[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. I.[1,2] AMINO ALCOHOLS DERIVED FROM 1,2,3,4-TETRAHYDROPHENANTHRENE

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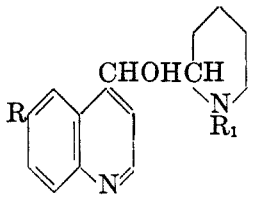
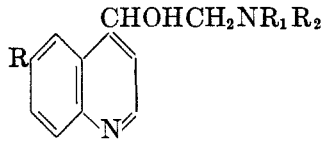
The most widely used and most effective antimalarials are at present quinine and Atabrine. Both the natural and the synthetic product are schizonticides, checking only the clinical symptoms of malaria. Plasmochin, less frequently used, appears to be the best known gametocide. A true causal prophylactic, attacking the parasite in the sporozoite-phase or shortly thereafter, has not been found as yet.

In January 1939, the Unit of Chemotherapy of the National Institute of Health was assigned the task of searching for new antimalarials with consideration of all three aspects of the chemotherapy of malaria, *i.e.*, the attack by chemicals of schizonts, gametocytes, and sporozoites. Atabrine and Plasmochin, the two outstanding antimalarials developed by the I. G. Farbenindustrie A.-G. of Germany, are structurally characterized by the aminodialkylaminoalkane side chain and a condensed aromatic-heterocyclic ring system. Whether a true causal prophylactic will have similar structural features appears doubtful. So far none of the active schizonticides or gametocides derived from acridine or quinoline have exhibited such an effect. Since the advent of these two synthetic drugs intensive efforts have been made by chemists, particularly in Great Britain, France, and Russia, to replace or improve them. This was attempted by changing, principally through minor variations, their structural features.

Attempts, however, to find substitutes for the natural product quinine, by adhering more closely to the alkaloid as a structural model, date back much further. These earlier efforts involved principally the synthesis of compounds of the two types I and II. In both structures the important feature of the alkaloid, *i.e.*, the amino alcohol grouping is retained.



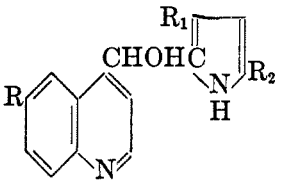
I



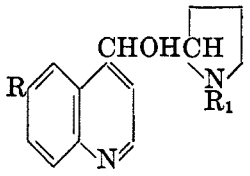
II

[1] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health.

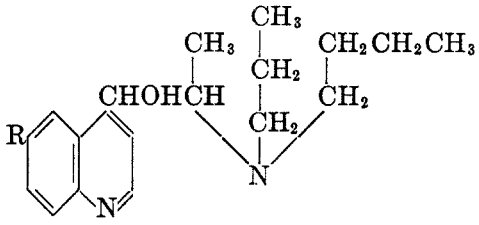
[2] Studies in the Phenanthrene Series XXVI. [Communication XXV, *J. Org. Chem.*, **5**, 313 (1940)].



Ia



Ib



III

R = H or Alkoxyl
R_1, R_2 = H or Alkyl

Thus Ruzicka and associates set forth to synthesize compounds of type I and Ib (1, 2, 3, 4). Karrer (5) prepared representatives of Ia, while Kaufmann (6) and Rabe (7, 8, 9) and their associates centered their synthetic efforts upon type II. Compounds of the latter type were then also prepared in the laboratories of the I. G. Farbenindustrie A.-G. (10). None of these efforts led to any chemotherapeutic success. It was eventually left to Ainley and King (11) to find in a series of compounds of type I, two members which showed a definite plasmodicidal effect in avian malaria. King and Work (12) then extended their searches for antimalarials, preparing compounds of type II. By increasing the size of the amino group, they succeeded in finding three members in that series which showed marked activity in avian malaria.

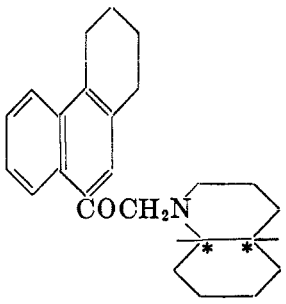
In the first stages of our search for new antimalarials, we had decided to prepare amino alcohols of type II carrying the side chain—CHOHCH(R_1)N(R_2R_3), and R_1, R_2, R_3 to be chosen in such manner that this portion could formally be considered a "quinuclidine with two C—C bonds disrupted"[3] (*e.g.*, III). While this work was under way it was largely anticipated by the paper of King and Work (12). In the meantime we also had submitted to antimalarial testing a considerable number of amino alcohols derived chiefly from phenanthrene, which had been prepared by Mosettig and co-workers[4] during the years 1929–1939 in attempting to find compounds with central narcotic properties. Surprisingly, a large percentage of these showed a significant plasmodicidal activity (*P. cathemerium*, *P. relictum*, *P. gallinaceum*, and *P. knowlesi*). We, therefore, immediately decided to exploit this field thoroughly, including also analogous derivatives of naphthalene and anthracene. It is obvious that by introducing one or more other substituents (*e.g.*, alkoxyl or halogen) into the nucleus, by partial saturation of the aromatic system, and by changes in the alkamine side

[3] Mosettig and Schmehl, unpublished results.

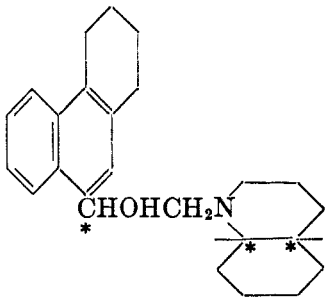
[4] See for Bibliography: "Studies on Drug Addiction," Small, Eddy, Mosettig, and Himmelsbach, Pub. Health Rep., Suppl., No. 138, 1938.

chain itself, the number of possible variations, even in one series only, becomes exceedingly large. As the work went on, however, the speedily carried out pharmacological and malarialogical tests enabled us to direct chemical efforts into the more promising channels, and consequently to avoid a good deal of superfluous work, seen in the light of therapeutic success.

The first paper of this series deals with amino alcohols derived from 1,2,3,4-tetrahydrophenanthrene. The starting point for this series was 9-acetyltetrahydrophenanthrene, which was prepared for the first time and elucidated in its structure by Bachmann and Struve (13). From this compound the alkamines were prepared in the customary manner *via* the bromo ketones and amino ketones.[4] Various difficulties were met with, particularly in the purification of amino ketones, further in their reduction, and in the purification of the final carbinolamines. In the catalytic reduction (PtO_2) of the *dl-trans*-decahydroquinolino ketone (IV), both of the possible diastereomeric amino alcohols (V) were obtained in an approximate ratio of 5:1.



IV



V

We also employed in this reaction *d-trans*-decahydroquinoline, but were able to detect in the reduction mixture of the amino ketone only one of the expected isomers.

The tolerated doses (chicks) of the drugs, varying roughly from 0.1–1.0 mg. per g. tend to increase from the dimethylamino derivative to the didecylamino derivative (Dr. Nathan B. Eddy, 14), while the effectiveness against *Plasmodium gallinaceum* tends to increase from the dimethylamino compound to the diheptylamino compound (Dr. G. Robert Coatney and Dr. W. Clark Cooper, 15). None of the drugs showed any activity towards sporozoite-induced *gallinaceum* malaria (15). SN 1796 (also recorded as NIH 204) and SN 5241 (also recorded as NIH 700) were investigated clinically. In spite of their high antimalarial activity in man, which equals approximately that of quinine, these two drugs have not been considered as practical competitors of quinine or Atabrine.[6] Some of the tetrahydrophenanthrene alkamines are very effective as inhibitors of plasma cholinesterase. This effectiveness is dependent upon the size of the dialkylamino group, passing through the maximum with the dipropylamino derivative (Dr. Charles I. Wright, 16).

[6] The clinical studies with these two drugs will be published by the several groups to whom these compounds were assigned by the Board for Coordination of Malaria Studies.

ACKNOWLEDGMENTS

We wish to thank Dr. R. C. Elderfield for a large supply of dihexylamine, and Mr. Edward A. Garlock, Jr., for carrying out the microanalyses.

TABLE I[5]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

SN	$C_{14}H_{13}$-9-	Q
1792	$CHOHCH_2N(CH_3)_2$	1/8
1793	$CHOHCH_2N(C_2H_5)_2$	1/2
1794	$CHOHCH_2N(C_3H_7)_2$	1/4
5868*	$CHOHCH_2N(i\text{-}C_3H_7)_2$	—
1798	$CHOHCH_2N(allyl)_2$	—
1795	$CHOHCH_2N(C_4H_9)_2$	1/8
5869*	$CHOHCH_2N(i\text{-}C_4H_9)_2$	—
1796 (NIH 204)	$CHOHCH_2N(C_5H_{11})_2$	1/4
6687*	$CH(OCOCH_3)CH_2N(C_5H_{11})_2$	—
8845	$CHClCH_2N(C_5H_{11})_2$	1/4
2673	$COCH_2N(C_5H_{11})_2$	—
3956	$CHOHCH_2N(i\text{-}C_5H_{11})_2$	1/4
5478	$CHOHCH_2N(C_6H_{13})_2$	1/4
5479*	$CHOHCH_2N(i\text{-}C_6H_{13})_2$	1/4
3957*	$CHOHCH_2N(C_7H_{15})_2$	1/2
3516	$CHOHCH_2N(C_8H_{17})_2$	1/2
5241* (NIH 700)	$CHOHCH_2N(C_9H_{19})_2$	1/4
5866*	$CHOHCH_2N(C_{10}H_{21})_2$	—
1799	$CHOHCH_2$piperidino	1/16
1803	$CHOHCH_2$morpholino	—
5990	$COCH_2$morpholino	—
2718	$COCH_2$tetrahydroquinolino	—
1800; 9930	$CHOHCH_2$*dl-trans*-decahydroquinolino	1/8
1800	$CHOHCH_2$*d-trans*-decahydroquinolino	1/8
1802	$CHOHCH_2$tetrahydro-*i*-quinolino	—

* See footnote 5.

EXPERIMENTAL

All melting points are uncorrected.

9-ω-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene (13). To a suspension of 20 g. of

[5] In Table I are listed the compounds which were submitted for biological investigations. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "Quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine. A dash indicates that the equivalent is less than $\frac{1}{16}$.

All compounds listed in the Table were administered as hydrochlorides, except SN 2718 which was administered as base.

The compounds marked with an asterisk were prepared, within a cooperative program, by Dr. Robert C. Elderfield at Columbia University. SN 8845 was prepared by Dr. Nelson K. Richtmyer of the National Institute of Health. The chemistry of these compounds will be described by the named authors in forthcoming issues of the Journal of Organic Chemistry.

9-acetyl-1,2,3,4-tetrahydrophenanthrene (13, 17)[7] in 100 cc. of dry ether cooled in an ice-salt bath was added dropwise with stirring 14.4 g. (4.8 cc.) of bromine over a period of thirty to forty-five minutes. While allowing the reaction mixture to warm to room temperature, air was blown over the surface to remove some hydrogen bromide. After cooling again to 0°, the pale yellow bromo ketone was filtered off and washed with a little cold ether. It weighed 18.5 g. and melted at 88–89°. By concentration of the filtrate 3.5 g. of an equally pure product was obtained, making the total yield 81%. This material was pure enough for the next step. A small sample recrystallized from methanol-ether melted at 91–92°, as reported by Bachmann and Struve (13).

In only one experiment out of an approximate total of twenty, a lower-melting, more soluble modification of the bromo ketone separated. It consisted of needles and melted at 70–72°. Upon dissolving it in warm ether, the higher-melting form separated immediately.

Amino alcohols. 9-ω-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene (one molecular equivalent) was suspended in four to five times its weight of ether and the secondary amine (two molecular equivalents) was added. The reactants were shaken together for two to fifteen hours depending upon the reactivity of the amine. In some cases, especially when large runs were made, it was necessary to cool during the initial stage of the reaction. After cooling in the ice-box, the precipitated secondary amine hydrobromide was filtered off, or washed out with water. From this point one of the four following procedures was used.

Procedure I (for compounds 2, 4, 6, 8, 15, 18, 24). The ether solution of the amino ketone was dried over sodium sulfate and made just acid to Congo red paper with alcoholic hydrogen chloride. The precipitated hydrochloride was recrystallized from the appropriate solvent combination (see Table). Unless Norit was used in this recrystallization the subsequent catalytic reduction proceeded sluggishly or not at all. The amino ketone hydrochloride was dissolved in methanol (or 95% ethanol) and the solution shaken under hydrogen with 0.025–0.05 g. of platinum oxide catalyst per gram of hydrochloride. The reductions required from eighteen to seventy-two hours and hydrogen absorption rarely came to a standstill but slowed to a constant rate after about one molecular equivalent had been absorbed. The catalyst was filtered off, the solvent evaporated under diminished pressure and the residual amino alcohol hydrochlorides were triturated with acetone or acetone-ether and purified by recrystallization. The yields (based on bromo ketone) were 40–70%.

Procedure II (for compounds 20, 21, 22, and 23). The ether solution of the *dl-trans*-decahydroquinolino (18)[8] ketone from which secondary amine hydrobromide had been filtered was concentrated somewhat, whence the crystalline base separated quantitatively. It was recrystallized from methanol, and hydrogenated in methanol solution (1.0 g. of base and 0.05 g. of platinum oxide in 50 cc. of methanol). At the end of fifteen to twenty hours, 1.2 molecular equivalents of hydrogen had been taken up, and absorption had slowed to the minimal constant rate. After removal of the catalyst, the solvent was evaporated under diminished pressure leaving a residue which crystallized on trituration with methanol. Upon standing in the ice-box overnight, 0.5 g. of solid separated. It was recrystallized from methanol to constant melting point (isomer A: see Table). Its hydrochloride was prepared by adding alcoholic hydrogen chloride to an acetone suspension of the amino alcohol base.

The original methanolic mother liquor was evaporated to dryness, and the oily residue was dissolved in the minimal amount of methanol and allowed to stand overnight. This yielded 0.1 g. of a diastereoisomer (B). Its hydrochloride was prepared as described above.

Procedure III (for compounds 2, 10, 11, 12). The dry ether solution of the amino ketone was treated with just enough dry gaseous hydrogen chloride to precipitate unchanged secondary amine as hydrochloride, which was filtered off. The amino ketone hydrochloride

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[7] We found the procedure by Bachmann and Struve (13) more advantageous for large scale preparation of this ketone, since in the subsequent bromination the 7-isomer is easily removed from the main product.

[8] The *trans*-decahydroquinoline was prepared according to Adkins and Cramer (18).

TABLE II

1,2,3,4-TETRAHYDROPHENANTHRENE DERIVATIVES

$C_{14}H_{13}$-9-	APPEARANCE	SOLVENT	M.P. °C.	FORMULA	% CARBON		% HYDROGEN		% CHLORINE	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
1. $COCH_2N(CH_3)_2 \cdot HCl$[a]	White diamond plates	Ethanol-acetone-ether	211–213*	$C_{18}H_{22}ClNO \cdot \frac{1}{2}H_2O$	69.09	68.68	7.41	7.20		
2. $CHOHCH_2N(CH_3)_2 \cdot HCl$	White prisms	Ethanol-acetone-ether	208–210	$C_{18}H_{24}ClNO$	70.69	70.37	7.91	7.91		
3. $COCH_2N(C_2H_5)_2 \cdot HCl$	Pale yellow needles	Ethanol-acetone-ether	190.5–192	$C_{20}H_{26}ClNO$	72.39	72.59	7.90	7.85		
4. $CHOHCH_2N(C_2H_5)_2 \cdot HCl$	White platelets	Acetone	161.5–163	$C_{20}H_{28}ClNO$	71.92	71.33	8.45	8.62	10.62	10.92
5. $COCH_2N(C_3H_7)_2 \cdot HCl$[b]	White needles	Acetone-ether	136–136.5	$C_{22}H_{30}ClNO \cdot H_2O$	69.91	69.69	8.54	8.11		
6. $CHOHCH_2N(C_3H_7)_2 \cdot HCl$	Broad white needles	Acetone-ether	171–173	$C_{22}H_{32}ClNO$	73.00	72.24	8.91	8.65		
7. $COCH_2N(C_4H_9)_2 \cdot HCl$[b]	White needles	Acetone-ether	91–98	$C_{24}H_{34}ClNO \cdot H_2O$	70.98	70.25	8.94	9.03	8.74	8.69
8. $CHOHCH_2N(C_4H_9)_2 \cdot HCl$	White prisms	Acetone-ether	136–137	$C_{24}H_{36}ClNO$	73.91	73.79	9.30	9.21		
9. $COCH_2N(C_5H_{11})_2 \cdot HCl$[b]	White rods	Ethyl acetate	147–150.5	$C_{26}H_{38}ClNO \cdot H_2O$	71.96	72.52	9.29	9.24		
10. $CHOHCH_2N(C_5H_{11})_2 \cdot HCl$	White prisms	Acetone-ether	134–135	$C_{26}H_{40}ClNO$	74.71	74.65	9.65	9.96	8.49	8.36
11. $CHOHCH_2N(C_6H_{13})_2 \cdot HCl$	White plates	Acetone-ether	136.5–137.5	$C_{28}H_{44}ClNO$	75.39	75.09	9.94	10.11		
12. $CHOHCH_2N(C_8H_{17})_2 \cdot HCl$	White rhombic plates	Ethyl acetate	110.5–112.5	$C_{32}H_{52}ClNO$	76.52	76.13	10.44	10.45		
13. $CHOHCH_2N(allyl)_2 \cdot HCl$	White square plates	Ethyl acetate	127–129	$C_{22}H_{28}ClNO$	73.82	73.45	7.88	8.19		
14. $COCH_2$-piperidino·HCl	White needles	Ethanol-ether	234*	$C_{21}H_{26}ClNO$	73.34	72.96	7.62	7.63		
15. $CHOHCH_2$-piperidino·HCl	White square plates	Ethanol-ether	235–235.5*	$C_{21}H_{28}ClNO$	72.91	72.67	8.16	8.12		
16. $COCH_2$-1,2,3,4-tetrahydroquinolino[c]	Yellow needles	Acetone	149.5–150.5	$C_{25}H_{25}NO$	84.47	84.10	7.09	7.35		
17. $COCH_2$-1,2,3,4-tetrahydroisoquinolino·HCl[d]	White needles	95% Ethanol	230–232*	$C_{25}H_{26}ClNO \cdot 2H_2O$					8.29	8.37
18. $CHOHCH_2$-1,2,3,4-tetrahydroisoquinolino·HCl	White plates	Ethanol-ether	221–223.5*	$C_{25}H_{28}ClNO$	76.22	76.05	7.16	7.32		

19. $COCH_2$-*dl-trans*-decahydroquinolino	Light yellow needles	Methanol	95–97	$C_{25}H_{31}NO$	83.07	82.70	8.64	8.65	
20. $CHOHCH_2$-*dl-trans*-decahydroquinolino (A)	White prisms	Ethanol	158.5–160	$C_{25}H_{33}NO$	82.60	82.38	9.15	9.17	
21. A·HCl	Short white needles	Ethanol-ether	229.5–230	$C_{25}H_{34}ClNO$	75.05	74.60	8.57	8.30	
22. $CHOHCH_2$-*dl-trans*-decahydroquinolino (B)	White hexagons	Methanol	139.5–141	$C_{25}H_{33}NO$	82.60	82.03	9.15	9.35	
23. B·HCl	Long white needles	Ethanol-ether	206–209	$C_{25}H_{34}ClNO$	75.05	74.98	8.57	8.82	
24. $CHOHCH_2$-*d-trans*-decahydroquinolino·HCl[e]	White needles	Ethanol-ether	216–218	$C_{25}H_{34}ClNO\cdot H_2O$	71.84	72.21	8.68	8.57	
25. $COCH_2$-Morpholino·HCl[f]	White needles	Ethanol-ether	225–228.5	$C_{20}H_{24}ClNO_2\cdot C_2H_5OH$	67.40	67.87	7.74	7.53	
26. $CHOHCH_2$-Morpholino·HCl	White prisms	95% Ethanol	230*	$C_{20}H_{26}ClNO_2$	69.04	68.83	7.53	7.74	

[a] Lost no water *in vacuo* at 77°. Decomposed at 110°. If m.p. is taken rapidly, it melts partially at 165°.

[b] Loss of water of crystallization was accompanied by decomposition. Thus, an accurate water determination could not be made.

[c] Reaction time was 48 hours for the preparation of this amino ketone. It absorbed 3 to 4 moles of hydrogen when reduced catalytically and no homogeneous crystalline products were isolable. Reduction with aluminum isopropoxide also failed to give the desired amino alcohol.

[d] The water determination was made by heating at 105–110° to constant weight. The m.p. after this was 239–241°. Calc'd for $2H_2O$, 8.42%. Found: 9.13%.

[e] Water determined by heating at 130° *in vacuo* (11 hrs.); m.p. 222–225°. Calc'd for H_2O, 4.31%. Found: 4.59%. *d-trans*-Decahydroquinoline was prepared essentially by the method of Mascarelli and Nigrisoli (20), and Mascarelli (21). Our m.p. for the *d*-bromocamphorsulfonate was 249–251°; reported, 239–240°. Our m.p. for the dextro base was the same as reported, but our rotation was $(\alpha)_D^{20}$ 8.28° (*c* 4.53, 95% EtOH); reported, $(\alpha)_D^{25}$ 4.86° (*c* 4.00). At present we cannot explain this discrepancy but intend to repeat the work in the near future.

[f] The analysis fits for one mole of alcohol of crystallization.

* Melts with decomposition.

was then precipitated as an oil by addition of gaseous hydrogen chloride in a very slight excess. On cooling and scratching, the hydrochloride crystallized and was collected. It was reconverted to the base with dilute aqueous ammonia. The base, after drying in ether, was dissolved in absolute ethanol (1.0 g. in 10 cc.) and the solution was shaken under hydrogen with platinum oxide catalyst (0.04 g. per gram of amino ketone). One molecular equivalent of hydrogen was absorbed in 25 to 35 hours, the reduction stopping at this point. After removal of catalyst and evaporation of solvent at reduced pressure, the residual oil was dissolved in ether and dry gaseous hydrogen chloride added in slight excess. The white amino alcohol hydrochloride precipitated in crystalline form on cooling. The yields were 60–70%.

9-(2-Dioctylamino-1-oxoethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride crystallized from ethyl acetate-ether in two forms. The less soluble one appeared as well-formed greenish prisms (m.p. 65–75°). It lost color slowly in the dry state and possibly contained a second mole of hydrogen chloride. The second form separated from the filtrate as hexagonal colorless plates (m.p. 81–83°). The latter could be converted to the prisms by recrystallizing in the presence of a little hydrogen chloride. Attempts to hydrogenate the compound melting at 65–75° resulted mainly in reductive fission, only a small amount of the expected amino alcohol hydrochloride being isolated. The second form (81–83°), on the other hand, absorbed hydrogen smoothly to give a 70% yield of the desired product. Either form when converted to the base could be reduced to the amino alcohol in 70% yield.

It may be generally stated, at this point, that the dialkylamino ketones, with the exception of dimethyl and diethyl, exhibited a green coloration in the presence of a large excess of alcoholic hydrogen chloride. This is believed to be due to the formation of a dihydrochloride of the amino ketone, the second molecule of hydrogen chloride being much less firmly held than that forming the normal hydrochloride.

Procedure IV (for compounds 10 and 13). In this procedure the amino ketones were reduced at the suggestion of Dr. E. M. Fry of this laboratory by the Meerwein-Ponndorf-Verley method, as modified by Lund (19), [see also "Organic Reactions" (22)]. The dried ether solution of the amino ketone was freed of solvent and reduced with 3 molecular equivalents of aluminum isopropoxide as a 3 *N* solution in isopropanol. Reaction time was one to two hours. The isopropanol was distilled under a water-pump vacuum, and the dark red oil remaining was partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water and dried over sodium sulfate and the solvent evaporated. The residual amino alcohol was evaporatively distilled at 180–190° (0.1–0.5 mm.). The almost colorless distillate was dissolved in dry ether and made just acid to Congo red paper with dry gaseous hydrogen chloride, whereupon the white crystalline hydrochloride precipitated. The average yield, based on bromo ketone was 60%.

It is now believed that the compounds described in procedure I could be more advantageously prepared by either procedure III or IV, especially by the latter. Time did not permit us to substantiate this by experiment.

SUMMARY

A series of amino alcohols carrying the side chain —$CHOHCH_2NR_2$ in position 9 of 1,2,3,4-tetrahydrophenanthrene has been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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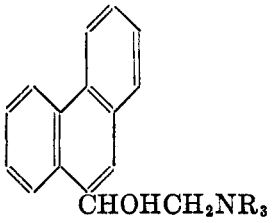
[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. II.[1,2] AMINO ALCOHOLS DERIVED FROM PHENANTHRENE

EVERETTE L. MAY AND ERICH MOSETTIG

Received December 12, 1944

In the foregoing paper (1) we described a series of amino alcohols carrying the ethanolamine side chain in position 9 of tetrahydrophenanthrene. This communication deals with amino alcohols in which the side chain is attached to the 9-position of phenanthrene itself (I).



I

The two series, thus, are structurally closely related, the difference consisting only in the degree of saturation of one of the terminal benzene rings of the phenanthrene nucleus. The amino alcohols were synthesized as described previously, namely, *via* the ω-bromomethyl ketones and amino ketones. The catalytic reduction of the amino ketones to the amino alcohols proved to be rather unsatisfactory. In the first place the hydrogen absorption took place considerably more slowly than was the case when the side chain was attached to the 2- or 3-position of the phenanthrene nucleus, or to the 9-position of tetrahydrophenanthrene. Secondly the tendency to absorb more than one molecular equivalent of hydrogen was quite pronounced. This surplus of hydrogen could not be accounted for by reductive fission. The desired amino alcohols, however, were obtained in good yields when aluminum isopropoxide in isopropanol was employed as the reducing agent. When 9-(2-*trans*-decahydroquinolino-1-oxoethyl)phenanthrene was reduced in this manner the two expected diastereomeric forms were obtained in the approximate ratio of 7:5.

The tolerated doses (chicks) of these compounds are approximately the same as those of their analogs in the "tetrahydro series". Also in this series one observes a definite decrease in toxicity with the increase in size of the dialkylamino group (Dr. Nathan B. Eddy) (2). In regard to effectiveness against *Plasmodium gallinaceum* it appears that, as a whole, the drugs of this series are somewhat superior to their "tetrahydro analogs" (Dr. G. Robert Coatney and Dr. W. Clark Cooper) (3). None of the drugs showed any activity towards

[1] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health.

[2] Studies in the Phenanthrene Series XXVII.

sporozoite-induced *gallinaceum* malaria (3). SN 8867 (also recorded as NIH 1111) was investigated clinically, and shown to have antimalarial activity

TABLE I[3]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

SN	$C_{14}H_9$-9-CHOHCH$_2$-	Q
1776	$N(CH_3)_2$	1/4
1777	$N(C_2H_5)_2$	1/2
1778	$N(C_3H_7)_2$	1/4
1779	$N(C_4H_9)_2$	1/4
5242	$N(C_5H_{11})_2$	1/4
5480	$N(C_6H_{13})_2$	1/4
6827	$N(C_7H_{15})_2$	1
6828	$N(C_8H_{17})_2$	1/2
8867 (NIH 1111)	$N(C_9H_{19})_2$	1/2
5970	*dl-trans*-decahydroquinolino (A)	1/8

(against *P. vivax*) greater than that of quinine.[4] The phenanthrene alkamines are more effective inhibitors of plasma cholinesterase than their "tetahydro analogs", but show the same general relationship between size of the dialkylamino group and inhibitory effect (Dr. Charles I. Wright) (4).

ACKNOWLEDGMENT

We wish to thank G. D. Searle and Company for the supply of large amounts of 9-acetylphenanthrene, Dr. R. C. Elderfield, Columbia University, for supplying us with dihexyl-, diheptyl- and dinonyl-amine, and Mr. Edward A. Garlock, Jr., of this Laboratory for carrying out the microanalyses.

EXPERIMENTAL[5]

9-Acetylphenanthrene was prepared by the method of Bachmann and Boatner (5).

9-ω-Bromoacetylphenanthrene (6) was prepared by adding one molecular equivalent of bromine dropwise to an ice-cooled stirred suspension of 9-acetylphenanthrene (1 g. in 5 cc. of ether). The bromo ketone was filtered off and washed with ether. The yield of product melting at 94–95° was quantitative.

9-(2-Dipropylamino-1-hydroxyethyl)phenanthrene hydrochloride. A mixture of 5 g. of 9-ω-bromoacetylphenanthrene, 3.5 g. of dipropylamine, and 30 cc. of dry ether was shaken mechanically overnight, cooled in the ice-box for one hour and the dipropylamine hydro-

[3] In Table I are listed the compounds which were submitted for biological investigations. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "Quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine. All compounds listed in the Table were administered as hydrochlorides, except SN 1777 which was administered as base. The synthesis of SN 1776 and SN 1777 has been described previously by Mosettig and van de Kamp (6).

[4] The clinical study with this drug will be published by the several groups to whom this compound was assigned by the Board of Coordination of Malaria Studies.

[5] All melting points are uncorrected.

bromide filtered off. The ether filtrate was made slightly acidic with 15% alcoholic hydrogen chloride, whence the amino ketone hydrochloride (4.4 g.) separated as an oil which soon crystallized. After one recrystallization from a methanol-ether mixture (Norit must be used to ensure success of the subsequent reduction) a yield of 3.1 g. was obtained. The melting point was 163–167°. When shaken under hydrogen with 0.14 g. of platinum oxide catalyst in 50 cc. of 80% aqueous methanol it absorbed 1.15 molecular equivalents of hydrogen in twenty hours. At this point hydrogenation had practically stopped. The syrup left after filtration and evaporation of solvent was dissolved in acetone, from which the amino alcohol hydrochloride separated in long white prisms (1.8 g.), m.p. 180–186°. From the mother liquor 0.3 g. of unchanged amino ketone hydrochloride was recovered.

It was not attempted to prepare this amino alcohol by the aluminum isopropoxide reduction method which was subsequently found more advantageous in this series of compounds.

Preparation of amino alcohols 2, 3, 4, 5, 6, 7, 8. 9-ω-Bromoacetylphenanthrene (1 molecular equivalent), the appropriate secondary amine (2 molecular equivalents), and dry ether (5 cc. per gram of bromo ketone) were mixed and the suspension shaken mechanically until all bromo ketone had disappeared (two to ten hours). After cooling in the ice-box for one to two hours, secondary amine hydrobromide was filtered off and the ether evaporated (the last few cubic centimeters *in vacuo*). To the oily residue was added 3 *N* aluminum isopropoxide (3.5 cc. per gram of bromo ketone employed in the preparation of the amino ketone) and the reduction carried out essentially by the procedure of Lund [See paper I (1)].

It was found advantageous when working with small amounts of material to use steam-bath heating and to replace liquid which distilled from the reaction mixture by dropwise addition of isopropanol. The time required for the reductions was one to two hours. Finally the isopropanol was evaporated *in vacuo* and the residue was partitioned between an excess of 10% sodium hydroxide and ether. The ether layer was washed twice with water, dried over sodium sulfate and the solvent evaporated. The dark-colored residue was evaporatively distilled at 190–210°/0.05 mm. The straw-colored distillate was dissolved in dry ether and the solution made slightly acidic with about 15% alcoholic hydrogen chloride. After some time (1 to 24 hrs.) the amino alcohol hydrochlorides crystallized. The yields ranged from 40% to 75%, based on bromo ketone.

9-(2-dl-trans-Decahydroquinolino-1-hydroxyethyl)phenanthrene. Thirty grams of 9-ω-bromoacetylphenanthrene, 28 g. of *dl-trans*-decahydroquinoline (7) and 150 cc. of U.S.P. ether were mixed, the whole was shaken mechanically for two hours and cooled in the ice-box. The *trans*-decahydroquinoline hydrobromide which separated was filtered off (21.5 g.). On standing overnight in the ice-box the ether filtrate yielded 25 g. of amino ketone melting at 93–95°. Twenty-two and five-tenths grams of this compound was reduced with 100 cc. of 3 *N* aluminum isopropoxide solution as described above. After about 3 hours the acetone test was negative. Upon distilling the solvent and partitioning the residue between an excess of 10% sodium hydroxide and about 100 cc. of ether, a crystalline solid separated in the ether layer. It was filtered off and the filtrate (X) was put aside. The precipitate (12 g., m.p. 143–145°) was suspended in acetone and treated with 11 cc. of 15% alcoholic hydrogen chloride. Overnight 5.7 g. of amino alcohol hydrochloride separated as clusters of fine white needles, m.p. 243–245°. One recrystallization raised the melting point to 249–250.5°, which did not change on further recrystallization. This compound is designated Isomer A. The corresponding base melted at 140–142°. The acetone filtrate of hydrochloride A yielded, on cooling in the ice-box, a 2.7 g. fraction of amino alcohol hydrochloride. By evaporation of the resulting filtrate to dryness and trituration of the residue with acetone, an additional 1.5 g. was obtained. These two fractions were combined and recrystallized from an absolute ethanol-ether mixture. The substance appeared in clusters of blade-like plates of m.p. 203–207° (Isomer B). It still contained a small amount of A which could be removed by conversion to the base (m.p. 154.5–156°) and recrystallization of the latter from alcohol. From the original ether filtrate X additional amounts of A (2.0 g.) and of B (1.5 g.) were obtained by acidification and fractional crystallization as described above. Thus the total yield of A was about 7.5 g. and of B about 5 g. of practically pure material.

TABLE II

PHENANTHRENE-9 AMINO ALCOHOLS

$C_{14}H_9$-9-$CHOHCH_2$-	SOLVENT	APPEARANCE[a]	M. P., °C.	FORMULA	CALC'D		FOUND	
					C %	H %	C %	H %
1. $N(C_3H_7)_2 \cdot HCl$	Acetone-ethanol-ether	Long prisms	189 –191	$C_{22}H_{28}ClNO$	73.82	7.89	73.73	8.02
2. $N(C_4H_9)_2 \cdot HCl$	Acetone-ether	Prisms	148 –149	$C_{24}H_{32}ClNO$	74.67	8.36	74.29	8.57
3. $N(C_4H_9)_2 \cdot H_2SO_4$	Acetone-ether	Prisms	118 –120	$C_{24}H_{33}NO_5S$	64.39	7.43	64.30	7.83
4. $N(C_5H_{11})_2 \cdot HCl$	Acetone-ether or ethyl acetate	Clusters of rods	129 –130	$C_{26}H_{36}ClNO$	75.43	8.77	75.43	8.97
5. $N(C_6H_{13})_2 \cdot HCl$[b]	Acetone-ether	Elliptical plates Prisms	128 –129.5 145 –146	$C_{28}H_{40}ClNO$	76.07	9.12	75.79	9.42
6. $N(C_7H_{15})_2 \cdot HCl$	Acetone-ether	Clusters of needles	126.5–129	$C_{30}H_{44}ClNO$	76.64	9.42	76.22	9.39
7. $N(C_8H_{17})_2 \cdot HCl$	Ethyl acetate-ether	Elliptical plates	133 –134.5	$C_{32}H_{48}ClNO$	77.14	9.71	76.67	9.69
8. $N(C_9H_{19})_2 \cdot HCl$	Acetone	Plates	133.5–135	$C_{34}H_{52}ClNO$	77.60	9.96	77.50	9.81
9. *d,l-trans*-Decahydroquinolino A	Ethanol	Prisms	140 –142	$C_{25}H_{29}NO$	83.52	8.13	83.38	8.25
10. Hydrochloride	Ethanol-ether	Fine needles	249 –250.5	$C_{25}H_{30}ClNO$	75.82	7.64	75.68	7.99
11. *d,l-trans*-Decahydroquinolino B	Ethanol	Prisms	154.5–156	$C_{25}H_{29}NO$	83.52	8.13	83.21	8.26
12. Hydrochloride	Ethanol-ether	Blade-like plates	200 –203	$C_{25}H_{30}ClNO$	75.82	7.64	75.74	7.83

[a] All compounds are white.

[b] Two interconvertible crystalline modifications.

SUMMARY

A series of amino alcohols carrying the side chain—$CHOHCH_2NR_2$ in position 9 of phenanthrene has been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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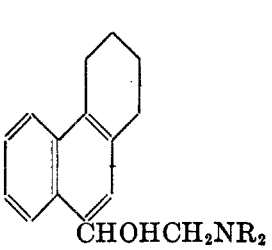
[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. III.[1,2] AMINO ALCOHOLS DERIVED FROM 3-METHOXYPHENANTHRENE

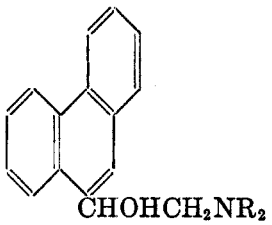
EVERETTE L. MAY AND ERICH MOSETTIG

Received January 1, 1945

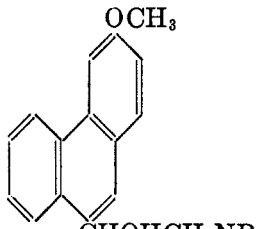
In the two foregoing communications (1, 2) we have shown that phenanthryl amino alcohols of the types I and II exhibit antimalarial activity to a high degree.



I



II



III

Since quinine as well as Atabrine and Plasmochin contain a methoxyl group, we thought that the introduction of a methoxyl group into I and II might enhance the efficacy of these amino alcohols. Mosettig and Burger (3) found that in the Friedel-Crafts reaction on 3-methoxyphenanthrene the acetyl group enters position 9 readily, the ketone being formed in 75% yield. From this compound we synthesized amino alcohols of type III as described in the foregoing papers, *via* bromo ketone and amino ketone. A great obstacle appeared to be the acquisition of 3-phenanthrol in large amounts. The hitherto most feasible preparation of 3-phenanthrol (sulfonation of phenanthrene and subsequent potassium hydroxide fusion) was developed by Werner and co-workers (4). Fieser (5) improved the process and was able to obtain this product in an over-all yield of 20–25%. Sandquist (6) prepared phenanthrene-3-sulfonic acid by sulfonation of 9-bromophenanthrene and subsequent debromination with zinc dust and ammonia. The results of Sandquist, however, could not be duplicated. Under the conditions given by this author, only the 3-sulfonic acid was obtained, but the yields were considerably lower than stated. Eventually we sulfonated 9-bromophenanthrene at steam-bath temperature as recommended by Anschütz and von Siemienski (7), and dehalogenated the reaction product catalytically. Phenanthrene-2- and 3-sulfonic acids were formed in over-all yields (from phenanthrene) of 8% to 10% and 40% to 45% respectively. A separation of the isomers was not necessary for our purpose. The 2-isomer is readily lost on the way to 3-methoxy-9-acetylphenanthrene,

[1] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health.

[2] Studies in the Phenanthrene Series XXVIII.

chiefly in the Friedel-Crafts reaction. The latter compound was obtained pure and in an over-all yield of about 40%, based on phenanthrene.

This series, as a whole, appears less effective against *Plasmodium gallinaceum* than the two previously described series (Dr. G. Robert Coatney and Dr. W. Clark Cooper) (8). The introduction of a methoxyl group into the 3-position of phenanthrene-9-alkamines proved to be therapeutically disadvantageous, while the toxicity (chicks) is not appreciably affected thereby (Dr. Nathan B. Eddy) (9). None of the drugs listed above showed any activity towards sporozoite-induced *galiinaceum* malaria (8).

ACKNOWLEDGMENTS

We wish to thank Dr. R. C. Elderfield, Columbia University, for the supply of dinonylamine, and Mr. Edward A. Garlock, Jr., for carrying out the microanalyses.

TABLE I[3]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

SN	$C_{14}H_8$ {3-OCH_3, 9-$CHOHCH_2$-}	Q
5985	$N(CH_3)_2$	1/4
5993	$N(C_2H_5)_2$	1/4
1780	$N(C_3H_7)_2$	1/4
1781	$N(C_4H_9)_2$	1/4
1782	$N(C_5H_{11})_2$	1/4
9470	$N(C_9H_{19})_2$	1/8
1784	morpholino	—
15046	*dl-trans*-decahydroquinolino (A)	1/16
1783	*dl-trans*-decahydroquinolino (B)	1/8

EXPERIMENTAL[4]

9-Bromophenanthrene (10). To an ice-cooled, well-stirred suspension of 200 g. of phenanthrene,[5] 400 cc. of chloroform and 400 cc. of absolute ether was added during fifteen minutes, 180 g. of bromine. The temperature remained at 10° to 15°. The mixture was then cooled to 3° for forty-five to sixty minutes, filtered, and the precipitate washed thoroughly with about 750 cc. of cold dry ether. This dibromo adduct was heated on the steam-bath with hand stirring until a clear melt was obtained (thirty to forty-five minutes). The yield of

[3] In Table I are listed the compounds which were submitted for biological investigations. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "Quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine. A dash indicates that the equivalent is less than 1/16. The compounds were administered as hydrochlorides.

[4] All melting points are uncorrected.

[5] A 98% pure Reilly product was used.

9-bromophenanthrene melting at 57–60° was 225 g. (87%). After one recrystallization from petroleum ether (b.p. 60–71°) it melted at 61.5–63°.

Sulfonation of 9-bromophenanthrene. A mixture of 103 g. of 9-bromophenanthrene (m.p. 57–60°) and 50 cc. of 96% sulfuric acid was heated in a steam-bath for one hour with frequent shaking. Sixteen cubic centimeters more of sulfuric acid was then added and the heating and shaking continued another hour. Finally, a second 16 cc.-portion of sulfuric acid was addd and the heating and shaking continued forty to sixty minutes until the reaction mixture had set to a grayish semi-solid mass. It was diluted with 1000–1500 cc. of water and made alkaline with 200 g. of potassium hydroxide. After cooling, the precipitated potassium salts of the sulfonation product were collected, washed with a 3% potassium chloride solution, and air-dried. This crude product weighed 170 g.

Phenanthrene-2- and 3-sulfonic acids. Fifty grams of the above crude sulfonation product (dried at 100°) and 5 g. of palladium-charcoal catalyst (5% Pd) were suspended in 300 cc. of 95% ethanol, 300 cc. of water, and 5 cc. of concentrated hydrochloric acid. The mixture was shaken under hydrogen at atmospheric pressure until absorption had ceased (about five hours). It was heated almost to the boiling point, filtered and the clear solution concentrated to 350–400 cc. Upon cooling to 10°, the isomeric potassium phenanthrene sulfonates precipitated and were collected. The yield was 27 g. When this mixture was separated according to Fieser (5), the 2- and 3-phenanthrene sulfonates were obtained in a ratio of 1 to 4. A potassium hydroxide fusion of the sulfonate mixture yielded 2- and 3-phenanthrols in a similar ratio. Their separation was effected by sublimation followed by fractional crystallization from a benzene-petroleum ether (30–60°) mixture and finally from benzene.

3-Methoxy-9-acetylphenanthrene. The mixture of the isomeric potassium phenanthrene sulfonates was fused as described by Fieser (5) for either of the pure isomers except that milder temperature conditions were used. The nickel crucible containing the potassium hydroxide melt was immersed in a metal-bath maintained at a temperature of 290–295°, and the temperature of the melt was 250–260° while adding the sulfonate mixture. During the following five-minute period, the bath temperature was 320–325° and the melt temperature remained at 280–285°. The yield of crude phenanthrol (m.p. 100–104°) was quantitative. Fifty grams of this material was dissolved in 125 cc. of 10% sodium hydroxide and the solution mechanically stirred while 25 cc. (35 g.) of dimethyl sulfate was added in twenty minutes without external cooling. After an additional one-half hour of stirring at room temperature, the reaction mixture was cooled to 0° and the methoxyphenanthrene filtered off. The air dried precipitate (46.5 g.) was distilled in a high vacuum to yield 42 g. of colorless product which solidified almost immediately. From the sodium hydroxide filtrate 5 g. of hydroxyphenanthrene was recovered by acidification with hydrochloric or acetic acids.

The 42 g. of distilled product was added in small portions to a stirred mixture of 54 g. of aluminum chloride, 180 cc. of nitrobenzene, and 18 g. of acetyl chloride. The temperature was maintained at −5° to 0°. Stirring was continued at 0° until the contents of the flask became rather pasty. The reaction product was then allowed to stand for twenty-four hours at +5°. It was decomposed with an ice-hydrochloric acid mixture and the nitrobenzene distilled with steam. The dark residual oil was dried in chloroform over sodium sulfate and distilled under a high vacuum. The distillate (45 g.) was recrystallized from methanol. The yield of 3-methoxy-9-acetylphenanthrene melting at 97–98.5° was 38.5 g. (over-all yield from phenanthrene, about 40%).

3-Methoxy-9-ω-bromoacetylphenanthrene (3b). To an ice-cooled, mechanically stirred mixture of 18 g. of 3-methoxy-9-acetylphenanthrene (m.p. 97–98.5°), 100 cc. of dry chloroform, and 100 cc. of dry ether was added 4.0 cc. of bromine during a fifteen-minute period. The reaction mixture was allowed to warm to room temperature, cooled again in ice and the precipitated bromo ketone collected and washed with cold ether. The yield of product melting at 116–117° was 15.4 g. By concentration of the mother liquor and dilution with methanol a second fraction of 3.6 g. melting at 114–116° was obtained.

3-Methoxy-9-(2-dipropylamino-1-hydroxyethyl)phenanthrene hydrochloride. Ten grams of 3-methoxy-9-ω-bromoacetyl phenanthrene, 6 g. of dipropylamine, and 60 cc. of dry ether were shaken together for about fifteen hours. After cooling in the ice-box, dipropylamine hydrobromide (5.5 g.) was filtered off. The filtrate was slowly acidified with 11 cc. of 12% alcoholic hydrogen chloride. The amino ketone hydrochloride separated as an oil which slowly crystallized. It was collected (8.6 g.) and recrystallized from an absolute ethanol-ether mixture. The use of Norit was necessary to ensure success of the subsequent reduction. The yield of recrystallized product (fine needles) was 7.5 g. It absorbed 85% of one molecular equivalent of hydrogen in 48 hours when shaken under hydrogen with 0.3 g. of platinum oxide catalyst in 100 cc. of 80% aqueous methanol. The catalyst was removed, the solvent evaporated *in vacuo*, and the syrupy residue dissolved in the minimal amount of warm acetone. On standing for some time, the amino alcohol hydrochloride crystallized. After cooling in ice a yield of 4.5 g., m.p. 200–202°, was obtained. By dilution of the filtrate with ether a second fraction of 0.8 g., melting at 125–135° was obtained. It was found to be a mixture of amino ketone and amino alcohol hydrochlorides and when subjected to reduction as described above yielded 0.5 g. more of amino alcohol salt. The latter fraction was combined with the 4.5 g. and the whole recrystallized from absolute ethanol-ether. Yield 4.1 g., m.p. 202.5–203°; clusters of large needles.

Anal. Calc'd for $C_{23}H_{30}ClNO_2$: C, 71.19; H, 7.79.
Found: C, 70.91; H, 8.15.

3-Methoxy-9-(2-dibutylamino-1-hydroxyethyl)phenanthrene hydrochloride. This compound was prepared essentially as described for the dipropyl homolog. Nine grams of bromo ketone yielded 7.7 g. of purified amino ketone hydrochloride. It absorbed 1.2 molecular equivalents of hydrogen in twenty-two hours when shaken with 0.4 g. of platinum oxide catalyst in 100 cc. of 80% aqueous methanol. From acetone-ether 4.6 g. of amino alcohol hydrochloride separated. It melted at 174.5–176°. From the mother liquor a 1.1 g. mixture of amino ketone hydrochloride and amino alcohol hydrochloride was obtained. Recrystallization of the 4.6 g. from acetone-methanol-ether gave 3.9 g. of clusters of large white needles melting at 176–177°.

Anal. Calc'd for $C_{25}H_{34}ClNO_2$: C, 72.18; H, 8.24.
Found: C, 71.90; H, 8.54.

3-Methoxy-9-(2-morpholino-1-hydroxyethyl)phenanthrene hydrochloride. This amino alcohol was prepared similarly to the two foregoing ones. The over-all yield from bromo ketone was about 60%. From methanol-ether the product crystallized in white hexagonal plates melting at 211–212° (decomp.).

Anal. Calc'd for $C_{21}H_{24}ClNO_3$: C, 67.45; H, 6.47.
Found: C, 67.45; H, 6.85.

It was not attempted to prepare the foregoing amino alcohols by the aluminum isopropoxide procedure described subsequently.

3-Methoxy-9-(2-dimethylamino-1-hydroxyethyl)phenanthrene hydrochloride. To 2.8 g. of a dry ethereal solution containing 3 g. of dimethylamine was added 5 g. of 3-methoxy-9-ω-bromoacetylphenanthrene. The mixture was alternately shaken and cooled in ice-water for a period of fifteen minutes, then allowed to stand at room temperature for two hours. After thorough cooling in the ice-box, dimethylamine hydrobromide (1.8 g.) was filtered off and washed with dry ether. The ether was evaporated (the last few cc. *in vacuo*) and the oily amino ketone remaining reduced with 25 cc. of 3 *N* aluminum isopropoxide as described previously (2). The time required for the reduction was 2.5 hours. After evaporating the isopropanol under a vacuum, the residue was partitioned between an excess of 10% sodium hydroxide and ether. The ether layer was washed twice with water, dried over sodium sulfate and acidified with 3 cc. of 20% alcoholic hydrogen chloride. The amino alcohol salt precipitated as a brown solid in a yield of 3.9 g. After one recrystallization from ethanol-ethyl acetate (Norit) 2.8 g. of product melting at 206–207° was obtained. Burger and Mosettig (3b) report 207–208°.

3-Methoxy-9-(2-diethylamino-1-hydroxyethyl)phenanthrene hydrochloride. A mixture of

5.6 g. of 3-methoxy-9-ω-bromoacetylphenanthrene, 2.9 g. of diethylamine and 40 cc. of dry ether was shaken for fifteen hours and cooled in the ice-box for one hour. Diethylamine hydrobromide (2.3 g) was filtered off and the ether filtrate washed twice with water, dried over sodium sulfate, and the solvent evaporated. The amino ketone residue was reduced as above with 25 cc. of 3 *N* aluminum isopropoxide solution. Reduction time was 1.5 hours and the yield of crude hydrochloride (m.p. 180–185°) was 3.7 g. Upon recrystallization from absolute ethanol (Norit) 2.6 g. of product melting at 189–191° was obtained. For analysis a small sample was recrystallized to the constant melting point 191–192° and dried at 110° for one hour.

Anal. Calc'd for $C_{21}H_{26}ClNO_2 \cdot \frac{1}{2}H_2O$: C, 68.37; H, 7.36; H_2O, 2.4.
Found: C, 68.70; H, 7.19; H_2O, 2.5.

3-Methoxy-9-(2-diamylamino-1-hydroxyethyl)phenanthrene hydrochloride. This compound was prepared essentially as described for the dimethyl and diethylamino homologs. The amino alcohol base was evaporatively distilled at 0.01 mm. pressure and at an air-bath temperature of 200–205°. The distillate was dissolved in ether and made slightly acidic with alcoholic hydrogen chloride. The over-all yield of hydrochloride from bromo ketone was about 40%. It crystallized from acetone-ether as white shining plates and melted at 124–125.5°.

Anal. Calc'd for $C_{27}H_{38}ClNO_2$: C, 73.03; H, 8.62.
Found: C, 73.01; H, 8.89.

3-Methoxy-9-(2-dinonylamino-1-hydroxyethyl)phenanthrene hydrochloride. This compound was prepared like the foregoing dimethyl, diethyl, and diamyl derivatives. Here, however, the reduction product was not distilled. On acidifiation of the dried ether solution of the crude base, 4.8 g. of hydrochloride (from 5 g. of bromo ketone) melting at 123–127° was obtained. One recrystallization from an acetone-ether mixture yielded 4.1 g. of needles which melted at 91–95°. Another recrystallization from acetone gave 3.0 g. of plates melting at 130–133°. Finally for analysis a small sample was recrystallized again from acetone. The melting point was 131–134°. The modification melting at 91–95° was not encountered after the recrystallization from acetone-ether.

Anal. Calc'd for $C_{35}H_{54}ClNO_2$: C, 75.56; H, 9.78.
Found: C, 75.56; H, 9.77.

3-Methoxy-9-(2-dl-trans-decahydroquinolino-1-hydroxyethyl)phenanthrene hydrochloride. A mixture of 3.8 g. of 3-methoxy-9-ω-bromoacetylphenanthrene, 3.4 g. of *dl-trans*-decahydroquinoline (11), and 25 cc. of dry ether was shaken for eighteen hours. After cooling in ice, 2.7 g. of *trans*-decahydroquinoline hydrobromide was filtered off, the filtrate was evaporated to dryness, and the residue reduced with 20 cc. of 3 *N* aluminum isopropoxide. The dried ether solution of the amino alcohol was evaporated to dryness and the residual oil triturated with a 2:1 ether-petroleum ether (30–60°) mixture, whereupon prisms separated. After cooling they were collected. The yield of base (Isomer A) melting at 148–154° was 1.3 g. It was suspended in acetone and neutralized with 15% alcoholic hydrogen chloride. The resulting hydrochloride weighed 1.3 g. and melted at 247–248° (decomp.). On recrystallization from 95% ethanol-ether it appeared as rectangular plates of m.p. 247–248° (decomp.).[6]

Anal. Calc'd for $C_{26}H_{32}ClNO_2$: C, 73.29; H, 7.58.
Found: C, 72.79; H, 7.37.

The base was prepared by adding aqueous ammonia to the hydrochloride followed by extraction with ether. It crystallized from absolute ethanol as prisms of m.p. 154–155°.

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[6] In a previous experiment the isomer A was isolated first as the hydrochloride and appeared as small prisms of m.p. 228.5–230° (decomp.). *Anal.* Found: C, 68.17; H, 7.25. It was dried for four hours at 130°. *Anal.* Found: C, 68.28; H, 7.28. The base, liberated from this salt melted at 154–155° and gave no depression in a mixture m.p. with that prepared from the hydrochloride of m.p. 247–248°. After about two years, the hydrochloride of m.p. 228.5–230° had changed to the one melting at 247–248°.

Anal. Calc'd for $C_{26}H_{31}NO_2$: C, 80.16; H, 8.02.
Found: C, 79.68; H, 8.02.

Another recrystallization from absolute ethanol did not change the melting point. The resulting sample gave C, 79.68; H, 8.17.

The ether-petroluem ether filtrate from base A was acidified with 3 cc. of 15% alcoholic hydrogen chloride, and the precipitated oil was just dissolved by addition of acetone. Overnight in the ice-box 2.0 g. of a crystalline hydrochloride melting at 229–233° (decomp.) separated. After two recrystallizations from 95% ethanol-ether the melting point was constant at 240–241° (decomp.). This is Isomer B. It was in the form of large needles.

Anal. Calc'd for $C_{26}H_{32}ClNO_2$: C, 73.29; H, 7.58.
Found: C, 73.09; H, 7.58.

The base could not be induced to crystallize.

SUMMARY

A series of amino alcohols carrying the side chain—$CHOHCH_2NR_2$ in position 9 and a methoxy group in position 3 of phenanthrene, has been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. I. AMINO KETONE METHOD[1]

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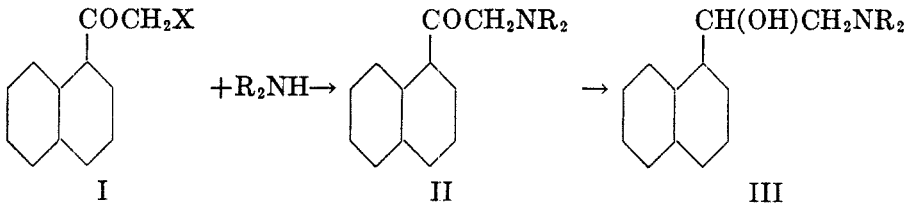
Attempts to discover an effective antimalarial drug have been based in part on modification of the structure of quinine. Among the simplest compounds examined were ethanolamine derivatives such as quinolyl-$CHOHCH_2NR_2$ and related substances in which other aryl groups, including naphthyl, replaced quinoline (1, 2, 3, 4). A thorough investigation of such compounds was undertaken at the National Institute of Health to determine the influence of various nuclei on antimalarial action (5). It was found that, among others, compounds of this type containing the α-naphthyl nucleus possessed some antimalarial activity in avian malaria (6), although King and Work (1) had not observed activity in similar substances. The corresponding β-naphthyl derivatives were much less active. As part of a cooperative project with the National Institute of Health, we have extended the work on the α-naphthyl compounds by synthesizing dialkylaminomethyl-1-naphthalenemethanols in which the naphthalene nucleus was substituted in various positions with halogen or methoxyl and in which the dialkylamino group varied from dimethylamino to di-*n*-decylamino.

The conventional synthesis of such ethanolamine derivatives involves the reaction of an α-halo ketone such as I with a dialkylamine to yield an amino ketone II which is then reduced.



I II III

All of the compounds reported in this paper were prepared thus, although yields were often poor and final products difficult to purify. These difficulties led us to devise other synthetic methods which are described in later papers of this series (7, 8). It is probable that the compounds reported in the present paper could have been prepared more readily by these alternative procedures.

The halo ketones, I, which served as starting materials for the synthesis, were

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

usually prepared in excellent yield by brominating the corresponding methyl ketones which were available from the Friedel and Crafts reaction. In the case of 4-methoxy-1-chloroacetonaphthone, however, it was easier to prepare the chloro ketone directly by a Friedel and Crafts reaction of 1-methoxynaphthalene and chloroacetyl chloride. The details of the synthesis of the 4-halogen-substituted acetonaphthones are given in a separate paper (9).

The reaction of naphthacyl halides with dialkylamines has been reported by Day and co-workers (10, 11) in addition to the investigators already mentioned (1, 5, 6) but the instability of the resulting amino ketones has not been emphasized. α-Amino ketones are known to be unstable when the amino group is primary or secondary (10, 12), but α-dialkylamino ketones are usually easy to isolate, although they are frequently reduced to amino alcohols without isolation, and in some cases the yields are poor (1). It was reported that piperidinomethyl 4-quinolyl ketone darkened on exposure to light (3) while α-tetrahydroisoquinolino-β-acetonaphthone turned pink on standing in air and the yield in its synthesis decreased if the reaction mixture stood too long (11). Small and co-workers (5, 6) noted the ease of decomposition of aryl dialkylaminomethyl ketones, especially on heating (as in attempted distillation), and reported that purification before reduction had never been necessary in their experience. We followed their directions with but few modifications, adding the α-haloacetonaphthone slowly to two molecular equivalents of dialkylamine in dry ether to avoid quaternary salt formation, $(RCOCH_2)_2NR_2^+X^-$. After removing the dialkylamine hydrohalide by filtration, the ether was evaporated under diminished pressure and the ketone reduced directly. It was always contaminated by a dark red impurity which made isolation of the final product difficult.

When the halo ketone was 4-methoxy-1-naphthacyl halide all attempts to isolate α-dialkylaminomethyl-4-methoxy-1-naphthalenemethanols failed until the reactions were carried out under nitrogen. In the presence of oxygen the products were largely intractable tars, although 4-methoxy-1-naphthoic acid was isolated in several instances. Time was not available for an examination of this side reaction, but it was found desirable to carry out both the condensation and reduction of the methoxyl-substituted compounds under nitrogen and even then the crude products were dark and purification difficult. With halogen-substituted naphthalene compounds the exclusion of air seemed to do little good.

The reduction of α-dialkylaminomethyl aryl ketones has usually been carried out catalytically (1, 2, 3, 4, 10, 11).[2] Among chemical methods of reduction may be mentioned sodium and alcohol (13, 14, 15), sodium amalgam (16), and sodium ethoxide in alcohol (17). Aluminum amalgam has given hydramine fission (2, 17). The aluminum isopropoxide-isopropyl alcohol method appears to have been tried first on this type of compound by Work (2), who reported that the reduction of 1,12-dipiperidino- or bisdiethylamino-2,11-diketododecane or the corresponding tetradecanes was impractical with this reagent. Burger

[2] These references are to the reduction of naphthyl and quinolyl compounds and represent only a few of the many examples in the literature.

and co-workers (18, 19, 20) used the method successfully on a number of heterocyclic dialkylaminomethyl ketones and Mosettig and co-workers (5, 6) applied it independently to a large variety of aryl dialkylaminomethyl ketones. In many cases it gives cleaner products and avoids cleavage of the C—N bond. Since most of our compounds contained nuclear halogen which might be removed by other reducing agents, aluminum isopropoxide was always used.

Table I summarizes the compounds which we prepared by the amino ketone method.

EXPERIMENTAL

All melting points are corrected unless marked otherwise.

Analyses were by Jack W. Ralls or Bruce Day.

ω-Bromo-1-acetonaphthones. To 0.5 mole of the substituted acetonaphthone in 450–500 ml. of anh. ether in a 1-liter, 3-necked flask equipped with mechanical stirrer and dropping-funnel was added 0.5 mole of bromine with stirring. The first drops of bromine were added at the b.p. of ether, and when the solution had decolorized, the flask was cooled in ice as bromine was added dropwise. The bulk of the bromine was added at 10–15° in fifteen to thirty minutes and the solution was then washed several times with water to remove hydrogen bromide and dried over anh. potassium carbonate or magnesium sulfate. This solution was usually diluted with anh. ether and used directly in the amine condensation, but the ether could also be removed and the solid product recrystallized. Table II gives the data on the compounds prepared. 2-Methoxy-ω-bromo-1-acetonaphthone was contaminated with an oily impurity which made purification necessary.

The synthesis of 4-haloacetonaphthones is described in the next paper (9). One trial of Noller and Adams' directions (21) for the synthesis of 2-methoxy-1-acetonaphthone by the Friedel and Crafts reaction between 2-methoxynaphthalene and acetic anhydride gave a low yield, and most of the material used was prepared from acetyl chloride (22) by a procedure involving remethylation of the crude reaction product with dimethyl sulfate before isolation. The yield was 50% and 21% of 2-methoxynaphthalene was recovered.

4-Methoxy-ω-halo-1-acetonaphthone (23, 24). The ω-chloro compound was prepared according to the directions of Madinaveitia and Puyal (23) in 64–70% yield, m.p. 70.5–71° after recrystallization from alcohol. The m.p. has been reported as 70° (23) and 85° (24). The product could be distilled at 1 mm. with some decomposition.

4-Methoxy-ω-bromo-1-acetonaphthone (25) was prepared similarly from bromoacetyl bromide in 70% yield, m.p. 72.5–73.0° (reported 70°). It was also obtained in lower yield by using acetyl chloride in the Friedel and Crafts reaction with 1-methoxynaphthalene and brominating the product.

ω-Dialkylamino-1-acetonaphthones. To 0.2 mole of dialkylamine[3] in 150–200 ml. of anh. ether in a 500 ml., 3-necked flask equipped with a mercury-sealed stirrer, condenser, and dropping-funnel, was added 0.1 mole of substituted ω-halo-1-acetonaphthone in 75 to 100 ml. of anh. ether during fifteen minutes or longer. It was sometimes necessary to cool the solution and to add more ether to facilitate stirring.

With 2- or 4-methoxy-ω-halo-1-acetonaphthones a nitrogen atmosphere was maintained throughout this reaction and the subsequent reduction, but with halogen-substituted ω-bromo-1-acetonaphthones this was usually not done. After further stirring and standing for one hour or longer the dialkylamine hydrohalide, usually pure (95–99% yield), was removed by filtration. If the ethereal filtrate does not remain free from crystalline precipitate the reaction is not complete. Any hydrobromide remaining may be removed by

[3] The dialkylamines were supplied in most cases by Dr. Elderfield and co-workers of Columbia University, although some were purchased commercially from Eastman or Sharples.

TABLE I

DIALKYLAMINOMETHYL-1-NAPHTHALENEMETHANOLS

SN*	SUBSTITUENT ON NAPHTHALENE	DIALKYLAMINO GROUP	YIELD BASED ON ω-HALOGEN COMPOUND, %	YIELD OF ACETONE IN THE REDUCTION, %	M.P., °C	SOLUBILITY AT 25° OF HYDROCHLORIDE, G./100 ML. WATER	ANALYSES			
							C		H	
							Calc'd	Obs.	Calc'd	Obs.
	4-Chloro	Dimethyl	22	35	[a]185–186.5	[a]2.52	[a]59.78	59.11	5.73	5.96
5277		Diethyl	31	52	[b]185.5–186.5	18.8 (?)	[d]61.15	61.57	6.74	6.91
5376		Dipropyl	19	65	[b]185–187	0.69	[d]63.15	63.43	7.36	7.45
5243		Dibutyl	37–45	65	[b]125–126	0.81	[d]64.86	65.01	7.89	7.98
6761		Dihexyl	34	77	[e] 48–48.5		[e]73.91	74.11	9.31	9.47
5375		Piperidino	18	28	[b]dec.	0.93	[d]62.58	62.58	6.49	6.18
8741	4-Fluoro	Diethyl	37		[b]150–151	137	[d]64.53	64.64	7.11	7.23
6716		Dibutyl	42	84	[b]119–121	2.2	[d]67.87	68.16	8.26	8.38
	4-Bromo	Dimethyl			[a]166–168		[a]54.08	54.16	5.17	5.30
5904		Diethyl	45	71	[c]92–93 [b]200–201	2.01	[d]53.57	53.54	5.90	5.99
6473		Dipropyl	45	68	[c]40–41 [b]181–183	0.60	[d]55.89	56.09	6.52	6.65
6453		Dibutyl	55	65	[c]44–45 [b,g]135–150	0.55	[d]57.91	57.91	7.05	7.11
6454		Dihexyl	25	74	[c]53–54 [b]101–103	0.00	[e]66.34	66.49	8.59	8.47
7734	2-Methoxy	Diethyl	23	37	[b]180.5–181.5	7.34	[d]65.90	65.69	7.81	7.51
7001		Dibutyl	46	63	[b]171–172	1.50	[d]68.93	68.66	8.81	9.02
7375		Dihexyl	47	70	[b,f]113–114 128–130	0.14	[d]71.14	70.91	9.55	9.73
5246	4-Methoxy	Diethyl	6–31	65	[b]180–182 unc.		[d]65.90	65.84	7.81	7.91
6409		[h]Dibutyl	8	54	[b]147–149 unc.		[d]68.93	68.45	8.81	8.90

* See footnote 1.

[a] Data for the *p*-toluenesulfonate. The hydrochloride could not be induced to crystallize.

[b] M.p. of the hydrochloride.

[c] M.p. of the free amine.

[d] Analysis of the hydrochloride.

[e] Analysis of the free amine.

[f] The compound exists in two crystalline forms.

[g] This broad m.p. is due to a change in crystalline form.

[h] This product was distilled in a molecular still at 10^{-4} mm. It has been prepared by other methods (7, 8).

extraction with a little dilute sodium hydroxide, but this step was often omitted and the ether removed from the filtrate directly under reduced pressure. The ether may also be removed at ordinary pressure, especially with the more stable 4-bromo-ω-dialkylamino-1-acetonaphthones. The condensation of tetrahydroquinoline with 4-chloro-ω-bromo-1-acetonaphthone was not successful using these directions; the yield of tetrahydroquinoline hydrobromide was only 25% after fifteen hours.

In early runs, when the reaction of 4-methoxy-1-naphthacyl chloride with di-*n*-propyl- or di-*n*-butyl-amine and subsequent reduction were carried out without exclusion of air, the only pure product isolated was 4-methoxy-1-naphthoic acid, m.p. 239.5–241.5°. The literature contains melting points ranging from 230° to 239° for this compound (23, 26, 27, 28). The mixture of our sample and one, m.p. 242–243°, obtained by the action of carbon dioxide on 4-methoxy-1-naphthylmagnesium bromide (29) showed the m.p. 240–243°.

Aluminum isopropoxide reduction. Isopropyl alcohol was dried by refluxing over and distillation from calcium oxide, followed by distillation from aluminum isopropoxide. Aluminum isopropoxide was prepared by the method of Young, Hartung, and Crossley (30) and usually distilled before use.

The dark red or brown dialkylaminoacetonaphthone was dissolved in 200–300 ml. of isopropyl alcohol in a 500-ml. flask (standard taper neck) and 110 ml. of 1 *M* aluminum isopropoxide in isopropyl alcohol was added. This solution was distilled at a moderate

TABLE II

ω-BROMOACETONAPHTHONES

SUBSTITUENT	YIELD %	M.P., °C	ANALYSES			
			% C		% H	
			Calc'd	Obs.	Calc'd	Obs.
4-Chloro[a]	92	50–51	50.83	51.07	2.84	3.03
4-Bromo[a]	92–95	68–68.5	43.95	43.97	2.46	2.61
4-Fluoro[b]	72–75	43–44	53.98	54.06	3.02	3.13
2-Methoxy[a]	60	100–101	55.95	55.91	3.97	4.03

[a] Recrystallized from hexane.

[b] Recrystallized from methanol.

rate (20–30 drops per minute) through a 40-cm. all-glass Vigreux column or from the apparatus described by Lund (31), and acetone determined in the distillate by the method of Marasco (32). If excess volatile dialkylamine is present (as diethylamine) it interferes with this determination. The distillation was continued until the distillate contained very little acetone (usually four to eight hours), more isopropyl alcohol being added if necessary. The yields of acetone are detailed in Table I. The isopropyl alcohol was then removed from the reaction mixture under reduced pressure and the dark red product treated by one of the following methods.

When the dialkylamine group was lower than dibutylamine or in all cases where the substituent on the naphthalene nucleus was methoxyl, the reduction product was treated with ice and 200 ml. of 10 *N* sodium hydroxide with stirring until all the solid had disappeared. With those methoxynaphthalene derivatives having dialkylamine groups above butyl this solution was steam distilled to remove the dialkylamine (for dihexylamine, under reduced pressure). The reaction mixture was then extracted several times with ether, the ether washed with water and dried thoroughly. The product was precipitated as the hydrochloride by using dry ethereal hydrogen chloride or by passing the dry gas over the surface. It was usually necessary to add the hydrogen chloride in several portions, separating the solid after each addition, and to avoid an excess of the reagent in order to avoid oils, but with the 4-bromo compounds these precautions were unnecessary. 4-Methoxy-α-dibutyl-

aminomethyl-1-naphthalenemethanol could not be obtained in a crystalline state by this method until it had been distilled in the molecular still. With the dimethylamino compounds the hydrochlorides were always obtained as oils and purification was accomplished through the *p*-toluenesulfonates.

4-Halo-dibutyl- or dihexyl-aminomethyl-1-naphthalenemethanols were more easily purified by treating the crude reduction product with 500 g. of ice and 200–250 ml. of 3 *N* sulfuric acid with stirring until no solid was present. The resulting 2-phase system was extracted several times with benzene, the benzene solution washed with water, three times with 5% sodium bicarbonate, again with water and concentrated on the steam-bath to 300 ml. Anh. ether was added and the hydrochloride precipitated as above. The yields of pure products, physical constants, and analyses are given in Table I.

SUMMARY

Eighteen α-dialkylaminomethyl-1-naphthalenemethanols containing halogen or methoxyl in the 2- or 4-position of the naphthalene nucleus have been synthesized by condensation of the corresponding ω-bromo- or -chloro-1-acetonaphthones with dialkylamines and reduction of the amino ketones by aluminum isopropoxide.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. II. 1-HALONAPHTHALENES IN THE FRIEDEL AND CRAFTS REACTION[1]

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4-Haloacetonaphthones were needed as starting materials for the synthesis of certain amino alcohols (1). It appeared probable that these could be synthesized most readily by the Friedel and Crafts reaction on halonaphthalenes, and this has proved to be the case.

Schweitzer (2) first prepared a bromoacetonaphthone by the reaction of 1-bromonaphthalene, acetyl chloride, and aluminum chloride in carbon disulfide but did not prove the structure of the product. Dziewonski and Sternbach (3) carried out the same reaction and showed that 4-bromo-1-acetonaphthone was the principal product, by oxidation to 4-bromo-1-naphthoic acid. Other examples of the Friedel and Crafts reaction with 1-halonaphthalenes have been reported by Mayer and Muller (4) and by Fieser and Desreux (5). The latter found that the reaction between 1-chloronaphthalene and 4-methylhydrindene-7-carboxylic acid chloride failed when excess 1-chloronaphthalene was used as the solvent, but in tetrachloroethane an 82% yield of a substituted benzanthrone was obtained. No account was taken of isomers present in minor amounts in any of these investigations.

We have found that reactions of 1-fluoro-, 1-chloro- and 1-bromo-naphthalene with acetyl chloride and aluminum chloride in carbon disulfide proceed smoothly. Table I gives the yields of ketone fraction and the amounts of 4-halo-1-acetonaphthone which could be isolated from this fraction in each case. The product from 1-fluoronaphthalene was shown to be mainly one isomer by oxidation to pure 4-fluoro-1-naphthoic acid and formation of a pure picrate in high yield. Its structure was proved by replacing the fluorine with ethoxyl to form the known 4-ethoxy-1-acetonaphthone.

The separation of 4-chloro-1-acetonaphthone from the ketone mixture from 1-chloronaphthalene was accomplished readily through the picrate; a similar separation of 4-bromo-1-acetonaphthone could be used, but the pure isomer was more readily obtained by crystallizing the ketone mixture from hexane. In the Friedel and Crafts reaction with 1-bromonaphthalene, tar formation was reduced by carrying out the reaction at 0° and the yield of the 1,4-isomer was greatly improved, but with 1-chloronaphthalene a corresponding temperature change had only slight effect.

After separation of 4-chloro-1-acetonaphthone, the residual ketone fraction from the 1-chloronaphthalene reaction failed to give a crystalline picrate. It

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California at Los Angeles.

was shown by oxidation to be a mixture, and semicarbazone formation permitted isolation of a pure ketone which was readily oxidized to a pure chloronaphthoic acid different from any known 1-chloronaphthoic acid. The ketone was shown to be 6-chloro-2-acetonaphthone by its degradation to 2,6-dichloronaphthalene. 6-Chloro-2-acetonaphthone was also obtained in 33% yield by the Friedel and Crafts reaction with 2-chloronaphthalene in nitrobenzene.

No success attended attempts to isolate a pure bromoacetonaphthone other than the 1,4-isomer, although the isolation of ketone derivatives with broad melting ranges indicated that other isomers were present.

It is not surprising that halogen migration occurs during the Friedel and Crafts reaction with 1-chloro- and 1-bromo-naphthalenes since it has been observed with a variety of aromatic halides (6). Although Roux (7) obtained no 2-chloronaphthalene when the 1-compound was refluxed with aluminum chloride in carbon disulfide, he did observe the rearrangement under these conditions with 1-bromonaphthalene, and the chloro derivative was rearranged by aluminum chloride at 100° in the absence of solvent. Fieser and Desreux (5) found that 1-chloronaphthalene was rearranged to the 2-isomer by standing

TABLE I

HALOACETONAPHTHONES

HALONAPHTHALENES	YIELD OF KETONE FRACTION (DISTILLED ONCE), %	% OF KETONE FRACTION ISOLATED AS 4-HALO-1-ACETONAPHTHONE
1-Fluoronaphthalene	92	>95
1-Chloronaphthalene	89–91	55–65
1-Bromonaphthalene		
at b.p. CS_2	84–88	52
at 0°	90–95	72

overnight at room temperature with aluminum chloride in tetrachloroethane. The conversion of 1,4- or 1,5-dibromonaphthalene to the 2,6-compound (8) and the isomerization of 1-bromonaphthalene by aluminum chloride in the presence of various metals (9) have also been reported.

We found that 1-chloronaphthalene was readily isomerized to the 2-isomer by refluxing with large amounts of aluminum chloride in carbon disulfide while anhydrous hydrogen chloride was passed in slowly. Considerable polymerization also occurred, and under the same conditions 1-bromonaphthalene gave a viscous tar from which only naphthalene could be isolated. These experiments confirm earlier observations (6) that isomerization of halogen compounds in the Friedel and Crafts reaction increases in the order F < Cl < Br.

The Friedel and Crafts reaction with 1-chloronaphthalene was carried out in nitrobenzene to observe the influence of another solvent, but much polymerization occurred, a ketone fraction was isolated in only 31% yield, and this gave a low yield of the picrate of 4-chloro-1-acetonaphthone, indicating that there is more isomerization in this solvent and that directive influences are different.

It was anticipated that in addition to 1,4-acetonaphthones and small amounts

of rearranged products, other isomers resulting from the introduction of the aceto group into the second ring would be obtained. These were not found and the high yields of 1,4-derivatives suggest that other isomers were formed in no more than minor amounts. This is somewhat surprising since halogen atoms, like meta-directing groups, are known to deactivate a benzene ring and might likewise be expected to lead to some heteronuclear electrophilic substitution in naphthalene. The nitration of 1-chloronaphthalene, which gives 31–63% of 1,4-, 30–65% of 1,8- and 0–20% of 1,5-isomer (10), and sulfonation which gives a mixture of 1,4- and 1,5-compounds (10b) support this expectation; but 1-fluoronaphthalene appears to give exclusively 4-substitution (11) and 1-bromonaphthalene is said to nitrate in the 4-position (10b). It would be interesting to know the relative rates of substitution reactions in naphthalene and halonaphthalenes, but further time was not available for the investigation of this and other questions involved in orientation and substitution in naphthalene systems.

EXPERIMENTAL

All melting points are corrected.

Analyses by Mr. Jack Ralls and Mr. Bruce Day.

4-Chloro-1-acetonaphthone. In a 5-liter, 3-n. flask fitted with an efficient, water-cooled condenser connected to a gas trap, a mechanical stirrer with a strong motor, and 250-ml. dropping-funnel were placed 357 g. (2.2 moles) of α-chloronaphthalene, 1500 ml. of carbon disulfide, and 350 g. (2.5 moles) of anh. aluminum chloride. The flask was immersed in an ice-bath and 172 ml. (2.3 moles) of acetyl chloride was added during forty-five minutes. The α-chloronaphthalene was redistilled Eastman best grade, b.p. 140–143°/20 mm. and the other materials were reagent grade. After the addition was complete the ice-bath was removed, the bright yellow mixture allowed to reach room temperature, and vigorous stirring continued for four hours. The reaction mixture was then refluxed for two hours on a water-bath, as much of the solvent decanted as possible and the yellow slush that remained decomposed in a 4-liter beaker with ice and 100 ml. of conc'd hydrochloric acid. The hydrolysis mixture was kept cold by adding more ice as needed.

The heavy oil layer was separated from the aqueous phase, which was extracted once with ether. The ether was combined with the oil, washed with water, 3 *N* sodium hydroxide, again with water and dried over anh. magnesium sulfate. The solvent was removed and the product distilled under reduced pressure, b.p. 155–165°/3–4 mm. The yield was 400–410 g. (89–91%).

The picrate was prepared by dissolving the ketone in 3200 ml. of alcohol and adding 494 g. of picric acid (containing about 10% water). Warming gave a clear solution from which the picrate crystallized on standing overnight in the refrigerator. The crystals were removed by filtration and the filtrate concentrated by removing 2 liters of alcohol on the water-bath. When the residue was cooled in ice it deposited an additional amount of the picrate which was recrystallized from alcohol and combined with the main fraction. This picrate (about 550 g.) melted at 87–88° and was satisfactory for further work, although the m.p. could be raised to 91–91.5° by further recrystallization. Further concentration of the filtrate was unprofitable, and the mixture of ketones recovered from it failed to yield a crystalline picrate.

In a 5-l., 3-n. flask fitted with a mechanical stirrer and thermometer were placed 318 g. (3.0 moles) of sodium carbonate in 3 liters of water. The solution was brought slowly to about 80° on a water-bath with stirring while the picrate was added in small portions during ninety minutes and heating was continued during thirty minutes more. The solution was

then cooled in ice to 35° and filtered to remove sodium picrate, which was washed twice with ether. The ethereal solution was washed with water, 3 *N* sodium hydroxide solution, and water and dried over anh. sodium sulfate. The solvent was removed and the product distilled under reduced pressure, b.p. 140–142°/1.5 mm., yield 230–270 g. (50–60% over-all). The compound solidified on long standing in the cold room and had the melting point 4–10°.

Essentially the same yields were obtained by adding the aluminum chloride to the chloronaphthalene, acetyl chloride and carbon disulfide.

The filtrate from the separation of 4-chloro-1-acetonaphthone picrate yielded only picric acid on concentration. It was treated with sodium carbonate and water, worked up as for the 4-chloro isomer and gave a ketone mixture (20–25% of the original ketone fraction), b.p. 157–162°/3 mm., which did not form a picrate under the conditions used above. A semicarbazone mixture was obtained, m.p. 204–216°, which gave a pure semicarbazone, m.p. 223.5–225.5°, by repeated crystallization from dioxane; a mixed m.p. with 4-chloro-1-acetonaphthone semicarbazone showed a large depression. The semicarbazone was decomposed with dil. sulfuric acid and the oily ketone oxidized by hypochlorite without purification to a chloronaphthoic acid, m.p. 283–284.5° after recrystallization from methanol, glacial acetic acid, and toluene.

Anal. Calc'd for $C_{11}H_7ClO_2$: C, 63.94; H, 3.41.
Found: C, 64.00; H, 3.47.

The amide was prepared, m.p. 206–207°.

4-Chloro-1-acetonaphthone semicarbazone, m.p. 224.5–225.5° after recrystallization from dioxane.

Anal. Calc'd for $C_{13}H_{12}ClN_3O$: C, 59.66; H, 4.62.
Found: C, 59.84; H, 4.68.

4-Chloro-1-acetonaphthone oxime, m.p. 124–125° from dilute methanol.

Anal. Calc'd for $C_{12}H_{10}ClNO$: C, 65.61; H, 4.59.
Found: C, 65.26; H, 4.65.

A Beckmann rearrangement of this oxime with phosphorus pentachloride gave 4-chloro-1-acetonaphthalide, m.p. 190–191° (reported 186.5°) (11) which was hydrolyzed with 3 *N* hydrochloric acid to 4-chloro-1-naphthylamine, m.p. 96–97° (reported, 98°) (12).

4-Chloro-1-naphthoic acid was obtained by hypochlorite oxidation of the ketone at 60–70° for three hours, and was recrystallized from glacial acetic acid. It had the m.p. 223–224°, compared with the value 210° reported by Friedländer and Weisberg (13), and was identical with the acid obtained by the action of carbon dioxide on 4-chloro-1-naphthylmagnesium iodide (14).

Anal. Calc'd for $C_{11}H_7ClO_2$: C, 63.94; H, 3.41.
Found: C, 63.88; H, 3.45.

The amide was prepared, m.p. 235–236°.

Anal. Calc'd for $C_{11}H_8ClNO$: C, 64.24; H, 3.92.
Found: C, 64.49; H, 4.18.

6-Chloro-2-acetonaphthone.[2] To a solution of 24.2 g. (0.15 mole) of 2-chloronaphthalene (20) in 100 ml. of nitrobenzene stirred and cooled in ice was added 13.2 g. (0.16 mole) of acetyl chloride (reagent grade), and then during fifty-five minutes 22.6 g. (0.17 mole) of anh. aluminum chloride. The red reaction mixture was stirred for two hours, allowed to stand for five hours and decomposed with ice and hydrochloric acid. The nitrobenzene layer was washed with water and the solvent removed by steam distillation. The product solidified, was recrystallized from alcohol which did not remove color and was distilled,

[2] Anderson and Johnson (15) obtained a 1:1 mixture of 6-bromo-2-acetonaphthone and 2-bromo-1-acetonaphthone from 2-bromonaphthalene in nitrobenzene, but in the chloro series the ease with which the 2,6-compound was purified suggests that relatively little of the 1,2-isomer was present. 2-Methoxyl (16, 17) and 2-methyl (18) are known to direct the aceto group to the 6-position in nitrobenzene solution. The procedure which we used was similar to that of Rivkin (19) for β-acetonaphthone.

b.p. 225–227°/4.2 mm., yield 13.5 g. (44%). The distillate was a solid which was recrystallized from methanol to give 10.2 g. of white needles, m.p. 83.5–84°.

Anal. Calc'd for $C_{12}H_9ClO$: C, 70.42; H, 4.43.
Found: C, 70.35; H, 4.53.

The oxime was prepared in 82% yield, m.p. 154–155° from aqueous methanol. It was rearranged with phosphorus pentachloride to 6-chloro-2-acetonaphthalide, which was hydrolyzed without purification by six-hour refluxing with 3 *N* hydrochloric acid, and the amine isolated as the hydrochloride. Diazotization and treatment with cuprous chloride gave 2,6-dichloronaphthalene, m.p. after recrystallization from alcohol 137–138°, over-all yield from 6-chloro-2-acetonaphthone, 31%, The m.p. of 2,6-dichloronaphthalene is given as 135° and 140–141° depending on the preparative method (21).

The carefully purified 6-chloro-2-acetonaphthone was oxidized with hypochlorite to 6-chloro-2-naphthoic acid for comparison with the acid obtained by oxidizing the by-product ketone above. Three recrystallizations from toluene gave colorless crystals, m.p. 285–286°, mixed m.p. with earlier sample, 284–285.5°. The amide was prepared, m.p. 206.5–207° and gave no depression with the earlier sample.

The isomerization of 1-chloronaphthalene was accomplished by adding during half an hour 23.8 g. (0.18 mole) of anh. aluminum chloride to a solution of 16.3 g. (0.1 mole) of 1-chloronaphthalene in 90 ml. of carbon disulfide with stirring and refluxing. The mixture turned red at once and was soon purple. Dry hydrogen chloride was passed in slowly for one-half hour, the mixture was refluxed for 1.5 hours and finally stirred for 3.5 hours at room temperature before decomposing with ice and dil. hydrochloric acid. The carbon disulfide layer was separated, washed with water, dried over anh. potassium carbonate and concentrated. Distillation at reduced pressure of the black oil which resulted gave 7.8 g. (48% recovery) of a yellow oil, b.p. 140–153°/22 mm. (bath 250–305°) and left 6–7 g. of a black solid in the distilling flask. The yellow oil solidified partially in an ice-bath and was recrystallized 3 times from alcohol to give 1 g. of 2-chloronaphthalene, m.p. 59–60°, no depression with authentic 2-chloronaphthalene (20).

4-Fluoro-1-acetonaphthone. In a 1-liter, 3-n. flask equipped with a mercury-sealed stirrer, a powerful motor, an efficient reflux condenser, and a short piece of large-diameter rubber tubing connected to a dry Erlenmeyer were placed 57.6 g. (0.4 mole) of 1-fluoronaphthalene (11), b.p. 139–141°/96 mm., 48 g. (0.6 mole) of acetyl chloride, and 350 ml. of carbon disulfide. The solution was brought to reflux on a water-bath, the bath removed, and 93 g. (0.7 mole) of anh. aluminum chloride added with stirring during half an hour so that gentle refluxing was maintained. The reaction mixture was refluxed on a water-bath with stirring for two hours, stirred for 3.5 hours longer without heating and worked up as usual. The product was an oil, b.p. 138–140°/4.5 mm., yield 65.5 g. (92%). On standing in the cold-room it crystallized, m.p. 36–38.5°. It could be recrystallized from hexane with excellent recovery, m.p. 38–39°.

The picrate of 4-fluoro-1-acetonaphthone was prepared using equimolar amounts of recrystallized ketone and picric acid in alcohol. An 88% yield of product, m.p. 90–91°, was obtained as a first crop, and systematic concentration and recrystallization produced an almost quantitative yield. Carefully recrystallized samples melted at 90.5–91.5°. The ketone was readily recovered from the picrate.

When the hexane filtrates from crystallization of distilled 4-fluoro-1-acetonaphthone were concentrated and converted to picrate, the yield of material, m.p. 90–91°, was 88% of that theoretically possible if the concentrate were pure 1,4-isomer. This indicates that the once-distilled product from the Firedel and Crafts reaction contained no more than traces of isomers of 4-fluoro-1-acetonaphthone.

4-Fluoro-1-naphthoic acid. Oxidation of 4-fluoro-1-acetonaphtone with hypochlorite at 60–70° gave an essentially quantitative yield of 4-fluoro-1-naphthoic acid, m.p. after two recrystallizations from toluene, 224.5–225°.

Anal. Calc'd for $C_{11}H_7FO_2$: C, 69.47; H, 3.71.
Found: C, 69.15; H, 3.84.

4-Ethoxy-1-acetonaphthone. A solution of 1.86 g. (0.01 mole) of 4-fluoro-1-acetonaphthone in 10 ml. of alcohol was added to 1.12 g. (0.02 mole) of potassium hydroxide in 5 ml. of alcohol and the mixture warmed fifteen minutes on the steam-bath. The orange-red reaction mixture was diluted with 20 ml. of water and the oil that separated soon solidified. It was taken up in ether and the ether solution washed twice with water, dried over anh. magnesium sulfate, filtered, evaporated to 10 ml. and cooled in ice, which gave 1.8 g. (84%) of beautiful white crystals, m.p. 76.5–77.5°. After one recrystallization from dry ether the m.p. was 77.5–78°. The m.p. of 4-ethoxy-1-acetonaphthone has been reported as 78–79° (22) and as 77° (23).

An analogous reaction with 4-nitro-1-fluoronaphthalene has been reported (11).

4-Bromo-1-acetonaphthone. In a 2-liter apparatus like that described for 4-fluoro-1-acetonaphthone were placed 207 g. (1 mole) of 1-bromonaphthalene (Eastman best grade), 82 ml. (1.1 moles) of acetyl chloride and 800 ml. of carbon disulfide. The solution was maintained at 0–2° while 173 g. (1.3 moles) of anh. aluminum chloride was added with stirring. Stirring was continued for seventy-five hours at 0–2° and six hours at 15–16°, or until the evolution of hydrogen chloride was negligible. The temperature was maintained at 0° with cooling and efficient stirring while 700 ml. of 3 *N* hydrochloric acid was added and the carbon disulfide layer was worked up as usual. The residual oil was distilled, b.p. 165–175°/2–4 mm., yield 230–240 g. (90–95%). The product was crystallized from 1300 ml. of hexane (Skellysolve B) with slow cooling to −10°, yield 162–172 g. (65–69%), m.p. 47.0–47.5°. Concentration of the mother liquors gave 65 g. of a mixture of isomers which was not separated successfully by crystallization or picrate formation.

The 4-bromo-1-acetonaphthone prepared by Dziewonski and Sternbach (3) was a liquid.

Similar runs at the b.p. of carbon disulfide gave 84–88% yields of ketone fraction from which only 52% could be recovered as pure 4-bromo-1-acetonaphthone by crystallization. The mother liquors were converted to picrate as for the 4-chloro compound. The first crop, 96 g., m.p. 89–91° (not improved by crystallization) was decomposed in the usual manner and gave 30 g. of pure ketone after 3 recrystallizations from hexane. The second crop of picrate, m.p. 70–80°, yielded no pure ketone. The over-all yield of 4-bromo-1-acetonaphthone was 54–57%.

Anal. Calc'd for $C_{12}H_9BrO$: C, 57.85; H, 3.64.
Found: C, 57.17; H, 3.79.

4-Bromo-1-acetonaphthone oxime was readily obtained in good yield and crystallized from 50% alcohol, m.p. 143–144° [reported 142° (3)]. The residual ketone mixture was also converted to a mixture of oximes, m.p. 90–120°, from which the only isolable pure product was the oxime of 4-bromo-1-acetonaphthone.

4-Bromo-1-acetonaphthonesemicarbazone was obtained in excellent yield, m.p. 225.5–226.5°, from alcohol [reported m.p. 215–217° (3)]. The residual ketone mixture gave a mixture of semicarbazones, m.p. 190–200°, which could not be separated.

An attempt was made to separate the ketone mixture by chromatographing the 2,4-dinitrophenylhydrazones, but without success.

4-Bromo-1-naphthoic acid. Hypochlorite oxidation of 4-bromo-1-acetonaphthone in dioxane at 60° gave 4-bromo-1-naphthoic acid, m.p. 217–219°, recrystallized from alcohol [reported 217–220° (24]. Similar oxidation of the residual ketone mixture gave a mixture of acids which could not be separated by crystallization.

SUMMARY

Excellent yields of 4-fluoro-, 4-chloro-, and 4-bromo-1-acetonaphthones have been obtained by the Friedel and Crafts reaction between acetyl chloride and the 1-halonaphthalene. It was necessary to purify the 4-chloro compound through the picrate, but the 4-bromo isomer was crystallized directly. The 4-fluoro compound was free from isomeric impurities. Some 6-chloro-2-aceto-

naphthone, resulting from halogen migration, was isolated from the residual ketone mixture from the synthesis of 4-chloro-1-acetonaphthone. A similar isomerization of 1-chloro- to 2-chloro-naphthalene was demonstrated under the influence of aluminum chloride and hydrogen chloride at the boiling point of carbon disulfide.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS OF SOME INDENE AND DIHYDRONAPHTHALENE DERIVATIVES RELATED TO STILBESTROL

MILTON SILVERMAN AND MARSTON TAYLOR BOGERT

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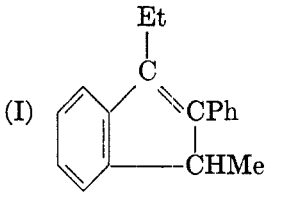
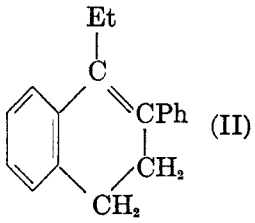
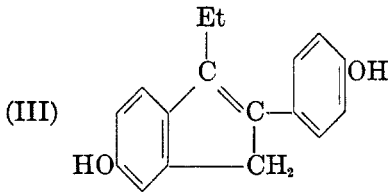
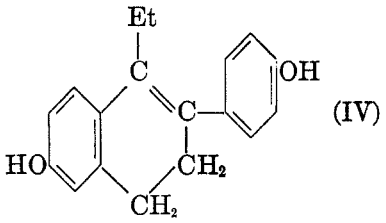
In April, 1941, Plentl and Bogert (1) published an article on the synthesis of tricyclic hydrocarbons related to stilbestrol, in which they described how compounds (I) and (II) were prepared from ethyl phenylcyanacetate and *alpha*- or *beta*-phenylethyl bromide, and mentioned the fact that experiments were already under way in these laboratories for the synthesis, by similar reactions, of the more important corresponding alkoxy and hydroxy (III, IV) derivatives.



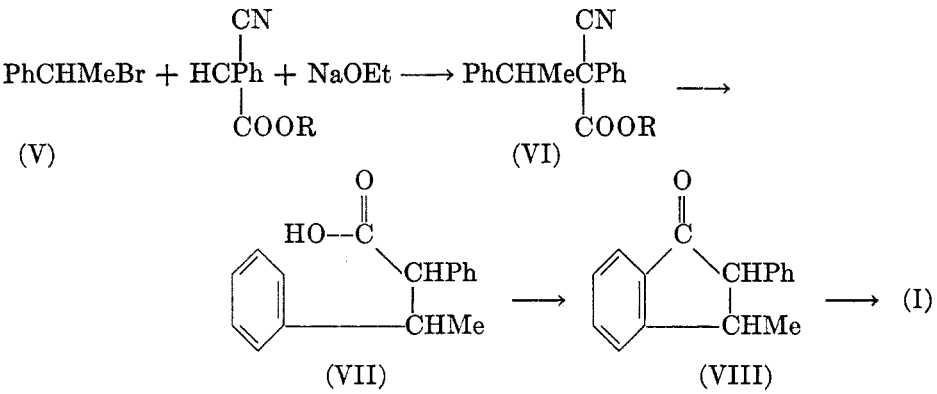




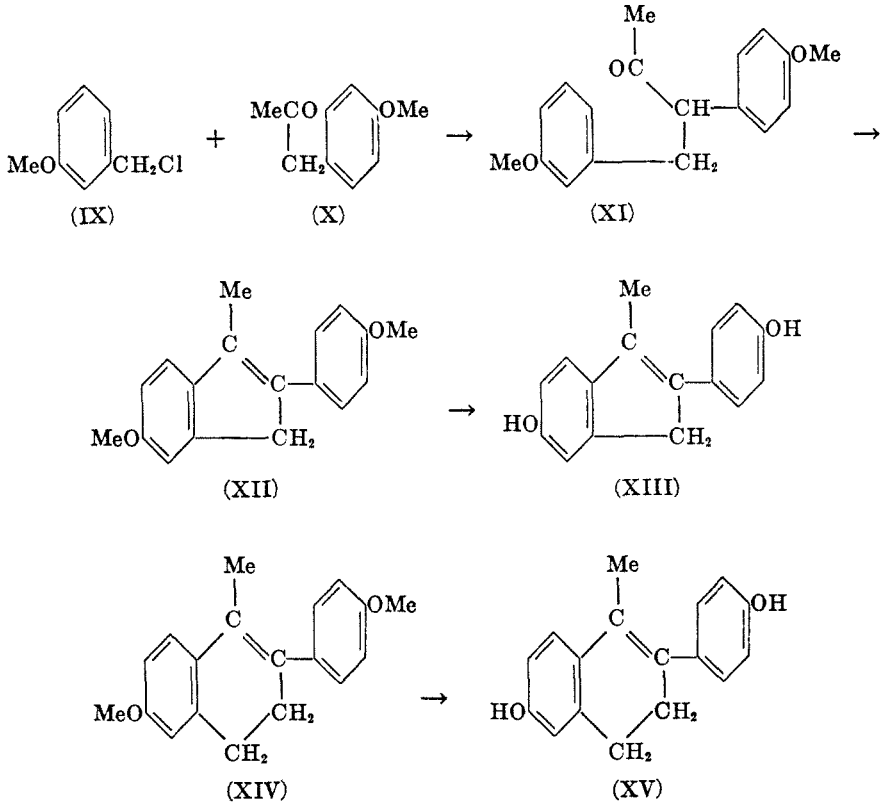


Unfortunately, both authors of the present communication were compelled, by various war duties, to interrupt these experiments temporarily and, before the resumed work could be completed, the articles by Salzer (2, 3) and by Solmssen (4) appeared, anticipating some of our own results, as explained beyond.

The Plentl and Bogert synthesis can be summarized as follows:



FLOW SHEET 1



When the isomeric $PhCH_2CH_2Br$ was used instead of (V), the product was the corresponding dihydronaphthalene derivative (II).

The method employed by Salzer (2, 3) for the synthesis of the indene derivative (XIII) is shown in Flow Sheet 1.

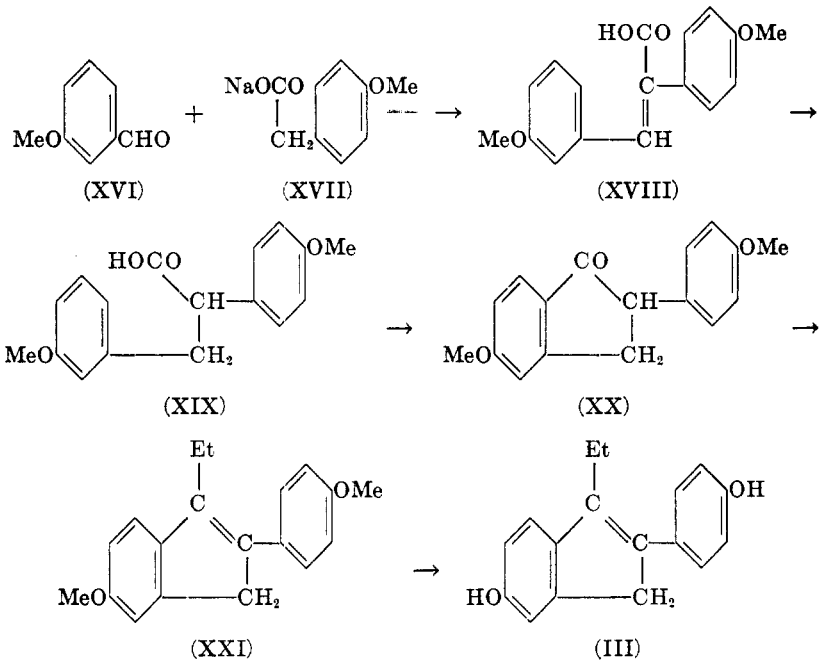
When the homologous (*m*) $MeOC_6H_4CH_2CH_2Br$ was used in place of (IX), the analogous dihydronaphthalene derivatives (XIV and XV) were formed.

Salzer failed to record the yield of several of his compounds and his final product (XIII) was obtained as an impure oil, which he identified by preparation of a crystalline diacetate (m.p. 131°) and by remethylation to (XII). He found it impossible to prepare any homologs of (XIII) or (XIV), with other substituents in position 3 of the indene, or position 1 of the dihydronaphthalene, since cyclization occurred only in the case cited.

He also concluded, without any apparent experimental proof, that ring closure of (XI) to (XII) occurred *para* to the methoxyl group, as shown in Flow Sheet 1, although his patent (3) indicates clearly that this may take place also *ortho* to the -OMe group in the formation of the indene cycle.

Solmssen (4) followed still another procedure in his synthesis of the indene derivatives:

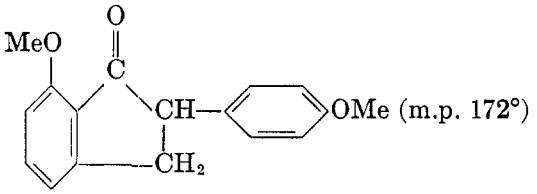
FLOW SHEET 2



In its general plan, this process differs from that of Plentl and Bogert (1), and in that pursued by us (Flow Sheet 3), only in the way in which the substituted hydrocinnamic acid (XIX) is prepared.

By hydrolysis of the dimethyl ether (XXI) with hydrobromic in glacial acetic acid, followed by a tedious chromatographic adsorption, he secured an impure dihydroxy derivative (III), from which he prepared a diacetate, but attempted purification through various esters proved unsatisfactory.

In the cyclization of the acid (XIX), he noted the formation of two isomeric indanones (m.p. 96° and 172°). Because the higher-melting form proved unreactive to the Grignard reagent, he ascribed to it the following formula:



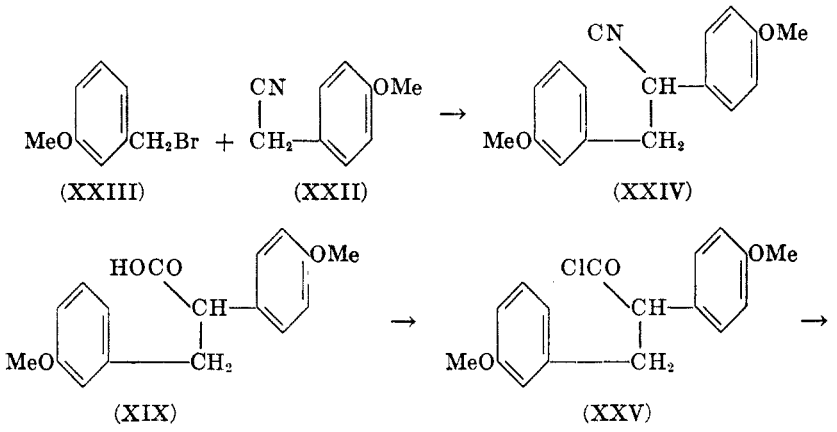
Further experimental work in this field, it seemed to us, should include additional proof of the constitution of these indanones, the preparation of the dihydroxy compound (III) in higher purity and better yield from its dimethyl ether (XXI), and corroborative identification of some of Salzer's products.

In continuing our own experimental work in this field, with the object of obtaining the desired alkoxy and hydroxy derivatives (III, IV), homoanisonitrile

(XXII) was selected as initial material. This was prepared from *p*-nitrobenzylcyanide in excellent over-all yield, as follows (5, 6): p-$O_2NC_6H_4CH_2CN$ → $H_2NC_6H_4CH_2CN$ → $HOC_6H_4CH_2CN$ → $MeOC_6H_4CH_2CN$ (XXII). The m-$MeOC_6H_4CH_2Br$ (XXIII) with which it was condensed was prepared from *m*-methoxybenzaldehyde by these steps: HOC_6H_4CHO → $MeOC_6H_4CHO$ → $MeOC_6H_4CH_2OH$ → $MeOC_6H_4CH_2Br$.

We synthesized the indene derivative (III) as shown in Flow Sheet 3.

FLOW SHEET 3



(XX) → (XXXI) → III (as in Flow Sheet 2).

For the synthesis of the corresponding dihydronaphthalene derivatives, m-$MeOC_6H_4CH_2CH_2Br$ was substituted for (XXIII) in the initial reaction above. This bromide was obtained by the following series of reactions:

m-$H_2NC_6H_4Br$ → HOC_6H_4Br → $MeOC_6H_4Br$ → $MeOC_6H_4CH_2CH_2OH$ → $MeOC_6H_4CH_2CH_2Br$ (XXX).

The *m*-bromoanisole was prepared by the process of Koelsch (10), and then converted into the alcohol and bromide as described by Bachmann and Thomas (8).

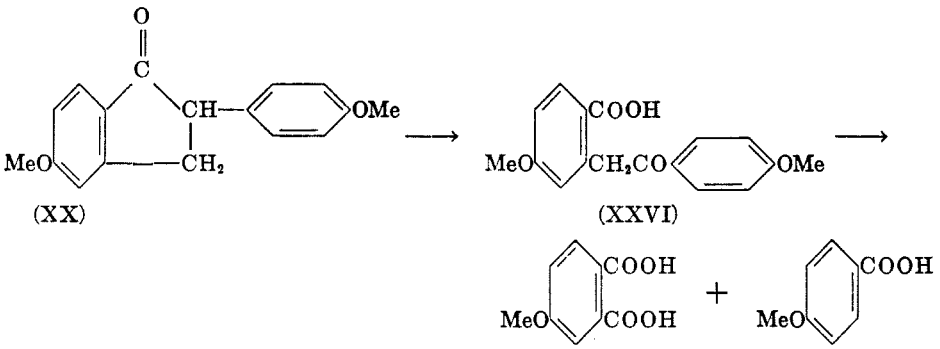
The sodium derivative of the homoanisic nitrile (XXII) was formed by reaction with a molar equivalent of sodamide in liquid ammonia, adding benzene and driving off the excess of ammonia. The sodamide was prepared fresh by the method of Vaughn, Vogt, and Nieuwland (7).

This sodium derivative was condensed with the bromide (XXIII) in dry benzene, and the resulting nitrile (XXIV) saponified by dilute alcoholic alkali to the acid (XIX).

The cyclization of this acid to the indanone (XX) was accomplished by the addition of stannic chloride to a benzene solution of the acyl halide (XXV), in much the same way as Bachmann and Thomas (8) prepared 6-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene. An excellent yield of the lower-melting isomer (m.p. 96–97°) was obtained as the sole product.

This product, on oxidation with chromic acid in dilute sulfuric acid solution, gave 2-(4′-methoxyphenacyl)anisic acid (XXVI). Oxidation of this acid by

30% hydrogen peroxide in alkali solution, yielded anisic and 4-methoxyphthalic acids:



(XX) (XXVI)

These results on the indanone (XX) support the structures (XXI and III) assigned by Solmssen (4) to his products.

We have also verified the correctness of Salzer's (2, 3) constitutional formula (XII) for the cyclization product of the ketone (XI), since we have obtained the same compound (m.p. 110–111°) by our process.

The conversion of the indanone (XX) into the indene derivative (XXI) was accomplished by refluxing it with ethylmagnesium iodide in toluene solution, the carbinol first formed undergoing dehydration at that temperature. In this way, not only the 2-ethyl (XXI), but also the 2-methyl, 2-phenyl, and 2-cyclohexyl derivatives were obtained.

In common with other investigators (2, 4, 9), we experienced great difficulty in demethylating these ethers, and we failed to isolate appreciable amounts of the pure dihydroxyindene by treatment with any of the following chemicals:

(a) Potassium hydroxide in alcohol, ethylene or propylene glycol, at 200°, 250°, or 300°, for 24 or 48 hours.

(b) Aluminum chloride in carbon disulfide, benzene, or chlorobenzene.

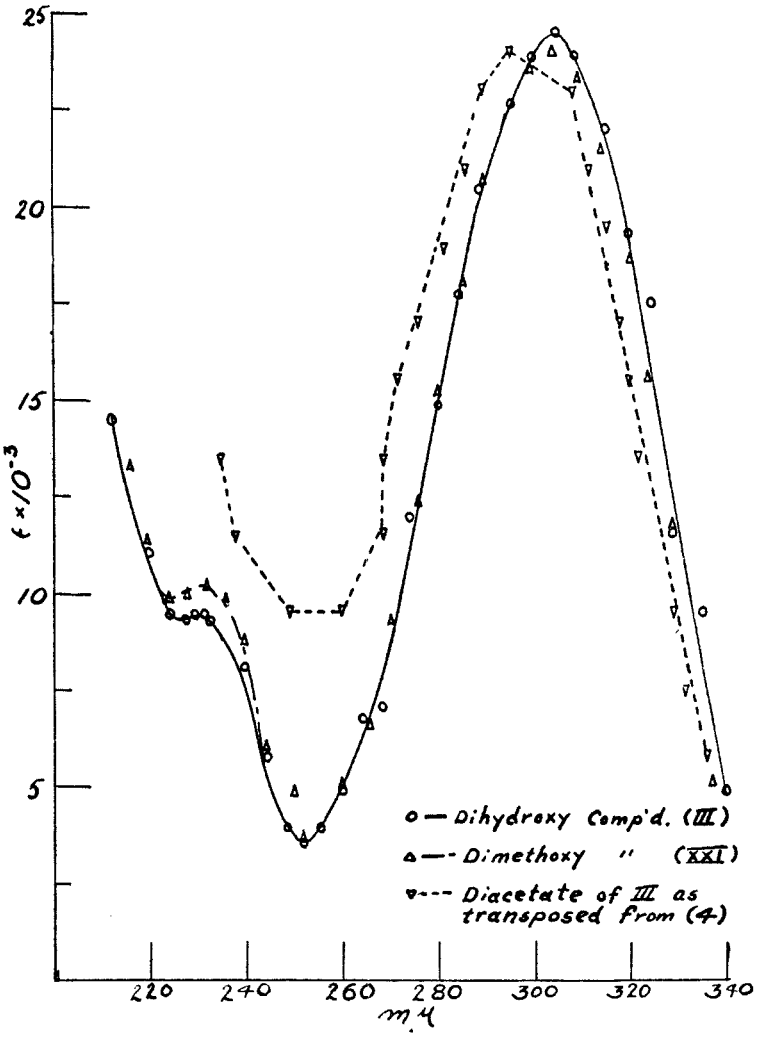
(c) The Grignard reagent, or aniline hydrochloride (alone, or in boiling tetralin).

Compound (III) was finally obtained by refluxing with a mixture of concentrated (48%) hydrobromic acid in glacial acetic acid, in an atmosphere of carbon dioxide, essentially as described by Solmssen (4), the proportion of reagents used being governed by the solubility of (III) in the acid mixture.

By treatment with suitable solvents, an anlytically pure product was secured, in small colorless needles, m.p. 176–177°, and the chromatographic adsorption used by Solmssen proved unnecessary. His product formed "slightly colored crystals," m.p. 136°, and gave analytical figures for carbon indicative of the presence of some impurity. The higher m.p. of our product may indicate that the compound is dimorphic. The diacetate prepared by us agreed closely with the one described by him. The pure diphenol (III), after standing for a few days in a sample bottle, darkened and apparently underwent some decomposition.

As a further check upon the identity and purity of our product (III), we have compared its ultraviolet absorption spectrum, and that of its dimethyl ether (XXI), with that of the diacetate as recorded by Solmssen (4), and found the

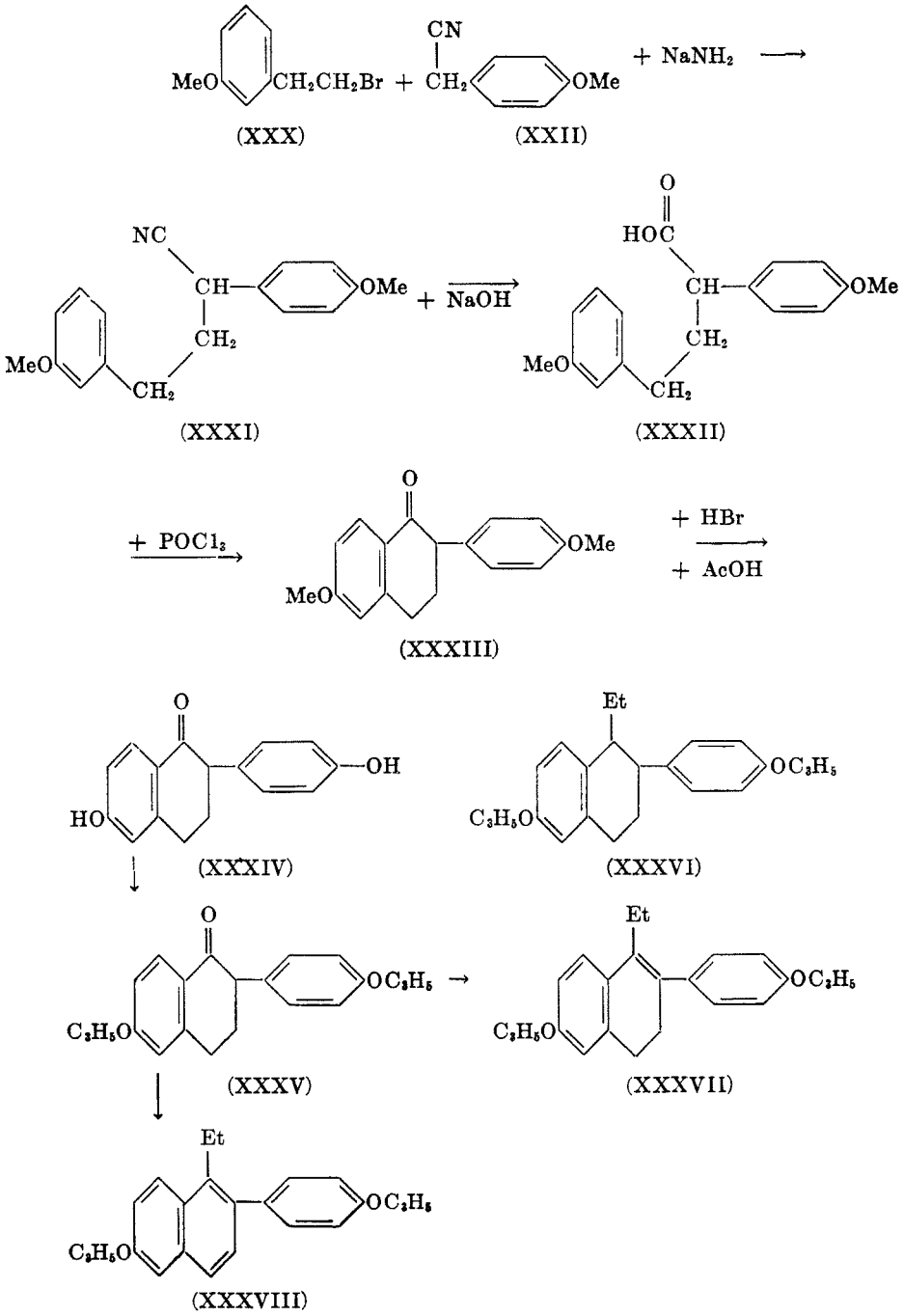
curves for all three compounds very similar, with a maximum at 305 mμ and a minimum at 252 mμ for (XXI) and (III), as compared with a maximum of 295 mμ and a minimum of about 255 mμ for the diacetate (4). The peak at 232 mμ has not hitherto been reported.



We owe these ultraviolet absorption curves to the skill and courtesy of Professor Erwin Brand of the Columbia University College of Physicians and Surgeons, to whom we wish to express our sincere thanks.

In some preliminary experiments seeking a more direct synthesis of (XXI), a Reformatsky reaction was attempted upon *p*-methoxypropiophenone with *alpha*-chlorohomoanisonitrile in benzene solution, but the only product isolated was the di-*p*-anisylsuccinonitrile (XXIX): (*p*-)$MeOC_6H_4COEt$ + ClCH(CN)

FLOW SHEET 4


MeO
CH2CH2Br
CN
CH2
OMe
+ NaNH2
(XXX)
(XXII)
NC
CH
OMe
CH2
MeO
CH2
+ NaOH
O
HOC
(XXXI)
(XXXII)
+ POCl3
+ HBr
+ AcOH
(XXXIII)
HO
OH
(XXXIV)
Et
OC2H5
C2H5O
(XXXVI)
(XXXV)
(XXXVII)
(XXXVIII)

$C_6H_4OMe(p)$(XXVIII) → (*p*-)$MeOC_6H_4CH(CN)CH(CN)C_6H_4OMe$(*p*-)(XXIX), obviously the result of the coupling of two molecules of (XXVIII).

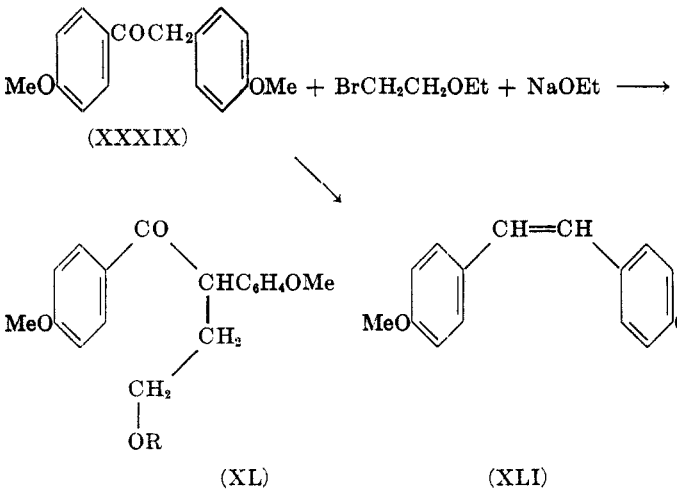
In the dihydronaphthalene series, the sodium derivative of homoanisic nitrile (XXII) was brought into reaction with *beta*-(*m*-anisyl)ethyl bromide (XXX), as mentioned above, and the substituted butyronitrile (XXXI) then saponified (XXXII) by alkali.

The cyclization to the tetralone was accomplished by means of phosphorus oxychloride, as described by Dodds *et al.* (9).

To avoid the troublesome problem of demethylating the dimethyl ether of (IV), a different line of approach was explored.

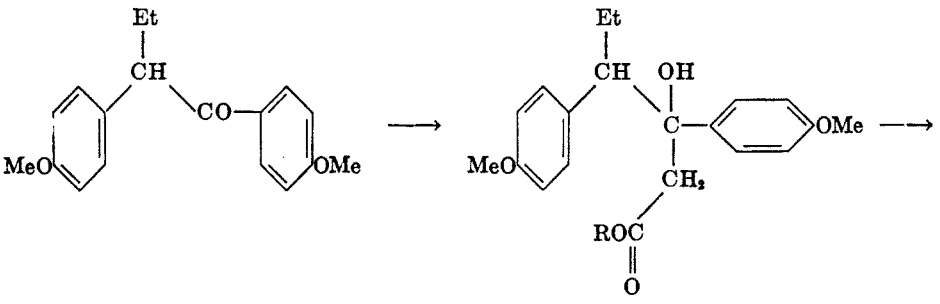
The diphenolic ketone (XXXIV), obtained from (XXXIII) by the action of concentrated hydrobromic acid in glacial acetic acid solution, was dissolved in anisole and treated with a slight excess of ethylmagnesium iodide. The interaction of the two phenolic groups with the Grignard reagent, however, precipitated the compound, so that the carbonyl group was not attacked and, upon working up the reaction mixture in the usual way, the initial compound was recovered.

An attempt was then made to take advantage of the observation of Luttringhaus and Saaf (11) that phenylallyl ethers are easily split by organometallic compounds at low temperatures. The diallyl ether (XXXV) was prepared by the Claisen method (12) and subjected to the action of ethylmagnesium iodide in benzene solution. From the reaction mixture, there were isolated the naphthalene derivative (XXXVIII), and either the di-(XXXVII) or tetrahydro (XXXVI) compound. It is suggested that compounds (XXXVI) and (XXXVIII) resulted from disproportionation of (XXXVII), although the evidence for the presence of the dihydro compound (XXXVII) was too incomplete to differentiate it satisfactorily from the tetrahydro derivative (XXXVI). No cleavage of (XXXVII) (or XXXVIII) resulted when it was subjected to the action of phenyllithium in ether at 50°.

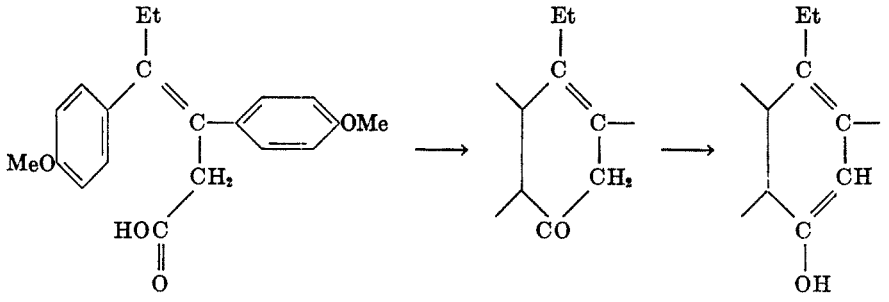


Experiments were also conducted for the condensation of *beta*-bromodiethyl ether with desoxyanisoin (XXXIX), in the presence of sodium ethoxide in benzene solution, to obtain the ether (XL), in the hope that this could be hydrolyzed to the corresponding alcohol, and the latter subjected to a cyclodehydration (13). The compound actually isolated, however, proved to be the di-anisal, (4,4′-dimethoxystilbene)(XLI), presumably formed by reduction of carbonyl to the secondary alcohol group, followed by dehydration. Whether this was the *cis* or *trans* form was not determined.

Some preliminary experiments were carried out in a different direction, involving the application of the Reformatsky reaction to *alpha*-ethyldesoxyanisoin (XLII), but these had to be interrupted before completion, because of the transfer of the junior author to other important work. The reactions completed included the condensation of ethyl bromoacetate with the ethyldesoxyanisoin to the expected hydroxy ester (XLIII), dehydration of the latter to the unsaturated ester, followed by saponification to the corresponding acid (XLIV).



(XLII) (XLIII)



(XLIV) (XLV) (XLVI)

Cyclization of (XLIV) should yield first the ketodihydro compound (XLV), which probably would rearrange promptly to the tautomeric *alpha*-naphthol derivative (XLVI), but it is uncertain when these experiments can be completed.

Acknowledgments. We are indebted to the General Aniline Co. of New York for a generous supply of *m*-hydroxybenzaldehyde. To Mr. Saul Gottlieb and Miss Frances Marx, we are under obligations for the analyses reported.

EXPERIMENTAL

All melting points reported are corrected for exposed stem.

m-Bromanisole. *m*-Bromaniline was diazotized according to the method of Koelsch (10). The bromophenol, b.p. 124–127°/22 mm., (lit. b.p. 125–130°/25 mm.) (10), was methylated by the procedure of Buck (14), who prepared veratric aldehyde from vanillin. The over-all yield was 65–70%, b.p. 108–110°/22 mm., [lit. b.p. 105°/16 mm. (15)].

beta-m-Anisylethyl bromide (XXX). The directions of Bachmann and Thomas (8) were followed, except that the Grignard reagent was prepared from *m*-bromoanisole instead of the corresponding iodo derivative. We were unable to obtain the excellent yield of the alcohol reported by these workers from the reaction between the Grignard reagent and ethylene oxide. The yield of alcohol obtained for conversion to the bromide was 59%, b.p. 110–115°/5 mm., [lit. 105–110°/1 mm. (16)]. The yield of bromide, based upon the alcohol used was 61%, b.p. 137–139°/13 mm. [lit. b.p. 138°/12 mm. (17)].

p-Methoxybenzyl cyanide (homoanisonitrile) (XXII). Koessler and Hanke (5) prepared *p*-hydroxybenzyl cyanide by the reduction of *p*-nitrobenzyl cyanide followed by diazotization. Their directions are based upon the earlier work of Pschorr, Wolfes, and Buckow (6). The yield of crude product was 71%, m.p. 65–70° (lit. m.p. 67–71°).

The methylation was carried out by the method of Meisenheimer and Weibezahn (18). The yield, based upon crude *p*-hydroxybenzyl cyanide, was 88%, b.p. 153–154°/15 mm. (lit. b.p. 152°/16 mm.).

m-Methoxybenzyl bromide (XXIII). This compound was prepared as directed by Woodward (19), except that the hydroxybenzaldehyde was methylated by the method of Buck (14). The carbinol was prepared by hydrogenation of *m*-methoxybenzaldehyde using the Adams catalyst in the presence of ferrous ions. The conversion to the bromide was easily carried out by passing hydrogen bromide into a benzene solution of the alcohol. The over-all yield of bromide was 85–90%; b.p. 127–129°/18 mm. [lit. b.p. 127°/16 mm. (20)].

alpha-(p-Anisyl)-beta-(m-anisyl)propionitrile (XXIV). A solution of sodamide was prepared by adding 4.25 g. of sodium in small pieces to 75 cc. of liquid ammonia containing 0.1 g. of ferric nitrate hexahydrate. As soon as all of the sodium had reacted, 27.2 g. of homoanisonitrile was added slowly to the well-stirred solution. A suspension of the sodium enolate formed immediately and the solution turned deep yellow in color. After standing for fifteen minutes, 200 cc. of benzene was carefully added and the mixture refluxed on the steam-bath for three hours. A solution of 37 g. of *m*-methoxybenzyl bromide in 50 cc. of benzene was added through the dropping-funnel. After refluxing for six hours, the benzene solution, containing a precipitate of sodium bromide, was cooled, washed with dilute hydrochloric acid and several times with water, then separated and dried over anhydrous sodium sulfate. The solvent was evaporated, after the solution had been filtered, and the dark brown oil was taken up in hot alcohol. On cooling, a copious precipitate came down which was recrystallized from alcohol. The glistening platelets melted at 93–94°; yield, 71%.

Anal. Calc'd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4.
Found: C, 76.5; H, 6.4.

alpha-(p-Anisyl)-beta-(m-anisyl)propionic acid (XIX). Hydrolysis was accomplished by refluxing a mixture of 29.0 g. of the nitrile (XXIV) dissolved in 110.0 cc. of alcohol and 58.0 g. of sodium hydroxide dissolved in 58.0 cc. of water on the steam-bath for thirty hours. After diluting with water, the alcohol was evaporated. The cold solution was filtered and acidified with dilute hydrochloric acid. The yellow oil which separated soon solidified. It was filtered, washed, and redissolved in dilute sodium carbonate solution. The insoluble material was filtered off, and the solution was then acidified with hydrochloric acid. The white solid was crystallized from alcohol, m.p. 105–106°; yield, 85%.

Anal. Calc'd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3.
Found: C, 71.5; H, 6.4.

Solmssen (4) recently prepared this compound by the catalytic hydrogenation of *m*-methoxy-*alpha*-(*p*-anisyl)cinnamic acid. He records the m.p. 106°.

2-(p-Anisyl)-6-methoxyindanone-3 (XX). Cyclization was carried out in a manner analogous to that of Bachmann and Thomas (8) in their preparation of 6-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene. The acid (XIX) (11.9 g.) was suspended in 50 cc. of dry ether containing two drops of pyridine. Thionyl chloride (5.5 g.)was added dropwise to the stirred suspension. The acyl chloride formed immediately and the reaction was ended by refluxing on the steam-bath for a few minutes. The ether was removed under reduced pressure, 10 cc. of benzene added, and this solvent also removed. The addition of benzene and its removal was repeated twice more. The oil was taken up in 100 cc. of benzene in a flask equipped with a dropping-funnel, stirrer, and reflux condenser. The solution was cooled to 5° and 12 g. of stannic chloride dissolved in 10 cc. of benzene was added dropwise. The insoluble complex separated as a dark brown oil which appeared to soldify as the mixture was stirred for ninety minutes at room temperature. This mixture was decomposed in the usual manner and the benzene layer separated, washed with water, dilute sodium carbonate solution, and finally with water again. After drying over anhydrous sodium sulfate, the solution was filtered and the solvent evaporated. The oil soon solidified and was crystallized from alcohol; m.p. 96–97°; yield, 82%.

Anal. Calc'd for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0
Found: C, 76.0; H, 6.0.

We were unable to obtain this indanone (XX) by the action of phosphorus oxychloride upon the acid (XIX), because the decomposition was so great that no pure product could be isolated. The use of sulfuric acid, dilute or concentrated, resulted always in products containing much alkali-soluble material. Attempts to effect ring closure by the action of aluminum chloride upon the acyl chloride in carbon disulfide, gave erratic results.

In the literature (4) this compound was obtained along with the isomeric 2-(*p*-anisyl)-4-indanone-3 by cyclizing (XIX) with phosphorus pentoxide in benzene. The m.p. is given as 96°.

Oxidative degradation of (XX). *2-(4'-Methoxyphenacyl)anisic acid* (XXVI). The ketone (XX) (1.65 g.) was oxidized with 70 cc. of a solution containing 10 g. of chromic acid and 10 cc. of sulfuric acid in 100 cc. of water. The reaction mixture was heated on the steam-bath for ninety minutes with frequent shaking. After cooling and filtering, the precipitate was washed with water and dissolved in dilute sodium carbonate solution. The liquid was filtered and acidified with 50% sulfuric acid until acid to Congo red paper. The solid was filtered off, washed with water and recrystallized twice from an alcohol-water mixture (1:1) yielding 0.67 g. of white hair-like needles melting at 181–183°.

Anal. Calc'd for $C_{17}H_{16}O_5$: C, 68.0; H, 5.3.
Found: C, 68.2; H, 5.5.

In another run, 2.0 g. of (XX) was oxidized by chromic acid as outlined above. After the filtered product was freed of chromic salts, it was dissolved in 25 cc. of 10% sodium hydroxide solution and slowly treated with 30 cc. of 30% hydrogen peroxide on the steam-bath. As soon as the excess peroxide had been decomposed (15 min.) the reaction mixture was cooled and acidified to Congo red paper. The precipitate which formed was filtered and twice recrystallized from water, yieldong 0.5 g. of colorless needles identified as anisic acid.

The filtrate, obtained after acidification of the peroxide-free solution, was evaporated to dryness and the residue extracted several times with ether. The solvent was removed and the solid material sublimed at 1/2 mm. (Wood's metal bath at 190–200°). The sublimate was recrystallized twice from glacial acetic acid to which a few drops of water were added, yielding 0.1 g. of white crystals melting at 95–96°. The compound was identified as 4-methoxyphthalic anhydride by analysis and by a mixed melting point with a specimen prepared from *m*-methoxybenzoic acid by the method of Chakravarti and Perkin (21); mixed m.p. 95–96°. [Lit. 95° (21)].

Anal. Calc'd for $C_9H_6O_4$: C, 60.7; H, 3.4.
Found: C, 60.7; H, 3.5.

3-Methyl-2-(p-anisyl)-6-methoxyindene (XII). The ketone (XX) (2.68 g.) was dissolved in 25.0 cc. of toluene. This solution was added dropwise to a Grignard reagent made from 0.24 g. of magnesium and 1.42 g. of methyl iodide in 25.0 cc. of ether. The solution became warm and turned orange in color. The ether was distilled off and the mixture refluxed for one hour at 105–110°. It was decomposed in the usual way with 20% iced sulfuric acid. The toluene extract was separated, washed, and dried over anhydrous sodium sulfate. The solvent was evaporated and the red oil soon solidified. It was crystallized from alcohol; m.p. 110–111.5°; yield, 60%.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8.
Found: C, 81.1; H, 6.7.

Salzer (2) has also prepared this substance by cyclizing 1-(*p*-anisyl)-1-(*m*-methoxybenzyl)acetone with concentrated sulfuric acid. The melting point 110° is in good agreement with that recorded above.

3-Ethyl-2-(p-anisyl-6-methoxyindene) (XXI). This compound was prepared from 2.68 g. of the ketone (XX) in 25.0 cc. of toluene and the required amount of ethylmagnesium bromide. The reaction mixture was refluxed for one hour and the decomposition and isolation was carried out as described above. The compound was recrystallized from alcohol; m.p. 87–88°; yield, 61%.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1.
Found: C, 81.4; H, 7.3.

In the literature (4) this compound was obtained by treating the indanone with ethylmagnesium iodide in benzene followed by dehydration with dilute sulfuric acid. It was purified by chromatographic adsorption on alumina and recrystallized from methanol. The m.p. is given as 87–88°.

2-(p-Hydroxyphenyl)-3-ethyl-6-hydroxyindene (II). One gram of the dimethyl ether (XXI) was refluxed for 70 minutes in a mixture containing 3.0 cc. of hydrobromic acid (48%) and 15 cc. of glacial acetic acid under carbon dioxide. The solution was made alkaline and the isoluble material removed by extraction with ether. The water layer was separated and acidified with hydrochloric acid. The precipitate was extracted with ether. The organic layer was washed several times with water, dried over sodium sulfate, and filtered. After evaporating the solvent, the oil remaining was taken up in benzene. The benzene solution was treated with Norit and filtered. After concentrating the solution to approximately 5 cc., 2–3 drops of alcohol were added and upon cooling a white crystalline material was filtered off. This was recrystallized once more from the benzene-alcohol mixture. The substance crystallized in clusters of small colorless, fibrous needles; m.p. 176–177°; yield, 2–3%.

Anal. The substance contained no methoxyl. Calc'd for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4.
Found: C, 80.6, 80.4; H, 6.4, 6.5.

This substance has previously been prepared by Solmssen (4) who records the melting point 136° for "slightly colored crystals." The analyses for the compound as given in his paper were: C, 79.8, 79.5; H, 6.5, 6.5.

The diacetate crystallized from dilute alcohol in small glistening platelets of m.p. 121–122° [lit. m.p. 118–120° (4)].

Anal. Calc'd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0.
Found: C, 75.0; H, 6.1

3-Cyclohexyl-2-(p-anisyl)-6-methoxyindene. This compound was prepared from 2.68 g. of the ketone (XX) in 25.0 cc. of toluene and the required amount of cyclohexylmagnesium bromide. After refluxing at 110° for two and one-half hours, the complex was decomposed. The organic layer was dried and the solvent removed. The straw colored oil was crystallized from alcohol. The long white fibrous needles melted at 137–139°; yield, 55%.

Anal. Calc'd for $C_{23}H_{26}O_2$: C, 82.6; H, 7.8.
Found: C, 82.2; H, 7.8.

3-Phenyl-2-(p-anisyl)-6-methoxyindene. This compound was prepared as described above by addition of the ketone (XX) dissolved in toluene, to the Grignard reagent and decomposed in the usual manner. The solid, after removal of the solvent, was crystallized

from alcohol. The long white fibrous needles, which turn pink on standing, melted at 115–117°; yield, 45%.

Anal. Calc'd for $C_{23}H_{20}O_2$: C, 84.2; H, 6.1.
Found: C, 84.0; H, 6.1.

alpha-(p-Anisyl)-gamma-(m-anisyl)-n-butyronitrile (XXXI). Sodium (3.13 g.) was added in small clean pieces to 100 cc. of liquid ammonia and 0.1 g. of ferric nitrate hexahydrate contained in a 500-cc. round-bottom flask. The deep blue color of the solution disappeared as soon as all of the sodium had reacted. To the mixture of sodamide was added, through the dropping-funnel, 20 g. of homoanisonitrile. A deep yellow color developed as the sodium salt was allowed to form during fifteen minutes. One hundred cubic centimeters of dry benzene was slowy added and the mixture refluxed on the steam-bath for three hours. The benzene was dark red in color and contained a suspension of the enolate. A solution of 29.2 g. of *m*-anisylethyl bromide in 50.0 cc. of benzene was added dropwise and the mixture refluxed for twenty hours. After washing with dilute hydrochloric acid, water, and drying over anhydrous sodium sulfate, the solvent was evaporated. The dark brown viscous oil was distilled and the fraction which boiled at 155–180°/.01 mm. was collected. The material was redistilled under vacuum and a very viscous lemon-colored oil came over at 198–203°/1 mm. The analytical sample was taken off at 199°/1 mm. and appeared colorless. The yield was 55%.

Anal. Calc'd for $C_{18}H_{19}NO_2$: C, 76.9; H, 6.8.
Found: C, 77.2; H, 6.9.

This compound has just recently been prepared by Mentzer and Urbain (23) who report the b.p. 205–210°/3 mm., but no yield.

alpha-(p-Anisyl)-gamma-(m-anisyl)butyric acid (XXXII). Thirty-one grams of the nitrile (XXXI) was dissolved in 125.0 cc. of alcohol. A solution of 62.0 g. of sodium hydroxide in 62.0 cc. of water was added. Two layers formed immediately and the mixture was refluxed for twenty-four hours. After dilution, the alcohol was evaporated and the cold solution acidified with dilute hydrochloric acid. The solid was filtered off and dissolved in dilute sodium carbonate solution. The latter was filtered from any undissolved material. The acid was precipitated and allowed to dry. It was crystallized from Skellysolve "D", m.p. 100–101°. Yield, 82%.

Anal. Calc'd for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7.
Found: C, 71.8; H, 6.7.

Dodds *et al.* (9) first prepared this compound by reducing *alpha*-(*p*-anisyl)-*beta*-(*m*-anisoyl)propionic acid *via* the Clemmensen procedure. They recorded the m.p. 98–99°.

2-(p-Anisyl)-6-methoxytetralone-1 (XXXIII). This compound was prepared from the acid (XXXII) in accordance with the direction of Dodds *et al.* (9); m.p. 124–126°. [Lit. 124–126° (9)]; yield, 80%.

2-(p-Hydroxyphenyl)-6-hydroxytetralone-1 (XXXIV). Demethylation of (XXXIII) was accomplished by dissolving 3.4 g. of the dimethoxy ketone in 75 cc. of glacial actic acid containing 75 cc. of concentrated hydrobromic acid (*d.* 1.49). The solution was refluxed for six hours, cooled and diuted with water. The granular precipitate was filtered off, washed with water and recrystallized from an alcohol-water mixture. The material melted at 266–271° with decomposition after darkening at 230°; yield, 73%.

Anal. Calc'd for $C_{16}H_{14}O_3$: C, 75.6; H, 5.5.
Found: C, 75.4; H, 5.8.

2-(p-Allyloxyphenyl)-6-allyloxytetralone-1 (XXXV). Two and one-half grams of XXXIV, 3.2 g. of allyl bromide, and 6 g. of anhydrous potassium carbonate were added to 25.0 cc. of dry acetone The mixture was refluxed on the steam-bath for eight hours and diluted with water. The acetone was boiled off; the residual oil taken up in ethyl acetate and dried over anhydrous sodium sulfate. After the solvent had been evaporated, the light yellow oil was dissoved in alcohol and refrigerated overnight. The colorless crystals melted at 69–70°; yield, 80%.

Anal. Calc'd for $C_{22}H_{22}O_3$: C, 78.6; H, 6.6.
Found: C, 78.5; H, 6.7.

1-Ethyl-2-(p-allyloxyphenyl)-6-allyloxynaphthalene (XXXVIII). One gram of the diallyloxyketone (XXXV) was dissolved in 10 cc. of dry benzene and added through a dropping-funnel to a Grignard reagent prepared from 0.072 g. of magnesium and 0.33 g. of ethyl bromide in ether. The solution turned yellow and a precipitate began to form immediately. The ether was distilled off and the mixture refluxed for three hours. It was decomposed in the usual way with ice cold 20% sulfuric acid. The benzene layer was separated, washed. and dried over anhydrous sodium sulfate. After evaporating the solvent, the light brown oil was taken up in alcohol and cooled The precipitate was filtered and recrystallized from alcohol The white platelets melted at 130–32°. Yield, 1–2%

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.6; H, 7.0.
Found: C, 83.2; H, 6.9.

1-Ethyl-2-(p-allyloxyphenyl)-6-allyloxy-1,2,3,4-tetrahydronaphthalene (XXXVI) or *1-Ethyl-2-(p-allyloxyphenyl)-6-allyloxy-3, 4-dihydronaphthalene* (XXXVII). After removal of the naphthalene derivative the alcohol solution was concentrated and refrigerated overnight. A second crop of crystals was obtained and these were also recrystallized from alcohol; m.p. 67–78°. Yield, 1–2%.

Anal. Calc'd for $C_{24}H_{26}O_2$: C, 83.2; H, 7.5.
Found: C, 83.0; H, 7.6.

Attempt to use alpha-chlorohomoanisonitrile in the Reformatsky reaction. A mixture of 3.04 g. of *p*-methoxypropiophenone, 3.62 g. of *alpha*-chlorohomoanisonitrile, 1.57 g. of zinc, and 15.0 cc. of dry benzene was refluxed on the steam-bath for one hour. The solution was separated from unreacted zinc and added to a cold dilute sulfuric acid solution. The benzene layer was separated, washed with water and finally dried over sodium sulfate. The solution was filtered and the solvent evaporated. The remaining oil was dissolved in alcohol and a solid precipitated on cooling. By recrystallization from alcohol a crop of fine colorless needles was obtained, melting at 230–230.5°.

Anal. Calc'd for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5.
Found: C, 74.1; H, 5.7.

The substance therefore appears to be *alpha,beta*-di-(*p*-anisyl)succinonitrile (XXIX).

Attempt to alkylate desoxyanisoin with beta-bromodiethyl ether. Sodium (0.9 g.) was dissolved in 20 cc. of absolute alcohol. Five grams of desoxyanisoin was added followed by 30.0 cc. of dry benzene. The mixture was distilled on the steam-bath until the temperature read 82°, the original volume being maintained by frequent addition of benzene. Six and two-tenths grams of *beta*-bromodiethyl ether was added all at once and the mixture refluxed until neutral to litmus. The reaction mixture was washed with water and the benzene layer separated and dried. After removal of the solvent the oil was taken up in hot acetic acid, from which glistening platelets precipitated on cooling. Upon recrystallization from this latter solvent the crystals melted at 211.5–212°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.6.
Found: C, 79.7; H, 6.6.

These constants agree with those in the literature for di-anisal (4,4′-dimethoxystilbene, XLI) (22).

Ethyl-beta-hydroxy-beta-(p-anisyl)-gamma-ethyl-gamma-(p-anisyl)butyrate (XLIII). A mixture of 5 g. of *alpha*-ethyldesoxyanisoin (XLII), 3.5 g. of ethyl bromoacetate, 1.3 g. of zinc, and 25 cc. of benzene was refluxed on the steam-bath for two hours. When most of the zinc had gone into solution, the reaction mixture was filtered and treated with 20% iced sulfuric acid until the solid matter which first appeared redissolved. The benzene layer was separated, washed with water, dried over sodium sulfate, and filtered. After the solvent had been removed, the oil was taken up in alcohol and cooled. The crystals were filtered and recrystallized from alcohol. Yield, 45%; m.p. 82–83°.

Anal. Calc'd for $C_{22}H_{28}O_5$: C, 71.0; H, 7.5.
Found: C, 70.9; H, 7.5.

beta-(p-Anisyl)-gamma-ethyl-gamma-(p-anisyl)-beta-butenoic acid (XLIV). Five-tenths gram of (XLIII) was added in small portions to 5 cc. of cold concentrated sulfuric acid. A deep red solution resulted immediately and stirring was continued for fifteen minutes in

the cold and for an equal length of time at room temperature. The solution was poured into ice-water, and the gum which separated extracted with ether. The ether solution was washed, dried, filtered, and the solvent evaporated. The resulting glass was refluxed for thirty minutes with 20% sodium hydroxide solution followed by filtration and acidification to Congo red paper. The precipitate was extracted with ether and the organic layer washed with water. It was dried and the solvent evaporated. The oil soon solidified and was recrystallized from alcohol yielding colorless crystals of m.p. 145–146°.

Anal. Calc'd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.8.
Found: C, 73.2; H, 6.8.

SUMMARY

1. The synthesis of indene and dihydronaphthalene derivatives, structurally related to stilbestrol, is described.

2. The path followed is that originally blazed by Plentl and Bogert for the synthesis of the corresponding tricyclic hydrocarbons. The processes used, and the products obtained, are compared with the recent work of Salzer, and of Solmssen, in this same field.

3. Experimental proof is supplied as to the structure of the indanones obtained by cyclization of the *beta*-(*m*-anisyl)propionic acids.

4. The 3-ethyl-2-(*p*-hydroxyphenyl)-6-hydroxyindene has been prepared analytically pure.

5. Corroborative identification of some of Salzer's products is reported.

6. The action of zinc upon a benzene solution of *p*-methoxypropiophenone and *alpha*-chlorohomoanisonitrile, results in the formation of di-(*p*-anisyl)succinonitrile.

7. Allyl ethers of 1-ethyl-2-(*p*-hydroxyphenyl)-6-hydroxy-3,4-dihydro-(or 1,2,3,4-tetrahydro-) naphthalene, are not split by phenyllithium in ether solution.

8. Desoxyanisoin, subjected to the action of *beta*-bromodiethyl ether, in the presence of sodium ethoxide, yields di-anisal.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

FUSION SYNTHESES OF ARYL POLYACYLGLYCOSIDES

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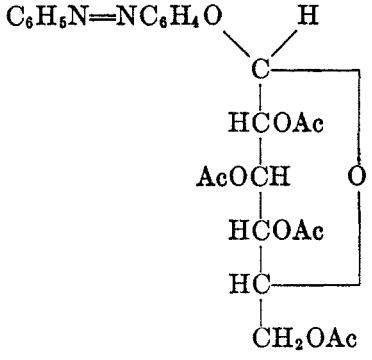
In 1933 Helferich and Schmitz-Hillebrecht (1) introduced a general method for the synthesis of aryl polyacetylglycosides, consisting of fusing a phenol and a fully acetylated sugar in the presence of a catalyst. When *p*-toluenesulfonic acid was utilized as catalyst with the simple phenols the formation of β-glycosides was noted, whereas zinc chloride favored the formation of the α-anomer. Subsequent investigators (2, 3) inaugurated improvements which led to better yields. An azo phenol such as *p*-hydroxyazobenzene has not been included among the phenols previously studied.

We wish to report (a) the application of this method of synthesis to the preparation of glycosides containing a chromophoric group in the aglycon; (b) the utilization of catalysts other than those previously reported; and (c) extension of the fusion procedure to the direct synthesis of an aryl thioglycoside.

β-D-Glucose pentaacetate underwent reaction with *p*-hydroxyazobenzene in the presence of *p*-toluenesulfonic acid to form crystalline *p*-phenylazophenyl tetraacetyl-β-D-glucoside (I) in good yields.



I

Assigning this compound to the β-series follows the results of earlier workers. *p*-(3-Nitrophenylazo)phenol also gave rise to a similarly constituted crystalline β-D-glucoside. Fructose or galactose pentaacetates with these two azo phenols, and also glucose pentapropionate, yielded only dark red syrups. From an analogous experiment with glucose pentaacetate and 4-phenylazo-1-naphthol the starting materials were recovered.

Pacsu (4) has shown that stannous chloride or titanium tetrachloride was capable of isomerizing methyl polyacetyl-β-glycosides into the α-form; and recently Montgomery, Richtmyer, and Hudson (3) have observed that the cor-

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responding aryl polyacetyl-β-glycosides could be anomerized similarly under conditions of the Helferich and Schmitz-Hillebrecht synthesis. These investigators presented directions for the preparation of the mixture of phenyl tetraacetyl-α- and -β-D-glucosides from α-D-glucose pentaacetate, phenol, and zinc chloride in yields of 64 and 26%, respectively. They reported also that in several related experiments "the yields estimated from the rotation of the ethylene dichloride solution were approximated by the total yields of the two isomers".

In the present work three other catalysts were studied, namely, aluminum chloride, ferric chloride, and boron trifluoride. Since the rotational method of analysis for anomers gave fair accuracy (3) in the reaction with the zinc chloride catalyst it was employed in the present work with these three catalysts: aluminum chloride, ferric chloride, and boron trifluoride. All three were found to catalyze the reaction between β-D-glucose pentaacetate and phenol. Ferric chloride yielded a mixture in which the α-glucoside predominated, whereas the other two catalysts appeared to yield approximately equal amounts of α-

TABLE I

THE ISOMERIZATION OF PHENYL TETRAACETYL-D-GLUCOSIDES

D-GLUCOSIDE	CATALYST	YIELD, %	%-*Alpha*	%-*Beta*
β	$ZnCl_2$	60	72	28
β	BF_3	1	13	87
β	$FeCl_3$	50	72	28
α	$AlCl_3$	92	84	16
α	p-$CH_3C_6H_4SO_3H$	95	67	33

and β-glucosides. Aluminum chloride gave the best yield of total product. Directions are given for its use with D-glucose and D-galactose pentaacetates and with D-glucose pentapropionate to obtain the aryl tetraacyl-β-D-glycosides.

These catalysts also have been shown to be effective in isomerizing pure samples of phenyl tetraacetyl-α- or -β-D-glucoside into mixtures of anomeric forms. Table I shows the ability of these catalysts to isomerize the acetates of optically pure phenyl α- or β-D-glucosides into anomeric mixtures under analogous conditions. The composition of the final mixture was determined in each case by its specific rotation. The α,β-percentages listed in Table I probably do not represent true equilibrium values, but are valid only for the reaction times stated in the Experimental Section.

Lastly, we have found that when β-D-glucose pentaacetate, thiophenol, and p-toluenesulfonic acid are fused together, phenyl tetraacetyl-β-D-thioglucoside is formed. This is the first extension of the Helferich and Schmitz-Hillebrecht reaction to the preparation of sulfur analogs of the glycosides. Previous syntheses (5) of thioglycosides have been by way of polyacetylglycosyl bromide and the potassium salt of thiophenol.

EXPERIMENTAL PART

p-Phenylazophenyl tetraacetyl-β-D-glucoside. β-D-Glucose pentaacetate (10 g.), crude *p*-hydroxyazobenzene (20 g.) (m.p. 147–154.5°), and about 0.1 g. of *p*-toluenesulfonic acid were mixed and melted at 145°. The melt was cooled at 130° and held at a pressure of 25 mm. for one-half hour. The melt was then taken up in ethylene chloride, and the red solution was washed with water, 10% sodium hydroxide solution (until no appreciable amount of color went into the aqueous layer), again with water, then dried over sodium sulfate. Removal of the solvent *in vacuo* left 8.8 g. of a dark, red syrup. This was taken up in ethanol from which 4.2 g., m.p. 168–171°, crystallized on cooling. A second crop of crystals weighing 2.2 g. melted at 105–112°. Another recrystallization of the first crop of crystals from ethanol yielded orange needles, which melted at 172.5–173°, corr.

Anal. (by T. S. Ma) Calc'd for $C_{26}H_{28}N_2O_{10}$: N, 5.30. Found: N, 5.40.

p-(3-Nitrophenylazo)phenyl tetraacetyl-β-D-glucoside. β-D-Glucose pentaacetate (10 g.), *p*-(3-nitrophenylazo)phenol (24.3 g.), and 0.1 g. of *p*-toluenesulfonic acid were melted and kept at 150° for forty minutes at 25 mm. An attempt was made to extract the product in the usual manner with ethylene chloride and to wash away the free phenol with excess sodium hydroxide solution. Addition of the alkali, however, caused the separation of a thick, red solid, which was filtered off and investigated later. The filtrate separated into two layers, and the ethylene chloride layer was treated as usual. Removal of the solvent gave 7.07 g. of a red solid which was recrystallized from a mixture of ethanol and ethyl acetate. The 4.1 g. of fine, orange needles obtained melted at 202.5–203°, corr.

Anal. (by T. S. Ma) Calc'd for $C_{26}H_{27}N_3O_{12}$: C, 54.4; H, 4.72.
Found: C, 54.22; H, 4.81.

High-melting modification of p-(3-nitrophenylazo)phenol. Several tests were made on the red solid mentioned above. It was slightly soluble in water, and acidification of the water solution gave an intense yellow precipitate (X) which melted at 162–162.5°. The original starting phenol melted at 146–147°. The isolated material (162°) proved to be the high-melting form of *p*-(3-nitrophenylazo)phenol, reported by Meldola and Hanes (6) to melt at 159°.

That this substance melts higher than 159° was established as follows. The phenol, prepared by coupling diazotized 3-nitroaniline and phenol, melted at 147–148°. After recrystallization from either toluene or dilute ethanol, with filtration through Celite while hot, it melted at 161.5–162.5°, corr. The melting point of a mixture of this substance with (X) was also at 161.5–162°.

Phenyl tetraacetyl-β-D-glucoside using aluminum chloride. β-D-Glucose pentaacetate (20 g.), phenol (18 g.), and anhydrous aluminum chloride (5 g.) were ground together and heated at 100° and diminished pressure for fifty minutes. It was necessary to control the pressure carefully, as the reaction frothed badly. The red mixture was taken up in ethylene chloride and washed with water. The voluminous precipitate of aluminum hydroxide which formed was dissolved in two subsequent washes with 10% sodium hydroxide solution. After several washes with water the solution was dried and the solvent removed. The crude, solid glucoside was obtained in almost quantitative yield. After recrystallization from 2-propanol approximately half of the material separated with the m.p. 123–124°; mixed m.p. with phenyl tetraacetyl-β-D-glucoside (m.p. 127°), 124.5–125.5°. After another recrystallization the melting point was 127–127.5°; $[\alpha]_D^{25}$ −21.5° (*c*, 1.444; $CHCl_3$). No attempt was made to isolate the α-anomer from the mother liquors.

1-Naphthyl tetraacetyl-β-D-glucoside using aluminum chloride. β-D-Glucose pentaacetate (10 g.), 1-naphthol (14 g.), and aluminum chloride (3 g.) were fused for thirty-five minutes at 135°. No vacuum was used, as frothing was excessive. The black reaction mixture was treated in the usual manner to yield 2.9 g. (23%) of crude syrup which crystallized spontaneously. This was recrystallized from 2-propanol to give 1.0 g. of pink needles, m.p. 175.5–176.5°; mixed m.p. with 1-naphthyl tetraacetyl-β-D-glucoside (m.p. 178–178.5°), 177–178°. Its specific rotation was −71.4° (*c*, 1.535; $CHCl_3$).

Phenyl tetraacetyl-β-D-galactoside using aluminum chloride. β-D-Galactose pentaacetate (10 g.), phenol (9 g.), and aluminum chloride (2.5 g.)were fused for forty-five minutes on the steam-bath at atmospheric pressure, then processed as usual to give 9.64 g. (88%) of crude galactoside which was recrystallized twice from 2-propanol; m.p. 124–125°; $[\alpha]_D^{25}$ 2.0° (*c*, 1.750; $CHCl_3$); yield, 3.5 g. The literature (1) gives m.p. 123–124°, $[\alpha]_D^{25}$ −0.7° for this compound.

Phenyl tetrapropionyl-β-D-glucoside. D-Glucose pentapropionate (83 g.), phenol (70 g.), and *p*-toluenesulfonic acid (1 g.) were fused at 100° for an hour, then extracted as before in ethylene chloride. Removal of the solvent from the final solution gave 78.7 g. of a clear syrup which failed to crystallize. The syrup was therefore distilled in a high vacuum (7). Most of the distillate was collected at 10^{-5} mm. with a bath temperature of 200–205°. To clarify the distillate which was somewhat dark, it was dissolved in ether and filtered through Norit. Removal of the ether and solution in ethanol (50 ml.) led to sparse crystallization, and further crystallization was induced by slow concentration in a gentle air stream. Thirteen grams of crystals, m.p. 70–72°, was obtained. A duplicate experiment led to 67 g. of crude syrup which could be crystallized directly from 2-propanol with the aid of seeds from the first experiment. After two recrystallizations from 2-propanol the combined products from above consisted of giant, tetragonal crystals, m.p. 72.0–72.5°; $[\alpha]_D^{25}$ −16.4° (*c*, 1.585; $CHCl_3$). An attempt was made to analyze this compound for propionyl by the

TABLE II

DATA FOR THE ISOMERIZATION OF PHENYL TETRAACETYL-D-GLUCOSIDES

D-GLUCOSIDE		PHENOL, G.	CATALYST		TIME, HRS.	TEMP. °C.	CRUDE PRODUCT, G.	$[\alpha]_D^{25}$	CONC. G./100 ML. $CHCl_3$
anomer	g.		name	g.					
β	0.5	0.5	$ZnCl_2$	0.15	3.00	120	0.3	114.3	0.481
β	2.0	2.0	BF_3	0.6	0.50	100	0.02	2.1	2.395
β	2.0	2.0	$FeCl_3$	0.4	1.00	100	1.0	114.3	1.791
α	0.5	0.5	$AlCl_3$	0.15	1.00	100	0.46	136.8	3.750
α	0.2	0.2	p-$CH_3C_6H_4SO_3H$	trace	1.00	100	0.19	103.9	1.710

method of Kunz and Hudson (8), but at 0° solution of the product in a mixture of acetone and 0.1 *N* sodium hydroxide could not be maintained. Consequently an attempt was made to run the analysis at room temperature instead of 0°. The solubility difficulty was thereby eliminated, and the following results were obtained. It should be pointed out that this room temperature modification of the Kunz and Hudson method of analysis is restricted to sugar derivatives, such as glycosides which resist hydrolysis to glycose under the conditions of the experiment.

Anal. 0.1544 g. required 13.02 ml. of 0.0984 *N* NaOH. Calc'd for $C_{12}H_{12}O_6(COC_2H_5)_4$: Propionyl, 47.4. Found: Propionyl, 47.5.

Anal. (by Mrs. M. M. Ledyard). Calc'd for $C_{24}H_{32}O_{10}$: C, 60.0; H, 6.71.
Found: C, 60.4; H, 7.05.

Use of aluminum chloride. D-Glucose pentapropionate (23.4 g.), phenol (18 g.), and aluminum chloride (5 g.) were heated in a Claisen flask for forty-five minutes on the steam-bath at a pressure just high enough to prevent the mixture from frothing over. From the mixture was obtained 21.8 g. of a colorless syrup after the usual steps of separation. This was taken up in 2-propanol and seeded. After several days there resulted 7 g. of coarse, white crystals, m.p. and mixed m.p. with the compound prepared above, 72.0–72.5°; $[\alpha]_D^{25}$ −14.7° (*c*, 3.410; $CHCl_3$).

Attempts to make the α-anomer using zinc chloride gave only non-crystallizable syrups.

Phenyl tetraacetyl-β-D-thioglucoside. β-D-Glucose pentaacetate (3.92 g.), thiophenol (5.5 g.), and 0.05–0.1 g. of *p*-toluenesulfonic acid were fused at 100° for one hour. The melt

was cooled, dissolved in ether, washed with 10% alkali, water, and dried. Removal of the solvent yielded 3.4 g. (68%) of crude syrup. Solution in 2-propanol and scratching yielded a seed which was removed. The solution was reheated and filtered through Norit. The filtrate was concentrated and seeded, giving 0.7 g. (14%) of crystalline material, m.p. 115.5°, $[\alpha]_D^{25}$ −15.1° (*c*, 2.515; $CHCl_3$). The literature (5) records m.p. 117°, $[\alpha]_D^{25}$ −17.5° for this thioglucoside. Attempts to make the α-anomer by the use of zinc chloride led only to small quantities of the β-compound described above.

The isomerization of phenyl tetraacetylglucosides with various catalysts. The general method used here was to heat the pure glucoside with phenol in the presence of the catalyst for the specified time. The melt was then taken up in ethylene chloride, washed with water, 10% sodium hydroxide solution, and again several times with water, and then dried over sodium sulfate. After decolorization by filtration through Norit the solvent was removed under diminished pressure and the specific rotation of the syrupy residue was determined. Table II gives a summary of the data.

Rotational analysis. In order to test the accuracy of specific rotation as a method of analyzing binary carbohydrate mixtures, several synthetic mixtures of known composition were made and their specific rotations taken. A graph was then made of specific rotation *vs.* percentage-composition by drawing a straight line between the specific rotations of the two pure components. The composition of the synthetic mixtures was then read from the graph, and the result compared with the known composition. A mixture of phenyl tetraacetyl-α-D-glucoside (27% by weight) and phenyl tetraacetyl-β-D-glucoside (73%) had the specific rotation 30.0° (*c*, 1.500; $CHCl_3$). From the graph the composition was read as 27.5% and 72.5% respectively, for the two components. A mixture of α-glucose pentaacetate (77.6%) and β-glucose pentaacetate (22.4%) had the rotation 78.9° (*c*, 1.965; $CHCl_3$). From the graph the composition was 77.5% and 22.5% respectively.

SUMMARY

Several arylazophenyl polyacylglycosides have been synthesized by fusing an azo phenol with acylated sugars in the presence of a catalyst. Both crystalline products and syrups were obtained.

Toluenesulfonic acid and zinc chloride have been shown to be capable of isomerizing pure aryl polyacylglycosides into a mixture of the α and β forms. Boron trifluoride, aluminum chloride, and ferric chloride are capable also both of catalyzing the formation and isomerization of aryl polyacylglycosides.

Phenyl tetraacetyl-β-D-thioglucoside has been prepared by the catalytic fusion method.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY]

SOME POTASSIUM AMIDE-ACTIVATED PHENYLATIONS IN LIQUID AMMONIA (1)

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The phenyl halides react readily with strong bases such as the alkali amides in liquid ammonia and the alkali dialkylamides in ether (2) but fail to react within a period of a day or so with less basic compounds of the type of potassium anilide, potassium diphenylamide, and potassium quinaldyl. Reaction nevertheless does occur if potassium amide is added to a solution of any of the salts enumerated above, provided that a phenyl halide is also present. Wright and Bergstrom (3) thus prepared 2-benzylquinoline, 2-benzohydrylquinoline, and 2-triphenylmethylquinoline in accordance with the equations below.

$$C_9H_6NCH_3 \xrightarrow{KNH_2} C_9H_6NCH_2K \xrightarrow[KNH_2]{C_6H_5Cl} C_9H_6NCH_2C_6H_5 \qquad (I)$$

Quinaldine

$$\xrightarrow{KNH_2} C_9H_6NCHKC_6H_5 \xrightarrow[KNH_2]{C_6H_5Cl} C_9H_6NCH(C_6H_5)_2 \xrightarrow{KNH_2}$$

$$C_9H_6NCK(C_6H_5)_2 \xrightarrow[KNH_2]{C_6H_5Cl} C_9H_6NC(C_6H_5)_3$$

The benzohydrylquinoline and triphenylmethylquinoline had the correct composition, but their structure was not definitely proved. It was for the purpose of orienting these compounds and of utilizing them in the preparation of free groups containing a quinoline nucleus that the present investigation was undertaken. Incidental to this a number of other catalytic phenylations have been studied.

The reactions of Wright and Bergstrom, shown in equation (I), have been confirmed. The 2-benzohydrylquinoline was oxidized to 2-quinolyldiphenylcarbinol, $C_9H_6NC(OH)(C_6H_5)_2$, which was found to be identical with the compound prepared by the action of an excess of phenylmagnesium bromide on ethyl quinaldate, thus proving its structure. Attempts to prepare 2-benzohydrylquinoline by reducing the carbinol, or by a Friedländer or Pfitzinger synthesis from 1,1-diphenylacetone, failed, as did also an attempt to make diphenyl-2-quinolylbromomethane from tribromoquinaldine, benzene, and aluminum chloride. It has not yet proved possible to synthesize 2-triphenylmethylquinoline. An interesting reduction of ω,ω,ω-tribromoquinaldine to ω,ω-dibromoquinaldine was effected by heating the former with concentrated sulfuric acid and a small amount of alcohol; presumably the reaction follows the equation,

$$C_9H_6NCBr_3 + C_2H_5OH = CH_3CHO + HBr + C_9H_6NCHBr_2 \qquad (II)$$

4-Methylquinoline (lepidine) forms alkali metal salts in liquid ammonia (4) which can be alkylated to give homologous 4-substituted quinolines. The

potassium salt of lepidine can be catalytically phenylated with chlorobenzene and potassium amide to give 4-benzylquinoline and 4-benzohydrylquinoline; 4-triphenylmethylquinoline has not been isolated in any of our experiments. The 4-benzohydrylquinoline is readily oxidized to the 4-quinolyldiphenylcarbinol of Remfrey and Decker (5). Since 2,4-dimethylquinoline has two reactive methyl groups, its potassium salt is doubtless a mixture, and a catalytic phenylation gave several products, none of which could be isolated in a state of purity. 2-*n*-Propylquinoline could not be phenylated in accordance with the present method, even though it had previously been alkylated in ether (but not in liquid ammonia) (6). 9-Methylphenanthridine forms a potassium salt which is not very soluble in ammonia at $-33°$; it is apparently this factor that prevents its catalytic phenylation.

On the other hand, 2-methylpyridine is readily phenylated to give a mixture of 2-benzylpyridine, 2-benzohydrylpyridine, and 2-triphenylmethylpyridine in fairly good over-all yield, but 2,4-dimethylpyridine is converted largely to tars under the same conditions.

o-Tolunitrile may be regarded as a vinylene homolog of acetonitrile, and therefore might be expected to have an active hydrogen atom in the methyl group. This was found to be true, since the potassium salt of *o*-tolunitrile was phenylated to give *o*-benzylbenzonitrile and *o*-benzohydrylbenzonitrile (*o*-cyanotriphenylmethane).

EXPERIMENTAL

The experimental method has been partly described in previous articles (7). Briefly, the apparatus consists of a 500-ml. 3-necked flask and a 1000-ml. 3-necked flask, so arranged that the contents of the former could be siphoned into the latter, which was fitted with a good mechanical stirrer. Potassium amide (from 6 g. or 0.15 atom of metallic potassium, with an iron oxide catalyst) was prepared in about 500 ml. of liquid ammonia in the larger flask, and to this was added an equivalent of quinaldine, lepidine or other compound whose potassium salt it was desired to form. Chlorobenzene (26–28 g., about 0.25 mole) was then introduced, and potassium amide solution (from 6 g. potassium, 0.15 atom) was forced over from the smaller flask with good stirring. Ammonium chloride equivalent to the potassium used (about 16 g.) was added at the end of about an hour to stop the reaction, and the ammonia was allowed to evaporate. Water was introduced to dissolve inorganic salts, and then benzene (100–150 ml.) to dissolve organic material. The treatment of the benzene solution depended upon the nature of the products that were formed; bases were generally removed by shaking with strong hydrochloric acid, and both the acid and the benzene solutions were worked up, as described later.

Phenylation of quinaldine. The catalytic phenylation of quinaldine gives 2-benzylquinoline, 2-benzohydrylquinoline, and 2-triphenylmethylquinoline in agreement with the work of Wright and Bergstrom (3). The relative amount of the triphenylmethylquinoline appeared to be increased by alternate addition of the chlorobenzene and the potassium amide to the solution of the potassium quinaldyl.

2-Benzohydrylquinoline (0.5 g.) was dissolved in 5 ml. of glacial acetic acid and the solution gently heated. Chromic anhydride was slowly added in small quantities until the brown color of the anhydride no longer changed to the green of the chromic ion. Half of the solvent was evaporated under suction and the solution cooled in ice. The needles that separated were crystallized from a 50–50 mixture of benzene and acetone; m.p. 188.5–189.5° corr.

Anal. Calc'd for $C_{22}H_{17}NO$: C, 84.88; H, 5.50; N, 4.50.
Found: C, 84.90; H, 5.93; N, 4.47.

Melting points of mixtures with the 2-quinolyldiphenylcarbinol prepared by the action of phenylmagnesium bromide on ethyl quinaldate were the same.

Ethyl quinaldate was prepared by refluxing for six hours a solution of quinaldic acid (80 g., 0.46 mole) in absolute ethanol (400 ml.) to which 50 cc. of conc'd sulfuric acid had been slowly added. The alcohol was distilled until a fairly viscous solution remained; this was poured into water and neutralized with ammonia. The heavy oil that separated was washed with water, dried, and distilled *in vacuo*; b.p. 180°/14 mm.; yield, 47 g., or 51%. Kindler (8) previously prepared this ester by the hydrochloric acid method, and gives the boiling point 186–188°/13 mm. (prob. corr.).

Phenylmagnesium bromide (0.50 mole) was prepared in 500 ml. of absolute ether in a 2-liter 3-necked flask fitted with reflux condenser, mercury sealed stirrer, and a dropping-funnel. Ethyl quinaldate (0.23 mole, 46.2 g.), dissolved in 200 ml. of absolute ether, was added over a period of an hour with stirring. At the end of this time the mixture was cautiously treated with dil. sulfuric acid (20 ml. in 300 ml. water). The white crystals that separated were filtered and washed with water, dried, and crystallized from a 50–50 acetone-benzene mixture. The melting point was 188.5–189.5°, and the yield was 47.3 g. (66%). The hydrochloride, prepared by passing dry hydrochloric acid gas through a solution of the carbinol in warmed benzene, melted, after crystallization from this solvent, at 178–179°, dec. It was sparingly soluble in hot benzene, and could not be crystallized from alcohol without hydrolysis to the carbinol.

Anal. Calc'd for $C_{22}H_{17}NO \cdot HCl$: C, 75.96; H, 5.22; Cl, 10.19.
Found: C, 76.04; H, 5.10; Cl, 9.71.

Phenylation of lepidine. The standard procedure was followed, except that in some of the experiments the amount of potassium amide added from the small flask was increased to 0.20–0.24 mole. The benzene solution of the reaction product was shaken for some time with 8 *N* hydrochloric acid in a thick-walled stoppered Erlenmeyer flask. The benzene and the aqueous acid solution were decanted from the tarry crystals of 4-benzohydrylquinoline hydrochloride, and the latter washed with 8 *N* hydrochloric acid. The benzene layer was separated and discarded (only tarry materials were obtained from it), the aqueous solution filtered to remove some benzohydryl quinoline hydrochloride, and then made basic with sodium hydroxide. The resulting oil was extracted with benzene, and the latter distilled; 4-benzylquinoline came over at 220–225° (uncor.) at 19 mm., or 180–190° at about 2 mm. The combined precipitates of benzohydrylquinoline hydrochloride were washed with a little acetone to remove tar, and either crystallized from water or dilute alcohol containing a little hydrochloric acid, or else converted to the free base by boiling with dilute sodium hydroxide solution. The benzohydrylquinoline was crystallized from 75% ethanol with the use of decolorizing carbon if necessary.

Alternately, the benzene extract of the reaction mixture was directly distilled, finally *in vacuo* to obtain 4-benzylquinoline (flask heated in an oil-bath). The tarry residue that did not distil was removed from the flask with warm acetone, and the latter almost entirely removed by distillation. Several volumes of ligroin were stirred in, giving crystals of benzohydrylquinoline, which were recrystallized from 75% alcohol with the use of Norit.

The yields were variable. In two experiments, the yield of 4-benzylquinoline was 37%, and that of 4-benzohydrylquinoline about 3%; in another experiment, 20.6% of crude benzohydrylquinoline hydrochloride was obtained, with only a small amount of 4-benzylquinoline.

4-Benzohydrylquinoline hydrochloride melts with decomposition at some temperature between 260° and 290° (rate of heating is important). For analysis it was crystallized several times from alcohol and dried at 100°.

Anal. Calc'd for $C_{22}H_{17}N \cdot HCl$: C, 79.62; H, 5.47; N, 4.22.
Found: C, 79.68, 79.61; H, 5.43, 5.51; N, 4.43, 4.39.

4-Benzohydrylquinoline melts at 146–147°, uncor.; for analysis it was crystallized several times from 80% alcohol.

Anal. Calc'd for $C_{22}H_{17}N$: C, 89.45; H, 5.80; N, 4.74.
Found: C, 89.33, 89.24; H, 5.90, 5.82; N, 4.85, 4.89.

The 4-benzylquinoline was identified by conversion to the picrate, m.p. 177–178° [literature (9), 178°]. 4-Benzohydrylquinoline was oxidized by chromic anhydride to the known (5) 4-quinolyldiphenylcarbinol, m.p. 247° (literature, 247.5°), following the directions for the preparation of 2-quinolyldiphenylcarbinol.

Phenylation of 2,4-dimethylquinoline. The phenylation of the potassium salt of 2,4-dimethylquinoline gave a complex mixture from which it was difficult to separate chemical individuals. One crystalline fraction (soluble in acetone but not in ether) melted at 163–165°; another fraction, m.p. 200–222°, was insoluble in both acetone and ether. One of the distilled fractions gave a picrate of the composition of a picrate of a methyl benzylquinoline.

Phenylation of 2-picoline. 2-Picoline (0.1 mole) was phenylated according to the standard procedure. The insoluble crystalline material from the benzene-water hydrolysate was filtered, the benzene layer evaporated, and finally heated under slightly reduced pressure to remove all solvent, 2-picoline, and chlorobenzene. A second crop of crystals separated from the cooled liquid. The total yield of material, crystallized from benzene and melting at 241° uncor., was 5.8 g., including the 2 g. recovered below (18%). This is undoubtedly the unknown triphenyl-2-pyridylmethane.

Anal. Calc'd for $C_{24}H_{19}N$: C, 89.68; H, 5.96; N, 4.36.
Found: C, 89.46; H, 5.96; N, 4.50.

The liquid separated from the second crop was extracted with 8 *N* hydrochloric acid, the latter made basic with sodium hydroxide, and in turn extracted with benzene. These extracts were distilled, finally at 12 mm., to obtain three fractions: 133–137° (5 cc.); 186–189° (5 cc.) and 210–215° (2 g.). The last fraction was crystallized from alcohol and proved to be triphenylpyridylmethane. The first two fractions were redistilled at 1 mm. to obtain 4.1 g. of an oil boiling at 93–94° (24%; 2-benzylpyridine) and 4.3 g. boiling at 163–164° (18%; 2-benzohydrylpyridine). The latter crystallized on standing and then melted at 62–63°, in agreement with the value given by Chichibabin and Benevolenskaya (10).

Anal. Calc'd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71.
Found: C, 88.12; H, 6.30; N, 6.25.

The oil boiling at 93–94°/1 mm. gave a picrate melting at 139°; 2-benzylpyridine picrate melts at 140° (11).

Phenylation of o-tolunitrile. The benzene solution of the reaction product was shaken with 8 *N* hydrochloric acid in a separatory funnel to remove aniline and other bases, and distilled, first at 760 mm. to remove solvent, and then at 2 mm. *o*-Benzylbenzonitrile came over at 158–160°, and was converted to *o*-benzylbenzoic acid m.p. 117° [literature, 117° (12)], by heating for 18 hrs. with methyl alcoholic sodium hydroxide, and acidifying with dil. sulfuric acid. *o*-Benzohydrylbenzonitrile came over as an oil at 200–210°; crystallizations from alcohol gave crystals melting at 88°. Drory (13) reports the melting point 89°.

Anal. Calc'd for $C_{20}H_{15}N$: C, 89.18; H, 5.61.
Found: C, 89.48; H, 5.87.

The yield of benzylbenzonitrile was 8.2 g. from 0.13 mole of *o*-tolunitrile (32%), and of *o*-benzohydrylbenzonitrile 3.1 g., or 8.8%.

ω,ω-Dibromoquinaldine. Tribromoquinaldine (18.9 g., 0.05 mole), ethyl alcohol (20 cc. of 95%), and conc'd sulfuric acid (5 cc.) were heated in a 100-cc. flask with take off of distillate. When the temperature (thermometer in the liquid) reached 102–105°, a brisk evolution of gas (mostly HBr) was observed, and the solid phase slowly dissolved. When the gas evolution had ceased, heating was continued for a few minutes to drive off dissolved hydrobromic acid, but was discontinued at the first sign of darkening of the liquid. After cooling, the product was poured into 500 cc. of cold water, and the flask rinsed out with the same solvent. The mixture was stirred for some time, and then filtered to remove dibromoquinaldine, which was crystallized from ethanol; yield, 14.7 g., or 98%; m.p. 119–120°. Hammick (14) reports the melting point as 120°.

Anal. Calc'd for $C_9H_6NCHBr_2$: Br, 53.0. Found: Br, 52.9.

Methyl alcohol, *n*-propyl alcohol, and isopropyl alcohol did not replace the ethanol in this preparation. Only with the two latter (and at about 130°) was dibromoquinaldine obtained, but there was much charring. Some acetal was also formed in the reaction with ethanol.

SUMMARY

1. 2-Picoline, quinaldine, lepidine, and *o*-tolunitrile are phenylated by adding potassium amide to a solution of their potassium salts and chlorobenzene in liquid ammonia. The following compounds were prepared in this manner: 2-Benzylpyridine, 2-benzohydrylpyridine, 2-triphenylmethylpyridine, 2-benzylquinoline, 2-benzohydrylquinoline, 2-triphenylmethylquinoline, 4-benzylquinoline, 4-benzohydrylquinoline, *o*-benzylbenzonitrile, *o*-benzohydrylbenzonitrile.

2. The structure of the 2-benzohydrylquinoline prepared by Wright and Bergstrom was confirmed by oxidizing it to diphenyl-2-quinolylcarbinol, which was also synthesized by the action of phenylmagnesium bromide on ethyl quinaldate.

3. 2-*n*-Propylquinoline, 2,4-dimethylquinoline, 2,4-dimethylpyridine, and 9-methylphenanthridine were not successfully phenylated by this method.

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THE ADDITION OF METHYLMAGNESIUM IODIDE TO BENZOYLDURENE

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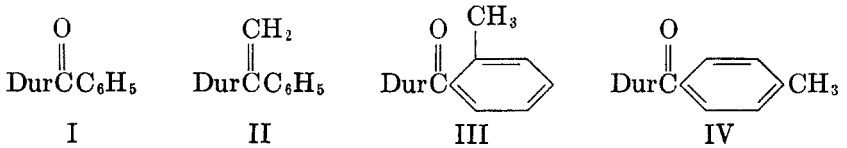
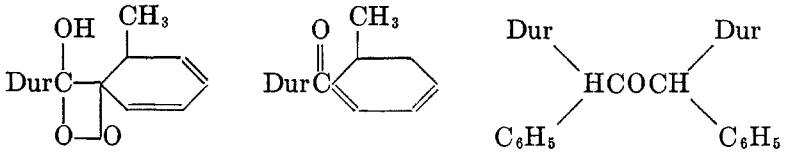
In earlier studies embracing benzoylmesitylene (1), benzoylisodurene (1), benzoyldurene (2), the mesitoylnaphthalenes (3), and similar diaryl ketones, it has been demonstrated that addition of Grignard reagents occurs in spite of the excessive crowding about the carbonyl group. The addition may be 1,2, 1,4, or 1,6, depending on the nature of the ketone and of the Grignard reagent which is used. Recently Young and Roberts (4) made the surprising discovery that 1,2 addition occurs when benzyl and *s*-butenyl Grignard reagents are condensed with acetomesitylene. These and methylmagnesium iodide are the only Grignard reagents which have been found to combine with mesityl ketones in this manner. In most cases addition takes place in the 1,4 manner. There is evidence, however, that even 1,4 addition is limited to reagents having small alkyl or aryl groups. In fact, in two instances 1,6 addition has been observed; benzyl- and *t*-butylmagnesium chloride react in this manner with benzoyldurene (2).

Thus it appears that in the condensation of Grignard reagents with highly hindered diaryl ketones 1,2, 1,4, and 1,6 addition may be competing reactions. It remained, however, to discover an example in which all three types of addition occurred simultaneously. The present paper deals with such a case—the condensation of methylmagnesium iodide with benzoyldurene (I).



I II III IV



V VI VII

When benzoyldurene was heated at 130° for six hours with three molar equivalents of methylmagnesium iodide in *n*-butyl ether solution, the product consisted of a mixture from which several pure compounds could be isolated. One of these was 1-duryl-1-phenylethylene (II), the olefin which would be formed by dehydration of the carbinol produced by 1,2 addition. This result is similar to those obtained with benzoylmesitylene, benzoylisodurene, and *p*-toluylmesitylene (1).

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The 1-duryl-1-phenylethylene (II) was converted by the action of ozone to a mixture of benzoyldurene and durylphenylacetic acid. The formation of the ketone is noteworthy inasmuch as similar hydrocarbons yielded, not the expected ketones, but the corresponding vinyl alcohols (5). The production of substituted acetic acids from olefins having terminal methylene groups has been observed repeatedly in chromic acid oxidations (6). Several examples of this type of change have been observed with ozone (5, 7). The identity of the 1-duryl-1-phenylethylene was confirmed by an independent synthesis; it was formed in low yield by the condensation of durylmagnesium bromide with acetophenone.

In the condensation of benzoyldurene with methylmagnesium iodide, *p*-toluyldurene (IV) was isolated also, though in small amount, showing that 1,6 addition had occurred. The chief product, however, was that formed by 1,4 addition. It was possible, by suitable procedures, to isolate the 1,4 addition product either in the form of the peroxide (V) of the enol or in the ketonized form, dihydro-*o*-toluyldurene. Two isomeric dihydro ketones were isolated from the reaction mixture; for convenience they have been designated as A (m.p. 123–124°) and B (m.p. 103–103.5°). The two isomers were never produced together. From the data at hand it is not clear what relationship exists between the method of conducting the condensation and the nature of the dihydro ketone formed. Possibly the acidity of the medium in which the enol is ketonized is the deciding factor. A third dihydro-*o*-toluyldurene (isomer C) was formed when isomer B was treated with platinum in an atmosphere of nitrogen.

The three isomeric dihydro-*o*-toluyldurenes gave positive tests for unsaturation and failed to evolve gas when tested for active hydrogen in the Kohler-Richtmyer apparatus (8). Each isomer underwent dehydrogenation when heated with palladium on charcoal, to yield *o*-toluyldurene (III). Dehydrogenation occurred spontaneously with isomers A and B but not with isomer C.

It is possible to write formulas for six dihydro-*o*-toluyldurenes which possess no *alpha* hydrogen atom. By use of the one known dihydro-*o*-toluic acid it has been possible to synthesize the ketone corresponding to formula VI. 2,3-Dihydro-*o*-toluic acid (9) was converted to the acid chloride and the latter condensed with durene by the Friedel-Crafts method. The product, obtained in 70% yield, melted at 123° and was identical with isomer A.

Whatever the exact structures of the other two isomers (B and C) may be, it is certain that they, like isomer A, have the skeletal arrangement of *o*-toluyldurene and that their formation likewise depends on initial 1,4 addition.

2,3,5,6-Tetramethylbenzohydryl ether (VII) was also isolated. It was probably formed from the durylphenylcarbinol produced by the reduction of benzoyldurene.

From the foregoing facts it is clear that the mode of addition of methylmagnesium iodide to benzoyldurene is chiefly 1,4 and that 1,2 and 1,6 addition also occur, though to a less extent.

EXPERIMENTAL

Condensation of methylmagnesium iodide with benzoyldurene. Experiment 1. To the Grignard reagent, prepared in ethyl ether from 34 g. of magnesium and 198 g. of methyl

iodide, was added 100 g. of solid benzoyldurene and 500 ml. of *n*-butyl ether. The flask was placed in an oil-bath and the temperature was gradually raised so that the ethyl ether was slowly distilled. Butyl ether was added from time to time to maintain the original volume. When the removal of the ethyl ether was almost complete, nitrogen was passed in and the temperature was raised to 130°. The reaction mixture was maintained at this temperature for six hours, with constant stirring. The reaction mixture was cooled to 0° and decomposed with ice and sulfuric acid. The organic layer was separated, washed twice with ice-water, and then shaken with 300 ml. of 2 *N* hydrochloric acid for eighteen hours to ketonize the enol. The organic layer was separated, extracted with 5% sodium carbonate, and washed with water. The solution was dried over magnesium sulfate and the butyl ether was distilled at the water-pump. The residual yellow oil was distilled at reduced pressure to separate the addition products from the polymeric material which was present. The residue in the flask weighed 25 g. Careful refractionation of the distillate yielded four fractions. The first consisted of 10 mg. of a solid with a phenolic odor which sublimed before the distillation started.

The second fraction, collected at 130–140° (2 mm.), weighed 22 g. Three distillations of this fraction yielded 15 g. of *1-duryl-1-phenylethylene* as a viscous oil which was induced to crystallize from absolute ethanol. It formed large prisms which, after three recrystallizations from this solvent, melted at 71–72°; yield 10 g.

Anal. Calc'd for $C_{18}H_{20}$: C, 91.47; H, 8.53.
Found: C, 91.32; H, 8.50.

The third fraction consisted of 50 g. of an oily solid distilling at 140–150° (2 mm.). After six recrystallizations from ethanol, 34 g. of the *dihydro-o-toluyldurene* (A), melting at 123–124°, was obtained.

Anal. Calc'd for $C_{18}H_{22}O$: C, 84.99; H, 8.72.
Found: C, 84.82; H, 8.67.

The fourth fraction, collected at 150–165° (4 mm.), weighed 3 g. By fractional crystallization of this material from ethanol, it was possible to separate a compound, m.p. 114–128°, from the dihydro-*o*-toluyldurene (A), m.p. 123–124°. After three recrystallizations the new product melted at 144–145°. It was shown by the method of mixture melting points to be *p-toluyldurene;* yield 0.5 g.

The residue, weighing 5 g., was recrystallized from ether, from absolute ethanol, and from butyl ether. Three grams of 2,3,5,6-tetramethylbenzohydryl ether, m.p. 174–175°, was obtained.

Anal. Calc'd for $C_{34}H_{38}O$: C, 88.26; H, 8.28.
Found: C, 88.08; H, 8.09.

Experiment 2. The condensation was run in the usual manner; 20 g. of benzoyldurene, 6.8 g. of magnesium, and 39.6 g. of methyl iodide were used. The reaction was effected in *n*-butyl ether by heating at 130° for six hours. The reaction mixture was cooled to 0° in an ice-salt bath and maintained at this temperature while a saturated solution of ammonium chloride was added slowly, with stirring. After the Grignard complex had been decomposed, the ether solution was decanted from the inorganic paste, and the latter washed with 100 ml. of cold ether. The combined extracts were washed three times with ice-water and dried with anhydrous magnesium sulfate. After the butyl ether had been distilled at the water-pump, the residue was fractionated at reduced pressure. Ten grams of distillate was obtained and approximately 10 g. of non-volatile material remained in the flask. Redistillation yielded 3 g. of crude *1-duryl-1-phenylethylene* and 6 g. of a *dihydro-o-tolyl duryl ketone* (B) boiling at 136–145° (2 mm.). After three recrystallizations from ethanol 4 g. of white platelets, m.p. 103–103.5°, was obtained. This ketone underwent dehydrogenation so readily that it was impossible to obtain a satisfactory analysis.

The high-melting dihydro-o-toluyldurene (A). This compound instantaneously decolorized a solution of bromine in carbon tetrachloride. It reacted with a 2% permanganate solution, and a Zerewitinoff determination showed the absence of active hydrogen. It was not isomerized by acid or alkali at room temperature.

Pentabromo derivative. To a solution of 2 g. of the dihydro compound (A) in carbon tetrachloride was added 8.5 g. of bromine in 20 ml. of carbon tetrachloride. The mixture was stirred at room temperature for three hours, at the end of which period it was washed once with a dilute aqueous solution of sodium bisulfite and once with water. The carbon tetrachloride was distilled and the residue was recrystallized several times from benzene. The pentabromo compound was a white crystalline solid; m.p. 195–196°; yield 4 g.

Anal. Calc'd for $C_{18}H_{21}Br_5O$: C, 33.09; H, 3.22; Br, 61.23.
Found: C, 32.66; H, 3.34; Br, 62.54.

Dehydrogenation. In a large test tube equipped with a cold-finger were mixed 1.5 g. of isomer A and 0.1 g. of 10% palladium-charcoal catalyst. The mixture was heated for thirty minutes at 350° in a metal-bath. It was then cooled, taken up in ethanol, and filtered to remove the catalyst. The brown filtrate was treated with Norit and cooled; 0.7 g. of white crystals, m.p. 100–107°, separated. Recrystallization of the compound from ethanol raised the melting point to 112–112.5°. A mixture melting point determination with an authentic sample of *o*-toluyldurene showed no depression.

The low-melting dihydro-o-toluyldurene (B). The compound instantaneously decolorized a solution of bromine in carbon tetrachloride and reacted with a 2% potassium permanganate solution.

Isomerization. In an attempted hydrogenation, 2 g. of the dihydro compound (B) was dissolved in 100 ml. of alcohol containing 0.2 g. of platinum oxide and the solution was shaken under 3 atm. of hydrogen at room temperature. The amount of hydrogen taken up was negligible. After the reaction mixture had been shaken for six hours it was filtered, and the alcohol was removed by evaporation. The residue was recrystallized from 95% ethanol. The product was a new form of dihydrotoluyldurene (Isomer C). It was a white crystalline solid melting at 117–118°; yield 1.5 g. This compound instantaneously decolorized a solution of bromine in carbon tetrachloride. It reacted with a 2% permanganate solution, and a Zerewitinoff determination showed the absence of active hydrogen. It was not isomerized by acid or alkali at room temperature. It had been isolated previously from the combined mother liquors of several runs of the reaction of methylmagnesium iodide with benzoyldurene.

Anal. Calc'd for $C_{18}H_{22}O$: C, 84.99; H, 8.72.
Found: C, 85.28; H, 8.63.

Similar results were obtained when the isomer (B) was shaken with platinum in an atmosphere of nitrogen.

The low-melting dihydro compound was not isomerized by 2 *N* hydrochloric acid at room temperature. Treatment with alkali caused dehydrogenation.

Dehydrogenation was carried out by the procedure that was employed in the dehydrogenation of isomer A; *o*-toluyldurene, m.p. 112–112.5°, was obtained.

Preparation of the peroxide of the enol. The condensation described in Experiment 2 was repeated but at the end of the six-hour period of heating 70 ml. of the reaction mixture was removed with a pipet, and cooled in an ice-salt bath. After decomposition of the solution with a saturated solution of ammonium chloride, the ether layer was removed and washed four times with ice-water. The solution was divided into two parts, one of which was allowed to stand for several hours. The ether was distilled and the product crystallized from ethanol; m.p. 102–103°. A mixture melting point determination showed it to be isomer B. Oxygen was bubbled for twelve hours through the remaining portion of the solution, which was kept in an ice-bath. The butyl ether was then evaporated in a stream of air and the residue was triturated with 100 ml. of low-boiling petroleum ether. The amorphous, white solid which would not dissolve in the petroleum ether was collected on a filter and recrystallized twice from a mixture of high- and low-boiling petroleum ether. The yellow, crystalline peroxide melted, with decomposition, at 126–128°; yield 3 g.

Anal. Calc'd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75.
Found: C, 75.28; H, 7.81.

Ozonization of 1-duryl-1-phenylethylene. One gram of the ethylene was dissolved in 100

ml. of glacial acetic acid and a stream of 2.5% ozone was bubbled through the solution at the rate of 50 ml. per minute for three hours. The solution turned green. The ozonide was heated under reflux for one hour with 400 ml. of water. The mixture was cooled and extracted with ether. The ether solution was extracted several times with 5% sodium hydroxide, washed with water, and dried over anhydrous magnesium sulfate. Removal of the ether left the benzoyldurene as a light brown oil. It was crystallized from absolute ethanol; m.p. 117–119°; yield 20 mg. A mixture melting point with a sample of benzoyldurene showed no depression.

The sodium hydroxide solution was acidified, extracted with ether, and washed repeatedly with water. The ether was evaporated, and the brown solid which remained was recrystallized several times from 95% ethanol. Needle-like crystals of an acid were obtained, which melted at 232–234°. This compound was identified as durylphenylacetic acid by comparison with an authentic specimen (10).

Preparation of 1-duryl-1-phenylethylene by the reaction of durylmagnesium bromide with acetophenone. The calculated amount of magnesium was added to a solution of 50 g. of bromodurene in 1 liter of anhydrous ether. The mixture was stirred for forty-eight hours under nitrogen, at the end of which time there was a copious precipitate of durylmagnesium bromide. A 20-ml. portion of the reaction mixture was removed with a pipet and poured on solid carbon dioxide. The amount of 2,3,5,6-tetramethylbenzoic acid formed indicated that 55% of the bromodurene had reacted with the magnesium.

Forty-two grams of acetophenone, dissolved in 200 ml. of anhydrous ether, was added slowly with vigorous stirring to the durylmagnesium bromide prepared as described above. Gentle refluxing occurred and a gummy precipitate formed which eventually prevented stirring of the reaction mixture. When the addition of acetophenone was completed, the Grignard complex was decomposed with saturated ammonium chloride solution and the product was isolated in the usual manner. It was a viscous yellow oil, fractional distillation of which yielded acetophenone, durene, bromodurene, and 1-duryl-1-phenylethylene. The amount of durene isolated indicated that 80% of the acetophenone had enolized. The olefin was obtained from the high-boiling fraction as a light yellow oil; yield 5 g. The oil was crystallized repeatedly from absolute ethanol; yield 3.5 g.; m.p. 71–72°.

Synthesis of 2,3-dihydro-o-toluyldurene. 2,3-Dihydro-*o*-toluic acid (9) was converted to the acid chloride by treatment with thionyl chloride. Eight and one-half grams of anhydrous aluminum chloride was added over a period of thirty minutes to a mixture of 8.5 g. of durene, 10 g. of the acid chloride, and 200 ml. of carbon disulfide. The mixture was stirred during the addition and for two hours afterward, then poured into a mixture of ice and hydrochloric acid. The 2,3-dihydro-*o*-toluyldurene, isolated by conventional procedures, was recrystallized from ethanol; m.p. 123–124°; yield 51%. A mixture with the compound obtained by treating benzoyldurene with methylmagnesium iodide showed no lowering of the melting point.

Preparation of the diaryl ketones. The ketones listed in Table I were prepared as reference compounds in connection with the identification of the various condensation products. They were all made by the same general procedure. One-tenth mole of anhydrous aluminum chloride was added in small portions over a period of one and one-half hours to a mixture of 1 mole of the aromatic compound (durene, bromodurene, or pentamethylbenzene), 1 mole of the acid chloride, and 200 ml. of carbon disulfide. The mixture was stirred during the addition and for three hours longer. After decomposition of the mixture, the organic layer was removed and the carbon disulfide was distilled. To the residue was added 200 ml. of 10% sodium carbonate solution and the mixture was steam distilled to remove the unchanged hydrocarbon. The contents of the flask were cooled and filtered. The solid ketone was dried and recrystallized from ethanol. In certain cases the product had a wide melting point range and a preliminary recrystallization from butyl ether was found to be helpful.

As indicated in the Table, several of the duryl ketones were also prepared by the reaction of durylmagnesium bromide with the appropriate acid chloride. The following procedure

was used. To a solution of the acid chloride in ether was added, dropwise, the equivalent amount of an ether suspension of durylmagnesium bromide. The solution was stirred for three hours after the addition and then was decomposed with ice and hydrochloric acid. The organic layer was removed and the ether was distilled. The product was freed from durene and bromodurene by steam distillation of the mixture formed by adding 200 ml. of a 10% sodium carbonate solution to the residue. The flask was then cooled and the solid ketone removed by filtration and recrystallized from ethanol.

Duryl-o-tolylmethane. Ten grams of *o*-toluyldurene was dissolved in absolute ethanol and 15 g. of sodium was added, in small amounts, at a rate sufficient to keep the mixture boiling vigorously. The reaction mixture was then poured into 400 ml. of water, and the

TABLE I

DIARYL KETONES

COMPOUND[a]	ACID CHLORIDE	YIELD %	M.P. °C	ANALYSIS
o-Toluyldurene[b]	*o*-Toluyl	76	112–112.5	Calc'd: C, 85.67; H, 7.99 Found: C, 85.59; H, 8.13
m-Toluyldurene	*m*-Toluyl	78	111–112	Calc'd: C, 85.67; H, 7.99 Found: C, 85.87; H, 7.93
p-Toluyldurene[b]	*p*-Toluyl	80	144–145	Calc'd: C, 85.67; H, 7.99 Found: C, 85.58; H, 8.15
p-Anisoyldurene	*p*-Anisoyl		143.4–144.5	Calc'd: C, 80.56; H, 7.51 Found: C, 80.88; H, 7.77
Benzoylpentamethylbenzene	Benzoyl	63	135–136	Calc'd: C, 85.67; H, 7.99 Found: C, 85.99; H, 7.97
m-Toluylbromodurene	*p*-Toluyl	61	131–132	Calc'd: C, 65.42; H, 5.76 Found: C, 65.63; H, 5.99
Duryl *trans*-2-methylcyclohexyl ketone	*trans*-2-Methylcyclohexanecarboxylic acid	78	132–134	Calc'd: C, 83.67; H, 10.14 Found: C, 83.70; H, 10.32

[a] All the ketones listed in this table were prepared by the Friedel-Crafts method.

[b] This compound was made by the Friedel-Crafts method and also by the Grignard method.

yellow-white solid which precipitated was collected on a filter and recrystallized from ethanol. The duryl-*o*-tolylmethane formed needle-like crystals melting at 94.5–95°; yield 4 g.

Anal. Calc'd for $C_{18}H_{22}$: C, 90.70; H, 9.30.
Found: C, 90.51; H, 9.57.

Durylphenylcarbinol. At one stage in the investigation it seemed possible that durylphenylcarbinol might be among the products formed by the action of the Grignard mixture on benzoyldurene. This carbinol was therefore made for reference. Benzoyldurene was reduced by the general method of Bachmann (11). To an amalgam prepared from 4.5 ml. of mercury and 1.2 g. of sodium were added 25 ml. of benzene, 25 ml. of dry ether, 2.5 ml. of absolute ethanol, and 4.76 g. of benzoyldurene. The container was stoppered and shaken

for twenty minutes. In the beginning the reaction mixture developed a deep, opaque red color which, at the end of the reaction, had given way to a pale, transparent green color. The mixture was poured into water contained in a separatory funnel, the mercury drawn off, and the organic layer washed with water and dried. The oil left after distillation of the solvent was distilled under diminished pressure, whereupon it crystallized; b.p. 185–186° (6 mm.); m.p. 66–69°.

Although the carbinol was not thought to be sufficiently pure for analysis, it formed an α-naphthylurethan, which served to identify it. The urethan was recrystallized from high-boiling petroleum ether; m.p. 177.5–178.5°.

Anal. Calc'd for $C_{28}H_{27}NO_2$: C, 81.92; H, 6.87.
Found: C, 82.23; H, 6.88.

Oxidation with chromic anhydride in glacial acetic acid converted the carbinol to benzoyldurene in 42% yield.

The gummy residue from the distillation of durylphenylcarbinol crystallized when allowed to stand overnight in contact with ether. Recrystallization from a mixture of benzene and chloroform yielded 650 mg. of 2,3,5,6-tetramethylbenzohydrylether, m.p. 174–175°.

SUMMARY

By treatment of benzoyldurene with methylmagnesium iodide under "forcing" conditions 1-duryl-1-phenylethylene, dihydro-*o*-toluyldurene, *o*-toluyldurene, and *p*-toluyldurene have been produced. These products demonstrate that 1,2, 1,4, and 1,6 addition of the Grignard reagent to the ketone take place concurrently.

The dihydro-*o*-toluyldurene was obtained from the reaction mixture in two isomeric forms, one of which was shown by an independent synthesis to be 2,3-dihydro-*o*-toluyldurene. The other isomer rearranged to a third isomer when treated with platinum in an atmosphere of nitrogen.

URBANA, ILL.

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[CONTRIBUTION FROM THE UNIVERSITY OF MARYLAND]

THE REACTION OF PHENANTHRENE WITH ETHYL DIAZOACETATE[1]

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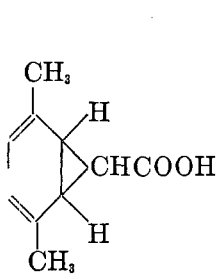
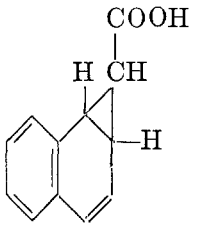
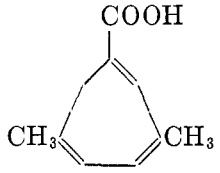
Ethyl diazoacetate adds to an ethylenic linkage to form a pyrazoline carboxylic ester, which loses nitrogen spontaneously when the reaction temperature is sufficiently high, to yield a derivative of the ethyl ester of cyclopropanecarboxylic acid. Extension of this reaction to certain aromatic hydrocarbons provides a general synthesis of the norcarane ring system. When benzene or certain of its derivatives are heated with ethyl diazoacetate, the primary product is the ethyl ester of a norcaradienecarboxylic acid (I). This ring system, with the exception of the one derived from naphthalene, benznorcaradienecarboxylic



I



II



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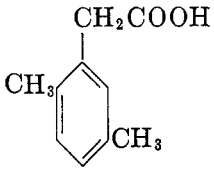

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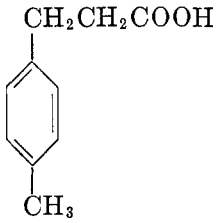

V

acid (II), exhibits a tendency to rearrange, especially at high temperatures or in the presence of alkali. Thus I rearranges into derivatives of cycloheptatrienecarboxylic acid (III), phenylacetic acid (IV), and hydrocinnamic acid (V), (1–16).

According to the rule of Buchner, the condensation of ethyl diazoacetate with an aromatic hydrocarbon always involves addition to a non-substituted carbon atom. If the nature of the hydrocarbon precludes this mode of addition,

[1] From a thesis submitted by Thomas R. Sweeney to the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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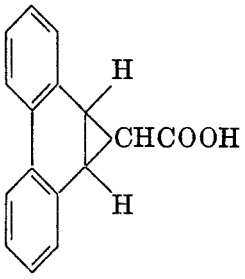
a rearrangement product of the bicyclic ester is obtained and not the bicyclic ester itself. Thus the primary product with mesitylene is a trimethylcycloheptatrienecarboxylic ester (14) while condensation with durene yields the ethyl ester of 2,4,5-trimethylhydrocinnamic acid (17).

The purpose of the present work was to extend this type of reaction to phenanthrene.

When ethyl diazoacetate was added slowly to phenanthrene at 145–150°, condensation took place smoothly with the evolution of nitrogen to yield the ethyl ester of dibenznorcaradienecarboxylic acid (VI). If the rate of addition of the diazo ester to the phenanthrene and the temperature was kept constant, nitrogen was evolved at a constant rate. The reaction started within a few



VI

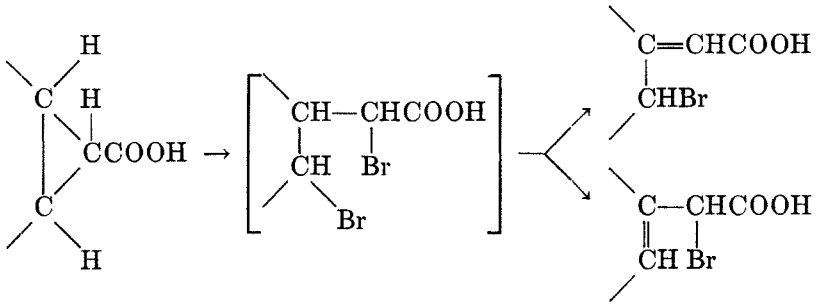
minutes after the addition of the first of the ester and was complete about fifteen minutes after the addition of the last of the ester. Without attempting to isolate the reaction product ester, the reaction mixture was saponified with alcoholic sodium hydroxide, the alcohol removed, and the sodium salt of the acid extracted from the residue with hot water. Acidification precipitated crude VI. The product was contaminated with a dark brown, gummy, acidic material. This resinous by-product was not identified in the present work; the formation of such a by-product, however, is usually observed in condensations involving ethyl diazoacetate. It consists of substances resulting from self-condensation of the diazo ester (18–25).

The ethyl ester of VI, like that of II, is stable to rearrangement when heated with alcoholic alkali whereas, in general, the esters of the bicyclic norcaradienecarboxylic acids undergo rearrangements into derivatives of cycloheptatrienecarboxylic acid when so treated (2, 12, 13). The acid VI is stable to rearrangement even under relatively severe conditions. When heated with sodium hydroxide in ethylene glycol at 170° for six hours, under which conditions rearrangement, decarboxylation, or both, might reasonably be expected, the original acid was recovered unchanged. Furthermore, the amide of VI was recovered unchanged after refluxing with thirty per cent sulfuric acid whereas this reagent brought about rearrangements of some of the bicyclic norcaradienecarboxylic acid amides into derivatives of phenylacetic acid (11, 12).

In an attempt to open the cyclopropane ring of VI by hydrogenation at 80°, a white, crystalline acid was obtained. Although the structure of this product

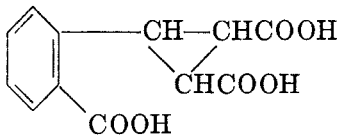
was not determined, it seems possible that it could be an octahydrophenanthreneacetic acid.

Unlike II, VI does not decolorize a chloroform solution of bromine at room temperature, nor does it react when the solution is held just below the boiling point of the chloroform for two hours. However, when VI is refluxed for two hours with bromine in glacial acetic acid considerable hydrogen bromide is evolved and the color of the reaction mixture slowly changes from the color of the bromine to a green and finally to a deep blue. From this solution can be isolated an almost colorless, crystalline acid which contains bromine and reduces alkaline permanganate immediately to a green solution, manganese dioxide being precipitated some time later. Although the exact structure of the product was not proved, it seems likely that the reaction involves cleavage of the cyclopropane ring with subsequent elimination of hydrogen bromide in one of two ways, namely from the side chain or the ring, thus



Of these two mechanisms, the formation of the completely aromatic phenanthrene nucleus seems the more probable. The analysis of the product agrees closely with that calculated for such isomers.

Unlike II, which declorizes an alkaline permanganate solution almost instantaneously at room temperature, VI is attacked only after prolonged standing. However, if the oxidation is forced, 1-(2′-carboxyphenyl)-2,3-cyclopropanedicarboxylic acid (VII) is obtained in extremely poor yields. Slightly better yields, although still very poor, can be obtained by oxidation with chromic anhydride



VII

in glacial acetic acid. The same acid, VII, is obtained in good yields from a permanganate oxidation of II.

From a consideration of the reaction of ethyl diazoacetate with other aromatic hydrocarbons, it seemed probable that the reaction with phenanthrene, if it occurred at all, would take the usual course, and that the addition product would consist of a cyclopropane ring fused with one of the benzene nuclei of the phenanthrene molecule. This sort of addition, or its equivalent, is supported by the

composition of the addition product. Furthermore, because of the pronounced reactivity and ethylenic character of the 9,10 bond of phenanthrene, it might be anticipated that condensation would take place in the 9,10 position and that the addition product would have the structure VI. That such was actually the case is proved by the fact that the condensation product on oxidation yields VII. None of the isomeric naphthonorcaradienecarboxylic acids that would have resulted from the condensation of ethyl diazoacetate across a double

TABLE I

COMPARISON OF OXIDATION PRODUCT OF II AND VI AND THEIR DERIVATIVES

	M.P., °C	MIXED M.P., °C	CARBON %		HYDROGEN %		NITROGEN %	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Oxidation product of (II)..	281–282 with decomp.	no change	57.60	57.72, 57.72	4.03	4.20, 4.07		
Oxidation product of (VI)..	281–282 with decomp.		57.60	57.68, 57.56	4.03	4.15, 4.04		
Tri-*p*-phenylphenacyl ester of oxidation product of (II).....	175–176	no change	77.87	77.98	4.84	4.95		
Tri-*p*-phenylphenacyl ester of oxidation product of (VI).....	175–176		77.87	77.84	4.84	4.88		
Tri-anilide of oxidation product of (II).....	decomp. 328–330 (block)	no change	75.77	75.77	5.30	5.19	8.84	8.71, 8.76
Tri-anilide of oxidation product of (VI).....	decomp. 328–330 (block)		75.77	75.65	5.30	5.33	8.84	8.82, 8.81

bond of a terminal ring in the phenanthrene molecule would reasonably be expected to yield VII on oxidation. Nor would the more improbable isomers that would result from condensation of the group $\diagdown CHCOOC_2H_5$ with the phenanthrene nucleus by means of a doubly bonded carbon, a meta bridge across a ring, or a para bridge across a ring, yield VII on oxidation.

The reluctance of the condensation product to react with permanganate and bromine at room temperature supports the structure VI. The isomeric naphthonorcaradienecarboxylic acids as well as any isomers having a four, five, or seven membered carbon ring would contain double bonds that would be expected to give the usual tests for unsaturation.

Proof that the oxidation product of VI actually has the structure shown in VII was obtained by comparing it with a sample of VII synthesized by an

independent method. Ethyl diazoacetate was allowed to react with naphthalene and the ester addition product saponified to yield II. The latter on oxidation with alkaline permanganate was converted to VII in good yield. That the oxidation product of VI was identical with the oxidation product of II was shown by a comparison of the analyses, melting points and mixed melting points of the two oxidation products as well as of their trianilides and tri-*p*-phenylphenacyl esters. These data are shown in Table I.

There are two possible geometric isomers of VI, one in which the carboxyl group is on the same side of the cyclopropane ring as the phenanthrene nucleus (cis), and one in which it is on the opposite side (trans). An isomer in which the two bonds that join the phenanthrene nucleus to the cyclopropane ring are on opposite sides of the ring would involve impossible strains and is, therefore, incapable of existing. Hence, these two bonds must necessarily bear a cis relation to each other. Since VII is a derivative of *trans*-cyclopropanedicarboxylic acid (10), the carboxyl group in VI probably bears a trans relation to the phenanthrene residue.

EXPERIMENTAL

Ethyl diazoacetate was prepared according to Curtius (26) as described by Gatterman and Wieland (27).

Purification of phenanthrene. Crude, 70% phenanthrene was converted to the pure crystalline product according to the method of Bachmann (28).

Action of ethyldiazoacetate on phenanthrene. The reaction was carried out in a 500-ml. three-necked flask, equipped with a mechanical stirrer, a small dropping-funnel, and a reflux condenser. In the top of the condenser was fitted a T-tube, one outlet of which was connected by rubber tubing to the top of the dropping-funnel to act as a pressure equalizer, while the other was connected to a Mariotte flask for collecting nitrogen. The water was allowed to flow from the Mariotte flask through a leveling bulb into a graduated cylinder. The reaction flask was immersed in an oil-bath.

A typical experiment is as follows. Phenanthrene (1 mole, 178 g.) was placed in the reaction flask and the outside temperature brought to 145–150°. After the phenanthrene had melted, the mechanical stirrer, geared down to 90–100 r.p.m., was started. Ethyl diazoacetate (0.2 mole, 22.8 g.) was then added dropwise from the dropping-funnel over a period of ten hours. Evolution of nitrogen started within a few minutes after the addition of the first drops of ester, and at the end of the first half hour 150 ml. had been collected. If a constant rate of addition was maintained, nitrogen was evolved at a constant rate. The rate of nitrogen evolution dropped sharply after the addition of the last of the ester. A total of 4600 ml. was collected. The reaction mixture was dissolved in alcohol and sufficient alcoholic sodium hydroxide was added to saponify the ester. The mixture was refluxed for two hours on the steam-bath, after which the alcohol was removed as completely as possible by distillation under reduced pressure. The residue was then extracted several times with hot water. The aqueous extract was cooled, filtered, and washed with ether. Acidification with hydrochloric acid precipitated the crude dibenznorcaradienecarboxylic acid, leaving the formerly brown solution almost water-clear. The precipitated acid was very sticky at this point, retained a large amount of water, and was very difficult to filter. It was allowed to stand overnight by which time it had turned granular and was easily filtered. The yield of crude, dry acid was 27.1 g., 57.4% of the theoretical based on the diazo ester used. The crude material was triturated quickly with cold dioxane and filtered. Most of the brown impurity and some of the product dissolved immediately in the dioxane and was filtered off. The product, after decolorization with Norit in dioxane solution, was crystallized from the same solvent; colorless needles, m.p. 257.5–258° with decomposition, were obtained.

Anal. Calc'd for $C_{16}H_{12}O_2$: C, 81.33; H, 5.12.
Found: C, 81.23, 81.26; H, 5.08, 5.18.

Recovery of phenanthrene. The residual phenanthrene, after extraction of the sodium dibenznorcaradienecarboxylate, had a color varying from a light to a dark brown. It was air-dried, taken up in an excess of 50–70° petroleum ether and treated with decolorizing carbon. The filtrate, which was still somewhat yellow, was then shaken for a few minutes with powdered alumina and filtered. The filtrate was then colorless; after evaporation of the solvent, pure, colorless phenanthrene crystallized.

Dibenznorcaradienecarboxylic acid. The acid dissolves in cold concentrated sulfuric acid with the formation of a green color which turns to a light blue in a few minutes, to a more intense blue in about an hour, and finally, in about twenty-four hours, to a purple. It forms crystalline sodium, ammonium, and silver salts.

Amide. The acid chloride was prepared with thionyl chloride. The amide was crystallized from alcohol; colorless needles, m.p. 334–335° with decomposition.

Anal. Calc'd for $C_{16}H_{13}NO$: C, 81.67; H, 5.57; N, 5.95.
Found: C, 81.64, 81.60; H, 5.59, 5.54; N, 5.90, 5.96.

para-Phenylphenacyl ester. This was prepared from sodium dibenznorcaradienecarboxylate and *p*-phenylphenacyl bromide in the usual way. Needles from alcohol, m.p. 169.5–170.5°.

Anal. Calc'd for $C_{30}H_{22}O_3$: C, 83.70; H, 5.13.
Found: C, 83.25, 83.30; H, 5.18, 5.27.

para-Nitrobenzyl ester. This was prepared from sodium dibenznorcaradienecarboxylate and *p*-nitrobenzyl bromide in the usual way. It was recrystallized from alcohol; m.p. 136–136.5°.

Anal. Calc'd for $C_{22}H_{17}NO_4$: C, 74.38; H, 4.62; N, 3.77.
Found: C, 74.12, 74.21; H, 4.66, 4.64; N, 3.83, 3.81.

Hydrogenation. Pure, crystalline sodium dibenznorcaradienecarboxylate (5.9 g.) was dissolved in dilute sodium hydroxide and the solution hydrogenated for two hours at 80° and 1700–1800 lbs. pressure using a Raney nickel catalyst. The catalyst was filtered from the reaction mixture and the filtrate acidified with hydrochloric acid. A gummy white solid was precipitated which was extracted from the aqueous medium with benzene. After the benzene had been evaporated and the residue freed of solvent over paraffin wax, the crude product weighed 4.7 g. It was purified by recrystallization from petroleum ether (b.p. 90–100°); colorless crystals, m.p. 144.5–145°.

Anal. Calc'd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25.
Found: C, 79.01, 78.44; H, 8.58, 8.38.

The product was a white crystalline acid which reduced alkaline permanganate almost instantaneously at room temperature, but only slowly decolorized bromine in chloroform solution. It gave only a faint yellow color with sulfuric acid. Oxidation with chromic anhydride in acetic acid yielded, what appeared to be from the wide melting range, a mixture of acids, which dissolved in sodium hydroxide solution with the formation of a blue color.

Bromination. The acid did not react with bromine in chloroform at room temperature nor when held just below the boiling point of the chloroform for two hours. However, the acid could be made to react as follows. To a solution of 1 g. of the acid in 30 ml. of acetic acid was added 0.3 ml. of bromine. The solution was refluxed for two hours, during which time the color changed slowly from the color of the bromine to a green and finally to a deep blue. Hydrogen bromide was evolved during the reaction. The reaction mixture was poured into several volumes of water whereupon a white solid was precipitated. After evaporation of the deep blue ether extract of this suspension, a mass of green and light yellowish brown crystals remained. These gave a green solution when taken up in hot benzene. To this solution, after treatment with decolorizing carbon with no change in color, was added an equal volume of hexane. A mass of slightly yellow crystals was obtained when the solution cooled. After recrystallization from benzene almost colorless

crystals were obtained, m.p. 182.5–184°. These crystals melted to a blue liquid which set to a blue solid on cooling.

Anal. Calc'd for $C_{16}H_{11}BrO_2$: C, 60.97; H, 3.52; Br, 25.36.
Found: C, 61.10, 61.03; H, 3.46, 3.54; Br, 26.26, 26.07.

The product was a bromo acid, insoluble in water, but soluble in dilute sodium hydroxide. The alkaline solution immediately reduced permanganate to a green solution, and slowly to manganese dioxide. It was only slowly soluble in concentrated sulfuric acid with the formation of a pale green solution which slowly turned to an intense green on standing.

The deep blue ether extract of the original reaction mixture on standing overnight faded to a faint yellowish green. However, if the original reaction mixture was allowed to stand for the same length of time and then extracted with ether, a blue extract was obtained. This indicated easy oxidation of the blue substance since the ether was known to contain peroxides.

Oxidation. To a solution of 1 g. of the acid in dilute sodium hydroxide was added a solution of 7.5 g. of potassium permanganate. The reaction mixture was allowed to stand at room temperature for twenty-four hours and was then heated on the steam-bath for two hours. It was then made distinctly acid with sulfuric acid and heated for another hour on the steam-bath with occasional shaking. The solution was cooled, filtered, and extracted several times with ether. The ether was evaporated and the residual 1-(2′-carboxyphenyl)-2,3-cyclopropanedicarboxylic acid recrystallized several times from water, m.p. 281–282°. The yield was very poor, about 0.1 g.

Anal. Calc'd for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03.
Found: C, 57.68, 57.56; H, 4.15, 4.04.

Slightly better yields, although still poor, were obtained using chromic anhydride in acetic acid as the oxidant. An excess of chromic anhydride (wt. ratio of 6:1) was used and the reaction mixture refluxed two hours.

Benznorcaradienecarboxylic acid. This acid was prepared by allowing ethyl diazoacetate to react with naphthalene, followed by saponification of the ester addition product essentially according to Buchner and Hediger (10).

1-(2′-Carboxyphenyl)-2,3-cyclopropanedicarboxylic acid. This acid was prepared by oxidation of benznorcaradienecarboxylic acid with alkaline permanganate according to the method of Buchner and Hediger (10). The melting point of our product, 281–282°, was slightly higher than that (273–275°) reported by Buchner. This discrepancy may possibly be accounted for by a difference in the methods used in determining the melting point or in the relative purity of the two products. Buchner and Hediger state that their compound was yellowish-white and did not melt sharply; the compound prepared in this work was pure white and melted sharply.

Anal. Calc'd for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03.
Found: C, 57.72, 57.72; H, 4.20, 4.07.

The tri-anilides and tri-*p*-phenylphenacyl esters of 1-(2′-carboxyphenyl)-2,3-cyclopropanedicarboxylic acid obtained from the oxidation of benznorcaradienecarboxylic and dibenznorcaradienecarboxylic acid were prepared in the usual way. The anilides were recrystallized from acetic acid and the *p*-phenylphenacyl esters from acetone. The melting points and analyses are given in Table I.

SUMMARY

1. Ethyl diazoacetate has been condensed with phenanthrene; the ethyl ester of dibenznorcaradienecarboxylic acid is formed.

2. The structure of the product has been proved.

3. Some of the chemistry of dibenznorcaradienecarboxylic acid has been described.

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ARYLAMINE-N-GLYCOSIDES. PART I. ARYLAMINE-N-D-RIBOPYRANOSIDES AND N-D-RIBOFURANOSIDES

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In the course of an investigation of the synthesis of N-ribityl-3,4-xylidine, an intermediate in the synthesis of vitamin B_2, a product was obtained from the condensation of 3,4-xylidine and D-ribose which did not correspond to the xylidine riboside obtained by Kuhn (1). A detailed study of this condensation product and related compounds indicated that a *new* form of N-riboside, *N-ribopyranoside*, was obtained. The synthesis, properties, and chemical potentialities of this form of N-pentoside form the basis of this paper, the first in a series of studies.

The condensation of aryl and alkyl amines with monosaccharides (also disaccharides) is well known and appears in the early literature. Schiff (2) first reported the condensation of aniline and toluidine with anhydrous D-glucose in 1870. Sachsse (3) prepared mono- and di-anilides of lactose in 1871 and Sorokin (4) prepared various anilides of other monosaccharides in 1886. The structure of these condensation products was an open question. Schiff and Straus (5) favored a "Schiff base" amine-aldehyde condensation product type linkage. Sorokin and Marchlewski (6) proposed an N-glycoside formula in 1894. In a series of papers, the first of which was published in 1908, Irvine and co-workers (7) demonstrated that the condensation product of glucose and aniline was an N-glycoside and not a Schiff's base.

Arylamine-N-glycosides are prepared by mixing a sugar and an amine in a solvent (usually a lower alcohol) and heating the mixture for several hours. Upon concentration of the solvent, the N-glycoside usually crystallizes. Other solvents such as water, benzene, or various mixtures, are often used. Various catalysts are employed such as HCl, NH_4Cl, excess base, etc.

Most N-glycosides are rather unstable, some decomposing in a few hours. Several species when absolutely pure remain unchanged for several months if kept cold. They usually crystallize with one or more molecules of water, alcohol, or even amine of crystallization (8). As a general class, N-glycosides are labile and undergo rearrangement as well as hydrolysis. The rearrangement of N-glycosides to isoglucosamines (the Amadori rearrangement) was studied and reported by Kuhn and co-workers (9) and Weygand (10) in a series of papers from 1936 through 1940.

In connection with the synthesis of riboflavin, vitamin B_2, the preparation of ribitylxylidine, which involved the condensation of an aryl amine and a pentose and subsequent reduction, gave impetus to the study of the preparation and properties of N-glycosides. Kuhn and Birkofer (1) prepared 3,4-xylidine-D-

riboside by refluxing a mixture of D-ribose and 3,4-xylidine for $\frac{3}{4}$ hour. The product obtained had the following characteristics: M.p. 118°; $[\alpha]_D^{21}$ +172°; (c = 0.5% in pyridine, without mutarotation).

Preparation of the above compound according to the directions of Kuhn and Birkofer yielded a product with the following characteristics: M.p. 128–130°; $[\alpha]_D^{24}$ +171.7° → +56.5°; (c = 0.5% in pyridine). However, if the condensation of 3,4-xylidine and D-ribose was carried out at room temperature in alcohol or aqueous alcohol, catalyzed with a trace of acid, an isomeric product was obtained which had the following characteristics: M.p. 110–112°; $[\alpha]_D^{25}$ +94.5° → +53.0°; (c = 1.0% in pyridine).[1]

Similarly, two isomeric products were obtained when aniline and ribose were condensed according to the two procedures. The product obtained from the hot alcoholic condensation had the following characteristics: M.p. 138–140°; $[\alpha]_{3D}^{27}$ +176.5° → +156.6°; (c = 3% in pyridine).

The product obtained from the cold alcohol condensation had the following characteristics: M.p. 125–127°; $[\alpha]_{3D}^{24}$ +63.4° → +48.6°; (c = 1.0% in pyridine).

It was found that the product obtained from the cold alcoholic condensation (lower melting and less positive rotation) could be converted quantitatively to the other form by refluxing for an hour in alcohol. It was also found that the transformation would also take place slowly at room temperature in the presence of traces of acid or basic catalysts, or other impurities.

In a study of the chemical nature of various aromatic N-ribosides, Kuhn and Ströbele (11) concluded that the products they had obtained were N-ribofuranosides, for acylation yielded triacetyl products, and tritylation indicated that the terminal hydroxyl group was free.

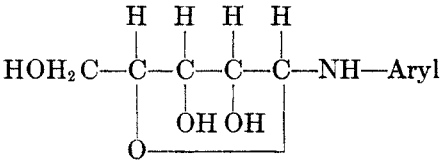
The isomeric products obtained by us could possibly be the β-furanoside, α- or β-pyranoside, a Schiff's base, or the Amadori rearrangement product. The direction of the mutarotation in pyridine (in the same direction and from positive to negative in both forms) and the different end-points reached on completion of the mutarotation (as shown by the isomeric aniline ribosides) eliminate the possibility of an α-, β-furanoside pair or a Schiff's base structure for these ribosides.

Both forms reduced hot Fehling's solution but did not give the dichlorophenol indophenol test for isoglucosamines (1). Hydrogenation of both forms under various conditions of pH and temperature gave the same ribitylamine indicating that Amadori rearrangement had not taken place. Thus α-xylidine-N-D-ribofuranoside, when hydrogenated in alcohol with Raney nickel, gave ribityl-xylidine, (1, 12); m.p. 144°; $[\alpha]_D^{25}$ −29.0°; (c = 5% in pyridine), $[\alpha]_D^{25}$ −37.5°; (c = 5% in 2 N HCl). α-Xylidine-N-D-ribopyranoside in anhydrous dioxane

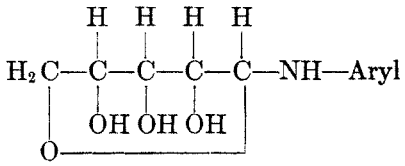
[1] The optical rotation of aromatic N-ribosides are more characteristic and reproducible than the melting point. As these compounds have a strong tendency to crystallize with solvent of crystallization, the melting point alone cannot be used as a criterion of purity, or to distinguish between pyranoside or furanoside forms. (Note difference in the melting point and similarity of the optical rotation of 3,4-xylidine-N-D-riboside obtained by Kuhn and Birkofer and our preparation of this compound.) The optical rotation, elementary analysis, moisture, and melting point all must be taken into account.

(which did not convert the pyranoside to the furanoside even at reflux temperature for several hours) on hydrogenation gave the identical ribitylxylidine. Similarly, both aniline ribosides gave the same ribitylaniline, m.p. 125–127°; $[\alpha]_D^{25}$ −42.3°; (c = 2.0% in pyridine).

The direction of the mutarotation in both forms indicated an α-pyranoside structure for the product obtained at room temperature and an α-furanoside structure for the product prepared in hot solution (on the assumption that the product prepared according to Kuhn is a furanoside).



Furanoside:
High m.p., more positive rotation, mutarotation (negative), α form



Pyranoside:
Low m.p., less positive rotation, mutarotation (negative), α form

That these designations were probably correct was confirmed by a study similar to that of Kuhn and Ströbele. The two aniline ribosides were acylated in pyridine to yield triacetyl products further indicating an N-glycoside structure. Both were tritylated in pyridine. The product obtained from the cold condensation (pyranoside) did not yield any identifiable tritylation product while the product obtained from the hot alcoholic condensation (furanoside), reacted under identical conditions, yielded a tritylated product as expected, and in agreement with the structure assigned by Kuhn.

Methylation of both aniline ribosides with methyl iodide and active silver oxide in acetone solution gave a mixture of partially methylated syrups. Subsequent remethylations of these syrups gave red oils, and analysis indicated that partial decomposition had taken place. Methylation of the aniline ribosides and the triacetyl aniline ribosides with methyl sulfate in alkaline solution was not possible, as warm alkali hydrolyzed the ribosides. Both isomers were instantly decomposed to tars with dilute periodate solution in an attempt to apply the method of Jackson and Hudson (13), and Lythgoe and Todd (14), for distinguishing between furanosides and pyranosides. The result was not entirely unexpected, as amino alcohols possessing a primary or secondary amino group react readily with the periodic acid reagent (15). Lythgoe and Todd record a similar experience with 4- or 6-glycosidaminopyrimidines.

Hydrolysis of both forms with water, water catalyzed with acids, or bases, or aldehydes such as formaldehyde and benzaldehyde, regenerated the original amine and ribose. This was further evidence that the products obtained were not Amadori rearrangement products.

The triacylated products prepared from the isomeric N-ribosides and their

hydrogenation products are assigned the tentative structures of 2,3,4- or 2,3,5-triacyl derivatives depending upon whether they were derived from the pyranoside or the furanoside form. It is assumed, however, that acyl migration did not take place in the course of acylation of the ribosides and their subsequent hydrogenation, although the similarity of the optical rotations of the two tribenzoylribitylanilines may indicate that ring opening and acyl migration had occurred in one of the ribosides.

α-Aniline-D-ribopyranoside and α-aniline-D-ribofuranoside were both more stable than the corresponding xylidine ribosides. Hanaoka (16) reported similar results in his studies on the rate of hydrolysis of various aniline and substituted aniline N-glycosides. Traces of impurities, high temperature, and moisture

TABLE I

PROPERTIES OF ARYLAMINE-N-GLYCOSIDES

RIBOSIDE	MELTING POINT, °C[a]	ROTATION
α-Aniline-N-D-ribopyranoside ($\frac{1}{2}$ H_2O)	125–127	$[\alpha]_D^{24}$ +63.4° → +48.6° c = 1.0% in pyridine (48 hrs.)
α-Aniline-N-D-ribofuranoside	138–140	$[\alpha]_D^{27}$ +176.5° → 156.6° c = 3.0% in pyridine (24 hrs.)
α-3,4-Xylidine-N-D-ribopyranoside	110–112	$[\alpha]_D^{25}$ +94.5° → +53.0° c = 1.0% in pyridine (48 hrs.)
α-3,4-Xylidine-N-D-ribofuranoside	128–130	$[\alpha]_D^{24}$ +171.7° → +56.5° c = 0.5% in pyridine (24 hrs.)
α-3,4-Xylidine-N-D-ribofuranoside (Kuhn, 1)	118	$[\alpha]_D^{21}$ +172° c = 0.5% in pyridine without mutarotation

[a] All melting points are uncorrected.

accelerated the decomposition of the ribosides. α-Aniline-D-ribopyranoside and -furanoside have been kept for over six months in a sealed container in the refrigerator at 5°.

EXPERIMENTAL

α-Aniline-N-D-ribopyranoside. A solution of 1.44 g. of crystalline D-ribose in 20 cc. of distilled water was prepared. The *p*H was adjusted to 4.0 with 3 *N* H_2SO_4.[2] One cubic centimeter of aniline in 10 cc. of absolute alcohol was added and the mixture stirred for 10 min. at 25°. The reaction mixture was then set in a refrigerator at 5° overnight (crystallized out in one hour). The crystalline precipitate was filtered off and washed with cold

[2] Acid catalysts accelerated the condensation but did not alter the direction nor affect the yield. The condensation at *p*H 6.0 to 8.0 (*p*H of base) gave excellent yields of the pyranoside but required several hours condensation at room temperature before being set in the refrigerator for crystallization.

alcohol and finally with ether. There was obtained 2.07 g. (96%) of colorless shining platelets, melting at 125–127°. The product contained 0.5 mole of water of crystallization; $[\alpha]_D^{24}$ +63.4° → +48.6°; (*c* = 1.0% in pyridine; 48 hrs.).

Anal. Calc'd for $C_{11}H_{15}NO_4 \cdot \frac{1}{2} H_2O$: C, 56.41; H, 6.84; N, 5.98.
Found: C, 56.71; H, 6.77; N, 5.78.

Under certain conditions the product may crystallize with different amounts of solvent of crystallization. This causes variations in the melting point and rotation, but when the latter is corrected on the basis of the above compound, it will correspond.

The purity of N-ribosides can be determined accurately by the ordinary Fehling titration method employed for sugars. The N-ribosides hydrolyze quantitatively under the conditions employed and the sugar liberated reduces Fehling solution in the normal manner.

For maximum accuracy in this titration, samples should contain or liberate 21.0 to 38.0 mg. of ribose for every 10 cc. of mixed Fehling solution used. The general procedure is as follows:

About 50 mg. of riboside is suspended in 10 cc. of mixed Fehling solution diluted with 15 cc. of distilled water in a 250-cc. Erlenmeyer flask. The flask is covered with a watch glass and set on a hot plate at 200–300° for exactly five minutes of *boiling*. The flask is cooled and 20 cc. of 10% KI (freshly prepared) and 20 cc. of 3 *N* H_2SO_4 are added. The liberated iodine is titrated with 0.1 *N* thiosulfate with soluble starch as an indicator in the usual manner. The titration of the Fehling solution is always run along with the test substance.

The ribose liberated is calculated as follows:

(a − b) 3.37 = mg. ribose[3]

a = cc. of 0.1 *N* thiosulfate used for Fehling solution alone.

b = cc. of 0.1 *N* thiosulfate used for test substance.

α-Aniline-N-D-ribopyranoside:

Ribose. Calc'd: 66.70%
Found: 66.80%
66.70%
66.70%

α-Aniline-N-D-ribofuranoside. (a) *By direct condensation.* A solution of 15.0 g. of D-ribose in 150 cc. of warm alcohol was prepared. Ten grams of aniline was added with stirring. The mixture was refluxed for two hours. On cooling, α-aniline-N-D-ribofuranoside crystallized out; the reaction was set in the refrigerator to complete the crystallization, and the white mass of crystals that formed was filtered off, washed with cold alcohol and ether, and air dried. There was obtained 19.0 g. (84.5%) of shining plates melting at 138–140°; $[\alpha]_D^{27}$ +176.5° → +156.6°; (*c* = 3% in pyridine; 24 hours).

Anal. Calc'd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.66; N, 6.22.
Found: C, 58.72; H, 6.66; N, 6.16.

Ribose. Calc'd: 66.70%
Found: 66.80%

(b) *By conversion of α-aniline-N-D-ribopyranoside.* Ten grams of α-aniline-N-D-ribopyranoside (m.p. 125–127°; $[\alpha]_D^{24}$ +63.4° → +48.6°) was dissolved in 80 cc. of boiling absolute alcohol and refluxed for one hour. The reaction flask was cooled, scratched with a glass rod, and set in the refrigerator for crystallization. After several hours the crystalline mass was filtered off, washed with alcohol and ether to yield 9.9 g. of α-aniline-N-D-ribofuranoside, m.p. 137–139°; $[\alpha]_D^{27}$ +177° → +156.5°; (*c* = 1.5% in pyridine; 24 hours).

The conversion of α-aniline-N-D-ribopyranoside to the furanoside is influenced by traces of impurities (both acidic and basic such as amine salts, amines, acids, etc.), water, or other hydroxylated solvents, heat, and sunlight. While attempting to remove the last traces of water of crystallization from α-aniline-N-D-ribopyranoside *via* high vacuum desiccation over P_2O_5, for 7 days, a 70% *conversion* to the furanoside occurred.

Original pyranoside: m.p. 125–127°; [α] +63° → 49°; (*c* = 1% in pyridine; analysis indicated ½ mole of H_2O).

[3] Factor determined with pure crystalline D-ribose.

Dried pyranoside (7 days): m.p. 120–123°; [α] +144°, initial; (*c* = 1% in pyridine).

Anal. Calc'd for $C_{11}H_{15}NO$ (anhydrous): C, 58.66; H, 6.66.

Found: C, 58.75; H, 6.67.

Refluxed in alcohol for twenty minutes; $[\alpha]_D^{28}$ +186° initial; (*c* = 1% in pyridine; complete conversion).

An attempt was made to recrystallize α-aniline-N-D-ribopyranoside from warm alcohol as rapidly as possible to avoid conversion to furanoside. One such crystallization lowered the melting point to 121–123° and the rotation to $[\alpha]_D^{25}$ +137.7° indicating over a 50% conversion to the furanoside.

α-3,4-Xylidine-N-D-ribopyranoside. A solution of 1.44 g. of crystalline D-ribose in 20 cc. of distilled water was prepared and the *p*H was adjusted to 4.0 with 3 *N* H_2SO_4. To this solution 1.3 g. of 3,4-xylidine dissolved in 10 cc. of ethyl alcohol was added, with stirring at 25° for ten minutes. The reaction mixture was then placed in the refrigerator overnight for crystallization. The crystalline product obtained was filtered off, washed with a small amount of cold alcohol and dry ether, to yield 1.2 g. (49%) of a colorless crystalline product; m.p. 110–112°; $[\alpha]_D^{25}$ +94.5° → +53.0°; (*c* = 1.0% in pyridine).

Anal. Calc'd for $C_{13}H_{19}NO_4$: N, 5.53.

Found: N, 5.44.

α-3,4-Xylidine-N-D-ribofuranoside (1). (a) *By direct condensation.* D-Ribose (8.8 g.) was dissolved in 100 cc. of absolute methanol containing 7.1 g. of 3,4-dimethylaniline and the solution was refluxed for forty minutes. The solution was cooled, seeded, and placed in the refrigerator for complete crystallization. The white crystalline product was filtered off, washed with cold methanol and ether, and air dried. There was 8.8 g. (60%) of α-3,4-xylidine-N-riboside melting at 127–129°; $[\alpha]_D^{25}$ +172° → 56.0°; (*c* = 0.5% in pyridine; 72 hours).

(b) *By conversion of α-3,4-dimethylaniline-N-D-ribopyranoside.* α-3,4-Xylidine-N-D-ribopyranoside (0.5 g.), m.p. 110–112°; $[\alpha]_D^{25}$ +94.9°, was refluxed with 5 cc. of absolute alcohol for one hour. The flask was cooled, scratched, seeded, and set aside for crystallization in the refrigerator. Forty-five hundredths gram of shiny papery crystals was filtered off, washed with cold alcohol and ether; m.p. 128–130°; $[\alpha]_D^{25}$ +171.7° → +56.5°; (*c* = 0.5% in pyridine; 48 hours).

2,3,4-Triacetyl-α-aniline-N-D-ribopyranoside. Twelve grams of α-aniline-N-D-ribopyranoside was dissolved in 100 cc. of dry pyridine, cooled to 0°, and 36.0 cc. of acetic anhydride was slowly added with stirring. Upon completion of the addition, the solution was kept at room temperature for one day. Heating for one hour at 40–50° completed the reaction.

The reaction mixture was poured into 500 cc. of cold water with stirring, and the syrupy mass that separated was extracted with ether. The ether solution was washed neutral, dried over anhydrous Na_2SO_4 overnight. The solvent was then removed to yield 14.0 g. (75%) of a hard yellow-orange glass which could not be crystallized. The product was readily soluble in all organic solvents, but insoluble in water and petroleum ether.

Anal. Calc'd for $C_{17}H_{21}NO_7$: C, 58.15; H, 5.98; N, 3.99; Acetyl, 36.75.

Found: C, 58.48; H, 6.18; N, 4.00; Acetyl, 33.2, 33.5.[4]

2,3,5-Triacetyl-α-aniline-N-D-ribofuranoside. Six grams of α-aniline-N-D-ribofuranoside was dissolved in 50 cc. of dry pyridine, cooled to 0°, and 18 cc. of acetic anhydride was added slowly with stirring. Upon completion of the addition, the solution was kept at room temperature for a day. One hour's heating at 40–50° completed the reaction.

The reaction mixture was poured into 250 cc. of cold water with stirring and the syrupy mass that separated was extracted with ether. The ether solution was washed neutral, dried overnight over anhydrous Na_2SO_4. The solvent was then removed to yield 8.3 g. (89%) of a hard yellow glass which began to soften and flow at 60°. The product could not

[4] Micro acetyl determination of the compounds in this series gave consistently low but reproducible values.

be crystallized. The product was readily soluble in all organic solvents, but insoluble in water and petroleum ether.

Anal. Calc'd for $C_{17}H_{21}NO_7$: C, 58.15; H, 5.98; N, 3.99; Acetyl, 36.75.
Found: C, 57.92; H, 6.31; N, 4.04; Acetyl, 33.7.[4]

2,3,4-Tribenzoyl-D-ribitylaniline. Fourteen grams of α-aniline-N-D-ribopyranoside was dissolved in 150 cc. of dry pyridine, cooled to 0°, and 28.7 g. of benzoyl chloride (3 moles excess) was slowly added with stirring. The acylation proceeded slowly. In about 35–40 minutes pyridine hydrochloride started to precipitate out. Upon completion of the addition, the reaction was kept at room temperature for a day and worked up in the usual manner.

A yellowish sticky glass, weighing 33 g. (quantitative yield) which could not be crystallized was obtained. The product was soluble in all organic solvents and separated as a thick oil from concentrated alcohol solution.

Fifteen grams of the above glass was dissolved in 120 cc. of ethyl alcohol, 1.5 g. of Raney nickel was added, and the reaction mixture was hydrogenated at 500 lbs. at 60° for two hours. The alcohol solution was filtered from the catalyst and evaporated to dryness. Fifteen grams of a glassy product was obtained which could not be crystallized. The product did not form a hydrochloride in ether solution with hydrogen chloride gas.

Anal. Calc'd for $C_{32}H_{29}NO_7$: C, 71.25; H, 5.38; N, 2.60.
Found: C, 71.41; H, 5.43; N, 2.46.

$[\alpha]_D^{28}$ −20.3° → ±1; (c = 1.67% in pyridine).

2,3,5-Tribenzoyl-D-ribitylaniline. Fourteen grams of α-aniline-N-D-ribofuranoside was acylated in 150 cc. of dry pyridine with 28.7 g. of benzoyl chloride at 0° as previously. In about 15–20 minutes pyridine salts started to precipitate out.[5] The reaction was worked up as previously to yield 34.0 g. of a yellow amorphous brittle solid which could not be crystallized. The product did not melt but liquefied at about 50°.

Fifteen grams of the glassy solid was dissolved in 120 cc. of ethyl alcohol, 1.5 g. of Raney nickel added, and the mixture hydrogenated at 500 lbs. at 60° for two hours. The alcohol solution was filtered from the catalyst and evaporated to dryness *in vacuo* to yield a light fluffy amorphous glass in quantitative yield. The product could not be crystallized.

Anal. Calc'd for $C_{32}H_{29}NO_7$: C, 71.25; H, 5.38; N, 2.60.
Found: C, 71.38; H, 5.40; N, 2.50.

$[\alpha]_D^{28}$ −22.1°; (c = 8.0% in pyridine).

D-*Ribitylaniline.* (a) *From α-aniline-N-D-ribopyranoside.* Four grams of α-aniline-N-D-ribopyranoside was suspended in 25 cc. of anhydrous dioxane and 0.3 g. of Raney nickel added. The mixture was hydrogenated at 65–75° at 500 lbs. for two hours. The catalyst was filtered off and the solution was concentrated *in vacuo* to ½ volume. The solution was scratched with a glass rod and set in the refrigerator for crystallization. Three and five-tenths grams (88%) of a colorless crystalline product was obtained which melted at 125–127°; $[\alpha]_D^{25}$ −42.3°; (c = 2.7% in pyridine).

Anal. Calc'd for $C_{11}H_{17}NO_4$: C, 58.19; H, 7.49; N, 6.17.
Found: C, 58.49; H, 7.26; N, 6.24.

(b) *From α-aniline-N-D-ribofuranoside.* Four grams of α-aniline-N-D-ribofuranoside was suspended in 25 cc. of absolute alcohol and hydrogenated at 60° at 500 lbs. for three hours in the presence of 0.3 g. of Raney nickel. The reaction was worked up as above to yield 3.60 g. (90%) of ribitylaniline, melting at 125–127°; $[\alpha]_D^{25}$ −42.7°; (c = 2.5% in pyridine).

N-D-Ribityl-3,4-dimethylaniline (*ribitylxylidine*). (a) *From α-3,4-xylidine-N-D-ribopyranoside.* Eight-tenths of a gram of α-xylidine-N-D-ribopyranoside was dissolved in 25 cc. of anhydrous dioxane and 0.1 g. of Raney nickel was added. The mixture was hydrogenated at 60° for three hours at 50 lbs. The catalyst was filtered from the solution, the solution concentrated and set aside for crystallization. There was obtained 0.72 g.

[5] The furanoside acylated more rapidly than the corresponding pyranoside as expected in view of the primary hydroxyl group present in the furanoside.

of ribitylxylidine, m.p. 143–144° (mixed with an authentic sample, gave no depression). $[\alpha]_D^{25}$ −29.0°; (c = 5% in pyridine); $[\alpha]_D^{25}$ −37.5° (c = 5% in 2 N HCl).

(b) *From α-3,4-xylidine-N-D-ribofuranoside (1).* Twenty-five and three-tenths grams of α-xylidine-N-D-ribofuranoside was suspended in 125 cc. of absolute alcohol and 2.5 g. of Raney nickel was added. The mixture was hydrogenated at 500 lbs. at 60° for one hour. The catalyst was filtered from the hot solution and the filtrate was set aside for crystallization; yield, 23.0 g. (90%) of colorless shiny platelets melting sharply at 144°; $[\alpha]_D^{25}$ −37.5°; (c = 5% in 2 N HCl).

Tritylation experiments with α-aniline-N-D-ribopyranoside and α-aniline-N-D-furanoside. α-Aniline-N-D-ribopyranoside and α-aniline-N-D-ribofuranoside (dried in high vacuum over P_2O_5 at 25° for 24 hours) were tritylated with trityl chloride (dried over anhydrous $CaCl_2$ for 24 hours) in dry pyridine solution at room temperature for five hours and at 5° for two days.

Five grams of the riboside was mixed with 6.2 g. of trityl chloride in 25 cc. of dry pyridine in a small ground-glass-stoppered bottle. The resultant brown solutions were poured into water in a fine stream.

The furanoside reaction mixture yielded a light brown amorphous product. This reaction product was dissolved in ether, extracted with dilute acid and finally washed neutral with water. The dried ether solution on evaporation yielded a small amount of crystalline matter (0.7 g.) of an undetermined by-product. Trituration of the residual syrup with alcohol removed the remainder of the crystalline matter. The alcoholic solution was treated with Norit and concentrated to dryness *in vacuo*. The resultant glass was dissolved in dry ether and precipitated with Skellysolve "B" to yield a light brown amorphous solid. The product was redissolved in ether and again precipitated with Skellysolve "B" to yield a tan amorphous powder which could not be obtained in crystalline form. The product on analysis corresponded to a monotrityl-α-aniline-D-riboside with water of crystallization.

Anal. Calc'd for $C_{30}H_{29}NO_4$ + 1.75 H_2O: C, 72.20; H, 6.25; N, 2.82.
Found: C, 72.06; H, 6.29; N, 2.96.

The pyranoside reaction mixture yielded a reddish oil which was dissolved in ether and worked up as previously. Concentration of the dried ether solution gave a tarry product which could not be purified nor could any product be isolated.

The above experiments were repeated with identical results. The furanoside yielded a tan amorphous product as previously which again gave analysis for the monotrityl product with water of crystallization.

Anal. Calc'd for $C_{30}H_{29}NO_4$ + 1.75 H_2O: C, 72.20, H, 6.52.
Found: C, 72.00; H, 6.27.

The pyranoside reaction mass yielded intractable tars.

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SUMMARY

1. Condensation of aryl amines with D-ribose in alcohol or aqueous alcohol (catalyzed with traces of acid) at low temperatures yields α-arylamine-N-D-ribopyranosides. If the reactants are condensed at the reflux temperature of the solvent, α-arylamine-N-D-ribofuranosides are formed.

2. α-Arylamine-N-D-ribopyranosides are converted quantitatively to the corresponding furanosides in boiling alcohol solution.

3. Hydrogenation of both the arylamine ribopyranoside and the corresponding arylamine ribofuranoside yields the identical ribitylamine.

4. Acylation of the furanoside and pyranoside forms yields triacyl derivatives. Hydrogenation of these triacyl arylamine ribosides yields triacyl ribityl amines.

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ARYLAMINE-N-GLYCOSIDES. PART II. ARYLAMINE-N-PENTOSIDES AND COMPLEX SALT FORMATION STUDIES

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3,4-Xylidine-N-D-ribofuranoside is an intermediate in the manufacture of riboflavin (vitamin B_2)(1). During the course of the technical development of its preparation, U. V. Solmssen of these laboratories observed that the addition of 3,4-xylidine in alcohol to a technical solution of D-ribose containing sodium sulfate resulted in the formation of an insoluble "complex salt". This salt could be hydrogenated directly to yield ribitylxylidine (2). The present authors undertook the investigation of the reaction in the absence of sodium sulfate and found that a new class of N-ribosides, which in all probability are α-arylamine-N-D-ribopyranosides, are formed when the sugar and the arylamine are condensed in alcohol or aqueous alcohol at low temperatures. The pyranosides are converted quantitatively to the corresponding furanosides merely by heating in alcoholic or aqueous alcoholic solution or can be prepared by direct condensation in hot alcoholic solution (3).

Kuhn and co-workers (1, 4) obtained good yields of arylamine-N-glycofuranosides by mixing the amine and the sugar in alcohol and boiling. Acid catalysts such as HCl or ammonium chloride were found desirable in most condensations and absolutely necessary in some. Aniline, toluidine, phenetidine, etc. condensed readily with pentoses and hexoses in hot alcoholic solution in good yield; however, *o*-nitroaniline did not react with pentoses and hexoses under these conditions. Two to five per cent of ammonium chloride catalyzed this reaction so that yields over 80% were obtained.

The yield of this condensation was influenced greatly by the presence of small amounts of water in the alcohol. Thus, when D-ribose was condensed with 2-nitro-4,5-dimethylaniline in 98% alcohol, a 30% yield of condensation product was obtained. If absolute alcohol was used the yield was increased to 60% or more.

As reported in the first paper in this series (3), aniline condensed with D-ribose in alcohol or aqueous alcohol solution at room temperature to form α-aniline-N-D-ribopyranoside in excellent yield (90–96%). The reaction was accelerated with a trace of acid (*p*H 4.0) without any change in actual yield. *o*-Nitroaniline was condensed with D-ribose under these conditions to yield *o*-nitroaniline-N-D-ribopyranoside in excellent yield (94.4%). Various other arylamines as orthochloroaniline, *p*-carboxyaniline, *p*-methylaniline, *p*-methoxyaniline, *m*-hydroxy-*p*-methoxyaniline, α-naphthylamine, and β-naphthylamine reacted with ribose under the same conditions to give the corresponding N-ribopyranoside in good yield. Arabinose condensed with aniline under these conditions to give α-aniline-N-D-arabinopyranoside in 50% yield. The product obtained occurred as colorless large prisms melting at 130°; $[\alpha]_D^{28}$ +8.9° → −13.2°; (c = 1.9% in methanol; 48 hrs.; $[\alpha]_D^{20}$ +68° → −4.3°; (c = 3% in pyridine; 48 hrs.).

This material differed from the aniline arabinoside prepared by Hanaoka (5) whose compound had the following characteristics: m.p. 130°; colorless plates; $[\alpha]_D^{20}$ +34.0° → +2.5°; (c = 1.0% in methanol).

A preparation of aniline arabinoside, according to the method described by Hanaoka, had the following characteristics: m.p. 130°; colorless plates; $[\alpha]_D^{29}$ +27.4° → −8.0°; (c = 1.6% in methanol; 24 hrs.); $[\alpha]_D^{29}$ +82° → +1.48°; (c = 2.0% in pyridine; 24 hrs.).

Following the observation of Solmssen, we have found that arylamine-N-D-ribopyranosides are characterized generally by the ability to form "complex salts" with the soluble salts of alkali metals (preferably at pH 4), which separate from aqueous alcohol,[1] and which contain the organic matter in a loose combination with the salt used. Sodium sulfate, lithium sulfate, sodium acid phosphate, sodium nitrate, potassium sulfate, sodium acetate, sodium citrate, etc. were among the salts that were used to form the "complex salt". The pyranoside was extracted quantitatively from the "complex salt" by extraction with dioxane (acetone or pyridine), filtering and adding carbon tetrachloride to precipitate the N-ribopyranoside with varying amounts of solvent of crystallization. The pyranoside was also isolated from the "complex salt" by trituration and digestion with cold water, but this was a tedious process accompanied with losses. Extractions of the "complex salt" with hot alcohol (which converted the pyranoside to the furanoside) gave the N-ribofuranoside in excellent yield.

Crystalline D-ribose was isolated in pure form from aqueous solutions containing crude D-ribose and salts in varying concentration (up to saturation) by utilization of this unique "complex salt" formation. Aniline was dissolved in sufficient alcohol to make a 30% aqueous alcohol solution when mixed with the aqueous crude sugar solution containing salts, and added to the solution (whose pH was brought to 4.0 with dilute H_2SO_4) with stirring. The reaction was kept at 25° for one hour and set in the refrigerator at +5° overnight. The "complex salt" obtained contained the ribose in the form of α-aniline-N-D-ribopyranoside loosely joined with varying amounts of salt. The yield of pyranoside (based on Fehling titration and/or extraction) ranged from 85% to 95%. The pyranoside, either in pure crystalline form or in the form of the "complex salt", was then hydrolyzed to regenerate D-ribose and aniline. A more detailed discussion of this reaction will be reported in another paper in this series.

The pyranoside in the "complex salt" form can be hydrogenated directly, and the reduction products then separated from the accompanying salts. Thus a solution of D-ribose, prepared by the electrolytic reduction of D-ribonolactone

[1] When acetone or dioxane was substituted for alcohol in the preparation of the "complex salt," there was a considerable drop in yield. However, aqueous alcoholic solutions containing as little as 5% alcohol were used successfully with little change in the resultant yield. It was found that enough alcohol to keep the amine in solution and still not precipitate much of the salts present was the most satisfactory mixed solvent and gave the maximum yields. An aqueous alcohol solution containing 30% water by volume was generally used.

in an electrolytic solution of sodium sulfate, was condensed with an alcoholic solution of aniline (also 3,4-xylidine) in the usual manner. The "complex salt" precipitate obtained was separated and hydrogenated in alcohol with Raney nickel to give N-ribitylaniline (or N-ribityl-3,4-xylidine) in excellent yields.

D-Glucose, D-arabinose, D-galactose, L-sorbose, D-xylose, and fructose did not form "complex salts" which separate when condensed with aniline in aqueous alcohol in the presence of sodium sulfate, whereas D-mannose and D-lyxose did form "complex salts" under these conditions. Indications are that sugars with hydroxyls in the 2- and 3-position in cis-configuration favor the formation of N-glycopyranoside "complex salts".

The ability to form these "complex salts" was used to separate a prepared mixture of ribose and arabinose in fair yield. Equal parts of ribose and arabinose were condensed with one mole of aniline in the presence of sodium sulfate in the usual manner. The complex obtained yielded α-aniline-N-D-ribopyranoside in 67% yield on extraction.

The utilization of this unique property of N-ribopyranosides (also N-manno- and N-lyxo-pyranosides) would perhaps facilitate the separation of these sugars from crude reaction liquors containing salts or other impurities.

EXPERIMENTAL

Preparation of substituted aniline-N-D-ribopyranosides. General procedure. Two grams of crystalline D-ribose was dissolved in 25 cc. of 95% ethyl alcohol. One drop of 3 *N* sulfuric acid was added. Two grams (slight excess) of the required amine (substituted aniline) was added with stirring. The reaction was kept at room temperature for two hours and then set in the refrigerator at 5° overnight. The product that crystallized out was filtered off, washed with cold alcohol, and finally with dry ether. The product was dried at room temperature and submitted for analysis as such. The yields were excellent; in some instances quantitative.

Table I lists the physical constants and the analysis of the compounds prepared.

α-Aniline-N-D-arabinopyranoside. Five grams of D-arabinose was dissolved in 35 cc. of water and 4 cc. of aniline dissolved in 15 cc. of alcohol was added with stirring. The mixture was set aside at 5° for two days after standing at room temperature for ten minutes. The reaction mixture was then concentrated to dryness *in vacuo* at 35°. The residual syrup was crystallized from alcohol and ether to yield 3.5 g. of large colorless prisms melting at 130°. The mother liquor gave another crop (1.0 g.) on concentration (total yield: 54%); $[\alpha]_D^{28}$ +8.9° → −13.2°; (c = 1.9% in methanol; 48 hrs.); $[\alpha]_D^{29}$ +68.0° → −4.3°; (c = 3.0% in pyridine; 24 hrs.).

α-Aniline-N-D-arabinofuranoside. Prepared according to the directions of Hanaoka (5) an aniline arabinoside was obtained which occurred as colorless plates (from alcohol) melting at 130°; $[\alpha]_D^{29}$ +27.4° → −8.0°; (c = 1.6% in methanol; 24 hrs.); $[\alpha]_D^{20}$ +82° → +1.48°; (c = 2.0% in pyridine; 24 hrs.).

Hanaoka (5) reported the melting point 130° (colorless plates); $[\alpha]_D^{20}$ +34.0° → +2.5°; (c = 1.0% in methanol).

A mixed melting point of the two aniline arabinosides gave no appreciable depression (129–130°). Aniline-N-D-ribopyranosides and -furanosides as a rule do not give depressions in mixed melting points.

α-Aniline-N-D-ribopyranoside-Na_2SO_4 complex. Crude D-ribose (1.39 g.) was dissolved in 25 cc. of 9% sodium sulfate solution and 7 cc. of alcohol was added. The *p*H was adjusted to 4.0 with 3 *N* sulfuric acid, and 1 cc. of aniline dissolved in 5.5 cc. of alcohol was added

TABLE I

PHYSICAL CONSTANTS OF NEW N-RIBOPYRANOSIDES

COMPOUND	CRYSTAL FORM	YIELD, %	M. P. (UNCORR.), °C.	ROTATION	NITROGEN ANAL.	
					Calc'd	Found
1. α-*o*-Chloroaniline-N-D-ribopyranoside	Large colorless cubes	91	152–153	$[\alpha]_D^{28}$ +136° → 125° c = 1.7% in pyridine, 72 hrs.	5.39	5.46
2. *o*-Nitroaniline-N-D-ribopyranoside	Yellow needles	94.5	183–185 decomp.	$[\alpha]_D^{28}$ −109° c = 1.0% in pyridine	10.36	10.39
3. α-*p*-Carboxyaniline-N-D-ribopyranoside	White powder	99	129–130 decomp.	$[\alpha]_D^{28}$ +231° → +70.2° c = 3.3% in pyridine, 72 hrs.	5.20	5.23
4. *p*-Methylaniline-N-D-ribopyranoside+2 C_2H_5OH	White powder	77	102–103 decomp.	$[\alpha]_D^{27.5}$ +53.2° c = 2.0% in pyridine	4.23	4.32
5. α-*p*-Methoxyaniline-N-D-ribonoside	Colorless cubes	99	109–110 decomp.	$[\alpha]_D^{27.5}$ +122° → +40.8° c = 1.8% in pyridine, 48 hrs.	5.49	5.64
6. α-*m*-Hydroxy-*p*-methylaniline-N-D-ribopyranoside+2 C_2H_5OH	Light yellow plates	88	133–135 decomp.	$[\alpha]_D^{27}$ +116° → +32.4° c = 1.0% in pyridine, 24 hrs.	4.65	4.76
7. α-(1-Naphthylamino)-N-D-ribopyranoside	Colorless plates	82	146–147 decomp.	$[\alpha]_D^{29}$ +122.0° → +29.2° c = 2.5% in pyridine, 48 hrs.	5.09	5.31
8. (2-Naphthylamino)-N-D-ribopyranoside+2 C_2H_5OH	White plates (papery)	30	119–120	$[\alpha]_D^{29}$ +96.6° c = 2.0% in pyridine	3.81	3.57

with stirring. The mixture was stirred at 25° for one hour, and set in the refrigerator at 5° overnight. The "complex salt" mass was filtered off, triturated with ten volumes of absolute alcohol, and filtered again. After drying *in vacuo* at 25°, the white precipitate (aniline ribopyranoside "complex salt") weighed 3.9 g. Analysis indicated that it contained 1.81 g. of riboside equivalent to an 87.5% yield.[2]

Other salts were used to form a similar "complex salt" in varying yields employing the above conditions, *e.g.*: lithium sulfate (20% yield), sodium hydrogen phosphate (43%), sodium nitrate (85%), potassium sulfate (36%), sodium acetate (68%).

D-Mannose and D-lyxose formed similar "complex salts" with aniline and sodium sulfate under the above conditions. D-Glucose, D-arabinose, D-galactose, D-xylose, as well as fructose, and L-sorbose did not react at all.

Isolation of α-aniline-N-D-ribopyranoside from "complex salt." α-Aniline-N-D-ribopyranoside-sodium sulfate "complex salt" (containing 1.81 g. riboside) was extracted with 20 volumes of dry acetone on the shaking machine for two hours. The salts were filtered off through a Hyflo matte and the solution was concentrated to dryness *in vacuo* to yield 1.78 g. of pure α-aniline-N-D-ribopyranoside, m.p. 124–126°; $[\alpha]_D^{25}$ +61.6°; (*c* = 4% in pyridine, initial rotation).

The pyranoside was also extracted quantitatively from the "complex salt" with anhydrous dioxane and recovered by precipitation with carbon tetrachloride to yield a riboside with varying amounts of dioxane of crystallization. Pyridine was also used to remove the organic matter from the "complex salt" but isolation of the pure pyranoside from the pyridine was difficult. The product was obtained in pure form from pyridine only if the solvent was removed in high vacuum at 0° to 5°. Higher temperatures caused excessive decomposition. The product obtained through pyridine decomposed more rapidly than the pyranoside isolated *via* acetone or dioxane.

α-Aniline-N-D-ribofuranoside from "complex salt." α-Aniline-N-D-ribopyranoside "complex salt" (50 g., containing the equivalent of 24.75 g. of pyranoside as determined by titration) was extracted with 400 cc. of boiling alcohol for thirty minutes. The hot solution was filtered through a Hyflo matte. The alcohol solution on cooling deposited 18.0 g. of α-aniline-N-D-*ribofuranoside*, m.p. 138–140°; $[\alpha]_D^{27}$ +176° → 156°. The alcoholic mother liquor was concentrated *in vacuo* to yield 6.3 g. of additional material melting at 137–139°. The total yield was 24.3 g., equivalent to 98%.

α-3,4-Xylidine-N-D-ribopyranoside "complex salt." α-3,4-Xylidine-N-D-ribopyranoside-sodium sulfate "complex salt" was prepared from an electrolyte solution containing D-ribose and sodium sulfate and 3,4-xylidine in alcohol, following the procedure for the corresponding aniline "complex salt." Excellent yields (85–95%) were obtained. The "complex salt" obtained was dried *in vacuo* at 25° and analyzed as follows:

Anal. Calc'd for 5 $C_{15}H_{19}NO_4 \cdot 3\ Na_2SO_4 \cdot 4\ H_2O$: C, 44.25; H, 5.84; N, 3.97; Na, 7.83.
Found: C, 44.08; H, 6.00; N, 4.07; Na, 7.96.

Subsequent runs contained varying amounts of salt and water depending upon the amount of salt present initially, the concentration of alcohol used, the temperature of precipitation, and the amount of drying.

Extraction of the "complex salt" with acetone (or dioxane) gave pure α-3,4-xylidine ribopyranoside, m.p. 110–112°; $[\alpha]_D^{25}$ +94.5° → +53.0°; (*c* = 1.0% in pyridine), in good yield. When extracted with hot alcohol, the corresponding furanoside, m.p. 128–129°; $[\alpha]_D^{25}$ +172°; (*c* = 6% in pyridine), was obtained.

Hydrogenation of α-aniline-N-D-ribopyranoside-sodium sulfate "complex salt." Twenty grams of α-aniline-N-D-ribopyranoside-sodium sulfate "complex salt" (70.05% riboside by weight) was suspended in 120 cc. of dry alcohol and 3 g. of Raney nickel added. The mixture was hydrogenated at 65° at 50 lbs. for eight hours. The catalyst and salts were filtered off and the solution was concentrated to dryness. The residue was extracted with boiling

[2] The amount of riboside in the "complex salt" was determined quantitatively by titration with Fehling solution (reference to preceding paper for method employed). Extraction of the riboside from the "complex salt" gave yields in agreement with titrated value.

alcohol and set aside for crystallization. On cooling, 13.0 g. (92%) of D-ribitylaniline, m.p. 125–127°; $[\alpha]_D^{25}$ −42.0°; (c = 2.7% in pyridine), was obtained.

Separation of D-*ribose from* D-*arabinose by means of aniline "complex salt" formation.* One gram of D-ribose and one gram of D-arabinose were dissolved in 14 cc. of 9% sodium sulfate solution. The *p*H was adjusted to 4.0 and 1 cc. of aniline in 3.5 cc. of alcohol was added. The mixture was stirred at room temperature for two hours and set in the refrigerator overnight. The complex formed was filtered off, washed with alcohol, and dried. Titration indicated that 1.0 g. of pentoside was present in the "complex salt" (67%). Extraction of the "complex salt" with acetone, concentration of the acetone solution to dryness, and trituration with alcohol yielded α-aniline-N-D-ribopyranoside +1/2 H_2O; m.p. 117–119°; $[\alpha]_D^{25}$ +55.7° → +47.3°; (c = 1.1% in pyridine).

Anal. Calc'd for $C_{11}H_{15}NO_4$: C. 56.40; H, 6.84.
Found: C, 56.14; H, 6.79.

Pure α-aniline-N-D-ribopyranoside +1/2 H_2O, melts at 125–127°; $[\alpha]_D^{25}$ +63.4° → +48.6°; (c = 1.0% in pyridine; 48 hrs.).

Pure α-aniline-N-D-arabinopyranoside melts at 130°; $[\alpha]_D^{29}$ +68.0° → −4.25°; (c = 3% in pyridine; 24 hrs.).

The melting point and the optical rotation indicated that the product that was isolated contained more of the *beta* form than usually present. A mixture with an authentic sample of α-aniline-N-D-ribopyranoside (m.p. 125–127°) melted at 120–122°. A mixed melting point with an authentic sample of α-aniline-N-D-arabinopyranoside (m.p. 130°) gave a depression (110–112°).

ACKNOWLEDGMENT

We wish to acknowledge our indebtedness to Dr. U. V. Solmssen for the preliminary investigations he performed and passed on to us, and for his continued interest in the study of the nature of the "complex salt". We also wish to thank Mr. Edward Wenis for technical assistance in the early phase of the investigation. The micro analyses were performed in the Microanalytical Division of these laboratories under the direction of Dr. Al Steyermark.

SUMMARY

1. Several substituted aniline bases (and naphthylamine) were condensed with D-ribose in aqueous alcohol solution at low temperatures to give the corresponding arylamine-N-D-ribopyranosides in excellent yield.

2. Aniline was condensed under these conditions with D-arabinose to yield α-aniline-N-D-arabinopyranoside.

3. Arylamine-N-D-ribopyranosides are characterized by the ability to form "complex salts" with the soluble salts of the alkali metals, which contain the pyranoside in a loose combination with the inorganic salt.

4. The N-D-ribopyranoside was obtained in almost quantitative yield by extraction of the "complex salt" with suitable solvents. Extraction of the "complex salts" with hot alcohol yielded the N-D-ribofuranoside in excellent yield.

5. The ribopyranoside "complex salt" was hydrogenated directly to the corresponding ribitylamine in excellent yield.

6. Sugars containing hydroxyls in the 2- and 3-position in cis-configuration as D-mannose and D-lyxose formed N-glycopyranoside "complex salts" while other sugars not possessing hydroxyls in that configuration did not form these "complex salts".

7. This unique property was used to separate a prepared mixture of D-ribose and D-arabinose.

NUTLEY, N. J.

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[CONTRIBUTION NO. 48 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LAROCHE, INC.]

ARYLAMINE-N-GLYCOSIDES. PART III. HYDROLYSIS OF ARYLAMINE-N-PENTOSIDES AND THE PREPARATION OF CRYSTALLINE D-RIBOSE

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The hydrolytic decomposition of arylamine-N-glycosides as a method for the preparation of rare sugars and their derivatives has not been reported, although the ease of hydrolysis and decomposition of aromatic N-glycosides is well known. Irvine and Moodie (1) determined the N-glycoside nature of glucose anilide by hydrolyzing a methylated glucose anilide with mineral acid and identifying the methylated glucose obtained. Irvine and McNicoll (2) reported that mannose anilide could be hydrolyzed with technical wet ether and in a later paper Irvine and Hynd (3) reported that glucose alanide could not be recrystallized, as it decomposed immediately on heating. Weygand (4) reported that *p*-toluidine-D-glucoside decomposed to a tarry mass when exposed to the vapors of a drop of glacial acetic acid in a vacuum desiccator.

As a result of a study of the rate of hydrolysis of various substituted aniline-N-glycosides, Hanaoka (5) reported that the introduction of the hydroxyl, methoxyl, ethoxyl, or methyl group on the ring decreased the stability of the N-glycoside linkage to acids, while chlorine, and especially the carboxyl group increased the stability. This has been confirmed with a study of the stability of the aniline ribosides and 3,4-dimethylaniline ribosides, whether in the pyranoside or furanoside form. The latter are comparatively unstable while the aniline-N-ribosides were stable for several weeks at room temperature and have been kept without noticeable decomposition in a sealed container at 5° for over six months. Traces of impurities, moisture, as well as high temperature accelerated the decomposition.

By a selection of mild conditions it was found that the hydrolysis of arylamine-N-D-ribopyranosides and arylamine-N-D-ribofuranosides could be effected practically quantitatively and the sugar easily obtained in a crystalline condition. The hydrolysis was effected by refluxing in water or aqueous alcohol solution or suspension, catalyzed by small amounts of dilute acetic acid. It was found convenient to remove the aniline formed by steam distillation, or by binding up with aldehydes such as formaldehyde and benzaldehyde in Schiff bases. The resultant aqueous sugar solution was concentrated to a clear syrup *in vacuo* and crystallized from absolute ethyl alcohol. The presence of a non-oxidizing atmosphere (as nitrogen) was advantageous but not necessary. The Schiff base formed when aldehydes were used, was extracted with benzene or ether, and subsequently hydrolyzed to regenerate aniline and the aldehyde. Recovery of these materials reduced the cost of operation in the preparation of large batches of ribose in this manner. The pyranoside was hydrolyzed also in the form of the

"complex salt" obtained from the condensation of the aromatic amine and D-ribose in the presence of alkali metal salts (6). The sugar obtained crystallized readily from ethyl alcohol in yields of 70–90% of pure crystalline D-ribose, m.p. 86–87°; $[\alpha]_D^{27}$ −19.6°; (c = 4.0% in H_2O.)

D-Ribose has been prepared by hydrolysis of nucleic acid, nucleotides, nucleosides, and their degradation products as guanosine or adenosine. Chemically, it has been synthesized from D-arabinose according to the method of Fisher and Piloty (7) and Alberda v. Ekenstein and Blanksma (8) by reduction of D-ribonolactone (prepared by epimerization of D-arabonic acid in aqueous pyridine) with sodium amalgam; or according to the method of Gehrke and Aichner (9), modified by Austin and Humoller (10), and Steiger (11), by oxidation of D-arabinal with perbenzoic acid to give a mixture of D-arabinose and D-ribose.

The syrupy ribose obtained by these methods could not be crystallized directly even in the presence of mere traces of impurities. The sugar was obtained in a crystalline state through decomposition of its *p*-bromophenylhydrazone, or diphenylhydrazone derivatives with formaldehyde or benzaldehyde. The yields of crystalline ribose obtained were low and the product obtained was usually of a low grade of purity and required several recrystallizations. The quality of the D-ribose obtained was improved when pure *p*-bromphenylhydrazine was prepared and condensed with the crude ribose and the hydrazone isolated was purified carefully by crystallizations (11).

In contrast, crystalline D-ribose was obtained directly in good yields from crude syrups obtained by the reduction of D-ribonolactone, by conversion to α-aniline-N-D-ribofuranoside (prepared in excellent yield by boiling the syrup in alcohol with a slight excess of aniline) and subsequent hydrolysis. D-Ribose was also isolated in a pure crystalline state in good yield from reduction liquors containing D-ribose and electrolyte salts by means of the α-aniline-N-D-ribopyranoside "complex salt" and direct hydrolysis of the "complex salt" obtained.

The hydrolysis method was applied to triacylated N-ribosides derived from two isomeric aniline ribosides (α-aniline-N-D-ribopyranoside and α-aniline-N-D-ribofuranoside) (12). These yielded triacyl derivatives which are tentatively designated as 2,3,4- or 2,3,5-triacyl derivatives of ribose depending upon whether they were derived from the pyranoside or the furanoside form, on the assumption that no acyl migration occurred during acylation of the ribosides or the subsequent hydrolysis. The acylated riboses were obtained in good yield. The products were hygroscopic syrups or glasses and could not be brought to crystallization.

The exact structure of these acylated riboses has not as yet been determined. The close agreement of the optical rotations of the two triacetylriboses obtained might seem to indicate that ring opening and acyl migration may have occurred in one of the ribosides. Methylation studies of these acylriboses gave mixtures of partially methylated syrups of undetermined structure, from which conclusions as the structure of the acyl sugars could not be drawn. The designation of the

products obtained as 2,3,4- or 2,3,5-triacylriboses is therefore to be regarded as tentative.

EXPERIMENTAL

Hydrolysis of α-aniline-N-D-riboside (pyranoside or furanoside). Method I. Four grams of α-aniline-N-D-ribopyranoside was suspended in 200 cc. of water containing 0.25% acetic acid. Steam was injected until all the aniline was removed. The light yellow solution was treated with a small amount of Norit, filtered, and concentrated to dryness *in vacuo* at 30–35°. The residual syrup was dissolved in absolute alcohol and dried by concentration *in vacuo*. A light yellow syrup weighing 3.0 g. was obtained. It was dissolved in 4–5 cc. of absolute alcohol with slight warming, seeded, and set in the refrigerator for crystallization. The whole mass crystallized in several hours, was filtered off, and washed with cold alcohol and ether There was obtained 2.3 g. of crystalline D-ribose (86% yield), melting at 86–87°; $[\alpha]_D^{27}$ −19.6°; (*c* = 4% in water); $[\alpha]_D^{29}$ −43.3°; (*c* = 1.5% in pyridine).

Method II. Forty-five grams of α-aniline-N-D-ribofuranoside was suspended in 2250 cc. of hot water in a 5-liter 3-neck flask equipped with a stirrer, dropping-funnel, and a condenser. The reaction mixture was heated until the glycoside dissolved, and 35 cc. of benzaldehyde was added at this point. The mixture was refluxed for one-half hour under nitrogen, cooled, and the solid benzalaniline filtered off. The aqueous layer was extracted with ether to remove the final traces of benzalaniline, decolorized with Norit, and concentrated to dryness *in vacuo* at 30–35°. The residual syrup was dried by alcohol reconcentrations and crystallized from absolute alcohol in the ratio of 5 g. of syrup to 5.6 cc. of absolute ethyl alcohol. On seeding, crystalline ribose was obtained in excellent yield (90%) melting at 86–87°.

Hydrolysis of α-aniline-N-D-ribopyranoside-sodium sulfate complex. To 200 cc. of water containing 0.25% acetic acid was added 16.0 g. of α-aniline-N-D-ribopyranoside-sodium sulfate "complex salt," equivalent to 7.9 g. of pure riboside. The solution was steam distilled under nitrogen until all the aniline was removed. The aqueous liquors were treated with a small amount of Norit, filtered, and concentrated to dryness *in vacuo* at 30–35°. The residue was extracted twice with warm alcohol, filtered, and evaporated to dryness *in vacuo*. The syrup obtained crystallized immediately on seeding to yield pure crystalline D-ribose in 73% yield, m.p. 84–86°; $[\alpha]_D^{26}$ −19.4°; (*c* = 1% in water).

The pyranoside complex was hydrolyzed according to method II to yield pure ribose in 71% yield.

Hydrolysis of α-2,3,4-triacetyl aniline-N-D-ribopyranoside. Ten grams of α-2,3,4-triacetyl aniline-N-D-ribopyranoside was dissolved in 25 cc. of ethyl alcohol and added to 400 cc. of a 0.5% acetic acid solution. The solution was steam distilled until all the aniline was removed. The aqueous solution was treated with Norit, filtered, and concentrated to dryness *in vacuo* as previously. The resultant syrup was dried *via* repeated alcohol distillations. There was obtained 5.0 g. of a clear colorless thick syrup that could not be crystallized. The syrup was readily soluble in alcohol and ethyl acetate (D-ribose is insoluble in cold alcohol and ethyl acetate). The syrupy 2,3,4-triacetylribose was dried at 100° for six hours and analyzed.

Anal. Calc'd for $C_{11}H_{16}O_8$: C, 47.82; H, 5.80; Acetyl, 46.7.
Found: C, 47.58; H, 5.86; Acetyl, 40.9.[1]

The 2,3,4-triacetylribose was very hygroscopic and adsorbed 8–10% of water on standing. Dried at room temperature *in vacuo* over P_2O_5, it retained 1/2 mole of water; $[\alpha]_D^{30}$ −26.3°; (*c* = 1.3% in water).

Hydrolysis of α-2,3,5-triacetyl aniline-N-D-ribofuranoside. Three grams of α-2,3,5-triacetyl-N-D-ribofuranoside was suspended in 200 cc. of water and 1 cc. of glacial acetic

[1] As reported in Part I (12), micro acetyl determinations of the compounds in this series gave consistently low values although the carbon and the hydrogen values agreed with the theoretical.

acid was added. The mixture was steam distilled to remove the aniline and worked up as above. The clear viscous syrup obtained was dried *via* repeated alcohol distillations. It was soluble in cold alcohol and ethyl acetate but could not be obtained in a crystalline state. The syrup was hygroscopic and gave up its water very slowly. It was dried at 100° in high vacuum over P_2O_5 for several hours and analyzed.

Anal. Calc'd for $C_{11}H_{16}O_8$: C, 47.82; H, 5.80; Acetyl, 46.7.
Found: C, 47.45; H, 6.06; Acetyl, 41.5.[1]

$[\alpha]_D^{30}$ −24.2°; (c = 0.8% in water).

*Hydrolysis of α-2,3,4-tribenzoyl aniline-N-*D*-ribopyranoside.* In a one-liter flask equipped with a stirrer, condenser, and gas inlet tube were placed 18.0 g. of α-2,3,4-tribenzoyl aniline-N-D-ribopyranoside, 50 cc. of benzaldehyde dissolved in 500 cc. of ethyl alcohol, and 100 cc. of water. The mixture was refluxed for one hour under nitrogen. The reaction was then brought to *p*H 3.5 with dilute acid, and apparatus arranged for steam distillation. The steam distillation was continued until all the volatile matter had been removed (four hours). The solution was then cooled and the mass that precipitated out was extracted with ether. The wet ether solution was treated with Norit to decolorize the brown solution and the solution was dried over anhydrous Na_2SO_4 overnight. On evaporation of the dry ether, there remained 9.9 g. of a yellow-brown glass which could not be brought to crystallization. Drying *in vacuo* for six hours over P_2O_5 at 100°, the glass was converted to a yellow amorphous powder.

Anal. Calc'd for $C_{26}H_{22}O_8$: C, 67.50; H, 4.76.
Found: C, 67.34; H, 4.96.

ACKNOWLEDGMENT

The micro analyses were performed in the Microanalytical Division of these laboratories under the direction of Dr. Al Steyermark.

SUMMARY

1. Hydrolysis of aromatic N-D-ribopyranosides and aromatic N-D-ribofuranosides with water, catalyzed with acids or bases, or in the presence of aldehydes as formaldehyde and benzaldehyde regenerated the original amine and D-ribose in good yield. The D-ribose was readily obtained in pure crystalline form from this reaction.

2. Aromatic N-D-ribopyranoside "complex salts" were hydrolyzed in this manner to yield crystalline D-ribose.

3. Triacyl aromatic N-ribosides were hydrolyzed to yield triacylriboses.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

METHONE DERIVATIVES OF ALDEHYDES

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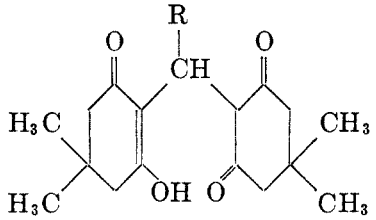
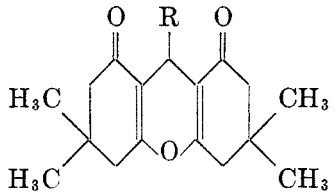
The use of methone (5,5-dimethyldihydroresorcinol) as a reagent for the identification and characterization of aldehydes is well known (1, 2, 3, 4, 5). A disadvantage attending the use of methone has been the lack of agreement on conditions recommended for the preparation of derivatives and a lack of data obtained by proposed general methods. A method for the characterization of aldehydes with methone, applicable to aliphatic and aromatic aldehydes, is described in the experimental section. The aldehyde is treated with methone in aqueous alcohol solution; a drop of piperidine is added as a catalyst, and a five minute reflux period suffices to complete the reaction. The crystalline methone derivatives (I) can be isolated readily and in good yield. The conditions de-

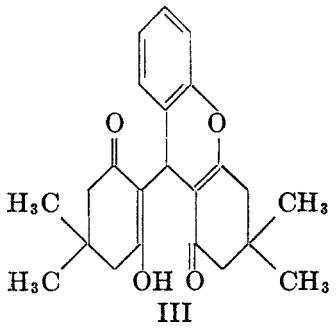


I

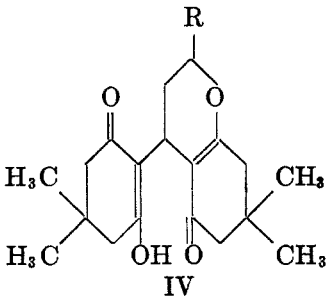


II

scribed were satisfactory in all cases which were examined. The melting points of the derivatives are in Tables I and II. α,β-Unsaturated aldehydes and *o*-hydroxy aromatic aldehydes yield products differing in structure from the normal derivatives (I), but these products are formed in excellent yield, and serve equally well as derivatives. The structure assigned to the salicylaldehyde product is that of an octahydroxanthene (II, R = *o*-hydroxyphenyl) (6), although an alternate structure (III) has also been suggested (7). There is no proof of structure at hand for the compounds obtained with α,β-unsaturated aldehydes, but since they do not undergo a dehydration reaction under conditions suitable for the usual derivatives we believe they may have a pyran structure as in IV.



III



IV

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It has been known for a long time that a variety of dehydration conditions will convert the normal derivatives (I) into octahydroxanthenes (II). Heating in acetic anhydride is the usual method; sulfuric acid and hydrogen chloride in alcohol have also been used. Prolonged heating in acetic acid alone has also been employed in some cases. An investigation of this reaction has shown that with one exception the cyclization can be effected through the relatively simple process of recrystallizing the methone derivative from aqueous alcohol to which a few drops of concentrated hydrochloric acid has been added. A routine

TABLE I

ALIPHATIC ALDEHYDES

ALDEHYDE	DERIVATIVE I		DERIVATIVE II	
	M.P., °C	Ref.	M.P., °C	Ref.
Formaldehyde[a]	191–191.5	1, 2, 3, 4	—	1, 2
Acetaldehyde[a]	141–142	1, 2, 3, 4	176–177	1, 2, 3
Glyoxal[b]	228	2	170	2
Glyoxylic acid[b]	239	2	245	2
Acrolein[b]	192	1	162–163	1
	135	2	170–188	2
Propionaldehyde[a]	157–158	2, 4	141.5–143	1, 2
Crotonaldehyde[a]	193–194	1, 2, 8, 9	—	1, 2
Butyraldehyde[a]	134–135	2, 4	135–136	2
Isobutyraldehyde[a]	153–154.5	2, 10	154–155.5	2
Allylacetaldehyde[b]	98	11	—	—
n-Valeraldehyde[a]	107–109	4	112–113[c]	—
Isovaleraldehyde[b]	154–155	1	172–173	1
	137	2	168	2
Hexanal[b]	108.5	4	—	—
Heptanal[a]	101–103	1, 2, 4	110.5–112	1, 2
Octanal[b]	89.8	4	—	—
Nonanal[b]	86.3	4	—	—
Decanal[b]	91.7	4	—	—
Citronellal[b]	77–79	1	173	1
	70–71	3		

[a] Melting point values are from this work and are corrected.

[b] Melting point values are from the literature.

[c] *Anal.* Calc'd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.31; H, 9.35.

procedure, described in the experimental section, has been applied to a number of derivatives, and the melting points of the products are listed in Tables I and II. All methone derivatives (I) yielded octahydroxanthenes except the compound derived from formaldehyde, which was recovered unchanged. Cyclization of this derivative requires more vigorous conditions (1, 2). It was also found that this cyclization procedure was not applicable to the products obtained from α,β-unsaturated aldehydes or to those from *o*-hydroxy aromatic aldehydes.

The cyclization requires a reaction period of approximately five minutes, and the yield is often very nearly quantitative. The octahydroxanthenes (II) are

TABLE II

AROMATIC ALDEHYDES

ALDEHYDE	DERIVATIVE I		DERIVATIVE II	
	M.P., °C	Ref.	M.P., °C	Ref.
Benzaldehyde[a]	194–195	6, 7, 12	204–205.5	6, 7, 12
Salicylaldehyde[a]	205–206	1, 3, 6, 7	—	6, 7
p-Hydroxybenzaldehyde[b]	188–190	1	246	1
	184	7	208–209	7
2,4-Dihydroxybenzaldehyde[b]	225–226	7	—	—
3,4-Dihydroxybenzaldehyde[b]	145 dec.	7	—	—
m-Nitrobenzaldehyde[a]	197–198[c]	7	171.5–172.5	7
p-Nitrobenzaldehyde[b]	188–190	7	222	7
o-Chlorobenzaldehyde[b]	205	1	224–226	1
o-Tolualdehyde[a]	166–167[d]	—	213.5–215[e]	—
m-Tolualdehyde[a]	171–172.5[f]	—	205–207[g]	—
Phenylacetaldehyde[b]	164–165	13	125–126	13
o-Methoxybenzaldehyde[a]	187–188	6	190–191	6
Anisaldehyde[a]	142–143	1, 3, 7	241–243	1, 7
Piperonal[a]	175.5–177	1, 3, 7	218.5–220	1, 7
2-Hydroxy-3-methoxybenzaldehyde[a]	232–234[h]	—	—	—
Vanillin[a]	195.5–196.5	1, 3, 7	226–228	1
Cinnamaldehyde[a]	215–217	1, 7	—	1, 7
2,3-Dimethoxybenzaldehyde[a]	149–150[i]	—	168–169[j]	—
Veratraldehyde[a]	173–174[k]	—	184–185.5[l]	—
p-Dimethylaminobenzaldehyde[a]	194.5–195.5	1, 14	220–222	14
Acetylvanillin[b]	167	3	148–149	7
Cuminal[b]	170–171	1	172–173	1

[a] Melting point values are from this work and are corrected.

[b] Melting point values are from the literature.

[c] *Anal.* Calc'd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58.
Found: C, 67.09; H, 6.59.

[d] *Anal.* Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91.
Found: C, 75.41; H, 8.02.

[e] *Anal.* Calc'd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74.
Found: C, 79.23; H, 7.83.

[f] *Anal.* Calc'd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91.
Found: C, 75.21; H, 7.90.

[g] *Anal.* Calc'd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74.
Found: C, 78.85; H, 7.81.

[h] *Anal.* Calc'd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12.
Found: C, 72.82; H, 7.27.

[i] *Anal.* Calc'd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53.
Found: C, 70.35; H, 7.74.

[j] *Anal.* Calc'd for $C_{25}H_{30}O_5$: C, 73.14; H, 7.37.
Found: C, 73.14; H, 7.25.

[k] *Anal.* Calc'd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53.
Found: C, 70.14; H, 7.65.

[l] *Anal.* Calc'd for $C_{25}H_{32}O_5$: C, 73.14; H, 7.37.
Found: C, 72.68; H, 7.32.

colorless crystalline products, varying considerably in melting point with variations in the R group. For purposes of identification of aldehydes, a combination of the two reactions offers the advantage that two derivatives may be obtained from one reaction of the original aldehyde. The methone derivative (I) may be prepared and after the melting point determination a cyclization can be carried out to yield a second derivative (II). This procedure may be of particular value when only small amounts of aldehyde are available.

EXPERIMENTAL

Reagents. Methone and piperidine were obtained from the Eastman Kodak Co. Aldehydes were commercial or laboratory preparations; liquid aldehydes were distilled before use.

Melting Points. Melting points up to 230° were taken in a stirred bath and are corrected. A metal block was used for higher temperatures.

Aliphatic aldehydes: Methone derivatives (I). To 4 cc. of 50% ethanol-water were added 400 mg. of methone and 0.10 cc. of the aliphatic aldehyde. One drop of piperidine[2] was added, and the mixture was heated under reflux on a steam-bath for 5 minutes. In cases where the solution was still clear at the end of this period, water was added dropwise to the cloud point. After chilling the reaction mixture, the derivative was separated by filtration, and washed with 50% ethanol-water.

The time required for crystallization of the product varied with individual aldehydes. In some cases crystalline derivatives separated during the reflux period; in other cases the addition of a little water was necessary; and in a few cases the derivative separated as an oil which crystallized readily on cooling and stirring. The yield was usually above 300 mg. Recrystallization, which was necessary in most cases, was effected from aqueous methanol. All derivatives were colorless.

Aliphatic aldehydes: Cyclization to 2,2,7,7-tetramethyl-4,5-diketo-9-alkyloctahydroxanthenes (II). One hundred milligrams of the methone derivative (I) was dissolved in 3 to 4 cc. (as required) of hot 80% ethanol-water, and one drop of conc'd hydrochloric acid was added. The solution was heated under reflux for 5 minutes. Water was added dropwise to the cloud point, and after cooling and chilling, the xanthenes were obtained by filtration and washing with aqueous ethanol.

These derivatives crystallized readily, and were obtained in good yield (usually over 80 mg.). They were of a high degree of purity, and usually did not require recrystallization. Where necessary, recrystallization was effected from aqueous methanol. All derivatives were colorless.

Aromatic aldehydes: Methone derivatives (I). The general procedure for aliphatic aldehydes was followed except that the amount of methone used was 300 mg. The amount of aldehyde was 0.10 cc. for liquids and 100 mg. for solids.

The derivatives usually appeared in crystalline form during the addition of water; oiling occurred in very few instances. Yields were usually nearly quantitative. Recrystallization, where necessary, was effected from aqueous methanol. All derivatives were colorless, except that from *p*-dimethylaminobenzaldehyde, which was bright yellow.

Aromatic aldehydes: Cyclization to 2,2,7,7-tetramethyl-4,5-diketo-9-aryloctahydroxanthenes (II). The procedure for aliphatic aldehydes was followed, but slightly larger amounts of solvent were required in some cases. These derivatives crystallized readily, in a high degree of purity, and usually were obtained in nearly quantitative yield. Recrystallization, where necessary, was effected from aqueous methanol. All derivatives were colorless.

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[2] The use of piperidine as a catalyst in dihydroresorcinol-aldehyde condensations was apparently first suggested by Desai (6).

In the case of the octahydroxanthene from *p*-dimethylaminobenzaldehyde, the solution was buffered with 4 *M* sodium acetate solution after cyclization was completed. This derivative was soluble in dilute hydrochloric acid.

SUMMARY

A general procedure for the preparation of methone derivatives of aldehydes has been applied to a number of aliphatic and aromatic aldehydes. It has been found that the cyclization of the derivatives to octahydroxanthenes may be accomplished readily by crystallization from aqueous alcohol containing a little hydrochloric acid, and that this procedure may be utilized for the preparation of a second set of derivatives.

ANN ARBOR, MICH.

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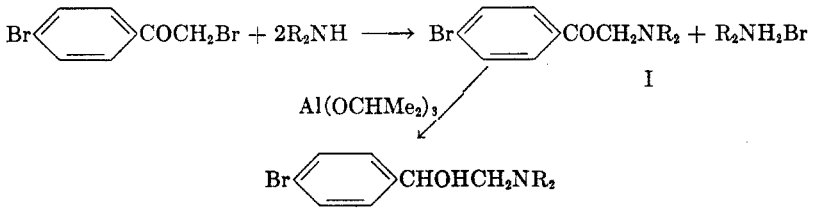
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MARYLAND]

SYNTHETIC ANTIMALARIALS. β-DIALKYLAMINOETHANOLS[1]

NATHAN L. DRAKE AND LEON GOLDMAN[2]

Received November 13, 1945

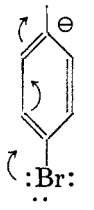
Certain amino alcohols, notably the cinchona alkaloids, *e.g.*, quinine, and some 4-quinoline methanols, *e.g.*, α-(6′-methoxy-1′-quinolyl)-β-di-*n*-butylaminoethanol, have been found to possess antimalarial activity (1, 2, 3, 4, 5). Both these types of compounds possess the grouping ArCHOHCHN—. In order to evaluate the β-dialkylaminoethanol moiety, compounds of structure (II) were synthesized according to the following scheme:



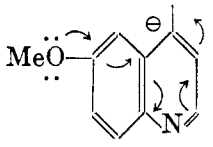
in I where NR_2 = $N(C_2H_5)_2$, III; hydrobromide, IV; hydrochloride, V
= $N(C_3H_7\text{-}n)_2$, VI; hydrobromide, VII; hydrochloride, VIII
= $N(C_4H_9\text{-}n)_2$, IX; hydrobromide, X
= NC_5H_{10},[3] XI; hydrochloride, XII

in II where NR_2 = $NH(C_2H_5)_2^+\ Br^-$, XIII
= $NH(C_3H_7\text{-}n)_2^+\ Br^-$, XIV
= $NH(C_4H_9\text{-}n)_2^+\ Br^-$, XV
= $NHC_5H_{10}^+\ Cl^-$, XVI

The *p*-bromophenyl group was chosen because of its nearly identical molecular weight to the methoxyquinolyl group, the former being 156 and the latter 158; and also because of the similar electron displacements of the two groups (XVII) and (XVIII).



XVII



XVIII

[1] Taken in part from a thesis submitted by Leon Goldman to the Graduate School of the University of Maryland in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, 1944.

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[3] NC_5H_{10} represents the piperidyl group.

The ω-dialkylamino-*p*-bromoacetophenones (III), (VI), (IX), and (XI), were prepared according to Marvel and du Vigneaud (6) and were isolated as their hydrobromide and hydrochloride salts, (IV), (V), (VII), (VIII), (X), and (XII), in yields of 87–100%.

The amino ketones (III), (VI), and (XI), were reduced as free bases by means of aluminum isopropoxide according to Meerwein and Schmidt (7) and Ponndorf (8) to produce the desired amino alcohols which were isolated as the salts (XIII), (XIV), and (XVI), in yields of 70, 70, and 81%, respectively. The free base of the di-*n*-butylamino ketone (IX) was too sensitive to this reagent, being decomposed by it even at room temperature. Acting on the suggestion of Dr. Lyndon F. Small of the National Institute of Health the hydrobromide salt (X), instead of the free base (IX), was reduced with aluminum isopropoxide. There was no sign of decomposition and the amino alcohol hydrobromide (XV) was obtained in 93% yield.

The amino ketones could not be reduced to amino alcohols by means of Adams' platinic oxide catalyst and hydrogen. The only crystallizable products from catalytic reduction of amino ketone hydrobromides (IV) and (X) were recovered starting material. Catalytic reduction of amino ketone hydrochlorides (V), (VIII), and (XII), gave products which proved to be mixtures of the hydrobromides and hydrochlorides of recovered amino ketones. Reductive fission of some bromine atoms in the *para* position must have occurred, producing hydrogen bromide. The unreacted amino ketone molecules were then obtained as crystalline mixed hydrobromides and hydrochlorides. Thus the product, m.p. 186.4–187.4°, isolated from catalytic reduction of (V) had the following analysis: C, 41.62; H, 4.97, which is not in agreement with the calculated values for the ethanolamine hydrochloride, $C_{12}H_{19}BrClNO$: C, 46.69; H, 6.20; but rather corresponds to a mixture of (IV) and (V). In fact, the product of the reduction, when treated with alkali, yielded a free base which was converted to a hydrochloride identical with (V). The aqueous solution from the liberation of the free base was found to contain bromide ions.

Compounds (XIII), SN 5668, (XIV), SN 5651, (XV), SN 5862, and (XVI), SN 5854, were submitted for antimalarial testing to the Survey of Antimalarial Drugs and were found to be active.

EXPERIMENTAL

Condensation of secondary amines with p-bromophenacyl bromide. To a solution of one mole of *p*-bromophenacyl bromide in the minimum amount of anhydrous benzene necessary for complete solution at 0° was added two moles of secondary amine. The mixture was shaken and cooled in ice to remove the heat of reaction. The secondary amine hydrobromide usually started to precipitate after several minutes. After refrigerating for two to twenty-four hours the suspension was treated with excess anhydrous ether and a nearly quantitative yield of secondary amine hydrobromide was obtained by filtration and washing with anhydrous ether until colorless.

The combined benzene-ether filtrate was chilled with ice and saturated with dry hydrogen bromide or hydrogen chloride and the precipitated amino ketone salt was removed by filtration, washed with anhydrous ether, and crystallized from absolute ethanol-anhydrous ether.

ω-Diethylamino-p-bromoacetophenone hydrobromide (*IV*). Reaction of 13.9 g. (0.05 mole) of *p*-bromophenacyl bromide with 7.3 g. (0.1 mole) of diethylamine in 150 cc. of anhydrous benzene for two hours at ice temperature yielded 7.5 g. (98%) of diethylamine hydrobromide. The yield of amino ketone hydrobromide, obtained as pale yellow crystals, was 17.5 g. (100%). Crystallization from absolute ethanol-anhydrous ether gave colorless crystals, m.p. 193.1–193.8°.

Anal. Calc'd for $C_{12}H_{17}Br_2NO$: C, 41.05; H, 4.88; Br,[4] 22.76.
Found: C, 41.57;[5] H, 4.88;[5] Br, 22.6.

ω-Diethylamino-p-bromoacetophenone hydrochloride (*V*). This compound was prepared in 96% yield from *p*-bromophenacyl bromide and diethylamine as described above, and from the hydrobromide salt (IV): a solution of 21.1 g. (0.06 mole) of ω-diethylamino-*p*-bromoacetophenone hydrobromide in 100 cc. of water was made alkaline with aqueous potassium carbonate to liberate the free amino ketone base as a yellow oil. The oil was extracted with ether, and the ether extract was dried over Drierite and saturated with dry hydrogen chloride. The resulting pale yellow gummy precipitate was dried in a vacuum desiccator over phosphorus pentoxide and crystallized from absolute ethanol-anhydrous ether, yielding 17.7 g. (97%) of colorless crystals. When recrystallized from absolute ethanol-anhydrous ether the product melted at 172.6–173.6°.

Anal. Calc'd for $C_{12}H_{17}BrClNO$: C, 47.00; H, 5.59; Cl,[4] 11.56.
Found: C, 46.51;[6] H, 5.69;[6] Cl, 11.5.

ω-Di-n-propylamino-p-bromoacetophenone hydrobromide (*VII*). A twenty-hour reaction of 13.9 g. (0.05 mole) of *p*-bromophenacyl bromide with 10.1 g. (0.1 mole) of di-*n*-propylamine in 150 cc. of anhydrous benzene, followed by addition of 300 cc. of anhydrous ether, yielded 8.8 g. (97%) of di-*n*-propylamine hydrobromide. The benzene filtrate was concentrated on the steam-bath to 200 cc., cooled in ice, and saturated with dry hydrogen bromide. After adding 300 cc. of anhydrous ether, 17.1 g. (90%) of pale green hydrobromide was obtained. Crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 184.2–184.8°.

Anal. Calc'd for $C_{14}H_{21}Br_2NO$: C, 44.35; H, 5.53; Br,[4] 21.09.
Found: C, 44.46, 44.60, 44.70; H, 5.38, 5.86, 5.54; Br, 21.3.

ω-Di-n-propylamino-p-bromoacetophenone hydrochloride (*VIII*). This compound was obtained in 95% yield (16.2 g.) by saturating an anhydrous benzene solution of ω-di-*n*-propylamino-*p*-bromoacetophenone (VI) (from reaction of 13.9 g. of *p*-bromophenacyl bromide and 10.1 g. of di-*n*-propylamine) with dry hydrogen chloride, with the addition of anhydrous ether. Crystallization from absolute ethanol-anhydrous ether gave colorless crystals, m.p. 171.7–172.6°.

Anal. Calc'd for $C_{14}H_{21}BrClNO$: C, 50.24; H, 6.32; Cl,[4] 10.59.
Found: C, 49.11, 49.73, 49.27; H, 6.08, 6.26, 6.03; Cl, 10.4.

ω-Di-n-butylamino-p-bromoacetophenone hydrobromide (*X*). Reaction of 13.9 g. (0.05 mole) of *p*-bromophenacyl bromide dissolved in 150 cc. of anhydrous benzene with 12.9 g. (0.1 mole) of di-*n*-butylamine for twenty-four hours in the refrigerator, followed by dilution with anhydrous ether, yielded 10.4 g. (99%) of di-*n*-butylamine hydrobromide. Saturation of the filtrate with dry hydrogen bromide yielded 35.3 g. (87%) of nearly colorless amino ketone hydrobromide. Crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 176.5–177.5° (transition point at 145–146°).

Anal. Calc'd for $C_{16}H_{25}Br_2NO$: C, 47.19; H, 6.19; Br,[4] 19.62.
Found: C, 47.23, 47.17; H, 6.21, 6.06; Br, 19.7.

ω-Piperidyl-p-bromoacetophenone hydrochloride (*XII*). Reaction of 27.8 g. (0.1 mole) of *p*-bromophenacyl bromide dissolved in 250 cc. of anhydrous benzene with 17 g. (0.2 mole) of freshly distilled piperidine for twenty-four hours in the refrigerator yielded 16.6 g.

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[4] Volhard titration of ionizable halogen.

[5] Analysis by courtesy of Dr. Robert C. Elderfield, Columbia University.

[6] Analysis by courtesy of Dr. Lyndon F. Small, National Institute of Health.

(100%) of piperidine hydrobromide. Saturation of the chilled filtrate with dry hydrogen chloride yielded 31.8 g. (100%) of cream-colored amino ketone salt. Crystallization from absolute ethanol yield colorless crystals, m.p. on slow heating 224.7–225.7°, on rapid heating 230.5–231.5°.

Anal. Calc'd for $C_{13}H_{17}BrClNO$: C, 49.00; H, 5.38; Cl,[4] 11.13.
Found: C, 48.96, 48.79; H, 5.05, 5.13; Cl, 10.9.

Reduction of amino ketones with aluminum isopropoxide. Amino ketones (III), (VI), and (XI), were reduced in the following manner: a solution of 0.05 mole of amino ketone and 15.3 g. (0.075 mole) of aluminum isopropoxide in 100 cc. of anhydrous benzene was slowly distilled through a helix-packed fractionating column with controlled take-off until most of the benzene was removed, care being taken not to distil to dryness. To the residue was added 100 cc. of isopropanol and distillation was continued until the distillate no longer gave a test for acetone with 2,4-dinitrophenylhydrazine reagent. The remainder of the solvent was removed at 20 mm. pressure and the red-brown semi-crystalline residue was chilled and acidified with 100 cc. of ice-cold 10% hydrochloric acid to decompose the aluminum complex. The resulting solution was made strongly alkaline with ice-cold potassium hydroxide solution to liberate the free base of the amino alcohol and keep the aluminum in solution as the aluminate ion. The amino alcohol was extracted with benzene, the benzene solution was washed with water and dried over Drierite or by distillation into a moisture-point receiver, and the hydrobromide or hydrochloride salt precipitated by saturation with dry hydrogen bromide or hydrogen chloride.

α-(p-Bromophenyl)-β-diethylaminoethanol hydrobromide (XIII). Saturation of the benzene solution of the free base with hydrogen bromide produced a brown oil. All the benzene was removed *in vacuo*, and the residual oily hydrobromide was dissolved in absolute ethanol. When the ethanol solution was cooled in a dry ice-acetone bath, 12.1 g. (70%) of tan crystalline product was obtained. Crystallization from absolute ethanol-anhydrous ether gave colorless crystals, m.p. 135.0–135.5°.

Anal. Calc'd for $C_{12}H_{19}Br_2NO$: C, 40.81; H, 5.42; Br,[4] 22.63.
Found: C, 40.93, 41.00; H, 5.28, 5.30; Br, 22.5, 22.5.

α-(p-Bromophenyl)-β-di-n-propylaminoethanol hydrobromide (XIV). The hydrochloric acid solution from decomposition of the aluminum complex contained a small amount of dark red oil in suspension. The oil was removed by extraction with ether. The amino alcohol hydrobromide was obtained as tan crystals which were crystallized from absolute ethanol-anhydrous ether to yield 13.4 g. (70%) of product. Further crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 138.3–139.3°.

Anal. Calc'd for $C_{14}H_{23}Br_2NO$: C, 44.11; H, 6.08; Br,[4] 20.97.
Found: C, 44.15, 44.20; H, 5.85, 5.96; Br, 20.9.

α-(p-Bromophenyl)-β-piperidylethanol hydrochloride (XVI). The hydrochloric acid solution from decomposition of the aluminum complex contained a tan precipitate. Addition of 800 cc. of warm water dissolved all except a small amount of dark-colored gummy material which was removed by filtration. Saturation of the benzene solution of the amino alcohol free base produced a cream-colored precipitate. After adding 200 cc. of anhydrous ether, 13.0 g. (81%) of the hydrochloride was obtained. Crystallization from absolute ethanol yielded colorless crystals, m.p. 237.7–238.2°.

Anal. Calc'd for $C_{13}H_{19}BrClNO$: C, 48.69; H, 5.97; Cl,[4] 11.06.
Found: C, 48.48, 48.53; H, 6.03, 6.10; Cl, 11.0.

α-(p-Bromophenyl)-β-di-n-butylaminoethanol hydrobromide (XV). A solution of 11.6 g. (0.0285 mole) of ω-di-*n*-butylamino-*p*-bromoacetophenone hydrobromide and 14.5 g. (0.071 mole) of aluminum isopropoxide in 100 cc. of anhydrous isopropanol was slowly distilled through a helix-packed fractionating column with controlled take-off until 60 cc. of distillate was collected. At this point the distillate gave a negative test for acetone with 2,4-dinitrophenylhydrazine reagent. The remainder of the isopropanol was removed by distillation at reduced pressure, leaving a colorless semi-solid residue. The residue was cooled in ice, acidified with 100 cc. of ice-cold 10% hydrochloric acid, and the resulting

suspension was completely dissolved by adding 700 cc. of water, yielding a colorless solution. The solution was cooled with ice and made strongly alkaline with ice-cold potassium hydroxide, causing a white solid to separate after the aluminum hydroxide, which first precipitated, redissolved. The suspension was extracted with five 50-cc. portions of benzene, and the colorless benzene extract was washed with water and then dried by distilling into a moisture-point receiver. The dry benzene solution was distilled to a volume of 150 cc. and then saturated with dry hydrogen bromide. The addition of 350 cc. of anhydrous ether caused a colorless oil to separate from solution. After standing overnight in the refrigerator the oil completely changed to colorless crystals weighing 10.8 g. (93%), m.p. 112–114°. Crystallization from absolute ethanol-anhydrous ether yielded colorless crystals, m.p. 113.0–114.0°.

Anal. Calc'd for $C_{16}H_{27}Br_2NO$: C, 46.96; H, 6.65; Br,[4] 19.54.
Found: C, 46.90, 46.92; H, 6.76, 6.70; Br, 19.6.

SUMMARY

Reactions of *p*-bromophenacyl bromide with secondary amines were used to synthesize the following compounds: ω-diethylamino-*p*-bromoacetophenone hydrobromide and hydrochloride, ω-di-*n*-propylamino-*p*-bromoacetophenone hydrobromide and hydrochloride, ω-di-*n*-butylamino-*p*-bromoacetophenone hydrobromide, and ω-piperidyl-*p*-bromoacetophenone hydrochloride.

Aluminum isopropoxide reduction of the amino ketones, as the free bases, produced the following compounds: α-(*p*-bromophenyl)-β-diethylaminoethanol hydrobromide, α-(*p*-bromophenyl)-β-di-*n*-propylaminoethanol hydrobromide, and α-(*p*-bromophenyl)-β-piperidylethanol hydrochloride. α-(*p*-Bromophenyl)-β-di-*n*-butylaminoethanol hydrobromide was obtained by aluminum isopropoxide reduction of the amino ketone hydrobromide. The amino alcohol salts were found to possess antimalarial activity.

COLLEGE PARK, MD.

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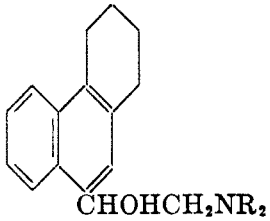
[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. IV.[1,2] AMINO ALCOHOLS DERIVED FROM PHENANTHRENE AND TETRAHYDROPHENANTHRENE

EVERETTE L. MAY AND ERICH MOSETTIG

Received January 25, 1945

We have shown in previous communications that a number of amino alcohols of type I (1) and type II (2) show a high antimalarial activity. We were interested to find out whether analogous compounds of type III (—$CHOHCH_2$-CH_2NR_2) would be of greater or lesser therapeutic value.



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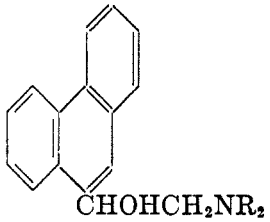

II

The simplest way of arriving at phenanthryalkamines of type III consists in the reduction of the corresponding amino ketones, which in turn are obtainable by the Mannich reaction. Previously (3, 4), isoamyl alcohol was used to advantage as medium in this reaction. By employing a modification as specified by Fry (5), the amino ketones were obtained in considerably higher yields. They were reduced catalytically in the form of their hydrochlorides. From the propylamino ketones upwards, fission in the alkamine side chain becomes more pronounced with increase in the size of the dialkylamino group, as shown by recovery of secondary amine hydrochloride and non-basic products. The Meerwein-Ponndorf-Verley method proved to be without value for the reduction of the amino ketones, since they were not stable under the conditions employed in this procedure.

The tolerated doses (chicks) of the "Mannich-type" amino alcohols are consistently lower (0.1–0.3 mg. per g.) than those of the corresponding ethanolamines (1, 2) (Dr. Nathan B. Eddy, 6). This results in a rather unfavorable chemotherapeutic index, and though these compounds have a high effectiveness against *Plasmodium gallinaceum* (Dr. G. Robert Coatney and Dr. W. Clark Cooper, 7), the study of this type was not further pursued. None of the drugs showed any activity towards sporozoite-induced *gallinaceum* malaria (7).

Acknowledgment. We are indebted to Mr. Edward A. Garlock, Jr. for carrying out the microanalyses.

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXIX.

TABLE I[3]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

SN	$C_{14}H_{13}$–9–$CHOHCH_2CH_2$	Q
1804	$N(CH_3)_2$	1/8
8861	$N(C_2H_5)_2$	1/4
8862	$N(C_3H_7)_2$	1/4
8863	$N(C_4H_9)_2$	1/4
7310	$N(C_5H_{11})_2$	1/2
1805	piperidino	1/8
	$C_{14}H_9$–9–$CHOHCH_2CH_2$–	
6824	$N(CH_3)_2$	1/4
6825	$N(C_2H_5)_2$	1/4
6826	$N(C_3H_7)_2$	1/2
7309	$N(C_4H_9)_2$	1/4
7308	$N(C_5H_{11})_2$	1/2

EXPERIMENTAL[4]

9-(3-Dimethylamino-1-oxopropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A mixture of 4.1 g. of dimethylamine hydrochloride, 1.5 g. of paraformaldehyde, 9 cc. of benzene, 9 cc. of nitrobenzene, and 2 drops of concentrated hydrochloric acid was stirred and boiled under reflux until the original solid became a light colored oil (ten to fifteen minutes). At this point 11 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene was added and the stirring and refluxing resumed. At the end of another ten-minute period, amino ketone hydrochloride began separating, whereupon a water-trap was inserted and during the next twenty minutes 0.75 cc. of water was collected. The reaction mixture was cooled, diluted with ether, then cooled in the ice-box and filtered. The precipitate (11.5 g.) was recrystallized from absolute ethanol-ether. The yield of hydrochloride melting at 187–189° was 9.8 g. (84% based on used ketone). After another recrystallization, the melting point was constant at 189–190°.

Anal. Calc'd for $C_{19}H_{24}ClNO$: C, 71.78; H, 7.61; Cl, 11.15.
Found: C, 71.11; H, 7.49; Cl, 11.47.

From the original filtrate 3 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene was recovered.

9-(3-Dimethylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. Nine and five-tenths grams of the above compound (m.p. 187–189°) absorbed one molecular equivalent of hydrogen in fifteen hours when shaken with 0.2 g. of platinum oxide and 110 cc. of 85% ethanol. The clear solution was filtered from catalyst, evaporated to dryness on the steam-bath under water-pump vacuum, and the syrupy residue dissolved in the minimum of warm acetone. After a few minutes the acetone solution of the amino alcohol hydrochloride was filtered from extraneous material, whereupon the compound slowly crystallized. It was cooled overnight in the ice-box and the material collected (6.2 g. of m.p. 150–162°). On recrystallization from absolute ethanol-ether, 5.1 g. of white platelets of m.p. 168–169° was obtained.

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[3] In Table I are listed the compounds which were submitted for biological investigations. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "Quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine.

All compounds listed in the Table were administered as hydrochlorides, except SN 1805 which was administered as base.

[4] All melting points are uncorrected.

Anal. Calc'd for $C_{19}H_{26}ClNO$: C, 71.33; H, 8.19.
Found: C, 71.05; H, 8.18.

9-(3-Dimethylamino-1-hydroxypropyl)phenanthrene hydrochloride (3). The intermediate amino ketone hydrochloride for this compound was prepared like the previous tetrahydrophenanthrene analog. The yield from 11 g. of 9-acetylphenanthrene was 10.5 g., m.p. 169–171° (3).

A mixture of 2.4 g. of this amino ketone hydrochloride, 0.07 g. of platinum oxide and 20 cc. of methanol absorbed 1.2 molecular equivalents of hydrogen in three to five hours. As described in the previous reduction, 1.7 g. of amino alcohol hydrochloride melting at 158–163° was obtained from acetone. Two recrystallizations from absolute ethanol-ether brought the melting point to the constant value 164–166°; prisms.

Anal. Calc'd for $C_{19}H_{22}ClNO$: C, 72.26; H, 7.03.
Found: C, 71.89; H, 7.25.

9-(3-Diethylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A stirred and refluxed mixture of 5.5 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene, 0.8 g. of paraformaldehyde, 2.8 g. of diethylamine hydrochloride, one drop of concentrated hydrochloric acid, 4 cc. of nitrobenzene, and 11 cc. of benzene became almost clear after one-half hour. A small amount (about 0.1 g.) of paraformaldehyde was then added and the reaction continued one-half hour. Thirty cubic centimeters of ether was added to the cooled reaction mixture, after which it was extracted three times with 50-cc. portions of water. The water solution was made alkaline and the liberated amino ketone base shaken into ether. The dried ether solution (Na_2SO_4) was freed of solvent, the residual base dissolved in about 40 cc. of acetone and 3.5 cc. of 25% alcoholic hydrogen chloride and a little ether were added. The yield of amino ketone hydrochloride was 4.1 g. (49%), m.p. 140–143°. It was pure enough for the subsequent reduction.

Seven grams of this product, with 0.2 g. of platinum oxide and 75 cc. of methanol absorbed one molecular equivalent of hydrogen in five hours. From acetone as described for the lower homolog, 5.0 g. of amino alcohol hydrochloride was obtained. After a recrystallization from absolute ethanol-ether the melting point was constant at 200–201°; white needles, yield 3.9 g.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.47; H, 8.69.
Found: C, 71.96; H, 8.68.

9-(3-Diethylamino-1-hydroxypropyl)phenanthrene hydrochloride (3). A mixture of 11 g. of 9-acetylphenanthrene, 1.5 g. of paraformaldehyde, 5.6 g. of diethylamine hydrochloride, 2 drops of concentrated hydrochloric acid, and 25 cc. of benzene was refluxed and stirred for one hour and forty minutes. The amino ketone hydrochloride resulting was isolated as its tetrahydrophenanthrene analog above. The yield was 7.5 g. (80% based on used ketone), m.p. 133–135° (3). Five grams of 9-acetylphenanthrene was recovered.

When ten grams of the hydrochloride of m.p. 133–135° was shaken under hydrogen with 0.2 g. of platinum oxide and 80 cc. of methanol, it absorbed 1.05 molecular equivalents of hydrogen in five hours, when uptake ceased. The yield of amino alcohol hydrochloride, isolated as above, was 6.9 g. From absolute ethanol-ether, 5.6 g. crystallized as fine white needles of m.p. 180–183°.

Anal. Calc'd for $C_{21}H_{26}ClNO$: C, 73.34; H, 7.62.
Found: C, 73.28; H, 7.75.

On examination of the filtrates of the amino alcohol hydrochloride, some diethylamine hydrochloride and non-basic material were found.

9-(3-Dipropylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A mixture of 11 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene, 1.5 g. of paraformaldehyde, 6.9 g. of dipropylamine hydrochloride, 2 drops of concentrated hydrochloric acid, and 25 cc. of benzene became clear upon refluxing and stirring for fifty minutes. After an additional twenty-five minute period the reaction was interrupted, cooled, and 20 cc. of ether was added. The small amount of oil which separated was dissolved by adding a few cubic centimeters of acetone and the solution was cooled in the ice-box for one-half hour. A

white solid separated, was collected (3.3 g.), and washed with a little acetone-ether mixture. The filtrate and washings deposited 8.9 g. of white, almost pure, amino ketone hydrochloride on standing two to three hours in the ice-box. The 3.3 g. above yielded on fractional crystallization from absolute ethanol-ether 1.2 g. of dipropylamine hydrochloride as a first fraction and 1.1 g. of amino ketone hydrochloride. From all of the filtrates an additional 0.8 g. of the latter was obtained making the total yield 10.8 (58%). It crystallized in leaflets with an indefinite melting point.

Four grams of this compound and 0.1 g. of platinum oxide in 40 cc. of methanol absorbed 0.95 molecular equivalents of hydrogen in 2.75 hours, when reduction ceased. From acetone-ether 3.0 g. of a white solid separated on cooling in ice. Upon recrystallization from absolute ethanol-ether 0.3 g. of dipropylamine hydrochloride (leaflets) separated first and was filtered quickly. From the filtrate 2.2 g. (m.p. 166–171°) of the desired amino alcohol hydrochloride crystallized after two hours at room temperature. An additional 0.2 g. was recovered from the filtrate. A second recrystallization gave 1.9 g. of m.p. 182.5–184°. The analytical sample melted at 183.5–184.5°.

Anal. Calc'd for $C_{23}H_{34}ClNO$: C, 73.46; H, 9.11.
Found: C, 73.19; H, 9.26.

9-(3-Dipropylamino-1-hydroxypropyl)phenanthrene hydrochloride. The amino ketone for this compound was prepared as the foregoing tetrahydrophenanthrene analog except that the reaction time was one hour. The yield of almost pure amino ketone hydrochloride (from 11 g. of 9-acetylphenanthrene) as it crystallized from the benzene reaction mixture after dilution with ether, was 13.3 g. (71%).

A mixture of 2.0 g. of this product, 0.05 g. of platinum oxide, and 20 cc. of methanol absorbed 0.9 molecular equivalents of hydrogen in ninety minutes. From acetone-ether, a small amount of dipropylamine hydrochloride separated at 0°. This was filtered, whereupon a white crystalline hydrochloride began to separate from the filtrate. After standing at room temperature overnight and one hour in the ice-box, 1.0 g. of amino alcohol hydrochloride of m.p. 131–138° was collected. After two recrystallizations from absolute ethanol-ether 0.85 g. of compound separated as fine white needles of m.p. 144.5–146.5° (turbid melt).

Anal. Calc'd for $C_{23}H_{30}ClNO$: C, 74.27; H, 8.13.
Found: C, 73.88; H, 7.86.

9-(3-Dibutylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The "Mannich" product for this compound was prepared essentially as described for the dipropylamino derivatives above. The reaction time using 11 g. of ketone was forty-five to sixty minutes. After diluting the reaction mixture with two-thirds its volume of ether and cooling in the ice-box, 3.4 g. of dibutylamine hydrochloride was collected. From the filtrate 9.4 g. (46%) of amino ketone hydrochloride (m.p. 129–132°) was obtained.

Six grams of this compound, 0.1 g. of platinum oxide, and 50 cc. of methanol absorbed the calculated amount of hydrogen in two hours, when uptake came to a standstill. From acetone-ether, dibutylamine hydrochloride (0.4 g.) separated. The filtrate deposited overnight, at room temperature, the desired amino alcohol hydrochloride in a yield of 2.5 g., m.p. 131–134°. After a recrystallization from acetone-ether and one from acetone, the product crystallized in blade-like needles of m.p. 138–139°.

Anal. Calc'd for $C_{25}H_{38}ClNO$: C, 74.32; H, 9.48.
Found: C, 74.14; H, 9.63.

9-(3-Dibutylamino-1-hydroxypropyl)phenanthrene hydrochloride. The Mannich reaction with 11 g. of 9-acetylphenanthrene and 8.4 g. of dibutylamine hydrochloride, carried out by a procedure similar to that described in the three foregoing experiments, required two hours. The yield of crude product was 14.5 g., which on recrystallization from absolute ethanol-ether gave 13.1 g. (77% based on used ketone). Two and five-tenths grams of 9-acetylphenanthrene was recovered.

Eight grams of the recrystallized product absorbed 0.95 molecular equivalent of hydrogen in eighty minutes when shaken with 0.15 g. of platinum oxide and 75 cc. of methanol.

The residue from filtration of catalyst and evaporation of solvent *in vacuo* was dissolved in 20 cc. of acetone and this solution diluted with 40 cc. of dry ether. After two hours in the ice-box 2.3 g. of dibutylamine hydrochloride separated. The filtrate was seeded with amino alcohol hydrochloride (crystallized by one week's standing and tedious manipulations), and on cooling in ice, 3.2 g. of hygroscopic product melting at 80–90° (with bubbling) was obtained. After two recrystallizations from acetone-ether 2.8 g. of white rectangular plates of m.p. 94–96° (frothy melt) was obtained. The compound was very hygroscopic and was dried in a vacuum desiccator before analysis.

Anal. Calc'd for $C_{25}H_{34}ClNO \cdot CH_3OH$: C, 72.29; H, 8.86; CH_3OH, 7.4.
Found: C, 72.49; H, 9.00; CH_3OH, 7.9.

The solvate methanol was determined by drying to constant weight at 77° *in vacuo*.

9-(3-Diamylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The Mannich reaction in this experiment was carried out with 11 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene as described for the foregoing dipropylamino and dibutylamino analogs and required ninety minutes. After diluting with an equal volume of ether the reaction mixture was cooled in ice for two hours and filtered from 2.0 g. of diamylamine hydrochloride. Since the amino ketone hydrochloride would not crystallize, the filtrate was evaporated to dryness and the residue washed twice with dry ether, 11.5 g. of crude oily material remaining. This was reduced in 75 cc. of methanol with 0.3 g. of platinum oxide, absorption 1.05 moles, 3 hours. From acetone-ether, diamylamine hydrochloride (2.2 g.) separated. The filtrate deposited gradually 3.6 g. of amino alcohol hydrochloride of melting point 100–105°. The substance was recrystallized twice from acetone-ether and appeared as clusters of long white prisms (3.0 g.) of m.p. 104–105.5°.

Anal. Calc'd for $C_{27}H_{42}ClNO$: C, 75.05; H, 9.80.
Found: C, 75.08; H, 9.61.

9-(3-Diamylamino-1-hydroxypropyl)phenanthrene hydrochloride. The amino ketone hydrochloride obtained from 11 g. of 9-acetylphenanthrene (ninety minutes reaction time) was isolated in the following manner. The benzene reaction mixture was evaporated to dryness *in vacuo*, the residue dissolved in 40 cc. of acetone and ether added carefully until no more unchanged diamylamine hydrochloride (3.0 g.) precipitated. After cooling the filtrate overnight in the ice-box 11.6 g. (60% based on used ketone) of the diamylamino ketone hydrochloride was obtained. Two grams of 9-acetylphenanthrene was recovered.

Fourteen grams of this hydrochloride when shaken with 100 cc. of methanol and 0.2 g. of platinum oxide absorbed 0.9 molecular equivalent of hydrogen in two hours. From acetone-ether 4.0 g. of diamylamine hydrochloride and 6.5 g. of amino alcohol hydrochloride were obtained. The latter melted at 112–118°, and after a recrystallization from acetone-ether, the yield of product melting at 122–125° was 5.0 g.; clusters of plates.

Anal. Calc'd for $C_{27}H_{38}ClNO$: C, 75.77; H, 8.95.
Found: C, 75.44; H, 8.87.

9-(3-Piperidino-1-oxopropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A mixture of 10 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene, 7 g. of paraformaldehyde, 5.5 g. of piperidine hydrochloride, and 50 cc. of isoamyl alcohol was boiled under reflux for one hour. The two-layered reaction mixture was cooled and diluted with ether, whereupon the amino ketone hydrochloride crystallized (5.3 g. or 33% of crude material). After two recrystallizations from absolute ethanol-ether, the melting point was 187.5–188.5°; white needles.

Anal. Calc'd for $C_{22}H_{28}ClNO \cdot H_2O$: C, 70.29; H, 8.04.
Found: C, 70.70; H, 7.91.

The material was dried at 100° *in vacuo* for two to three hours.

Anal. Calc'd for $C_{22}H_{28}ClNO$: C, 73.82; H, 7.89.
Found: C, 73.34; H, 7.77.

9-(3-Piperidino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene. The 5.3 g. of hydrochloride above, with 0.2 g. of platinum oxide and 100 cc. of 95% ethanol absorbed the calculated amount of hydrogen in 24 hours. The residue remaining after filtration from catalyst and evaporation of solvent was partitioned between an excess of dilute sodium hydroxide

and ether. The dried ether layer (Na_2SO_4) was concentrated to 15 cc., whereupon the base crystallized. After cooling, 1.8 g. of amino alcohol was obtained, m.p. 114.5–115.5°. The melting point was not changed by a recrystallization from ether; white needles.

Anal. Calc'd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04.
Found: C, 81.31; H, 8.77.

SUMMARY

A series of amino alcohols derived from phenanthrene and tetrahydrophenanthrene, and carrying the side chain —$CHOHCH_2CH_2NR_2$ in position 9, has been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

9-ALKYLAMINO CARBINOLS DERIVED FROM 9-ACYL-1,2,3,4-TETRAHYDROPHENANTHRENE DERIVATIVES[1]

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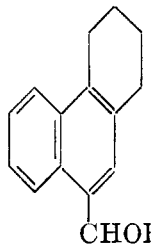
The work here presented was undertaken as a cooperative project with the National Institute of Health as part of a broader general program, the main object of which was a thorough exploration of the synthesis of as wide a variety of N,N-dialkylamino carbinols derived from 1,2,3,4-tetrahydrophenanthrenes of the general type shown in I as possible. It was desired to synthesize the



$CHOHCHR_1NR_2R_3$

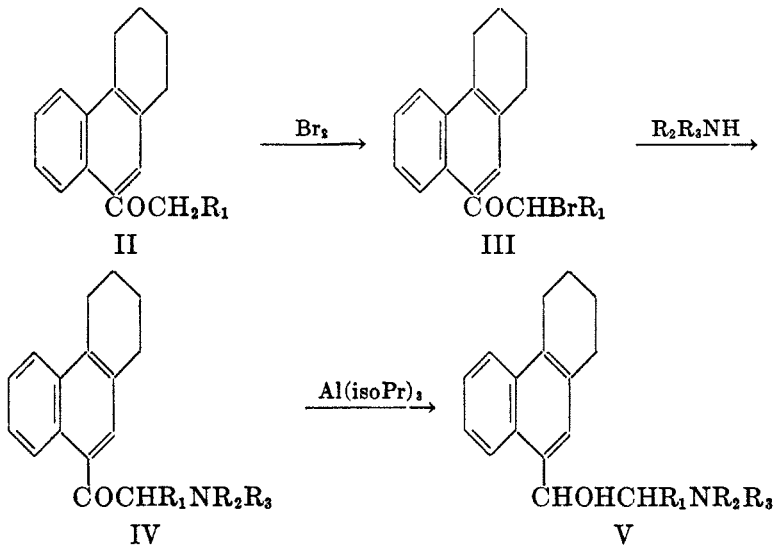
I

entire homologous series with respect to R_2 and R_3, in the case where R_1 = hydrogen and R_2 = R_3, up to the didodecyl compound, and also to introduce branched chain groups for R_2 and R_3 in so far as possible. At the time the work was begun, some of the lower members of the series had already been prepared by the group at the National Institute of Health laboratories, and shown to possess marked antimalarial action (1), so that the substances here reported are those necessary to complete the series. In addition, other representative variations in R_2 and R_3 have been introduced in order to acquire experience in the synthesis of such types, should a further exploration of these other types be demanded as the result of future work. Such variations include the case where R_2 = hydrogen and R_3 = a benzyl group. Similarly, variations in R_1 included the synthesis of representative amino carbinols in the series where R_1 = methyl and ethyl.

The general mode of synthesis used is shown in formulas II–V. In all cases a 9-acyl-1,2,3,4-tetrahydrophenanthrene was brominated in ether solution; the resulting α-bromoalkyl ketone was then condensed with the desired amine and finally the amino ketones were reduced with aluminum isopropoxide to yield the desired amino carbinols. 9-Acetyl- and 9-propionyl-tetrahydrophenanthrene have been previously described by Bachmann and Struve (2) and Bachmann and Cronyn (3). 9-Butyryltetrahydrophenanthrene appears to be new,

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

and its synthesis is described in detail. Likewise, bromoacetyltetrahydrophenanthrene has also been described (2). In general it was found to be neither desirable nor necessary to isolate the unstable amino ketones. Rather, these were reduced either as the free bases or as the hydrochlorides without purification, and the final amino carbinols were isolated as the hydrochlorides.



While at first glance it might appear that all of the reactions would proceed in a similar fashion in all cases, actually in practice it developed that each individual amino carbinol required its own individual experimental conditions and that in no two cases could exactly the same experimental procedure be used with optimum results. As a result of the present study, it has become possible to make some generalizations regarding the synthesis of such compounds. A similar study of amino carbinols in the naphthalene series has recently appeared (5).

In cases where R_1 is hydrogen, condensation of the bromo ketone with secondary amines took place readily at room temperatures provided R_2 and R_3 were straight chain alkyl or benzyl groups. However, in the cases where R_2 and R_3 contained branched chains with the branching in the vicinity of the secondary amino group, as in the case of diisopropyl and diisobutylamine, reaction was much more sluggish and required higher temperatures and longer reaction times. In many cases it was found that the amination reaction proceeded more readily in benzene than in ether. As would be expected, branching of the alkyl chain at a distance from the amino group, as in diisoamyl- and diisohexylamine, had comparatively little effect on the ease of the amination reaction. Not expected was the complete failure of the amination reaction in the cases of di-2-ethylbutyl- and di-2-ethylhexylamine, in which the branching of the carbon chains is at the second carbon atom from the nitrogen atom. It has been found impossible to carry out the amination under any conditions which did not also involve decomposition of the other reactant. However, a study of

TABLE I

PROPERTIES OF AMINO CARBINOLS REPRESENTED BY TYPE FORMULA I

All amino carbinols are described in this table as the hydrochlorides

SN[2]	R_1	R_2	R_3	M.P.°C	ANAL. Calc'd C	ANAL. Calc'd H	ANAL. Found C	ANAL. Found H	CRYSTALLINE FORM
5868	H	iso-C_3H_7	iso-C_3H_7	191–192	73.0	8.9	72.9	9.0	Prisms
5869	H	iso-C_4H_9	iso-C_4H_9	140–141	73.9	9.4	73.9	9.4	Hexagonal plates
3956	H	iso-C_5H_{11}	iso-C_5H_{11}	181–182	74.7	9.7	74.8	9.8	Micro needles
5479	H	iso-C_6H_{13}	iso-C_6H_{13}	118–119	75.4	9.9	75.3	10.2	Long plates
3957	H	n-C_7H_{15}	n-C_7H_{15}	122–123	76.0	10.2	76.2	10.2	Rectangular prisms
5241	H	n-C_9H_{19}	n-C_9H_{19}	125.5–126	77.0	10.6	76.9	10.7	Flat needles
5866	H	n-$C_{10}H_{21}$	n-$C_{10}H_{21}$	116.5–117.5	77.4	10.8	77.1	11.1	Plates
8608	H	n-$C_{11}H_{23}$	n-$C_{11}H_{23}$	111.5–113	77.8	11.0	77.6	11.1	Flat prisms
6901	H	n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	107.5–109	78.2	11.2	78.0	11.5	Rectangular plates
5919	H	n-C_4H_9	$CH_2C_6H_5$	178–179	76.5	8.1	76.6	8.0	Fluffy needles
6903	H	n-C_4H_9	p-$OCH_3CH_2C_6H_4$	165–166	74.1	8.0	74.1	7.7	Micro needles
5921	H	H	iso-C_5H_{11}	193.5–194.5	72.5	8.7	72.3	8.5	Needles
6902	H	H	n-C_9H_{19}	171–172.5	74.3	9.5	74.6	9.4	Long flat needles
5920	H	H	n-$C_{10}H_{21}$	158.5–159.5	74.7	9.6	74.6	9.9	Prisms
7426	CH_3	Tetrahydroisoquinolino		224–225 d.	76.5	7.4	76.2	7.3	Stout prisms
	C_2H_5	C_2H_5	C_2H_5	195.5–196.5	73.0	8.9	72.9	8.8	Prisms

[2] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

an atomic model of the two amines in question showed that the steric arrangement in them is such as to block effectively the secondary amine hydrogen atom as far as the reaction under consideration is concerned. In the cases where R_2 = hydrogen and R_3 = alkyl, reaction of the bromo ketone with the primary amines was so rapid that external cooling was necessary.

In so far as the effect of the nature of R_1 on the amination reaction is concerned, it was found that branching of the chain of the acyl group attached to the ring system exerted a strong inhibitory effect on the amination reaction with the result that the reaction of the 9-α-bromopropionyl and 9-α-bromobutyryl derivatives of tetrahydrophenanthrene with straight chain secondary amines approached the reaction of 9-bromoacetyltetrahydrophenanthrene with diisopropyl- or diisobutyl-amine in sluggishness. In other words, it makes little difference in a qualitative sense on which reactant the chain is branched. In contrast to the circumstances encountered when groups R_2 and R_3 contained a long chain branched at the end, similar branching in R_1 exerted a very pronounced inhibitory effect on the amination reaction. Thus, when the condensation of 9-α-bromoisocaproyltetrahydrophenanthrene with diethylamine was attempted, a period of about six months at room temperature was required for complete reaction. This observation was entirely unexpected, since it seemed reasonable to predict that the isocaproyl derivative would approximate the propionyl or butyryl derivative in its behavior.

$$RCOCH_2Br + C_5H_{11}NSO_2C_6H_4CH_3 \rightarrow RCOCH_2NSO_2C_6H_4CH_3$$
$$\qquad\qquad\qquad\qquad\quad | \qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\quad K \qquad\qquad\qquad\qquad\qquad\quad C_5H_{11}$$

In the reduction of the amino ketones to the carbinols, the major difficulties are caused by the instability of the amino ketones or the tendency of the amino carbinols to undergo hydramine fission. Under the experimental conditions used in the present work, it was difficult to separate one factor from the other when poor yields were encountered. However, previous experience (4) has shown, that where extensive amine cleavage may be expected when the ketones are reduced catalytically, this may be minimized by the use of the Meerwein method of reduction. No particular difficulty was encountered in the reduction of the amino ketones except in the cases where R_2 = hydrogen. Here the yields of carbinols were very poor. Accordingly, an alternate synthesis for this type of substance, involving condensation of isoamyl *p*-toluenesulfonamide with the bromo ketone followed by hydrolysis of the sulfonamide either before or after reduction of the carbonyl group, was explored. However, acid hydrolysis of the sulfonamide of either the amino ketone or amino carbinol resulted in the formation of large amounts of tar from which none of the expected products could be isolated.

The amino carbinols thus prepared are summarized in Table I.

We are indebted to Mr. Saul Gottlieb and to Misses Lois May and Frances Marx for all microanalyses reported in this paper.

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure, unless otherwise stated.

9-α-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene. This was prepared by the bromination of 9-acetyl-1,2,3,4-tetrahydrophenanthrene according to the method of Bachmann and Struve (1). The material used in the condensation with amines was recrystallized once from methanol and melted 89.5–90.5°.

9-(2-Diisoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The method used for the preparation of this compound was used in the synthesis of most of the amino carbinol hydrochlorides, although in some cases, with certain amines, modification of the procedure was necessary.

A solution of 28 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene in 225 cc. of anhydrous ether was shaken mechanically with 29.4 g. (two equiv.) of diisoamylamine for twelve hours. The solution was filtered, after standing for one hour in the refrigerator, and 21.0 g. of diisoamylamine hydrobromide (95%) was obtained. The ether solution was washed once with 250 cc. of water, once with a 1% sodium hydroxide solution and again with water. The ether solution was then dried over magnesium sulfate and the ether was removed, the last traces being taken off *in vacuo*. The oily orange colored residue was reduced directly according to the Meerwein method, using a mixture of 90 cc. of 1 *M* aluminum isopropoxide solution and 100 cc. of anhydrous isopropyl alcohol. The acetone formed during the reduction was distilled off through a 12-in. Vigreux column, additional isopropyl alcohol being added from time to time to maintain the level of the solution. After three to four hours, the 2,4-dinitrophenylhydrazine test for acetone was negative. The reduction was continued for an additional thirty minutes and the isopropyl alcohol removed under the water-pump vacuum. The dark red residue was cooled somewhat and shaken with 50 cc. of 10% sodium hydroxide solution and 200 cc. of anhydrous ether. After the solid had dissolved completely, the aqueous layer was drawn off and the ether layer washed twice with water and dried over magnesium sulfate. The volume of the solution at this point should be about 350 cc.

The solution was cooled in an ice-salt bath and the amino carbinol precipitated by the very slow addition of a dry ethereal hydrogen chloride solution. The precipitate which formed upon the addition of the first small portions of the hydrogen chloride solution possessed the crystalline character of the amine hydrochloride and the small amount of material thus formed was filtered off and discarded. The amino carbinol hydrochloride was then precipitated by addition of more ethereal hydrogen chloride solution to the filtrate until the solution became turbid. The solution was placed in an ice-salt bath and scratched vigorously to induce crystallization. The light brown crystalline precipitate which formed was filtered off and washed with ether. The weight of crude amino carbinol hydrochloride was 23 g. (60%). Three recrystallizations from acetone-ether or ethyl acetate gave 15 g. of material of analytical purity. Yields of the same order were obtained in the cases of other amino alcohols prepared according to this general method.

9-(2-Diisopropylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. Condensation of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with diisopropylamine did not take place as readily as with diisoamylamine and other longer chained amines. A solution of 24.0 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene in 90 cc. of benzene was refluxed with three equivalents (24 g.) of diisopropylamine for six hours. The solution was allowed to cool to room temperature and the theoretical amount (14.5 g.) of diisopropylamine hydrobromide was filtered off.

The solution was evaporated under vacuum to remove the last traces of diisopropylamine and benzene and the straw colored residue reduced in the manner described for the above diisoamyl compound, yielding 16.0 g. (58.2%) of crystalline crude amino carbinol hydrochloride. The light tan powder was recrystallized once from acetone-ether, followed by an additional recrystallization from alcohol-ether to give a sample of analytical purity. This

compound was found to be less soluble in most organic solvents than the amino alcohol hydrochlorides of the longer-chained amines.

9-(2-Diisobutylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A solution of 25 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 9.5 g. (2 equiv.) of diisobutylamine in acetone was refluxed for six hours. Most of the acetone was removed *in vacuo* and the diisobutylamine hydrobromide which separated out was filtered off and washed with ether. The remainder of the acetone and ether was then removed under vacuum.

The oily amino ketone was reduced in the manner described for the previous compounds. The amino carbinol hydrochloride precipitated as an oil when dry hydrogen chloride gas was passed slowly over the surface of the ether solution of the amino alcohol cooled in an ice-bath. By dissolving a small portion of the oil in ethyl acetate-alcohol and adding petroleum ether (Skellysolve B) to slight turbidity, crystals were produced when the solution was allowed to stand overnight at room temperature. The crystals were used for seeding the remainder of the oil. Eight grams (21%) of amino carbinol hydrochloride was obtained by this method. Two recrystallizations of the crude product from ethyl acetate gave a sample of analytical purity.

9-(2-Diisohexylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The general method used for the preparation of 9-(2-diisoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene was followed. The yield of crude amino alcohol hydrochloride starting with 25.0 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was 24.0 g. (65%). Four recrystallizations from acetone-ether with one charcoal treatment gave 8.4 g. of product of analytical purity. This substance is quite hygroscopic and increases in weight slightly upon standing.

9-(2-Diheptylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the diisoamyl compound was followed.

9-(2-Dinonylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the diisoamyl compound was followed. Somewhat better yields were obtained in larger runs. Thus when 101 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was condensed with 2 equivalents (179 g.) of dinonylamine and the amino ketone reduced in the usual way, using 380 cc. of 1 *M* aluminum isopropoxide in isopropanol solution, the acetone formed being distilled off through a one-meter Vigreux column, the yield of product, melting at 125–126° after two recrystallizations from ethyl acetate, was 108 g. (61%).

9-(2-Didecylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the diisoamyl compound was followed.

9-(2-Diundecylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The same general procedure as above was used, the reaction being slower.

In the condensation of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with diundecylamine, reaction took place to the extent of about 96% after twenty-four hours mechanical shaking and twenty-four hours additional standing in the refrigerator. Purification of the amino carbinol hydrochloride was rather difficult, probably due to the fact that it was contaminated with a small amount of diundecylamine hydrochloride. Three recrystallizations from acetone followed by four recrystallizations from ethyl acetate were necessary to produce an analytical sample.

Diundecylamine was obtained along with undecylamine by the reduction of decylcyanide. Four hundred six grams (500 cc.) of decylcyanide (b.p. 128–131°/10 mm.) was reduced in a pressure bomb with 15 g. of Raney nickel at 125° and an initial pressure of 1300 lbs. After the theoretical amount of hydrogen had been taken up, the reduction was stopped. The product of the reaction was distilled under vacuum. The first crude fraction boiled at 90–100°/0.8 mm. and the second fraction boiled at 190–200°/0.8 mm. Both fractions were redistilled separately. The first fraction gave 226 g. of undecylamine boiling at 94–96°/1 mm., and the second fraction gave 62.5 g. of diundecylamine boiling at 190–194°/0.8 mm. The

second fraction, a white solid, when recrystallized three times from benzene-ethanol under nitrogen gave small colorless needles melting at 51.5–52.5°.

Anal. Calc'd for $C_{22}H_{47}N$: C, 81.1; H, 14.6.

Found: C, 80.8; H, 14.6.

9-(2-Didodecylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. When 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and didodecylamine were condensed together under the conditions used with diundecylamine, condensation took place to the extent of 93%. The product of the reaction was worked up according to the method described previously. The crude amino carbinol hydrochloride was purified by four recrystallizations from ethyl acetate.

p-Methoxybenzal-n-butylamine was prepared according to the directions of Einhorn and Pfeiffer (6). A mixture of 25 g. of *n*-butylamine, 75 cc. of water, and 50.5 g. of *p*-anisaldehyde was thoroughly shaken and allowed to stand overnight at room temperature. The mixture was extracted with ether and the ether solution dried over anhydrous potassium carbonate. Evaporation of the ether gave a colorless oil which was distilled *in vacuo*, yielding 65.6 g. (92%) of a colorless oil boiling at 108–109°/1.0 mm. n_D^{25} 1.5384

Anal. Calc'd for $C_{12}H_{17}NO$: C, 75.4; H, 9.0.

Found: C, 75.5; H, 8.8.

p-Methoxybenzyl-n-butylamine was prepared by the reduction of *p*-methoxybenzalbutylamine. Four hundred fifty cubic centimeters (440 g.) was reduced in a high pressure bomb using 10 g. of Raney nickel at an initial pressure of 1200 lbs. and at a temperature of 80°. After one and one-half hours, the reaction was stopped after the calculated amount of hydrogen had been taken up. To the filtrate from the catalyst was added 500 cc. of water and 400 cc. of conc'd hydrochloric acid and the mixture was warmed on the steam-bath for two hours. The solid amine hydrochloride was filtered off and treated with alkali to liberate the free base. The free base was purified by distillation under vacuum from sodium and gave 240 g. of a colorless liquid boiling at 120–125°/0.7 mm. n_D^{25} 1.5081.

Anal. Calc'd for $C_{12}H_{19}NO$: C, 74.6; H, 9.9.

Found: C, 74.8; H, 10.1.

9-(2-p-Methoxybenzyl-n-butylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. This compound was prepared according to the general method. Thirty-five grams of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 44.6 g. of *p*-methoxybenzylbutylamine were allowed to stand together in 1000 cc. of ether for three days, after which the amine hydrobromide was filtered off and the product worked up in the usual way. The reduction of the amino ketone was complete after five hours. Upon passing gaseous hydrogen chloride over the ethereal solution of the amino carbinol, an oil separated. Hydrogen chloride gas was passed over the surface until precipitation was complete and then a stream of dry air was blown through the mixture to remove excess hydrogen chloride. The oil-ether mixture was allowed to stand overnight in the refrigerator, after which some crystals had formed. The ether layer was decanted off and the oil taken up in hot acetone and ether added to slight cloudiness. The solution was scratched vigorously in an ice-salt bath, whereupon the whole mass solidified. The yield of light tan product was 27.3 g. (52%). Three recrystallizations of the crude material from acetone-ether gave 15 g. of product melting 165–166°.

9-(2-n-Butylbenzylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The general method used for the preparation of the diisoamyl compound was followed using 50 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 54 g. of benzylbutylamine. There was obtained 40 g. (57%) of crude amino carbinol hydrochloride. One recrystallization from acetone containing 10% alcohol gave 35 g. of pure product.

9-(2-Isoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. To a solution of 25.9 g. of isoamylamine in 500 cc. of anhydrous ether was added 45 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene. The flask was allowed to stand at room temperature, with cooling, for fifteen minutes, with occasional shaking, at the end of which all of the 9-bromoacetyltetrahydrophenanthrene had gone into solution. After six hours

in the refrigerator the solution was red in color. The isoamylamine hydrobromide was filtered off and washed with a small amount of ether, the washings being added to the filtrate, yielding 23.2 g. (93%). The filtrate was treated immediately with a saturated ethereal hydrogen chloride solution and 28.5 g. of crude amino ketone hydrochloride was obtained. If the ether solution was allowed to stand before adding the ethereal hydrogen chloride solution, a yellow precipitate began to form slowly; consequently, the hydrogen chloride was added immediately. The crude amino ketone hydrochloride was stirred well with about one liter of water and filtered. The process was then repeated using 200 cc. of ether. The pure white product thus obtained was reduced in the manner described previously using 150 cc. of 1 *M* aluminum isopropoxide solution and 150 cc. of dry isopropyl alcohol. After two hours a negative acetone test was obtained and the reduction was continued for an additional hour and stopped. The reduced product was worked up as described previously. The amino alcohol hydrochloride was precipitated by the slow addition of dry gaseous hydrogen chloride. Nine and one-tenth grams of a white precipitate formed immediately. Three recrystallizations from ethyl acetate gave an analytical product.

Preparation of the above compound was attempted over the *p*-toluene sulfonamide as follows: To 300 cc. of an ether solution of 33.2 g. of isoamylamine in a 1-liter 3-necked flask fitted with a reflux condenser, mechanical stirrer and dropping-funnel, was added dropwise over the course of two hours, 34.6 g. of *p*-toluene sulfonyl chloride dissolved in 200 cc. of ether. After a short time isoamylamine hydrochloride began to precipitate out. The reaction mixture was stirred at low temperature for five hours and the amine hydrochloride filtered off. The filtrate was washed with dilute hydrochloric acid, then with water, and dried over magnesium sulfate. Upon evaporation of the ether a colorless residue (40 g.) remained; this was distilled under vacuum and gave 36 g. (82%) of a colorless liquid boiling at 178–180°/1 mm. n_D^{25} 1.5171.

Anal. Calc'd for $C_{12}H_{19}NO_2S$: C, 59.7; H, 7.9.
Found: C, 59.8; H, 7.7.

To 36 g. of isoamyl-*p*-toluenesulfonamide dissolved in 300 cc. of anhydrous benzene was added 5.8 g. of potassium. The reaction mixture was heated to reflux and stirred mechanically until complete reaction was effected. The benzene was removed *in vacuo* and the potassium salt dissolved in anhydrous ether. To a stirred ethereal solution of 25 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was added an ether solution of 23.2 g. of potassium isoamyl-*p*-toluene sulfonamide. The reaction mixture was refluxed for four hours, the potassium bromide filtered off, and the ether evaporated, leaving a thick yellow oil. The condensation product was soluble in ether and benzene, but insoluble in ethyl and methyl alcohol. Attempts at recrystallization were unsuccessful.

When the condensation product was refluxed with 25% hydrochloric acid for twenty hours, only tarry products were obtained.

A portion of condensation product was reduced in the usual way with aluminum isopropoxide and isopropyl alcohol according to the Meerwein method. The resulting product upon hydrolysis with dilute acid again gave only tarry products.

9-(2-n-Nonylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The method used for the preceding monoisoamyl compound was followed. Starting with 31.8 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and 30.1 g. of *n*-nonylamine, there was obtained 20 g. of crude amino ketone hydrochloride. This was reduced as described previously and gave 9.5 g. (22.5%) of crude amino carbinol hydrochloride. Two recrystallizations from absolute ethanol-ether gave 8.4 g. of pure product.

9-(2-n-Decylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. The procedure used for the monoisoamyl compound was followed. From 30 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene there was obtained 14.5 g. of crude amino ketone hydrochloride, which upon reduction gave 8.5 g. of crude amino carbinol hydrochloride. One recrystallization from alcohol-acetone gave 6 g. (14.5%) of pure product.

Attempted condensation of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with di-2-

ethylbutylamine and di-2-ethylhexylamine. When a solution of 10 g. of 9-α-bromoacetyl-1,2,3,4-tetrahydrophenanthrene and the theoretical amount of di-2-ethylbutylamine or di-2-ethylhexylamine in 100 cc. of ether was shaken mechanically for twenty-four hours, practically no condensation took place. Negative results were also obtained when the solution was refluxed under nitrogen for eight hours or when the reactants were refluxed under nitrogen in benzene for eight hours.

9-(2-Diamylamino-1-acetoxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A mixture of 25 g. of 9-(2-di-*n*-amylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride, 75 cc. of acetic anhydride, and 150 cc. of dry pyridine was refluxed for two hours. The solution was then allowed to stand at room temperature for forty-eight hours. The solvents were removed under reduced pressure and the residue crystallized from ethyl acetate to give 10 g. of acetoxy compound. After two additional recrystallizations from ethyl acetate, with charcoal decolorization, small colorless needles, melting at 152–154°, were obtained.

Anal. Calc'd for $C_{28}H_{42}ClNO_2$: C, 73.1; H, 9.3.
Found: C, 72.9; H, 9.3.

9-α-Bromopropionyl-1,2,3,4-tetrahydrophenanthrene. A solution of 20 g. of 9-propionyl-1,2,3,4-tetrahydrophenanthrene (m.p. 42–43°), prepared according to the directions of Bachmann and Cronyn (2), in 150 cc. of dry ether in a 500-cc. 3-necked flask fitted with mechanical stirrer, small dropping-funnel, and reflux condenser fitted with a calcium chloride tube, was heated to boiling on a steam-bath. A few drops of bromine were added and after decoloration had taken place, the flask was cooled in an ice-bath to 15° and the remainder of the bromine (13.0 g. in all) was added over the course of twenty minutes. The ether solution was washed with water, then with sodium bisulfite solution, and again with water, and dried over magnesium sulfate. After standing overnight in the ice-box, 10 g. of slightly yellow crystals precipitated from the ethereal solution and were filtered off (m.p. 77–78°). Concentration of the ethereal filtrate and cooling gave four more grams of crystalline bromo ketone. The weight of bromo ketone obtained was thus 14 g. (52.5%). Two recrystallizations from methanol gave translucent rectangular prisms melting at 77–78°.

Anal. Calc'd for $C_{17}H_{17}BrO$: C, 64.4; H, 5.4.
Found: C, 64.1; H, 5.5.

9-(2-Tetrahydroisoquinolino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. A solution of 40 g. (0.126 mole) of 9-α-bromopropionyl-1,2,3,4-tetrahydrophenanthrene in 200 cc. of dry benzene was allowed to stand with 2 equivalents (33.5 g.) of tetrahydroisoquinoline for 48 hours. Condensation took place to the extent of 85%, as determined by the amount of amine hydrobromide precipitating out. The filtrate was washed twice with water and dried over magnesium sulfate. The ethereal solution was cooled in an ice-bath, ethereal hydrogen chloride was added slowly, and the precipitate which formed was filtered off. This was washed twice with water to dissolve any tetrahydroisoquinoline hydrochloride present, and converted back to the free amino ketone by treatment with 10% sodium hydroxide solution and ether. After redrying with magnesium sulfate and evaporation of the ether, the resulting residue was reduced as described previously, using 240 cc. of aluminum isopropoxide solution. Reduction was complete in ten hours. The reduced product was worked up in the usual manner, and the amino carbinol hydrochloride precipitated by the addition of ethereal hydrogen chloride solution. After three recrystallizations from acetone-methanol-ether, with charcoal decolorization, 20 g. of pure material remained.

9-Butyryl-1,2,3,4-tetrahydrophenanthrene. The procedure of Bachmann and Cronyn (2) for 9-propionyl-1,2,3,4-tetrahydrophenanthrene was followed using 66.9 g. of 1,2,3,4-tetrahydrophenanthrene, 123 g. of anhydrous aluminum chloride, 750 cc. of carbon disulfide, 500 cc. of tetrachloroethane, and 83 g. of butyryl chloride. The tetrahydrophenanthrene was added dropwise to the stirred solution of the other reagents at −15°. Stirring was continued for one hour and the flask was allowed to stand twenty-four hours in the refrigerator. The brown complex was filtered off, washed with a small amount of carbon disulfide, al-

lowed to dry for ten minutes in the air, and hydrolyzed with ice and dilute hydrochloric acid. A light brown oil separated out, which did not solidify upon standing in the refrigerator for some time. The oil was separated off and the aqueous layer extracted twice with 250-cc. portions of ether. The oil was added to the ether extracts and the combined ether solution was dried over magnesium sulfate, the ether distilled off, and the black residue distilled under vacuum, yielding 40.1 g. (43%) of a colorless liquid which boiled at 200–205°/1.1 mm. Upon standing in the refrigerator, the liquid solidified. One recrystallization from ethanol-methanol gave needles melting at 44–45.5°. Two additional recrystallizations from the same solvent mixture gave needles melting at 46–47°.

When the reaction was carried out using nitrobenzene as a solvent, a mixture of two isomers was obtained. Small amounts of both isomers could be obtained by recrystallization. The procedure of Bachmann and Struve (1) for 9-acetyl-1,2,3,4-tetrahydrophenanthrene was followed using 75 g. of 1,2,3,4-tetrahydrophenanthrene, 45.8 g. of butyryl chloride, and 101 g. of anhydrous aluminum chloride. The nitrobenzene layer, after hydrolysis of the product with ice and dilute hydrochloric acid, was separated off and the aqueous layer extracted with benzene. The benzene extracts were added to the nitrobenzene layer and the benzene and nitrobenzene were removed by steam distillation. The residue was vacuum distilled, yielding 73.7 g. of colorless liquid, boiling at 185–195°/0.7 mm., which solidified upon standing overnight in the refrigerator. One recrystallization from methyl alcohol followed by four recrystallizations from petroleum ether (Skellysolve B) gave colorless needles melting at 140–141°. This is probably the 7-isomer.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.7; H, 8.0.
Found: C, 86.0; H, 7.8.

The methyl alcohol mother liquors obtained from the above recrystallization, upon standing for some time in the refrigerator precipitated long slender needles. One additional recrystallization from methyl alcohol gave long, colorless, slender needles melting at 46–47°. This product was identical with the product obtained by the previous method employing carbon disulfide and tetrachloroethane, inasmuch as mixed melting points of several compositions of the two showed no depression.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.7; H, 8.0.
Found: C, 85.5; H, 7.9.

9-α-Bromobutyryl-1,2,3,4-tetrahydrophenanthrene. To a solution of 15 g. of 9-butyryl-1,2,3,4-tetrahydrophenanthrene in 50 cc. of anhydrous ether in a 200-cc. 3-necked flask fitted with dropping-funnel, reflux condenser fitted with a calcium chloride tube, and mechanical stirrer, cooled to 10° in an ice-salt bath, was added the calculated amount (3.1 cc.) of bromine, dropwise. The reaction was instantaneous. The ether solution was washed with water, dried with magnesium sulfate, and the ether removed, leaving a yellow oil. One recrystallization of this oil from methanol gave 14.8 g. (75%) of crystalline material melting at 54.5–55.5°. Three additional recrystallizations from methanol gave long transparent needle-like prisms melting at 55.5–56.5°. The yield of product, based upon the weight of oil obtained after evaporation of the ether, was practically quantitative.

Anal. Calc'd for $C_{18}H_{19}BrO$: C, 65.3; H, 5.8.
Found: C, 65.3; H, 5.7.

9-(2-Diethylamino-1-hydroxybutyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride. To a solution of 10 g. of 9-α-bromobutyryl-1,2,3,4-tetrahydrophenanthrene in 50 cc. of dry benzene was added a large excess (50 cc.) of diethylamine and the resulting solution was allowed to stand, with occasional shaking, for twenty-one days. The amine hydrobromide was filtered off and washed with ether. The benzene, ether, and excess amine were distilled off from the filtrate under reduced pressure. To the residue was added 75 cc. of anhydrous ether and the small amount of diethylamine hydrobromide separating out was filtered. The ethereal filtrate was washed twice with water, dried over magnesium sulfate, and the ether distilled off, the last traces being taken off under reduced pressure. The dark oily residue was reduced in the usual manner using 45 cc. of 1 *M* aluminum isopropoxide solution and 45 cc. of dry isopropyl alcohol. A negative acetone test was obtained after

four hours. The reduced product was worked up in the usual manner and upon addition of an ethereal hydrogen chloride solution, an oil separated. Upon addition of 100 cc. of acetone to the flask containing the oil, after the ether layer had been decanted off, an immediate precipitation of a white solid occurred. After the flask had been allowed to cool for several hours in the refrigerator, the precipitate was filtered off; it weighed 4.2 g. (43%). Two recrystallizations from absolute ethanol-ether, with charcoal decolorization, gave 3 g. of colorless prisms melting at 194–196°. Three additional recrystallizations from an absolute ethanol-ethyl acetate-ether mixture gave an analytical product melting at 195.5–196.5°.

9-Isocaproyl-1,2,3,4-tetrahydrophenanthrene. The procedure described for the preparation of 9-butyryl-1,2,3,4-tetrahydrophenanthrene was followed using the appropriate quantities of reagents for 110 g. of 1,2,3,4-tetrahydrophenanthrene. The solvent was carbon disulfide-tetrachloroethane. The light brown oily product of the reaction was distilled under vacuum, yielding 85.9 g. (51%) of a colorless liquid boiling at 195–200°/0.6 mm. The oil solidified upon standing for some time in the refrigerator, after seeding with a crystal obtained by freezing a small part of the oil in a "dry-ice" bath. Two recrystallizations from ethanol-methanol (1:2) gave large colorless needles melting at 33–33.5°.

Anal. Calc'd for $C_{20}H_{24}O$: C, 85.7; H, 8.6.
Found: C, 85.7; H, 8.7.

9-α-Bromoisocaproyl-1,2,3,4-tetrahydrophenanthrene. The procedure described for the preparation of 9-α-bromobutyryl-1,2,3,4-tetrahydrophenanthrene was followed using the appropriate quantities of reagents for 49.1 g. of 9-isocaproyl-1,2,3,4-tetrahydrophenanthrene. After the addition of bromine was complete, the solution was washed with water. At this point a white precipitate began to form. After standing overnight in the refrigerator, the precipitate was filtered off. From the mother liquors additional product was obtained. Recrystallization of the total product thus obtained from methanol-absolute ethanol (2:1) gave 53.8 g. (85%) of material melting at 88–90°. Two additional recrystallizations gave long colorless needles melting at 89.5–90.5°.

Anal. Calc'd for $C_{20}H_{23}BrO$: C, 66.9; H, 6.5.
Found: C, 67.1; H, 6.5.

Reaction of 9-(α-bromoisocaproyl)-1,2,3,4-tetrahydrophenanthrene with secondary amines. A mixture of 15 g. of 9-α-bromoisocaproyl-1,2,3,4-tetrahydrophenanthrene and 61.0 g. (20 equivs.) of diethylamine in 100 cc. of benzene was allowed to stand under nitrogen for six months, at the end of which condensation was complete. The benzene and excess amine were distilled off and the amino ketone residue was reduced according to the usual Meerwein procedure. Only a faint acetone test was obtained. When the reduction product was worked up according to the method described for 9-(2-diisoamylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride, an impure amino carbinol hydrochloride was obtained. This could not be obtained in the pure state, probably because of incomplete reduction of the amino ketone, due to the steric effect of the isocaproyl group.

SUMMARY

1. A variety of new amino carbinol hydrochlorides derived from 1,2,3,4-tetrahydrophenanthrene, with the amino carbinol side chain in the 9-position, has been prepared.

2. 9-Butyryl- and 9-isocaproyl-1,2,3,4-tetrahydrophenanthrene have been prepared by the Friedel-Crafts reaction between the corresponding acid chlorides and 1,2,3,4-tetrahydrophenanthrene.

3. 9-α-Bromopropionyl-, 9-α-bromobutyryl-, and 9-α-bromoisocaproyl-1,2,3,4-tetrahydrophenanthrene have been prepared by bromination of the corresponding ketones.

4. Diundecylamine and *p*-methoxybenzylbutylamine have been prepared by catalytic reduction of decylcyanide and *p*-methoxybenzalbutylamine, respectively.

5. *p*-Methoxybenzalbutylamine has been prepared.

NEW YORK 27, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

7-METHOXY-8-ACETYL- AND 7-METHOXY-9-ACETYL-1,2,3,4-TETRAHYDROPHENANTHRENE AND AMINO CARBINOLS DERIVED FROM THEM[1]

JOHN M. GRIFFING AND ROBERT C. ELDERFIELD

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Since dialkylamino carbinols derived from 1,2,3,4-tetrahydrophenanthrene have been shown to possess distinct antimalarial activity against avian malaria, it became of importance to study the effect of nuclear substituents on this activity. The present paper records the results of an investigation of the synthesis of certain methoxytetrahydrophenanthrene derivatives which was undertaken as part of a broad general program in collaboration with the National Institute of Health.

A study of the synthesis of 7-methoxytetrahydrophenanthrene according to the methods used by Hill, Short, and Higginbottom (1) to synthesize 7-methoxy-8-methyltetrahydrophenanthrene and by Short, Stromberg, and Wiles (2) to synthesize 1-methyl-7-methoxytetrahydrophenanthrene was carried out. However, this method, utilizing in the first step the requisite naphthalene nucleus in a condensation with succinic anhydride under the conditions of a Friedel-Crafts reaction, proved to be impractical after a very thorough study carried out independently from the present work (3). Therefore, the direct introduction of substituents into the tetrahydrophenanthrene molecule has been investigated.

Previous work by Bachmann and Cronyn (4) had shown that the direct halogenation of tetrahydrophenanthrene results in the formation of the 9-halogeno derivatives, which are obviously of no use in so far as the present objective is concerned. Of possible use for the introduction of a substituent in the 7-position is the 7-aminotetrahydrophenanthrene described by Bachmann and Cronyn (4), which was obtained by Beckmann rearrangement of the oxime of 7-acetyltetrahydrophenanthrene followed by hydrolysis of the resulting acetamino derivative. However, in the Friedel-Crafts reaction between tetrahydrophenanthrene and either acetyl chloride or acetic anhydride, the 7-acetyl derivative constitutes but a minor part of the total reaction product, and its separation from the larger amount of 9-acetyl derivative, which is the major product, requires a long and tedious fractional crystallization.

No reference occurs in the literature to the direct sulfonation of tetrahydrophenanthrene, and since the sulfonic acid group can be readily converted to a variety of other groups, this approach appeared to be worthy of study. As a dialkyl naphthalene derivative, tetrahydrophenanthrene on sulfonation could be expected to lead to a series of sulfonic acids: the 6-, 7-, or 10-sulfonic acid by

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

sulfonation in one of the β-positions, or the 5-, 8-, or 9-sulfonic acid by sulfonation in one of the α-positions, depending on the temperature at which the sulfonation is carried out.

When tetrahydrophenanthrene was sulfonated under experimental conditions which would be expected to lead to the β-sulfonic acid (5), a good yield of tetrahydrophenanthrene-7-sulfonic acid (II) was obtained. The position of the sulfonic acid group was demonstrated by conversion of the sodium salt to the phenol, 7-hydroxytetrahydrophenanthrene (III) by fusion with potassium hydroxide. Methylation of III with dimethylsulfate yielded 7-methoxytetrahydrophenanthrene (IV), which was then dehydrogenated with selenium to 2-methoxyphenanthrene (V).

The low temperature sulfonation of tetrahydrophenanthrene was not successful despite the use of a number of experimental conditions in which the temperature, strength of sulfuric acid, and time of reaction was varied. Likewise the use of a variety of salts for the isolation of the reaction product led to no uniform material.

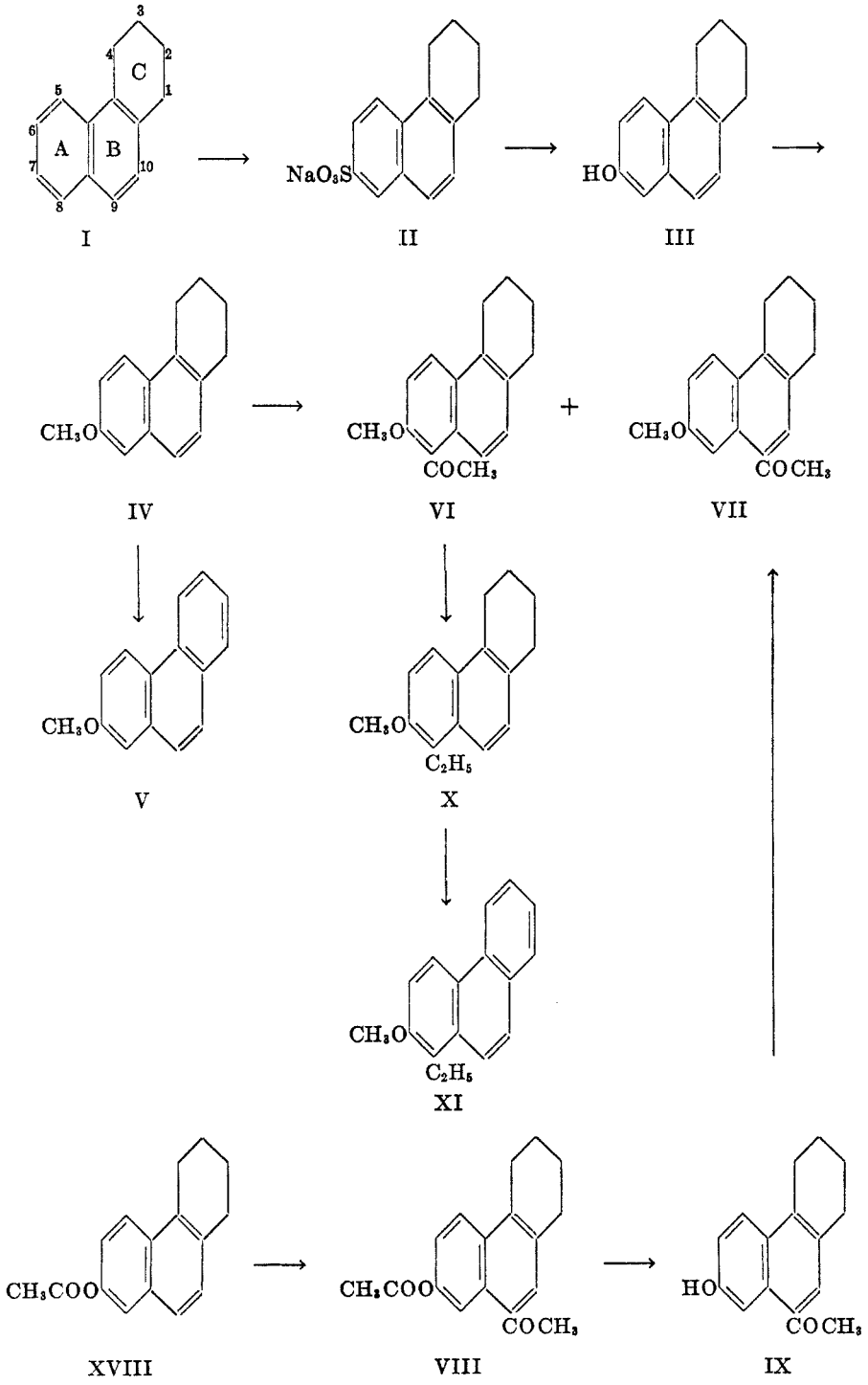
With the successful preparation of 7-hydroxy- and 7-methoxytetrahydrophenanthrene in reasonably good yield, the route to the desired final derivatives, N,N-dialkylamino carbinols of the general type shown in XXII containing nuclear substituents was open. In the present paper the synthesis of representative members of two series of such amino carbinols derived from 7-methoxytetrahydrophenanthrene is described. Other nuclear substituted amino carbinols will be described in another communication (6).

When 7-methoxytetrahydrophenanthrene is treated with either acetyl chloride or acetic anhydride under the conditions of the Friedel-Crafts reaction, a mixture of 7-methoxy-8-acetyltetrahydrophenanthrene (VI) and 7-methoxy-9-acetyltetrahydrophenanthrene (VII) results. These can be separated by fractional crystallization, although it was found more convenient to prepare both acetyl derivatives as indicated below. Changing the solvent in which the reaction was carried out and other conditions did not appear to affect markedly the proportions of isomers obtained.

For the preparation of the 9-acetyl derivative, it was found that if the Friedel-Crafts reaction is carried out on 7-acetoxytetrahydrophenanthrene, only 7-acetoxy-9-acetyltetrahydrophenanthrene (VIII) results. Hydrolysis of the acetoxy group in VIII followed by methylation of IX gives VII in good yield. Likewise, it proved to be more convenient to prepare VI by Fries rearrangement of 7-acetoxytetrahydrophenanthrene (XVIII), followed by methylation of 7-hydroxy-8-acetyltetrahydrophenanthrene (XIX).

The position of the acetyl group in VI was established by reduction of VI to oily 7-methoxy-8-ethyltetrahydrophenanthrene (X) by the Clemmensen method. X has been described as an oil by Miyasaka and Nomura (7), who prepared no solid derivatives. In order to place the ethyl group in X definitely, it was dehydrogenated to 1-ethyl-2-methoxyphenanthrene (XI). This was identical with an authentic sample.

Alternate unsuccessful methods to place the acetyl group in VI involved application of the Gattermann reaction to 7-hydroxytetrahydrophenanthrene


3
4
C
2
5
1
6
A
B
7
10
8
9
I
NaO3S
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HO
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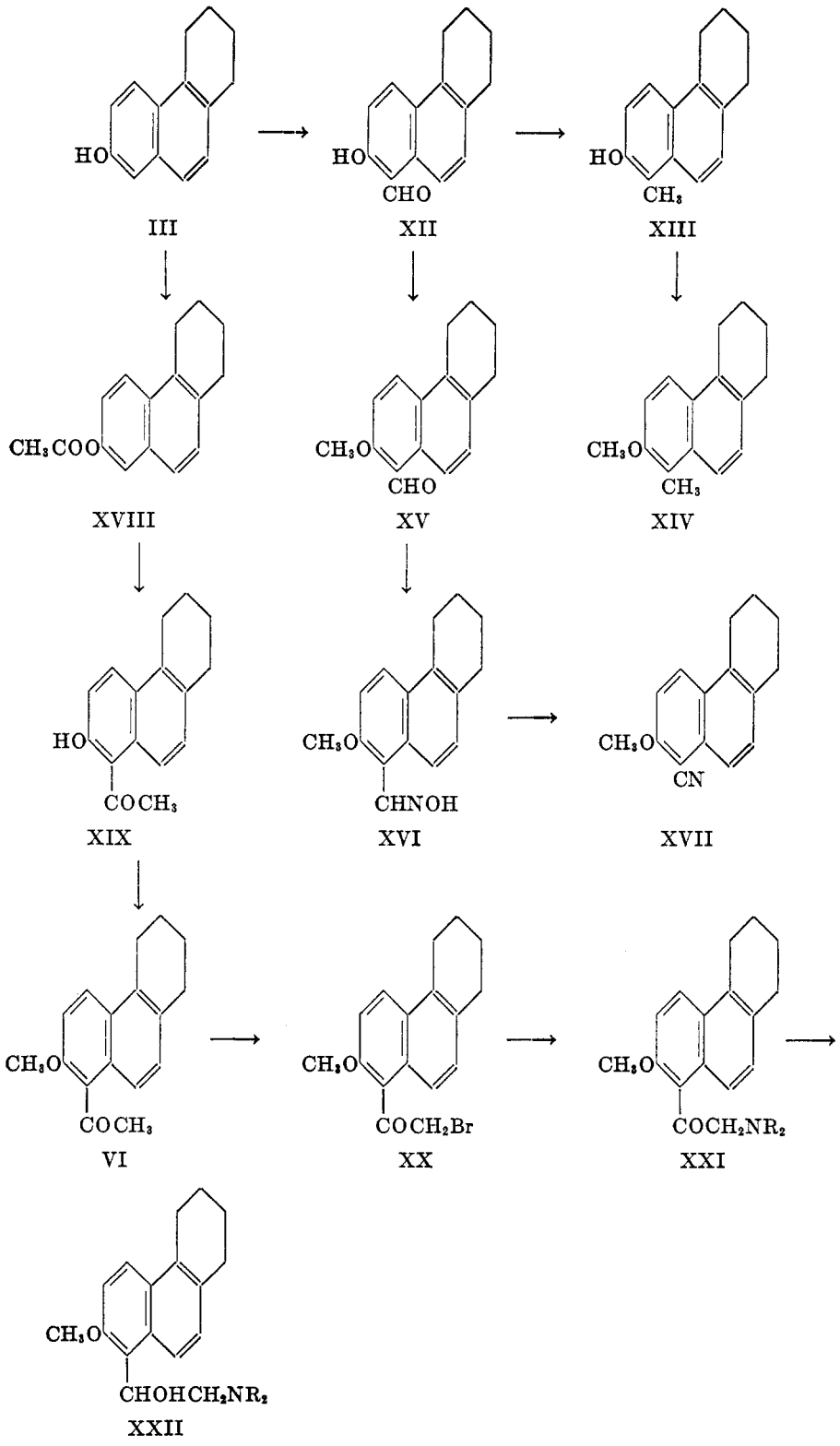
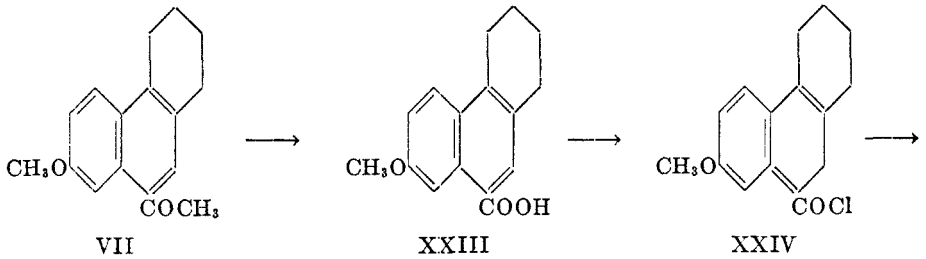
CH3O
IV
CH3O
COCH3
VI
CH3O
COCH3
VII
CH3O
V
CH3O
C2H5
X
CH3O
C2H5
XI
CH3COO
XVIII
CH3COO
COCH3
VIII
HO
COCH3
IX


HO
III
HO
CHO
XII
HO
CH3
XIII
CH3COO
XVIII
CH3O
CHO
XV
CH3O
CH3
XIV
HO
COCH3
XIX
CH3O
CHNOH
XVI
CH3O
CN
XVII
CH3O
COCH3
VI
CH3O
COCH2Br
XX
CH3O
COCH2NR2
XXI
CH3O
CHOHCH2NR2
XXII

(III). This yielded 7-hydroxytetrahydrophenanthrene-8-aldehyde (XII). That the course of the Gattermann reaction on III paralleled that with β-naphthol was shown by reduction of XII to 7-hydroxy-8-methyltetrahydrophenanthrene (XIII) and methylation of XIII to the corresponding methoxyl derivative (XIV). On dehydrogenation with selenium, XIV gave a substance agreeing in properties with the 1-methyl-2-methoxyphenanthrene described by Hill, Short, and Higginbottom (1). The plan then was to oxidize the aldehyde group in XV to carboxyl and to compare the acid obtained in this way with the acid obtained by oxidation of the acetyl group in VI. However, all attempts at oxidation of the aldehyde group in XV failed. It was possible to prepare an oxime of XV (XVI) and from this to prepare a nitrile (XVII) by the action of acetic anhydride. Again all attempts at hydrolysis of the nitrile in XVII to carboxyl failed. An attempt to oxidize the acetyl group in VI to the desired acid gave a very poor yield. In contrast, the acetyl group in VII was readily oxidized to the acid with hypochlorite solution.

The position of the acetyl group in VII has been proved by Mighton and Elderfield (8).



VII XXIII XXIV

XXV XXVI XXVII

For the synthesis of the amino carbinols, two general methods are available, both of which have been found advantageous in the present work. The more convenient and direct method (XX–XXII) was satisfactory for the preparation of amino carbinols derived from VI. This involves bromination of the acetyl derivative, condensation of the bromo ketone with an appropriate amine, and reduction of the amino ketone with aluminum isopropoxide to the carbinol.

In the series of amino carbinols derived from VII, the formation of bromomethyl ketones (XXVI) by direct bromination of VII was accompanied by a considerable amount of nuclear bromination, presumably in the 8-position. The ease of halogenation of the 8-position in 7-methoxytetrahydrophenanthrene is evidenced by the ready formation of 7-methoxy-8-chlorotetrahydrophenan-

threne by fusion with phosphorus pentachloride (6) and by the bromination of the analogous 2-propionyl-6-methoxynaphthalene (9), which yields 2-(2-bromopropionyl)-5-bromo-6-methoxynaphthalene. Therefore, XXVI was prepared by oxidation to the acid and conversion of this to the bromo ketone through the acid chloride and diazo ketone (XXIII–XXVI). The amino carbinols (XXVII) were then prepared in the same manner as those from XX.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Sodium tetrahydrophenanthrene-7-sulfonate (II). To 150 g. (0.825 mole) of 1,2,3,4-tetrahydrophenanthrene brought quickly to a temperature of 160–165°, 90 cc. of concentrated sulfuric acid (sp. gr. 1.84) was added over a period of three minutes with vigorous stirring. The mixture was heated at 160–165° for three additional minutes and then poured into 800 cc. of water. The aqueous solution was boiled with charcoal and filtered with suction. The excess sulfuric acid was neutralized with 35 g. of sodium carbonate, and the solution was then saturated with 80–100 g. of sodium chloride at the boiling point and then boiled for fifteen minutes. The suspension was cooled to 0° and the sodium sulfonate filtered. The salt was recrystallized from as small an amount of boiling water containing another 20 g. of sodium chloride as was required to dissolve the sulfonate. The product, a white flaky solid (approximately 100 g.), was obtained by cooling to 0°, filtering, and drying in an oven.

To characterize the sulfonic acid, the *p*-toluidine salt (5) was made. To 0.5 g. of the purified sodium salt, dissolved in boiling water, 0.5 g. of *p*-toluidine and 2 cc. of concentrated hydrochloric acid was added. Needles separated almost at once; m.p. with decomposition 293–295° after recrystallization from boiling water.

Anal. Calc'd for $C_{21}H_{23}NO_3S$: C, 68.3; H, 6.3.
Found: C, 68.5; H, 6.2

Potassium hydroxide fusion of sodium 1,2,3,4-tetrahydrophenanthrene-7-sulfonate: 7-hydroxytetrahydrophenanthrene (III). In a 500-cc. nickel crucible, fitted with a copper stirrer and a thermometer sheathed with copper, were placed 300 g. of potassium hydroxide and 5 cc. of water. The crucible was heated with a burner and 100 g. of dry recrystallized sodium tetrahydrophenanthrene sulfonate, well pulverized, was added with stirring, when the temperature of the molten potassium hydroxide was 220–230°. The temperature was raised quickly to 300–305° and maintained at this temperature for five minutes, after which the reaction product, while still hot, was carefully poured into a liter of ice. The aqueous solution was acidified with concentrated hydrochloric acid, cooled by adding ice, and filtered. The product was redissolved in the minimum amount of aqueous sodium hydroxide solution and the solution filtered. The phenol was reprecipitated with acetic acid, washed with water, dilute sodium bicarbonate solution, and finally with water. The yield of crude dried phenol was 85–93%. It crystallized in the form of colorless needles from carbon tetrachloride, and melted at 133–134°.

Anal. Calc'd for $C_{14}H_{14}O$: C, 84.8; H, 7.1.
Found: C, 84.7; H, 7.3.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene (IV). To a solution of 183 g. (0.93 mole) of crude dry phenol, obtained as above, in 500 cc. of water and 500 cc. of acetone containing 62 g. of 85% potassium hydroxide (0.94 mole), 89 cc. (118 g., 0.94 mole) of dimethyl sulfate was added dropwise, with vigorous stirring at room temperature. The reaction mixture was warmed to reflux for two hours after the final addition, and allowed to stand overnight at room temperature. The acetone layer was separated, and the aqueous layer was extracted with three 100-cc. portions of ether. The extracts and original acetone solution were combined, washed with water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the product was distilled *in vacuo* using a short Vigreux column

and the fraction boiling at 160–163°/0.5 mm. was collected. The yield of crystalline solid from methanol was 184.5 g. (84%). It melted at 59–60°. Cook, Hewett, and Robinson (10), who prepared this compound in an impure state from the corresponding methyl ether of the octahydrophenanthrol (unsaturated only in the ring containing the methoxyl group) by partial dehydrogenation over platinum black at 300°, report the melting point 60–61°.

Dehydrogenation of 7-methoxy-1,2,3,4-tetrahydrophenanthrene. A mixture of 2.2 g. of 7-methoxy-1,2,3,4-tetrahydrophenanthrene and 2 g. of selenium in a two-foot Pyrex tube was heated at 300° for eight hours, after which another 0.5 g. of selenium was added and the reaction continued for six more hours. There was no further evolution of hydrogen selenide, and the solidified methoxyphenanthrene was extracted with ether and filtered. Evaporation of the solvent and recrystallization of the solid residue from 95% ethanol gave 1.8 g. of product melting at 96–97°. The picrate (from ethanol) melted at 124–125°. Mixtures of varying percentage samples of 2-methoxyphenanthrene prepared from 7-methoxytetrahydrophenanthrene and 2-methoxyphenanthrene (courtesy of Dr. E. Mosettig) melted at 96–97°. Mixtures of varying percentages of the picrates melted at 124–125°.

Acetyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (VI and VII). To an ice-salt cooled, well stirred mixture of 78 g. (0.58 mole) of aluminum chloride, 1000 cc. of carbon disulfide, 700 cc. of *sym.*-tetrachlorethane, and 57 g. (0.56 mole) of dry acetic anhydride, prepared according to the method of Bachmann and Cronyn (4) by dissolving the aluminum chloride in the solvents warmed to 45° followed by cooling to 0° in an ice-salt bath, a solution of 59 g. (0.278 mole) of 7-methoxy-1,2,3,4-tetrahydrophenanthrene in 200 cc. of carbon disulfide was added dropwise. Stirring was continued for two hours after the final addition, and the reaction mixture was placed in the refrigerator for twenty-four hours. After decanting off the solvent and air drying the residue, the complex was hydrolyzed by the addition of ice and 5% hydrochloric acid. The product was extracted with three 200-cc. portions of ether; the extracts were combined, washed with water, and dried. The product was distilled *in vacuo*, the fraction boiling at 155–160°/.002 mm. being collected. The yield of a mixture of plates and needles, which separated when the distillate was crystallized from 95% ethanol, was 58 g. (82%). The mixture was separated in poor yields by fractional crystallization from 95% ethanol and gave plates and needles:

VI, m.p. of colorless plates 101.5–102.5°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.2; H, 7.2.

VII, m.p. of colorless needles 90–91°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.3; H, 7.1.

Low temperature favored the predominance of isomer (VI), while higher temperatures gave lower total yields, with isomer (VII) predominating.

7-Methoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene (VII). Owing to the difficulty of obtaining pure isomer (VII) by the above method, it was prepared by methylation of 7-hydroxy-9-acetyltetrahydrophenanthrene, which was obtained by hydrolysis of the corresponding 7-acetoxy derivative the synthesis of which will be described by Mighton and Elderfield (8). From 40 g. of the acetoxy derivative (VIII), 32.7 g. of the hydroxy derivative (IX) was obtained.

To a solution of 85 g. (0.354 mole) of 7-hydroxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 500 cc. of acetone was added a solution of 23.4 g. of 85% potassium hydroxide (0.354 mole) in 100 cc. of water. The mixture was heated to reflux and 34 cc. (45.4 g. or 0.354 mole) of dimethyl sulfate was added with stirring. Heating was continued for six hours followed by the addition of the same amounts of potassium hydroxide solution and dimethyl sulfate as before. The reaction mixture was allowed to stand at room temperature overnight. The crystalline product remaining after the removal of acetone was filtered by suction and gave 69 g. (77%) of needles melting at 90–91° after two recrystallizations from 95% ethanol. This material when mixed with varying percentages of isomer (VII) melted at 90–91°.

7-Methoxy-8-acetyl-1,2,3,4-tetrahydrophenanthrene (VI). In this case also in order to avoid the troublesome separation of isomers when the Friedel-Crafts reaction was carried out directly on IV, the rearrangement of Fries (11) was applied to 7-acetoxy-1,2,3,4-tetrahydrophenanthrene (XVIII). A solution of 50 g. (0.208 mole) of the acetoxy compound (VIII) (8) in 100 cc. of carbon disulfide was cooled in an ice-bath and 29 g. (0.216 mole) of anhydrous aluminum chloride was added slowly with stirring. The reaction mixture was refluxed for one hour on the steam-bath. The carbon disulfide was removed and the residue was heated at 120–130° for four hours. The cake was hydrolyzed with ice and 5% hydrochloric acid and the product was filtered, dissolved in aqueous sodium hydroxide, reprecipitated with hydrochloric acid, and washed. The yield of crude product was 30 g. (60%). For purification it was distilled *in vacuo* and boiled at 160–170°/0.2–0.3 mm. After recrystallization from ethanol and water, from which it separated as lustrous plates, it melted at 86.5–87.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 80.2; H, 6.9.

To a solution of 10 g. (0.04 mole) of the acetyl phenol in 100 cc. of water and 100 cc. of acetone containing 2.7 g. (0.041 mole) of 85% potassium hydroxide, 5.3 g. of dimethyl sulfate (0.042 mole) was added dropwise with stirring at room temperature, and the mixture was refluxed six hours and allowed to stand overnight. The acetone was distilled off and the product filtered after cooling. Recrystallization from ethanol using decolorizing carbon (Norit-A) gave lustrous plates melting at 101.5–102.5°. Melting points of varying percentage samples of the product and isomer (VI) obtained from the Friedel-Crafts reaction, showed no depression.

7-Methoxy-8-ethyl-1,2,3,4-tetrahydrophenanthrene (X). Fifty grams of mossy zinc in a 500-cc. flask was washed with 10% hydrochloric acid and amalgamated by shaking for five minutes with a solution of 5 g. of mercuric chloride and 10 cc. of concentrated hydrochloric acid in 100 cc. of water. A mixture of 3 g. of 7-methoxy-8-acetyl-1,2,3,4-tetrahydrophenanthrene, 100 cc. of glacial acetic acid, 100 cc. of concentrated hydrochloric acid, 100 cc. of water, and 40 cc. of toluene was added, and the mixture was refluxed for twenty-four hours. Two additional 40-cc. portions of concentrated hydrochloric acid were added after sixteen and twenty hours. The solution was cooled, the toluene layer drawn off, and the zinc washed with ether. The aqueous solution was extracted with four 200-cc. portions of ether, and the ether and toluene solutions combined and washed with 10% sodium hydroxide and then with water. After drying the combined extracts, the solvents were removed, leaving a viscous, pale yellow oil. This compound is reported an oil by Miyasaka and Nomura (7).

1-Ethyl-2-methoxyphenanthrene (XI). A mixture of the pale yellow oil obtained above and 3 g. of selenium powder was heated at 300–310° for fifteen hours in a two-foot Pyrex glass tube (fitted with a gas outlet to the hood). The cooled residue was extracted with ether, and the ether filtered. The residue, after removal of the ether, was taken up in methanol, from which 1.5 g. (54% from the acetyl-methoxy compound) of 1-ethyl-2-methoxyphenanthrene separated. It melted at 126–128°.

1-Ethyl-2-methoxyphenanthrene was synthesized according to the method of Miyasaka and Nomura (7). From 11 g. of 4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (courtesy of Dr. L. Goldman of Cooper Union), 3.5 g. of 4-keto-7-methoxy-8-acetyl-1,2,3,4-tetrahydrophenanthrene, melting at 155–157° after recrystallization from methanol (Miyasaka and Nomura report 155–157°), and 4.5 g. of free phenol from the basic extract, were obtained. Three grams of 4-keto-7-methoxy-8-acetyl-1,2,3,4-tetrahydrophenanthrene was reduced by the Clemmensen method to give the oil described by Miyasaka and Nomura. This was subjected to dehydrogenation with selenium, as they describe, and 1-ethyl-2-methoxyphenanthrene melting at 126–128° was obtained. Mixed melting points of varying percentage samples of the compound obtained as described above and 1-ethyl-2-methoxyphenanthrene were 126–128°, indicating their identity and establishing the position of the original acetyl group.

7-Hydroxyl-1,2,3,4-tetrahydrophenanthrene-8-aldehyde (*XII*). Following the procedure of Adams and Levine (12), 34.7 g. (0.175 mole) of 7-hydroxy-1,2,3,4-tetrahydrophenanthrene, 31 g. (0.265 mole) of zinc cyanide, and 4.3 g. of potassium chloride were added to 300 cc. of anhydrous ether. Dry hydrogen chloride gas was passed rapidly into the well stirred suspension for four hours, during which an oil separated out and solidified. After decanting off the ether, the residue was taken up in 150 cc. of ethanol and 50 cc. of water and refluxed for ten minutes. The light tan product was filtered off after cooling, and after purification through the bisulfite addition product and recrystallization from 95% ethanol using decolorizing carbon (Norit-A), 26.8 g. (68%) of light yellow needles melting at 116.5–117.5° was obtained.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2.
Found: C, 79.8; H, 6.2.

The oxime was prepared by refluxing a solution of 25 g. (0.11 mole) of the aldehyde and 12.5 g. (0.153 mole) of hydroxylamine sulfate in 150 cc. of dry pyridine and 500 cc. of absolute ethanol for twenty-four hours on the steam-bath. After removing the alcohol, the pyridine solution was poured into ice. The yield of colorless micro needles, melting at 221–222° was 25.2 g. (95%).

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3.
Found: C, 74.6; H, 6.2.

7-Hydroxy-8-methyl-1,2,3,4-tetrahydrophenanthrene (*XIII*). Twenty-four grams (0.106 mole) of 7-hydroxy-1,2,3,4-tetrahydrophenanthrene-8-aldehyde, 48 g. of amalgamated zinc, 83 cc. of concentrated hydrochloric acid, 40 cc. of toluene, 20 cc. of acetic acid, and 30 cc. of water was heated to reflux for thirty-four hours. The toluene layer was separated while still hot, and the aqueous layer and zinc residue were washed with two 50-cc. portions of toluene. From the combined toluene extracts 7 g. of crystalline material melting at 170–172° was obtained on cooling to 0°. From the mother liquor only unreduced starting material could be isolated. Recrystallization of the product from toluene gave glistening plates melting at 171–172°.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.9; H, 7.6.
Found: C, 85.2; H, 7.7.

7-Methoxy-8-methyl-1,2,3,4-tetrahydrophenanthrene (*XIV*). Two and one-tenth grams (0.01 mole) of 7-hydroxy-8-methyl-1,2,3,4-tetrahydrophenanthrene was added to a solution of 1 g. of 85% potassium hydroxide (0.015 mole) in 20 cc. of water and 10 cc. of acetone. To the stirred solution, 1.45 cc. (0.0153 mole) of dimethyl sulfate was added dropwise. After stirring for three hours, the solution was allowed to stand overnight at room temperature, 200 cc. of water was added, and the product filtered. From ethanol 1.5 g. (67%) of glistening scales, melting at 111–112°, was obtained. Hill, Short, and Higginbottom report the melting point 111–112°.

1-Methyl-2-methoxyphenanthrene. A mixture of 1.7 g. of 7-methoxy-8-methyl-1,2,3,4-tetrahydrophenanthrene with 2 g. of selenium was heated in a two-foot Pyrex tube for seventeen hours at 300°. The reaction mixture was thoroughly extracted with hot benzene, filtered, and the residue recrystallized from chloroform-petroleum ether, and finally from 95% ethanol, giving colorless plates melting at 160.5–161°. Hill, Short, and Higginbottom (1) report 161°. The corresponding phenol was prepared according to the method of Hill, Short, and Higginbottom. It melted at 196–197.5°. They report 196–197°.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-8-aldehyde (*XV*). Following aprocedure of Mundici (13), 1.9 g. of 7-hydroxy-1,2,3,4-tetrahydrophenanthrene-8-aldehyde was converted to the sodium salt by dissolving the compound in the necessary amount of hot ethanol and to this adding another solution containing the theoretical amount of sodium dissolved in ethanol. One and nine-tenths grams of a fine yellow precipitate formed, which was filtered and dried in an oven at 120° for fifteen minutes. To a stirred boiling suspension of 1.9 g. (0.0077 mole) of the sodium salt in 20 cc. of anhydrous toluene was added dropwise 0.9 cc. (0.0095 mole) of dimethyl sulfate, and refluxing was continued for two hours. After adding 100 cc. of water, the toluene layer was washed with 2% sodium hydroxide solution

followed by water. The residue from evaporation of the toluene crystallized from acetone and gave 1 g. (55%) of light yellow prisms melting at 142.5–143.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 79.9; H, 6.9.

All attempts to convert the methoxy aldehyde into the methoxy acid resulted only in the recovery of starting material. Likewise, a variety of conditions failed to hydrolyze the methoxy nitrile to the methoxy acid.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-8-aldehyde oxime (XVI). A solution of 10 g. (0.0415 mole) of the aldehyde and 4.9 g. (0.06 mole) of hydroxylamine sulfate in 60 cc. of dry pyridine and 200 cc. of absolute ethanol was refluxed for twenty-four hours on the steam-bath. The alcohol was removed and the pyridine solution poured into water. The yield of highly refractive needles from ethanol, melting at 198–199°, was 9.3 g. (87.5%).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.2; H, 6.7.
Found: C, 75.3; H, 6.9.

7-Methoxy-8-cyano-1,2,3,4-tetrahydrophenanthrene (XVII). A solution of 5 g. of 7-methoxytetrahydrophenanthrene-8-aldehyde oxime in 125 cc. of dry acetic anhydride was held at reflux for eight hours. The reaction mixture, after cooling, was poured into 500 cc. of cold water with stirring, and the solid material filtered. Recrystallization from 95% ethanol gave 4.1 g. (88.5%) of arborescent plates melting at 186–187°.

Anal. Calc'd for $C_{16}H_{15}NO$: C, 81.0; H, 6.4.
Found: C, 80.8; H, 6.4.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid (XXIII). Sixty-eight grams (0.96 mole) of chlorine was bubbled into a well stirred mixture of 82 g. (2.02 mole) of sodium hydroxide in 400 cc. of water and 800 g. of crushed ice. The reaction mixture tested alkaline to litmus. Fifty and eight-tenths grams (0.2 mole) of 7-methoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene and 100 cc. of purified dioxane were added. The mixture was warmed to 75°, and after a few minutes a vigorous exothermic reaction took place, requiring external cooling. The reaction was maintained at 75–80° for an additional one-half hour, followed by distillation of 300 cc. of the solution, filtration hot, decomposition of excess hypochlorite with 20 g. of sodium bisulfite in aqueous solution with stirring, and acidification with 80 cc. of concentrated hydrochloric acid. The precipitated acid was filtered after cooling and air dried. Recrystallization from ethanol yielded 48 g. (94%) of colorless needles which melted at 227–229°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.
Found: C, 75.3, 74.8; H, 6.3, 6.4.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-9-acid chloride (XXIV). A mixture of 50 cc. (83 g., 0.7 mole) of purified thionyl chloride, 70 cc. of dry, thiophene-free benzene, and 40 g. (0.156 mole) of 7-methoxy-1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid was heated to reflux for two hours with careful exclusion of moisture, followed by removal of solvent and excess thionyl chloride by distillation *in vacuo*. Another 100 cc. of dry benzene was distilled from the residue, which was then taken up in 70 cc. of hot benzene and filtered. The acid chloride crystallized in fine colorless needles, melting at 139–141°, and was used in the subsequent reaction at once to avoid hydrolysis.

To characterize the acid chloride, the *p*-toluide was made. The residue left after removing the benzene from the reaction mixture of equivalent amounts of the acid chloride and *p*-toluidine crystallized in slender colorless needles from 95% ethanol, m.p. 207–208°.

Anal. Calc'd for $C_{23}H_{23}NO_2$: C, 80.0; H, 6.7.
Found: C, 79.9; H, 6.5.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-9-diazomethyl ketone (XXV). To an ice cold, well stirred solution of diazomethane [from 30 g., (0.29 mole) of nitrosomethylurea] in 500 cc. of dry ether and 200 cc. of dry benzene, was added 20 g. (0.073 mole) of the acid chloride in small portions. After the addition was complete, the solution was allowed to come to room temperature and stirring was continued for five hours. Excess diazomethane and ether were removed *in vacuo* below 30°, and the diazo ketone crystallized from the cold

benzene in clusters of fine colorless needles, melting with decomposition at 125–126°. The diazo ketone decomposes on standing at room temperature and was therefore used at once to prepare the bromo or chloro ketones.

7-Methoxy-9-(ω-bromoacetyl)1,2,3,4-tetrahydrophenanthrene (XXVI). The benzene solution of the diazo ketone from the previous reaction was filtered and transferred to a 500-cc. three-necked flask immersed in a water bath at 15–20°. Fifteen cubic centimeters of 48% hydrobromic acid was added dropwise with stirring, and stirring was continued for one hour after the final addition. Excess hydrobromic acid was neutralized with aqueous potassium carbonate; the benzene solution was washed with water and dried over anhydrous magnesium sulfate. The benzene was concentrated to 100 cc., maintaining the temperature of the bath below 60°, and to the warm solution 100 cc. of pentane was added. The crystalline bromo ketone separated in clumps of pale yellow needles which melted at 95–96°. Yield, 15 g. (62% from the acid chloride). The chloro ketone, which is more stable, was made in the same way, using concentrated hydrochloric acid (sp. gr. 1.19) in place of hydrobromic acid. It crystallized in fine, pale yellow needles from isopropyl ether, and melted at 102–103°. Varying percentage samples of the bromo ketones prepared as above and by the method described for XX melted at 95–96°.

To characterize the bromo ketone, the benzoate was made by refluxing equivalent amounts of sodium benzoate and the bromo ketone in 50% ethanol for two hours. On cooling, a silky mass of fine needles of the benzoate crystallized and melted, after recrystallization from 95% ethanol, at 145–146°.

Anal. Calc'd for $C_{24}H_{22}O_4$: C, 77.0; H, 5.9.
Found: C, 76.7; H, 5.9.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-9-chlorohydrin. A method furnished by Dr. T. L. Jacobs (14) was followed. Twenty grams (0.069 mole) of the chloro ketone was refluxed for thirty minutes with a solution of 70.4 g. (0.345 mole) of aluminum isopropoxide in 200 cc. of dry isopropyl alcohol. The reaction mixture was then poured into a mixture of ice and 200 cc. of 1:1 hydrochloric acid with stirring, followed by dilution to 2 liters. Upon recrystallization from 95% ethanol, 18 g. (89%) of the chlorohydrin separated in clusters of micro needles, melting at 157–158°.

Anal. Calc'd for $C_{17}H_{19}ClO_2$: C, 70.2; H, 6.6.
Found: C, 69.9; H, 6.8.

7-Methoxy-9-(2-dimethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. To a well stirred solution of 6 g. (0.133 mole) of dimethylamine in 60 cc. of anhydrous ether in a flask cooled below 10° in a cold water-bath, and provided with a nitrogen inlet tube, 11 g. (0.33 mole) of (XXVI) was added slowly and the stirring was continued for three hours. The dimethylamine hydrobromide was filtered off, after bringing the temperature of the ether to −5°. The ether solution was washed with water and dried over anhydrous magnesium sulfate. After removing the solvent and excess dimethylamine *in vacuo* from the oily free base in the flask used for reduction, 60 cc. of 1 *M* aluminum isopropoxide and 50 cc. of dry isopropyl alcohol were added, and the flask was fitted with a 12-inch Vigreux column provided with a dropping-funnel for continuous addition of dry isopropyl alcohol. Distillation was continued for an hour after the distillate gave a negative test for acetone with 2,4-dinitrophenylhydrazine reagent. The isopropyl alcohol was removed and the residue treated with an excess of 10% sodium hydroxide with warming to ensure complete solution of the aluminum salts. The amino carbinol was extracted with ether after cooling, and the ether extract dried thoroughly with anhydrous magnesium sulfate. The dimethylamino carbinol hydrochloride was precipitated by adding dry ethereal hydrogen chloride to the ice cold solution, allowing the first turbidity to crystallize before adding any additional hydrogen chloride gas. Eight grams (72%) of crude amino carbinol hydrochloride precipitated and was washed with anhydrous ether. After recrystallization from ethyl acetate and acetone, 5 g. of analytically pure clusters of colorless needles was obtained, which melted at 183–184.5°.

Anal. Calc'd for $C_{19}H_{26}ClNO_2$: C, 67.9; H, 7.8.
Found: C, 67.8; H, 7.8.

7-Methoxy-9-(2-diethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. The procedure was essentially that outlined above, using an excess of diethylamine, except that stirring was continued in a stream of nitrogen for eight hours. From 2 g. of bromo ketone, 1.1 g. (50.5%) of amino carbinol hydrochloride was obtained, which crystallized from ethyl acetate in clumps of needles and melted at 180–181°.

Anal. Calc'd for $C_{21}H_{30}ClNO_2$: C, 69.3; H, 8.3.
Found: C, 69.3; H, 8.3

Attempts to synthesize the corresponding diamylamino carbinol both from the bromo ketone and the chlorohydrin (14) resulted only in the precipitation of an oil with ethereal hydrogen chloride, which did not crystallize.

7-Methoxy-8-(ω-bromoacetyl)-1,2,3,4-tetrahydrophenanthrene (*XX*). To a well stirred mixture of 4 g. (0.0156 mole) of 7-methoxy-8-acetyl-1,2,3,4-tetrahydrophenanthrene in 75 cc. of glacial acetic acid cooled to 10° in a cold water-bath, 5 drops of acetic acid saturated with hydrogen bromide at 0° was added, followed by 0.85 cc. of bromine, dropwise, while a stream of carbon dioxide gas was passed through the solution. The mixture was stirred fifteen minutes after the final addition, and then the mixture was poured over 100 g. of ice with stirring. The crude crystalline product was filtered off and recrystallized from isopropyl ether using decolorizing carbon (Norit-A) and avoiding heat as much as possible. The yield of micro prisms melting at 96.5–97.5° was 4.5 g. (86%). The bromo ketone decomposes slowly on standing at room temperature, and rapidly if heated. For this reason it was used at once in the subsequent reactions.

7-Methoxy-8-(2-dimethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. The procedure was essentially that outlined for 7-methoxy-9-(2-dimethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene, with the exception that the 8-bromo ketone is less reactive and required a longer period of standing under a nitrogen atmosphere to get an almost complete theoretical recovery of amine hydrobromide. The bromo ketone was added to excess dimethylamine in ether contained in a bottle. The air was replaced by nitrogen and the bottle stoppered and allowed to stand with occasional shaking for twelve hours. The amine hydrobromide was filtered off after cooling in ice, and the procedure outlined in detail previously followed. A 50% yield of micro needles melting at 224–225° was obtained.

Anal. Calc'd for $C_{19}H_{26}ClNO_2$: C, 67.9; H, 7.8.
Found: C, 67.9; H, 7.9.

7-Methoxy-8-(2-diethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. The procedure outlined above was followed, but condensation required forty-eight hours. A 40% yield of micro needles from acetone-ethyl acetate, melting at 177–178°, was obtained.

Anal. Calc'd for $C_{21}H_{30}ClNO_2$: C, 69.3; H, 8.3.
Found: C, 69.1; H, 8.4.

7-Methoxy-8-(2-di-n-amylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. The procedure outlined above was followed except that an equivalent amount of di-*n*-amylamine was used instead of an excess, and after decomposing the reduction product with sodium hydroxide, the alkaline solution was steam distilled to remove unreacted diamylamine, and the aqueous layer was extracted with ether to recover the amino alcohol. A 32% yield of micro needles, melting at 183–184°, was obtained after recrystallizing the product from ethyl acetate.

Anal. Calc'd. for $C_{27}H_{42}ClNO_2$: C, 72.4; H, 9.4.
Found: C, 72.2; H, 9.5.

The microanalyses here reported were done by the Misses Frances E. Marx and Lois E. May.

SUMMARY

1. 7-Methoxy-1,2,3,4-tetrahydrophenanthrene has been prepared from tetrahydrophenanthrene-7-sulfonic acid.

2. Since acetylation of 7-methoxy-1,2,3,4-tetrahydrophenanthrene by the Friedel-Crafts method leads to a difficultly separable mixture of the 8- and 9-acetyl derivatives, alternate syntheses of the two latter compounds are described.

3. The synthesis of representative 7-methoxy-1,2,3,4-tetrahydrophenanthrene-8- and 9-N,N-dialkylamino carbinols is described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

7-CHLORO- AND 7-METHOXY-8-CHLORO-1,2,3,4-TETRAHYDRO-PHENANTHRENE AND AMINO CARBINOLS DERIVED FROM THEM[1]

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In other communications (1, 2) the synthesis of N,N-dialkylamino carbinols derived from 7-hydroxy- and 7-methoxy-1,2,3,4-tetrahydrophenanthrene as well as the synthesis of the parent nuclear substituted tetrahydrophenanthrenes is described. In the present paper, we wish to present the results of further study of the preparation and reactions of other nuclear substituted tetrahydrophenanthrene derivatives. The work forms part of a broad general program dealing with tetrahydrophenanthrene derivatives as antimalarials.

For the introduction of nuclear substituents into the 7-position of tetrahydrophenanthrene, the 7-hydroxy derivative (I) described by Griffing and Elderfield (2) provides perhaps the most convenient starting point. By use of the Bucherer reaction, this was readily converted into 7-aminotetrahydrophenanthrene (II). The latter compound was obtained as a solid. Bachmann and Cronyn (3) describe 7-aminotetrahydrophenanthrene, obtained by Beckmann rearrangement of a mixture of the oximes of 7- and 9-acetyltetrahydrophenanthrene and fractional crystallization of the resulting acetylamines, as an oil.

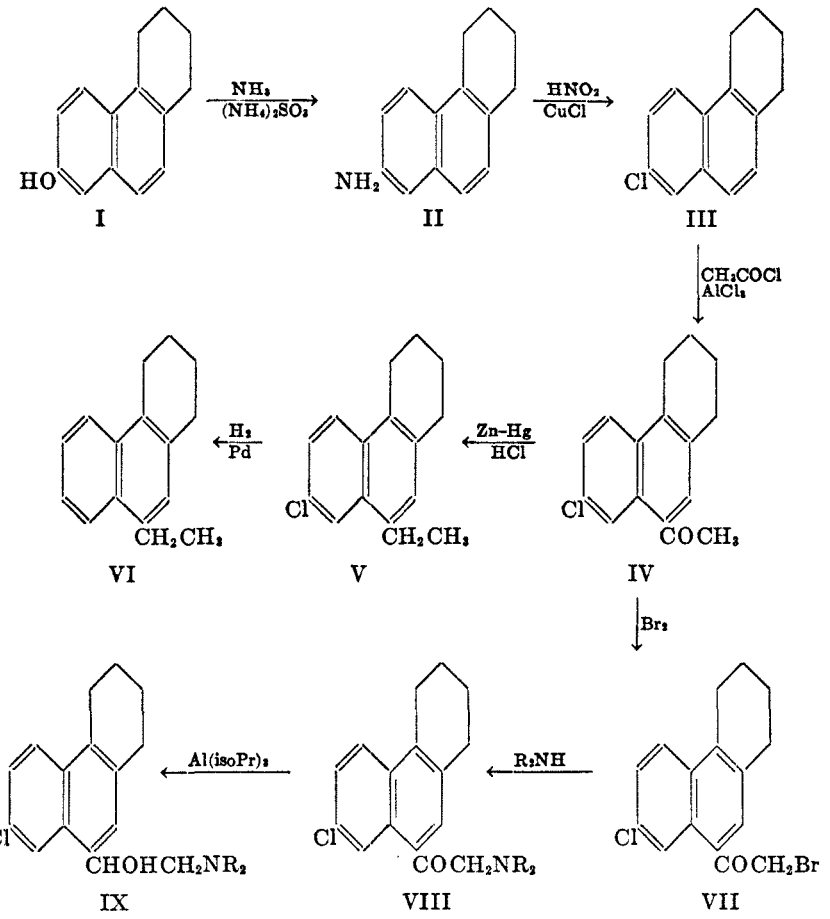
Diazotization of II and reaction of the diazonium salt with cuprous chloride according to a modification of the Sandmeyer method worked out in these laboratories for application to phenanthrene derivatives (4) resulted in a good yield of 7-chlorotetrahydrophenanthrene (III). By the Friedel-Crafts reaction between III and acetyl chloride, 7-chloro-9-acetyltetrahydrophenanthrene (IV) was prepared. The position occupied by the acetyl group in IV was shown by reduction of IV to 7-chloro-9-ethyltetrahydrophenanthrene (V) by the Clemmensen method, followed by removal of the chlorine in V by hydrogen and palladium on calcium carbonate to yield the known 9-ethyltetrahydrophenanthrene (VI) (5).

From IV by established methods shown in VII–IX, representative 7-chlorotetrahydrophenanthrene-N,N-dialkylamino carbinols were prepared (IX–XII).

A second series of nuclear substituted tetrahydrophenanthrenes investigated was that derived from 7-methoxy-8-chlorotetrahydrophenanthrene (XIV). This substance is readily prepared by a reaction applied to 2-methoxynaphthalene by Autenrieth and Mühlinghaus (6) and involves fusing 7-methoxytetrahydrophenanthrene (XIII) with phosphorus pentachloride. Although the position assigned to the chlorine in XIV can be argued by analogy to the naphtha-

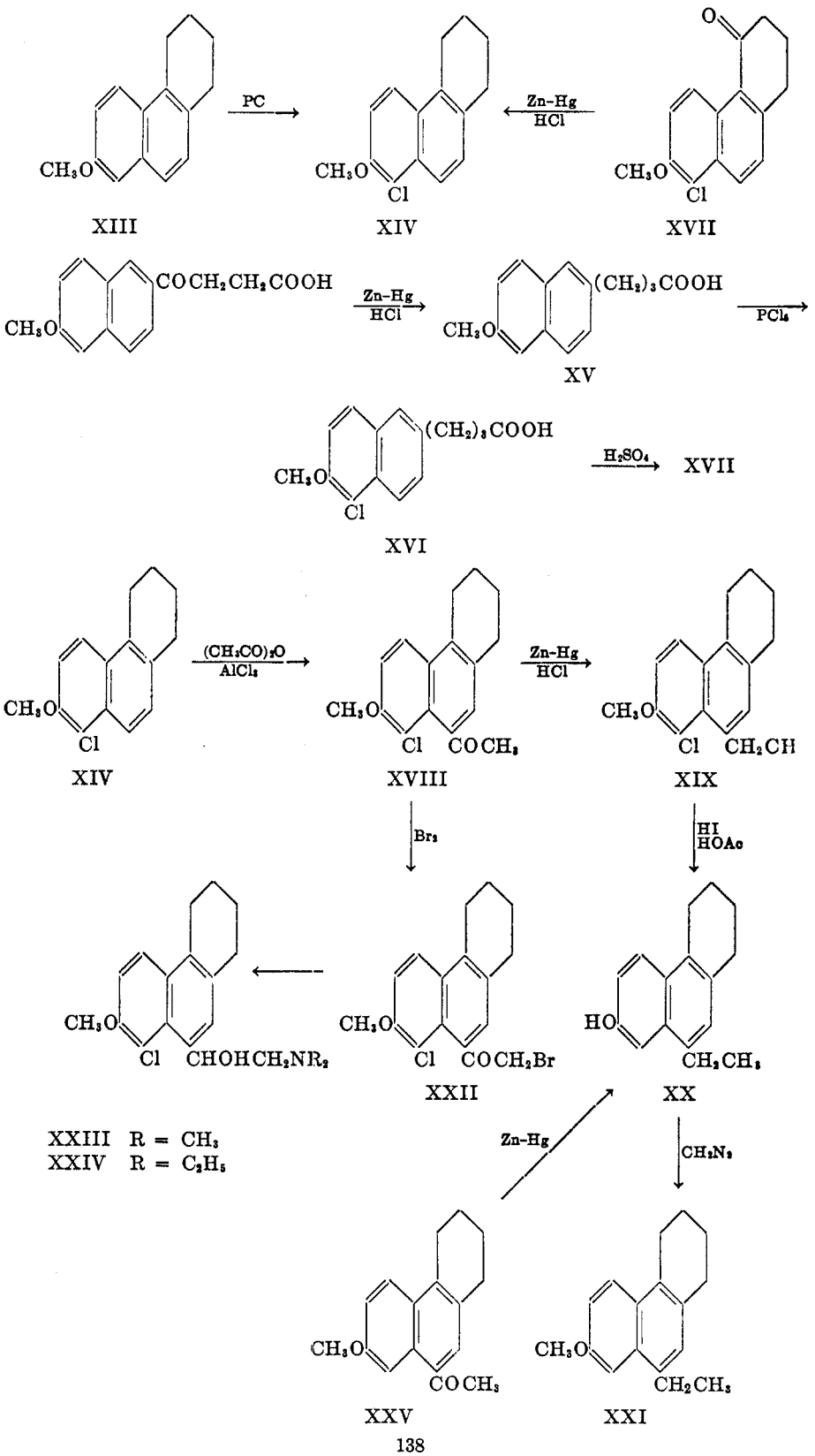
[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

lene derivative described by Autenrieth and Mühlinghaus, it was possible to confirm this by an independent synthesis of XIV. Robinson and Thompson (7) have described the synthesis of γ-(5-chloro-6-methoxy-2-naphthyl)butyric



IX R = CH_3
X R = C_2H_5
XI R = n-C_5H_{11}
XII R = n-C_6H_{13}

acid (XVI) in which the positions of the chlorine and methoxyl group are established. The same workers have also described 4-keto-7-methoxy-8-chlorotetrahydrophenanthrene (XVII). By application of the phosphorus pentachloride reaction to γ-(6-methoxy-2-naphthyl)butyric acid (XV), XVI was obtained which agreed in properties with the compound described by Robinson and Thompson. Ring closure of XVI with sulfuric acid gave XVII, again agreeing in properties with the material described by Robinson and Thompson. Clemmensen reduction of XVII gave XIV, which was identical with the substance prepared directly from 7-methoxytetrahydrophenanthrene.


PC
Zn-Hg
HCl
XIII
XIV
XVII
Zn-Hg
HCl
PCl5
XV
H2SO4
XVII
XVI
(CH3CO)2O
AlCl3
Zn-Hg
HCl
XIV
XVIII
XIX
Br2
HI
HOAc
XXII
XX
XXIII R = CH3
XXIV R = C2H5
Zn-Hg
CH2N2
XXV
XXI

Acetylation of XIV by the Friedel-Crafts method led to an excellent yield of 7-methoxy-8-chloro-9-acetyltetrahydrophenanthrene (XVIII). The position of the acetyl group in XVIII was shown by reduction of the acetyl group to ethyl followed by simultaneous cleavage of the ether and reduction with hydriodic acid to give the previously known 7-hydroxy-9-ethyltetrahydrophenanthrene (XX) (1). From XVIII representative dialkylamino carbinols (XXIII and XXIV) were prepared by the same general method shown in IV–IX.

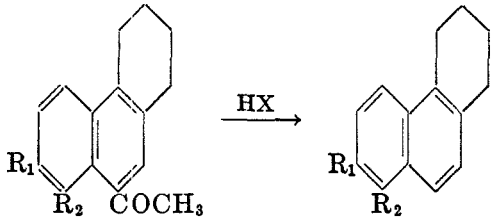
The experience of Robinson and Willenz (8) on the action of halogen acids on 8-chloro-3′-keto-4-acetoxy-7-methoxy-1,2-cyclopentenophenanthrene prompted us to study the action of such acids on XIV and XVIII in order to see whether the reactions described by the English workers are characteristic of the phenanthrene system or whether they are also applicable to a naphthalene nucleus (tetrahydrophenanthrene can best be regarded as a 1,2-dialkylnaphthalene rather than as a true phenanthrene). In summary, Robinson and Willenz noted that when their 7-methoxy-8-chlorophenanthrene derivative was boiled with hydriodic acid, reductive removal of the chlorine occurred in addition to cleavage of the ether; on the other hand, hydrobromic acid merely cleaved the ether and left the chlorine intact.

In the naphthalene series as indicated by the present experiments, the conclusions of Robinson and Willenz were substantiated in the case of the hydriodic acid reaction. In addition, some interesting observations on the hydrolytic fission of tetrahydrophenanthrene ketones by acids were made. Reaction of 7-methoxy-8-chloro-9-ethyltetrahydrophenanthrene (XIX) with hydriodic acid, as shown above, led to removal of the chlorine as well as cleavage of the ether. When XVIII was refluxed with hydriodic acid, the ether was cleaved and both the chlorine and acetyl groups were removed with the formation of 7-hydroxytetrahydrophenanthrene (I) as the product of the reaction. When the reaction was applied to 7-methoxy-9-acetyltetrahydrophenanthrene (XXV) and to 9-acetyltetrahydrophenanthrene (XXVI) the acetyl group was removed in both cases, leading to 7-hydroxytetrahydrophenanthrene (I) and tetrahydrophenanthrene (XXVII), respectively.

In the reaction of 7-methoxy-8-chloro-9-ethyltetrahydrophenanthrene (XIX) with hydrobromic acid in acetic acid, our results do not parallel strictly those of Robinson and Willenz on the removal of chlorine from the nucleus. Thus, when XIX was treated with hydrobromic acid, removal of the chlorine occurred to a certain extent as evidenced by the isolation of a small amount of XX from the reaction products. On the other hand, when XVIII and XIV were treated with hydrobromic acid, 7-hydroxy-8-chlorotetrahydrophenanthrene (XXVIII) was obtained. Reaction of 9-acetyltetrahydrophenanthrene (XXVI) with hydrobromic acid, like the reaction with hydriodic acid, caused cleavage of the ketone, and gave tetrahydrophenanthrene (XXVII).

Our experiences on the behavior of 1,2-dialkylnaphthalene derivatives in so far as tetrahydrophenanthrene derivatives may be taken as representative may be summarized as follows: In the case of 5-chloro-6-methoxy-1,2-dialkylnaphthalenes, treatment with hydriodic acid results in complete reductive re-

moval of the chlorine in addition to cleavage of the ether; treatment with hydrobromic acid may result in partial removal of the chlorine in addition to cleavage of the ether. Both hydrobromic and hydriodic acids cause hydrolytic fission of an acetyl group in the 4-position of the 1,2-dialkylnaphthalene.



Hydriodic Acid

XVIII $R_1 = OCH_3$; $R_2 = Cl \longrightarrow I$ $R_1 = OH$; $R_2 = H$
XXV $R_1 = OCH_3$; $R_2 = H \longrightarrow I$ $R_1 = OH$; $R_2 = H$
XXVI R_1 and $R_2 = H \longrightarrow$ XXVII R_1 and $R_2 = H$

Hydrobromic Acid

XVIII $R_1 = OCH_3$; $R_2 = Cl \longrightarrow$ XXVIII $R_1 = OH$; $R_2 = Cl$
XXVI R_1 and $R_2 = H \longrightarrow$ XXVII R_1 and $R_2 = H$

Hill and Short (11), in their study of the hydrolytic fission of aromatic ketones in the desoxybenzoin series with hydrobromic acid, concluded that fission occurs only when the aromatic nucleus possesses a hydroxyl or methoxyl group. They suggested that the influence of the hydroxyl (or methoxyl) group may be caused by the electromeric shift of electrons to the carbon which is the point of attachment of the acetyl group to the ring, effecting the acceptance of a proton by that carbon. Apparently, the electron density around the 9-carbon in tetrahydrophenanthrene is high enough to permit cleavage of unsubstituted 9-acetyltetrahydrophenanthrene without further activation by a hydroxyl or a methoxyl group. The high electron density is attested to by the reactivity of the 9-position in tetrahydrophenanthrene in bromination and Friedel-Crafts reactions (1, 2, 3, 5) and by the similarly high reactivity of the analogous 4-position in 1,2-dimethylnaphthalene (12, 13) and in 1-methylnaphthalene (14). Further investigation of the scope of this reaction is planned.

A pronounced steric hindrance of the 8-chlorine and of the 9-acetyl group in XVIII is indicated by the nonreactivity of the two groups toward reagents with which they would normally be expected to react. Thus catalytic removal of the chlorine with hydrogen over a palladium on calcium carbonate catalyst, a reaction which proceeded quantitatively with V, failed completely with XVIII. The presence of the methoxyl group in the ortho position undoubtedly caused this failure, since Robinson and Willenz (8) experienced the same difficulty in their 7-methoxy-8-chlorophenanthrene derivative in which the 9-position is unoccupied. The resistance of 7-methoxytetrahydrophenanthrene-8-aldehyde to oxidation (2) can be attributed to the same effect. Likewise, the acetyl group in XVIII was resistant to the action of hydroxylamine and to oxidation with

sodium hypochlorite. That this non-reactivity of the acetyl group may be attributed to the chlorine is evidenced by the successful outcome of the two latter reactions with the analogous chlorine-free compound (XXV) (2).

The microanalyses reported in this paper were performed by Miss Frances E. Marx and Miss Lois E. May of these laboratories.

EXPERIMENTAL

All melting points are corrected for stem exposure.

7-Amino-1,2,3,4-tetrahydrophenanthrene (II). A mixture of 280 g. (1.4 moles) of finely ground crude 7-hydroxy-1,2,3,4-tetrahydrophenanthrene (2) and 700 cc. of aqueous ammonia (sp. gr. 0.9) containing 150 g. of sulfur dioxide was heated with stirring at 150–155° for thirty hours in a one-gallon mechanically stirred high pressure autoclave (Will Corporation, Cat. No. 1734). After cooling, the contents of the autoclave were washed out with water. The main product was a heavy mass of tar. This was added to a small amount of material which was filtered from the water washings of the autoclave, and the combined product was dissolved in a mixture of 600 cc. of alcohol and 300 cc. of concentrated hydrochloric acid. The mixture was digested until uniform and then decanted from a small amount of tarry material into 2.5 l. of water. The tan solid which separated was filtered off and suspended in 600 cc. of 3 *N* sodium hydroxide solution and extracted with three 500-cc. portions of ether. A small amount of 7-hydroxy-1,2,3,4-tetrahydrophenanthrene was recovered on acidification of the water layer. The ether layer was dried with magnesium sulfate and the amine hydrochloride was precipitated by passing hydrogen chloride gas over the surface of the stirred ethereal solution until no further precipitate separated. There was thus obtained 163–174 g. of light pink product which melted at 289–291° dec. The yield was 50–53% based on crude 7-hydroxy-1,2,3,4-tetrahydrophenanthrene. The hydrochloride was recrystallized from ethanol, from which it separated as colorless needles which melted at 290–292° dec.

Anal. Calc'd for $C_{14}H_{16}ClN$: C, 71.9; H, 6.9.
Found: C, 71.8; H, 7.1.

The free base was liberated by treating a sample of the hydrochloride with 1 *N* sodium hydroxide and extracting with ether. The ether was dried over magnesium sulfate and then evaporated to dryness. The residue was crystallized from petroleum ether (Skellysolve B), from which it separated as prisms melting at 76.5–77.5°.

Anal. Calc'd for $C_{14}H_{15}N$: C, 85.2; H, 7.7.
Found: C, 85.3; H, 7.7.

Bachmann and Cronyn (3) report that 7-amino-1,2,3,4-tetrahydrophenanthrene is an oil and that its hydrochloride melts at 238–239°. Unfortunately, we had none of their compound for comparison.

7-Chloro-1,2,3,4-tetrahydrophenanthrene (III). To a suspension of 98 g. (0.42 mole) of 7-amino-1,2,3,4-tetrahydrophenanthrene hydrochloride in 1600 cc. of glacial acetic acid and 650 cc. of concentrated hydrochloric acid cooled to −2° in an ice-salt bath, was added a solution of 49 g. (0.7 mole) of sodium nitrite in 70 cc. of water, over a period of an hour. During this time the reaction mixture darkened to a red-brown color. After the addition of the nitrite, stirring was continued for two hours, at −2 to −5°. A solution of 36 g. (0.6 mole) of urea in 100 cc. of water was then added over a period of thirty minutes. After continued stirring for two and one-half hours, the solution gave a negative starch-iodide test for nitrous acid.

Meanwhile a solution of cuprous chloride was prepared by adding a hot solution of 84 g. (0.8 mole) of sodium bisulfite and 56 g. (1.4 moles) of sodium hydroxide in 550 cc. of water to a hot solution of 385 g. (1.5 moles) of cupric sulfate ($CuSO_4 \cdot 5H_2O$) and 100 g. (1.7 moles) of sodium chloride in 1100 cc. of hot water with stirring. After cooling, the cuprous chloride was filtered off and dissolved in 650 cc. of concentrated hydrochloric acid.

The diazonium solution at 0° was rapidly poured into the cuprous chloride solution at −2°. Some solid separated and the temperature rose to 4°. The green-black solution was stirred for three hours at room temperature and then for one hour at 70°. After cooling overnight in the refrigerator, the aqueous solution was decanted from the solid on the bottom and sides of the flask. The aqueous layer was extracted with benzene twice, and the crude solid product was then dissolved in the benzene extracts. The benzene solution was concentrated under reduced pressure and the residue was distilled at 147–149°/0.4 mm. The yield was 61 g. (67%) of material which melted at 51–52°. Recrystallization from ethanol gave transparent, irregular plates which melted at 53–53.5°.

Anal. Calc'd for $C_{14}H_{13}Cl$: C, 77.6; H, 6.1.
Found: C, 77.4; H, 6.1.

7-Chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene (IV). The general method of Bachmann and Cronyn (3) was used. To a suspension of 64 g. (0.48 mole) of anhydrous aluminum chloride in 600 cc. of pure carbon disulfide was added 30 g. (0.38 mole) of acetyl chloride and the mixture was stirred for fifteen minutes. After the addition of 400 cc. of tetrachloroethane, the solution was stirred for another fifteen minutes and then warmed to 45° for a few minutes. A solution of 43.5 g. (0.2 mole) of 7-chloro-1,2,3,4-tetrahydrophenanthrene in 60 cc. of carbon disulfide was added to the solution at 10°. Hydrogen chloride was evolved, and a precipitate separated from the deep green solution. After stirring for thirty minutes longer at room temperature, the mixture was placed in the refrigerator for twenty hours. The yellow complex was filtered off, washed with carbon disulfide, and spread out on filter paper to dry for an hour. It was decomposed by adding it in portions to 5% hydrochloric acid and crushed ice. The tan solid which separated was recrystallized from ethanol with charcoal (Norit-A) decolorization. The yield was 39 g. of 7-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene which melted at 86.5–88°. Concentration of the ethanol solution gave 5 g. more, or 44 g. in all (85%). Recrystallization from ethanol gave colorless needles melting at 88–89°.

Anal. Calc'd for $C_{16}H_{15}ClO$: C, 74.3; H, 5.8.
Found: C, 74.6; H, 6.0.

7-Chloro-9-ethyl-1,2,3,4-tetrahydrophenanthrene (V). A mixture of 7 g. of 7-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 30 g. of amalgamated zinc, 60 cc. of glacial acetic acid, 60 cc. of concentrated hydrochloric acid, and 30 cc. of toluene was refluxed for twenty-four hours, an additional 45 cc. of concentrated hydrochloric acid being added in portions over this period. After cooling, the toluene was separated; the zinc and then the aqueous layer were extracted with ether and the organic solvents were combined. The solution was washed with water, dried with magnesium sulfate and concentrated to dryness. The residue was sublimed at 180° at 0.2 mm. and 5 g., or 76% yield was obtained. Recrystallization from alcohol-acetone gave elongated prisms melting at 37–37.5°.

Anal. Calc'd for $C_{16}H_{17}Cl$: C, 78.5; H, 7.0.
Found: C, 78.7; H, 6.9.

9-Ethyl-1,2,3,4-tetrahydrophenanthrene (VI). A solution of 1.5 g. of 7-chloro-9-ethyl-1,2,3,4-tetrahydrophenanthrene in 60 cc. of absolute alcohol containing 1.0 g. of potassium hydroxide was shaken with hydrogen in the presence of a palladium on calcium carbonate catalyst (9). The theoretical volume of hydrogen was taken up within twenty minutes. The alcohol was removed under reduced pressure and the residual oil was distilled at 200° and 0.2 mm. in a molecular still. The crude distillate crystallized on cooling in the refrigerator overnight and melted at 21–23°. The picrate crystallized from ethanol as bright orange needles melting at 125.5–126.5°.

9-Ethyl-1,2,3,4-tetrahydrophenanthrene was prepared by Clemmensen reduction of 9-acetyl-1,2,3,4-tetrahydrophenanthrene according to Bachmann and Struve (5). It melted at 21–23° and the picrate prepared from it melted at 125–126°. Mixed melting point determinations with mixtures of varying compositions of samples of the hydrocarbon and its picrate prepared by the two procedures showed no depression.

7-Chloro-9-(ω-bromoacetyl)-1,2,3,4-tetrahydrophenanthrene (VII). To a solution of 26

g. (0.1 mole) of 7-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene in one liter of anhydrous ether was added dropwise with constant stirring 5.14 cc. (16 g. or 0.1 mole) of bromine. The first few drops were added very slowly to the solution at room temperature. After the color had disappeared, the remainder of the bromine was added more rapidly to the ethereal solution cooled in an ice-water bath. When the reaction was complete, the mixture was chilled and 22 g. of bromo ketone was filtered off. Concentration of the ether solution to 100 cc. gave an additional 7 g., or a total of 29 g. (86%). Recrystallization from absolute alcohol with charcoal (Norit-A) treatment gave long, colorless needles which melted at 124–125°.

Anal. Calc'd for $C_{16}H_{14}BrClO$: C, 56.9; H, 4.2.
Found: C, 56.9; H, 4.4.

7-Chloro-9-(2-dimethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (IX). A solution of 6.8 g. (0.02 mole) of (VII) in 140 cc. of benzene was added slowly with stirring to a solution of 2.7 g. (0.06 mole) of dimethylamine in 30 cc. of ether. The mixture was shaken by hand for fifteen minutes and was then allowed to stand for forty-eight hours. The mixture was cooled and the dimethylamine hydrobromide which separated was filtered off. The solvent was evaporated from the filtrate under reduced pressure, and the residual oil was taken up in ether and washed twice with water. After drying the ether with magnesium sulfate, the solvent was removed under reduced pressure and the residue was reduced with 45 cc. of a hot molar solution of aluminum isopropoxide in anhydrous isopropyl alcohol. The reduction was run in a flask equipped with a 10-inch Vigreux column, and at the start the mixture was heated so that a fairly rapid distillation ensued for about fifteen minutes. The distillation was then slowed down and continued until a negative 2,4-dinitrophenylhydrazine test for acetone in the distillate was obtained. The result of the test was regarded as negative only when the first few drops of distillate after refluxing without distillation for fifteen minutes failed to give a cloudy solution with 2,4-dinitrophenylhydrazine test solution. The reaction mixture was then concentrated *in vacuo* to a paste. Excess 10% sodium hydroxide solution was added and the mixture was heated with stirring on the steam-bath until all the aluminum salts were in solution. After cooling, the amino carbinol was extracted with ether and the ether solution was dried over magnesium sulfate. The amino carbinol was precipitated as the hydrochloride by cautiously adding a dilute solution of dry hydrogen chloride in ether to the ice cold ethereal solution to slight turbidity. Three and five-tenths grams (52%) of crystalline product separated on cooling in the refrigerator overnight. Upon recrystallization from acetone-methanol-ether, it formed colorless plates which melted at 224–225°.

Anal. Calc'd for $C_{18}H_{23}Cl_2NO$: C, 63.5; H, 6.8.
Found: C, 63.3; H, 6.8.

7-Chloro-9-(2-diethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (X). Reaction of 6.8 g. (0.02 mole) of VII with 4.4 g. (0.06 mole) of diethylamine in the manner described above gave 3.5 g. (48%) of amino carbinol hydrochloride. Recrystallization from acetone-ether gave colorless rectangular plates which sintered at 168° and melted at 170–171°

Anal. Calc'd for $C_{20}H_{27}Cl_2NO$: C, 65.2; H, 7.4.
Found: C, 65.3; H, 7.2.

7-Chloro-9-(2-di-n-amylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (XI) SN-12,853).[2] Six and eight-tenths grams (.02 mole) of VII and 6.3 g. (.04 mole) of di-*n*-amylamine were combined in the manner described above up to the final precipitation of the amino carbinol hydrochloride. Ethereal hydrogen chloride was carefully added to the ether solution of the amino carbinol until precipitation of unreacted diamylamine was complete, as indicated by no further formation of an immediate precipitate on addition of

[2] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

fresh hydrogen chloride. The diamylamine hydrochloride was filtered and ethereal hydrogen chloride was added to the filtrate which now became turbid and only slowly deposited crystals on the walls of the flask. After cooling in the refrigerator overnight, 3.6 g. (40%) of crystalline product was obtained. Recrystallization from ethyl acetate gave needles melting at 155–156°.

Anal. Calc'd for $C_{26}H_{19}Cl_2NO$: C, 69.0; H, 8.7.
Found: C, 68.7; H, 8.5.

7-Chloro-9-(2-dihexylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (XII). Reaction of 6.8 g. (0.02 mole) of VII with 7.5 g. (0.04 mole) of dihexylamine in the manner described for the dimethylamine condensation produced 4.9 g. (51%) of amino carbinol hydrochloride. Colorless needles, melting at 143–144°, were obtained by recrystallization from acetone-ether.

Anal. Calc'd for $C_{28}H_{43}Cl_2NO$: C, 70.0; H, 9.0.
Found: C, 70.2; H, 9.0.

7-Methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene (XIV). To a stirred melt of 48 g. (0.23 mole) of 7-methoxy-1,2,3,4-tetrahydrophenanthrene heated in an oil-bath to 80° was added 48 g. (0.23 mole) of finely powdered phosphorus pentachloride in small quantities. The temperature of the oil-bath was raised slowly to 135° to prevent solidification of the reaction mixture. After all the phosphorus pentachloride had been added, heating at 135° with stirring was continued for thirty minutes, after which time the initially copious evolution of hydrogen chloride gas had subsided. The reaction mixture was cooled somewhat and cold water was added slowly. A vigorous reaction ensued with hydrogen chloride evolution, and a greenish-white solid separated. The solid was broken up into lumps, filtered, and finally crushed in a mortar. After washing with water, the crude product was dried in a desiccator overnight. The product was recrystallized from 700 cc. of absolute alcohol, giving 46 g. or 80% of material which melted at 124–125.5°. Recrystallization from absolute alcohol gave colorless prisms melting at 126–126.5°.

Anal. Calc'd for $C_{15}H_{15}ClO$: C, 73.0; H, 6.1.
Found: C, 73.3; H, 6.2.

γ-(6-Methoxy-2-naphthyl)butyric acid (XV). This reduction was run by the method of Sherman, Goldman, and Clayton (10). A mixture of 18 g. (0.07 mole) of β-(6-methoxy-2-naphthoyl)propionic acid (kindly furnished us by Dr. C. S. Sherman), 50 g. of amalgamated zinc, 3 cc. of acetic acid, 100 cc. of concentrated hydrochloric acid, and 90 cc. of toluene was refluxed for twenty-four hours, an additional 60 cc. of hydrochloric acid being added in portions over this period. After decantation, the zinc and aqueous layer were washed with toluene, and the combined toluene solution was washed with water and then with one 100-cc. portion and three 50-cc. portions of 1 *N* sodium hydroxide solution containing some sodium hydrosulfite. The sodium hydroxide solution was heated to 80° and 5 cc. of dimethyl sulfate was added dropwise with stirring. After allowing it to stand overnight, the solution was acidified with dilute hydrochloric acid, and the precipitate was filtered off. The gummy solid was taken up in hot benzene, concentrated and distilled under vacuum. Eight grams of solid (47%) boiling at 175–178°/0.3 mm. was obtained. After recrystallization from acetone-petroleum ether, the product melted at 134–135° (10).

γ-(5-Chloro-6-methoxy-2-naphthyl)butyric acid (XVI). An intimate mixture of 1.2 g. (0.005 mole) of γ-(6-methoxy-2-naphthyl)butyric acid and 2.1 g. (0.01 mole) of phosphorus pentachloride was warmed on the steam-bath. A vigorous reaction started almost immediately, with evolution of hydrogen chloride gas. After ten minutes, the reaction mixture was cooled somewhat, and decomposed with water. The yellow-white solid which separated was dissolved in 2 *N* sodium hydroxide solution. The sodium hydroxide solution was filtered, and the acid was reprecipitated from the filtrate with dilute hydrochloric acid. One and two-tenths grams (93%) of product melting at 133–136° was obtained, which was pure enough to be used in the next reaction. Recrystallization from aqueous alcohol gave colorless plates melting at 137–138°. Robinson and Thompson (7) report that this compound melts at 137–138°.

4-Keto-7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene (*XVII*). Ring closure of 0.9 g. of γ-(5-chloro-6-methoxy-2-naphthyl)butyric acid by the method described by Robinson and Thompson (7) gave 0.5 g. of 4-keto-7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene melting at 169–170°.

7-Methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene (*XIV*). A mixture of 0.4 g. of 4-keto-7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene, 5 g. of amalgamated zinc, 10 cc. of glacial acetic acid, 10 cc. of concentrated hydrochloric acid, 10 cc. of water, and 4 cc. of toluene was refluxed for twenty-four hours, two additional 2-cc. portions of hydrochloric acid being added after fifteen and eighteen hours. The toluene was separated; the zinc and aqueous layer were washed with ether. The combined toluene-ether solution was washed with water, then with 1 *N* sodium hydroxide solution and then with water again. The organic layer was dried with magnesium sulfate and evaporated to dryness under reduced pressure. Recrystallization of the crystalline residue from hot absolute alcohol gave 0.2 g. of crystalline solid melting at 123.5–125°. After another recrystallization, the product melted at 124.5–125.5°. The melting points of mixtures of varying percentage compositions of this sample and the material prepared as above showed no depression.

7-Methoxy-8-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene (*XVIII*). To a solution of 43 g. (0.175 mole) of 7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene in 400 cc. of carbon disulfide (dried over phosphorus pentoxide) cooled to 5° in an ice-water bath was added 56 g. (0.42 mole) of anhydrous aluminum chloride. The cooling bath was then removed and 26.8 g. (0.26 mole) of acetic anhydride was added dropwise over the course of an hour, with continuous stirring. The temperature rose sufficiently during the addition of the acetic anhydride to boil the carbon disulfide, and refluxing was continued for one-half hour after all the acetic anhydride had been added, by warming on the steam-bath. Decomposition of the complex was accomplished by dropping 5% hydrochloric acid into the carbon disulfide and boiling the solvent off with the heat generated by the decomposition reaction. The last traces were removed by heating on the steam-bath under reduced pressure. The green-black solid which remained was heated with about 1200 cc. of benzene and 400 cc. of 20% hydrochloric acid. The benzene was washed twice with 3 *N* sodium hydroxide solution, then twice with water, and was dried over magnesium sulfate. The hot, dried solution was then treated with decolorizing carbon (Norit-A), filtered, and allowed to stand in the refrigerator overnight. The precipitate was filtered off and washed with ether. Forty-seven grams (94%) of crude material melting at 121–124° was obtained. Repeated recrystallization from ethanol with charcoal (Norit-A) decolorization, gave 41 g. of transparent, colorless elongated plates melting at 127.5–128°.

Anal. Calc'd for $C_{17}H_{17}ClO_2$: C, 70.7; H, 5.9.

Found: C, 70.9; H, 6.1.

7-Methoxy-8-chloro-9-ethyl-1,2,3,4-tetrahydrophenanthrene (*XIX*) *and its reaction with hydriodic acid.* A mixture of 4 g. of 7-methoxy-8-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 30 g. of amalgamated zinc, 60 cc. of acetic acid, 60 cc. of concentrated hydrochloric acid, and 30 cc. of toluene was refluxed for twenty-four hours, an additional 45 cc. of hydrochloric acid being added in portions over this period. The toluene was separated; 30 cc. of warm toluene was used to wash the zinc and the aqueous layer. The combined toluene solution was washed twice with water, twice with 5% potassium hydroxide solution, and again with water. Acidification of the alkaline extract caused no precipitation. The toluene solution was evaporated to dryness under reduced pressure, leaving an oil which resisted all attempts at purification by sublimation or crystallization. It was found to be insoluble in hot 5% potassium hydroxide solution, and failed to give any coloration with 1% ferric chloride solution.

To the oily product above were added 25 cc. of hydriodic acid (sp. gr. 1.7), 90 cc. of glacial acetic acid, and 3 cc. of water, and the mixture was refluxed for twenty-four hours. After cooling slightly, the reaction mixture was poured into 150 cc. of ice-water, and the free iodine present was removed by bubbling sulfur dioxide through the solution. The green semi-solid mass which separated was dissolved in 5% potassium hydroxide solution and

reprecipitated, after filtration, with dilute hydrochloric acid. The yellow gummy solid was taken up in benzene, concentrated to dryness under reduced pressure, and vacuum sublimed at 160° and 0.1 mm. The sublimate was crystallized from carbon tetrachloride, and 1.7 g. (54%) of yellow-white solid was obtained, melting at 157–160°. Recrystallization from carbon tetrachloride gave colorless, glistening, flat prisms melting at 165–166°.

Anal. Calc'd for $C_{16}H_{18}O$: C, 84.9; H, 8.0.
Found: C, 84.8; H, 8.0.

Mixed melting points of mixtures of varying percentage compositions of this sample and an analytical sample of 7-hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene prepared from 7-acetoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene (1), were 164.5–165.5°.

Reaction of 7-methoxy-8-chloro-9-ethyl-1,2,3,4-tetrahydrophenanthrene (XIX) with hydrobromic acid. Seven grams of 7-methoxy-8-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene was reduced by the method described above. The oily product was refluxed with 150 cc. of hydrobromic acid (sp. gr. 1.5) and 150 cc. of acetic acid for four hours. The reaction product was worked up in the same manner as in the hydriodic acid reaction. Sublimation and crystallization from carbon tetrachloride gave 0.7 g. (12%) of product melting at 163–164°. Mixed melting points of mixtures of varying percentage compositions of this compound and the analytical samples of 7-hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene showed no depression.

7-Methoxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (XXI). Clemmensen reduction of 7-methoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene (2) by the procedure described above for 7-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene gave 7-hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (1). Five and five-tenths grams of 7-hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene was added slowly to an ethereal solution of diazomethane prepared from 7.5 g. of N-nitrosomethylurea. After standing at room temperature overnight, the ether and excess diazomethane were evaporated. The residue solidified on cooling, and upon crystallization from methanol, yielded 4.8 g. of crude product. Recrystallization of a portion from methanol gave colorless, long needles melting at 60–61°.

Anal. Calc'd for $C_{17}H_{20}O$: C, 84.9; H, 8.4.
Found: C, 84.6; H, 8.3.

Chlorination and reduction of 7-methoxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (XXI). The crude 7-methoxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (4.8 g.) obtained above was chlorinated with 5 g. of phosphorus pentachloride, following the general procedure described above for 7-methoxy-1,2,3,4-tetrahydrophenanthrene. The crude oily product was then treated with 75 cc. of hydrobromic acid and 75 cc. of acetic acid exactly as described above, and 0.6 g. of 7-hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene was obtained.

Reaction of 7-methoxy-8-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene (XVIII) with hydrobromic acid; 7-hydroxy-8-chloro-1,2,3,4-tetrahydrophenanthrene (XXVIII). A mixture of 2.5 g. of XVIII, 50 cc. of hydrobromic acid, and 50 cc. of acetic acid was refluxed for four hours. The reaction product was cooled and poured into 100 cc. of ice-water, whereupon a flaky precipitate separated. The solid was sublimed at 160° at 0.3 mm. The sublimate was taken up in 5% potassium hydroxide solution, and, after filtration of the alkaline solution, the product was reprecipitated with dilute hydrochloric acid. One and three-tenths grams (65%) of crude product was obtained. Recrystallization from methanol-water gave colorless rods melting at 111–112°.

Anal. Calc'd for $C_{14}H_{13}ClO$: C, 72.3; H, 5.6.
Found: C, 72.5; H, 5.8.

Reaction of 7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene (XIV) with hydrobromic acid. Reaction of 2.5 g. of XIV exactly as described above gave 1.4 g. (60%) of product melting at 106–109°. Recrystallization of the material from methanol-water brought the melting point to 110–111°. Mixed melting points of varying percentage compositions of this product and the analytical sample of 7-hydroxy-8-chloro-1,2,3,4-tetrahydrophenanthrene showed no depression.

Reaction of 7-methoxy-8-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene (XVIII) with hydriodic acid. A mixture of 3 g. of XVIII, 25 cc. of hydriodic acid, 90 cc. of acetic acid, and 3 cc. of water was refluxed for twenty hours. After cooling, the reaction mixture was diluted with water, treated with sulfur dioxide to remove free iodine, and filtered. The crude product obtained was vacuum sublimed at 150° and 0.1 mm., yielding 1.5 g. (75%) of sublimate, which, after recrystallization from carbon tetrachloride, melted at 132–133°. Mixed melting points of several mixtures of this sample and an analytically pure sample of 7-hydroxy-1,2,3,4-tetrahydrophenanthrene (2) showed no depression. One-half gram of the above product was acetylated with acetic anhydride and sodium acetate, as described by Mighton and Elderfield (1). Two crystallizations from alcohol gave a product melting at 77–78°. Acetylation of pure 7-hydroxy-1,2,3,4-tetrahydrophenanthrene under the same conditions gave a product which, after two recrystallizations, also melted at 77–78°. Mixed melting points of several different mixtures of the two preparations showed no depression.

Reaction of 7-methoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene (XXV) with hydriodic acid. Reaction of 2.5 g. of XXV with hydriodic and acetic acids as described above, and recrystallization of the crude product from ethanol-water gave 1.8 g. (90%) of product melting at 127–130°. Recrystallization from carbon tetrachloride gave colorless needles melting at 133–134°. Mixed melting points of mixtures of varying percentage compositions of this sample and pure 7-hydroxy-1,2,3,4-tetrahydrophenanthrene remained 133–134°.

Reaction of 9-acetyl-1,2,3,4-tetrahydrophenanthrene (XXVI) with hydriodic acid. Reaction of 2.5 g. of XXVI with hydriodic acid and acetic acid as described above produced a semi-solid product on cooling the diluted reaction mixture. This product was extracted with ether and, after drying with magnesium sulfate, the solvent was removed under reduced pressure. The residue was dissolved in ethanol-methanol (1:2) and cooled, yielding plates melting at 32–33°. Mixed melting points of mixtures of varying compositions of this compound and 1,2,3,4-tetrahydrophenanthrene showed no depression.

To the filtrate from the above crystals, a warm saturated solution of picric acid in ethanol was added. Three grams (66%) of picrate, melting at 109–111° was obtained. Recrystallization from ethanol gave a product melting at 110.5–112°. Mixed melting points of mixtures of varying percentage compositions of this sample and pure 1,2,3,4-tetrahydrophenanthrene picrate melting at 111–112° showed no depression.

Reaction of 9-acetyl-1,2,3,4-tetrahydrophenanthrene (XXVI) with hydrobromic acid. Reaction of 2.5 g. of XXVI with hydrobromic acid by the method used with XVIII above produced a brown semi-solid product on cooling the diluted reaction mixture. Extraction with ether, followed by crystallization from methanol, gave plates melting at 31–32°. Melting points of mixtures of this material with authentic 1,2,3,4-tetrahydrophenanthrene of varying composition showed no depression. The picrate (yield 50%) melted at 110–112° after crystallization from alcohol and showed no depression in melting point when mixed with an authentic sample.

7-Methoxy-8-chloro-9-(ω-bromoacetyl)-1,2,3,4-tetrahydrophenanthrene (XXII). To a suspension of 28.9 g. (0.1 mole) of 7-methoxy-8-chloro-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 750 cc. of ether and 75 cc. of chloroform was added dropwise with stirring 5.1 cc. (16 g. or 0.1 mole) of bromine. After the addition of the first few drops, the solution was warmed slightly to start the reaction. The solution decolorized rapidly after a short while, and the flask was cooled in cold water during the remainder of the addition of the bromine. The clear solution which remained after addition of all the bromine was rapidly washed with water, and dried over magnesium sulfate. On standing in the refrigerator 32 g. (87%) of solid separated, melting at 147–150°. Recrystallization from ethanol gave fluffy, colorless needles, which melted at 152–153°.

Anal. Calc'd for $C_{17}H_{16}BrClO_2$: Br, 21.7; Cl, 9.6.

Found from total AgX, assuming molecule has 1 Br and 1 Cl: Br, 22.0; Cl, 9.8.

7-Methoxy-8-chloro-9-(2-dimethylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (XXIII) (SN-9050).[2] A solution of 5.5 g. (0.015 mole) of XXII in 100 cc. of acetone and

100 cc. of dry benzene was added to a three molar quantity (2.02 g.) of dimethylamine in ether. The mixture was stirred for three hours and was then allowed to stand overnight. The solvents were removed under reduced pressure, and the residue was taken up in ether. The ether was cooled in the refrigerator for an hour, decanted from amine hydrobromide, and then was washed well with water. After drying over magnesium sulfate, the ether was concentrated under reduced pressure, and the residue was reduced with 30 cc. of 1 *M* aluminum isopropoxide in anhydrous isopropyl alcohol. The reduction was run for two hours, although the acetone test was negative after one hour. After evaporation of the solvent, the residue was treated with 3 *N* sodium hydroxide solution and then extracted with ether. The ether layer was washed twice with water, dried over magnesium sulfate and the filtrate was cooled in an ice-water bath. Addition of ethereal hydrogen chloride precipitated an oil, which crystallized from acetone on scratching, yielding 2.3 g. (41%) of crude product. Recrystallization from methanol-ether produced colorless prisms which melted at 242–244° dec.

Anal. Calc'd for $C_{19}H_{25}Cl_2NO_2$: C, 61.6; H, 6.8.
Found: C, 61.9; H, 6.6.

7-Methoxy-8-chloro-9- (2-diethylamino-1-hydroxyethyl) -1,2,3,4-tetrahydrophenanthrene (XXIV). Reaction of 5.5 g. (0.015 mole) of XXII with 3.6 g. (0.045 mole) of diethylamine in the manner described above produced 2.1 g. (35%) of amino carbinol hydrochloride. Recrystallization from acetone-methanol-ether gave rectangular prisms melting at 209–210°.

Anal. Calc'd for $C_{21}H_{29}Cl_2NO_2$: C, 63.3; H, 7.3.
Found: C, 63.4; H, 7.1.

Condensation of 7-methoxy-8-chloro-9-(ω-bromoacetyl)-1,2,3,4-tetrahydrophenanthrene (XXII) with higher dialkylamines. Several attempts were made to condense dipropylamine and diamylamine with the bromo ketone in the same manner as the dimethyl compound. In all cases, only intractable oils were formed, along with a very considerable amount of dialkylamine hydrochloride. The amination step was found to proceed slowly, and 90% of dialkylamine hydrobromide was usually obtained after two weeks' standing at room temperature. The reduction, however, was found to be extremely slow, and the distillate was found to contain some acetone even after thirty hours' reduction. Condensation and reduction in an atmosphere of nitrogen produced no significant change in the results.

SUMMARY

1. Two series of dialkylaminomethyl-1,2,3,4-tetrahydrophenanthrene-9-methanols derived from 7-chloro-1,2,3,4-tetrahydrophenanthrene, and from 7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene have been prepared.

2. The reactivity of the chlorine in 7-methoxy-8-chloro-1,2,3,4-tetrahydrophenanthrene derivatives toward hydriodic and hydrobromic acids has been studied.

3. The hydrolytic fission of 1,2,3,4-tetrahydrophenanthrene-9-methyl ketones by hydriodic and hydrobromic acids has been described.

NEW YORK 27, N. Y.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. III. REDUCTION OF SUBSTITUTED NAPHTHYL HALOMETHYL KETONES TO HALOHYDRINS. DERIVED AMINO ALCOHOLS[1]

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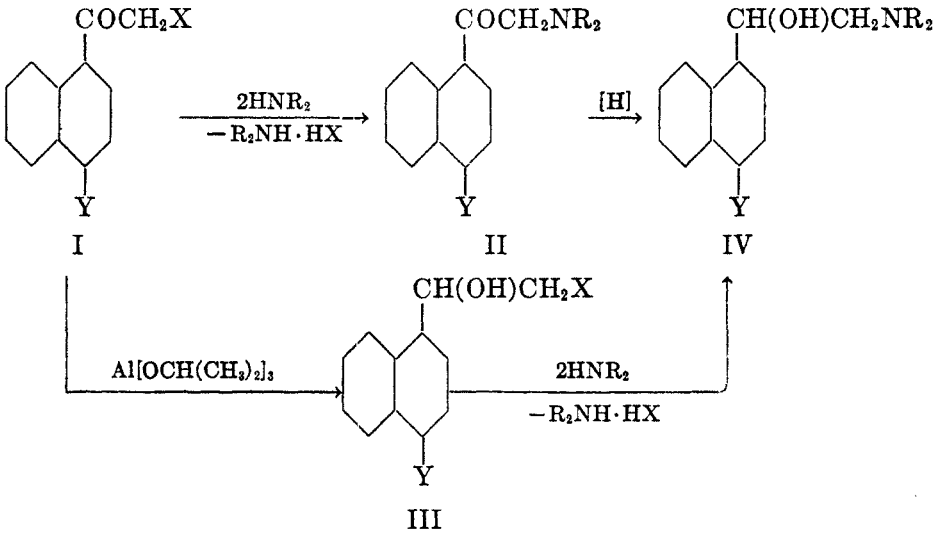
Received October 16, 1945

In the course of work in this laboratory we have had occasion to prepare substituted α-dialkylaminomethyl-1-naphthalenemethanols from the relatively easily available haloketones I. Difficulties (1) with the traditional method of preparing amino alcohols from haloketones by way of the amino ketones II led us to the alternate route by way of the halohydrins III, members of a type



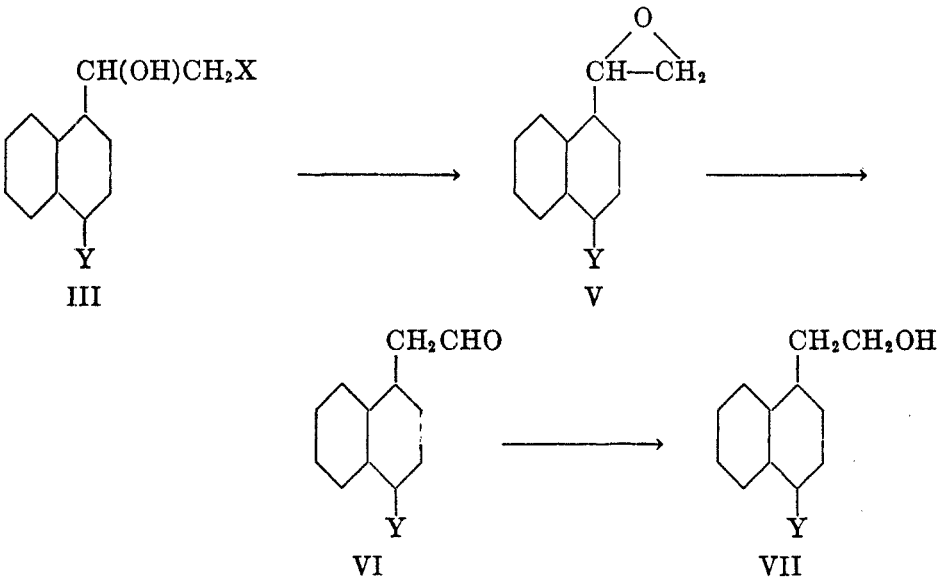
substance often converted to amino alcohols. This route finally proved very satisfactory after we learned how to reduce the haloketones in high yield. Our syntheses with the 4-substituted naphthyl derivatives by this method are reported in this article.

The initial attempts at the key step, the reduction with aluminum isopropoxide of the haloketones I, were carried out with 4-methoxy-1-naphthyl chloromethyl ketone (1). A conventional procedure (2), which involved distilla-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

tion of acetone and isopropyl alcohol through a column jacketed with refluxing methanol, was employed in these first attempts. Our results were discouraging and very different from those obtained with the somewhat analogous haloketone, phenacyl bromide, by Lund (3), who reported a yield of 85%. Instead they recalled the low yields of halohydrin reported by Stevens and co-workers (4) and by one of us (5) from the aluminum isopropoxide reduction of the other monohaloketones, α-bromopropiophenone, α-bromoisobutyrophenone, 2-bromocholestene-4-one-3 (4), and α-bromocyclohexanone (5).

In the early reduction attempts the analysis for acetone in the distillate greatly exceeded the theoretical. Treatment of the difficult reaction mixture either with base in an attempt to isolate oxide V or with acid to isolate chlorohydrin

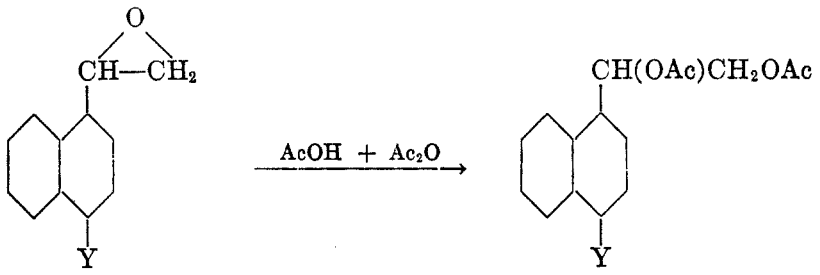


III did not yield these materials in any kind of purity. There was isolated repeatedly a product of over-reduction which corresponded in melting point and analysis to β-(4-methoxy-1-naphthyl)ethyl alcohol VII previously reported by Kon and Ruzicka (6). Stevens and co-workers (4), in the work cited above, isolated materials which could have arisen from an oxide. Similarly, our naphthylethyl alcohol VII probably arose, by way of the aldehyde VI, from oxide V which was produced in the reaction mixture from halohydrin III.

Although at least 130% of the theoretical amount of acetone could be obtained from the reduction of the 4-methoxynaphthalene derivative, a plot of the amount of acetone collected against time revealed that the distillation of acetone was fairly slow after approximately 85% had been collected. In an attempt to avoid some of the destruction of halohydrin III after its formation, the reaction was interrupted after 85% of the theoretical acetone had been distilled. Only then was it possible to obtain substantial amounts of the desired product.

Treatment of the reaction mixture with base gave a product which contained oxide V and which yielded a solid derivative on treatment with acetic acid and acetic anhydride, analyzing correctly for the corresponding glycol diacetate VIII. Treatment of the reaction mixture with hydrochloric acid gave a product from which a moderate yield of crystalline chlorohydrin III was obtained.

Further experimentation revealed that the rate of distillation of acetone was a very poor indication of its rate of formation. In fact, the reduction is very rapid. A series of experiments (Table III) revealed that much shorter reaction times gave improved yields by decreasing the subsequent reaction of the halohydrin. Yields of 97% were obtained consistently with a reaction time of



V VIII

approximately eighteen minutes and the use of 5 moles of isopropoxide to 1 mole of haloketone. With this short reaction time no attempt was made to distill off acetone. While we have not inquired further into the situation, it is clear that the use of a large excess of aluminum isopropoxide and a short reaction time in our work makes possible complete reduction without appreciable destruction of halohydrin.

We have used the type procedure described above for the haloketone reduction on the 4-bromo- and 4-chloro-1-naphthyl bromomethyl ketones (1, 7) and 4-chloro-1-naphthyl chloromethyl ketone without exploring for optimum conditions, yields of 85–89 % being obtained. The properties of the 4-substituted α-naphthylethylene halohydrins are summarized in Table I. In addition we have applied the method in this laboratory to the preparation of other substituted α-naphthylethylene halohydrins to be described in detail elsewhere (8). Yields of 90–99% have been obtained. Table IV summarizes all the haloketone reductions.

The conversion of the halohydrins to amino alcohols proceeded satisfactorily, Table II summarizing the compounds together with melting points and analyses. The conversion of a halohydrin to an amino alcohol sometimes definitely involves an oxide intermediate (9, 10) and possibly does so generally (4). Because an unsymmetrical oxide may conceivably be opened in two different directions, the amino alcohol may sometimes not correspond to the original halohydrin (10). Fortunately, this ambiguity does not exist in the present situation since the structure IV is expected (11) whether or not the oxide is an intermediate.

TABLE I

HALOHYDRINS $YC_{10}H_6CH(OH)CH_2X$ FROM ALUMINUM ISOPROPOXIDE REDUCTION OF HALOKETONES

Y	X	M.P. °C	ANALYSIS			
			Calc'd		Found	
			% C	% H	% C	% H
4-OCH_3	Cl	98–99[a]	65.95	5.53	65.78	5.69
4-Br	Br	89–90	43.61	3.05	43.51	3.16
4-Cl	Cl	75–76.5	59.78	4.18	59.67	4.27
4-Cl	Br	68–69	50.46	3.53	50.59	3.63

[a] Another crystalline modification, m.p. 66–67°.

TABLE II

AMINO ALCOHOLS $YC_{10}H_6CH(OH)CH_2NR_2$ FROM HALOHYDRINS

SN	Y	R	M.P. °C	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
6409	4-OCH_3	n-C_4H_9[a]	151–154	68.93	8.81	68.65	8.83
8990	4-OCH_3	n-C_5H_{11}[a]	125–127	70.10	9.21	70.24	9.35
8725	4-Br	n-C_5H_{11}[a]	106–108[c] 126.5–128.0	59.66	7.51	59.53	7.39
8679	4-Br	n-C_7H_{15}[b]	44	67.51	8.72	67.56	8.68
8678	4-Br	n-C_9H_{19}[b]	39–40	69.47	9.33	69.43	9.23
8736	4-Cl	n-C_5H_{11}[a]	100–101	66.32	8.35	66.12	8.35

[a] Hydrochloride.

[b] Free amino alcohol.

[c] Two crystalline modifications.

EXPERIMENTAL

All melting points are corrected. Analyses were by Jack W. Ralls or Bruce Day.

Preparation of haloketones. The haloketones are described elsewhere (1, 8) with the exception of 4-chloro-1-naphthyl chloromethyl ketone which was prepared by chlorination of 4-chloro-1-acetonaphthone (7). To a solution of 0.1 mole of ketone in 125 ml. of glacial acetic acid was added a few drops of ethereal hydrogen chloride. Then an equivalent amount of chlorine in 125 ml. of glacial acetic acid was added over a period of approximately a half hour. The reaction mixture was poured into 2.5 l. of ice-water and stirred for half an hour. The solid was filtered and air-dried. Recrystallization from hexane gave 90% yield of product, m.p. 69–70°.

Anal. Calc'd for $C_{12}H_8Cl_2O$: C, 60.28; H, 3.37.
Found: C, 60.18; H, 3.48.

Reduction of haloketones. Distilled aluminum isopropoxide and isopropanol, distilled from this reagent, were employed. An apparatus similar to the one described by Wilds (2) was used, involving the use of a condenser jacketed with refluxing methanol as a column. Analysis for acetone in the isopropanol-acetone distillate was carried out by Marasco's method (12). Table III summarizes some of the unsuccessful attempts with 4-methoxy-1-naphthyl chloromethyl ketone (1) and then illustrates the variation in the yield with the experimental conditions. Experiment 1 yielded no crystalline product and was not carried

through to any characterized material. In experiment 2, 0.10 mole of chloro ketone was treated until 118% acetone was evolved, then the reaction mixture was treated with water and the product was extracted with ether. The ether extract yielded no crystalline material. Molecular distillation yielded a product which was treated with alcoholic sodium hydroxide and then subjected to an attempted vacuum distillation. No distillate was obtained at expected pressures and temperatures. Extraction of the residues with ligroin, b.p. 60–70°, gave about 2 g. of a brown solid, m.p. 70–80°. Three recrystallizations from carbon tetrachloride yielded a white solid, m.p. 83–84°. Kon and Ruzicka (6) report 87° as the melting point of β-(4-methoxy-1-naphthyl)ethyl alcohol.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98.
Found: C, 76.83; H, 7.04.

From the behavior of halohydrin on treatment with base and distillation of the oxide as described in the following article (11) it is clear that the β-(4-methoxy-1-naphthyl)ethyl

TABLE III

SUMMARY OF REDUCTIONS OF 4-METHOXY-1-NAPHTHYL CHLOROMETHYL KETONE WITH ALUMINUM ISOPROPOXIDE

EXP.	ISOPROPANOL ML.[a]	Al(*i*-PrO)$_3$ MOLES[a]	TIME HRS.: MIN.	% ACETONE	% YIELD
1	1600	0.50		130	0
2	3000	3.0		118	0[b]
3	3000	0.33		85	[c]
4	3000	0.78		87	37
5	2400	2.0	2:15	88	42
6	2400	2.0	1:35	79	62
7	10000	5.0	1:25	68	66
8	4000	5.0	0:50	63	67
9	4000	5.0	0:25		74
10	10000	5.0	0:18		97
11	5000	2.5	0:05		25[d]

[a] Per mole of haloketone.
[b] β-(4-methoxy-1-naphthyl)ethyl alcohol found.
[c] Oxide identified as glycol diacetate.
[d] Mostly starting material obtained.

alcohol did not arise from halohydrin during the treatment for working up the reaction mixture.

In experiment 3, 0.10 mole of chloro ketone was treated until 85% acetone was distilled, then the reaction mixture was treated with sodium hydroxide and extracted with ether. Evaporation of the ether left an impure oil. A portion, 0.50 g., of this oil was treated with a mixture of 5.0 ml. of glacial acetic acid and 5.0 ml. of acetic anhydride on the steam-bath. Water was added, the mixture was extracted with ether, the ether extract was washed with carbonate solution and dried over potassium carbonate. Evaporation of the ether and recrystallization from ligroin, b.p. 75–135°, yielded *ca.* 50 mg. of glycol diacetate, m.p. 86–87.5°.

Anal. Calc'd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00.
Found: C, 67.23; H, 5.92.

In the remaining experiments of Table III the reaction mixture was cooled and poured into a slush of ice and 6 *N* hydrochloric acid in 10% excess over the isopropoxide used. Further dilution with water and cooling gave an oil in the cases where the product was impure. The oil was extracted with ether, the extract was washed with water, then carbonate solution, and dried over potassium carbonate. Evaporation of the ether left an

oil which was recrystallized from ligroin, b.p. 60–70°. The yields in Table III reflect a loss of material in the recrystallization.

In the experiment using the 18-minute reaction time separate solutions of the chloro ketone and aluminum isopropoxide, previously brought to a boil, were mixed and held under reflux the specified time. No attempt was made to distill off acetone. The reaction mixture was cooled and treated with a slush of 6 *N* hydrochloric acid and ice. The mixture was then diluted and left in the cold room or agitated for an hour or two with a motor-driven stirrer in an ice-bath. Filtration and washing of the crystalline product yielded practically pure material after drying in a vacuum desiccator over sulfuric acid.

Essentially this latter procedure was used in the reduction of the 4-chloro-1-naphthyl and the 4-bromo-1-naphthyl halomethyl ketones (1, 7) and also in connection with other halo-1-acetonaphthones (8). There was no attempt in these cases to find optimum conditions. Table IV summarizes the conditions and yields of material directly isolated in nearly pure form (m.p. only 1 to 6° low).

For purification, the halohydrins were recrystallized from ligroin (b.p. 60–70°) or diisopropyl ether.

TABLE IV

REDUCTION OF $YC_{10}H_6COCH_2X$ BY ALUMINUM ISOPROPOXIDE

Y	X	*i*-PrOH L.[a]	Al(*i*-PrO)$_3$ MOLES[a]	TIME MIN.	% YIELD
4-OCH_3	Cl	10	5	18	97
2-Cl	Br	7	5	25	90
4-Cl	Cl	15	5	18	88
4-Cl	Br	5	5	18	85
6-Cl	Cl	5	5	18	95
7-Cl	Cl	3	3	18	99
2-Br	Br	6	5	20	94
4-Br	Br	2	2	35	89

[a] Per mole of haloketone.

Conversion of halohydrins to amino alcohols. A mixture of halohydrin and dialkylamine[2] was kept twelve to twenty-four hours at 120°. When the amine was dibutyl- or diamylamine, four moles of amine were used per mole of halohydrin. The reaction mixture was treated with 6 *N* sodium hydroxide and freed from excess amine by steam distillation. The amino alcohol was taken up in ether and the ether extract was dried over potassium carbonate. The amino alcohol hydrochloride was precipitated by the addition of ethereal hydrogen chloride and recrystallized from acetone, methanol, or ethanol by addition of ether. Yields were 56–78%.

For the action of diheptyl- and dinonyl-amine on the 4-bromo-1-naphthylethylene chlorohydrin the procedure, which is capable of improvement was as follows: Two moles of amine were employed per mole of halohydrin. After being heated, the reaction mixture was stirred with ether and solid was removed. The ether solution was washed with sodium hydroxide, then water, and was then dried over magnesium sulfate. Distillation of the ether left an oil which solidified on cooling. Three recrystallizations of the amino alcohol from alcohol left a 37% yield in the case of the diheptyl and a 32% yield in the case of the dinonyl derivative.

The addition of water to the mixture of amine and 4-methoxy-1-naphthylethylene chlorohydrin produced a two-phase initial reaction mixture and lower yields were obtained.

[2] The dialkylamines were supplied in some cases by Dr. Elderfield and co-workers at Columbia University.

The addition of dioxane to give an initially homogeneous reaction mixture did not remedy the situation. Water tended to produce glycol as in the following case.

A mixture of 0.05 mole of 4-methoxy-1-naphthylethylene chlorohydrin, 0.10 mole of dipropylamine, 0.3 mole of water and enough dioxane to give one phase was held in a sealed tube forty-five hours at 127°. The contents of the tube and 10 ml. of 6 *N* sodium hydroxide were freed of amine by vacuum distillation on a water-bath. When the residue was taken up in ether, a white solid, not very soluble in this solvent, remained. More was obtained by concentrating the ether extract to bring the total to 1.9 g., m.p. 142–143°, after recrystallization from alcohol.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47.
Found: C, 71.39; H, 6.52.

SUMMARY

The aluminum isopropoxide reduction of substituted 1-naphthyl halomethyl ketones has been studied and adapted to the preparation of the corresponding halohydrins in excellent yields.

Dialkylaminoethanols have been prepared from the 4-methoxy-, 4-bromo-, and 4-chloro-1-naphthylethylene halohydrins by reaction with secondary amines.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. IV. SUBSTITUTED α-NAPHTHYLETHYLENE OXIDES AND DERIVED AMINO ALCOHOLS[1]

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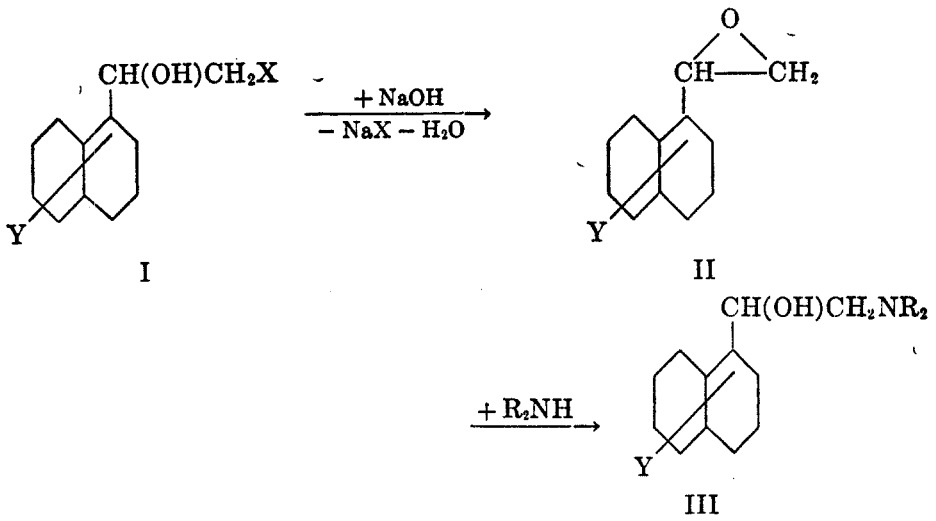
Received October 15, 1945

In the preparation of substituted α-dialkylaminomethyl-1-naphthalenemethanols of the type III from halohydrins I (1) derived from the corresponding haloketones, there were in some cases advantages in the preliminary preparation and isolation of the corresponding naphthylethylene oxide II. Thus, several oxides of this type have been prepared by us and used for the purpose mentioned. The results are reported in this paper.



Short treatment of the halohydrins (1) with alcoholic alkali at room temperature gave rise to the oxides in nearly quantitative yield. Their properties are summarized in Table I. Of the five oxides described here, four are low-melting solids, the 4-methoxy derivative being an oil.

Naphthylethylene oxides of the type II have apparently not been studied previously, but can be handled well if ordinary precautions are taken. These substances are quite sensitive to heat and traces of acid. Thus molecular distil-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

lation of 4-methoxy-1-naphthylethylene oxide II (Y = 4-OCH_3) at 5×10^{-5} mm. was successful. However, distillation at 0.5–1.0 mm. yielded the rearranged aldehyde which formed a bisulfite addition compound and an oxime and gave a positive Schiff's test immediately. The oxide gave only a faint Schiff's test, the color deepening slowly. The residue in the flask after the distillation at 0.5–1.0 mm. consisted largely of a high-melting solid which had the composition of the dioxane IV, a type substance sometimes produced from oxides (2).

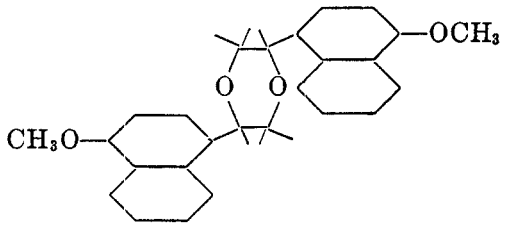
In the case of the 4-bromo-1-naphthylethylene oxide one preparation gave rise, apparently through the action of water and an accidental trace of acid, to a dif-

TABLE I

OXIDES $YC_{10}H_6CHOCH_2$ FROM HALOHYDRINS

Y	M.P. °C	ANALYSIS			
		Calc'd		Found	
		%C	%H	%C	%H
4-OCH_3	oil[a]	77.98	6.04	77.78	5.90
4-Cl	49	70.41	4.43	70.43	4.61
4-Br	49–50	[b]			
6-Cl	32.5–32.8	70.41	4.43	70.13	4.57
7-Cl	40.2–41.0	70.41	4.43	70.37	4.59

[a] n_D^{20} 1.625–1.626.
[b] Not analyzed.



IV

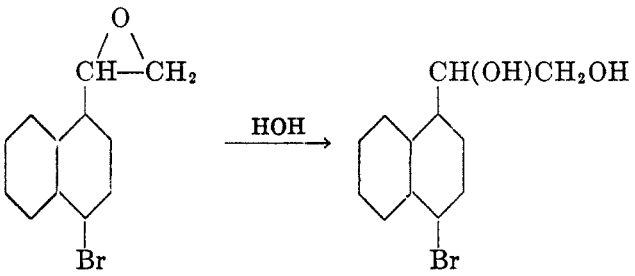
ferent substance whose analysis corresponded to the glycol V. The molecular weight of the material and the analysis of the acetate ester were confirmatory.

The conversion of the oxides to the amino alcohols was accomplished in high yield very conveniently by heating an equimolar mixture of the oxide and dialkylamine for the requisite time. The progress of the ring-opening reaction may be followed easily by measurement of the refractive index of the reaction mixture. This method was used to follow the course of the reaction of several amines with the 4-methoxy-1-naphthyl- and the 4-bromo-1-naphthyl-ethylene oxide. The results are shown graphically in Fig. 1. For these oxides a working temperature of 100–125° gave a convenient rate of reaction.

There are some advantages to the preparation of the amino alcohols through the oxides rather than directly from the halohydrin. First, there is no necessity

to remove excess secondary amine by steam-distillation or otherwise, this separation being difficult with the higher amines. Second, the product is more nearly pure and is usually obtained in higher yield. Table II summarizes the amino alcohols prepared from the substituted naphthylethylene oxides.

Although an unsymmetrical oxide theoretically may open to give one or the other or a mixture of two isomeric amino alcohols, there is little doubt that III



V

TABLE II

AMINO ALCOHOLS $YC_{10}H_6CH(OH)CH_2NR_2$ FROM OXIDES

SN	Y	R	M.P. °C	ANALYSIS			
				Calc'd		Found	
				%C	%H	%C	%H
6409	4-OCH_3	n-C_4H_9[a]	151–154	Reference 1 (a)			
9053	4-OCH_3	n-C_8H_{17}[a]	137–139	72.84	10.12	73.09	10.05
8725	4-Br	n-C_5H_{11}[a]	106–108[c] 126.5–128.0	Reference 1 (a)			
8680	4-Br	n-C_8H_{17}[b]	40.5–41.3[d]	68.55	9.04	68.81	8.93
8677	4-Br	n-$C_{10}H_{21}$[b]	35.0–36.5[e]	70.30	9.59	70.22	9.53
10267	4-Cl	n-C_8H_{17}[b]	34.4–34.8	75.38	9.94	75.18	10.00
8732	4-Cl	n-$C_{10}H_{21}$[b]	33.5–34.5	76.53	10.44	76.43	10.45
7522	6-Cl	n-C_4H_9[a]	151–154	64.86	7.89	64.83	7.97
13264	7-Cl	n-C_4H_9[a]	123–125	64.86	7.89	64.72	8.14

[a] Hydrochloride.
[b] Free amino alcohol.
[c] Two crystalline modifications.
[d] M.p. of hydrochloride 106–108.5°.
[e] M.p. of hydrochloride 93–94°.

correctly represents the structure of the ethanolamines prepared by us. The opening of the oxide ring by an amine appears to be a bimolecular displacement (3) of the ring oxygen by an amine molecule. The available evidence is that when the oxide is of the type VI (*e.g.*, propylene oxide, isobutylene oxide, styrene oxide), reaction takes place at the primary carbon atom in preference to the secondary or tertiary carbon atom (4, 5) even when this latter carbon atom carries an aromatic group (6).

EXPERIMENTAL

All melting points are corrected. Analyses were by Jack W. Ralls or Bruce Day.

Preparation of oxides. To a solution of 0.10 mole of halohydrin (1) in 50 ml. or more of alcohol was added a solution of 0.15 mole of sodium or potassium hydroxide in 50–75 ml. of alcohol. Both solutions were at room temperature, and the mixture was shaken occasionally at room temperature for fifteen minutes. Then 500 ml. of water was added and the oxide was extracted with two 200-ml. portions of ether. The combined ethereal extracts were washed with three 500-ml. portions of water and then dried over potassium carbonate. The product was reduced to constant weight by distillation of solvent first at atmospheric

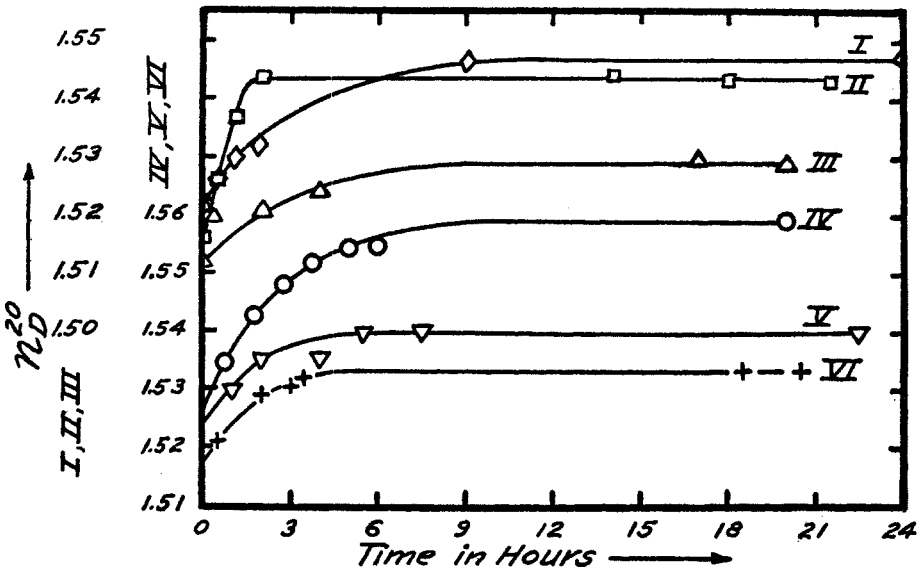
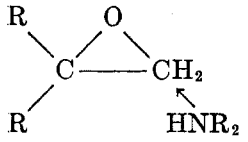


FIG. 1. Plots of n_D^{20} *vs.* time for reactions of oxides with amines

Curves I, II and III: 4-Methoxy-1-naphthylethylene oxide with di-*n*-amylamine at 100° (I) and 127° (II) and di-*n*-octylamine at 100° (III).

Curves IV, V and VI: 4-Bromo-1-naphthylethylene oxide with di-*n*-amylamine at 104° (IV), di-*n*-octylamine at 120° (V) and di-*n*-decylamine at 120° (VI).



VI

pressure, then at partially reduced pressure and finally at approximately 2 mm., with the aid of a water-bath kept below 50°.

In the case of the 4-methoxy-1-naphthylethylene oxide, the residue from the above treatment constituted a 96% yield of essentially pure material. The crude products from the preparations of the other ethylene oxides were recrystallized from petroleum ether, b.p. 60–70°, and dried in a vacuum desiccator which contained some paraffin. The yields were about 80%. The solid oxides turned to oils on exposure to air for a number of days but kept well for longer periods in closed bottles.

It is advisable to rinse the required glassware with ammonia before drying in order to guard against the contamination of the oxide by acid.

One preparation of 4-bromo-1-naphthylethylene oxide by the above method yielded an oil insoluble in hexane and easily recrystallized from benzene to give a solid, m.p. 126.5–128.0° and Rast (7) molecular weight 271 ± 15 (theoretical for glycol 266).

Anal. Calc'd for $C_{12}H_{11}BrO_2$: C, 53.95; H, 4.15.
Found: C, 53.97; H, 4.03.

A 1.0-g. portion of this material was acetylated with acetyl chloride in pyridine at room temperature to yield an ester, m.p. 103.0–104.5°, 0.89 g., (60%), after several recrystallizations from hexane.

Anal. Calc'd for $C_{16}H_{15}BrO_4$: C, 54.72; H, 4.31.
Found: C, 54.38; H, 4.18.

Distillation and rearrangement of 4-methoxy-1-naphthylethylene oxide. Molecular distillation of crude oxide n_D^{20} 1.6252, at 5×10^{-5} mm. on an apparatus of the type described by Riegel (8) yielded a clear colorless product, n_D^{20} 1.6255.

Distillation of oxide at 0.5–1.0 mm. from a modified Claisen flask gave a clear distillate at 142–144°, n_D^{20} 1.6208, which soon solidified; m.p. 47.5–48.5° after recrystallization from ligroin of b.p. 60–70°. This distillate formed a bisulfite addition product, and an oxime, m.p. 132–134°.

Anal. Calc'd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09.
Found: C, 72.23; H, 6.40.

The solid distillate, dissolved in alcohol, gave an immediate deep purple color with Schiff's reagent; the oxide only a light pink which became purple only on standing overnight.

The residue from the above distillation at 0.5–1.0 mm. yielded, on washing with ether, a white solid, m.p. 240–241°, after recrystallization from benzene.

Anal. Calc'd for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04.
Found: C, 77.78; H, 6.01.

Conversion of oxides to amino alcohols. An equimolar mixture of oxide and dialkylamine[3] was warmed and shaken until homogeneous and then kept in a sealed tube or a stoppered flask heated, usually at 120°, for eight to twenty-four hours either in a furnace or an oil-bath. In judging the extent of the reaction, the refractive index was measured either on separate samples in small sealed tubes or on a sample withdrawn from the main flask. Plots of the data obtained in this way are given in Fig. 1.

After the heating period, the amino alcohols were either recrystallized one or more times from methyl or ethyl alcohol or alcohol-hexane mixtures, or taken up in anhydrous ether and precipitated as the hydrochlorides with ethereal hydrogen chloride. The hydrochlorides were recrystallized from methanol-ether, acetone-ether, or ethanol-ether. The crude yields of amino alcohol were usually very high, the yield of recrystallized amino alcohol or its hydrochloride usually about 80%.

SUMMARY

A series of substituted α-naphthylethylene oxides (4-methoxy-, 4-chloro-, 4-bromo-, 6-chloro-, and 7-chloro-) has been prepared.

The oxides have been converted smoothly to a number of dialkylaminoethanols.

LOS ANGELES, CALIF.

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[3] The dialkylamines were supplied in some cases by Dr. Elderfield and co-workers at Columbia University.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE UNIVERSITY OF SOUTHERN CALIFORNIA]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. V. THE PREPARATION OF SOME α-DIALKYLAMINOMETHYL-2-CHLORO- AND BROMO-1-NAPHTHALENEMETHANOLS[1]

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This article describes the preparation of several α-dialkylaminomethyl-2-halo-1-naphthalenemethanols, VII, which was carried out as part of a program of synthesis of amino alcohols containing substituted naphthalene nuclei (1). Since such ethanolamines could be prepared readily from the 2-halo-1-acetonaphthones IV, the practical synthesis of the latter materials was our main problem. Several approaches were examined.

The most direct approach to the substances would appear at first to involve the Friedel-Crafts reaction on 2-halonaphthalene, just as we found it to be in the case of the 4-halo-1-acetonaphthones (2). We explored this first with 2-bromonaphthalene. Acetyl chloride and aluminum chloride gave rise in 66% yield to a mixture of the 1- and 6-acetylphthones as previously reported by Dziewonski and Sternbach (3) who accomplished the difficult separation of isomers through the phenylhydrazones. However, we found it preferable to add phenylhydrazine roughly equivalent to the 1-isomer which reacts more rapidly than the 1-isomer in acetic acid solution. After the precipitation of the 2-bromo-6-acetonaphthone phenylhydrazone was complete the 2-bromo-1-acetonaphthone IV (X = Br) was obtained with a 38% recovery of crude material and a 26% recovery of pure material after recrystallization. Since β-bromonaphthalene was obtained in 50–55% yield from β-naphthylamine, the over-all yield of 2-bromo-1-acetonaphthone was approximately 9% from β-naphthylamine.

The Friedel-Crafts reaction on 2-chloronaphthalene gave rise to a mixture of ketones from which the 2-chloro-1-acetonaphthone IV (X = Cl) was isolated rather easily by simple crystallization. The over-all yield of pure product from β-naphthylamine was 32%.

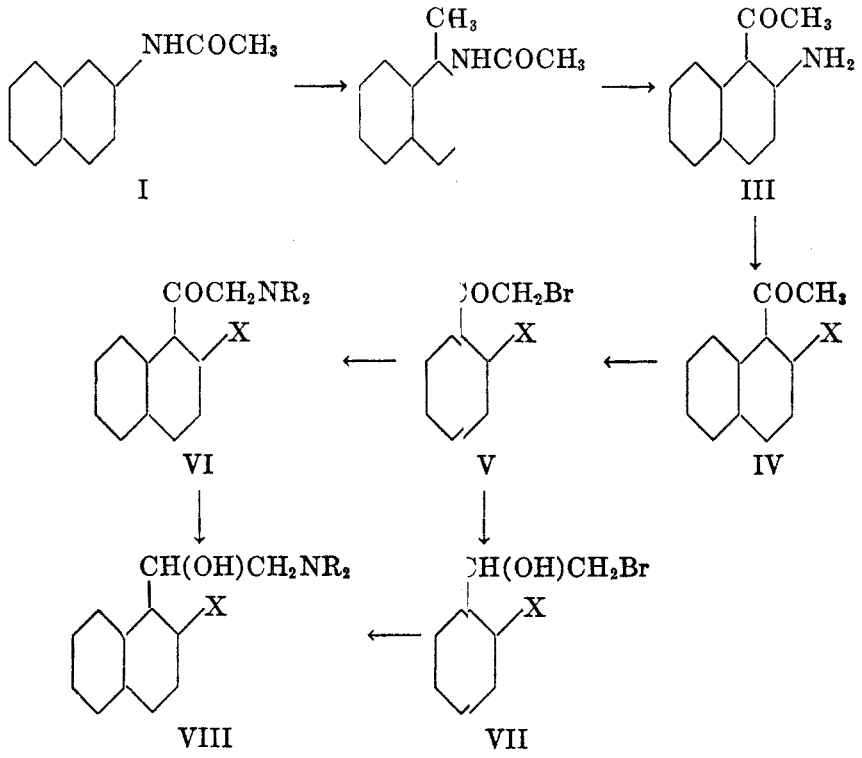
A preliminary attempt at chloromethylation (4) of β-bromonaphthalene to produce 2-bromo-1-chloromethylnaphthalene was discouraging. The latter substance was to be oxidized to 2-bromo-1-naphthoic acid which was to be built up to the bromomethyl ketone V by way of the diazoketone (5).

The best synthesis we found for 2-halo-1-acetonaphthones IV involved 2-amino-1-acetonaphthone which was easily diazotized and converted to IV.

[1] This work was done under contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles, and the University of Southern California. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

Attempts to prepare 2-amino-1-acetonthone by a Bucherer reaction (6) on 2-hydroxy-1-acetonaphthone or by a Fries-type rearrangement (7) of 2-acetamidonaphthalene I were unsuccessful but satisfactory conditions were found for the Friedel and Crafts reaction on II hydrolysis of the product (II to III).

A number of satisfactory Friedel and Crafts reactions on acetanilide and substituted acetanilides have been reported in the literature (8). Also, Dziewonski and co-workers (9) obtained 2-benzamido-1-benzoylnaphthalene in 30–40% yield from treatment of β-naphthylamine with benzoyl chloride and zinc chloride. Similarly we eventually obtained satisfactory acetylation of 2-acetamidonaphthalene I by regulation of experimental conditions. The proportion of alumi-



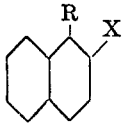
num chloride catalyst was crucial, no product being obtained in carbon disulfide or benzene with mole ratios of aluminum chloride to acetic anhydride to acetamidonaphthalene of 2.5:1.25:1. Also, starting material was obtained with acetyl chloride in carbon disulfide where corresponding mole ratios were 1.25:1.25:1. When, with acetic anhydride in carbon disulfide, the above mole ratios were 8:2:1, a product was obtained which had the correct composition for the 2-acetamido-1-acetonaphthone II (Table I), yielded a 2,4-dinitrophenylhydrazone, gave an iodoform test, and failed to give a test for a primary amine. The yield in this step was improved to 4 and with approximately an 80% yield on the hydrolysis of II to the 2-amino-1-acetonaphthone III (Table I) the over-all yield of III from acet-β-naphthalide I was about 38%.

The over-all yield of III from I was improved to 45% by avoiding isolation of II and further improved by use of acetyl chloride instead of acetic anhydride, acetyl chloride being added to a suspension of the amide and aluminum chloride in carbon disulfide. This modified procedure gave rise to yields of III of 60–70%.

The structure of the 2-amino-1-acetonaphthone III was clear from the subsequent diazotization and conversions to the 2-halo-1-acetonaphthones IV. The bromo compound was identical with the material prepared from β-bromonaphthalene by Dziewonski and Sternbach's method (3). In addition to the 2-amino-1-acetonaphthone III, m.p. 110–111°, from the modified procedure in which the 2-acetamido-1-acetonaphthone was not isolated, there was obtained a

TABLE I

PROPERTIES AND ANALYSES OF COMPOUNDS



SN	X	R	M.P. °C	ANALYSIS			
				%C		%H	
				Calc'd	Found	Calc'd	Found
	$NHCOCH_3$	$COCH_3$	151	73.99	73.58	5.76	5.77
	NH_2	$COCH_3$	110–111	77.81	77.60	5.99	6.21
	Cl	$COCH_3$	64–65	70.42	69.95	4.43	4.55
	Cl	$COCH_2Br$	97–98	50.83	50.35	2.84	2.94
	Br	$COCH_2Br$	116–117	43.94	43.94	2.46	2.51
	Cl	$CH(OH)CH_2Br$	80–81	50.47	50.30	3.53	3.51
	Br	$CH(OH)CH_2Br$	78.5–79.5	43.67	43.70	3.05	3.10
5905	Cl	$CH(OH)CH_2N(C_2H_5)_2$	64–64.5	69.18	69.12	7.26	7.21
6620	Cl	$CH(OH)CH_2N(C_4H_9)_2 \cdot HCl$	136.5–137[a]	64.86	65.08	7.89	7.76
			124.5–125[a]		64.71		7.99
8100	Cl	$CH(OH)CH_2N(C_5H_{11})_2 \cdot HCl$	121–126	66.32	66.60	8.35	8.38
7936	Cl	$CH(OH)CH_2N(C_6H_{13})_2 \cdot HCl$	121–122	67.59	67.46	8.75	8.64
8681	Br	$CH(OH)CH_2N(C_4H_9)_2 \cdot HCl$	134–135	57.90	57.78	7.05	7.13

[a] Two crystalline modifications.

small amount of a material, m.p. 163–164°, with the correct composition of an isomer of III, probably 2-amino-6-acetonaphthone.

The 2-chloro-1-acetonaphthone IV (X = Cl, Table I) was prepared in yields of 65–70% from the amino ketone III by the Sandmeyer reaction. Thus the over-all yield from β-naphthylamine by this approach was 41%. For the 2-bromo-1-acetonaphthone IV (X = Br, Table I) the yield was low, but, since only one amino alcohol VIII corresponding to it was needed, the preparation was not further investigated. Bromination of the 2-halo-1-acetonaphthones IV to bromo ketones V (Table I) was easily accomplished.

The bromo ketones V were converted to amino alcohols VIII (Table I) by routes already described (1, 10).

EXPERIMENTAL

Melting points are uncorrected. Analyses by Jack W. Ralls and Bruce Day.

β-Bromonaphthalene. This material, m.p. 56.0–56.5°, was prepared in 50–55% yield from β-naphthylamine following directions of Geissman and Tulagin (11) and recrystallized from aqueous methanol.

Preparation of 2-bromo-1-acetonaphthone from β-bromonaphthalene. The mixture of ketones was prepared in 66% yield from β-bromonaphthalene, acetyl chloride, and aluminum chloride in carbon disulfide essentially by the method of Dziewonski and Sternbach (3). Since hydrolysis of the phenylhydrazones was accompanied by formation of considerable tarry material, the separation of the ketones was carried out by converting most of the 6-isomer to phenylhydrazone, leaving the 1-acetonaphthone unreacted. It is difficult to judge the composition of the mixed ketone. Anderson and Johnston (12) estimate the ketone mixture is approximately one-tenth 6-bromo-2-acetonaphthone. However, treatment of the crude ketone with the equivalent amount of phenylhydrazine in glacial acetic acid precipitated about one-third of the ketone and we proceeded on this basis.

The ketone mixture (73.7 g., 0.296 mole) was dissolved in 150 ml. of glacial acetic acid and into this solution was washed 12.8 g. (0.118 mole) of phenylhydrazine with the aid of 50 ml. of glacial acetic acid. In about one minute a yellow precipitate began to form. When precipitation appeared complete, the phenylhydrazone was collected on a filter and washed with ether. The phenylhydrazone weighed 34.8 g. (0.103 mole). The combined filtrate and washings were diluted with 500 ml. of water and extracted with ether. The ether extract was washed in turn with carbonate solution, twice with 5% hydrochloric acid, and twice with water. After the ether solution was dried over potassium carbonate and the ether removed on the steam-bath, the residue was distilled at 1 mm. The fraction of b.p. 145–155° weighed 27.7 g. (0.111 mole), 37%. Recrystallization from a petroleum ether-ligroin mixture yielded 19.2 g. of 2-bromo-1-acetonaphthone, m.p. 63–64° [literature (3) 64–65°].

Preparation of 2-chloro-1-acetonaphthone from β-chloronaphthalene. The Friedel-Crafts reaction at 0° between β-chloronaphthalene (13), acetyl chloride, and aluminum chloride in carbon disulfide was carried out similarly to the conversion of the β-bromonaphthalene, an 84% yield of the mixture of isomeric ketones being obtained. Distillation at reduced pressure was not necessary in this case, the product crystallizing soon after the removal of solvent. Recrystallization of 12.5 g. of the mixed ketone from 140 ml. of 80% ethanol yielded 6.3 g. of 2-chloro-1-acetonaphthone, m.p. 62.5–64.0°.

2-Acetamidonaphthalene. This material, m.p. 131–132° was prepared in 90–97% yield by the method of Kaufmann (14).

2-Acetamido-1-acetonaphthone. In a one-liter 3-necked flask in a good hood were placed 18.5 g. (0.10 mole) of 2-acetamidonaphthalene, 20.4 g. of acetic anhydride, and 200 ml. of anhydrous carbon disulfide. The flask was equipped with an efficient stirrer, an efficient reflux condenser protected with a drying tube, and a short length of ¾-inch rubber tubing connected to a conical flask for addition of 107 g. (0.80 mole) of aluminum chloride.

The contents of the flask were warmed to the reflux temperature with a pan of warm water. Then the aluminum chloride was added in small portions over a two-hour period to the well-stirred mixture. Refluxing was continued for two more hours and then the flask was allowed to stand for three hours.

The reflux condenser and the addition tube were removed and the flask was fitted with a dropping-funnel and a condenser for downward distillation. Dropwise addition of 250 ml. of water with stirring caused rapid distillation of carbon disulfide. Residual traces of carbon disulfide were distilled by warming the flask in warm water. Then, 200 ml. of 1.5 *N* hydrochloric acid was added rapidly and the flask was allowed to cool. The brown solid was removed by filtration and air-dried. A solution of this solid in hot 50% by vol. ethyl alcohol was filtered, treated with Norit, and cooled slowly. Two more recrystallizations of the deposited crystals yielded 10.9 g., 48%, of white crystalline product, m.p. 151°. The material yielded a 2,4-dinitrophenylhydrazone, m.p. 244° and gave a positive iodoform test.

2-Amino-1-acetonaphthone. (*a*) *From 2-acetamido-1-acetonaphthone.* The latter material was mixed with 5 times its weight of glacial acetic acid and 10 ml. of 18 *N* sulfuric acid per gram of amide and the mixture was held under reflux for two hours. The mixture was then chilled and neutralized with concentrated sodium hydroxide. The precipitated amine was dissolved in ether and the solution was dried over potassium carbonate. Bubbling hydrogen chloride gas into the ether solution precipitated the hydrochloride, which was filtered, dissolved in warm water, decolorized with Norit, and reprecipitated by dropwise addition of 10% sodium hydroxide until the solution was basic. The amine was dissolved in dilute acid, decolorized again, and reprecipitated. One recrystallization from water containing about 10% methanol yielded light golden platelets, m.p. 110–111°, in 80% yield.

(*b*) *Directly from 2-acetamidonaphthalene.* In a one-liter 3-necked flask were placed 18.5 g. (0.10 mole) of 2-acetamidonaphthalene, 67 g. (0.50 mole) of aluminum chloride, and 400 ml. of carbon disulfide. The flask was equipped with a powerful mercury-sealed stirrer, an efficient reflux condenser, and a dropping-funnel protected by a drying tube. The reflux condenser was fitted with a drying tube followed by a hydrogen chloride trap. The flask was cooled with an ice-bath and 9.3 g. (0.125 mole) of redistilled acetyl chloride was added in twenty minutes to the well-stirred mixture. Stirring was continued for three hours, at the end of which a gummy complex was formed. The flask and contents were allowed to come to room temperature and stand overnight. The next day, the mixture was heated to reflux in warm water and stirring was carried on as well as possible for one hour. Hydrogen chloride was copiously evolved at this point.

The flask was cooled and the carbon disulfide layer was decanted and discarded. To the residue in the flask was added about 300 g. of chopped ice and the mixture was left in the hood with occasional stirring until the vigorous hydrolysis was complete. Concentrated hydrochloric acid (100 ml.) was added and the mixture was warmed on the steam-bath to expel carbon disulfide. Then the mixture was held under reflux until the oil disappeared and a clear red-brown solution formed. The liquid was poured into an Erlenmeyer flask and the reaction flask was rinsed with hot hydrochloric acid (100 ml. of water and 50 ml. of conc'd hydrochloric acid). The rinsings were added to the Erlenmeyer flask, and its contents cooled. The deposited hydrochloride of 2-amino-1-acetonaphthone was dissolved in the minimum amount of boiling water. The solution was filtered and added to a mixture of 20 g. of sodium hydroxide, 50 ml. of water and 300 g. of chopped ice. The precipitated amine was removed by filtration and air-dried. Recrystallization with the use of Nuchar XXX from 100 ml. benzene yielded 11.1–13.0 g. (60–70%) of product, m.p. 110–111°, including a small second crop obtained by concentration of the mother liquor to about half the volume.

Further concentration of the mother liquor yielded a small amount of material, m.p. 163–164°, probably a position isomer of the main product.

Anal. Calc'd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99.
Found: C, 78.30; H, 6.03.

Conversion of 2-amino-1-acetonaphthone to 2-chloro-1-acetonaphthone. In a 600-ml. beaker, 46.2 g. (0.25 mole) of 2-amino-1-acetonaphthone[2] and 125 ml. of concentrated hydrochloric acid were stirred into a thin paste with a motor-driven stirrer. The mixture was cooled to −5° by an ice-salt bath and the diazotization was carried out with a solution of 17.3 g. (0.25 mole) of sodium nitrite in 100 ml. of water. The diazotization required about an hour, the temperature being kept below 0° during this time and for an additional fifteen minutes, while the mixture was stirred. A test for nitrous acid at this time was usually negative. When it was positive, a little urea was added.

The diazonium chloride solution was poured rapidly into a solution of cuprous chloride in concentrated hydrochloric acid maintained at 70°. The cuprous chloride (15) was prepared from 78.2 g. of cupric sulfate pentahydrate and dissolved immediately in 110 ml. of concentrated hydrochloric acid. After refluxing the whole mixture one hour, the dark liquid was left overnight.

[2] We are indebted to Dr. Elderfield at Columbia University, Dr. Hartshorn at Dartmouth College, and their co-workers for the preparation of some of this material.

After this, the crude product, a black tar, was filtered out and washed free from acid with water. It was dried in an evaporating dish in an oven at 70° for twenty-four hours, after which, on cooling, it solidified to a crumbly black solid. This was then distilled from a Claisen flask with a wide side-arm at 5 mm. The distillate soon solidified to a nearly white solid, which was recrystallized from alcohol or a mixture of petroleum ether and ligroin, to yield 33.2–35.8 g., 65–70%, of material, m.p. 64–65°, b.p. 158–160° (4 mm.).

Conversion of 2-amino-1-acetonaphthone to 2-bromo-1-acetonaphthone. 2-Amino-1-acetonaphthone (46.2 g., 0.25 mole) suspended in 100 ml. of 48% hydrobromic acid, was diazotized in the usual manner with a solution of 17.3 g. (0.25 mole) of sodium nitrite in 100 ml. of water. A cuprous bromide solution was prepared by adding a hot solution of 16.6 g. of sodium bisulfite and 11.0 g. of sodium hydroxide to a hot solution of 78.2 g. of cupric sulfate pentahydrate and 41.6 g. of potassium bromide. The precipitated cuprous bromide was filtered, washed, and dissolved in 100 ml. of 48% hydrobromic acid. The cold diazonium bromide solution was added to the cuprous bromide solution heated to 70°. Foaming was prevented with a few drops of caprylic alcohol.

The black tarry product, obtained as in the case of the chloro analog was distilled at 3 to 4 mm. from a Claisen flask with a wide side-arm, b.p. 164–166°. Recrystallization from hexane yielded 13.4 g., 22%, of light yellow crystals, m.p. 63–64°, mixed m.p. with 2-bromo-1-acetonaphthone prepared by the Friedel-Crafts reaction on β-bromonaphthalene, 63–65°.

Preparation of ω-bromo-2-haloacetonaphthones. 2-Chloro-1-acetonaphthone (35.0 g., 0.171 mole) was dissolved in 250 ml. of anhydrous ether in a 500-ml. 3-necked flask equipped with a stirrer, a small burette, and a thermometer. Approximately 50 ml. of roughly 2 *N* ethereal hydrogen chloride was added and 27.5 g. (0.172 mole) of bromine was added from the burette in about one hour. The reaction was started at 30° and the rest of the bromination was carried out below 15°. A white precipitate began to form after about half of the bromine had been added. After the bromination, the product was removed on a Büchner funnel and washed with cold, dry ether. The ethereal solution was washed with water, dried over potassium carbonate and evaporated to yield more crude product, the total crude yield being about 95%. Recrystallization from absolute alcohol yielded 41.2 g., 85%, of needles, m.p. 97–98°.

Analogous bromination of 2-bromo-1-acetonaphthone gave rise to crude product in 97% yield and, after recrystallization from hexane to final product, m.p. 114–116.5° in 72% yield. The analytical sample, m.p. 116–117°, was obtained after two more recrystallizations from hexane.

Reduction of bromo ketones to bromohydrins. 2-Chloro-1-naphthacyl bromide and 2-bromo-1-naphthacyl bromide were reduced to bromohydrins with aluminum isopropoxide as described elsewhere (10) in crude yields of 90 and 94% respectively. Recrystallization from hexane gave rise to the pure materials in yields of 77 and 88% respectively.

Preparation of amino alcohols. (*a*) *From bromo ketones* (*1*). The reaction between 2-chloro-1-naphthacyl bromide and diethyl-, dibutyl- or dihexyl-amine[3] was carried out in benzene or ether, the yields of dialkylammonium bromide being 84–95%. The yield of acetone on reduction with aluminum isopropoxide was 81–85%. The products were isolated either as free base or as the hydrochloride. The diethylamino compound as the free base was recrystallized from pet. ether (b.p. 30–60° or 60–70°). In the other two cases, the hydrochlorides were recrystallized from acetone-ether or acetone-pet. ether. Yields of pure materials were 18–36%.

(*b*) *From bromohydrins* (*10*). The mixtures of 1 mole of bromohydrin to 4 moles of dibutyl-, diamyl- or dihexyl-amine were held at 120° for 16–24 hours. Steam distillation from basic solution removed the excess amine. The products were taken up in ether, the solutions were dried and dry ethereal hydrogen chloride was used to precipitate the products in crude yields of 73–91%. Recrystallization from ethyl acetate-ether, acetone-pet. ether, or absolute alcohol-ether gave rise to pure materials in yields of 56–70%.

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[3] The dialkylamines were supplied in some cases by Dr. Elderfield and co-workers at Columbia University.

SUMMARY

Several approaches to the 2-halo-1-acetonaphthones have been examined, the best of which appears to involve the Friedel-Crafts reaction with 2-acetamidonaphthalene followed by hydrolysis and a Sandmeyer reaction.

A number of α-dialkylaminomethyl-2-chloro- and bromo-1-naphthalenemethanols have been prepared as possible antimalarials from the 2-halo-1-acetonaphthones.

LOS ANGELES, CALIF.

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DERIVATIVES OF 6-METHOXY-8-NITROQUINOLINE. CHLORINATION WITH SULFURYL CHLORIDE

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Since it was of interest, in connection with work on antimalarial drugs, to prepare derivatives of 6-methoxy-8-nitroquinoline containing chlorine in the hetero ring, it was decided to investigate the reaction between the N-oxide of this substituted quinoline and sulfuryl chloride. Unfortunately we were unable to isolate the N-oxide by the usual methods. However 6-methoxy-8-nitroquinoline itself was found to react with sulfuryl chloride to yield a mixture of chlorinated products. We were able to isolate five of these compounds; a dichloromethoxynitroquinoline, a trichloromethoxyquinoline, a trichlorohydroxyquinoline, a trichloromethoxynitroquinoline, and a tetrachloromethoxyquinoline.

The first of these was identified, by nitric acid oxidation to the known 5-chloronicotinic acid, as 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline.

The tetrachloromethoxyquinoline was also oxidized to 5-chloronicotinic acid with nitric acid. This indicates that three chlorine atoms enter the benzene ring, one replacing the nitro group, and the fourth enters the hetero ring in the 3-position. This compound is therefore 3,5,7,8-tetrachloro-6-methoxyquinoline. (Survey Number 13,480).[2]

The trichlorohydroxyquinoline, on the basis of its analysis, melting point, and melting point of its acetyl derivative appears to be identical with a compound prepared by Zincke and Müller (1). This compound was prepared by these investigators by a series of chlorinations starting with 6-hydroxyquinoline and was identified by them, mainly by analogy with the same reactions starting with β-naphthol, as 5,7,8-trichloro-6-hydroxyquinoline. Since this evidence appeared inconclusive, a sample of our trichlorohydroxyquinoline was oxidized by means of nitric acid to yield nicotinic acid (identified by melting point and melting point of its nitrate). Therefore this substance may be presumed to be 5,7,8-trichloro-6-hydroxyquinoline (SN 13,479).

By methylation of our trichlorohydroxyquinoline (SN 13,479) with dimethyl sulfate, we obtained a substance shown to be identical with our trichloromethoxyquinoline (SN 13,478). The latter is therefore identified as 5,7,8-trichloro-6-methoxyquinoline.

The remaining compound isolated from the sulfuryl chloride reaction was a trichloromethoxynitroquinoline whose structure we did not determine. This substance is accordingly designated x,y,z-trichloro-6-methoxy-8-nitroquinoline.

The 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline and the x,y,z-trichloro-

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[2] The Survey Number is the identification number assigned by the Malaria Survey Office of the National Research Council.

6-methoxy-8-nitroquinoline were reduced to the corresponding amines and several attempts were made by the usual methods for similar compounds to couple the dichloromethoxyaminoquinoline (SN 13,482) with 1-diethylamino-4-bromopentane. A portion of this dichloromethoxyaminoquinoline was also converted into the corresponding dichloromethoxyiodo compound (SN 13,483) and an attempt was made to couple this with 1-diethylamino-4-aminopentane. None of these coupling reactions succeeded, and will not be described. No attempt was made to couple the x,y,z-trichloro-6-methoxy-8-aminoquinoline (SN 13,481) with 1-diethylamino-4-bromopentane.

A number of these compounds were tested for antimalarial activity by the Malaria Research Group at the National Institute of Health. The following compounds tested showed no antimalarial action against *P. gallinaceum* in the chick when administered orally in the highest tolerated dose (Test A-1 of the Malaria Survey):

5,7,8-trichloro-6-methoxyquinoline (SN 13,478)
5,7,8-trichloro-6-hydroxyquinoline (SN 13,479)
3,5,7,8-tetrachloro-6-methoxyquinoline (SN 13,480)
x,y,z-trichloro-6-methoxy-8-aminoquinoline (SN 13,481)
3,5 (or 7)-dichloro-6-methoxy-8-aminoquinoline (SN 13,482)
3,5 (or 7)-dichloro-6-methoxy-8-iodoquinoline (SN 13,483)

EXPERIMENTAL[3, 4]

Chlorination of 6-methoxy-8-nitroquinoline. (Experiment I). To 40 g. of 6-methoxy-8-nitroquinoline in a 2-liter, round bottomed flask equipped with a reflux condenser, the top of which was protected by a calcium chloride tube and led to a gas absorber, was added 800 cc. of redistilled sulfuryl chloride (b.p. 68.5–70°). The mixture was refluxed gently (large quantities of SO_2 and HCl were evolved) for 15 minutes. It was then allowed to cool and divided between two 4-liter beakers, each containing about 500 g. of ice and 500 cc. of water. The mixture was stirred frequently until a vigorous reaction set in. The reaction was kept under control by the addition of ice. Finally precipitation was completed by adding more water to bring the total volume to approximately 7.5 liters. The mixture was then heated on the steam-bath for 1.5 hours, cooled, and filtered. This procedure was repeated with 40 g. then 20 g. of starting material, combining all filtrates and all precipitates.

5,7,8-Trichloro-6-hydroxyquinoline. The above filtrate was heated to about 80°, made alkaline with 40% sodium hydroxide, and filtered while hot from the precipitated starting material, which amounted to 20 g. The alkaline filtrate was acidified to *p*H about 5 and 16 g. of 5,7,8-trichloro-6-hydroxyquinoline filtered off. After recrystallization from dilute alcohol, then from methanol it was obtained as colorless needles m.p. 241–241.5° after slight sintering at 235°; lit. 244° (1).

Oxidation of 5,7,8-trichloro-6-hydroxyquinoline. A solution of 1.0 g. of 5,7,8-trichloro-6-hydroxyquinoline in 40 cc. of concentrated nitric acid was boiled gently for one hour. The solution was then evaporated almost to dryness on the water-bath in a current of air. The residue was dissolved in a small volume of hot water and allowed to cool. Light yellow crystals (0.37 g. 50%) of nicotinic acid nitrate, m.p. 189–191° were obtained.

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[3] We are indebted to the Winthrop Chemical Co. for the 6-methoxy-8-nitroquinoline used in this work.

[4] All C, H, and N analyses were done by Dr. T. S. Ma.

The nicotinic acid nitrate was dissolved in about 10 cc. of water, the solution neutralized to methyl red with dilute sodium hydroxide solution and an excess of copper sulfate solution added. The precipitated nicotinic acid copper salt was filtered off, washed free of sulfate with water and then suspended in about 25 cc. of water containing 0.10 g. of ammonium nitrate. H_2S was passed into the suspension to precipitate the copper, the solution of nicotinic acid was filtered off and concentrated to small volume. On cooling, about 0.2 g. (40%) of colorless nicotinic acid crystals, m.p. 229–231°, separated. Recrystallization from water raised the melting point to 231–232°.

5,7,8-Trichloro-6-acetoxyquinoline. Acetylation of the 5,7,8-trichloro-6-hydroxyquinoline with acetic anhydride gave colorless needles m.p. 138.5–139.5°; lit. 139° (1).

x,y,z-Trichloro-6-methoxy-8-nitroquinoline. The original precipitate was extracted with 1500 cc. of hot concentrated hydrochloric acid, leaving a residue of about 20 g. From this material there was obtained by recrystallization from benzene, then dioxane, about 10 g. of a trichloro-6-methoxy-8-nitroquinoline in the form of pale yellow needles, m.p. 203.5–204°.

Anal. Calc'd for $C_{10}H_5Cl_3N_2O_3$: C, 39.0; H, 1.62; N, 9.10.
Found: C, 38.44; H, 1.81; N, 8.90.

x,y,z-Trichloro-6-methoxy-8-aminoquinoline. To a solution of 70 g. of stannous chloride in 130 cc. of hydrochloric acid and 130 cc. of water was added a solution of 18 g. of the x,y,z-trichloro-6-methoxy-8-nitroquincline in 450 cc. of dioxane, with cooling so that the temperature did not exceed 50°. The mixture was allowed to stand 24 hours at room temperature, and the precipitated complex filtered off and washed with dilute hydrochloric acid. The complex was decomposed with aqueous sodium hydroxide and the amine extracted with ether. The ethereal solution was evaporated to dryness and the residue recrystallized from alcohol to yield about 9 g. of yellow needles; m.p. 212.5–213°.

Anal. Calc'd for $C_{10}H_7Cl_3N_2O$: N, 10.10. Found: N, 10.24.

3,5 (or 7)-Dichloro-6-methoxy-8-nitroquinoline. The hot, concentrated hydrochloric acid filtrate from extraction of the trichloromethoxyquinoline was diluted with a large amount of water and yielded a precipitate of 31.6 g. Crystallization from isopropanol gave 12.5 g. of yellow needles, m.p. 213–219°. Recrystallization raised the m.p. to 223.5–224.5°.

Anal. Calc'd for $C_{10}H_6Cl_2N_2O_3$: C, 44.00; H, 2.20; Cl, 26.0.
Found: C, 43.98; H, 2.34; Cl, 25.95.

Oxidation of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline. A solution of 8 g. of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline in 300 cc. of concentrated nitric acid was refluxed for 20 hours, when a small sample showed no precipitation with dilute sodium hydroxide. The solution was then evaporated to dryness and the residue taken up in 200 cc. of water. The *p*H was adjusted to 2 with sodium hydroxide solution; crystallization at 0° overnight yielded 1.32 g. (28.5%) of yellow crystals, m.p. 168–169.5°. Two recrystallizations from water raised the melting point to 170–171°. This corresponds to the reported melting point of 5-chloronicotinic acid (2).

Anal. Calc'd for $C_6H_4ClNO_2$: Cl, 22.5; Neutral Equiv., 157.5.
Found: Cl, 22.6; Neutral Equiv., 157.5.

3,5 (or 7)-Dichloro-6-methoxy-8-aminoquinoline. To a solution of 94 g. of stannous chloride in 170 cc. of hydrochloric acid and 250 cc. of water was added a solution of 24 g. of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline in 500 cc. of hydrochloric acid. The mixture was cooled during the addition to maintain the temperature at about 45°. The mixture was allowed to stand for 24 hours at room temperature and the resulting complex filtered off and washed with dilute hydrochloric acid. The complex was decomposed with aqueous sodium hydroxide and the amine extracted with ether. The ethereal solution was evaporated to dryness and the residue crystallized from alcohol to yield 17.5 g. of pale yellow needles; m.p. 130.5–131.5°.

Anal. Calc'd for $C_{10}H_8Cl_2N_2O$: N, 11.5. Found: N, 11.39.

3,5 (or 7)-Dichloro-6-methoxy-8-iodoquinoline. A solution of 10 g. of 3,5 (or 7)-dichloro-6-methoxy-8-aminoquinoline in 100 cc. of concentrated sulfuric acid was diazotized at 5–10° with 3.4 g. of sodium nitrite in 40 cc. of sulfuric acid and 500 cc. of glacial acetic acid.

The solution was allowed to stand 20–25 minutes and then diluted with 500 cc. of ice and water. A solution of 3.5 g. of urea in a little water was then added and the solution allowed to stand 20 minutes longer. A solution of 8.2 g. of potasium iodide in 80 cc. of water was then added. The mixture was allowed to stand for 30 minutes, then heated on the steam-bath till evolution of nitrogen ceased.

The precipitate was filtered off and thoroughly washed with water and dried. The solid was crystallized from benzene (using carbon) to yield 9.7 g. of pale buff colored needles, m.p. 218–219°.

Anal. Calc'd for $C_{10}H_6Cl_2INO$: I, 35.9. Found: I, 35.8.

3,5,7,8-Tetrachloro-6-methoxyquinoline. From the isopropanol mother liquors (crystallization of the 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline) was obtained by fractional crystallization from acetone about 1.8 g. of fine colorless needles, m.p. 188–188.5°.

Anal. Calc'd for $C_{10}H_5Cl_4NO$: C, 40.4; H, 1.68; M.W., 297.
Found: C, 40.38; H, 2.07; M.W. (Rast), 292.

Oxidation with nitric acid yielded 5-chloronicotinic acid, which did not depress the melting point of the chloronicotinic acid obtained from 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline.

Experiment II. To 50 g. of 6-methoxy-8-nitroquinoline in a 1-liter round bottomed flask with a distilling head, condenser, and receiver was added 350 cc. of sulfuryl chloride. The flask was placed in a water-bath at 60° and the temperature was raised gradually to keep up a rapid distillation. After about 10 minutes, the lumps of solid which had formed were broken up, after which distillation was continued. After 35 minutes, the mixture had become practically dry. The solid cake which remained was extracted with about 700 cc. of conc'd hydrochloric acid in several portions, the mixture being heated to boiling with each portion of acid, cooled, and filtered.

A residue of 9.5 g. of acid-insoluble matter was obtained. Crystallization from benzene or isopropanol gave about 4.5 g. of the same x,y,z-trichloro-6-methoxy-8-nitroquinoline isolated in Experiment I (m.p. 202.5–204°).

The hydrochloric acid solution at this point had a volume of about 750 cc. and was 11 *N* in HCl. Water (180 cc.) was added, the solution left in the refrigerator overnight and a small gummy precipitate filtered off. One hundred twenty cc. of water was added to the filtrate and 2.24 g. of precipitate m.p. 150–188° removed. The solution was now diluted to about 2500 cc. with water and 19 g. of precipitate melting at 190–217° obtained. One crystallization from benzene-hexane yielded 10.3 g. of 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline, melting at 223.5–224.5° with sintering at 219°. The mother liquor from this crystallization was evaporated to dryness. Fractional crystallization of the residue from acetone yielded 1 g. of 3,5,7,8-tetrachloro-6-methoxyquinoline, m.p. 183–186°. Recrystallization from ethyl acetate raised the melting point to 188–188.2°.

The acid solution from the precipitation of the crude 3,5 (or 7)-dichloro-6-methoxy-8-nitroquinoline was concentrated to about 60 cc. *in vacuo*, diluted, made alkaline with sodium hydroxide solution, and extracted with benzene. At this point, 14.2 g. of material insoluble in alkali or benzene was filtered off. By extraction with boiling dilute alkali, a residue of 5.4 g. of 6-methoxy-8-nitroquinoline was obtained, together with an alkaline solution which on adjusting the *p*H to 5 precipitated about 7 g. of 5,7,8-trichloro-6-hydroxyquinoline, m.p. 225–235°. The benzene solution was evaporated to dryness leaving a residue of 10.7 g. Fractional precipitation from hydrochloric acid followed by crystallizations from benzene, then methanol yielded about 1.5 g. of 5,7,8-trichloro-6-methoxyquinoline, m.p. 144.5–145.0° (slight sintering at 144.0°). About 3 g. of 6-methoxy-8-nitroquinoline was also recovered in the course of the fractional precipitations.

Anal. Calc'd for $C_{10}H_6Cl_3NO$: C, 45.7; H, 2.38; N, 51.33; Cl, 40.6; M.W., 262.5.
Found: C, 45.64; H, 2.69; N, 5.23; Cl, 39.2; M.W. (Rast), 257.

A sample of the 5,7,8-trichloro-6-hydroxyquinoline on methylation with dimethyl sulfate, gave 5,7,8-trichloro-6-methoxyquinoline, which did not depress the melting point of the above material.

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SUMMARY

1. A study of the reaction between 6-methoxy-8-nitroquinoline and sulfuryl chloride has been made.

2. A number of chlorinated quinoline derivatives not previously described have been prepared.

3. A number of chlorinated quinoline derivatives have been evaluated as antimalarials.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. V. STUDIES IN THE ACRIDINE SERIES. 9-N-HETEROCYCLIC ACRIDINES AND 9-ACRIDYLSULFANILAMIDES[1]

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With the synthesis of Atabrine and the demonstration of its high antimalarial activity a little over a decade ago (1), interest in compounds of related structure has expanded tremendously. Significantly, nearly all the effort expended in these researches was concerned with derivatives of 9-aminoacridine. This was principally due to the fact that only the 9-N-substituted aminoacridines exhibited plasmodicidal activity to any appreciable degree. By far, the bulk of the acridine compounds studied carried aminoalkamino groups of the type $-NH(CH_2)_nNR_2$ in the 9-position. Some notable exceptions were the heterocyclic substituted acridines recently described by Burckhalter (2). However, even in these latter cases the 9-amino nitrogen was part of an aliphatic and not a heterocyclic system. In view of this it was thought of interest to prepare certain substituted 9-aminoacridines in which the nitrogen atom of the amino group was an integral part of a heterocyclic system, *viz.* 6-methoxy-1,2,3,4-tetrahydroquinoline. In addition, the introduction of certain substituted sulfanilamido groups in the 9-position of the acridine molecule was carried out in order to determine the effect of these groups upon antimalarial activity.

With the exception of 9-chloroacridine, where anhydrous ether was employed as a solvent, 6-methoxytetrahydroquinoline was condensed with the variously substituted acridines in phenol at 90–100°. The condensation of 3,9-dichloro-7-methoxyacridine with sulfanilamide, sulfapyridine, and sulfathiazole gave best results in *n*-amyl alcohol at 120° yielding, in all cases, the corresponding hydrochlorides. With 2-aminothiazole, phenol proved to be the better solvent.

Antimalarial activity towards *P. gallinaceum* (chick infection) (3) was found present, in small degree, in compounds SN[2] 2762, 2667, and 2514 at the respective maximum tolerated doses. The remainder of the compounds were devoid of this property.

EXPERIMENTAL[3]

9-(6-Methoxytetrahydroquinolino)acridine (SN-2716). A solution of 5 g. of 9-chloroacridine (4) in 225 ml. of anhydrous ether was treated with 7.6 g. (2 moles) of 6-methoxytetrahydroquinoline[4] in 50 ml. of anhydrous ether and the mixture kept at room temperature

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] The Survey Numbers (SN) are the identification numbers assigned by the Malaria Survey Office of the National Research Council.

[3] Analyses by Ass't Chemists L. R. Modlin and E. A. Garlock; m.p.'s are uncorrected.

[4] Prepared by high-pressure hydrogenation over copper chromite catalyst of 6-methoxyquinoline; for preparation of latter see Skraup, *Monatsh.*, **6**, 760 (1885).

for 60 hrs. The resulting orange solution was filtered from a small amount of insoluble matter, washed with water, dried over sodium sulfate and concentrated to small volume *in vacuo*. The residual, dark colored, oily crystals were covered with 40 ml. of ethanol and kept in the refrigerator for 12 hours, yielding a bright orange, crystalline product which was filtered, washed with a little cold ethanol, and dried; 5.2 g. (65%). Three recrystallizations from acetone afforded stout, orange prisms, m.p. 190–191.5°.

Anal. Calc'd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92.
Found: C, 81.35; H, 5.95.

3-Chloro-9-(6-methoxytetrahydroquinolino)acridine (SN-2637). A mixture of 8.1 g. of 3,9-dichloroacridine (5), 5.85 g. (1.1 moles) of 6-methoxytetrahydroquinoline, and 74 g. of phenol was heated in an oil-bath at 90–100° for 2 hours. After cooling, the melt was poured into 300 ml. of cold 10% sodium hydroxide and the resulting colored syrup taken up in ether. The latter solution was washed with water, dried over sodium sulfate, and concentrated to small volume *in vacuo*, yielding 2.6 g. (crop I) of dark red prisms, m.p. 192–194°. The concentrated mother liquor was freed of excess 6-methoxytetrahydroquinoline by steam distillation. The residual reddish-purple syrup, after trituration with ether and seeding, afforded 3.2 g. (crop II) of crystalline material. After one recrystallization from methanol 2.4 g. of dark red prisms, m.p. 191–193°, was recovered. Total yield of pure material 5 g. (42%).

Anal. Calc'd for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.11.
Found: C, 73.43; H, 5.27.

7-Methoxy-9-(6-methoxytetrahydroquinolino)acridine (SN-2634). Twelve and seven-tenths grams of 7-methoxy-9-chloroacridine (4), 9.4 g. (1.1 moles) of 6-methoxytetrahydroquinoline, and 80 g. of phenol were heated together at 90–100° for 2 hours. The colored melt was poured into 350 ml. of cold 10% sodium hydroxide and the product extracted with ether. After washing the latter solution successively with dilute sodium hydroxide and water, concentration (*vacuo*) yielded a syrup from which the excess 6-methoxytetrahydroquinoline was removed by steam distillation. The resulting oil was taken up in ether and dried. From the ether a semi-crystalline mass was obtained which, after one trituration with 30–60° petroleum ether, followed by recrystallization from 50% methanol, yielded 8.5 g. of a bright orange powder of indefinite melting range 118–135°. Upon crystallization from absolute methanol the product separated as reddish-orange prisms which, however, were soon contaminated by the appearance of a by-product which crystallized in clusters of amber prisms. Owing to the marked difference in color as well as in crystalline form, the two substances were readily separated mechanically. Recrystallization of 6.6 g. of the orange prisms from methanol gave 5.7 g. of pure material, m.p. 138–140°.

Anal. Calc'd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99.
Found: C, 77.69; H, 6.03.

The amber colored by-product (1.1 g.) after recrystallization from methanol, melted at 151–153° and was identified as the intermediate 7-methoxy-9-phenoxyacridine by mixed m.p. with an authentic specimen, as well as by analysis.

3-Chloro-7-methoxy-9-(6-methoxytetrahydroquinolino)acridine (SN-2762). Seven and one-tenth grams of 3,9-dichloro-7-methoxyacridine (5) was condensed with 4.6 g. (1.1 moles) of 6-methoxytetrahydroquinoline in 45 g. of phenol as described above. The cooled, colored reaction mixture was poured into 200 ml. of 10% sodium hydroxide and the precipitated gum taken up in ether. From the dried ethereal solution there separated, on concentration *in vacuo*, a dark orange, crystalline powder which was recrystallized from ethanol, yielding 4.3 g. (crop I) of bright orange plates, m.p. 168–170°. The alcoholic mother liquor yielded, upon further concentration, 3.5 g. of less pure product which was recrystallized from acetone affording 2.5 g. (crop II) of relatively pure material, m.p. 161–164° (total yield, 6.8 g. or 65%). Crops I and II were combined and recrystallized from ethanol yielding 5.7 g. of pure product, m.p. 172–174°.

Anal. Calc'd for $C_{24}H_{21}ClN_2O_2$: C, 71.20; H, 5.23.
Found: C, 71.35; H, 5.45.

3-Chloro-7-methoxy-9-(8-amino-6-methoxyquinolino)acridine (SN-2667). The condensation of 7 g. of 3,9-dichloro-7-methoxyacridine with 4.4 g. (1 mole) of 6-methoxy-8-aminoquinoline[5] in 45 g. of phenol was carried out as previously described. The cooled melt was poured into 250 ml. of 10% sodium hydroxide and the yellow precipitate collected. It was successively washed by decantation with 5% sodium hydroxide then with water and finally air-dried. The crude material was purified by dissolving in 450 ml. of a hot mixture of chloroform-methanol (60:40) and concentrating to the point of incipient crystallization. After 24 hours (room temperature), 6.3 g. (60%) of bright yellow needles was collected; m.p. 244–245°.

Anal. Calc'd for $C_{24}H_{18}ClN_3O_2$: C, 69.16; H, 4.35.
Found: C, 69.43; H, 4.29.

3-Chloro-7-methoxy-9-(2-aminothiazolyl)acridine (SN-1440). Five grams of 3,9-dichloro-7-methoxyacridine was heated with 1.8 g. (1 mole) of 2-aminothiazole in 32 g. of phenol at 90–100° for 2 hours. The dark red melt was cooled, poured into 250 ml. of cold 10% sodium hydroxide and the red precipitate collected and washed several times with water by decantation. The yield of crude, air-dried product was 5.5 g. (86%). Recrystallization from ethanol afforded 2.3 g. of dark red microprisms, m.p. 246–247° (decomp.).

Anal. Calc'd for $C_{17}H_{12}ClN_3OS$: C, 59.73; H, 3.54.
Found: C, 59.41; H, 3.99.

N^4-[9-(3-Chloro-7-methoxyacridyl)]sulfanilamide hydrochloride (SN-188). A mechanically stirred mixture of 7 g. of 3,9-dichloro-7-methoxyacridine and 4.35 g. (1 mole) of sulfanilamide in 50 ml. of *n*-amyl alcohol was heated at 120° (oil-bath) for 2.25 hours. The bright orange, microcrystalline precipitate was filtered, triturated with hot (100°) amyl alcohol, washed with ether, and dried; the yield was 9.2 g. (80%). Recrystallization from a large volume of ethanol, in the presence of a few drops of alcoholic HCl to prevent hydrolysis of the salt, afforded minute, bright orange plates, m.p. 305–307° (decomp.).

Anal. Calc'd for $C_{20}H_{17}Cl_2N_3O_3S$: C, 53.34; H, 3.81.
Found: C, 53.00; H, 3.90.

N^1-(2-Thiazolyl)-N^4[9-(3-chloro-7-methoxyacridyl)]sulfanilamide hydrochloride (SN-2514). The condensation of 7 g. of 3,9-dichloro-7-methoxyacridine with 6.42 g. (1 mole) of sulfathiazole in 50 ml. of *n*-amyl alcohol was carried out as described in the preceding preparation. The washed and dried product consisted of a yellow-orange powder, 11 g. (81%). It was recrystallized from a large volume of ethanol, in the presence of a little alcoholic HCl and recovered as golden-yellow leaves, m.p. 301–303°.

Anal. Calc'd for $C_{23}H_{18}Cl_2N_4O_3S_2$: C, 51.78; H, 3.40.
Found: C, 51.71; H, 3.46.

N^1-(2-Pyridyl)-N^4[9-(3-chloro-7-methoxyacridyl)]sulfanilamide hydrochloride (SN-2515). Seven grams of 3,9-dichloro-7-methoxyacridine and 6.27 g. (1 mole) of sulfapyridine were condensed in 50 ml. of *n*-amyl alcohol in the above manner. The bright yellow, crystalline product, 10 g. (75%) crystallized from ethanol in minute, yellow, rhombic plates, m.p. 302–303° (decomp.).

Anal. Calc'd for $C_{25}H_{20}Cl_2N_4O_3S$: C, 56.93; H, 3.82.
Found: C, 56.99; H, 3.96.

SUMMARY

The synthesis of several N-substituted heterocyclic as well as certain 9-acridylsulfanilamides is described. A few of these compounds showed slight antimalarial activity.

BETHESDA 14, MD.

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[5] Prepared by reduction ($SnCl_2$+HCl) of 6-methoxy-8-nitroquinoline; for latter see *Chem. Absts.*, **22**, 1216 (1928).

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. VI. SOME HETEROCYCLIC SULFANILAMIDE DERIVATIVES[1]

LEWIS J. SARGENT AND LYNDON SMALL

Received November 15, 1945

The remarkable bacteriostatic powers of the sulfanilamide group are so well established that it was logical that this class of compounds should be considered when orientation experiments were undertaken in a search for new antimalarials. The therapeutic effect of several sulfonamide derivatives has been demonstrated in connection with simian as well as avian malaria (1, 2, 3, 4). In some cases a residual immunity was found to persist for periods up to three months (2), but it was questionable if any complete cure was effected. Moreover, recent studies in this laboratory (5) showed that sulfadiazine and, to a lesser extent, sulfaguanidine exhibit definite prophylactic properties in avian infections. These interesting findings justified further exploration of this field of compounds. The availability of the following heterocyclic amines: 6-methoxy-1,2,3,4-tetrahydroquinoline,[2] 6-methoxy-8-aminoquinoline,[2] 1,2,3,4-tetrahydroquinoline,[2] 1,2,3,4-tetrahydroisoquinoline (6), *trans*-decahydroquinoline (7), and 9,10-dihydroacridine (8), prepared in connection with other work in progress in this laboratory, made it possible to prepare a mixed series of sulfonamide derivatives with the view of studying their possible antimalarial properties.

The condensation of the various heterocyclic amines with N^4-acetylsulfanilyl chloride was effected in one-half minute in boiling pyridine solution, from which the crude N-acetylsulfanilamides were precipitated with hot water. In the case of dihydroacridine a longer period of heating (3 minutes) was required to complete the reaction. Hydrolysis of the N-acetyl groups proceeded smoothly with either aqueous or alcoholic HCl (8–15%); alcoholic alkali proved ineffective.

The following experimental details (condensation as well as hydrolysis) were generally adhered to in the preparation of the several compounds described below. We are indebted to Ass't Chemist E. A. Garlock for the analytical data; m.p.'s are uncorrected.

EXPERIMENTAL

N^4-Acetyl-N^1-(6-methoxy-1,2,3,4-tetrahydroquinolyl)sulfanilamide. An intimate mixture of 6 grams of 6-methoxy-1,2,3,4-tetrahydroquinoline and 9 grams (5% in excess of 1 mole) of N^4-acetylsulfanilyl chloride was covered with 25 ml. of purified, anhydrous pyridine, and the red solution boiled for one-half minute. The reaction mixture was poured

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] 6-Methoxy-1,2,3,4-tetrahydroquinoline was prepared by high-pressure reduction (copper-chromite) of 6-methoxyquinoline; for latter see Skraup, *Monatsh.*, **6**, 760 (1885). 6-Methoxy-8-aminoquinoline was prepared by reduction ($SnCl_2$ + HCl) of 6-methoxy-8-nitroquinoline; for latter see *Chem. Abstr.*, **22**, 1216 (1928). 1,2,3,4-Tetrahydroquinoline was prepared by high-pressure reduction (copper-chromite) of quinoline.

TABLE I

SULFANILAMIDE DERIVATIVES

S.N.*	COMPOUND	APPEARANCE	FORMULA	M.P., °C	ANALYSES			
					Calc'd		Found	
					C	H	C	H
	N^4-Acetyl-N^1-(6-methoxy-1,2,3,4-tetrahydroquinolyl) sulfanilamide	Stout prisms[a]	$C_{18}H_{20}N_2O_4S$	223–224	59.98	5.59	59.95	5.94
2511	N^1-(6-Methoxy-1,2,3,4-tetrahydroquinolyl)-sulfanilamide	Prisms[a]	$C_{16}H_{18}N_2O_3S$	153.5–155	60.35	5.70	60.60	5.78
	N^4-Acetyl-N^1-(8-amino-6-methoxyquinolyl) sulfanilamide	Silky needles[b]	$C_{18}H_{17}N_3O_4S$	211–213	58.21	4.61	58.15	4.66
190	N^1-(8-Amino-6-methoxyquinolyl)sulfanilamide	Slender prisms[b]	$C_{16}H_{15}N_3O_3S$	190–192	58.34	4.59	58.13	4.55
	N^4-Acetyl-N^1-(1,2,3,4-tetrahydroquinolyl) sulfanilamide	Irreg. shaped prisms[a]	$C_{17}H_{18}N_2O_3S$	178–179	61.80	5.49	61.78	5.63
2512	N^1-(1,2,3,4-Tetrahydroquinolyl)sulfanilamide	Striated prisms[a]	$C_{15}H_{16}N_2O_2S$	129–130.5	62.48	5.59	62.27	5.63
	N^4-Acetyl-N^1-(1,2,3,4-tetrahydroisoquinolyl)sulfanilamide	Stout prisms[c]	$C_{17}H_{18}N_2O_3S$	181.5–183	61.80	5.49	62.06	5.81
2502	N^1-(1,2,3,4-Tetrahydroisoquinolyl)-sulfanilamide	Flat, rect. prisms[a]	$C_{15}H_{16}N_2O_2S$	179–180.5	62.48	5.59	62.39	5.64
	N^4-Acetyl-N^1-(*trans*-decahydroquinolyl) sulfanilamide	Irreg. shaped prisms[a]	$C_{17}H_{24}N_2O_3S$	145–146	60.69	7.19	60.91	6.90
2510	N^1-(*trans*-Decahydroquinolyl)sulfanilamide	Plates[a]	$C_{15}H_{22}N_2O_2S$	128–129.5	61.19	7.53	60.83	7.29
	N^4-Acetyl-N^1-(9,10-dihydroacridyl)sulfanilamide	Minute rhombic-shaped prisms[c]	$C_{21}H_{18}N_2O_3S$	233–234	66.65	4.79	66.58	4.98
	N^1-(9,10-Dihydroacridyl)sulfanilamide	Hexagonal plates[a]	$C_{19}H_{16}N_2O_2S$	203–204.5	67.84	4.79	67.61	4.51

* The Survey Numbers (SN) are the identification numbers assigned by the Malaria Survey Office of the National Research Council.
[a] 70% Ethanol.
[b] Ethanol.
[c] Methanol.

into 200 ml. of boiling water and the product filtered, washed with water, and dried. Recrystallization from slightly diluted ethanol (Norit) afforded 11.6 grams of stout prism clusters, m.p. 222–224°.

N^1-(6-Methoxy-1,2,3,4-tetrahydroquinolyl)sulfanilamide. To a suspension of 8.4 grams of the above material in 68 ml. of ethanol, 17 ml. of concentrated HCl was added and the mixture heated under reflux (steam-bath) for 30 minutes. The resulting solution was poured into 500 ml. of cold water containing an excess of ammonium hydroxide, and the product filtered, washed with water, and dried. After two recrystallizations from 70% ethanol, 6.8 grams of colorless prisms was obtained, m.p. 153.5–155°.

N^4-Acetyl-N^1-(9,10-dihydroacridyl)sulfanilamide. In the condensation of 3.4 grams of 9,10-dihydroacridine with 4.6 grams of N^4-acetylsulfanilyl chloride in 18 ml. of anhydrous pyridine, it was necessary to boil the solution for at least three minutes to ensure complete reaction.

N^1-(9,10-Dihydroacridyl)sulfanilamide. A suspension of one gram of N^4-acetyl-N^1-(9,10-dihydroacridyl)sulfanilamide in 8 ml. of absolute ethanol with 2 ml. of conc'd HCl was heated on the steam-bath (reflux) for 20 minutes. The dark-colored solution was filtered from a small amount of insoluble material and the filtrate poured into cold water (50 ml.). The gum which separated solidified when triturated with a little warm 2 *N* HCl—probably the hydrochloride. The latter was collected and converted to the free base by digesting with warm 2 *N* NH_4OH. Crystallization from 70% ethanol yielded colorless leaves contaminated with some prisms; the mixture melted over the range 155–175°. It was found that the prismatic material could readily be removed by sublimation at 125–130°/0.5 mm.; this proved to be 9,10-dihydroacridine, identified by its melting point (172–173°) alone or mixed with an authentic specimen. The non-volatile or desired product crystallized from 70% ethanol in glistening, hexagonal plates, m.p. 203–204.5°.

SUMMARY

A series of heterocyclic substituted sulfanilamide derivatives has been prepared. Two members of the series, SN 190 and SN 2510, showed slight plasmodicidal activity towards *P. gallinaceum* (chick infection).

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

ARYLSULFONYL ESTERS OF NITRO ALCOHOLS

J. L. RIEBSOMER[1]

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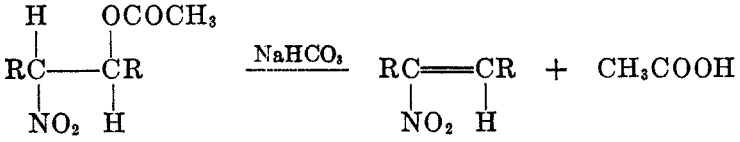
Nitrate (1) and phosphate (2) esters of certain aliphatic nitro alcohols have been reported. Organic esters may be obtained by the reaction of the nitro alcohols with organic acids, acid anhydrides, or acid halides. The most extensive series of organic esters was prepared by Tindall (3). In view of the interest in the use of these compounds as plasticizers it seemed worth while to prepare a series of arylsulfonyl esters which might be useful for the same purpose.

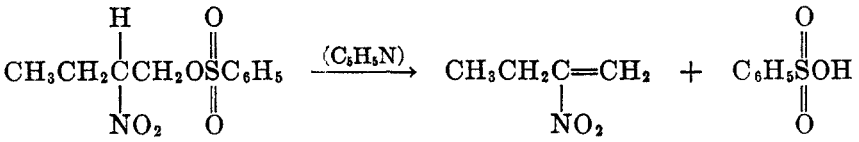
The appropriate arylsulfonyl chloride was mixed with the nitro alcohol and pyridine was added to react with the hydrogen chloride formed. The following represents a typical reaction:

The best yields were obtained with one of the monohydric nitro alcohols. The diols and triols gave less satisfactory yields. 2-Nitro-1-butanol gave none of the expected ester with benzenesulfonyl chloride and only a low yield with *p*-toluenesulfonyl chloride. This behavior can probably be accounted for by the observation made by Schmidt and Rutz (4) that nitro olefins form readily when nitro esters of type (I) are warmed with sodium bicarbonate.



(I)

It is to be noted that the carbon atom attached to the nitro group has a single hydrogen atom attached. The hydrogen atom attached to the carbon bearing the nitro group is activated. In the example under discussion it is possible that the ester (II) was formed, but in the presence of pyridine was transformed into



(II)

2-nitro-1-butene and benzenesulfonic acid.

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TABLE I

ARYLSULFONYL ESTERS OF NITRO ALCOHOLS

COMPOUND	M.P., °C	YIELD, %	ANALYSES			
			Found		Calc'd	
			%N	%S	%N	%S
1. $(CH_3)_2C(NO_2)CH_2OSO_2C_6H_4CH_3$-*p* 2-Nitroisobutyl *p*-toluenesulfonate	73–74	76.7	5.38	12.28	5.13	11.72
2. $C_2H_5CH(NO_2)CH_2OSO_2C_6H_4CH_3$-*p*..... 2-Nitrobutyl *p*-toluenesulfonate	52.5–53	20.0	5.18	12.11	5.13	11.72
3. *p*-$CH_3C_6H_4SO_2OCH_2C(CH_3)(NO_2)$-$CH_2OSO_2C_6H_4CH_3$-*p* ..... 2-Nitro-2-methyltrimethylene *p*-toluenesulfonate	98.5–99	48.0	3.61	14.46	3.15	14.43
4. *p*-$CH_3C_6H_4SO_2OCH_2C(C_2H_5)(NO_2)$-$CH_2OSO_2C_6H_4CH_3$-*p*..... 2-Nitro-2-ethyltrimethylene *p*-toluenesulfonate	153–154	68.9	3.53	14.42	3.04	13.99
5. $(p\text{-}CH_3C_6H_4SO_2OCH_2)_3CNO_2$..... Tris(*p*-toluenesulfonoxymethyl)nitromethane	122–123	39	2.32	15.40	2.28	15.66
6. $(CH_3)_2C(NO_2)CH_2OSO_2C_6H_5$..... 2-Nitroisobutyl benzenesulfonate	56	67.9	5.47	12.63	5.44	12.34
7. $C_6H_5SO_2OCH_2C(CH_3)(NO_2)CH_2OSO_2$-$C_6H_5$..... 2-Nitro-2-methyltrimethylene benzenesulfonate	114	58.1	3.64	15.60	3.35	15.40
8. $C_6H_5SO_2OCH_2C(C_2H_5)(NO_2)CH_2OSO_2$-$C_6H_5$..... 2-Nitro-2-ethyltrimethylene benzenesulfonate	69–69.5	44.2	3.53	15.50	3.26	14.90
9. $(C_6H_5SO_2OCH_2)_3CNO_2$..... Tris(benzenesulfonoxymethyl)nitromethane	122–123	28.1	2.88	17.90	2.45	16.8
10. $(CH_3)_2C(NO_2CH_2OSO_2C_6H_4NHCOCH_3$-*p* 2-Nitroisobutyl *p*-acetamidobenzenesulfonate	153–154	45.6	9.21		8.86	
11. [*p*-$CH_3CONHC_6H_4SO_2OCH_2]_2C(CH_3)$-$(NO_2)$..... 2-Nitro-2-methyltrimethylene *p*-acetamidobenzenesulfonate	198	14.4	8.10		7.93	

The relatively low yields with the diols and triols would be expected because of the possibility of the formation of a mixture of esters thus increasing the difficulty of purification.

EXPERIMENTAL

In the general procedure for the preparation of these esters, equivalent quantities of the nitro alcohol and arylsulfonyl chloride were mixed and to this mixture was added slightly more than the equivalent quantity of pyridine. The pyridine was added slowly with stirring to prevent too great a temperature rise. The reaction mixture was warmed over steam for from 5 minutes to one hour depending upon the example involved. After the reaction mixture had cooled, water was added to dissolve any unreacted alcohol and the pyridine hydrochloride. At this stage the ester usually solidified, and the solid was filtered and washed with more water. The crude products were crystallized from methanol, ethanol, or benzene.

A number of variations of the above procedure were tried but with less satisfactory results. Sodium carbonate and sodium hydroxide were used instead of pyridine to remove the hydrogen chloride. The resulting yields were about 20% as compared with yields as high as 76% when pyridine was used. Benzene, chloroform, and xylene were tried as reaction media but in all instances the yields were lowered. Heating above the temperature of a steam-bath likewise reduced the yields.

The effect of time of heating was studied carefully in the reaction of 2-nitro-2-methyl-1-propanol and *p*-toluenesulfonyl chloride. Keeping all other conditions constant and warming the reactants over steam for the indicated period of time, the yields were as follows: one hour, 76.7%; 2 hours, 68%; 3 hours, 65%; 15 hours, 40%.

One typical procedure will be described in detail. Six grams (0.05 mole) of 2-nitro-2-methyl-1-propanol, 9.5 g. (0.05 mole) of *p*-toluenesulfonyl chloride, and 5 ml. of pyridine were mixed in a flask and warmed over steam one hour. After cooling to room temperature, 20 ml. of water was added and the mixture was stirred thoroughly. The ester solidified, was filtered, and washed with cold water. This crude product was crystallized from methanol. Yield, 10.4 grams (76.7%); m.p. 73–74°.

The compounds prepared, together with the yields, melting points, and analyses, are listed in Table I.

ACKNOWLEDGMENT

The author wishes to express his thanks to Commercial Solvents Corporation for assistance in carrying out this work. Thanks are also due Dr. P. J. Baker, Jr. of Commercial Solvents Corporation who suggested this problem.

SUMMARY

Eleven arylsulfonyl esters of nitro alcohols have been synthesized. Some of these compounds may be useful plasticizers.

GREENCASTLE, IND.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS CHEMISTRY LABORATORY,
NEW YORK UNIVERSITY]

2-PHENYLINDOLE-3-ALDEHYDE AND CERTAIN OF ITS CONDENSATION PRODUCTS

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Received November 30, 1945

The original purpose of this study was to accomplish the ring closure to the 4-position of indole-3-acrylic acid derivatives to yield compounds belonging to the benz[cd]indole ring system. While this objective was not realized, a number of condensation products were prepared.

The first attempt to prepare the substituted acrylic acid was by the condensation of malonic acid with 2-phenylindole-3-aldehyde (1) under Perkin conditions; this failed, as did attempts to condense these reagents using organic bases as catalysts. In the hope of obtaining the acrylic acid derivative indirectly, ethyl cyanoacetate and cyanoacetamide condensation products were prepared. However, hydrolytic treatment of these products regenerated the 2-phenylindole-3-aldehyde.

2-Phenylindole-3-aldehyde was oxidized by heating for two hours with 30% hydrogen peroxide. The resulting acid was not the expected 2-phenylindole-3-acid but N-benzoylanthranilic acid; this was proved by analysis and by comparison with an authentic sample. Other attempts to oxidize the aldehyde with less concentrated hydrogen peroxide or with alkaline potassium permanganate gave only smaller yields of benzoylanthranilic acid. It has been reported previously that 3-nitro-2-phenylindole (2), 1-hydroxy-2-phenylindole (3), and 3-nitroso-2-phenylindole (2) are oxidized by alkaline permanganate to give N-benzoylanthranilic acid. 2-Methylindole-3-aldehyde yields N-acetylanthranilic acid under these conditions (4). Angeli and Alessandri (5) ascribed this result to the hydroxymethylene form of the aldehyde.

2-Phenylindole-3-aldehyde fails to give a sodium bisulfite addition product or a positive fuchsin test. It does not give a silver mirror with Tollens reagent nor does it reduce Fehling solution. The failure of these characteristic aldehyde tests with indole-3-aldehyde has been reported (6). However, the successful preparation of the oxime, semicarbazone, and *p*-nitrophenylhydrazone have been reported (7).

EXPERIMENTAL

Ethyl 2-phenylindole-3-(α-cyano)acrylate (II). 2-Phenylindole-3-aldehyde (I) (2.2 g.; 0.01 mole) was refluxed for twenty minutes in a solution consisting of 6 cc. of isopropyl alcohol, 3 cc. of pyridine, 0.5 cc. of piperidine, and 1.5 cc. (0.012 mole) of ethyl cyanoacetate. Crystals separated after dilution with an equal volume of 70% alcohol. Recrystallized from 95% alcohol. (See Chart II).

2-Phenylindole-3-(α-cyano)acrylamide (III). A mixture consisting of I (0.10 g.; 0.0045 mole), cyanoacetamide (0.1 g.), piperidine (0.25 cc.), and absolute alcohol (2.0 cc.) was

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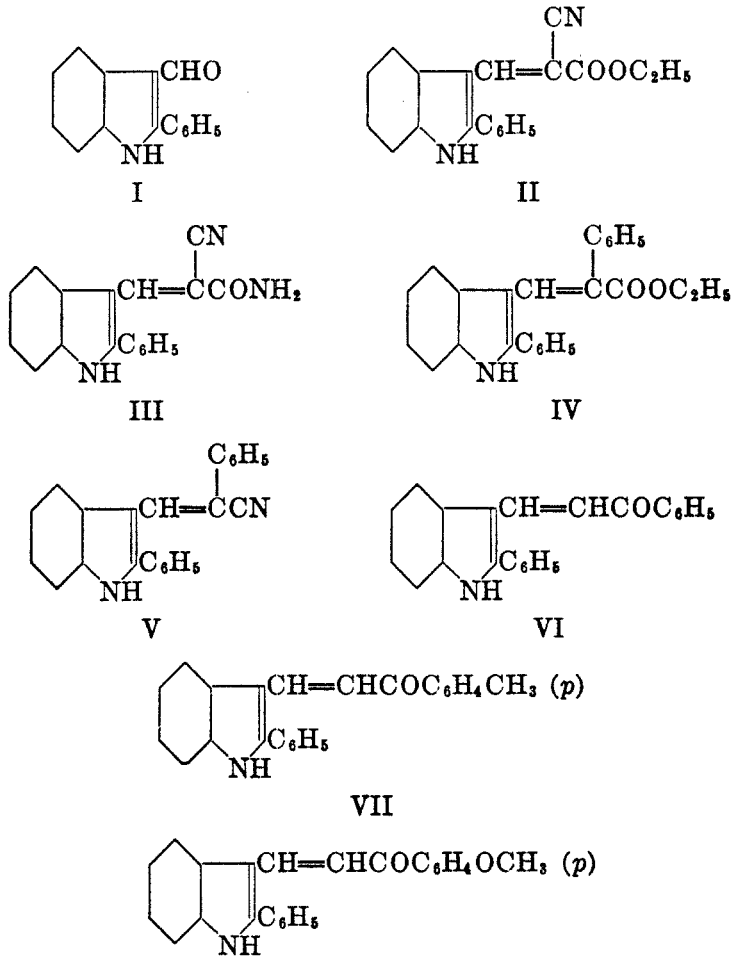
heated on the steam-bath for one-half hour. The product which separated was recrystallized from 50% pyridine-alcohol.

Ethyl 2-phenylindole-3-(α-phenyl)acrylate (IV). Compound I (0.50 g.; 0.0023 mole), ethyl phenylacetate (1 cc.), and piperidine (1 cc.) were refluxed together for one-half hour. Dilution with alcohol, neutralization with acetic acid, and precipitation with water followed. The product was recrystallized from ethyl alcohol.

CHART I



2-Phenylindole-3-(α-phenyl)acrylonitrile (V). Compound I (0.50 g.; 0.0023 mole), benzyl cyanide (0.5 cc.), in 1 cc. of pyridine containing 3 drops of piperidine, were refluxed for six hours. Dilution with 4 cc. of alcohol and addition of water gave a yellow oil which slowly solidified. Recrystallized from alcohol containing ligroin.

β-(2-Phenylindolyl-3)-acrylophenone (VI). Compound I (1 g.; 0.0045 mole), 1 cc. of acetophenone, and 10 drops of piperidine were refluxed for ten minutes. The resulting oil was washed, while hot, with 25 cc. of hot 10% acetic acid. The residue was recrystallized from 15 cc. of alcohol.

p-Methyl-β-(2-phenylindolyl-3)-acrylophenone (VII). A mixture of I (0.50 g.), methyl *p*-tolyl ketone (1 cc.), and 1 cc. of piperidine was refluxed for one-half hour. To the resulting solution were added successively: 8 cc. of alcohol, 1 cc. of glacial acetic acid, and water to the point of cloudiness. The crystals, which formed were recrystallized from ethyl alcohol.

p-Methoxy-β-(2-phenylindolyl-3)-acrylophenone (VIII). A mixture of I (0.5 g.), *p*-methoxyacetophenone (0.50 g.), and 0.5 cc. of piperidine was refluxed for forty minutes. To the red melt were added successively: 3 cc. of alcohol, 1 cc. of glacial acetic acid, and water to the point of cloudiness. The product was recrystallized from ethyl alcohol.

CHART II

CONDENSATION PRODUCTS OF 2-PHENYLINDOLE-3-ALDEHYDE

WITH:[a]	PRODUCT	% YIELD	COLOR AND FORM	M.P. °C	ANAL.					
					Calc'd			Found		
					C	H	N	C	H	N
Ethyl cyanoacetate	(II) $C_{20}H_{16}N_2O_2$	89	Yellow needles	219–220	75.9	5.06	8.86	75.7	5.19	8.87
Cyanoacetamide	(III) $C_{18}H_{12}N_2O_2$	84	Yellow needles	292	75.3	4.53		75.0	4.59	
Ethyl phenylacetate	(IV) $C_{24}H_{21}NO_2$	52	Yellow needles	199–201	81.1	5.92	3.94	81.4	5.96	3.83
Benzyl cyanide	(V) $C_{22}H_{16}N_2$	76	Lemon-yellow needles	176–177[b]			8.75			8.73
Acetophenone	(VI) $C_{22}H_{17}NO$	67	Orange needles	170–171	85.5	5.26	4.34	85.4	5.60	4.36
Methyl *p*-tolyl ketone	(VII) $C_{24}H_{19}NO$	67	Orange platelets	200–201			4.15			4.15
p-Methoxyacetophenone	(VIII) $C_{24}H_{19}NO_2$	78	Orange prisms	176–177			3.97			3.82

[a] See Experimental Part for details of proportions, time of heating, etc.

[b] Partial sintering at 167°.

Oxidation of 2-phenylindole-3-aldehyde (I). Compound I (1 g.) was heated on the steam-bath with 20 cc. of 30% hydrogen peroxide for two hours. The cooled suspension was cautiously made alkaline with dilute sodium hydroxide. The alkaline solution was filtered and the N-benzoylanthranilic acid was precipitated by acidification with hydrochloric acid. After recrystallization from water and from benzene the product melted at 175–176.5°. Mixture with an authentic sample caused no lowering of the melting point.

Anal. Calc'd for $C_{14}H_{11}NO_3$: N, 5.81. Found: N, 5.74.

SUMMARY

1. Condensation products of 2-phenylindole-3-aldehyde with certain active methylene compounds have been prepared using basic catalysts.

2. 2-Phenylindole-3-aldehyde does not have the reducing properties characteristic of aldehydes.

3. Oxidation of 2-phenylindole-3-aldehyde with hydrogen peroxide yields N-benzoylanthranilic acid.

NEW YORK 53, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

THE CHEMISTRY OF CITRININ. I. THE SYNTHESIS OF 2,4-DIMETHOXY-3-ETHYLBENZOIC ACID, AND 2,6-DIMETHOXY-3-METHYLBENZOIC ACID[1]

R. D. SPRENGER[2] AND P. M. RUOFF

Received December 12, 1945

In the course of certain citrinin studies begun in 1940 (1) it seemed advisable to examine some of the evidence presented by Coyne, Raistrick, and Robinson (2) in support of their proposed structure of citrinin (A), a metabolic product of the mold, *Penicillium citrinum.*

According to these investigators the course of the degradation of citrinin was as shown in Figure 1.

Since none of the degradation products (B—F) was known at the time, they based these structural deductions upon chemical behavior and the analysis of certain derivatives. In the case of the two acids (E) and (F), they relied rather heavily upon the divergent chemical behavior of certain pure specimens of the dimethyl ethers of orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) and *p*-orsellinic acid (2,6-dihydroxy-4-methylbenzoic acid) which they had on hand.

Since the major portion of their arguments for the structure of citrinin is based on the correctness of these deductions, a comparison of the properties of the corresponding synthetic compounds is highly desirable.

Accordingly, we have synthesized the acids, 2,4-dimethoxy-3-ethylbenzoic acid (IV) and 2,6-dimethoxy-3-methylbenzoic acid (VII) using straightforward methods as shown in Figure 2 and Figure 3, respectively.

A marked divergency in the melting points of the acids (E) and (F) as obtained by Coyne, Raistrick, and Robinson and the synthetic acids (IV) and (VII) is to be noted. See Table I.

Such results would indicate that the proof of structure based on synthesis of the degradation products of citrinin as well as of citrinin, itself, has yet to be accomplished.[3]

[1] From a thesis to be submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, Syracuse University.

[2] Eaton Foundation Fellow, 1943–46.

[3] The synthesis of 2-ethyl-4-methylresorcinol (C) has now been reported (3, 4, 5), but Robinson and Shah (3) were unable to establish its identity with the corresponding phenolic degradation product of citrinin since the latter, as they stated, "had deteriorated; originally of m.p. 98–99°, it had m.p. 65–70° after an interval of two or three years."

We have also synthesized the dialkyl resorcinol (C) using the methods of Yanagita, Shah and Shah, and Robinson and Shah, starting in the latter case, however, with 2-ethylresorcinol as prepared by the method of Russell, Frye, and Mauldin (6). In each case the same product (m.p. 100–101°, after sublimation) was obtained as confirmed by mixed melting points. Its color reactions however corresponded to those reported by Yanagita.

It is of interest, also, to note that in our hands an attempt to obtain the phenolic degradation product (C) from citrinin, itself, gave us a product whose melting point was 67–70° (see above) instead of 97–99° as previously reported (2).

TABLE I

COMPARISON OF PHYSICAL PROPERTIES

COMPOUND	M.P.°C (UNCOR.)
Acid (E)	97–99 (2)
2,4-Dimethoxy-3-ethylbenzoic acid (IV)	128–129
Acid (F)	142–146 (2)
2,6-Dimethoxy-3-methylbenzoic acid (VII)	117–118

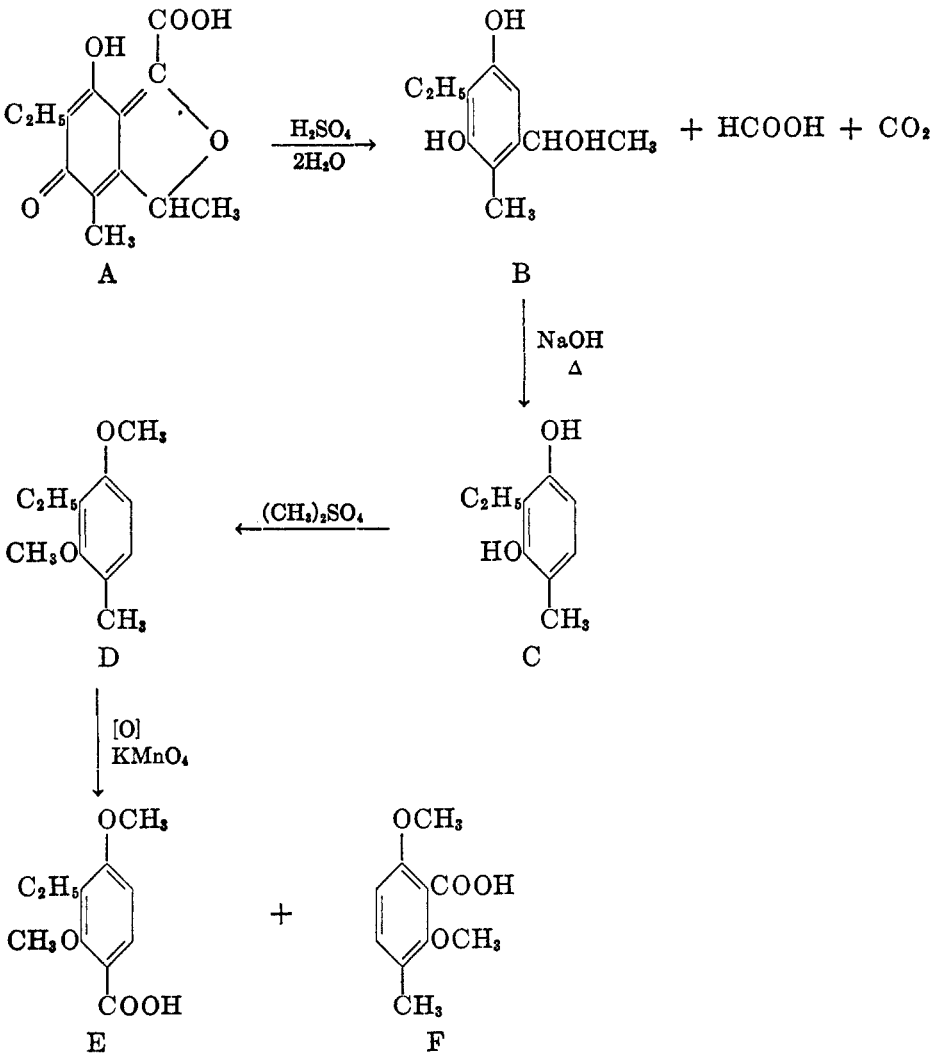

FIG. 1. DEGRADATION OF CITRININ

Acknowledgment. This investigation was made possible by the generous action of the Eaton Laboratories, Norwich, N. Y., in establishing at Syracuse University the Eaton Foundation Research Fellowships. We wish to thank Dr. A. B. Scott and Dr. F. Austin of the Eaton Laboratories for their interest and encouragement.

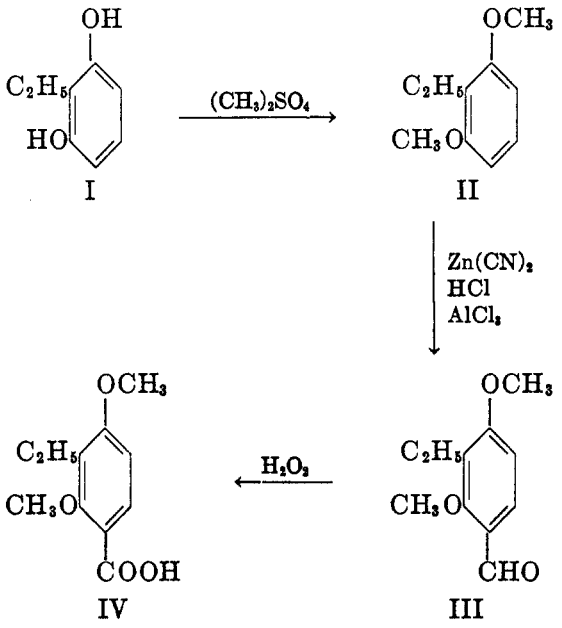

FIG. 2. SYNTHESIS OF 2,4-DIMETHOXY-3-ETHYLBENZOIC ACID

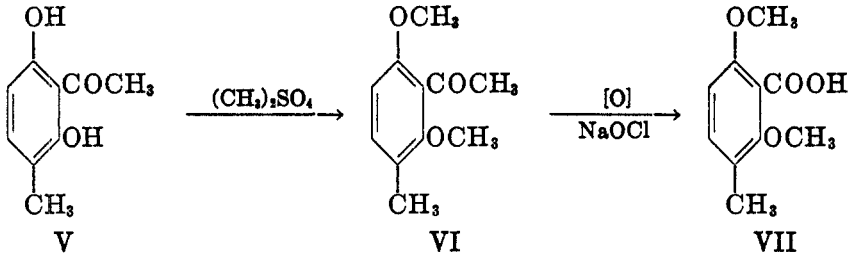

FIG. 3. SYNTHESIS OF 2,6-DIMETHOXY-3-METHYLBENZOIC ACID

EXPERIMENTAL

An attempt to prepare 2,4-dimethoxy-3-ethylbenzoic acid (IV) by the direct methylation of 2,4-dihydroxy-3-ethylbenzoic acid was unsuccessful. Although the latter compound has not been reported in the literature it was readily obtained by the carboxylation of 2-ethylresorcinol. Methylation with dimethyl sulfate or with methyl iodide gave a crystalline compound but the product melted over a wide range and the neutral equivalent indicated only a monomethoxy compound. A strong color reaction with ferric chloride

also indicated incomplete methylation. Use of diazomethane gave an alkali-insoluble compound but hydrolysis of the ester resulted in a compound which corresponded again to the monomethoxy derivative. Accordingly, the following synthesis was utilized.

2,6-Dimethoxyethylbenzene (II). 2-Ethylresorcinol (I) (m.p. 94–95°) as prepared by the method of Russell, Frye, and Mauldin (6) was methylated in the usual fashion with dimethyl sulfate and alkali giving the methoxy compound, which melted at 57–58° after recrystallization from 80% alcohol (70% yield).

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49.
Found: C, 71.98; H, 8.12.

2,4-Dimethoxy-3-ethylbenzaldehyde (III). To a mechanically stirred solution of 7 g. (0.042 mole) of the 2,6-dimethoxyethylbenzene in 40 cc. of dry ether cooled by a freezing mixture, 10 g. (0.085 mole) of zinc cyanide was added followed by 11.3 g. of aluminum chloride (0.085 mole) in 40 cc. of dry ether. Dry hydrogen chloride was passed in for four hours. After keeping the mixture in the refrigerator for 24 hours, the ether was decanted, the aldimine hydrochloride washed with ether and decomposed by heating with 75 cc. of water on the steam-bath for 30 minutes. When cooled, a pale yellow oil separated which crystallized on standing. Decolorization and recrystallization from alcohol gave 5 g. (50%) of yellow needles melting at 59–60°.

The *p*-nitrophenylhydrazone was prepared and crystallized from glacial acetic acid giving orange-red needles melting at 219–220°.

Anal. Calc'd for $C_{17}H_{19}N_3O_4$: N, 12.76. Found: N, 12.98.

2,4-Dimethoxy-3-ethylbenzoic acid (IV). To a solution of 30 cc. of 5% sodium hydroxide and 60 cc. of 3% hydrogen peroxide warmed to 65–70° was added 2 g. (0.01 mole) of the aldehyde (III). After addition of 20 cc. of alcohol the mixture was shaken and heated at 70–75° for twenty minutes. An additional 20 cc. of hydrogen peroxide was added and the mixture warmed for two minutes longer. After cooling, the solution was ether extracted to remove unreacted aldehyde and the aqueous layer made acid to Congo Red with hydrochloric acid. Recrystallization of the precipitated acid from ligroin gave colorless needles (1 g., 47% yield), melting at 128–129°.

Anal. Calc'd for $C_{11}H_{14}O_4$: Mol. wt. 210.2: C, 62.84; H, 6.71.
Found: C, 62.32; H, 6.54; N. E., 208.4.

The acid thus obtained gave no color reaction with either aqueous or alcoholic ferric chloride. It was soluble in alcohol and benzene, slightly soluble in cold and moderately soluble in hot water.

2,6-Dimethoxy-3-methylbenzoic acid (VII). 2,6-Dihydroxy-3-methylacetophenone (V) (m.p. 138–139°) as prepared by the method of Yanagita (4) was methylated in the usual manner with dimethyl sulfate and alkali. A pale yellow oil was obtained which solidified on standing in the cold (m.p. 20–22°) (70% yield). The methoxy ketone (VI) was oxidized directly without further purification as follows:

Chlorine gas was passed into a solution of 18.4 g. (0.46 mole) of sodium hydroxide in a mixture of ice (120 g.) and water (30 cc.) until the solution was neutral to litmus. A solution containing 3.4 g. of sodium hydroxide in 10 cc. water was then added. The mixture was warmed to 60–70° and 6 g. (0.03 mole) of the methoxy ketone (VI) added with vigorous stirring. After stirring for two hours at 60–70° the solution was cooled and treated with 10 g. of sodium bisulfite in 30 cc. of water to destroy excess hypochlorite. Following an ether extraction to remove unreacted ketone, the aqueous layer was acidified with hydrochloric acid. The precipitated acid (3 g., 50% yield) on recrystallization from a benzene-petroleum ether mixture was obtained in the form of colorless prisms which melted at 117–118°. It was soluble in benzene and alcohol, slightly soluble in cold water, and moderately soluble in hot water. No color was given with ferric chloride in either aqueous or alcoholic solution.

Anal. Calc'd for $C_{10}H_{12}O_4$: Mol. wt. 196.2; C, 61.21; H, 6.17.
Found: C, 60.83; H, 6.04; N. E. 197.

SUMMARY

2,4-Dimethoxy-3-ethylbenzoic acid and 2,6-dimethoxy-3-methylbenzoic acid have been prepared. Their melting points do not correspond to those reported for the degradation products of citrinin.

SYRACUSE, N. Y.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

ALKYLATION OF ETHYL MALONATE WITH DIETHOXYMETHYL ACETATE[1]

REYNOLD C. FUSON, WILLIAM E. PARHAM, AND LESTER J. REED

Received December 26, 1945

In an attempt to improve the yield of ethyl ethoxymethylenemalonate (I) by the Claisen method (1), a study has been made of the mechanism of the reaction. The original procedure involved treatment of ethyl malonate with ethyl orthoformate in the presence of acetic anhydride and zinc chloride. It was believed that the two esters underwent condensation with the elimination of ethanol, and that the function of the anhydride was to remove the ethanol.

$$C_2H_5OCH(OC_2H_5)_2 + H_2C(CO_2C_2H_5)_2 \rightarrow \underset{\text{I}}{C_2H_5OCH{=}C(CO_2C_2H_5)_2} + 2C_2H_5OH$$

An entirely different mechanism was suggested by the discovery of Post and Erickson (2) that ethyl orthoformate reacts with acetic anhydride to form diethoxymethyl acetate (II) and that the latter can be condensed with ethyl acetoacetate to give ethyl α-(ethoxymethylene)acetoacetate (III).

$$(C_2H_5O)_2CHOC_2H_5 + (CH_3CO)_2O \rightarrow \underset{\text{II}}{(C_2H_5O)_2CHOCOCH_3} + CH_3CO_2C_2H_5$$

$$CH_3COCH_2CO_2C_2H_5 + \underset{\text{II}}{(C_2H_5O)_2CHOCOCH_3} \longrightarrow CH_3COCCO_2C_2H_5 + CH_3CO_2H + C_2H_5OH$$

$$\underset{\text{III}}{\overset{\|}{CHOC_2H_5}}$$

These observations indicate that in the Claisen process the ethyl malonate might undergo alkylation with diethoxymethyl acetate to yield ethyl diethoxymethylmalonate (IV), which by loss of a molecule of ethanol would yield ethyl ethoxymethylenemalonate (I).

$$\underset{\text{II}}{(C_2H_5O)_2CHOCOCH_3} + CH_2(CO_2C_2H_5)_2 \rightarrow \underset{\text{IV}}{(C_2H_5O)_2CHCH(CO_2C_2H_5)_2} + CH_3COOH$$

In the present work it has been shown that this alkylation does occur. When diethoxymethyl acetate (II) was heated with ethyl malonate in the absence of a catalyst, a new ester, ethyl diethoxymethylmalonate (IV) was obtained in a

[1] The work described in this paper was done under a contract, recommended by the National Defense Research Committee and the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

yield of 17%. The presence of a small amount of zinc chloride increased the yield considerably. In this case, however, the product was a mixture of ethyl diethoxymethylmalonate (IV) and ethyl ethoxymethylenemalonate (I). If it is assumed that the latter is formed by way of the diethoxymethylmalonate, the extent of diethoxymethylation corresponds to 53% of the theoretical amount.

The alkylation of an active methylene compound by an ester of a carboxylic acid rarely has been observed. Ethyl acetoacetate was found by Hauser and Breslow (4) to undergo isopropylation when treated with isopropyl acetate in the presence of boron trifluoride. Metal derivatives of monoalkylated malonic esters were found by Wallingford and Jones (5) to undergo alkylation when treated with alkyl carbonates. It appears that esters of alcohols of the allyl type are able to alkylate ethyl acetoacetate in a similar way. This hypothesis affords a satisfactory explanation of the formation of the esters of β-phenylpropionic and allylacetic acids when the sodium derivative of ethyl acetoacetate is treated with benzyl or allyl acetate, respectively, in the presence of sodium ethoxide (6).

It would appear that the new example of alkylation is closely related to that which occurs with allyl and benzyl esters, in which the release of the alkyl radicals occurs with unusual readiness. In diethoxymethyl acetate the release of the diethoxymethyl group as a carbonium ion is facilitated by the presence of the ethoxy groups on the carbon atom which is the electron-accepting component in the alkylation.

The new ester (IV) also was isolated by careful fractionation of ethyl ethoxymethylenemalonate prepared by the Claisen method,[2] a fact which is in harmony with the belief that it is formed as an intermediate in that process. It was prepared also in 90% yield by the addition of a molecule of ethanol to ethyl ethoxymethylenemalonate in the presence of sodium ethoxide.

$$\underset{\text{I}}{C_2H_5OCH{=}C(CO_2C_2H_5)_2} + C_2H_5OH \rightleftarrows \underset{\text{IV}}{(C_2H_5O)_2CHCH(CO_2C_2H_5)_2}$$

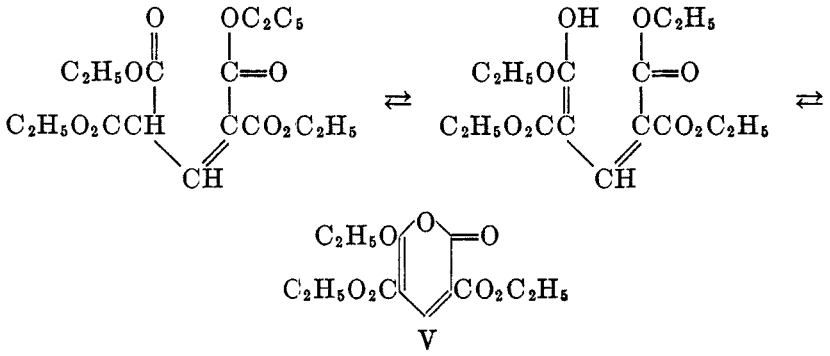
The reaction was found to be reversed by heating in the presence of zinc chloride; however, the main product under these conditions was not ethyl ethoxymethylenemalonate (I) but 3,5-dicarbethoxy-6-ethoxy-α-pyrone (V), a compound the structure of which was established by Guthzeit and Dressel (3). Since ethyl orthoformate was identified as a product of this decomposition, it seems likely that the formation of V may have occurred in the following way.

$$\underset{\text{IV}}{(C_2H_5O)_2CHCH(CO_2C_2H_5)_2} \xrightarrow[\text{heat}]{ZnCl_2} \underset{\text{I}}{C_2H_5OCH{=}C(CO_2C_2H_5)_2} + C_2H_5OH$$

$$(C_2H_5O)_2CHCH(CO_2C_2H_5)_2 + C_2H_5OH \rightarrow (C_2H_5O)_3CH + CH_2(CO_2C_2H_5)_2$$

$$C_2H_5OCH{=}C(CO_2C_2H_5)_2 + CH_2(CO_2C_2H_5)_2 \rightarrow$$

[2] The authors are indebted to Dr. Wesley Minnis of the National Aniline Division of the Allied Chemical and Dye Corporation for carrying out this fractionation.



V

When ethyl diethoxymethylmalonate (IV) was heated with zinc chloride in the presence of acetic anhydride the main product was ethyl ethoxymethylenemalonate (I). It is probable that under these conditions the acetic anhydride removes the ethyl alcohol which is formed, thus preventing the liberation of ethyl malonate and in turn formation of the pyrone.

On the basis of this observation it seemed likely that the yield of ethyl ethoxymethylenemalonate from the Claisen procedure might be improved simply by heating the reaction product, without removal of the zinc chloride, in order to decompose the ethyl diethoxymethylmalonate. Experiment has verified this expectation. The heating converts the diethoxymethyl compound to the ethoxymethylene derivative, thus at once destroying a troublesome contaminant and increasing the yield of the desired product.

EXPERIMENTAL

Condensation of diethoxymethyl acetate with ethyl malonate. Diethoxymethyl acetate, prepared by the method of Post and Erickson (2), was condensed with ethyl malonate by the following procedure. An equimolecular mixture of the two esters (80 g. of each) was heated until the temperature reached 116° (forty-five minutes). After four hours at this temperature the mixture was distilled under reduced pressure; fraction 1, b.p. 69–92° (14–18 mm.), n_D^{20} 1.3810–1.4150 (124 g.), consisted of a mixture of diethoxymethyl acetate and ethyl malonate; fraction 2, collected up to 125° (7.5 mm.), n_D^{20} 1.4150 (3 g.), was mainly ethyl diethoxymethylmalonate; fraction 3, b.p. 126–129° (7 mm.), n_D^{20} 1.4220 (22 g. or 17% of the theoretical amount), was pure ethyl diethoxymethylmalonate.

When the foregoing experiment was carried out with 0.2 g. of anhydrous zinc chloride in the reaction mixture the yield of alkylation product was much greater. The product was separated by fractional distillation into three fractions. Fraction 1, b.p. 70–100° (15 mm.), n_D^{20} 1.3980–1.4180 (54 g.), consisted mainly of unchanged reactants; fraction 2, b.p. 126–131° (8 mm.), n_D^{20} 1.4180–1.4225 (17 g.), was ethyl diethoxymethylmalonate; fraction 3, b.p. 107–115° (0.5 mm.), n_D^{20} 1.4275–1.4550 (53 g.), was a mixture of ethyl diethoxymethylmalonate and ethyl ethoxymethylenemalonate.

Ethyl diethoxymethylmalonate. To a mixture of 108 g. (0.5 mole) of ethyl ethoxymethylenemalonate and 5 ml. of a 10% solution of sodium ethoxide was added 41.4 g. (0.9 mole) of anhydrous ethanol during the course of ten minutes. The temperature was maintained at 30–40° during the addition of ethyl alcohol and for one hour afterward. The reaction mixture was neutralized with acetic acid and distilled under reduced pressure. The yield of ethyl diethoxymethylmalonate, b.p. 88–89° (0.18 mm.), was 118 g. (90% of the theoretical amount). A redistilled sample, n_D^{25} 1.4209, was submitted for analysis.

Anal. Calc'd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45.
Found: C, 54.75; H, 8.36.

The compound isolated by fractional distillation of ethyl ethoxymethylenemalonate, prepared according to the Claisen method, had the boiling point 133–134° (7–9 mm.); n_D^{25} 1.4209, n_D^{20} 1.4220.

Anal. Calc'd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45.
Found: C, 54.97; H. 8.15.

Pyrolysis of ethyl diethoxymethylmalonate. A. In the presence of zinc chloride. A mixture of 30 g. of ethyl diethoxymethylmalonate and 0.1 g. of anhydrous zinc chloride was heated at 95–125° for two and one-half hours and then at 125–130° for two hours, while a slow stream of nitrogen gas was bubbled through it. During the heating process 12 ml. of distillate was collected. The reaction mixture was distilled under reduced pressure; fraction 1, b.p. 100–104° (0.19 mm.), n_D^{20} 1.4530, weighed 1.7 g. and consisted mainly of ethyl ethoxymethylenemalonate; fraction 2, b.p. 104° (0.19 mm.), n_D^{20} 1.4605 (6.5 g.), was pure ethyl ethoxymethylenemalonate; the residue (10.0 g.), solidified on cooling. After recrystallization from toluene and then from petroleum ether (90–110°), it melted at 94–96° and did not depress the melting point of an authentic sample of 3,5-dicarbethoxy-6-ethoxy-α-pyrone (V).

During the vacuum distillation 4 g. of volatile material was collected in the dry-ice trap. This material and that collected during the pyrolysis were combined and redistilled to give 5.4 g. of ethyl alcohol, b.p. 77°, n_D^{20} 1.3610 and 1 g. of ethyl orthoformate, b.p. 140–145°, n_D^{20} 1.3950. The latter compound was characterized by conversion to trianilinomethane, m.p. 137–138° (2). A mixed melting point with an authentic sample was not depressed.

B. In the presence of zinc chloride and acetic anhydride. A mixture of 75 g. (0.286 mole) of ethyl diethoxymethylmalonate, 35 g. (0.343 mole) of acetic anhydride, and 0.1 g. of anhydrous zinc chloride was heated at 150–160° for two hours in a 200-ml. distilling flask equipped with a 6-in. column, still-head, and condenser. During the heating process 19 g. (0.21 mole) of ethyl acetate distilled and was collected. The reaction mixture was cooled, filtered, and distilled under reduced pressure; fraction 1, b.p. 85–109° (0.5 mm.), n_D^{20} 1.4300–1.4585 (18 g.), consisted of ethyl ethoxymethylenemalonate contaminated with unchanged ethyl diethoxymethylmalonate; fraction 2, b.p. 109° (0.5 mm.), n_D^{20} 1.4602 (37 g. or 62%), consisted of pure ethyl ethoxymethylenemalonate.

Ethyl ethoxymethylenemalonate. This ester was made by a modification of the procedure of Claisen (1). A mixture of 1000 g. (6.75 moles) of ethyl orthoformate, 1260 g. (12.3 moles) of acetic anhydride, 960 g. (6.0 moles) of ethyl malonate, and 0.5 g. of zinc chloride was placed in a 5-l. three-necked flask equipped with a thermometer and a 12-in. column packed with Berl saddles. The column was attached to a still-head and condenser. The mixture was well agitated and then heated as follows.

Reaction Temp., °C.	*Time (Hrs.)*
102–115	2.5
115–127	7
127–145	2
145–155	2

After eight hours of heating, 250 g. (2.45 moles) of acetic anhydride and 200 g. (1.35 moles) of ethyl orthoformate were added. The eleventh hour of heating was carried out at slightly reduced pressure (735 mm.) to aid in the removal of the last traces of volatile materials. The mixture was cooled to room temperature, filtered, and distilled under reduced pressure. A forerun, collected up to 70° (17 mm.), contained very little malonic ester. A second fraction was collected from 70–100° (17 mm.); when redistilled it yielded 148 g. (15.3%) of malonic ester, n_D^{20} 1.4142. The residue then was distilled *in vacuo*. In addition to a small forerun (15 g.), 818 g. of ethyl ethoxymethylenemalonate was collected; b.p. 108–110° (0.25 mm.); n_D^{20} 1.4600–1.4620. The weight of residue was 35 g. The yield of ethyl ethoxymethylenemalonate was 63%, based upon the amount of malonic ester employed, or 75%, based upon the malonic ester which was consumed in the reaction.

SUMMARY

It has been shown that ethyl malonate is alkylated when heated with diethoxymethyl acetate. The yield of diethoxymethylation product is increased by the presence of a small amount of zinc chloride. The alkylation product, ethyl diethoxymethylmalonate, is a new compound; it has been prepared also by the addition of ethanol to ethyl ethoxymethylenemalonate in the presence of sodium ethoxide.

URBANA, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

DIMORPHISM OF HIGH MOLECULAR WEIGHT SYMMETRICAL NORMAL ALIPHATIC SECONDARY AMINES

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Polymorphism of aliphatic compounds evidently occurs more widely than has previously been thought. In recent years there have been reports concerning the polymorphic behavior of some members of almost all of the common classes of paraffin-chain compounds. It is quite possible that under certain conditions all of the higher alkyl derivatives may exist in more than one crystalline modification. In view of the influence of this phenomenon upon melting points, solubilities, and other related physical properties, it is becoming increasingly important that the organic chemist be aware of the polymorphic behavior of the long-chain compounds.

The occurrence of polymorphism may be demonstrated by a variety of physico-chemical measurements. Of these, the most direct are the determination of the respective freezing and melting points of the several crystalline modifications, measurements of their corresponding solubility curves in a variety of solvents, determination of the respective liquidus and solidus curves of the temperature-concentration diagrams of binary homologs, and x-ray investigation of the crystal spacings. By such methods, two or more crystalline modifications have been definitely established for many of the triglycerides (1–4), the ethyl esters of saturated fatty acids (5–8), the primary aliphatic alcohols (9–11), and for oleic acid (12). In all of these instances, the compounds investigated exhibit two (or more) definite melting points, or at least, as in the case of many of the triglycerides (4), sharp breaks in the heating curves of the compounds. Several x-ray investigations (13, 14) have shown that the higher saturated fatty acids exist in two crystalline modifications, although only one melting point has been reported for each of these acids. It has been suggested that the two forms of palmitic and stearic acids have identical melting points (13), but no explanation has been proposed for such a thermodynamic paradox. Other instances of polymorphism have been reported for the higher alkylammonium acetates, chlorides, and bromides (15–18), and for several of the substituted fatty acid amides (19). In these cases, however, the polymorphic modifications are evidenced only in relatively dilute aqueous or alcoholic solutions, while at higher concentrations only one crystalline form is exhibited.

While the phenomena cited above were exhibited by reputedly pure compounds, several investigators (20, 21) have proved that in many instances polymorphism is attributable to the presence of impurities, chiefly closely related homologs, which tend to stabilize a metastable modification to such an extent that transformation to the corresponding stable crystalline form is impeded, or even prevented. For example, it has been shown (22) that a small amount (less than 5%) of octadecane produces two crystalline modifications in hexadec-

ane, although no evidence of polymorphism is found in the latter hydrocarbon in its pure state (23). The higher alkyl halides behave in a similar manner (22). Although it has been stated (24) that the higher aliphatic nitriles are polymorphic, a recent report from this laboratory (25) shows that less than 1% of palmitonitrile in stearonitrile (or *vice versa*) produces not only two crystalline modifications, but several mesomorphic forms in addition. Such behavior is not exhibited by the pure components. Other recent studies in this laboratory (26) indicate that the behavior of the higher saturated fatty acids may likewise be attributable to the presence of small amounts of homologs, in view of the marked similarity between the temperature-concentration diagram of binary mixtures of the acids and the corresponding diagrams of the nitriles.

A previous investigation of the secondary amines (27) dealt with the solubilities of several of the higher homologs in a variety of organic solvents. It was found that dioctylamine presented two solubility curves in the non-polar and slightly polar solvents, one curve representing the solubility of a lower-melting, more soluble form, and the other a higher-melting, less soluble modification. In the more highly polar solvents, dioctylamine presented only one solubility curve, that of the higher-melting form. While didodecylamine exhibited two melting points, it presented only one solubility curve since a rapid transformation from the low-melting to the higher-melting form precluded determination of the solubility curve of the lower-melting form. The higher homologs appeared to exist in only one crystalline modification. Further investigation of this class of compounds revealed certain apparent inconsistencies which form the basis of the present paper.

EXPERIMENTAL

Dihexylamine, didecylamine, and dihexadecylamine were prepared by heating their respective primary amines for 5–6 hours at 200° in the presence of Raney nickel catalyst as described previously (27). The two lower homologs were purified by fractionation *in vacuo* in a Stedman-packed column. The distillates were cooled without access to the atmosphere, and transferred to small, tightly capped bottles under an atmosphere of nitrogen to prevent contamination with carbon dioxide. The dioctylamine employed in the previous studies was subjected to a further vacuum distillation in the Stedman-packed column and several fractions were bottled in the above manner. In addition, about 50 ml. of the middle fraction were distilled directly into a Pyrex test tube (25 mm. diam.) which was then sealed off while under vacuum. The hexadecylamine, as well as the tetradecylamine which was employed in the previous studies, was repeatedly crystallized from mixtures of freshly distilled ethanol and benzene and filtered under an atmosphere of nitrogen. The precipitates were dried by heating well above their melting points under a vacuum and were bottled as above.

The freezing and melting points of the several crystalline forms of these compounds were determined by direct measurement with a calibrated thermometer immersed in 10–25 g. samples of the amines without exposure to atmospheric carbon dioxide. For temperature below 10° a calibrated iron-constantan thermocouple was used. The equipment and general procedures for determining the freezing and melting points and for several additional solubility measurements have been described previously (15–18). The observed freezing and melting points are listed in Table I.

The earlier report (27) that dioctylamine forms a carbamate with the freezing point 36.6° has been verified. In addition, small amounts of didodecylamine and dioctadecyla-

mine were thoroughly exposed to the atmosphere, and subsequent analyses showed that one mole of carbon dioxide reacts with two moles of secondary amines. The melting points of didodecylamine and dioctadecylamine carbamates determined by means of a small, electrically heated hot-plate were 58.3° and 74.4°, respectively. Hence, it is probable that some of the reference melting points listed in Table I may be the melting points of secondary amines which had been contaminated by exposure to carbon dioxide.

TABLE I

FREEZING AND MELTING POINTS OF SECONDARY AMINES

	NO. OF C ATOMS	F.P., °C	M.P., °C		LIT. M.P., °C	
			α	β		
Dihexylamine	12	−13.06	−13.06	0.5*		
Diheptylamine	14				1	(28)
Dioctylamine	16	14.62	14.62	26.7*	14.60	(27)
					26.7	(27)
					36.5	(29)
					35	(30)
					34	(31)
Didecylamine	20	32.60	32.60	41.5*	42–42.5	(31)
Didodecylamine	24	46.95	46.95	51.8	46.9	(27)
					51.8	(27)
					58	(30)
					51–53	(31)
					55–56	(32)
					44.4	(33)
					52–53	(34)
					53	(35)
Ditridecylamine	26	53.5	53.5	56.5	56.5	(27)
Ditetradecylamine	28	60.62	60.62		60.6	(27)
					56–58	(31)
					56	(35)
Dipentadecylamine	30	63.3	63.3		63.3	(27)
Dihexadecylamine	32	67.03	67.03		65	(30)
					64–65	(31, 36)
					64	(35)
Dioctadecylamine	36	72.3	72.3		72.3	(27)
					71–72	(31)
					73–74	(34)

* Values obtained both by extrapolation of solubility curves and from melting point determination of slightly impure amine (see text).

RESULTS AND DISCUSSION

The freezing and melting points of a number of high molecular weight symmetrical normal aliphatic secondary amines are shown graphically in Fig. 1, the temperatures being plotted against the total number of carbon atoms in the amine molecule. This diagram shows that these temperatures fall on two curves which intersect at the freezing (and melting) point of ditetradecylamine. While the lower homologs, under certain conditions, exhibit two crystalline forms

as evidenced by their different melting points, ditetradecylamine and its higher homologs appear to exist in only one crystalline form.

The behavior of didodecylamine is typical of aliphatic compounds possessing two melting points. Upon cooling, this compound begins to freeze at 46.95°

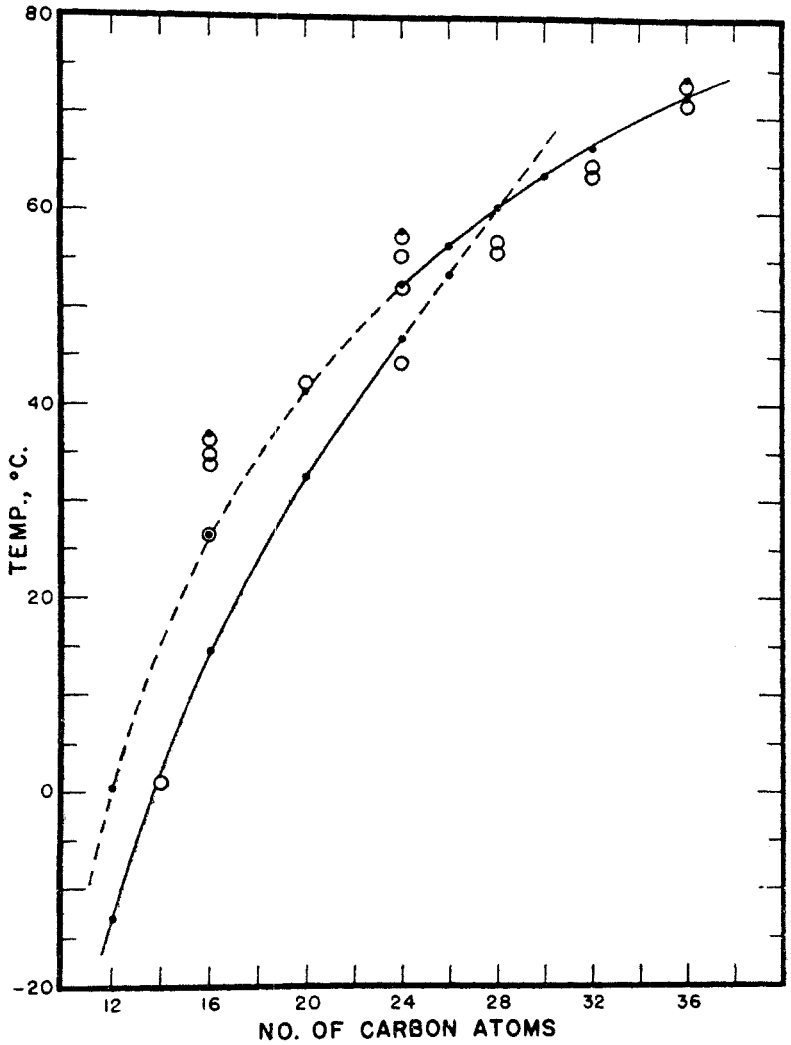


FIG. 1. Freezing and Melting Points of the Symmetrical Normal Aliphatic Secondary Amines. The solid circles represent the authors' data, and the open circles refer to data in the literature.

in the form of small, transparent crystals, which, if heated rapidly, will melt at this temperature. If the temperature is kept constant at the freezing point for several minutes, however, this amine transforms to a dense, opaque crystalline form which melts at 51.8°. The lower-melting form is generally designated the α-modification, while the higher is called the β-modification. Similar behavior

of many long-chain compounds has been observed (7, 10, 22, 25, 37, 38). While ditridecylamine appears to present a similar behavior, its transformation is so rapid as to preclude accurate determination of the freezing point. Since the purity of this amine was below that of the other homologs (as indicated by its melting point being 0.2° below the curve), the upper portion of the lower curve in Fig. 1 has been extrapolated to its intersection with the other curve.

The lower homologs, dihexylamine, dioctylamine, and didecylamine, present an anamolous behavior in that only the relatively impure samples exhibited the type of dimorphism described above. The very highly purified fractions of these three amines repeatedly freeze and melt only at the temperatures represented by the lower curve in Fig. 1. A small amount of impurity, however, permits the realization of the higher-melting form. This impurity may be

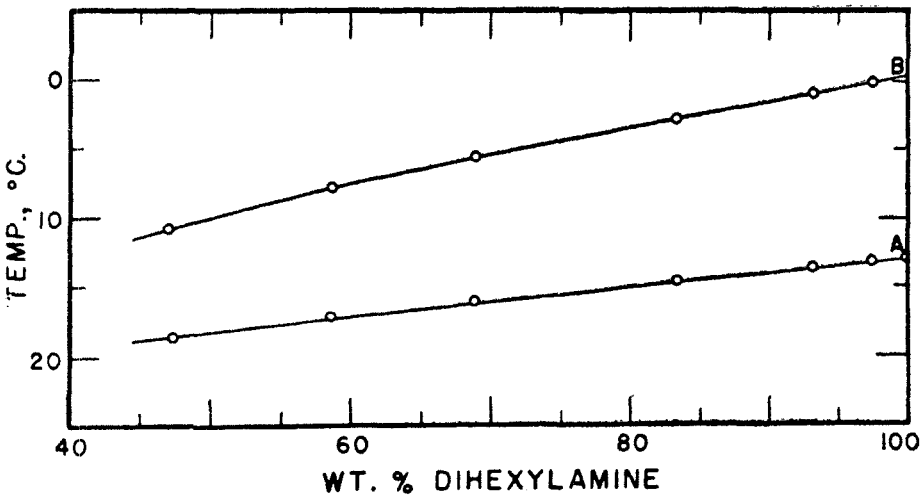


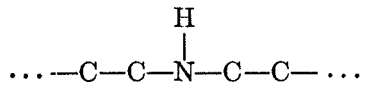
FIG. 2. Solubility of Dihexylamine in *n*-Hexane. The lower curve represents the solubility of the α-form, and the upper curve that of the β-modification.

either carbon dioxide, a homolog of the secondary amine, or an organic solvent. In the case of dioctylamine, less than 0.1% of any of these impurities was sufficient to bring about formation of the higher-melting crystals. It is evident that this behavior contradicts the generally accepted opinion that the presence of an impurity necessarily stabilizes the lower-melting form and retards its transformation to the higher-melting form (20, 21). The melting points of the higher form of dihexylamine, dioctylamine, and didecylamine were quite accurately located by determining the solubilities of these amines in several organic solvents as illustrated by Fig. 2, which represents the solubility of dihexylamine in hexane. In this case, the various concentrations of amine precipitate from solution at temperatures on the lower curve which intersects the freezing point of the pure amine at A(−13.06°). In a short time (usually only a few seconds at the lower concentrations), the amine has transformed to the second crystalline form which, upon heating, redissolves at temperatures on the higher curve.

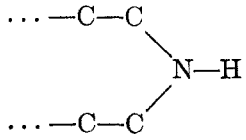
Extrapolation of this curve to 100% solute gives the melting point of the higher-melting crystalline form at B(0.5°). The melting points of this β-form of the lower homolog determined in this manner fall on the continuation of the curve through the melting points of the higher homologs. Since these higher melting points cannot be observed directly for the lower homologs, the curve below didodecylamine has been drawn as a broken line in Fig. 1.

The results of this investigation are paralleled to some extent by studies of the higher primary aliphatic alcohols (11). The latter compounds also exhibit two melting point curves which intersect at the melting point of tetradecyl alcohol. In this case, the higher alcohols, as well as their lower homologs, possess two melting points. The absence of a higher melting point curve in the case of the higher secondary amines may be due to failure in ascertaining the proper conditions necessary to effect the transformation, although consideration was given to this possibility, in view of its prediction by the configuration of the curves in Fig. 1. It was established, however, that the factor which brings about the dimorphism of the lower secondary amines, namely, the presence of impurities, does not function in the same manner for the higher homologs.

It appears to be of some significance that the melting point curves of the aliphatic alcohols intersect at the melting point of tetradecanol, while the corresponding curves of the higher secondary amines intersect at the melting point of ditetradecylamine, which contains exactly twice as many carbon atoms as does the alcohol. This phenomenon suggests that the secondary amines may not exist in a linear molecular configuration,



but rather, in some manner in which the paraffin chains are parallel,

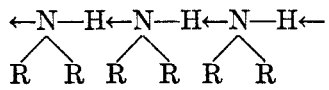


The latter structure would result in the secondary amines presenting certain physical properties approximately those of other aliphatic compounds containing half as many carbon atoms.

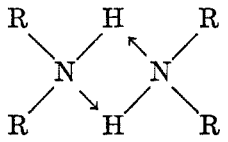
X-ray studies of the alcohols (9) have demonstrated that these compounds, as well as the fatty acids and their esters, exist in two crystalline forms, one in which the molecules are arranged in bimolecular layers with their polar groups adjacent and their paraffin chains aligned perpendicularly to the plane of the polar groups, and the other in which the parallel carbon chains are tilted at an angle to the plane of the polar groups. It has generally been found that this tilted form is characteristic of the lower-melting, unstable polymorphs, while the higher-melting, stable crystals possess the vertical configuration, except in the case of the aliphatic alcohols above tetradecanol, which present the opposite

phenomenon. It is highly probable that the dimorphism of the high molecular weight secondary amines is attributable to similar changes in their molecular structures.

A unique feature of the dimorphism of the lower homologs, noted particularly in the case of dioctylamine, is the fact that the slightly impure samples appear never to transform completely to the higher-melting form even after several months. A further peculiarity is the failure to observe directly a transformation from the α- to the β-form; the higher form seems to appear spontaneously from the liquid state at temperatures between the melting points of the lower and higher forms. This behavior, and the marked differences in the slopes of the respective solubility curves (27) indicate that the two crystalline forms differ by more than a variation in the angles of tilt of their molecules. Such behavior suggests that the two forms differ in the nature of their molecular association due to hydrogen bondings. Thus, one form may be associated linearly,



and the other form may possess a cyclical structure,



Since the entropies of these structures would be practically identical, the failure to realize a transition from one to the other is understandable. It is possible that one of the polymorphic forms of the solid possesses a different type of association from that encountered in the liquid state. The inability to realize complete solidification of the lower secondary amines in their β-form may be attributable to an equilibrium between the molecular arrangements of the higher-melting crystals and the liquid.

It is evident from this discussion that the determination of the melting points of the higher secondary amines involves many factors which preclude the use of this physical property as a means of identification. This property, however, appears to present an excellent criterion of ultimate purity for the amines below ditetradecylamine in this series. By accurate titration of these lower amines with carefully standardized hydrochloric acid, by estimation of cooling curves, and by the addition of known amounts of impurity to highly purified secondary amines, it was found that samples containing in excess of only 0.05% impurity exhibited dimorphism, while samples of greater purity presented only one crystalline form.

SUMMARY

The freezing and melting points of a series of high molecular weight aliphatic secondary amines have been accurately determined. It is found that the amines

below ditetradecylamine in the series present dimorphic tendencies, except in a very highly purified condition.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

HYDROXAMIC ACIDS FROM ALIPHATIC DICARBOXYLIC ACIDS

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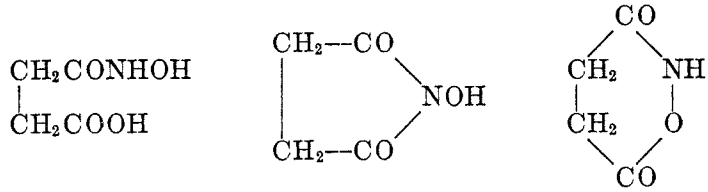
Most of the story about hydroxamic acids has been developed from work with derivatives of the monocarboxylic acids, although the first hydroxamic acid discovered was that of a dicarboxylic acid. Lossen (1) obtained oxalohydroxamic acid in 1869 by the interaction of ethyl oxalate and hydroxylamine. Other workers (2) have extended its chemistry, including rearrangement of its benzoyl derivative to hydrazine (3).

The terminology of the hydroxamic acids is patterned after that of amides because the former are but hydroxyamides with acid properties. Hence, just as $CH_2(CONH_2)_2$ is named malonamide (not malonodiamide) so also $CH_2(CONHOH)_2$ is named malonohydroxamic acid (not -dihydroxamic acid). The name malonobenzoylhydroxamic acid, $CH_2(CONHOCOC_6H_5)_2$, follows precedent of substituted amides, *e.g.* malonomethylamide for $CH_2(CONHCH_3)_2$. Half hydroxamic acids are named as derivatives of half amides. An illustration is N-hydroxysuccinamic acid, $HONHCOCH_2CH_2COOH$, derived from succinamic acid.

Hydroxamic acids related to higher aliphatic dicarboxylic acids were known prior to this study but their rearrangement had not been reported. Malonohydroxamic acid was synthesized both from ethyl malonate (2) and from carbon suboxide (4). Suberohydroxamic acid was made (7) by interaction of suberaldehyde and sodium nitrohydroxamate. Both succinohydroxamic acid and N-hydroxysuccinamic acid (I) were prepared, the former (5) from ethyl succinate and the latter (6) from either succinic anhydride or succinyl chloride. Acetic anhydride causes cyclization of I.



I II III

Structure III seems more plausible for the ring structure than II because III conforms to the pattern of the diacylated hydroxylamines or "dihydroxamic acids", RCONHOCOR. The product actually isolated by Errera was an acetate of III for which he proposed structure IV. Another reasonable structure is V. The same substance was formed also by reaction of acetic anhydride on succinohydroxamic acid.

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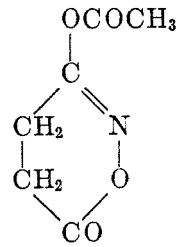
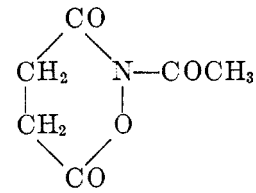


IV



V

Two years after the completion (1942) of the present work announcement was made (8) of the syntheses of adipohydroxamic acid and sebacohydroxamic acid by using the established general method involving reaction of the corresponding esters with hydroxylamine in the presence of sodium methoxide. Rearrangement to tetramethylene isocyanate and octamethylene isocyanate, respectively, was accomplished by suspending the hydroxamic acids in xylene and treating with phosgene or thionyl chloride.

The present work deals with the hydroxamic acids of malonic, succinic, adipic, and sebacic acids. Crystalline sodium salts, usually containing solvent of crystallization, of all these compounds were prepared by interaction of the appropriate ethyl ester with hydroxylamine and an alcoholic solution of sodium ethoxide. The malonic and succinic salts were extremely deliquescent.

Cupric salts were prepared by interaction of the sodium salts with aqueous cupric acetate solutions. Cupric malonohydroxamate remained in colloidal suspension but the succinohydroxamate and adipohydroxamate separated readily. Treatment of the last two cupric salts with hydrogen sulfide represented one method of conversion to the free hydroxamic acids. Succinohydroxamic acid was a waxy solid, which is in contrast to the oil reported by Hantzsch and Urbahn (5). An insoluble ammonium salt was obtained by adding ammonium hydroxide to an alcoholic solution of the acid. It is characteristic of hydroxamic acids (9) to form insoluble acid ammonium salts.

Sebacohydroxamic acid was sufficiently insoluble in water that precipitation of it in good yields occurred when a solution of the sodium salt was acidified. To obtain adipohydroxamic acid from aqueous solution the latter was evaporated to dryness and the residue extracted with alcohol. To prepare malonohydroxamic acid from the sodium salt an alcohol solution was used. Even with this precaution it was found necessary to concentrate the solution at room temperature to avoid decomposition. Lachrymatory vapors, including formaldehyde, were formed if a boiling temperature was used. This is understandable if rearrangement to methylene isocyanate occurred:

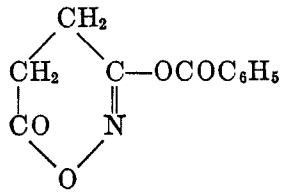
$$CH_2(CONHOH)_2 \rightarrow CH_2(NCO)_2 + 2H_2O$$

because it should hydrolyze readily to formaldehyde.

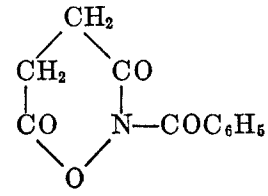
Simple benzoylation occurred when suspensions or solutions of the sodium salts of malono-, adipo-, or sebaco-hydroxamic acids were treated with benzoyl chloride. The derivatives formed were malonobenzoylhydroxamic acid, CH_2-

$(CONHOCOC_6H_5)_2$, adipobenzoylhydroxamic acid, and sebacobenzoylhydroxamic acid. To make the first of these three derivatives it was necessary to use anhydrous conditions. If an aqueous solution of sodium malonohydroxamate was taken, dibenzohydroxamic acid was formed instead, a process evidently involving preliminary hydrolysis to hydroxylamine (10) and benzoylation of the latter.

Sodium succinohydroxamate underwent cyclization into benzoylsuccinylhydroxylamine (VI or VII) when treated with benzoyl chloride. The hydroxylamine which was detached in this process reacted with benzoyl chloride to form dibenzohydroxamic acid. No carbanilide was



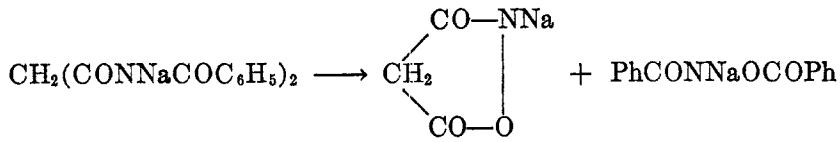
VI



VII

found on heating this substance with sodium hydroxide solution, an observation which may be explained from either VI or VII. If carbanilide had been found the observation would have supported VII.

Malonobenzoylhydroxamic acid underwent cold alkaline hydrolysis into benzoic acid and malonohydroxamic acid. Boiling of a solution of sodium malonobenzoylhydroxamate caused the precipitation of carbanilide. Evidently sodium dibenzohydroxamate is detached to cause this rearrangement:



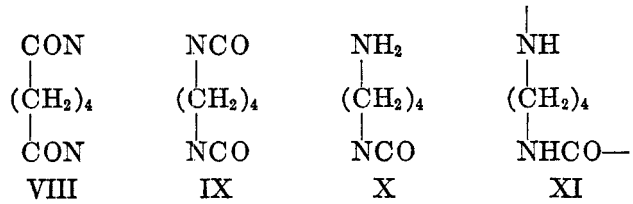
$$2PhCONNaOCOPh + H_2O \longrightarrow CO(NHPh)_2 + CO_2 + 2PhCOONa$$

It is reasonable to infer that malonylhydroxylamine was formed as shown in the first equation but no direct evidence for it was obtainable.

Precipitation of a white, fluffy solid was noticed when an aqueous solution of sodium adipobenzoylhydroxamate was boiled. The filtrate contained sodium benzoate. The solid product was ash-free, high-melting (above 310°), insoluble in water and in ordinary organic solvents, but moderately soluble in phenol. It behaved like a polymeric amide. Hydrolysis of the product was difficult, but concentrated hydrochloric acid at 150° gave rise to putrescine in an amount equivalent to 93% of the nitrogen in the sample. A little benzoic acid was isolated also.

The general appearance of the rearrangement product of sodium adipobenzoylhydroxamate, its high fusion point, and resistance to hydrolysis all pointed to an amide of high molecular weight. In view of the fact that the solid was hydrolyz-

able to putrescine this suggests that rearrangement occurred at both ends of the molecule. To visualize this, one may consider detachment of sodium benzoate to form the hypothetical intermediate (VIII) which rearranges to tetramethylene isocyanate (IX), partial hydrolysis of which should give rise to 4-aminobutyl isocyanate (X). This should polymerize to a urea containing the recurring unit (XI).



VIII IX X XI

Such a urea, however, would contain 24.56% nitrogen, in contrast to the 15.08 actually found. It is fruitless to speculate now concerning the composition of this polymer but work is going forward towards its characterization. It is of interest to note that Cupery (8) obtained an impure sample of IX by interaction of phosgene with adipohydroxamic acid, suspended in xylene. An important difference in our conditions was the presence of water which would react with IX.

Similar observations were found for the rearrangement of sodium sebacobenzoylhydroxamate. The insoluble precipitate, formed by boiling the aqueous solution, possessed a nitrogen content of 12.4% as contrasted to 16.5% for a polymer containing the —$NH(CH_2)_8NHCO$— nucleus. The product was inhomogeneous, since hot alcohol was capable of extracting part of it. The material broke down on drastic hydrolysis into 1,8-octanediamine and a small amount of benzoic acid. Work on the characterization of the polymer is being continued.

EXPERIMENTAL PART

Preparation of the sodium hydroxamates. The general method of preparation was to mix one mole of ester, two or more moles of hydroxylamine, and two moles of sodium ethoxide with absolute alcohol as solvent. The hydroxylamine solution was prepared by adding the calculated quantity of sodium ethoxide in absolute alcohol to an alcoholic solution (or suspension) of hydroxylammonium chloride. Phenolphthalein indicator was used for the end point. Sodium chloride was filtered off and the solution of hydroxylamine was poured directly into the ester. Precipitation of the desired sodium salt began soon after the sodium ethoxide solution was added but the mixture was usually left several hours to ensure complete reaction. Ethanol was favored as solvent over methanol because of the greater solubility of the salt in methanol. If 95% alcohol was used with the malonate or succinate only gummy or sirupy products resulted. These two salts were extremely deliquescent. Details of some representative runs are presented in Table I. Except for the adipic derivative, analysis revealed solvent of crystallization in all these salts.

Preparation of the hydroxamic acids. To prepare malonohydroxamic acid 17 g. of the sodium salt was added to an equivalent amount of hydrogen chloride in ethanol (50 ml. of 2.8 *N*). After two hours, during which the mixture was shaken occasionally, it was filtered to remove sodium chloride, and evaporated at 20 mm. pressure and 25°. The crude residue melted at 144–147°. Pure malonohydroxamic acid (4) is known to melt at 155°. Cupric succinohydroxamate precipitated when aqueous solutions of cupric acetate and sodium

succinohydroxamate were mixed. This was separated, washed with water and methanol, suspended in methanol, and the latter was saturated with hydrogen sulfide. On filtration and evaporation a syrupy residue was left, which changed to a low-melting waxy solid on desiccation over sulfuric acid. When 0.2 g. of this succinohydroxamic acid was treated with 2 ml. of conc'd ammonium hydroxide an ammonium salt separated which melted at 180–181°.

Adipohydroxamic acid was prepared in like manner from the cupric salt, but it was more convenient to prepare it by acidification of an aqueous solution of the sodium salt with two equivalents of glacial acetic acid or with the calculated quantity of dil. hydrochloric acid. The mixture was evaporated to dryness at 100° and the residue extracted with hot alcohol. Several crystallizations from alcohol were required to bring the m.p. to 165–165.5°; yield, 75–85%. Analytical values obtained on this compound were satisfactory for adipohydroxamic acid monohydrate. That both nitrogens in this material were of hydroxamic acid character was demonstrated by the fact that it reacted only very slowly with

TABLE I

SYNTHESIS OF SODIUM HYDROXAMATES

ETHYL ESTER			HYDROXYL-AMINE		SODIUM ETHOXIDE			SODIUM HYDROXAMATE					
					Sodium					Anal. for Na			
Name	g.	moles	moles	abs. alc., ml.	g.	moles	abs. alc., ml.	g.	Method of drying	Found	Calc'd[b]	Calc'd[c]	Calc'd[d]
Malonate	80	0.50	1.0	1000	25	1.1	500	78	*vacuo*	19.6, 20.1	25.8	20.5	
Succinate	79.5	.46	1.0	850	23	1.0	450	99	*vacuo*	19.0	24.0	19.3	
Adipate	88	.43	1.2	1050	20	0.87	450	123	air				
Adipate	93	.46	1.8	1000[a]	21	.92	450[a]	91	*vacuo*	20.4	20.9		
Sebacate	59	.23	0.55	500	11	.48	250	49.5	*vacuo*	15.5	16.6	14.3	15.6

[a] Methanol solvent. This was concentrated to 400 ml. before collecting sodium salt.

[b] Anhydrous salt.

[c] Salt + $1C_2H_5OH$ of crystallization.

[d] Salt + $1H_2O$ of crystallization.

a 2% potassium permanganate solution. If one of them had been a hydroxylammonium salt (as $—CO_2NH_3OH$) it would have reacted quickly (11).

Anal. Calc'd for $C_6H_{12}N_2O_4 \cdot H_2O$: N, 14.43. Found (Dumas): N, 14.04, 14.03.

Sebacohydroxamic acid monohydrate was prepared similarly in 7.9 g. yield (crude) from 10 g. of the sodium salt in 90 ml. of water treated with 4 g. of glacial acetic acid. Two recrystallizations from 95% alcohol yielded 4.4 g. (52%) of the hydrate, m.p. 134–136°. The m.p. of the anhydrous acid (8) is listed as 164°.

Anal. (by T. S. Ma) Calc'd for $C_{10}H_{20}N_2O_4 \cdot H_2O$: N, 11.19. Found, (Dumas, micro): N, 10.94.

Benzoyl derivatives. Benzoyl derivatives of malono- and succino-hydroxamic acids were prepared by adding 2.5 molar parts of benzoyl chloride to a suspension of the sodium salt in an 8-fold quantity of ether. After the initial exothermic reaction subsided, the mixture was refluxed (4 hrs., malonic; 0.5 hr., succinic). The solid which separated was collected on a filter, washed with water to remove sodium chloride, dried, and crystallized from alcohol. Details of representative runs are listed in Table II.

Benzoylsuccinylhydroxylamine was also prepared in 98% yield by refluxing for two hours a mixture of succinohydroxamic acid (4.2 g.), pyridine (5.9 g.), benzoyl chloride (6.7 g.), and benzene (120 ml.). The pyridine hydrochloride was separated, the solvent removed, and the residue was crystallized from ethanol; m.p. 134–135°.

The adipic and sebacic derivatives were prepared by shaking benzoyl chloride with aqueous solutions of the sodium salts for about fifteen minutes. The insoluble benzoyl derivative was filtered off and crystallized from alcohol. See Table II for data on specific runs.

Sodium salts of the malonic, adipic, and suberic benzoyl derivatives were prepared by suspending about 1–2 g. of the acid in question in 25–50 ml. of absolute alcohol and adding 2 molar parts of sodium ethoxide in 25–30 ml. of absolute alcohol. This caused the benzoyl derivative to dissolve, but 75-98% separations of the sodium salts appeared after a day at 0°.

Analyses of benzoyl derivatives. Malonobenzoylhydroxamic acid. Calc'd for $C_{17}H_{14}N_2O_6$: N, 8.18; mol. wt., 342; neutr. equiv. 171. Found: N, 7.80 by Dr. T. S. Ma; mol. wt. (cryoscopic in dioxane), 336; neutr. equiv., 169.6, by titration to phenolphthalein end point. The cryoscopic constant of dioxane was found to be 4.62 using dibenzohydroxamic acid as solute. *Sodium salt.* Calc'd for $C_{17}H_{12}N_2Na_2O_6$: Na, 11.9. Found: Na, 11.4.

Benzoylsuccinylhydroxylamine. Calc'd for $C_{11}H_9NO_4$: N, 6.40; mol. wt., 219. Found: N, 6.39, 6.27; mol. wt. (dioxane, solvent), 226.

Adipobenzoylhydroxamic acid. Calc'd for $C_{20}H_{20}N_2O_6$: N, 7.29; neutr. equiv., 192. Found: N, 7.04, 7.44; neutr. equiv., 192.2 (ave. of five determinations). *Sodium salt.* Calc'd for $C_{20}H_{18}N_2Na_2O_6$: Na, 10.75. Found: Na, 10.41.

TABLE II

BENZOYL DERIVATIVES

SODIUM SALT		BENZOYL CHLORIDE	BENZOYL DERIVATIVE		
Name	g.	g.	g.	%	m.p., °C
(M)	50	58	47	66	177–179
(Suc.)	10	16	8	88	135–136
(A)	4.5	5.7	4.2	70	187
(Seb)	13.8	16.8	13.7	66	162–163

M, malonohydroxamate A, adipohydroxamate
Suc., succinohydroxamate Seb., sebacohydroxamate

Sebacobenzoylhydroxamic acid. Calc'd for $C_{24}H_{28}N_2O_6$: N, 6.36; neutr. equiv. 220. Found: N, 6.20; neutr. equiv., 226. *Sodium salt.* Calc'd for $C_{24}H_{26}N_2Na_2O_6$: Na, 9.49. Found: Na, 9.29.

Rearrangement of benzoyl derivatives. Sodium malonobenzoylhydroxamate. The salt was made by dissolving 0.05 mole of the acid (17.1 g.) with 0.10 mole of sodium hydroxide solution in 202 ml. of water. This clear solution was heated to boiling till the precipitate of *sym*-diphenylurea which appeared had coagulated. When cool it was filtered off. The yield was 1.28 g. or 24%; m.p. 237–238°.

When an excess of alkali was taken (0.01 mole of the acid, 0.04 mole sodium hydroxide in 73 ml. of water) and the solution kept for ten hours at room temperature there was hydrolysis of the benzoyl groups and not rearrangement. Acidification with acetic acid (0.05 mole) caused the separation of 1.3 g. (0.01 mole) of benzoic acid. One gram of sodium acetate was added to the filtrate, the solution was then concentrated at 100° and, when cool, 3 ml. of strong ammonium hydroxide was added. The ammonium hydrogen malonohydroxamate which separated was crystallized from a mixture of ethyl acetate and ethanol; m.p. and mixed m.p. 142–143°. The value reported by Lossen (1b) was 141°. Our salt depressed the m.p. of the ammonium salt of dibenzohydroxamic acid from 146–147° to 128–135°.

Sodium adipobenzoylhydroxamate. The sodium salt from 18.1 g. of adipobenzoylhydroxamic acid was dissolved in 190 ml. of water. Boiling the solution rapidly caused pre-

cipitation of 4.63 g. (dry weight) of white solid. Concentration of the filtrate gave rise to 13.6 g. of impure sodium benzoate.

The white solid was high-melting (above 310°) but melted on platinum foil. It was insoluble in alcohol, acetone, dioxane, camphor, 5% hydrochloric acid, and 5% sodium hydroxide solution. It was partially soluble in boiling acetic acid, and was moderately soluble in phenol. Kjeldahl analysis revealed 15.08% nitrogen.

Two grams of the substance and 25 ml. of conc'd hydrochloric acid was heated in a sealed tube at 150° for nineteen hours. Much gas escaped when the cooled tube was opened and 0.05 g. of benzoic acid (m.p. 121–122°) was suspended in the solution. Evaporation of the filtrate yielded 2.32 g. of crude putrescine hydrochloride. This was dissolved in water, made alkaline, and benzoyl chloride was added. Recrystallization of the precipitate from a 3:1 mixture of ethyl acetate and ethanol yielded 2.94 g. of benzoylputrescine, m.p. 176–177°, the N-content of which is 0.279 g. Based on the N-analysis, the 2.00 g. of substance taken contained 0.300 g. of nitrogen. Hence, 93% of the nitrogen present in the sample appeared as putrescine.

Sodium sebacobenzoylhydroxamate. The sodium salt from 5.0 g. of sebacobenzoylhydroxamic acid, dissolved in 45 ml. of water, produced 2.90 g. (dry) of precipitate on boiling the solution. Its melting range was 165–220°. No ash was left on ignition. This material was a light, white powder, insoluble in dilute acids or alkalies. It was partially soluble in conc'd hydrochloric acid or hot alcohol, and it dissolved in phenol. Analysis (by T. S. Ma) by the Dumas method showed 12.44% N.

Hydrolysis of 2.12 g. of the product by 25 ml. of conc'd hydrochloric acid heated to 150° for twenty-one hours gave rise to 0.24 g. of benzoic acid and 2.10 g. of what was presumably impure 1,8-octanediammonium chloride. Sodium hydroxide solution liberated an oil which was acetylated by acetic anhydride to an acetyl derivative melting at 127–128° after crystallization from water. Naegeli and Landorff (12) mention the m.p. of this acetyl derivative as 121–122°. They precipitated their compound from alcohol by addition of ether. We also obtained a benzoyl derivative, using benzoyl chloride and aqueous sodium hydroxide, and purified it by crystallization from ethanol. This substance melted if dipped in a bath at 155° but it solidified an instant later to remelt at 171°. Muller and Kindlmann (13) report 173° as the m.p. of the benzoyl derivative of 1,8-octanediamine.

SUMMARY

Consideration is given to the preparation and properties of hydroxamic acids related to malonic, succinic, adipic, and sebacic acids. Benzoylation of succinohydroxamic acid yields the cyclic compound benzoylsuccinylhydroxylamine, whereas benzoylation of the other three hydroxamic acids gives rise to open-chain benzoyl derivatives of the general structure: $C_6H_5COONH—CO—(CH_2)_n—CO—NHOCOC_6H_5$. The study included rearrangement of the sodium salts of these derivatives by boiling their aqueous solutions. The malonic derivative gave rise to *sym*-diphenylurea. The adipic and sebacic derivatives changed into substances with the properties of high polymeric amides capable of hydrolysis into putrescine and 1,8-octanediamine, respectively.

EVANSTON, ILL.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENE-METHANOLS. VI. SOME MANNICH KETONES AND DERIVED PROPANOLAMINES[1]

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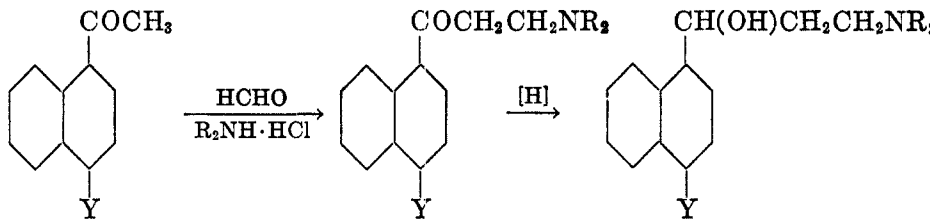
In the search for antimalarial drugs, the group at the National Institute of Health has investigated as well as ethanolamines, the amino alcohols of type III with the propanolamine side chain. At the suggestion of Dr. Lyndon F. Small, we undertook the preparation of the propanolamines in which the naphthalene nucleus was substituted with a methoxyl group or a halogen atom just as we did in the case of the ethanolamines (1).



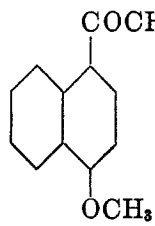
I II III

The most direct approach to compounds of the type III is, of course, through the Mannich ketones II. This is the method used at the National Institute of Health, and the one we used for the preparation of several propanolamines. Our preparations in this connection and some observations on the Mannich reaction are reported in this paper. In certain cases, sometimes for interesting reasons, the preparation by way of the Mannich ketones proved impossible, and a number of propanolamines were prepared by other methods discussed in the following article (2).

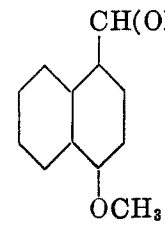
In the course of our work we prepared Mannich ketones II from 4-methoxy- and 4-chloro-1-acetonaphthone and several dialkylamines (Table I). In these preparations nitromethane possessed advantages over several more conventional (3) solvents and is recommended for trial in other cases.

In attempting to prepare an amino ketone from 4-methoxy-1-isobutyronaphthone IV in order to arrive eventually at a branched chain amino alcohol V,

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.



IV



V

we came across an interesting structural limitation of the Mannich reaction. The isobutyronaphthone was recovered unchanged even when conditions were very vigorous. Similarly, isobutyrophenone survived the conditions of the

TABLE I

AMINO KETONES $YC_{10}H_6COCH_2CH_2NR_2 \cdot HCl$ FROM SUBSTITUTED 1-ACETONAPHTHONES

Y	R	YIELD, %	M.P., °C	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
4-OCH_3	CH_3	44	172.7–173.7	65.41	6.86	65.79	6.96
4-OCH_3	C_2H_5	63	105.3–106.3[a]	63.61	7.71	63.43	7.62
			152.3–152.8[b]	67.17	7.52	66.83	7.59
4-OCH_3	n-C_4H_9	69	137.5–139.0	69.91	8.54	69.87	8.59
4-OCH_3	n-C_5H_{11}	74	126.0–126.5	71.00	8.94	71.10	8.89
4-Cl	CH_3	64	155–156.5	60.41	5.75	60.28	5.74
4-Cl	C_2H_5	70	128–129	62.58	6.49	62.31	6.49
4-Cl	n-C_4H_9	60	131–132	65.96	7.64	65.70	7.75

[a] Monohydrate.

[b] Anhydrous.

Mannich reaction. Methyl aryl ketones undergo the Mannich reaction smoothly as demonstrated by this and considerable earlier work (3). A substance such as 4-methoxypropiophenone with one more carbon atom in the side chain undergoes the Mannich reaction smoothly, although there is evidence that the reaction is a little slower than for 4-methoxyacetophenone (4). However, there is apparently a much more marked effect of the second methyl group when one goes to the branched chain aryl ketones.

The branched chain isobutyraldehyde is known to undergo the Mannich reaction smoothly (2, 5) and we thought it worth while to try diisopropyl ketone in this reaction. As expected, this carbonyl compound seemed to fall in a position intermediate between isobutyraldehyde and the branched chain aryl ketones. Judging by the equivalent weight and nitrogen analysis, the product contained an 8% yield of the Mannich ketone VI and a 12% yield of the di-dialkylaminomethane VII from the formaldehyde and dibutylamine. The mixed product yielded formaldehyde dinitrophenylhydrazone from an acidic medium.

$(CH_3)_2CHCOC(CH_3)_2CH_2N(C_4H_9)_2$

VI

$(C_4H_9)_2NCH_2N(C_4H_9)_2$

VII

A satisfactory explanation of the behavior of the branched chain aryl ketones in attempts to carry out the Mannich reaction must await further evidence on the mechanism of the reaction. This evidence we hope to produce when time permits. However, it is interesting to notice the behavior of isobutyrophenone in other reactions involving the *alpha* hydrogen atom. For example, this ketone is halogenated satisfactorily, the rate of acid-catalyzed halogenation being slower than the one for acetophenone by a factor of approximately fifty in the case of iodination in aqueous perchloric acid solution (6) and approximately ten in the case of bromination in an acetic acid solution of hydrochloric acid (7). On the other hand, isobutyrophenone appears not to condense with ethyl phthalate with sodium ethoxide as a catalyst (8). Most interesting in connection with our work is the observation that isobutyrophenone reacts with formaldehyde by a complex process which must, however, involve condensation with the formaldehyde (9).

The amino alcohols (Table II) which we prepared as possible antimalarials were derived by reduction of the Mannich ketones II. Catalytic hydrogenation

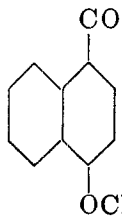
TABLE II

AMINO ALCOHOLS $YC_{10}H_6\ CHOHCH_2CH_2NR_2 \cdot HCl$

SN	Y	R	M.P., °C	YIELD, %	ANALYSIS	
					Calc'd	Found
					% C % H	% C % H
8991	4-OCH_3	*n*-C_4H_9	125.8–127.8	52	69.54 9.02	69.61 9.27
10200	4-OCH_3	*n*-C_5H_{11}	117.7–118.7	53	70.65 9.39	70.31 9.49
8744	4-Cl	C_2H_5[a]	112–114	8	58.96 7.28	59.06 7.51

[a] Monohydrate.

of the 4-methoxyamino ketone hydrochlorides using Adams' catalyst gave rise to fair yields of the products together with some of the hydrogenolysis product, 4-methoxy-1-propionaphthone VIII. When Raney nickel or palladium catalysts were used only hydrogenolysis occurred. When the free amino ketone was subjected to hydrogenation, only hydrogenolysis occurred in line with the greater tendency toward this cleavage displayed by free β-amino ketones over the corresponding salts (10). It is of some interest in connection with the mechanism of the hydrogenolysis that the free Mannich base IX from isobutyraldehyde and dipropylamine, which we describe in another article (2), is hydrogenated with Adams' catalyst in quantitative yield to the neopentyl alcohol X.



VIII

$(n\text{-}C_3H_7)_2NCH_2C(CH_3)_2CHO$

IX

$(n\text{-}C_3H_7)_2NCH_2C(CH_3)_2CH_2OH$

X

Catalytic hydrogenation of the 4-chlorodibutylamino ketone hydrochloride with Adams' catalyst gave a large proportion of cleavage of the nuclear halogen and was therefore unsuccessful. Although the nuclear halogen-substituted amino alcohols were best prepared by another method reported elsewhere (2), we did prepare one of them in poor yield by aluminum isopropoxide reduction of the Mannich ketone. We found as Fry (11) did in similar cases that somewhat better yields were obtained with the hydriodide. The aluminum isopropoxide reduction did not succeed with the 4-methoxydibutylamino ketone II (Y = OCH_3; R = n-C_4H_9). Neither did the use of sodium amalgam in acid solution or isobutylmagnesium bromide give anything but uncharacterized oils.

Reduction of a 4-methoxyamino ketone II (Y = OCH_3 ; R = n-C_4H_9) with activated aluminum gave rise to two diastereomeric glycols XI (SN-9860). This behavior is common with arylamino ketones (4, 12).

$$\begin{array}{l} CH_3OC_{10}H_6C(OH)CH_2CH_2N(C_4H_9)_2 \\ | \\ CH_3OC_{10}H_6C(OH)CH_2CH_2N(C_4H_9)_2 \end{array}$$

XI

EXPERIMENTAL

All melting points are corrected. Analyses were by Jack W. Ralls and Bruce Day.

Mannich reactions with 1-acetonaphthones. The best procedure used nitromethane as a solvent and is illustrated in detail for the preparation of 4-methoxy-1-(β-diethylaminopropio)naphthone.

In a 250-ml., three-necked flask equipped with a thermometer, a Hershberg stirrer (13) and a reflux condenser attached through a gravity type water separator, were placed 20.0 g. (0.10 mole) of 1-aceto-4-methoxynaphthone (1), 11.0 g. (0.10 mole) of diethylammonium chloride, 4.5 g. (0.15 mole) of paraformaldehyde, 0.23 ml. of conc'd hydrochloric acid, 35 ml. of nitromethane, 5 ml. of absolute alcohol, and 10 ml. of toluene. The mixture was stirred and refluxed for one-half hour during which the inside temperature rose from 92° to 93° and 2.1 ml. of water was collected in the separator. The mixture was poured into a flask, allowed to cool, and diluted to about 300 ml. with anhydrous ether. The solution was stored overnight in the refrigerator. The crystallized product was filtered, washed on the filter several times with water and dried over phosphorus pentoxide. Further dilution of the mother liquors with ether brought the total yield of material to 21.4 g. (63%). One recrystallization from a mixture of acetone and absolute alcohol yielded 19.1 g. (56%) of material, m.p. 105.3–106.3°, which proved to be a monohydrate. Storage *in vacuo* over phosphorus pentoxide for a week converted the hydrate to a white hygroscopic powder, m.p. 152.3–152.8°, which had the composition of the anhydrous amino ketone hydrochloride.

A procedure similar to the above was also used with the dibutyl and the diamyl analogs from 4-methoxy-1-acetonaphthone. The crude yields were 69 and 74% respectively, the yields of pure material, 62 and 60%.

The Mannich reaction involving 4-methoxy-1-acetonaphthone and diethylammonium chloride was also carried out in nitrobenzene-benzene as a solvent, as suggested to us by Dr. E. M. Fry (11, 14). The proportions of materials were the same as those above except that the solvent contained 2 ml. of absolute alcohol, 24 ml. of nitrobenzene, and 24 ml. of benzene. After the proper reflux period, the reaction mixture was worked up in a manner which differed in some details from the procedure outlined above. The yields varied markedly with the length of the reflux period, a one-hour period giving a crude yield of 55%, a two-hour period 47% and a three-hour period 29%. These results parallel those of Fry (14) in similar cases.

For the Mannich reaction with 4-methoxy-1-acetonaphthone and dimethylammonium chloride, isoamyl alcohol was used for the solvent. The materials employed consisted of 0.05 ml. conc'd hydrochloric acid, 2.78 g. (0.034 mole) of dimethylammonium chloride, 1.02 g. (0.034 mole) of paraformaldehyde, 6.8 g. (0.034 mole) of 4-methoxy-1-acetonaphthone, and 16 ml. of absolute isoamyl alcohol. A 5.5-hour reflux period was allowed. The reaction mixture was cooled in the refrigerator and the product filtered and washed with cold isoamyl alcohol. Dilution of the mother liquors with cold ether gave enough additional product to bring the total crude yield to 44%. Purification was effected by conversion to free base, reprecipitation of the hydrochloride from anhydrous ether by the addition of ethereal hydrogen chloride, and recrystallization of the hydrochloride from alcohol-ether. A similar procedure was used for the Mannich reaction with 4-chloro-1-acetonaphthone and dimethylammonium chloride. A two-hour reflux period was allowed and the product was purified by crystallization from ethanol. The yield was 64%.

The Mannich ketones from 4-chloro-1-acetonaphthone and diethyl- and di-*n*-butylammonium chloride were prepared in nitromethane as described above. The di-*n*-butylamino ketone was purified by washing with water and recrystallizing from ethyl acetate, yield 60%. With the diethyl analog it was necessary to convert to the free base and steam distill at water-pump pressure to remove diethylamine. The base was then reconverted to the hydrochloride. Further purification was unnecessary; yield 70%.

1-Isobutyro-4-methoxynaphthone. This material was prepared similarly to 4-methoxy-1-acetonaphthone (1) from isobutyryl chloride, α-methoxynaphthalene and aluminum chloride in carbon disulfide. There was obtained after two recrystallizations from ligroin, b.p. 60–70°, a 72% yield of pale yellow prisms, m.p. 96–98° (m.p. after three more crystallizations 97.0–97.5°).

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06.
Found: C, 78.95; H, 6.90.

A sample of this material was oxidized with potassium ferricyanide (15) at 65° for 95 hours. The product was recrystallized from alcohol to yield 40% of the theoretical amount of 4-methoxy-1-naphthoic acid, m.p. 237–239° (uncorr.). No depression was observed on admixture with material prepared in this laboratory (16) by carbonation of the Grignard reagent from 4-methoxy-1-bromonaphthalene.

Attempted Mannich reactions with 1-isobutyro-4-methoxynaphthone and isobutyrophenone. Di-*n*-butylammonium chloride was used in these attempts. The reaction was tried in nitromethane in a manner similar to that used with 1-aceto-4-methoxynaphthone. With the 1-isobutyro-4-methoxynaphthone, after a one-hour reflux period, the cooled solution was diluted with anhydrous ether and stored in the ice chest. Only di-*n*-butylammonium chloride was obtained. This was filtered and from the filtrate, after suitable purification, there was isolated 76% of unreacted ketone.

Other attempts gave a 92% recovery of naphthone after a 12-hour reaction period in nitromethane, an 88% recovery after a 2.5-hour reflux period in 1-nitropropane, and a 91% recovery after a 3.5-hour reflux period in isoamyl alcohol.

With isobutyrophenone (17) after a 1.25-hour reflux period, there were obtained an 84% recovery of dibutylammonium chloride and a 78% recovery of isobutyrophenone, m.p. and mixed m.p. of 2,4-dinitrophenylhydrazone 163–164° (7). Hold-up and still bottoms in the distillation of isobutyrophenone added an estimated 13% to the recovery.

The Mannich reaction with diisopropyl ketone. Di-*n*-butylammonium chloride was used in this reaction and the procedure was similar to that of Mannich (5). The diisopropyl ketone was kindly supplied by Dr. J. D. Roberts of this laboratory. After a 3.25-hour refluxing period, the cooled reaction mixture was poured into water and the organic layer separated. The aqueous layer was made alkaline and extracted with ether. The solvent was evaporated after drying and the residue was distilled *in vacuo*. Several cuts were taken but no pure material was obtained and the largest fraction was redistilled. The two main fractions still possessed a wide boiling range and they were combined and redistilled. At 3 mm. the main fraction, 5.2 g. (20%), had the following properties: b.p. 112–114° (3 mm.), n_D^{20} 1.4437.

Anal. Calc'd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48.
Calc'd for $C_{17}H_{35}N_2$: C, 75.48; H, 14.16; N, 10.36.
Found: C, 75.24; H, 13.71; N, 8.59.

The equivalent weight of this fraction was obtained by titration with acid to the methyl red end-point.

Equiv. Wt. Calc'd for $C_{16}H_{33}NO$: 255.
Calc'd for $C_{17}H_{38}N_2$: 135.
Found: 166, 168, 169.

When the 2,4-dinitrophenylhydrazone of this fraction was prepared in alcohol containing hydrochloric acid, the only product obtained was formaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 164.8–165.3°. This fraction gave a silver mirror when warmed with ammoniacal silver nitrate.

The ready production of formaldehyde in acid solution from compounds of the type VII is well known (18). As a control, we treated the Mannich base from isobutyraldehyde and diamylamine (2) in acid solution with dinitrophenylhydrazine. No hydrazone was precipitated.

Hydrogenation of amino ketones over Adams' catalyst. The reactions were carried out at atmospheric pressure and were interrupted at about 100% absorption. In the case of the 4-methoxydibutylamino ketone hydrochloride, the reaction mixture was filtered and the solution was concentrated under reduced pressure. The resulting syrup was triturated with dry ether and the solid collected on a filter, washed with ether, and dried. The combined filtrate and washings on evaporation gave a green oil which, on crystallization from methanol, yielded 22% of 4-methoxy-1-propionaphthone, m.p. 56–57° [literature: 57°, 58° (19)], m.p. of oxime 172–174° [literature: 172° (19c)].

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59.
Found: C, 73.33; H, 6.60.

The crude solid from above was washed on the funnel with water. From the water washings there was obtained 20% of di-*n*-butylammonium chloride identified through the phenylthiourea derivative. The crude amino alcohol hydrochloride (52%), m.p. 124–126°, on the funnel was recrystallized from ethyl acetate-alcohol-ether, to yield 46% of pure product, m.p. 126–128°.

From the reduction of the 4-methoxydiamylamino ketone hydrochloride, there was obtained the amino alcohol hydrochloride, m.p. 114.6–115.6° in a yield of 69% of crude and 53% of pure material.

When the 4-methoxydibutyl- and diamyl-amino ketones, as the free bases, were hydrogenated over Adams' catalyst, the only products isolated were dialkylamine and 4-methoxy-1-propionaphthone.

When the 4-chloro-di-*n*-butylamino ketone was hydrogenated and the catalyst removed by filtration, gravimetric determination of chloride on an aliquot portion indicated 71% hydrogenolysis of the ring chlorine. No pure product could be isolated.

The hydrogenation of 14.0 g. (0.0756 mole) of α,α-dimethyl-β-di-*n*-propylaminopropionaldehyde, prepared as described elsewhere (2) was carried out in ethyl alcohol. After removal of solvent, the residue was distilled at 20 mm. through a 4-inch Vigreux column. The following cuts were taken: (a) 0.4 g., b.p. 114–118°, n_D^{20} 1.4434; (b) 5.7 g., b.p. 118.0–119.5°, n_D^{20} 1.4449; (c) 6.8 g., b.p. 119.5–119.5°, n_D^{20} 1.4449; (d) still bottoms and hold-up, wt. 0.6 g. Fractions (b) and (c) make a combined yield of 88%.

Anal. Calc'd for $C_{11}H_{25}NO$: C, 70.53; H, 13.45.
Found: C, 70.60; H, 13.56.

Hydrogenation of amino ketones over Raney nickel. These experiments were performed with 4-methoxy-1-(β-dibutylaminopropio)naphthone. The hydrogenations were carried out in a Parr hydrogenator at 3 to 4 atmospheres. When the hydrochloride of the amino ketone was used, there was obtained 97% of di-*n*-butylammonium chloride and 97% of 4-methoxy-1-propionaphthone. When the hydrogenation was performed on the free base, there was obtained 78% of di-*n*-butylammonium chloride and 97% of 4-methoxy-1-propionaphthone

Hydrogenation of amino ketone over palladium-charcoal. Hydrogenation of the 4-methoxy-di-*n*-butylamino ketone hydrochloride at atmospheric pressure with 10% palladium-charcoal catalyst was incomplete even after 6.5 days. There were isolated 66% of unreacted starting material, 13% of di-*n*-butylammonium chloride, and 17% of 4-methoxy-1-propionaphthone.

Reduction with aluminum amalgam. The 4-methoxy-di-*n*-butylamino ketone was reduced in the usual way (12) in moist ether. After 27 hours the ether layer was separated and the solids extracted with ether for 15 hours. The combined ether solutions were dried, concentrated, and cooled. There was obtained 14% of a white crystalline product *A*, m.p. 171.1–172.5°. Evaporation of the ether left an oil which yielded 84% of a hydrochloride *B*, m.p. 231.4–232.4°.

Anal. *A* Calc'd for $C_{44}H_{64}N_2O_4$: C, 77.15; H, 9.42.
Found: C, 76.99; H, 9.37.
B Calc'd for $C_{44}H_{66}Cl_2N_2O_4$: C, 69.72; H, 8.78.
Found: C, 69.66; H, 8.81.

The molecular weight of *A* by the micro-Rast method (20) was 695, 575, 648, theoretical for $C_{44}H_{64}N_2O_4$ being 685.

Addition of ethereal hydrogen chloride to a benzene solution of *A* yielded the dihydrochloride, m.p., after crystallization from alcohol-ether, 231.9–232.4°, mixed m.p. with *B* 227.5–228.0°.

Reductions with sodium amalgam. These were carried out with the 4-methoxydiethyl- and di-*n*-butylamino ketone hydrochlorides according to the method of Cromwell (21). The mixtures were worked up in the usual way but only oils were obtained.

Reduction with isobutylmagnesium bromide. The 4-methoxy-di-*n*-butylamino ketone as an ether solution was added to the isobutyl Grignard reagent. About 34% of what appeared to be isobutane was collected in a dry ice trap. From a concentrated sulfuric acid trap there was obtained a small amount of hydrocarbon.

The Grignard reaction mixture was treated in the usual way to yield a basic product. However, neither this basic material nor its hydrochloride could be crystallized.

Reductions with aluminum isopropoxide. The reduction of the 4-chlorodiethylamino ketone hydriodide is typical. It was carried out under nitrogen in an all-glass apparatus (1). After an hour 95% of the theoretical amount of acetone was obtained. The mixture was poured on an excess of iced sodium hydroxide solution and steam distilled at reduced pressure until there was no longer a detectable odor of diethylamine. The residual oil was converted to the hydrochloride, m.p. 109–111° after recrystallization from acetone-ether and 112–114° after further recrystallization from ethyl acetate; yield 5%.

Another reduction was carried out with the diethylamino ketone hydriodide at 250 mm. pressure. After eight hours, 72% of the theoretical amount of acetone was obtained. The mixture was worked up as before and the yield of amino alcohol, m.p. 110–111°, was 8%.

Several other similar experiments were carried out. Four reductions of the diethylamino ketone hydrochloride were run at atmospheric pressure. The yield in each case was 0% except one in which a 2% yield of amino alcohol was obtained. When the reduction was repeated but at 250 mm. pressure, the yield of crude amino alcohol was 5%. Where the reduction was run with the free base, no amino alcohol was obtained.

When the 4-methoxydiethylamino ketone hydrochloride was reduced, 56% of the theoretical amount of acetone was obtained in 13 hours. The reaction mixture was treated in the usual way but the basic fraction, isolated as a black oily hydrochloride, gave no crystalline material. A neutral, amorphous apparently polymeric material, which accounted for about 87% of the starting amino ketone, was also isolated.

SUMMARY

A number of Mannich bases have been prepared from 4-methoxy- and 4-chloro-1-acetonaphthone. These Mannich bases have been reduced to α-(2-dialkylaminoethyl)-4-chloro- and -4-methoxy-1-naphthalenemethanols.

An interesting structural limitation of the Mannich reaction is the failure of the branched chain ketones 4-methoxy-1-isobutyronaphthone and isobutyrophenone to give a Mannich base even under vigorous conditions. Diisopropyl ketone seems to represent a borderline case.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. VII. SYNTHESIS OF SOME PROPANOLAMINES BY MEANS OF GRIGNARD REAGENTS[1]

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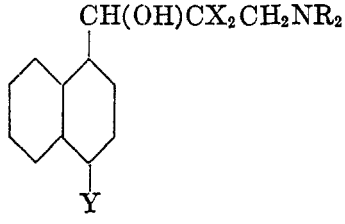
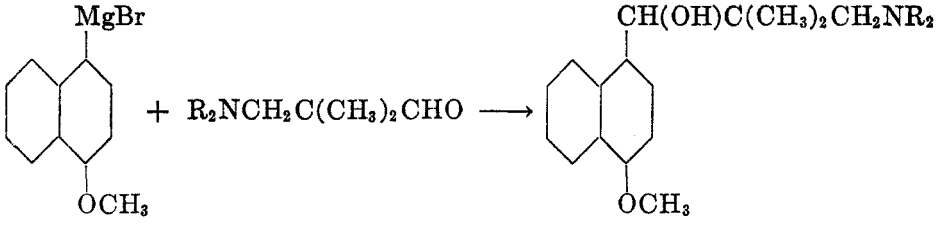
In the synthesis of β-dialkylaminoethyl-1-naphthalenemethanols, I,



I

the failure of the method involving preparation and reduction of the Mannich ketones (1) in those cases where Y = Cl, X = H or Y = CH_3O, X = CH_3 led to the investigation of other methods.

The synthesis of compounds representative of this second case (Y = CH_3O, X = CH_3) was accomplished successfully by treatment of α,α-dimethyl-β-dialkylaminopropionaldehyde with 4-methoxy-1-naphthylmagnesium bromide:



The α,α-dimethyl-β-dialkylaminopropionaldehydes were readily prepared according to the method of Mannich, Lesser, and Silten (2). The preparation of several of these compounds has been recorded in the literature: methylamino (3), dimethylamino (2), diethylamino (2), piperidino (2), and morpholino (4). We have extended the series to include those amino aldehydes containing the di-*n*-propyl, di-*n*-butyl, and di-*n*-amyl groupings. The properties of these compounds are summarized in Table I.

The Grignard reagent prepared from 1-bromo-4-methoxynaphthalene (5) re-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

TABLE I

PROPERTIES OF α,α-DIMETHYL-β-DIALKYLAMINOPROPIONALDEHYDES

NR_2 R =	YIELD, %	B.P., °C	n^{20}	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
C_3H_7	70	103–107/20 mm.	1.4363	71.30	12.51	71.23	12.38
C_4H_9	57	120–125/15 mm.	1.4415	73.18	12.76	73.10	12.72
C_5H_{11}	49	138–146/10 mm.	1.4440	74.62	12.94	74.71	13.12

TABLE II

PROPERTIES OF α-(2-DIALKYLAMINO-*tert.*-BUTYL)-4-METHOXY-1-NAPHTHALENEMETHANOLS

SN	R	YIELD, %	M.P. OF HYDROCHLORIDE, °C	ANALYSIS			
				Calc'd		Found	
				% C	% H	% C	% H
8768	C_2H_5	72[a]	(α) 107.5–109.0[b] (β) 170.0–170.4	68.26	8.59	68.11	8.71
8364	C_3H_7	51[a]	182.0–182.5	69.54	9.02	69.02	8.98
7993	C_4H_9	52[a]	166.0–167.0	70.64	9.39	70.68	9.13
8989	C_5H_{11}	45[c]		78.14	10.34	77.83	10.55

[a] This figure represents the yield of crude product.

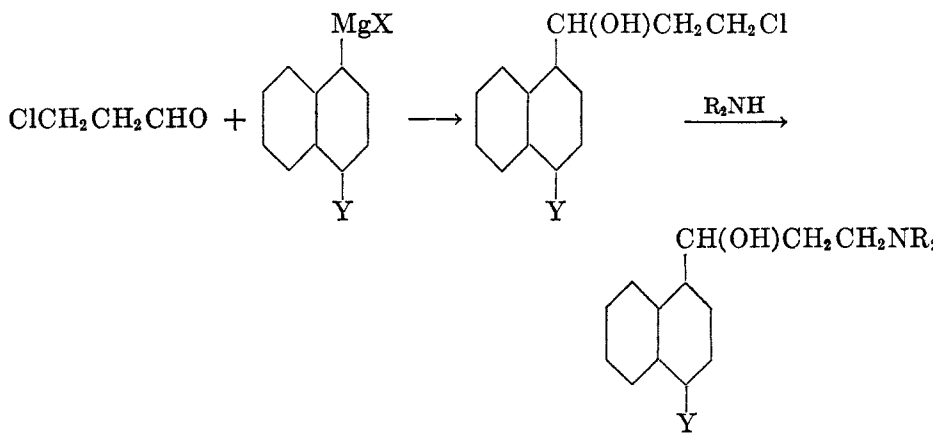
[b] Two dimorphic forms were obtained in this case. Mixed melting point was 169–171°.

[c] This figure represents the yield of distilled product. The hydrochloride could not be obtained solid.

acted smoothly with these aldehydes and four amino alcohols were prepared.[2] Table II lists the properties of these compounds.

The method of Fourneau (7, 8) was used to prepare the compounds where Y = CH_3O or Cl, X = H. This method is represented by the following equations:

$$CH_2{=}CHCHO + HCl \longrightarrow ClCH_2CH_2CHO$$



[2] Evidently the only other study of the reaction of a Grignard reagent with β-amino aldehydes is that of Matti and Barman (6) who treated α,α-dimethyl-β-dimethyl- and -diethyl-aminopropionaldehydes with ethyl, butyl, and phenyl Grignard reagents.

The synthesis of β-chloropropionaldehyde from acrolein and hydrogen chloride has been described several times (7, 8, 9). This compound is relatively unstable and readily polymerizes to a trimer (10) or decomposes into acrolein and hydrogen chloride. It has usually been prepared by saturation of acrolein with hydrogen chloride cold, followed by distillation of the monomer, sometimes at reduced pressure. The distillate was then used directly in the Grignard reaction. The rapid polymerization of the monomer to trimer was troublesome, since the latter did not react smoothly with Grignard reagents. This trimerization was prevented by distillation of the monomer at reduced pressure into ether or toluene immersed in a dry ice-alcohol bath. This solution was not allowed to warm up until ready for use in the next step.

TABLE III

PROPERTIES OF α-(2-DIALKYLAMINOETHYL)-4-CHLORO OR METHOXY-1-NAPHTHALENEMETHANOL HYDROCHLORIDES, I

SN	Y	R	YIELD, %[c]	M.P., °C	ANALYSIS			
					Calc'd		Found	
					% C	% H	% C	% H
8744	Cl	C_2H_5[a, b]	33	112.0–113.0	58.96	7.28	58.67	7.36
8738	Cl	C_4H_9	30	147.5–149.0	65.61	8.13	65.63	8.14
8991	CH_3O	C_4H_9[b]	7	121.3–122.8	69.54	9.02	69.65	9.22

[a] This compound was isolated as a monohydrate. A crystalline anhydrous form could not be obtained.

[b] These compounds were shown to be identical, by analysis and mixed m.p., with those prepared by reduction of the corresponding Mannich ketones (1).

[c] This figure represents the yield of pure material.

The Grignard reagents used in this synthesis were 4-methoxy-1-naphthylmagnesium bromide and 4-chloro-1-naphthylmagnesium iodide. The 1-chloro-4-iodonaphthalene required for the latter was conveniently prepared through the chlorination of α-acetamidonaphthalene based on the method of Reverdin and Crepieux (11), with subsequent replacement of the amino group with iodine.

The intermediate chlorohydrins were not isolated in a pure state but were treated directly with the desired dialkylamine. The amino alcohols so produced were isolated and purified as hydrochlorides. Table III lists the properties of these compounds.

EXPERIMENTAL

All melting points are corrected. Analyses were performed by Mr. Jack Ralls and Mr. Bruce Day.

α,α-Dimethyl-β-(di-n-alkylamino)propionaldehydes. These compounds were prepared according to the method of Mannich, Lesser, and Silten (2) for α,α-dimethyl-β-diethylaminopropionaldehyde.

An attempt was made to prepare the 2,4-dinitrophenylhydrazone of the di-*n*-amyl compound by treating 1 ml. of the aldehyde in 50 ml. of 95% ethyl alcohol with 0.7 g. of 2,4-dinitrophenylhydrazine, heating to boiling, adding 3 ml. of concentrated hydrochloric acid, and refluxing for six minutes. On cooling, no crystalline material was obtained. No attempt was made to obtain the free base by neutralizing the reaction mixture.

α-(2-Dialkylamino-tert.-butyl)-4-methoxy-1-naphthalenemethanols. These compounds were all prepared in a completely analogous manner. As an example, the preparation of the hydrochloride of the diethylamino derivative is given.

In a well dried one-l. three-necked flask, kept under slight nitrogen pressure, fitted with a Hershberg stirrer (12), a reflux condenser, and a dropping-funnel were placed 6.0 g. (0.25 g. atom) of magnesium turnings and 50 ml. of anhydrous ether. Then 47.4 g. (0.20 mole) of 1-bromo-4-methoxynaphthalene (5), dissolved in 150 ml. of anhydrous ether and 50 ml. of anhydrous thiophene-free benzene was added dropwise, over the course of ¾ hour, with stirring and refluxing. A small amount of methylmagnesium iodide was added to start the reaction. Refluxing was continued for 3.25 hours longer.

The solution of the Grignard reagent was filtered, under nitrogen, into a one-l. three-necked flask equipped with a Hershberg stirrer, a reflux condenser, and a dropping-funnel. A solution of 23.6 g. (0.15 mole) of α,α-dimethyl-β-diethylaminopropionaldehyde (2) in 80 ml. of anhydrous ether was added dropwise over the course of thirty minutes to the Grignard reagent. A yellow precipitate soon appeared in the flask. The mixture was refluxed and stirred 7.5 hours longer.

The complex was decomposed with ice and saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted with two 100-ml. portions of ether which were combined with the organic layer, washed twice with saturated ammonium chloride solution, and dried over anhydrous potassium carbonate.

The dry ether solution was treated with an excess of ethereal hydrogen chloride, the ether decanted and the gummy residue taken up in the minimum amount of alcohol. Addition of dry ether caused the product to crystallize. The yield was 37.8 g. (72%) of crude material m.p. 162–164°. Four recrystallizations from alcohol-ether yielded 18.6 g., m.p. 169.0–169.5°. A small sample for analysis was crystallized three more times from alcohol-ether. Tiny, colorless, granular crystals were obtained, m.p. 170.0–170.4°. A dimorphic modification crystallizing in the form of rosettes of tiny needles, m.p. 107.5–109° was also obtained on one occasion.

The isolation and purification of the di-*n*-propyl- and the di-*n*-butyl-amino compounds was almost identical with the above. The hydrochloride of the di-*n*-amyl compound, however, could not be crystallized. The dark red oil resulting from the Grignard reaction was subjected to molecular distillation at 4×10^{-5} mm. pressure and 140–145°. There was obtained 21.7 g. (45%) of an orange-red oil. All attempts to crystallize the hydrochloride of the distilled base failed.

1-Chloro-4-iodonaphthalene. Preparation of 1-amino-4-chloronaphthalene. In a 3-l., three-necked flask fitted with a mechanical stirrer and a condenser attached to a gas trap were placed 243 g. (1.7 moles) of α-naphthylamine (technical), 730 ml. of glacial acetic acid and 174 ml. (188 g., 1.85 moles) of acetic anhydride (technical). The dark purple solution was refluxed for two hours, the reaction mixture cooled in an ice-bath until the temperature reached 35°, and 150 ml. of concentrated hydrochloric acid added. This prevented the α-acetamidonaphthalene from setting to a semi-solid mass. When the temperature reached 21°, 500 ml. more of conc'd hydrochloric acid was added.

With an ice-bath the temperature was kept at 20–24° while a solution of 78.2 g. (0.735 mole) of sodium chlorate in 150 ml. of water was added with stirring over a period of one hour. The mixture was stirred one hour longer in the ice-bath, then two hours at room temperature and left overnight.

The mixture was refluxed for two hours to hydrolyze the amide, the condenser set for distillation and 1100 ml. distilled while 750 ml. of water was added. The reaction mixture was cooled, basified with saturated sodium hydroxide, and allowed to cool overnight after removal of the stirrer.

The product, which had settled as a black oil and solidified, was transferred to a 500-ml. Claisen flask and distilled with superheated steam (the temperature of the issuing vapors being 130–135°) until the organic phase almost stopped distilling (about six hours). The product, which had distilled as a light purple oil and solidified in the receiver was air dried.

The yield of crude 1-amino-4-chloronaphthalene was 155 g. (51%). This was crystallized once from hexane (Skellysolve B, b.p. 60–70°) and yielded 106 g. (35%), m.p. 95–97°. This material was pure enough for the next step.

Diazotization of the amino group and replacement with iodine. In a 2-l., three-necked flask fitted with a mechanical stirrer, dropping-funnel, and thermometer, were placed 65.5 g. (0.369 mole) of 1-amino-4-chloronaphthalene and a solution of 31 ml. of concentrated sulfuric acid in 1000 ml. of water. The mixture was cooled to 0° and a solution of 27.4 g. (0.385 mole) of sodium nitrite (97%) in 80 ml. of water was added over a two-hour period, the temperature being kept below 5°. The mixture was allowed to stand in the ice-bath for a half hour, filtered quickly through glass wool and added cautiously to a solution of 90 g. (0.54 mole) of potassium iodide in 100 ml. of water in a 4-l. beaker fitted with a mechanical stirrer. The reaction mixture foamed very badly.

After about one hour, most of the reaction was over. The reaction mixture was stirred one hour longer, then heated until the black product melted and settled to the bottom. On cooling, the black oil solidified and was removed and air dried. This material was extracted three times with 500-ml. portions of boiling methanol and a black tarry residue was discarded. The methanol solution was decolorized with Nuchar until light yellow, and the product was crystallized by concentration. The yield of light yellow 1-chloro-4-iodonaphthalene was 72 g. (68% based on 1-amino-4-chloronaphthalene), m.p. 52.5–53.8°. Beattie and Whitmore (13) report m.p. 54.5°.

Several other syntheses of 1-chloro-4-iodonaphthalene were investigated but the above is in our opinion the best. Although the method of Beattie and Whitmore (13) gave a higher over-all yield (39% from sodium naphthionate), it was tedious, and the intermediate mercury compound produced an unpleasant skin rash. The nitration of α-chloronaphthalene to yield 1-chloro-4-nitronaphthalene, which could be readily reduced to 1-amino-4-chloronaphthalene, was attempted by the method of Ferrero and Caflisch (14). The desired compound could only be obtained in very low yield. The method reported by Pajak (15) of treating α-naphthylhydroxylamine with concentrated hydrochloric acid to yield 1-amino-4-chloronaphthalene could not be repeated. We have prepared 1-chloro-4-iodonaphthalene in 31% over-all yield (based on 1-aceto-4-chloronaphthalene), by preparing 1-amino-4-chloro-naphthalene by a Beckmann rearrangement of methyl 4-chloro-1-naphthyl ketoxime (16).

α-(2-Diethylaminoethyl)-4-chloro-1-naphthalenemethanol hydrochloride. Preparation of β-chloropropionaldehyde. In a 50-ml. flask in an ice-salt bath at −10° was placed 14.5 ml. (12.1 g., 0.216 mole) of redistilled acrolein. Dry hydrogen chloride gas was passed over the acrolein with occasional swirling. When 7.6 g. (96% theory) had been taken up, the contents of the flask were transferred to a 50-ml. modified Claisen flask with the aid of a little ether, and a few crystals of hydroquinone and *p*-toluenesulfonic acid were added.

The mixture was distilled under nitrogen at 20 mm. in an oil-bath at 75° until the distillate was one phase (no more water distilling). The distillate was about 4 ml. The receiver was then changed to a tared 125 ml. distilling flask containing 75 ml. of absolute ether, which had been weighed and immersed in a dry ice-alcohol bath; the distillation was then continued until the distillate practically stopped coming over. The increase in weight of the receiver was 8.3 g. (0.090 mole, 43% yield assuming the weight increase to be pure β-chloropropionaldehyde). The solution was left immersed in the dry ice-alcohol bath while the Grignard reagent was being prepared.

Reaction of β-chloropropionaldehyde with 4-chloro-1-naphthylmagnesium iodide. In a 500-ml. three-necked flask fitted with a reflux condenser, a dropping-funnel and a mechanical stirrer were placed 28.9 g. (0.10 mole) of 1-chloro-4-iodonaphthalene, 150 ml. of absolute ether, and 2.3 g. (0.095 mole) of magnesium turnings. The reaction started immediately and the mixture was refluxed until all the magnesium had reacted.

The ethereal aldehyde solution was warmed to about 10° and added to the Grignard solution dropwise at a rate to maintain refluxing; after one hour of further refluxing the solution was cooled in ice and hydrolyzed with 40 ml. of 3 *N* sulfuric acid. The ether solution was separated, washed, and dried.

Condensation of the chlorohydrin with diethylamine. The solvent was removed from the above solution at reduced pressure, the light-colored oil taken up in 100 ml. of acetone and 22 ml. (15.5 g., 0.21 mole) of diethylamine and 7.5 g. (0.05 mole) of sodium iodide added. The solution was refluxed seventeen hours.

The reaction mixture was transferred to a 500-ml. Claisen flask with 200 ml. of 3 *N* sodium hydroxide solution and distilled at 140 mm. pressure, under nitrogen, until there was no odor of diethylamine in the distillate. The residual dark oil was taken up in ether, washed, and dried.

The addition of excess ethereal hydrogen chloride to the ether solution precipitated a brown taffy. This material was treated with 50 ml. of boiling ethyl acetate and absolute ethanol was added until all was in solution. On cooling, the solution deposited 5.5 g. of nearly colorless product, m.p. 112–114°. Concentration of the mother liquor produced 5.5 g., m.p. 103–108°, which was recrystallized from ethyl acetate-ethanol to yield 4.2 g., m.p. 112–113°. The total yield was 9.7 g. (33%, based on β-chloropropionaldehyde).

α-(2-Dibutylaminoethyl)-4-chloro-1-naphthalenemethanol hydrochloride was prepared in a completely analogous manner.

α-(2-Dibutylaminoethyl)-4-methoxy-1-naphthalenemethanol hydrochloride. By a procedure similar to that used for the above 4-chloro compounds, 4-methoxy-1-naphthylmagnesium bromide was treated with β-chloropropionaldehyde (in toluene) and the crude chlorohydrin was treated with di-*n*-butylamine. The crude product was subjected to molecular distillation at 5×10^{-5} mm. pressure and after a forerun of α-methoxynaphthalene (excess Grignard used) there was obtained a fraction of crude base from which was obtained 4.4 g. (7%) of the product desired.

SUMMARY

Four α-(2-dialkylamino-*tert.*-butyl)-4-methoxy-1-naphthalenemethanols were prepared by the reaction of 4-methoxy-1-naphthylmagnesium bromide and α,α-dimethyl-β-dialkylaminopropionaldehydes. The aldehydes were prepared by the Mannich reaction.

The reaction of β-chloropropionaldehyde with 4-methoxy- or 4-chloro-1-naphthylmagnesium bromide gave chlorohydrins which were readily converted into α-(2-dialkylaminoethyl)-4-chloro- or -methoxy-1-naphthalenemethanols.

Los Angeles, Calif.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENE-METHANOLS. VIII. 5-, 6-, AND 7-CHLORO DERIVATIVES[1]

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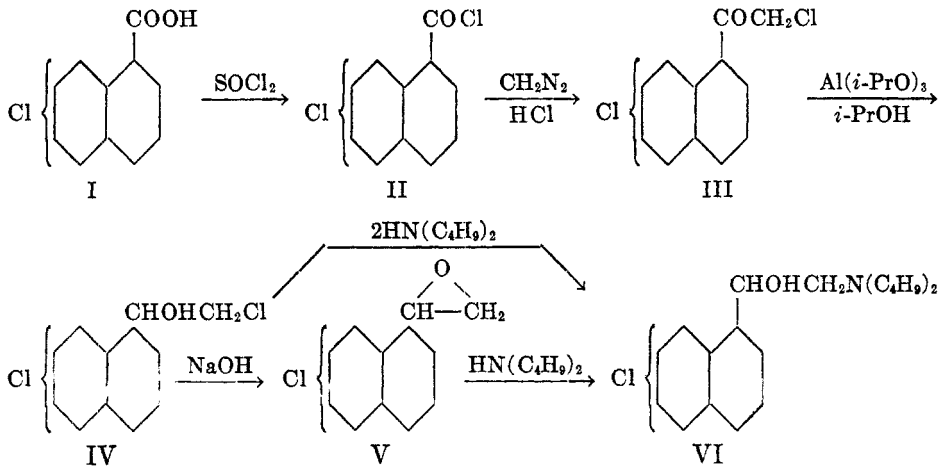
Since certain α-dialkylaminomethyl-2 or 4-chloro-1-naphthalenemethanols (1, 2, 3, 4) possessed considerable antimalarial activity, it was desirable to study the effect of further varying the position of the halogen. This paper reports the 5-, 6-, and 7-chloro derivatives which were prepared from the corresponding 1-naphthoic acids by the following reactions:



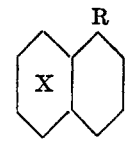
All of the chloronaphthoic acids needed as starting materials have been reported previously, but the substance, m.p. 188–189°, prepared by the condensation of methyl furoate and chlorobenzene in the presence of aluminum chloride (5, 6, 7), and believed to be 6-chloro-1-naphthoic acid is an eutectic mixture of the 6- and 7-chloro acids. It is not surprising that the reaction produces such a mixture and the only structure proof heretofore attempted, decarboxylation to 2-chloronaphthalene, merely shows that the halogen occupies a β-position.

We repeated the synthesis of the acid mixture according to the directions of Price and Huber (7), converted it to acid chloride, II, and prepared the chloro ketone, III. A chloro ketone, m.p. 94–95°, was usually obtained in 25–50% yield but in one case an isomeric ketone, m.p. 98.5–99.5°, was isolated. A mixed melting point determination indicated that these compounds were different.

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

Hypochlorite oxidation of the first of these ketones (m.p. 94–95°) gave pure 6-chloro-1-naphthoic acid, m.p. 215.8–216.2°, and similar treatment of the second

TABLE I

SUMMARY OF PROPERTIES OF DERIVATIVES OF THE TYPE  OF 6- AND 7-CHLORO-1-NAPHTHOIC ACIDS

COMPOUND		M.P.	ANALYSIS			
			Calc'd		Found	
X	R	°C	% C	% H	% C	% H
6-Cl	—$COOCH_3$	66.0–66.5 165–170/2 mm. (7)[a]	65.32	4.11	65.62	4.28
6-Cl	—$CONH_2$	215–216	64.24	4.02	64.62	4.17
6-Cl	—$CONHC_6H_5$	196–197	72.47	4.29	72.02	4.27
6-Cl	—$COCH_3$	140/1 mm.[a]				
6-Cl	—C=NOHCH_3	130.5–131.5	65.61	4.59	65.23	4.50
6-Cl	—$NHCOCH_3$	210–211	65.61	4.59	65.19	4.71
6-Cl	—NH_2	62–64 63–64 (10)[b]				
6-Cl	—CHO	83–84 120–160/2 mm.[a, c]	69.30	3.70	69.11	3.86
6-Cl	—CH=NOH	126–127	64.24	3.92	64.63	4.16
7-Cl	—$COOCH_3$	53–54 54 (8)[b]				
7-Cl	—$CONH_2$	231.5–233.5 237 (8)[b]				
7-Cl	—$CONHC_6H_5$	184.5–185.5 185 (8)[b]				

[a] Boiling point.
[b] Literature melting point.
[c] Crude, m.p. 45–46°.

gave slightly impure 7-chloro-1-naphthoic acid, m.p. 233.5–236.5°. Goldstein and Fisher (8) found the m.p. 243° for this compound and we have prepared a sample m.p. 239.7–243.1° by the separation method described below. Table I

summarizes the derivatives which we have prepared of these 6- and 7-chloro acids. The melting point-composition diagram for mixtures of the two acids is given in Fig. 1.

A superior method of separating the acid mixture was sought. Recrystallization of this mixture from a variety of solvents effected no separation and partial precipitation from carbonate solution did not help much. It proved to be most convenient to recover the 7-chloro isomer by crystallization of the mixture of acid chlorides and to convert the residual acid chlorides to methyl esters from which methyl 6-chloro-1-naphthoate was readily crystallized. This procedure gave 35–40% of 6-isomer and 10–18% of 7-isomer based on the amount of acid mixture used.[2]

Distillation at reduced pressure of the acid chloride mixture mentioned above gave a low-boiling forerun which on hydrolysis yielded 5–8% of *o*-chlorobenzoic acid. This substance probably arose from *o*-chlorotoluene, since it failed to

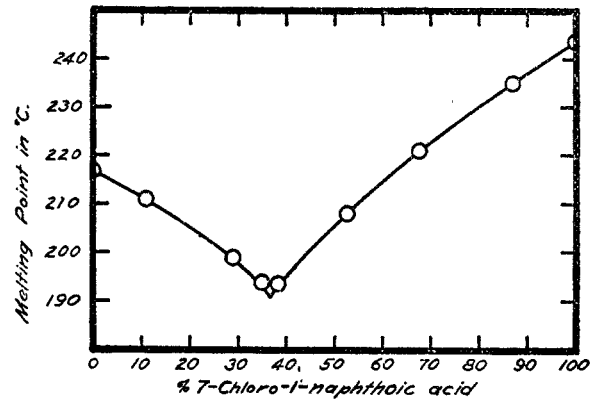


FIG. 1. MELTING POINT-COMPOSITION DIAGRAM FOR MIXTURES OF 6- AND 7-CHLORO-1-NAPHTHOIC ACIDS

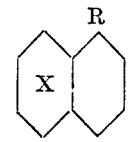
appear when carefully purified chlorobenzene was used as the starting material in the synthesis.

During this work a need arose for 6-chloro-1-naphthaldehyde and an attempt was made to prepare it by the Rosenmund reduction of the acid chloride from the 188–189° acid mixture. It was possible to obtain pure 6-chloro aldehyde by careful recrystallization of the oximes of the mixed aldehydes but it was more practical to prepare pure 6-chloro-1-naphthoic acid by hydrolysis of the methyl ester described above and to make the acid chloride from this for the reduction.

The structure of 6-chloro-1-naphthoic acid was established by conversion of its acid chloride to methyl ketone using dimethylcadmium, Bechmann rearrangement of the oxime of this ketone and hydrolysis of the resulting substituted aceta-

[2] Although we have obtained approximately this recovery of 6- and 7-isomers on several runs, the proportions of each may depend rather critically on the method of conducting the reaction. Hurd and co-workers (9) at Northwestern University have repeated this synthesis and separation, obtaining 23–27% of 6- and 25% of 7-chloro acid.

TABLE II

SUMMARY OF PROPERTIES OF COMPOUNDS OF TYPE  USED IN SYNTHESIS OF THE DESIRED DI-*n*-BUTYLAMINOMETHYL-X-CHLORO-1-NAPHTHALENEMETHANOLS

COMPOUND		M.P.	ANALYSIS			
			Calc'd		Found	
X	R	°C	% C	% H	% C	% H
5-Cl	—COOH	245 245 (11)[a]				
6-Cl		215.8–216.2	63.93	3.41	63.78	3.61
7-Cl		240–241 243 (8)[a]				
5-Cl	—COCl	146–148 160–165/2 mm.[b]				
6-Cl		69–70 140–150/1 mm.[b]	58.69	2.69	59.63	3.32
7-Cl		106–107 106 (8)[a] 140–150/1 mm.[b]				
5-Cl	—$COCH_2Cl$	147–148	60.28	3.37	60.55	3.60
6-Cl		95–96	60.28	3.37	60.18	3.56
7-Cl		98.5–99.5	60.28	3.37	60.03	3.56
5-Cl	—$CHOHCH_2Cl$	153–154				
6-Cl		74–75	59.77	4.18	59.88	4.43
7-Cl		77.0–77.5	59.77	4.18	59.86	4.26
5-Cl[c]	—$CHOHCH_2N(C_4H_9)_2 \cdot HCl$	157–159	64.86	7.89	64.66	7.94
6-Cl[d]	—$CHOHCH_2N(C_2H_5)_2 \cdot HCl$	174–176	61.15	6.74	60.70	6.78

[a] Literature melting point.
[b] Boiling point.
[c] SN 8739.
[d] SN 8069.

mide to the known 6-chloro-1-naphthylamine (10). A preliminary attempt to accomplish the proof by a Hofmann degradation of 6-chloro-1-naphthoic amide was not promising.

For 5-chloro-1-naphthoic acid we chose the method of Eckstrand (11), involving chlorination of 1-naphthoic acid in glacial acetic acid. This gives a mixture of 5-chloro, 8-chloro, and 5,8-dichloro acids from which the 5-isomer can be separated readily as the ester. The 8-chloro compounds fail to esterify by the Fischer procedure. Dichlorination can be largely prevented by chlorinating at room temperature for a limited time, but when the 5-isomer alone is desired, it is simpler to overchlorinate slightly at higher temperatures, which converts most of the 8-compound to 5,8- without removing much of the 5-derivative (11).

The 5-, 6-, and 7-chloro-1-naphthoic acids, I, were converted to acid chlorides, II, with thionyl chloride in 90–98% yields. Treatment of the acid chlorides with diazomethane followed by hydrogen chloride produced x-chloro-1-naphthyl chloromethyl ketones, III, in 65–86% yields. Reduction of these α-chloro ketones with aluminum isopropoxide gave 94–99% of the chlorohydrins, IV, which were used to prepare the corresponding x-chloro-1-naphthyl ethylene oxides, V, in 90–99% yields. The oxides were opened with di-*n*-butyl amine to give 70–76% of the desired α-di-*n*-butylaminomethyl-(x-chloro)-1-naphthalenemethanols, VI.

In some cases the halohydrins were treated with two moles of di-*n*-butyl amine and the final products obtained directly. Usually this procedure gave slightly lower yields than the method involving isolation of the oxides. α-Diethylaminomethyl-6-chloro-1-naphthalenemethanol was also prepared by this method.

Table II summarizes the compounds prepared.

EXPERIMENTAL

All melting points are corrected. Analyses were done by Jack W. Ralls or Bruce Day.

1-Naphthoic acid. The method of Gilman (12) was used to prepare 1-naphthoic acid. Use of solid rather than gaseous carbon dioxide in the decomposition of 1-naphthylmagnesium bromide raised the yields to 80–90%.

5-Chloro-1-naphthoic acid. Fifty grams (0.29 mole) of 1-naphthoic acid, 0.5 gram of iodine, and 500 ml. of glacial acetic acid were placed in a one-liter, three-necked flask equipped with a thermometer and an inlet tube extending to the bottom of the flask. Chlorine was passed in slowly at room temperature. Heat was evolved during the reaction and the temperature rose to 50–60°. When it had returned to room temperature the reaction was complete. Excess chlorine and acetic acid were removed at 30 mm., the residue was dissolved in 500 ml. of ether and this solution washed several times with 200 ml. of water to remove the remaining acetic acid. After drying over magnesium sulfate the solution was evaporated. The chlorinated naphthoic acids remaining were dissolved in 500 ml. of methanol saturated with hydrogen chloride and the solution refluxed twenty-four hours. The methanol was removed at reduced pressure leaving methyl 5-chloro-1-naphthoate, 8-chloro- and 5,8-dichloro-1-naphthoic acids. The acids were dissolved in saturated sodium bicarbonate solution, and the ester taken up in 500 ml. ether. The layers were separated and the ethereal solution evaporated. The ester thus obtained was hydrolyzed by refluxing overnight with aqueous alcoholic sodium hydroxide (10% excess). The resulting solution was poured slowly onto a vigorously stirred mixture of ice and 25% excess of concentrated hydrochloric acid. The precipitated 5-chloro-1-naphthoic acid was collected, washed with water, pressed as dry as possible, and air dried. This acid was crystallized from ligroin (Skellysolve S, b.p. 150–200°) to give 27 g. (0.13 mole, 48%) of a tan solid, m.p. 237–242°, sufficiently pure for further work. Two recrystallizations raised the melting point to 245°, which is that reported by Eckstrand (11).

It was possible but less satisfactory to purify by distillation of the crude methyl 5-chloro-

1-naphthoate b.p. 130° at 2 mm. The distillate solidified on standing and this solid was recrystallized from ethanol to give the pure ester, m.p. 42°. Hydrolysis of the crude distillate gave acid sufficiently pure for further use. Decomposition losses during distillation were prohibitively large except on small runs.

6- and 7-Chloro-1-naphthoic acids. The method of Price and Huber (7) was used with some modification.

In a 3-liter, 3-neck flask fitted with a mercury-sealed stirrer, a reflux condenser, and an aluminum chloride addition tube were placed 150 g. (1.18 moles) of methyl furoate and 900 ml. of dry Eastman practical grade chlorobenzene. The solution was cooled to 5° and 325 g. (2.44 moles) of aluminum chloride was added with stirring. The reaction mixture was stirred for thirty minutes at 5°, for one hour at room temperature, and at 95–105° for twenty-nine hours. The solution was cooled and poured into an excess of ice and hydrochloric acid. The resulting emulsion was stirred one hour, and the chlorobenzene was removed by steam-distillation. After decanting the water, the tarry product was dissolved in 1.5 liters of boiling glacial acetic acid, the solution filtered while hot, and diluted to 4.5 liters with water. The resulting solid was collected and dried. This material contained up to 15% methyl 6- and 7-chloro-1-naphthoate; the ester was separated by extraction with three 500-ml. portions of boiling petroleum ether (b.p. 60–70°, Skellysolve B). The solvent was evaporated, the esters hydrolyzed and added to the material remaining after these extractions. The acids were dissolved in bicarbonate, the solution boiled with decolorizing carbon, and filtered. Acidification with 6 *N* hydrochloric acid precipitated the acid mixture. This gave 135–145 g. (55–60%) of crude mixed acids, m.p. 160–180°, containing roughly 60% 6-chloro-1-naphthoic acid, 30% 7-chloro-1-naphthoic acid, 5–8% *o*-chlorobenzoic acid, and some inorganic salts.

Two liters of practical chlorobenzene was fractionated through a three-foot column packed with $\frac{1}{8}''$ glass helices at a reflux ratio of 5:1 to 8:1. Nine hundred milliliters of a middle cut boiling 130.0–130.6° (uncorr.) was used in one condensation with methyl furoate. No *o*-chlorobenzoic acid could be detected among the products of the reaction. In addition to the chlorobenzene and a small forerun the fractionation yielded about 100 ml. of material boiling at 157–160°.

Separation of 6- and 7-chloro-1-naphthoic acids. In a 1-liter glass-jointed flask 100 g. of the crude acids and 400–500 ml. of thionyl chloride were refluxed eight to twelve hours. The excess thionyl chloride was removed first at atmospheric pressure then under an aspirator vacuum. Distillation of the residue at 1 mm. from a 250-ml. Claisen flask gave 30–40 g. of material boiling under 140° and 60–70 g. boiling at 140–150°. The high-boiling fraction was dissolved in 1 liter of hexane (b.p. 60–70°, Skellysolve B) and allowed to crystallize overnight at 0°. One-third to one-half of the solute was precipitated by this procedure. The precipitate was richer in the 7-chloro isomer and melted at 60–90°. Recrystallization once from Skellysolve B (14–15 ml. per g. of acid chlorides) raised the melting point to 80–100° and another recrystallization to 100–104°. The mother liquors were combined and the solvent evaporated, then 200 ml. methanol was added and the solution boiled ten to fifteen minutes. A crystalline methyl ester deposited on standing, m.p. 50–60°. Recrystallization from methanol gave pure methyl 6-chloro-1-naphthoate, m.p. 66.0–66.5°. This procedure gave 35–40% of the 6-isomer and 10–18% of the 7-isomer. All residues were hydrolyzed and the products added to the original crude acid mixture for recycling.

Three and seventy-eight hundredths grams of the low-boiling fraction from the acid chloride distillation was boiled with 200 ml. water. The solution was filtered while hot. Upon cooling the filtrate deposited 1.16 g. of *o*-chlorobenzoic acid, m.p. 137–139°, mixed melting point with authentic sample 138–140°, anilide 116–117° [reported m.p. 114°, 117.5–118° (13)]; equivalent weight: 156.7, 157.8; calculated for $C_7H_5ClO_2$: 156.57. The fraction insoluble in hot water was presumed to be chloronaphthoic acids and was returned for recycling.

Preparation of 5-, 6-, and 7-chloro-1-naphthoyl chlorides. The acids were refluxed in glass-jointed equipment for several hours with four to five times their weight of thionyl

chloride [Eastman White Label or purified by Fieser's method (14)] for four to twelve hours. The excess thionyl chloride was removed first at atmospheric pressure then under an aspirator vacuum. Distillation at 1 to 2 mm. of the residues gave the acid chloride in 95–99% yield. The distillation was not required for satisfactory results; after removal of most of the thionyl chloride as above, ten ml. of benzene was added to a preparation of 6 g. of 6-chloro-1-naphthoyl chloride and removed first at atmospheric pressure, then under an aspirator vacuum to give a crude acid chloride sufficiently pure for the next step. (Table II lists the physical properties.)

Preparation of 5-, 6-, and 7-chloro-1-naphthyl chloromethyl ketones. To a cold solution of about 12.6 g. (0.30 mole) of diazomethane in 450 ml. of dry ether (15) was added a solution of 22.5 g. (0.10 mole) of the acid chloride prepared as above. Nitrogen was evolved vigorously for 15–30 minutes. After standing overnight, the diazo ketone was decomposed, either by adding an ether solution of hydrogen chloride, or by passing in dry hydrogen chloride until the evolution of nitrogen ceased. The ether was evaporated, leaving 22 to 22.5 g. (0.092–0.098 mole, 92–98%) of chloro-1-naphthyl chloromethyl ketone as a crude yellow solid. Recrystallization from hexane (b.p. 60–70°, Skellysolve B) gave the pure materials in 86% yield of the 5-chloro isomer, 65% yield (from undistilled 6-chloro-1-naphthoyl chloride) of the 6-chloro isomer, and 75% of the 7-chloro isomer. These compounds are described in Table II.

During preliminary work this reaction was performed repeatedly using distilled mixed 6- and 7-chloro-1-naphthoyl chlorides prepared from the 188–189° acid mixture and gave a crude, semi-solid, yellow-to-red product in 90–98% yield. From this material pure 6-chloro-1-naphthoyl chloromethyl ketone could be obtained in 30–50% yield by repeated recrystallizations from methanol. During a decolorization with 2 g. of Nuchar XXX and recrystallization from 200 ml. of methanol of 29.5 g. of this mixture, crystals other than the needles of the 6-chloro isomer were noted and separated. This gave 13.2 g. of nearly pure material, m.p. 97–99°. This substance gave a melting point depression with the 6-chloro-chloro ketone and with methyl-6-chloro-1-naphthoate.

Anal. Calc'd for $C_{12}H_8Cl_2O$: C, 60.28; H, 3.37.
Found: C, 60.03; H, 3.60.

One and two-tenths grams (0.005 mole) of this material was oxidized with sodium hypochlorite using the directions of Newman and Holmes (16) to give 0.93 g. (0.0045 mole, 90%) of an acid, m.p. 231–233.5°; neutral equivalent: calc'd for $C_{11}H_7ClO_2 \cdot H_2O$, 224.6; obs. 220. Recrystallization from benzene raised the melting point to 233.4–236.6° [reported for 7-chloro-1-naphthoic acid: 243° (8)], mixed melting point with 5-chloro-1-naphthoic acid (241–244°), 203–212°. Treatment of 0.2727 g. of this acid with thionyl chloride gave, after recrystallization from hexane (b.p. 60–70°, Skellysolve B), 29% of an acid chloride, m.p. 102–104° [reported for 7-chloro-1-naphthoyl chloride, 106° (8)]. By reaction of 0.0322 g. of this acid chloride with aniline, 0.0409 g. (100%) of a crude anilide was obtained. After recrystallization from ethanol this anilide melted at 178–180° (7-chloroanilide m.p. 185°). Ammonia converted 0.0450 g. of the acid chloride to 0.0303 g. (74%) of the corresponding amide; after recrystallization from ethanol, m.p. 227–229° (7-chloroamide, m.p. 237°). Later larger amounts of the acid were obtained and purified by recrystallization of the methyl ester from methanol and these derivatives were prepared in a purer state. These compounds are listed in Table I.

From a solution of 42 g. of mixed chloro ketones in 300 ml. of methanol 3.0 g. of a compound, m.p. 136.0–142.5°, crystallized. An additional crystallization raised the melting point to 145.7–146.2°. Tests for sulfur and nitrogen after sodium fusion were negative. The material was recovered unchanged after an aluminum isopropoxide reduction of eighteen minutes duration.

Anal. Found: C, 58.73; H, 5.31.

Preparation of α-chloromethyl-5-, 6-, and 7-chloro-1-naphthalenemethanols. The pure chloro ketones were reduced to the corresponding chlorohydrins by reduction with aluminum isopropoxide in isopropanol by a technique previously described (2), in 94–99% yields. These compounds are listed in Table II.

Preparation of 5-, 6-, and 7-chloro-1-naphthyl ethylene oxides. The procedure detailed previously was used to prepare the ethylene oxides in 94–99% yields in the case of the 6- and 7-isomers and the properties of these compounds have been reported (3). The 5-chloro-1-naphthyl ethylene oxide was used without determining the yield.

Preparation of α-di-n-butylaminomethyl-5-, 6-, and 7-chloro-1-naphthalenemethanols. A. By treatment of the appropriate oxides with molecular equivalents of di-*n*-butyl amine at 100–120° for eight to twelve hours the corresponding amino ethanols were obtained. The free bases were dissolved in ether and precipitated as the hydrochloride by adding ethereal hydrogen chloride. These salts were recrystallized from acetone by adding enough ether to cause precipitation. After purification the 5-isomer was obtained in 70% yield, based on chlorohydrin; the 6-isomer in 74% yield and the 7-isomer in 76% yield based on oxide. This method is described in detail in another paper (3).

B. The amino alcohol was prepared in the case of the 6-chloro isomer not only by treatment of oxide with amine, but also by allowing 98.0 g. (0.760 mole) of di-*n*-butyl amine to react with 45.8 g. (0.192 mole) of chlorohydrin for twenty hours in 200 ml. of refluxing xylene. A precipitate of hydrochloride salt appeared and the flask was swirled occasionally to break up the crust which formed. The contents of the flask were transferred to a 2-l. round-bottom flask, 75 ml. of 6 *N* sodium hydroxide and 200 ml. of water were added, and steam distillation was carried on until all the dibutylamine had been distilled. It was safe to stop when *ca.* 3 l. of distillate had been obtained. The residual mixture in the flask was cooled and extracted with two 300-ml. and one 100-ml. portions of ether. After being washed with water the combined ether solutions were dried over anhydrous potassium carbonate overnight. This solution of the free base in ether was treated as described above. The yield after recrystallization was 51–52.5 g. (70–72%). The compounds thus obtained are listed in Table II except when they have been given earlier (3).

α-Diethylaminomethyl-6-chloro-1-naphthalenemethanol. This compound was prepared from the chlorohydrin by heating in dilute dioxane with diethyl amine in a bomb tube at 125° for twenty-four hours. The yield was only 33%, but modification of the methods given above should lead to great improvement. The compound was also obtained in low yield by the amino ketone method described earlier (1).

Preparation of 6-chloro-1-naphthaldehyde. Hydrolysis of 45.5 g. (0.206 mole) of pure methyl 6-chloro-1-naphthoate gave 43.0 g. of 6-chloro-1-naphthoic acid. This acid was converted to the acid chloride with thionyl chloride, and the acid chloride distilled at reduced pressure. A Rosenmund reduction following the directions of Hershberg and Cason (17) gave 25.0 g. (0.131 mole, 63.6% on the basis of ester used) of 6-chloro-1-naphthaldehyde, m.p. 83–84°. Reduction of acid chloride mixture from the 188–189° acid mixture gave crude mixed aldehydes which were distilled b.p. 120–160°/2 mm., m.p. 45–46°. Treatment of 25 g. of this mixture with sodium bisulfite gave the addition product from which 18 g. of aldehydes melting 69–72° could be recovered. Mixed oximes were prepared from this latter material. Recrystallization three times from carbon tetrachloride gave pure 6-chloro-1-naphthaldehyde oxime, m.p. 126–127°, in good yield. Decomposition of 5.0 g. (0.024 mole) of pure oxime with pyruvic acid, acetic acid, and hydrochloric acid gave 3.6 g. (0.019 mole, 78%) of pure 6-chloro-1-naphthaldehyde, m.p. 82.5–83.5°. Oxidation of 5.0 g. (0.024 mole) of the oxime with basic permanganate gave 0.3 g. (0.0015 mole, 6.3%) of 6-chloro-1-naphthoic acid, m.p. 212–214°.

The Rosenmund method has also been used to prepare 4-chloro-1-naphthaldehyde, m.p. 81.5–82.0°. The yield from 4-chloro-1-naphthoic acid (18) was 75%.

Anal. Calc'd for $C_{11}H_7OCl$: C, 69.30; H, 3.70.
Found: C, 68.78; H, 3.69.

Preparation of 6-chloro-1-acetonaphthone. Pure 6-chloro-1-naphthoic acid was refluxed with thionyl chloride for four hours. The excess thionyl chloride was removed, and the product poured on a watch glass to solidify and to allow residual thionyl chloride to evaporate. Nine and four-tenths grams (0.039 mole) of this acid chloride was suspended in 50 ml. of dry ether and added to a solution of 0.030 mole of dimethylcadmium in 150 ml. of

ether, prepared according to the directions of Gilman and Nelson (19). The reaction mixture was refluxed an hour and then treated as described by Gilman and Nelson. The product, a light-yellow oil, was converted directly to an oxime.

Preparation of 6-chloro-1-acetonaphthone oxime. The ketone was dissolved in 80 ml. of alcohol and 11 ml. of water and 4.4 g. (0.063 mole) of hydroxylamine hydrochloride and 8 g. (0.20 mole) of sodium hydroxide were added. The mixture was allowed to stand overnight, then refluxed fifteen minutes. After cooling, the suspension was poured into 25 ml. of conc'd hydrochloric acid and 400 ml. of water was added. The yield was 7.02 g. (0.0321 mole, 82.3% from crude acid chloride) m.p. 120–140°. By extracting this crude product with 200 ml. of boiling Skellysolve B and chilling the extracts, a product melting at 125–128° was obtained. Three recrystallizations from Skellysolve B gave 1.5 g. of pure oxime, m.p. 130.5–131.5°. Recrystallization of the material insoluble in Skellysolve B from methanol or ethyl acetate gave two grams of a solid melting at 180–182°.

Anal. Found: C, 59.33; H, 3.75.

This substance would not dissolve in aqueous base nor give a precipitate with alcoholic silver nitrate.

Beckmann rearrangement of 6-chloro-1-acetonaphthone oxime. In 30 ml. of dry ether was placed 1.0066 g. of oxime and 1.00 g. of phosphorus pentachloride. The solution was refluxed one hour, then poured on ice and stirred. By warming the ether and ice mixture on a steam-bath the ether was evaporated and the product precipitated. This substituted acetamide had the m.p. 185–200°, wt. 1.102 g. (contaminated with phosphorous acid). Half of this crude material was recrystallized three times from ethyl acetate to give pure N-acetyl-6-chloro-1-naphthylamine, m.p. 210–211°.

Preparation of 6-chloro-1-naphthylamine. Five hundred milligrams (0.0023 mole) of crude N-acetyl-6-chloro-1-naphthylamine was refluxed with 30 ml. of 6 *N* hydrochloric acid for four hours. The solution was neutralized with sodium hydroxide and extracted with three 100-ml. portions of ether. After drying over anhydrous potassium carbonate, the ether solution was concentrated to twenty ml. Addition of ethereal hydrogen chloride precipitated 0.1934 g. (0.0009 mole, 39%) of 6-chloro-1-naphthylamine hydrochloride. This hydrochloride was recrystallized from an alcohol-ether mixture. Fifty milligrams of the purified hydrochloride was shaken with dilute base and ether. Evaporation of the ether left 0.0386 g. (95%) of 6-chloro-1-naphthylamine, m.p. 62–64°.

The above compounds are listed in Table I.

SUMMARY

α-Di-*n*-butylaminomethylchloronaphthalenemethanols with chlorine in position 5, 6, and 7 have been prepared from the corresponding chloro-1-naphthoic acids. The substance, m.p. 188–189° obtained by the reaction of chlorobenzene, methyl furoate, and aluminum chloride and believed to be 6-chloro-1-naphthoic acid has been shown to be the eutectic mixture of the 6- and 7-chloro compounds. A satisfactory method of separation has been devised.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

THE USE OF THE FUSED EUTECTIC OF SODIUM AMIDE AND POTASSIUM AMIDE IN ORGANIC SYNTHESES

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According to Sachs (1), 1-naphthylamine is formed in good yield by heating naphthalene and phenol with sodium amide at temperatures above the melting point of the latter; the phenol is reduced to benzene in the process. Germuth (2), in a short note without experimental detail, claims that pure 1-naphthylamine may be prepared by heating naphthalene and sodium amide in the absence of phenol. The well known reaction of Chichibabin, in which α-amino derivatives of pyridine, quinoline, and isoquinoline are obtained by the action of sodium amide upon the heterocyclic base in heated xylene or other inert solvent, has been reviewed elsewhere (3, 4). An important modification, suggested by Ostromislenski (5) and later adopted by Leffler (4) consists in the use of dimethylaniline instead of a hydrocarbon, in which both the sodium amide and the sodium salt of the reaction product are generally insoluble. It was thought that difficulties could be partly avoided by the use of the fused eutectic of sodium amide and potassium amide, which contains 33 mole per cent of the latter and melts at about 92° (6). It was also believed that primary amines might prove to be better media for these reactions than a tertiary amine, such as dimethylaniline, whose effectiveness is thought by Leffler (4) to be partly due to its ability to dissolve appreciable amounts of sodium amide at high temperatures.

Attempts were first made to find an easily reducible organic or inorganic compound that would take the place of the phenol in the reaction of Sachs (1), or of the potassium nitrate in the equation below (7).

$$C_9H_7N + 2KNH_2 + KNO_3 \rightarrow C_9H_6N\cdot NHK + KNO_2 + KOH + NH_3 \quad (I)$$
(in liquid ammonia at 20°)

It was found that the yield of 2-aminoquinoline obtained in the reaction between quinoline and the fused amide eutectic in boiling xylene was poor and could not be sensibly improved by the addition of any one of the following substances: sodium nitrate, potassium nitrate, sodium azide, phenol, nitrobenzene (caution: nitrobenzene and sodium amide explode if heated to too high a temperature), benzalaniline, or acetamide. Mercury did not improve the yield of 1-aminoisoquinoline under similar conditions.

1-Aminoisoquinoline was obtained in 69% yield by refluxing a xylene solution of isoquinoline with the fused amide eutectic; Chichibabin and Oparina (8) report a 38% yield with the use of sodium amide alone. Fairly good yields of α-alkylaminopyridines and α-alkylaminoquinolines were obtained by heating pyridine or quinoline with the fused amide eutectic in a primary alkylamine; no aminopyridine or aminoquinoline was isolated. The following compounds have been

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prepared in this manner: 2-methylaminopyridine, 2-methylaminoquinoline, 2-*n*-butylaminopyridine, 2-*n*-butylaminoquinoline (in an impure state), 2-cyclohexylaminopyridine, 2-cyclohexylaminoquinoline, and 2-*n*-heptylaminopyridine. Potassium nitrate was generally unnecessary, though it appeared to be helpful in some cases. A typical reaction, representing the formation of 2-cyclohexylaminoquinoline, is shown in the following equation.

$$C_9H_7N + MNH_2 + C_6H_{11}NH_2 \rightarrow C_9H_6N \cdot N(M)C_6H_{11} + H_2 + NH_3 \quad \text{(II)}$$

When hydrolyzed,

$$C_9H_6N \cdot N(M)C_6H_{11} + H_2O \rightarrow C_9H_6N \cdot NHC_6H_{11} + NaOH$$

MNH_2 represents the amide eutectic.

Attempts to prepare alkylamino pyridines and quinolines by heating a solution of a primary amine and pyridine or quinoline in xylene with the eutectic mixture of amides failed in one case, but succeeded in another, where a moderate yield of 2-*n*-heptylaminopyridine was isolated. It is interesting to find that isoquinoline and the fused amide eutectic reacted in boiling cyclohexylamine to give 1-aminoisoquinoline in 57% yield, apparently without the formation of 1-cyclohexylaminoisoquinoline. Under similar conditions, acridine was converted to a tar. In the comparatively small scale experiments described in this article, pyridine and quinoline reacted with the fused amide eutectic in secondary amines only to give 2-aminopyridine (possibly with some 2,6-diaminopyridine) and 2-aminoquinoline. Attempts to make 2-anilinoquinoline by heating quinoline and aniline with the amide eutectic were unsuccessful. Chichibabin and Seide (9) were able to prepare 2-anilinopyridine in poor yield by heating sodium anilide with pyridine.

THE REACTION MECHANISM

Bradley and Robinson (10) warmed a mixture of nitrobenzene, piperidine, and sodium amide, thereby obtaining a 27% yield of 4-N-piperidinonitrobenzene, in accordance with the equation,

$$C_6H_5NO_2 + C_5H_{10}NH + NaNH_2 \rightarrow C_5H_{10}N \cdot C_6H_4NO_2 + NH_3 + (NaH) \quad \text{(III)}$$

An electronic interpretation is given, based on the assumption that sodium-N-piperidide, $C_5H_{10}NNa$, is formed as an intermediate. The highly active anion of this compound attacks the nitrobenzene molecule in the para position, at a point that can become positively charged because of the (−) electromeric effect of the nitro group. Bergstrom, Granara, and Erickson (11) have similarly prepared *p*-nitrotriphenylamine by the action of sodium diphenylamide on nitrobenzene.

According to the mechanism of Bradley and Robinson, the formation of sodium cyclohexylaminoquinoline should follow the equations,

$$NaNH_2 + C_6H_{11}NH_2 \rightarrow C_6H_{11}NHNa + NH_3 \quad \text{(IV, a)}$$

$$C_6H_{11}NHNa + C_9H_7N \rightarrow C_9H_6N \cdot NNaC_6H_{11} + H_2 \quad \text{(IV, b)}$$

However, when cyclohexylamine was refluxed with the amide eutectic, very little ammonia was formed, indicating lack of appreciable reaction, an equilibrium

with very little sodium cyclohexylamide present, or, less probably, the formation of a salt, $C_6H_{11}NHNa \cdot NH_3$, with ammonia of crystallization. The equilibrium of (IV, a) should be gradually displaced toward the right if ammonia is lost during the refluxing.

In view of these facts, it is worth while to suggest an alternate mechanism, in which the amide ion first attacks the carbimide group (—CH=N—) of quinoline to form (A), equation (V); this is of course equivalent to an addition compound of quinoline with potassium amide. The amino group is then exchanged for —NHR in a reaction that is doubtless favored by an excess of the primary alkylamine; reasons why this is a logical step are discussed in a previous article (12).

$$\begin{aligned} CH{=}N + NH_2^- &\rightarrow CH(NH_2){-}N^- \quad (A) \\ CH(NH_2)N^- + RNH_2 &\rightleftarrows CH(NHR)N^- + NH_3 \end{aligned} \qquad (V)$$

The formation of a 2-alkyl-quinoline or -pyridine then will be expressed by the following over-all equation,

$$\begin{aligned} CH(NHR){-}N^- &\xrightarrow{M^+} C(NMR){=}N + H_2 \\ C(NMR){=}N + H_2O &\longrightarrow C(NHR){=}N + MOH \end{aligned} \qquad (VI)$$

where M=Na or K

The mechanism whereby this is accomplished is not yet clear in all of its aspects; a tentative suggestion for a related liquid ammonia reaction has been made in a previous paper (13).

EXPERIMENTAL PART

Sodium amide-potassium amide eutectic was prepared by bubbling ammonia gas through a mixture of 77 g. (3.4 atoms) of sodium and 64.5 g. (1.6 atoms) of potassium at 350°, in accordance with directions given in Organic Syntheses (14). The mixture was cooled toward the end to about 200°, and ammonia gas passed through for about half an hour to diminish the amount of hydride; thereafter, the inlet tube was raised above the level of the melt and the latter allowed to cool to room temperature in a slow stream of ammonia. Pouring of the molten amide on a metallic pan, as suggested in previous directions (14), will result in a bad fire. When cool, the nickel crucible containing the amides was inverted on a metal plate and tapped to dislodge the solid, which was broken up and stored in a wide-mouth bottle filled with ammonia gas (the ground stopper must fit tightly and be greased near the top). After each removal of amide, the bottle was again filled with ammonia and stoppered. The average "molecular weight" of this mixture, or, more precisely, the weight containing 16 g. of amide ion, is calculated to be 45.

All reagents were of high purity and were dried before use either by desiccation or, if a liquid, by fractional distillation. The melting points are uncorrected.

1-Aminoisoquinoline. Fifteen grams of the amide eutectic was well ground in a mortar under 200 cc. of xylene, and then transferred, along with the xylene, to 500-cc. three-necked round-bottomed flask. The mixture was heated at 100° on a boiling water-bath and mechanically stirred while 10 g. of isoquinoline was slowly added from a dropping-funnel. After heating and stirring for an additional two hours, the flask was cooled and the xylene decanted as well as possible. The excess of amide was destroyed by passing over it a current of moist air, obtained by passing air through two wash bottles of water maintained at a temperature of 60–70°.

The hydrolyzed residue was crystallized from hot water; a dark colored oil separating at this stage was largely 1-aminoisoquinoline, which could be dissolved by adding more hot water. In four experiments, the yield of 1-aminoisoquinoline varied between 63.5 and 69.7%, while in one run a 76% yield of hydrogen was obtained. With 6 g. of the eutectic and 10 g. of isoquinoline in 200 cc. of xylene at 100°, the following yields of 1-aminoisoquinoline were recorded; with 10 minutes heating, 23%; with 2 hrs. heating, 41%. When 26 g. of isoquinoline and 15 g. of the eutectic were heated for 2 hrs. in 200 cc. of xylene at 100°, the yield of 1-aminoisoquinoline dropped to 37%, showing that it is better to operate in the more dilute solutions.

Twenty grams of the amide eutectic and 100 cc. of dry cyclohexylamine were heated with 5.5 g. of isoquinoline and 5 g. of potassium nitrate for 1.5 hours at 135°. After careful hydrolysis the upper amine layer was separated and steam distilled to remove the amine; 3.5 g. or 57% of 1-aminoisoquinoline, m.p. 122–123°, separated from the steam non-volatile liquid on cooling.

2-Aminopyridine. Ten grams of the amide eutectic, 3 cc. (2.95 g.) of pyridine, and 50 cc. of diethylamine were heated in a small autoclave for two hours at 120°. After cooling, water (30 cc.) was slowly added to the contents of the bomb, and the aqueous layer extracted several times with benzene. Distillation of these extracts, first at atmospheric pressure to remove benzene and diethylamine, and then *in vacuo* gave 1.6 g. of 2-aminopyridine (46%), m.p. 50–52°, b.p. 91–93° at 8 mm. One-half gram of a substance, probably 2,6-diaminopyridine, was obtained at 144° and 6 mm. When crystallized from benzene the melting point became 121–122°; according to Chichibabin and Seide (9), the melting point of 2,6-diaminopyridine is 122°.

Pyridine (16 g.), the amide eutectic (10 g.), and xylene (30 cc.) were heated for seven hours at 140–150° (oil-bath temperature). After cooling, 20 cc. of saturated sodium carbonate solution was cautiously added to hydrolyze the excess of amide. The xylene layer was separated and combined later with two benzene extracts of the aqueous solution, and then distilled as described in the paragraph above to give 7.2 g. (38%) of 2-aminopyridine; better yields have been reported with the use of sodium amide alone (9). No increase in yield was obtained in dibutylamine as a solvent, though the reaction time appeared to be decreased.

2-Aminoquinoline. The yield of 2-aminoquinoline obtained by heating quinoline with an excess of the amide eutectic in xylene at 100° for six hours was inferior to that reported by Chichibabin and Zatzepina (15), who used sodium amide alone. The replacement of the xylene by diethylamine or by dibutylamine offered no advantages.

Alkylamino Pyridines and Alkylamino Quinolines

Procedure A. 2-Cyclohexylaminoquinoline. Twenty grams (0.45 mole) of the sodium amide-potassium amide eutectic was well ground under benzene and transferred to a 500-cc. reaction flask with standard taper ground glass joints (A of Fig. 1). The benzene was decanted as well as possible and replaced by 100 cc. of cyclohexylamine which had been dried over sodium ribbon and fractionated. Five grams (0.05 mole) of dry and powdered potassium nitrate was added to the mixture. The levelling bulb, H, was lowered to the level of the mercury seal, I, and the reactants heated at 100–110° (oil-bath temperature) for thirty minutes, or until no more air was expelled into the nitrometer, F. Air in the latter was then displaced by raising H and opening the stopcock, G. With the latter closed, H was again lowered to the level of the mercury surface in I, and 5.5 g. of quinoline (0.043 mole) added dropwise from the burette, B, over a period of about half an hour, with stirring. (The stirrer passed through a packed gland.) A fairly vigorous reaction took place with the evolution of hydrogen; a total of 740 cc. (0.0330 mole) of gas, calculated to standard conditions, was obtained, a yield of 77%. The mixture was stirred and heated for about 15 minutes after the gas evolution had ceased. The flask, A, was now disconnected from the nitrometer, cooled, and the contents hydrolyzed by the slow addition of water, a total of about 500 cc. being used in order to dissolve the bulk of the cyclohexylamine. The floccu-

lent gray solid that separated was filtered and crystallized from 200 cc. of 50% ethanol to give 5.7 g. (59%) of white needles melting at 125–126°.

Anal. Calc'd for $C_{15}H_{18}N_2$: C, 79.62; H, 8.02.
Found: C, 79.36; H, 8.27.

A repetition of this experiment with the omission of the potassium nitrate, and one hour heating gave 5.4 g. (56%) of 2-cyclohexylaminoquinoline melting at 124–125°, but the yield

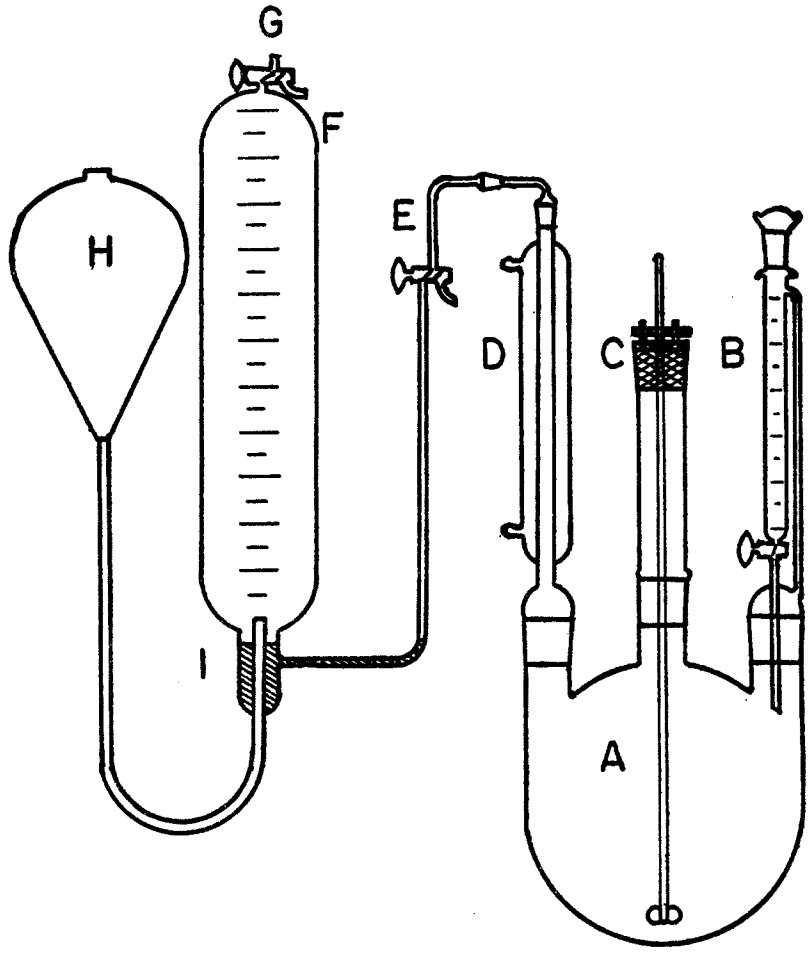

FIG. 1

occasionally dropped practically to zero. More consistent results were obtained when potassium nitrate was used.

2-Cyclohexylaminoquinoline was also prepared by heating 2-chloroquinoline (4.1 g.) with cyclohexylamine (15 cc.) for six hours at 200° in a sealed tube, with the addition of one gram of copper powder. The cooled reaction product was poured into water and the resulting precipitate crystallized from 50% ethanol as above. The yield was 3.3 g., or 58%. The melting point and the mixed melting points with material prepared by the action of the eutectic on quinoline in cyclohexylamine were 125–126°.

2-Cyclohexylaminopyridine. In accordance with the procedure outlined above, 20 g. of

the eutectic, 5 g. of potassium nitrate, 5.9 g. of pyridine, and 100 cc. of cyclohexylamine reacted at 100–120° for one hour. There was obtained 4.5 g., or 34%, of cyclohexylaminopyridine melting at 123–124° and 1,230 cc. of gas, calculated to standard conditions (74%). The isolation followed the scheme given above for cyclohexylaminoquinoline; the precipitate was crystallized several times from dilute alcohol.

Anal. Calc'd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.90.
Found: C, 74.92; H, 9.35; N, 16.12.

2-Bromopyridine (2.7 g.) was heated with cyclohexylamine (4.5 g.) at 180° for five hours in a sealed glass tube. Water was added to the reaction mixture and the resulting precipitate filtered and washed with small quantities of the same solvent to remove cyclohexylammonium bromide. The yield of 2-cyclohexylaminopyridine melting at 123–124° was 1.2 g., or 40%. The melting points of three mixtures of this with the material prepared by the first method were the same.

2-n-Butylaminoquinoline. Procedure (A) was followed, with the use of 100 cc. of *n*-butylamine, 20 g. of the eutectic, 5 g. of potassium nitrate, and 5.5 g. of quinoline. There was collected 1120 cc. of gas under standard conditions in place of a theoretical 950 cc. The supernatant oily layer left after the hydrolysis with a small volume of water was dried over potassium hydroxide and distilled, first to remove butylamine, and then at 145–170° and 4 mm. to obtain crude 2-*n*-butylaminoquinoline. The yield was about 40% of the theoretical. A picrate, crystallized several times from methyl isobutyl ketone, melted at 201.5–202.5°.

Anal. Calc'd for $C_{19}H_{19}N_3O_7$: C, 53.15; H, 4.46; N, 16.31.
Found: C, 53.43; H, 4.84; N, 16.13.

A much better method of preparation is the following: Four grams of 2-chloroquinoline, 25 cc. of *n*-butylamine, and 0.2 g. of copper powder were heated in a sealed glass tube at 170° for five hours. Isolation of the product in accordance with the above directions, gave 3.8 g. of a yellowish liquid boiling at 168–170° at 4 mm., a 78% yield. The picrate recrystallized from methyl isobutyl ketone, melted at 199–200°, and at 200–201° when mixed with the picrate whose analysis is given above. It is possible that some isomerization of the free base occurred during distillation.

2-n-Butylaminopyridine. In accordance with procedure (A), 5.9 g. of pyridine and 130 cc. of *n*-butylamine were heated for one and one-half hours with 5 g. of potassium nitrate and 20 g. of the amide eutectic. The initial temperature was 110°, finally rising to about 125° at the end of the reaction. A small amount (50 cc.) of water was added to the cooled mixture to hydrolyze the excess of amide. The butylamine layer was separated, dried over potassium hydroxide, and distilled to yield unchanged amine, and then 2-*n*-butylaminopyridine at 125° and 14 mm. The yield of material melting at 42° was 7.2 g. or 64%. The picrate melted at 135.5°, in fair agreement with the value of Slotta and Franke (16), 138°, who give 45° as the melting point of the free base.

In a repetition of this experiment with omission of the potassium nitrate, 1,600 cc. of gas (under standard conditions) was collected, as compared with a theoretical of 1,680 cc. The yield of butylaminopyridine was 60%. If sodium amide alone was used, the reaction time was trebled, but the amount of gas collected was very close to the theoretical. The yield of butylaminopyridine in this case was 57%. The yield dropped to 50% when equivalent molar quantities of the amide eutectic and pyridine were used.

Procedure B. 2-n-Heptylaminopyridine. A mixture of 23 g. of *n*-heptylamine, 5.5 g. of the sodium amide potassium amide eutectic, 3.95 g. of pyridine, and 50 cc. of xylene was heated under reflux (at about 140°) for three hours, with mechanical stirring. The excess of amide was cautiously decomposed with water and the water layer extracted once with benzene. The combined benzene and xylene solutions were extracted with 180 cc. of dilute acetic acid to remove pyridine and then with 12% hydrochloric acid to remove heptylaminopyridine, which was subsequently precipitated by the addition of excess sodium carbonate. The oil was extracted with ether, the latter evaporated, and the residue crystallized from low-boiling ligroin. The yield of white needles was 2.0 g. or 21%; the melting point was 45.5–46.0°.

Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.96; H, 10.48; N, 14.57.
Found: C, 75.36; H, 10.37; N, 14.29.

An attempt to prepare 2-cyclohexylaminoquinoline by this method was unsuccessful.

Procedure C. 2-Methylaminoquinoline. Twenty-eight grams of the amide eutectic (0.62 mole), 25.7 g. (0.199 mole) of quinoline, and 22.7 g. (0.224 mole) of potassium nitrate were placed in an autoclave (17) into which 97 g. of anhydrous methylamine was distilled. The reactants were heated for four hours at 100–135°, allowed to cool during about two hours to 70°, and finally cooled to room temperatures by immersion in water. The methylamine was distilled into a small supply tank, held at 0°, through a connecting lead tube, and the solid remaining hydrolyzed by adding benzene, followed by a small amount of water. The thick liquid left after evaporating the benzene was extracted repeatedly with boiling ligroin (b.p. 55–85°). When each extract had reached a temperature of about 30°, a sticky oil had deposited; the supernatant liquid was decanted, cooled further to 0°, and stirred, whereupon white crystals separated. The melting point varied between 68° and 81°, since there are two crystalline modifications of 2-methylaminoquinoline melting at 71° and at 81–82° (18). The complete separation of the crystals from the sticky impurity was very tedious. The yield was 8.1 g. or 26%.

Anal. (m.p. 79–82°). Calc'd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71.
Found: C, 75.96; 75.97; H, 6.36, 6.30; N, 17.70, 17.80.

In a repetition of this experiment on a smaller scale, the methylaminoquinoline was distilled at 6 mm. and 158°, but did not solidify when cool; it was converted to a picrate of about the right melting point (230–233°; correct, 234–236°).

A second (full scale) repetition with a longer period of heating (5.5 hours at 105° with approximately 5 hours consumed in heating and in cooling the autoclave) gave a benzene extract from which brownish crystals separated on concentration. When recrystallized from benzene (the hot solution was filtered), there was obtained 3.36 g. of crude material melting at 120–125°, and at 127–128° after several recrystallizations from the same solvent.

Anal. Calc'd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49.
Found: C, 74.93, 74.95; H, 7.44, 7.53; N, 17.49, 17.61.

A mixed melting point determination showed that this could not be 2-aminoquinoline; it may be a monomeric or polymeric dihydromethylaminoquinoline, or perhaps 3-methyl-2-methylaminoindole, even though a pine splinter reaction was negative.

2-Methylaminopyridine. 2-Methylaminopyridine, b.p. 100–102° at 18 mm. or 85–88° at 4 mm. was prepared in 2.9 g. (73%) yield by heating pyridine (2.95 g.), methylamine (about 20 g.), potassium amide (14 g.), and potassium nitrate (2.5 g.) for one and one-half hours at 90° in a small glass lined tube autoclave. The methylamine was evaporated and the solid hydrolyzed with a mixture of benzene and a little ice-water; the benzene layer was distilled in the usual manner. The picrate melted at 188–192°, and at 193–194° after several crystallizations from methyl isobutyl ketone. Chichibabin (19) reports that the picrate melts at 190°, and the free base boils at 90° at 9 mm. Almost identical results were obtained with the use of the amide eutectic.

SUMMARY

1. The eutectic of sodium amide and potassium amide, which melts at about 92° (6), is occasionally a better reagent than sodium amide in organic syntheses since reactions may be carried out with the fused material at moderate temperatures, thereby avoiding surface effects. The yield of 1-aminoisoquinoline has been improved to about 70%, but no advantage was found in the use of the eutectic to prepare aminopyridine or aminoquinoline.

2. 2-Alkylaminopyridines and 2-alkylaminoquinolines are obtained in fairly good yields by heating the eutectic mixture of sodium amide and potassium amide with pyridine or quinoline dissolved in a primary aliphatic amine. The following compounds have been prepared in this manner: 2-methylaminopyridine,

2-*n*-butylaminopyridine, 2-*n*-heptylaminopyridine, 2-cyclohexylaminopyridine, 2-methylaminoquinoline, 2-butylaminoquinoline (in a crude state), and 2-cyclohexylaminoquinoline. 1-Aminoisoquinoline appears to be the only product formed when isoquinoline and the amide eutectic are heated in cyclohexylamine. The theoretical aspects of the reaction are discussed.

3. 2-Aminopyridine (and possibly also 2,6-diaminopyridine) are formed when pyridine is heated with the amide eutectic in either diethylamine or in dibutylamine; dialkylaminopyridines have not been isolated.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

7-ACETOXY-9-ACETYL-1,2,3,4-TETRAHYDROPHENANTHRENE AND DIALKYLAMINO CARBINOLS DERIVED FROM IT[1]

HAROLD R. MIGHTON AND ROBERT C. ELDERFIELD

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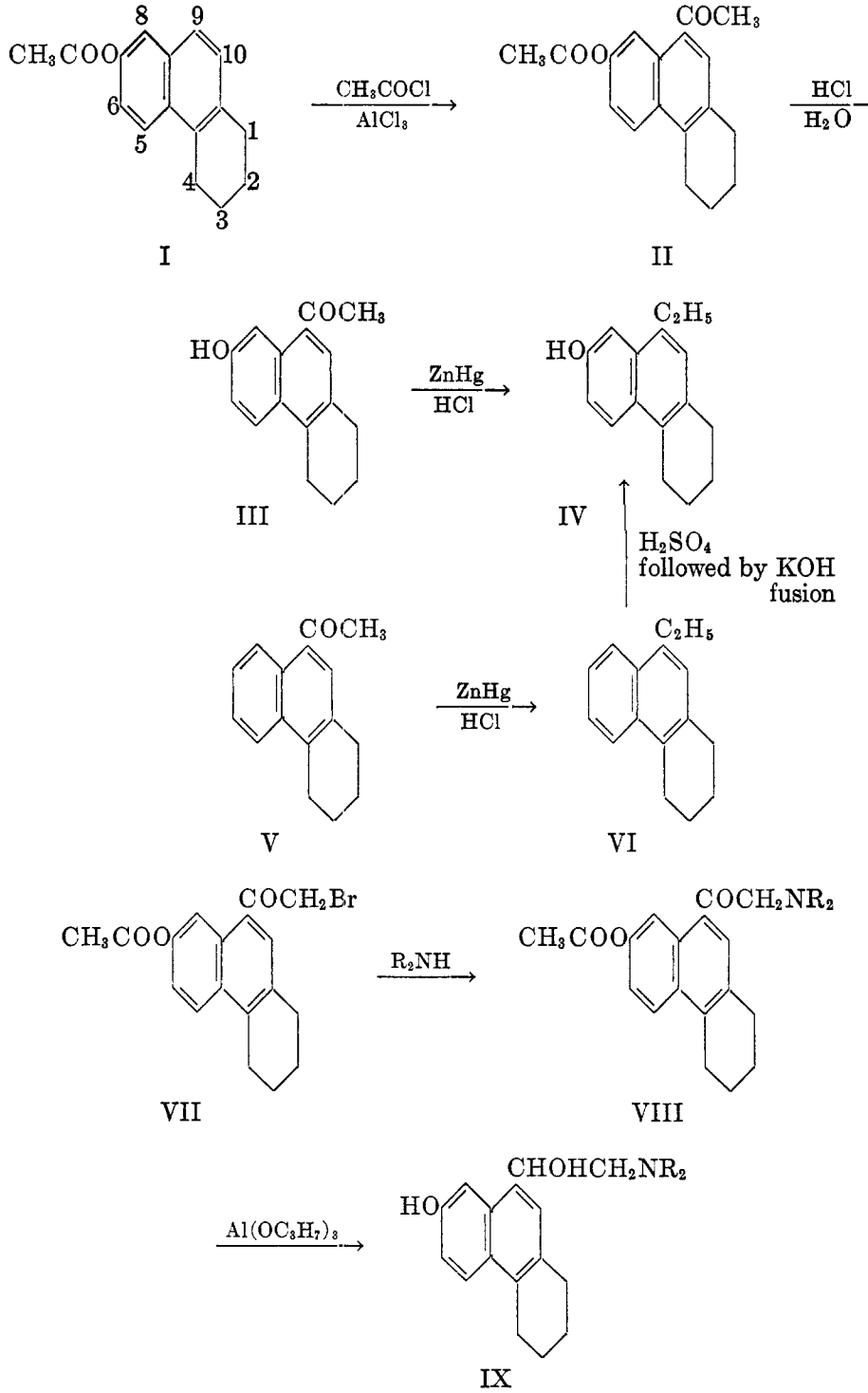
In another communication (1) the synthesis of a series of non-nuclear substituted 9-(2-dialkylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrenes is reported. Since certain of these substances possessed marked antimalarial activity against avian malaria, it became of importance to prepare a variety of similar nuclear substituted tetrahydrophenanthrene derivatives in order to examine the effect of such substituents on antimalarial action. The present communication presents a portion of a cooperative attack on this phase of the problem and describes the synthesis and proof of structure of representative dialkylamino carbinols derived from tetrahydrophenanthrene carrying a hydroxyl group in the 7-position. Other substituted amino carbinols will be described elsewhere.

Acetylation of 7-hydroxytetrahydrophenanthrene (2) yielded 7-acetoxytetrahydrophenanthrene (I). When this was subjected to the Friedel-Crafts reaction with acetyl chloride according to the general procedure of Bachmann and Cronyn (3), 7-acetoxy-9-acetyltetrahydrophenanthrene (II) along with a small amount of 7-hydroxy-9-acetyltetrahydrophenanthrene (III) resulted. The position of the new acetyl group was demonstrated by the following reactions. On hydrolysis with hydrochloric acid, II yielded 7-hydroxy-9-acetyltetrahydrophenanthrene (III) which on reduction by the Clemmensen method gave 7-hydroxy-9-ethyltetrahydrophenanthrene (IV). On the other hand, when 9-acetyltetrahydrophenanthrene (V) in which the position of the acetyl group has been proved by Bachmann and Struve (4), was similarly reduced, 9-ethyltetrahydrophenanthrene (VI) resulted. The latter on sulfonation and fusion of the resulting sulfonic acid with potassium hydroxide yielded 7-hydroxy-9-ethyltetrahydrophenanthrene, identical with the substance, IV, obtained by steps I–IV as shown by mixed melting point determinations. Since the position of the ethyl group in VI, and hence in IV, has been established by Bachmann and Struve (4), and since the position of the acetoxy group in I, or the hydroxyl group in IV, has been established by Griffing and Elderfield (2), it follows from the identity of VI with IV that the acetyl group in II must occupy the 9-position. In this connection, it is interesting that no 8-acetyl derivative was found in the products of the Friedel-Crafts reaction, since in the corresponding reaction with 7-methoxytetrahydrophenanthrene, considerable amounts of the 8-acetyl derivative are formed (2).

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.


8
9
CH3COO
10
6
1
5
4
2
3
CH3COCl
AlCl3
COCH3
CH3COO
HCl
H2O
I
II
COCH3
HO
ZnHg
HCl
C2H5
HO
III
IV
H2SO4
followed by KOH
fusion
COCH3
ZnHg
HCl
C2H5
V
VI
COCH2Br
CH3COO
R2NH
COCH2NR2
CH3COO
VII
VIII
CHOHCH2NR2
HO
Al(OC3H7)3
IX

Bromination of II proceeded smoothly in ether to yield 7-acetoxy-9-(ω-bromoacetyl)tetrahydrophenanthrene (VII), which on condensation with an appropriate secondary amine gave the amino ketones (VIII). The amino ketones were then reduced with aluminum isopropoxide to the corresponding amino carbinols. However, either during the reduction or on subsequent working up, the acetoxy group was cleaved so that the final products were 7-hydroxy-9-(2-dialkylamino-1-hydroxyethyl)tetrahydrophenanthrenes (IX). Evidence for this cleavage of the acetoxy group is presented in the experimental part of this communication. The method of synthesis of the amino carbinols was that successfully used for the preparation of other substances of this general type (1, 2, 5), with some modifications to fit the particular circumstances encountered. Amino carbinols of the type represented by IX wherein R is *n*-amyl (SN-8756),[2] *n*-hexyl, and *n*-nonyl (SN-8758) have been prepared.

EXPERIMENTAL

7-Acetoxy-1,2,3,4-tetrahydrophenanthrene (I). To 15 g. of 7-hydroxytetrahydrophenanthrene was added 250 cc. of acetic anhydride and 26 g. of fused sodium acetate, and the mixture was refluxed for ten hours. After cooling, it was poured into water. The oil which separated solidified on stirring and partial neutralization with sodium bicarbonate. The solid was filtered off, dried and distilled, the fraction boiling at 165–170° at 0.4 mm. being collected. After recrystallization from alcohol, the acetate formed needles which melted at 82–83°. The yield was practically quantitative.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 79.9; H, 6.8.

7-Acetoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene (II). The general method of Bachmann and Cronyn (3) was used. To a suspension of 28.2 g. of anhydrous aluminum chloride in 340 cc. of carbon disulfide was added 15.5 cc. (0.206 mole) of pure acetyl chloride, and the mixture was stirred for fifteen minutes. To the mixture was added 220 cc. of *sym.*-tetrachloroethane. The mixture was stirred for another fifteen minutes and then warmed to 45–50° for a few minutes until all the aluminum chloride was dissolved. The solution was then cooled to 5° and a solution of 25 g. of 7-acetoxytetrahydrophenanthrene (0.103 mole) in the minimum amount of carbon disulfide was added. The complex separated almost immediately and stirring was continued for an hour, after which the flask was tightly stoppered and placed in the refrigerator for twenty-four hours. The crystalline yellow complex was then filtered off, washed with carbon disulfide and air dried. The weight of the crude complex was 40 g. It was added with stirring to excess 5% hydrochloric acid and ice, and after breaking up the lumps, the crude acetylacetoxytetrahydrophenanthrene was collected, washed with water, and dried. The yield at this point was 26.4 g. On crystallization from alcohol, pure 7-acetoxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene was obtained as plates which melted at 130–131°. The yield was 70%.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4.
Found: C, 76.7; H, 6.5.

From the mother liquors of the acetylacetoxy derivative, about 5% of 7-hydroxy-9-acetyl-1,2,3,4-tetrahydrophenanthrene was obtained as needles melting at 221.5–222.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 80.1; H, 7.0.

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[2] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

The above 7-hydroxy-9-acetyltetrahydrophenanthrene was also readily obtained from the corresponding acetoxy compound by refluxing the latter (3.5 g.) in 50 cc. of hydrochloric acid (sp. gr. 1.19) and 50 cc. of alcohol for three hours. On refrigerating, the phenol separated as needles identical with those obtained above.

7-Hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IV). 7-Hydroxy-9-acetyltetrahydrophenanthrene (5 g.) was reduced in the usual Clemmensen procedure using amalgamated zinc (25 g.), acetic acid (45 cc.), toluene (25 cc.), and HCl (45 cc.). The mixture was refluxed for twenty-four hours, during which period three additions of HCl (11 cc. per addition) were added. After cooling, the toluene layer was separated,the water layer extracted with ether, and the combined toluene-ether solution dried. The solvent was evaporated under reduced pressure and the residue recrystallized from carbon tetrachloride. The yield was 2 g., and the compound melted at 165–166°.

Anal. Calc'd for $C_{16}H_{18}O$: C, 84.9; H, 8.0.
Found: C, 84.7; H, 8.2.

9-Acetyl-1,2,3,4-tetrahydrophenanthrene (V) was reduced by the Clemmensen procedure to give 9-ethyl-1,2,3,4-tetrahydrophenanthrene (3), which was sulfonated in the usual manner for the sulfonation of naphthalene in the β-position, to give sodium 9-ethyltetrahydrophenanthrene-7-sulfonate. The product obtained was fused with potassium hydroxide at 310–320° and the material recrystallized from carbon tetrachloride. The melting point was 165–166°.

Mixed melting points with varying percentage compositions of the 7-hydroxy-9-ethyl-1,2,3,4-tetrahydrophenanthrenes prepared by the two methods were found to be identical.

7-Acetoxy-9-(ω-bromoacetyl)-1,2,3,4-tetrahydrophenanthrene (VII). To a suspension of 7 g. of 7-acetoxy-9-acetyltetrahydrophenanthrene in 125 cc. of anhydrous ether was added dropwise, with constant stirring, 1.37 cc. of bromine. The first few drops of bromine were added very slowly. After the color had disappeared, the remainder of the bromine was added more rapidly. Bromination proceeded smoothly at room temperature. When the reaction was complete, the mixture was chilled and the solid bromo ketone was filtered off and washed with small portions of cold, dry ether. The crude substance was used for subsequent reactions. The yield was 7 to 8 g. On recrystallization from alcohol the compound formed needles which melted at 154–155°.

Anal. Calc'd for $C_{18}H_{17}BrO_3$: C, 59.8; H, 4.7.
Found: C, 60.0; H, 5.0.

7-Hydroxy-9-(2-di-n-amylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (IX, R = n-C_5H_{11}) (SN-8756). In a 200-cc. 3-necked flask equipped with a stirrer, gas inlet tube and soda-lime tube, was placed a solution of 7 g. of the above bromo ketone in 50 cc. of dry benzene. To this was added 6.1 g. (2 equivalents) of di-n-amylamine and the mixture was stirred for three hours at room temperature under nitrogen. After standing overnight, the separated amine hydrobromide was filtered off and thoroughly washed with dry ether. The solvent was removed from the filtrate at reduced pressure under nitrogen, and the residue was taken up in dry ether, whereupon more diamylamine hydrobromide separated on refrigerating. This was filtered off and washed with dry ether. If a total of 75% or more of the calculated amine hydrobromide separated the reaction was considered complete. The ether solution was washed twice with water and then with dilute hydrochloric acid, on which the amino ketone hydrochloride separated in crystalline form. The yield was 5 to 6 g.

The amino ketone hydrochloride was placed in a 250 cc. flask and 60 cc. of 3 N aluminum isopropoxide solution and 80 cc. of dry isopropyl alcohol was added. The flask was then connected to an 8-inch Vigreux column and the mixture was fractionated from a steam-bath under nitrogen until the distillate no longer gave a positive test for acetone with 2,4-dinitrophenylhydrazine. Isopropyl alcohol was added intermittently so that the flask was always about half full. When the reduction was complete (1 to 3 hours), heating was continued for another thirty minutes and the contents of the flask were evaporated to dryness under

reduced pressure. The dark red residue was cooled and shaken with 75 cc. of ether and 50 cc. of 10% sodium hydroxide solution. After decanting the liquid, the residue was again shaken with ether and sodium hydroxide solution. The combined ether layers were separated, and the aqueous layer extracted twice with ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Dry hydrogen chloride was slowly passed over the surface of the cooled solution, and crystals of the amino alcohol hydrochloride slowly formed. After chilling for a few hours, the crystalline material was filtered off and the ether filtrate again cautiously treated with hydrogen chloride, yielding a second crop. ether filtrate again cautiously treated with hydrogen chloride, yielding a second crop. The combined hydrochloride was recrystallized from a mixture of acetone and ethyl acetate. It formed micro needles which melted at 173.5–174.5° with decomposition.

Anal. Calc'd for $C_{26}H_{40}ClNO_2$: C, 71.9; H, 9.3; Cl 8.2.
Calc'd for $C_{28}H_{42}ClNO_3$: C, 70.6; H, 8.9; Cl, 7.4.
Found: C, 72.0; H, 9.4; Cl, 7.9.

Confirmation of the loss of the acetyl group either during the reduction or in working up the product was provided by saponification experiments.

A solution of 0.3058 g. of the amino carbinol hydrochloride in 20 cc. of 1.4 *N* alcoholic sodium hydroxide was refluxed for 3.5 hours. The solution was made acid to phenolphthalein with sulfuric acid and distilled to dryness, the distillate being collected quantitatively and titrated for free acid against 0.1042 *N* sodium hydroxide solution. Calc'd for the phenol: 6.7 cc. For the acetyl phenol: 12.06 cc. Found: 6.61 cc.

In another experiment 0.2995 g. of the hydrochloride was saponified with sodium hydroxide, the solution was made acid to litmus with sulfuric acid and 0.8 g. of silver sulfate was added to precipitate the chloride ion. The solution was then distilled to dryness and the distillate titrated for free acid as before. Calc'd for the phenol: 0.00 cc. For the acetyl phenol: 7.35 cc. Found: 0.51 cc.

A blank determination with 0.2910 g. of 7-acetoxy-9-acetyltetrahydrophenanthrene using the silver sulfate method gave the following figures: Calc'd for the acetyl phenol: 9.40 cc. Found: 8.01 cc.

Although the above tests are semi-quantitative, we feel that taken in conjunction with other data, the presence of the free phenolic hydroxyl group has been demonstrated. The amino carbinol gave a negative Davidson test (6) for esters, whereas 7-acetoxytetrahydrophenanthrene gave a positive test.

7-Hydroxy-9-(2-di-n-hexylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (IX, R = n-C_6H_{13}). This was prepared exactly as was the di-*n*-amyl derivative with the following exceptions. The amino ketone hydrochloride crystallized from ethyl acetate as micro needles and melted at 169.5–170.5° with decomposition.

Anal. Calc'd for $C_{28}H_{44}ClNO$: C, 72.8; H, 9.6.
Found: C, 72.5; H, 9.6.

7-Hydroxy-9-(2-di-n-nonylamino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (IX, R = n-C_9H_{19}) (SN-8758). This was prepared as was the di-*n*-amyl derivative except that the amino ketone hydrochloride was reduced as an oil. The amino carbinol hydrochloride crystallized from ethyl acetate and melted at 130–131° with decomposition.

Anal. Calc'd for $C_{34}H_{56}ClNO_2$: C, 75.0; H, 10.4.
Found: C, 75.1; H, 10.6.

The microanalyses here reported were carried out by the Misses Frances Marx and Lois May.

SUMMARY

1. Acetylation of 7-acetoxy-1,2,3,4,-tetrahydrophenanthrene by the Friedel-Crafts method yields 7-acetoxy-9-acetyltetrahydrophenanthrene.

2. Representative 7-hydroxy-9-(2-dialkylamino-1-hydroxyethyl)tetrahydrophenanthrenes have been prepared.

NEW YORK 27, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

3-(2-DIALKYLAMINO-1-HYDROXYETHYL) RETENE DERIVATIVES[1]

THOMAS N. DODD, JR., CHARLES H. SCHRAMM, AND ROBERT C. ELDERFIELD

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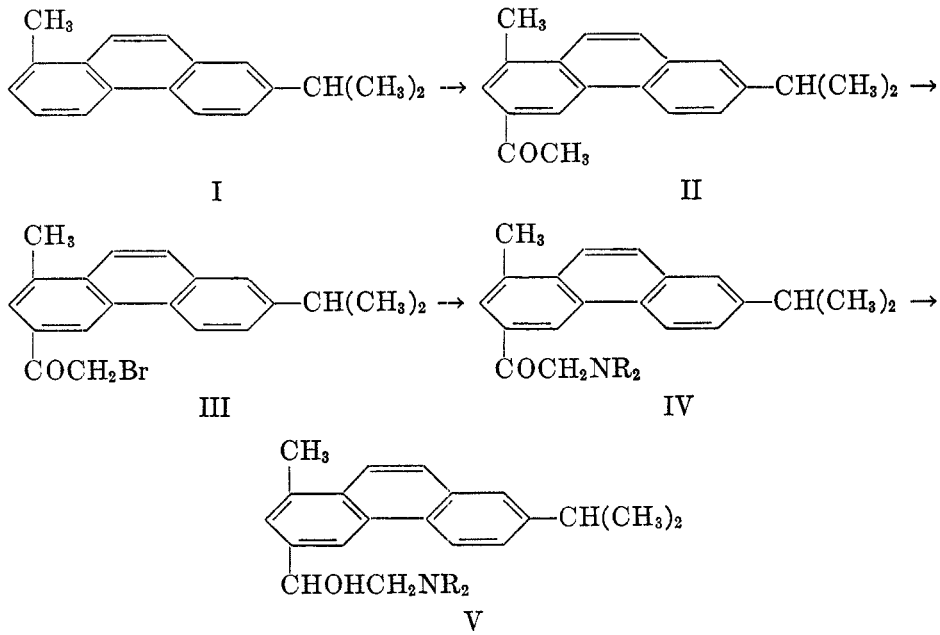
The observation that certain dialkylamino carbinols derived from phenanthrene possess high antimalarial activity (1) suggested the possibility that similar derivatives of retene (1-methyl-7-isopropylphenanthrene), I, might also possess the same property. The use of retene presents obvious advantages over phenanthrene for a variety of reasons. Retene is potentially available in practically unlimited amounts at a low cost, and, perhaps more important, in its reaction to yield acetylretene, the primary compound leading to dialkylamino carbinols, it yields but one isomer. Phenanthrene, on the other hand, yields at least two acetyl derivatives under the same conditions, and the isolation of one or more of these as a pure compound involves at best a long and tedious procedure. Accordingly, a series of retene-3-amino carbinols derived from 3-acetylretene has been prepared.



I II III IV V

3-Acetylretene (II) was prepared by a modification of the procedure of Campbell and Todd (2) and 3-(ω-bromoacetyl)retene (III) was prepared according to Adelson and Bogert (3). Reaction of bromoacetylretene with an appropriate secondary amine led to retene-3-dialkylamino ketones (IV) which were in turn

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

reduced to retene-3-dialkylamino carbinols (V) by the use of aluminum isopropoxide (4). Most of the latter were obtained as crystalline salts only with great difficulty, and in most cases it was necessary to distill the free bases in a molecular still in order to secure adequate purification. The properties of the hydrochlorides of the amino carbinols thus prepared are shown in Table I.

Screening tests against avian malaria on several retene-3-dialkylamino carbinols have been carried out, and the details will be reported elsewhere. It will be sufficient at this point to state that none of the substances showed significant antimalarial activity. Whether this is due to the presence of the two alkyl groups in positions 1 and 7 or whether it is due to the introduction of the dialkylamino carbinol group in position 3 in contrast to position 9 in the active phenanthrene derivatives is not apparent at present.

TABLE I

HYDROCHLORIDES OF 3-(2-DIALKYLAMINO-1-HYDROXYETHYL)RETENE DERIVATIVES

SN[2]	ALKYL GROUPS	M.P. °C.	ANAL.			
			Calc'd		Found	
			C	H	C	H
6601	CH_3	253–258	74.0	7.9	74.4	8.1
5998	C_2H_5	129–129.5	74.7	8.4	74.9	8.5
	n-C_3H_7	204.5–205.5	75.4	8.8	75.3	8.8
5481	*n*-C_5H_{11}	146–147	76.6	9.4	76.5	9.3
6905	*iso*-C_5H_{11}	171.5–172.5	76.6	9.4	76.5	9.4
6600	*n*-C_6H_{13}	126–127	77.2	9.6	77.3	9.6
6906	*iso*-C_6H_{13}	149–150	77.2	9.6	77.6	9.6
7165	*n*-C_8H_{17}	79–80	78.0	10.2	77.7	10.5
	n-C_9H_{19}	86–87	78.4	10.4	78.4	10.6

EXPERIMENTAL

All boiling and melting points are corrected for stem exposure.

3-Acetylretene. This was prepared by a modification of the procedure described by Campbell and Todd (2). Since the present method includes what at first sight appear to be minor variations, but also since it gives almost double the yield reported by Campbell and Todd, it is given in detail. In order to secure satisfactory yields, it is vital that pure retene be used.

Enough crude retene (m.p. 80–85°) to fill a 2-liter Claisen flask two-thirds full was melted and poured into such a flask. The retene was then distilled at 1 mm. pressure, the fraction boiling at 175–189° being collected. The solidified retene in the receiver was melted and poured into 5.5 l. of alcohol contained in a 12-l. flask, and warmed until all the retene was in solution. After cooling, the retene was filtered off and dried *in vacuo* over calcium chloride for forty-eight hours. As so obtained, retene melts at 98° with preliminary softening at 96°. It is vital that all traces of alcohol and moisture be removed from the retene for subsequent success in the Friedel-Crafts reaction.

A 3-liter three-necked flask was equipped with a mercury sealed mechanical stirrer, a trap for hydrogen chloride, an internal thermometer, and a 500-ml. Erlenmeyer flask at-

[2] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

tached by a short length of Gooch tubing. To a solution of 250 g. (1.067 moles) of purified retene in 1200 ml. of dry nitrobenzene contained in the flask was added 150 ml. (2.134 moles) of acetyl chloride (distilled from dimethylaniline). The flask was then immersed in an ice-salt freezing-bath and the contents chilled to −5°. Anhydrous aluminum chloride (290 g.) was then added very gradually with stirring and cooling from the Erlenmeyer flask at such a rate that the internal temperature did not exceed −5°. The addition of the aluminum chloride required from 1.5 to 3 hours, depending on the efficiency of the cooling-bath. When all of the aluminum chloride had been added, the mixture was stirred for an additional 5 hours at −5° and then allowed to stand in the refrigerator at 5° for 40 hours. If the temperature is properly controlled, the reaction mixture is reddish-orange in color throughout the addition of the aluminum chloride and finally becomes bright orange. Otherwise, the color varies from dark brown to pitch black and the yield suffers accordingly.

The mixture was then poured very slowly into a vigorously stirred mixture of 3200 g. of cracked ice and 500 ml. of hydrochloric acid (sp. gr. 1.19) at a temperature below 0°. The hydrolysis must take place below 0°; otherwise, undesirable side reactions occur with sudden evolution of hydrogen chloride. Ice should always be present during the hydrolysis. Stirring was continued for another hour. After decanting most of the aqueous layer, the oily nitrobenzene layer, which varied in color in different experiments from orange to dark brown, was steam distilled until the nitrobenzene was *completely* removed. With an efficient system, this distillation requires 5–6 hours.

After cooling, the solidified crude acetylretene was filtered off, air dried, and treated with decolorizing carbon in 1.5–2.5 l. of boiling ether. The filtered solution was concentrated to about 700 ml. and on cooling deposited 200 g. of 3-acetylretene which melted at 98–99°. On concentration of the mother liquors, a second crop of 30–40 g. melting at 96–98° was obtained. The yield of first crop material was 68% and the total yield was 78–82%. Campbell and Todd (2) report 3-acetylretene melting at 99.5–100°.

3-(2-Dialkylamino-1-hydroxyethyl)retene derivatives (*V*). The synthesis of 3-(2-di-*n*-hexyl-1-hydroxyethyl)retene may be taken as typical of the method used for the synthesis of the amino carbinols. A solution of 14 g. of 3-(ω-bromoacetyl)retene (III) (3), and 14.6 g. of di-*n*-hexylamine in 400 ml. of anhydrous ether was shaken mechanically overnight. After chilling in an ice-bath, 10 g. of di-*n*-hexylamine hydrobromide was filtered off. The ether filtrate was washed three times with water and dried over anhydrous magnesium sulfate. On removal of the ether at the water-pump, the amino ketone remained as a thick syrup. This was reduced directly with 165 ml. of *N*-aluminum isopropoxide solution in dry isopropanol, the acetone formed during the reduction being driven off through a short Vigreux column. From time to time additional isopropanol was added to the reaction flask so that the volume of the mixture was substantially constant. Reduction was complete in 1.5 hours (negative test for acetone with 2,4-dinitrophenylhydrazine in the distillate). The isopropanol was removed from the reaction mixture at the water-pump, and the dark residue was worked up with 250 ml. of ether until all soluble material had dissolved. The ether solution was washed with two 65-ml. portions of 10% sodium hydroxide solution, then with three 200-ml. portions of water, and finally dried over anhydrous sodium sulfate. To the ether solution of the amino carbinol, a dilute ethereal solution of hydrogen chloride was carefully added until no further immediate precipitation occurred. After refrigerating overnight, 1.1 g. of di-*n*-hexylamine hydrochloride was filtered off. More ethereal hydrogen chloride was added to the filtrate until a distinct turbidity appeared. After refrigerating overnight, 8.8 g. of the amino carbinol hydrochloride had crystallized. This was recrystallized from dry ethyl acetate, yielding 6.8 g. or 34% of the carbinol hydrochloride. The melting points and analyses of this and the other carbinols prepared are shown in Table I.

In the cases of some of the carbinols, it was necessary to subject the free bases to distillation in a molecular still at about 0.01 mm. pressure before salts could be obtained. In one or two cases, preliminary purification over the picrates aided in securing crystalline salts.

As a general rule, the amino ketones were not purified but were reduced directly. However, it was possible to secure analytically pure samples of two of them.

3-(ω-Di-n-butylaminoacetyl)retene picrate was obtained by fusing 0.5 g. of the crude oily ketone with 0.5 g. of picric acid on the steam-bath. On taking the melt up in hot alcohol and cooling, the picrate crystallized. After recrystallization from alcohol, it melted at 152–152.5°.

Anal. Calc'd for $C_{34}H_{40}N_4O_8$: C, 64.3; H, 6.3.
Found: C, 64.6; H, 6.2.

Despite the fact that the amino ketone could be satisfactorily purified in this manner, it was not possible to obtain a well-defined salt of the carbinol after reduction.

3-(ω-Diethylaminoacetyl)retene hydrobromide. Dry hydrogen bromide gas was very carefully passed over the surface of a dry ether solution of the amino ketone. At first a light granular precipitate settled out. This soon changed to an oil. The oily amino ketone hydrobromide readily crystallized from ethyl acetate and melted at 163–164° after recrystallization from the same solvent.

Anal. Calc'd for $C_{24}H_{30}BrNO$: C, 67.3; H, 7.1.
Found: C, 67.0; H, 7.0.

The microanalyses here reported were done by the Misses Frances Marx and Lois May.

SUMMARY

Nine 3-(2-dialkylamino-1-hydroxyethyl)retene derivatives have been prepared for examination as antimalarial drugs.

Details of an improved procedure for preparing 3-acetylretene are given.

NEW YORK 27, N. Y.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ANTITUBERCULAR STUDIES. HETEROCYCLIC FATTY ACIDS

EDITH GRAEF,[1] JAMES M. FREDERICKSEN,[2] AND ALFRED BURGER

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A number of branched aliphatic acids isolated from the metabolic waxes and lipids of mycobacteria not only cause the formation of lesions similar to those produced by the bacteria, but also inhibit the growth of the organisms (1). The cyclopentenyl fatty acids from chaulmoogra oil, which can be interpreted as unsaturated branched fatty acids, as well as some synthetic cyclic or aliphatic analogs (2), have shown a similar behavior. It appeared interesting to study the effect of long-chain acids containing heterocyclic basic rings on acid-fast organisms, and this investigation was undertaken in order to explore methods for the synthesis of such compounds.

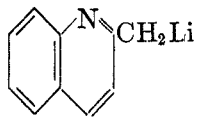
Some time after work on this problem had begun, Brody and Bogert published two articles (3) in which they described syntheses of 10-(α-pyridyl)-decanoic, and 11-(α-piperidyl)-, 11-(α-pyridyl)- and 11-(2-thiazolyl)-undecanoic acid and announced that these compounds would be tested as leprocidal agents. We were especially interested in polycyclic fatty acids, derived, for example, from quinoline, acridine, or benzothiazole, because so many drugs containing these ring systems have proved to be of therapeutic value. After consulting Professor Bogert, it was decided that we continue our study, since the polynuclear systems would provide us with an opportunity to introduce in the molecules of the fatty acid derivatives quinonoid groups which might interfere with bacterial oxido-reductions. A similar idea has been proposed by Fieser (4), who prepared a number of homocyclic quinonyl fatty acids, and by Buu-Hoï and Cagniant (5) who synthesized dihydrochaulmoogryl naphthoquinones as potential antitubercular agents. The significance of quinonoid structures in heterocyclic chemotherapeutics has also been pointed out by Schönhöfer (6) in his biochemical studies of antimalarials in the quinoline series.

The condensation of long-chain carboxy aldehydes with active methyl groups α or γ to cyclic nitrogen atoms, and saturation of the olefinic acids formed in such reactions, appeared a reasonable approach to some of the desired heterocyclic acids. We studied the reaction of aliphatic aldehydes with quinaldine as an exploratory measure, and found it proceeded well in a number of cases in ethanol solution in the presence of a trace of zinc chloride. The alkenylquinoline thus formed was readily saturated. However, when the same reaction was tried with various aldehydic esters, no satisfactory results were observed, perhaps because of the instability of the aliphatic components over the necessary periods of heating.

It was therefore considered advisable to try out the condensation of quinaldyllithium (I) with esters of ω-bromo acids (II) which are readily accessible by the

[1] duPont Fellow, 1945; Merck Fellow, 1944.

[2] Merck Fellow, 1943; at present Ensign, U. S. N. R.

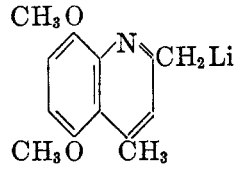


I

$$Br(CH_2)_nCOOR$$

II

Hunsdiecker reaction (7). Although 12-(2-quinolyl)dodecanoic acid was formed in the reaction with ethyl 11-bromoundecanoate (II, n = 10), the low yield (7.5%) did not recommend this procedure for general use. Likewise, 4-methyl-5,8-dimethoxyquinaldyllithium (III) and ethyl 5-bromovalerate (II, n = 4) gave



III

only an unsatisfactory yield of 6-(4-methyl-5,8-dimethoxy-2-quinolyl)-caproic acid.

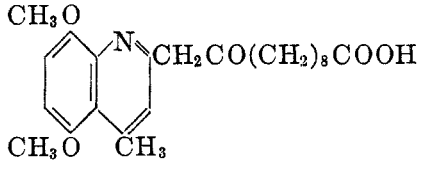
The metalation of 2,4-dimethyl-5,8-dimethoxyquinoline with phenyllithium could lead, conceivably, to a lithium derivative of either the quinaldyl (III) or lepidyl type. While no definite proof of its structure has been obtained, formula III is supported by analogous reactions involving one enolizable methyl group in 2,4-dimethylquinoline. Koenigs and Mengel (8) have shown that the 2-methyl group of this compound reacts with formaldehyde, since oxidation of the condensation product, and decarboxylation of the resulting methylquinolinecarboxylic acid, yielded lepidine.

When esters of monochlorides of dicarboxylic acids (IV) were substituted for

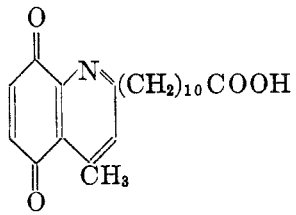
$$ROOC(CH_2)_nCOCl$$

IV

those of ω-halogeno acids (II), the over-all yields of heterocyclic aliphatic acids were improved considerably in several cases. The synthesis proceeded in two stages, since the keto acids first formed had to be reduced to the fatty acid derivatives. Thus, 10-keto-11-(4-methyl-5,8-dimethoxy-2-quinolyl)undecanoic acid (V), obtained from III and ethyl sebacyl chloride (IV, n = 8), was reduced to 11-(4-methyl-5,8-dimethoxy-2-quinolyl)undecanoic acid; the two methoxyl groups of this compound were hydrolyzed with hydrobromic acid, and the *p*-dihydroxy compound oxidized to the colorless quinonoid acid VI with ferric chloride (9).



V



VI

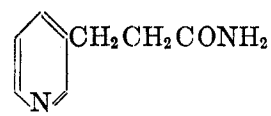
The chief difficulty in this synthesis was to find a satisfactory method for the reduction of the keto acid V. Although keto and keto acid derivatives of pyridine and similar azine systems sensitive to zinc and hydrochloric acid have been reduced in a few cases by the Clemmensen method, or catalytically (10) without attacking the nucleus, we looked for a catalytic method which might be simpler to execute, and more generally applicable in these series. Hydrogenations reported in the literature seemed to imply that the complete reduction of keto groups without reduction of the pyridine ring would be difficult. For example, Strong and McElvain (11) hydrogenated 3-acetylpyridine in an acid medium in the presence of Adams' catalyst and obtained 3-ethylpiperidine. Similar results were observed by Prelog (12), who hydrogenated ethyl nicotinyl acetate hydrochloride in ethanol solution with the same catalyst and isolated ethyl β-(3-piperidyl)propionate in a yield of 33.5% from this reaction.

Rosenmund and Karg (13) used palladized barium sulfate in hydrogenating aromatic alcohols, ketones, and nitrogenous ketones to hydrocarbons or amines, respectively, in glacial acetic acid, or propionic acid solution containing a small amount of an activator acid. We have applied their method to the reduction of quinoline keto acids and found the keto groups could be reduced consistently in excellent yields to methylene without affecting the nucleus. Moreover, neither uncondensed pyridine rings, regardless of their position relative to the carbonyl group, nor the benzothiazole ring, are attacked by this method.

In explaining the mechanism of their reduction method, Rosenmund and Karg suggested that the ketones are first reduced to the corresponding alcohols, and these tend to esterify under the influence of the activator acid. The esters, actually formed or potentially present, are then reduced to the hydrocarbon stage. Perchloric acid proved better than other "esterification catalysts," which is in agreement with its superior ability to bring about esterification of cellulose (14).

This mechanism seems supported by observations in one of our experiments. Encouraged by the smooth reduction of several quinoline keto acids, we decided to test the method with some pyridyl ketones. In the absence of perchloric acid, 2-acetonyl-6-methylpyridine absorbed only one mole of hydrogen; when a small amount of the activator acid was then added, hydrogenation was resumed immediately, and absorption was complete as soon as 2-*n*-propyl-6-methylpyridine had formed.

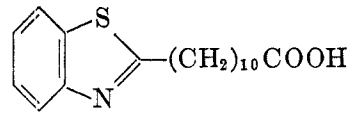
As an example of a pyridyl keto ester containing a carbonyl group conjugated with the ring, ethyl nicotinyl acetate could be reduced to ethyl β-(3-pyridyl)propionate without further hydrogenation to the piperidyl derivative (*cf.* 12). From the ester, the hitherto unknown pyridine-3-propionic acid and its amide (VII) were prepared.



VII

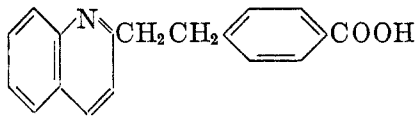
It was considered of interest to compare quinolyl fatty acids with isosteric benzothiazole derivatives, and 11-(2-benzothiazolyl)undecanoic acid (VIII) was

synthesized for this purpose. Lithium 2-methylbenzothiazole (15) reacted normally with ethyl sebacyl chloride, and the resulting keto acid was reduced readily to VIII. This indicates the value of the Rosenmund and Karg method even in a series containing cyclic sulfur stabilized by the resonance energy of the aromatic ring.

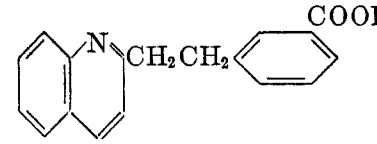


VIII

Since the role of aliphatic acid chains in mycobacteriostatic compounds may be purely physical, and may perhaps parallel the surface-tension-depressing properties of compounds containing these groups (16), we prepared the acids IX and X for comparison with aliphatic-type derivatives.[3]



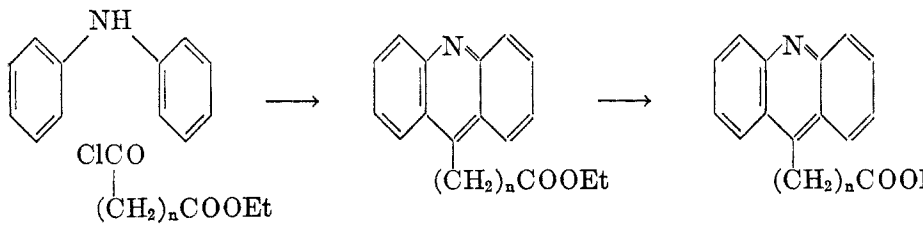
IX



X

The syntheses of these compounds started from the corresponding 2-(*p*- or *m*-nitrostyryl)quinolines which were reduced to the aminostyryl derivatives with stannous chloride, or with hydrogen activated by Raney nickel or Adams' catalyst. The unsaturated amines yielded 4′ - or 3′ - amino-2-phenethylquinoline, respectively, by hydrogenation over palladized charcoal; the saturated amines could also be obtained by direct catalytic hydrogenation of the nitrostyrylquinolines with the same catalyst. They were then subjected to a Sandmeyer nitrile synthesis, and the nitriles hydrolyzed to the acids IX and X.

Two fatty acid derivatives of acridine, 5-(9-acridyl)valeric acid (XIa), and 9-(9-acridyl)pelargonic acid (XIb) were prepared by a variation of the Bernthsen synthesis of 9-alkylacridines (17). Diphenylamine was heated with ethyl adipyl chloride, and ethyl sebacyl chloride, respectively, and the acids XI isolated from the hydrolysate of their esters.



XI a: n = 4
b: n = 8

[3] It may be noted that a similar relation exists between the angostura alkaloids, galipine, galipoline, and cusparine which contain the phenethylquinoline skeleton, and 2-*n*-amylquinoline isolated from the same source by Späth and Pikl [*Monatsh.*, **55**, 352 (1930)].

In the course of this work we also attempted to prepare quinoline quinone fatty acids having the aliphatic chains attached to the homocyclic ring. It seemed that 5,8-dihydroxyquinoline-6-(or 7-)carboxylic acid could serve as a starting material towards such compounds, and we tried to apply the Homeyer and Wallingford synthesis (18) of 5,8-dihydroxy-6-naphthoic acid to diethyl quinolinate. However, we were unable to condense this ester with diethyl succinate.

Preliminary *in vitro* tuberculostatic tests of a few of the acids reported in this article have been carried out by Professor Frederick Bernheim of Duke University Medical School. His observations will be published elsewhere.

The authors wish to thank E. I. duPont de Nemours and Co., and Merck and Co. for Fellowships in the Graduate School of the University of Virginia which were of aid in this study.

EXPERIMENTAL

All melting points are corrected.

2-(3-Ethyl-1-heptenyl)quinoline. A solution of 25.0 g. (0.14 mole) of quinaldine hydrochloride and 58 g. (0.42 mole) of freshly distilled 2-ethylhexaldehyde in 500 cc. of absolute ethanol was heated under reflux in the presence of about 0.1 g. of anhydrous zinc chloride for eight hours and then allowed to stand for three days at 25° in order to permit a favorable shift of equilibrium. Fifteen grams of 2-(3-ethyl-1-heptenyl)quinoline hydrochloride was filtered off. By repeating this procedure twice with the mother liquor, adding each time a trace of zinc chloride, another 20 g. of the condensation product was obtained. Recrystallization of the hydrochloride from methanol-ether furnished 35 g. (87%) of colorless needles, m.p. 242–244°.

Anal. Calc'd for $C_{18}H_{23}N \cdot HCl$: N, 4.83. Found: N, 4.99.

2-(1-Octenyl)quinoline. This compound was prepared from quinaldine hydrochloride and heptaldehyde under analogous conditions, but the heating was not repeated since the first crop of the condensation product amounted to 62% of the calculated yield. The colorless hydrochloride crystallized from ethanol-ether, m.p. 248–252°.

Anal. Calc'd for $C_{17}H_{21}N \cdot HCl$: N, 5.08. Found: N, 5.27.

2-(3-Ethylheptyl)quinoline. 2-(3-Ethyl-1-heptenyl)quinoline hydrochloride, dissolved in 60 times its weight of methanol, absorbed one mole of hydrogen with Adams' catalyst under atmospheric pressure in two hours. The colorless hydrochloride was obtained in the customary manner and recrystallized from methanol-ether. It melted at 247.5–249°.

Anal. Calc'd for $C_{18}H_{25}N \cdot HCl$: N, 4.80. Found: N, 4.70.

12-(2-Quinolyl)dodecanoic acid. Seven grams of quinaldine (0.049 mole) was added over a period of five minutes to a stirred solution of phenyllithium prepared from 7.9 g. of bromobenzene and 0.8 g. of lithium in 15 cc. of dry ether under an atmosphere of nitrogen. Agitation was continued for two hours, and the quinaldyllithium (19) turned dark red. A solution of 14.7 g. (0.049 mole) of ethyl 11-bromoundecanoate in 30 cc. of ether was added, and the mixture boiled spontaneously. After refluxing for ten hours, and standing overnight, it was decomposed with ice-hydrochloric acid, and the unreacted ethyl 11-bromoundecanoate extracted into ether. The acid solution was made alkaline with sodium carbonate, and extracted with five portions of ether, the extract dried over sodium sulfate, and the solvent evaporated. The oily residue, consisting of the desired ester and some unchanged quinaldine, was refluxed for five hours with 50 cc. of an 8% ethanolic potassium hydroxide solution. The alcohol was removed under reduced pressure, the residue taken up in water, and the basic mixture extracted with ether to remove quinaldine. The aqueous solution was acidified to *p*H 6.5 with acetic acid, and 12-(2-quinolyl)dodecanoic acid extracted with three portions of ether. The oil from this extract crystallized from ether-

petroleum ether and weighed 1.2 g. (7.5%). After several recrystallizations, the colorless material melted at 84–84.5°.

Anal. Calc'd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93.
Found: C, 76.70, 76.37; H, 9.17, 8.91.

The *hydrochloride*, prepared in dry ether, and recrystallized from ethanol-ether, appeared as a colorless solid, m.p. 134–135°.

Anal. Calc'd for $C_{21}H_{29}NO_2 \cdot HCl$: N, 3.85. Found: N, 4.37.

4-Methyl-5,8-dimethoxyquinaldine. The condensation of 2,5-dimethoxyaniline with acetylacetone (8) yielded a brown solid which was distilled and recrystallized for purification. It boiled at 195–200° (6 mm.), and crystallized from ethanol or ethyl acetate as colorless needles, m.p. 95–96°. This melting point remained unchanged despite repeated distillations and crystallizations which were carried out in view of the reported melting point 107° (8).

Anal. Calc'd for $C_{13}H_{15}NO_2$: N, 6.45. Found: N, 6.16.

The *hydrochloride* crystallized as yellow platelets and melted at 235–235.5° as reported (8).

Anal. Calc'd for $C_{13}H_{15}NO_2 \cdot HCl$: Cl, 13.97; N, 5.52.
Found: Cl, 13.95; N, 5.77.

Methyl 6-(4-methyl-5,8-dimethoxy-2-quinolyl)caproate. Using the same conditions as in the synthesis of 12-(2-quinolyl)dodecanoic acid, the lithium derivative of 12.3 g. (0.057 mole) of 4-methyl-5,8-dimethoxyquinaldine was condensed with 12.0 g. (0.057 mole) of ethyl 5-bromovalerate which was prepared from silver ethyl adipate (7). The reaction mixture was worked up as described before, and the crude solid mixture of unreacted 4-methyl-5,8-dimethoxyquinaldine and ethyl 6-(4-methyl-5,8-dimethoxy-2-quinolyl)-caproate saponified. Unchanged starting material was removed by extraction of the alkaline solution of the hydrolysate, and 6-(4-methyl-5,8-dimethoxy-2-quinolyl)caproic acid extracted from the solution at *p*H 6.5. The red oily acid from the ether extract weighed 0.25 g., and did not lend itself readily to purification. It was therefore esterified with 0.2 g. of diazomethane in ether solution, and the crude brown methyl ester purified by sublimation at 75° and 0.1 mm. pressure. The pale yellow sublimate melted at 79–80°.

Anal. Calc'd for $C_{19}H_{25}NO_4$: N, 4.23. Found: N, 4.54.

6-Keto-7-(4-methyl-5,8-dimethoxy-2-quinolyl)heptanoic acid. To a stirred solution of the lithium derivative of 10.62 g. (0.049 mole) of 4-methyl-5,8-dimethoxyquinaldine in 50 cc. of ether was added a solution of 9 g. (0.049 mole) of ethyl adipyl chloride in 75 cc. of ether in several small portions under an atmosphere of nitrogen. After the initial spontaneous reaction the mixture was refluxed for three hours, allowed to stand overnight, poured onto 200 g. of ice containing 5 cc. of hydrochloric acid, and some oily ethyl hydrogen adipate extracted into ether. The aqueous solution was made alkaline with sodium carbonate and extracted with ether. The crude keto ester from the extract was hydrolyzed with 100 cc. of a 10% ethanolic potassium hydroxide solution, the solvent was removed, and the residue treated with water. Some unreacted starting material was removed by ether extraction, and the solution neutralized to *p*H 6.5. The reaction product was extracted into ether, the dried extract concentrated, and the brown crystalline residue, weighing 4.9 g. (32%), was recrystallized from about 50 cc. of ethyl acetate. The pale tan feathery needles melted at 136–137°.

Anal. Calc'd for $C_{19}H_{23}NO_5$: N, 4.06. Found: N, 3.71.

The *methyl ester*, prepared with diazomethane in ether solution, was purified by sublimation at 75° (0.1 mm.). The reddish semi-solid material was analyzed.

Anal. Calc'd for $C_{20}H_{25}NO_5$: N, 3.90. Found: N, 3.55.

Methyl 7-(4-methyl-5,8-dimethoxy-2-quinolyl)heptanoate. A solution of 4 g. of the keto acid in 100 cc. of glacial acetic acid containing one drop of perchloric acid was hydrogenated in the presence of 0.5 g. of palladized barium sulfate (20) under atmospheric pressure. Absorption of two moles of hydrogen was complete after one hour; the catalyst was filtered, the solution poured onto 25 g. of ice, and neutralized with saturated sodium carbonate solution. The heptanoic acid derivative was extracted into several portions of ether; an

additional amount of the water-soluble reduction product was obtained by evaporating the neutral solution to dryness, and extracting the residual salt mixture in a Soxhlet apparatus. The brown residue from the ether extracts was not purified but was esterified with diazomethane. The yellowish methyl ester sublimed at 50° and 0.1 mm., and melted at 65–66°.

Anal. Calc'd for $C_{20}H_{27}NO_4$: N, 4.05. Found: N, 3.83.

10-Keto-11-(4-methyl-5,8-dimethoxy-2-quinolyl)undecanoic acid (V). Following the directions given above for the preparation of the homologous ketoheptanoic acid derivative, 4-methyl-5,8-dimethoxyquinaldyllithium from 21 g. (0.1 mole) of the base was combined with 28.6 g. (0.1 mole) of ethyl sebacyl chloride, and the mixture worked up as described before. The brown solid crude undecanoic acid derivative was recrystallized from ethanol, and then several times from ethyl acetate. The faintly tan colored needles melted at 134–135°; the yield was 11 g. (27%).

Anal. Calc'd for $C_{23}H_{31}NO_5$: N, 3.49. Found: N, 3.20.

The waxy *methyl ester*, prepared with diazomethane, was sublimed at 50° (1 mm.), and the yellow material melted at 59–60°.

Anal. Calc'd for $C_{24}H_{33}NO_5$: N, 3.37. Found: N, 3.13.

11-(4-Methyl-5,8-dimethoxy-2-quinolyl)undecanoic acid. Five grams of the keto acid, dissolved in 100 cc. of acetic acid containing one drop of perchloric acid, absorbed two moles of hydrogen in the presence of 1 g. of palladized barium sulfate at atmospheric pressure in four hours. The reaction mixture was worked up as described in the analogous case above. The brown crude reduction product obtained in quantitative yield was recrystallized four times from hot water. 11-(4-Methyl-5,8-dimethoxy-2-quinolyl)undecanoic acid appeared as colorless platelets, m.p. 126–127°.

Anal. Calc'd for $C_{23}H_{33}NO_4$: N, 3.62. Found: N, 3.34.

11-(4-Methyl-5,8-dihydroxy-2-quinolyl)undecanoic acid. A suspension of 5.0 g. of the dimethoxy acid in 25 cc. of 48% hydrobromic acid was boiled under an atmosphere of nitrogen for nine hours, the mixture was evaporated to dryness under diminished pressure, and the residue dissolved in about 10 cc. of water containing a little sodium bisulfite. The solution was buffered with ammonium acetate to *p*H 6.0, the precipitated colorless dihydroxy acid filtered, and a small amount of the same material recovered from the filtrate by continuous extraction with ether. Four recrystallizations from hot water furnished 4.2 g. (97%) of colorless crystals, m.p. 233–234° (decomp.).

Anal. Calc'd for $C_{21}H_{29}NO_4$: N, 3.89. Found: N, 3.53.

11-(4-Methyl-5,8-quinonyl-2-quinolyl)undecanoic acid (VI). To a solution of 1.0 g. of 11-(4-methyl-5,8-dihydroxy-2-quinolyl)undecanoic acid in 11 cc. of 1 *N* hydrochloric acid was added 6 cc. of a 20% ferric chloride solution. The yellow mixture turned red, and after one-half hour was neutralized with ammonium hydroxide to *p*H 6.5. Exhaustive extraction with ether, and distillation of the solvent, gave brown crystals which were recrystallized four times from water. The colorless quinonoid acid melted at 128–128.5°; the yield was 0.6 g. (60%).

Anal. Calc'd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61.
Found: C, 70.30; H, 7.71.

10-Keto-11-(2-benzothiazolyl)undecanoic acid. The yellow ethereal solution of lithium 2-methylbenzothiazole, prepared from 29.8 g. (0.2 mole) of 2-methylbenzothiazole and phenyllithium in the customary manner (15), was treated with a solution of 50 g. (0.2 mole) of ethyl sebacyl chloride in 50 cc. of dry ether with vigorous stirring under nitrogen. After the spontaneous reaction had subsided, the mixture was stirred and refluxed for five hours, allowed to stand overnight, and worked up as in the case of the quinoline analogs. After saponification of the ester and removal of the alcohol, the alkaline residue was dissolved in 25 cc. of water and extracted with ether to remove unchanged 2-methylbenzothiazole. The aqueous solution was buffered to *p*H 6.5, and the yellow precipitate extracted into ether. In order to avoid any loss of the water-soluble reaction product, the aqueous solution was evaporated to dryness under reduced pressure, and the residue exhaustively extracted with ether. Concentration of the combined ether extracts yielded a reddish oil which was dis-

solved in 10 cc. of hot water and cleared with Darco. On cooling, 1.9 g. of glistening colorless plates precipitated out which melted, after three more crystallizations, at 128.5–129.5°.

Anal. Calc'd for $C_{18}H_{23}NO_3S$: N, 4.20. Found: N, 3.97.

11-(2-Benzothiazolyl)undecanoic acid (VIII). Absorption of two moles of hydrogen by the keto acid with palladized barium sulfate in an acetic acid-perchloric acid medium as described above was complete after five hours. The reduction product was isolated in the usual manner at *p*H 6.5, and recovered in quantitative yield by continuous extraction with ether. Four recrystallizations from a little 50% ethanol, and washing with benzene, rendered colorless rods, m.p. 119.5–120°.

Anal. Calc'd for $C_{18}H_{25}NO_2S$: N, 4.39. Found: N, 4.20.

2-(m-Nitrostyryl)quinoline. (a) Quinaldine was condensed with *m*-nitrobenzaldehyde by the method of Wartanian (21). The yield of 2-(*m*-nitrostyryl)quinoline of m.p. 153–154° was 83%.

(b) In an application of the method of Koelsch (22), 13.3 g. of *m*-nitrobenzaldehyde and one drop of piperidine were added to a solution of 25 g. of quinaldine methiodide in 300 cc. of absolute ethanol. The mixture was allowed to stand overnight; 9 g. of the crude crystalline product was filtered, and another 18 g. was obtained on concentration of the mother liquors. Four recrystallizations from water yielded 25 g. (70%) of yellow plates of 2-(*m*-nitrostyryl)quinoline methiodide, m.p. 253–254° (decomp.).

Anal. Calc'd for $C_{18}H_{15}IN_2O_2$: N, 6.70. Found: N, 6.66.

Decomposition of this methiodide by distillation at 3 mm. pressure, and recrystallization of the distillate from ethanol, yielded 76% of the calculated amount of 2-(*m*-nitrostyryl) quinoline which was characterized by melting and mixture melting points. The over-all yield in this two-step reaction was thus 53%.

Anal. Calc'd for $C_{17}H_{12}N_2O_2$: N, 10.14. Found: N, 9.95.

2-(m-Aminostyryl)quinoline. Reduction of 2-(*m*-nitrostyryl)quinoline with stannous chloride and hydrochloric acid (21, 23) gave 89% of the amino compound, m.p. 167–168°. Because the previous investigators had observed lower melting points (158–159°, 160–161°) the amine was analyzed.

Anal. Calc'd for $C_{17}H_{14}N_2$: N, 11.38. Found: N, 11.33.

The reduction of the nitro derivative may be carried out more advantageously by hydrogenation over a Raney nickel or Adams catalyst in ethanol suspension or solution under atmospheric pressure over periods of one to six hours. The yields varied from 96–99%.

The *acetyl derivative*, prepared from the hydrochloride of the amine with acetic anhydride and sodium acetate in aqueous solution, crystallized as colorless needles from ethanol, m.p. 152–154°.

Anal. Calc'd for $C_{19}H_{16}N_2O$: N, 9.72. Found: N, 9.54.

The *dipicrate* was prepared in ethanol solution, and recrystallized from the same solvent as yellow needles melting at 225–227°.

Anal. Calc'd for $C_{17}H_{14}N_2 \cdot 2C_6H_3N_3O_7$: N, 15.91. Found: N, 15.76.

3'-Amino-2-phenethylquinoline. A solution of 1 g. (0.0041 mole) of 2-(*m*-aminostyryl)-quinoline in a mixture of 30 cc. of 0.12% hydrochloric acid and 30 cc. of acetic acid absorbed 0.0041 mole of hydrogen with palladized charcoal (24) at atmospheric pressure in five hours. The catalyst was filtered and the solution neutralized with sodium carbonate. The saturated amine was thus obtained in quantitative yield as yellow rods, m.p. 165–166°. The melting point was not changed by repeated recrystallizations from water.

Anal. Calc'd for $C_{17}H_{16}N_2$: N, 11.28. Found: N, 11.27.

The *dipicrate* crystallized from ethanol as yellow needles, m.p. 226–228°.

Anal. Calc'd for $C_{17}H_{16}N_2 \cdot 2C_6H_3N_3O_7$: N, 15.86. Found: N, 15.57.

The *acetyl* derivative appeared as colorless needles which were recrystallized from ethanol, and melted at 222–225°.

Anal. Calc'd for $C_{19}H_{18}N_2O$: N, 9.65. Found: N, 9.64.

It is noteworthy that neither mixtures of 2-(*m*-aminostyryl)quinoline and 3'-amino-2-phenethylquinoline, nor those of their respective dipicrates, exhibited definite depressions

of their melting points. However, the widely different melting points of the two acetyl derivatives served to distinguish the two compounds.

3'-Cyano-2-phenethylquinoline. The diazo solution obtained by treating a solution of 7 g. of 3'-amino-2-phenethylquinoline in 390 cc. of ice-cold 5.9% hydrochloric acid with 64 cc. of 3.44% sodium nitrite solution was neutralized to litmus with sodium carbonate, and added slowly to a stirred ice-cold mixture of a solution of 5.6 g. of cuprous cyanide and 3 g. of sodium cyanide in 240 cc. of water and 80 cc. of benzene (25). After one-half hour, the solution was warmed to 50° and kept at this temperature for fifteen minutes. It was cooled, the layers were separated, and the water solution was extracted with ether. The combined benzene-ether extracts were concentrated. The residual oil was dissolved in dilute acid, and reprecipitated with sodium carbonate solution. The resulting brown platelets melted, after recrystallization from ethanol, at 198–199°; the yield was 46%.

Anal. Calc'd for $C_{18}H_{14}N_2$: N, 10.84. Found: N, 10.89.

3-[2-(2-Quinolyl)ethyl]benzoic acid (X). A solution of 5 g. of the nitrile just described in 85 cc. of 4.5 *N* sulfuric acid was refluxed for one-half hour, cooled, and neutralized to *p*H 6.5 with sodium carbonate. The oily carboxylic acid was extracted into ether, the residue from the ether extract dissolved in alkali, and the benzoic acid derivative reprecipitated with acid. The now amorphous material weighed 5 g. and crystallized from ethanol. Repeated recrystallizations from water furnished tan-colored plates, m.p. 214–216° (decomp.).

Anal. Calc'd for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.20.

4'-Amino-2-phenethylquinoline. A solution of 4 g. of 2-(*p*-nitrostyryl)quinoline (26) in 150 cc. of ethanol was hydrogenated in the presence of palladized charcoal under atmospheric pressure. The nitro compound absorbed four moles of hydrogen in four and one-half hours. The catalyst was filtered, the solvent distilled, the residue taken up in dilute alkali, and a pinkish precipitate filtered. After reprecipitation with alkali from its acid solution, the saturated amine weighed 3.1 g. (88%). It was purified further by sublimation at 75° (1 mm.), and melted at 107–108°.

Anal. Calc'd for $C_{17}H_{16}N_2$: N, 11.28, Found: N, 10.99.

Bergstrom, Norton, and Seibert (27), who recently prepared this amine by reduction of 4'-nitro-2-phenethylquinoline with stannous chloride, reported the melting point 107–109°.

4-[2-(2-Quinolyl)ethyl]benzoic acid (IX). Twenty-five grams of 4'-amino-2-phenethylquinoline was diazotized and converted to the nitrile as described above for the meta isomer. The crude oily nitrile was hydrolyzed with 150 cc. of 4.5 *N* sulfuric acid, and 12 g. of the brown amorphous carboxylic acid precipitated when the solution was neutralized. After repeated crystallization from ethanol, 1.5 g. of tannish platelets, m.p. 185–187°, was obtained.

Anal. Calc'd for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 4.83.

Ethyl nicotinyl acetate. The hydrochloride of this keto ester was dissolved in water, the solution made slightly alkaline and extracted with ether. The ether extract was fractionated. After distilling off a considerable amount of lower-boiling materials, the yellow keto ester boiled at 148–150° (2 mm.). Clemo and Holmes (28) reported b.p. 125–135° (1 mm.).

The *picrate* crystallized from ethanol as yellow needles, m.p. 133–134°.

Anal. Calc'd for $C_{10}H_{11}NO_3 \cdot C_6H_3N_3O_7$: N, 13.27. Found: N, 13.21.

Ethyl β-(3-pyridyl)propionate. A solution of 8.0 g. (0.042 mole) of ethyl nicotinyl acetate in 75 cc. of glacial acetic acid containing two drops of perchloric acid absorbed 2.1 l. (0.084 mole) of hydrogen under the influence of 0.5 g. of palladized barium sulfate under atmospheric pressure in two hours. The mixture was worked up in the usual way, and the reduced ester extracted into ether. After removing the solvent, the ester was distilled; it boiled at 138–140° (3 mm.), and showed n_D^{21} 1.5138. The yield was 6.8 g. (92%).

The yellow *picrate* crystallized from ethanol as long needles and melted at 103–104°.

Anal. Calc'd for $C_{10}H_{13}NO_2 \cdot C_6H_3N_3O_7$: N, 13.72. Found: N, 13.61.

β-(3-Pyridyl)propionamide (VII). Two grams of ethyl β-(3-pyridyl)propionate was shaken with 5 cc. of 20% ammonium hydroxide overnight, the solution was evaporated to

dryness, and the yellow solid residue recrystallized from a little dioxane. The colorless rods melted at 136.5–137°.

Anal. Calc'd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66.

Found: C, 64.04; H, 6.41; N, 18.59.

β-(3-Pyridyl)propionic acid. The ethyl ester was saponified with a 10% ethanolic solution of potassium hydroxide, and the hydrolysate worked up in the customary manner. We did not succeed in purifying the free acid, but the *picrate* crystallized readily from ethanol. The orange needles melted at 112–113°.

Anal. Calc'd for $C_8H_9NO_2 \cdot C_6H_3N_3O_7$: N, 14.73. Found: N, 14.45.

2-n-Propyl-6-methylpyridine. One gram of 2-acetonyl-6-methylpyridine,[4] dissolved in 30 cc. of glacial acetic acid, was reduced by the method of Rosenmund and Karg (13); two moles of hydrogen was absorbed in nine hours. The catalyst was filtered, the solution made alkaline with sodium hydroxide, and the oily reaction product extracted with ether. The yellow oily residue from this extract weighed 0.9 g. Its *picrate* crystallized from ethanol as long yellow needles, m.p. 134–134.5°.

Anal. Calc'd for $C_9H_{13}N \cdot C_6H_3N_3O_7$: N, 15.38. Found: N, 15.09.

5-(9-Acridyl)valeric acid (XI a). A mixture of equimolecular amounts of ethyl adipyl chloride and diphenylamine was heated with a small amount of anhydrous zinc chloride at temperatures ranging between 180° and 220° for thirty hours. The dark brown liquid mixture was saponified by boiling with 8% ethanolic sodium hydroxide solution for three hours the solid sodium salt dissolved in water, and unreacted diphenylamine removed by ether extraction. The alkaline solution was acidified, again extracted to remove adipic acid, and then carefully neutralized to phenolphthalein. A brownish solid precipitated; it was filtered and recrystallized from boiling pyridine. The yield was 12%. The compound dissolved to give a yellow solution in alkali, and showed a green fluorescence in acids. It melted at 265–269° (decomp.) after some sintering.

Anal. Calc'd for $C_{18}H_{17}NO_2$: N, 5.01. Found: N, 4.88.

The hydrochloride crystallized from ethanol-ether solution as colorless needles, m.p. 179–180°.

Anal. Calc'd for $C_{18}H_{17}NO_2 \cdot HCl$: N, 4.44. Found: N, 4.60.

When ethyl hydrogen adipate was substituted for ethyl adipyl chloride (*cf.* ref. 17 and similar directions), the yield dropped to 5%.

9-(9-Acridyl)pelargonic acid (XI b). Equimolecular quantities of ethyl sebacyl chloride and diphenylamine were condensed as described above for the lower homolog. The reaction product crystallized as faintly violet needles from pyridine, m.p. 207–208° (decomp.); the yield was 31%.

Anal. Calc'd for $C_{22}H_{25}NO_2$: N, 4.18. Found: N, 4.29.

The *hydrochloride* crystallized from ethanol-ether as glistening colorless needles, m.p. 178.5–179.5°.

Anal. Calc'd for $C_{22}H_{25}NO_2 \cdot HCl$: N, 3.77. Found: N, 3.73.

The acid exhibits a yellow-green fluorescence in dilute acid solution while alkaline solutions display a purple color.

SUMMARY

1. Aliphatic aldehydes were condensed with quinaldine under mild conditions, and the olefinic reaction products saturated catalytically.

2. Quinaldyllithium, and 4-methyl-5,8-dimethoxyquinaldyllithium reacted with esters of ω-halogeno acids to yield small amounts of the corresponding quinolyl fatty acids.

3. Substituting esters of monochlorides of dicarboxylic acids for those of ω-halogeno acids, keto acids were obtained which were hydrogenated to fatty acid derivatives by the method of Rosenmund and Karg (13).

[4] The preparation of this ketone will be reported in a later communication.

4. Lithium 2-methylbenzothiazole, subjected to similar reactions as quinaldine, yielded a 2-benzothiazolyl fatty acid.

5. Ethyl nicotinyl acetate was reduced to ethyl β-(3-pyridyl)propionate by the method of Rosenmund and Karg, and other pyridyl ketones could be reduced likewise without hydrogenating the pyridine ring.

6. Two ω-(9-acridyl) fatty acids, and two quinoline derivatives with an aliphatic-aromatic acid chain were prepared.

7. A 5,8-quinonoid quinolyl fatty acid was synthesized.

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[COMMUNICATION NO. 1061 FROM THE KODAK RESEARCH LABORATORIES

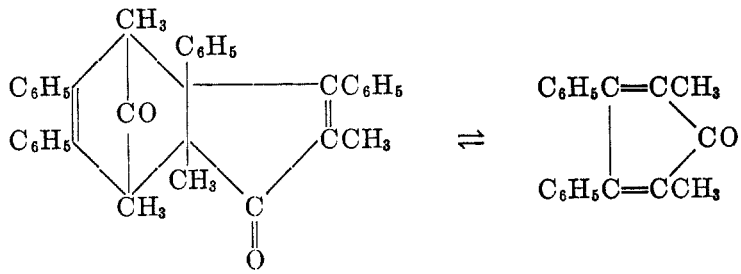
THE ACTION OF ALKALINE REAGENTS UPON CARBONYL BRIDGE COMPOUNDS. II

C. F. H. ALLEN, J. E. JONES, AND J. A. VANALLAN

Received January 16, 1946

The action of alkaline reagents upon a considerable variety of phenylated carbonyl bridge compounds has been described in previous papers (1, 2, 3). In each instance the bridge was cleaved at one end, with consequent formation of a carboxyl group. Bridged compounds in which the phenyl groups at the ends of the bridge are replaced by methyl groups are conveniently considered together, because they exhibit other reactions in addition to cleavage of the bridge at one end.

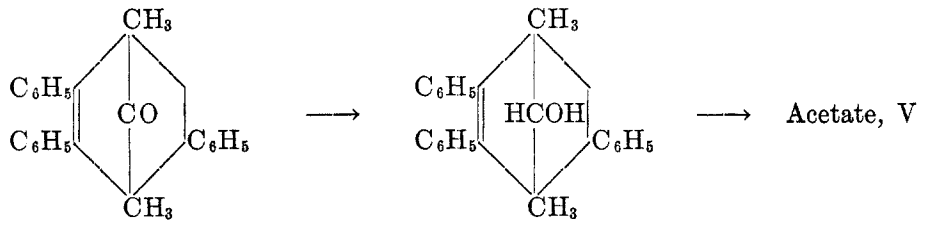
It was previously recorded (4) that the bimolecular product, I, obtained from α,β-dimethylanhydroacetonebenzil appeared to dissociate in most reactions so that in solution it was equivalent to 2,5-dimethyl-3,4-diphenylcyclopentadienone, II. A number of addition products from the latter, already described, were treated with alkaline reagents. Observations were complicated in some instances by the presence of secondary products resulting from a primary dissociation of the substances into their components. However, it was usually possible to isolate some of an acid, formed by cleavage of the bridge at one end. The characteristic reaction of alkaline reagents is, thus, observed in this series where the phenyl groups at the bridgehead are replaced by methyl groups.



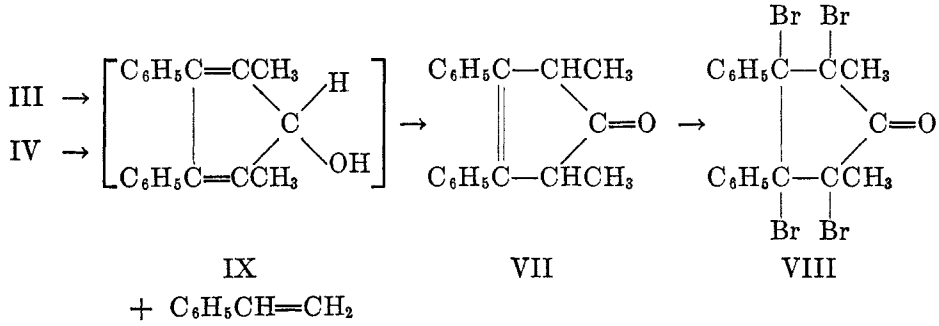
I ⇌ II

The most striking difference between the methylated and phenylated series is the occurrence of reduction of the carbonyl bridge in the former. An endocarbinol is obtained in certain instances. Hitherto no reduction products of carbonyl bridge compounds, in which either the carbonyl group or the double bond of the ring is reduced (5), have been prepared by the action of reducing agents.

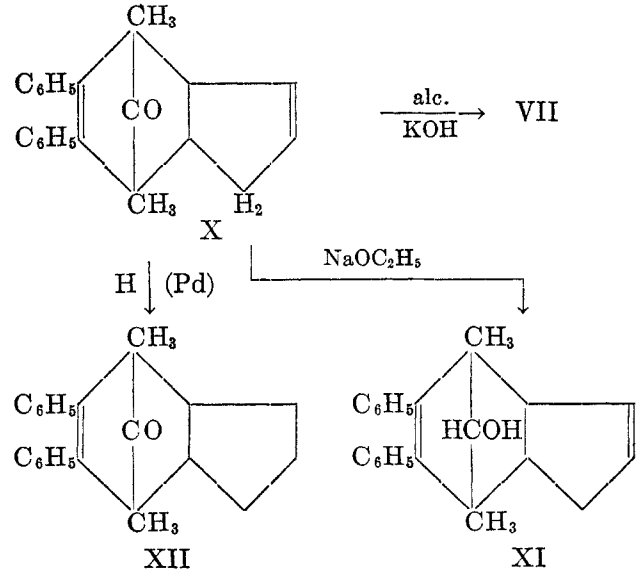
The ketone, III, is smoothly reduced to the carbinol, IV, by sodium or sodium ethoxide in dry ethanol. Piperidine is without action. The carbinol can be distilled *in vacuo* unchanged; it forms an acetate, V, when treated with acetyl chloride, and a chloride, VI, with thionyl chloride; it evolves one equivalent of methane from methylmagnesium iodide.



With ethanolic potassium hydroxide, however, the ketone, III, appears to undergo a dissociation, for the principal product is 2,5-dimethyl-3,4-diphenyl-3-cyclopentenone, VII (6). It was identical with a specimen prepared as described in the literature, and it gave the same tetrabromide, VIII, and 2,4-dinitrophenylhydrazone.



When the carbinol, IV, was heated at atmospheric pressure, it distilled in two fractions; the first was styrene (identified by physical properties and conversion

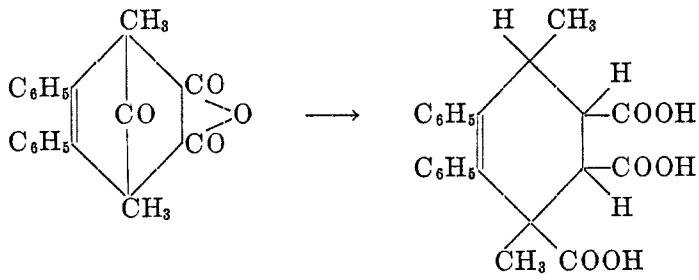


to the dibromide), while the second was this same cyclopentenone, VII. The mechanism is assumed to be a dissociation of the carbinol into styrene and the cyclopentadienol, IX, which rearranges into the stable cyclopentenone, VII. A similar case was recently described (7) in which an endocarbinol dissociated into styrene and an enol, which was stable enough to be isolated.

This series of reactions was confirmed by use of the indene derivative, X. With sodium ethoxide this gives a carbinol, XI, but with alcoholic potassium hydroxide, the same cyclopentenone, VII.

To make sure that reduction had proceeded as indicated, the indene, X, was catalytically reduced to XII, using palladium charcoal; the two reduction products were different and isomeric. The carbinol has one active hydrogen, as expected, while the ketone, XII, gives a 2,4-dinitrophenylhydrazone, as does X.

The bridged anhydride, XIII, gives no evidence of reduction, the formation of a tricarboxylic acid, XIV, taking place quantitatively when it is treated with alkaline reagents.

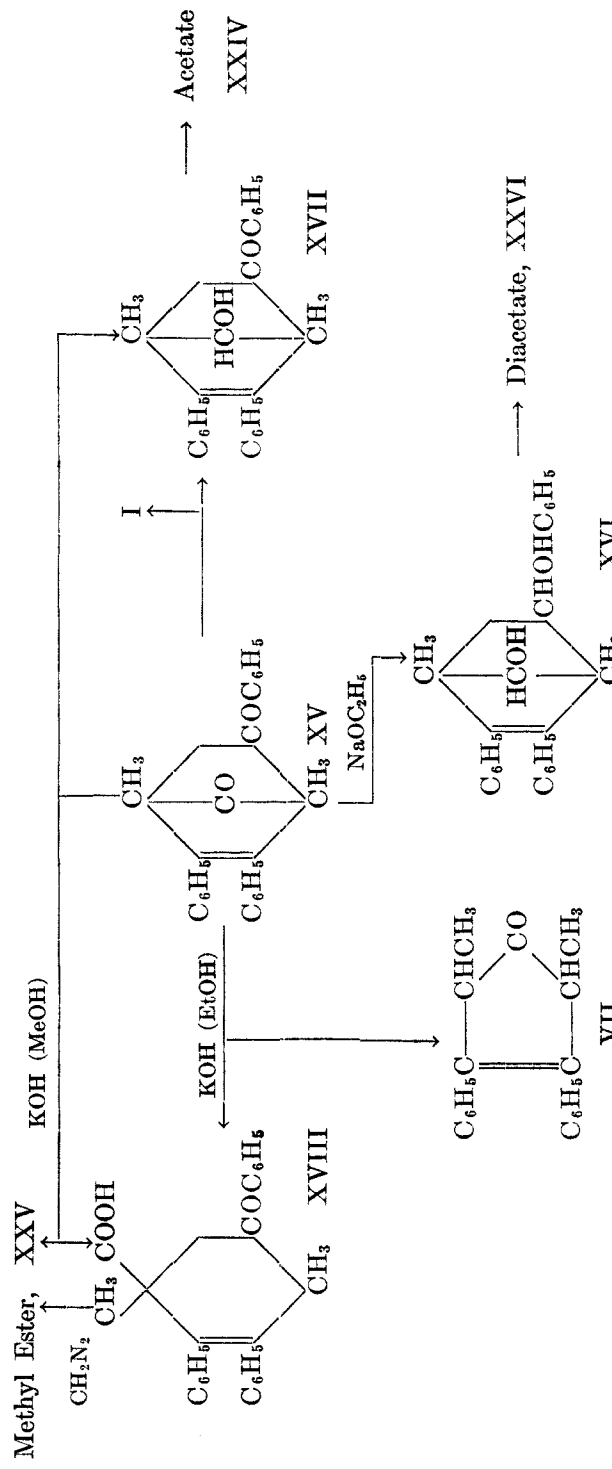


XIII XIV

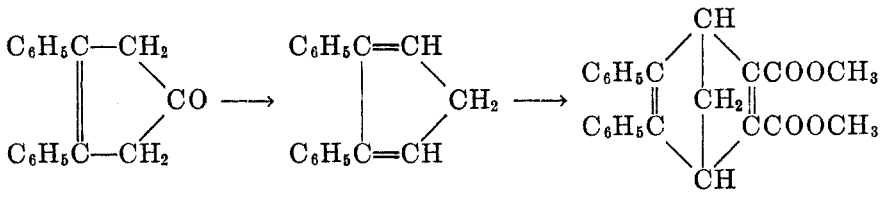
With the bridged ketone, XV, however, all types of reaction already described occur. With ethanolic sodium ethoxide, reduction to the carbinol, XVI, takes place; this diol readily formed a diacetate, XXVI. With methanolic sodium methoxide, reaction is very slow; there is but a slight change after a short time. Longer refluxing results in mixtures from which can be isolated a monocarbinol, XVII, and a little bimolecular product, I. The latter presumably results from dimerization of the dienone formed by dissociation of the starting material. The monocarbinol is assigned the structure, XVII, because it can be heated to 250° without change; no carbonyl bridge compound is known that would withstand such treatment (5).

The use of methanolic potassium hydroxide gave mixtures. From these were isolated the acid, XVIII, its methyl ester, XXV, and the monocarbinol, XVII. The acid, XVIII, could not be esterified by means of thionyl chloride, followed by methanol, but readily formed the methyl ester, XXV, with diazomethane.

The bimolecular product, I, obtained from α,β-dimethylanhydroacetonebenzil can be distilled *in vacuo*; the relatively low boiling point and red color indicate that it is distilling as the dissociated monomer, II. It is not surprising, therefore, to find that with alcoholic alkali it likewise gives the cyclopentenone, VII, though in a low yield.

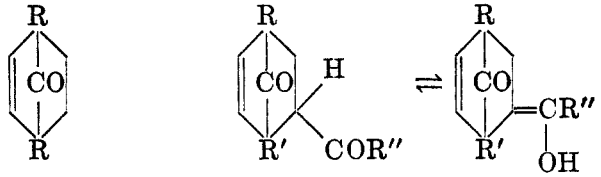

Methyl Ester, XXV
CH_2N_2
KOH (MeOH)
KOH (EtOH)
$NaOC_2H_5$
I
Acetate XXIV
Diacetate, XXVI
XVIII
XV
XVII
XVI
VII
CO
HCOH
$CHOHC_6H_5$
$CHCH_3$
C_6H_5
CH_3
COC_6H_5
COOH

The lower homolog, XIX, of the cyclic ketone was refluxed for 15 hours with ethanolic potassium hydroxide; the intensely red solution was diluted and after appropriate manipulation and vacuum distillation, a hydrocarbon, $C_{17}H_{14}$, was obtained. This hydrocarbon is represented as 3,4-diphenylcyclopentadiene, XX, because it easily adds methyl acetylenedicarboxylate to form an ester, XXI, and because of the production of a blue fluorescence with concentrated sulfuric acid; this latter behavior was noted with the isomeric 2,4-diphenylcyclopentadiene (8).



XIX XX XXI

When the results described in this and in the preceding papers are compared certain conclusions can be drawn as to the course of reaction that may be expected between carbonyl bridge compounds and alkaline reagents. If there are phenyl groups at the ends of the bridge (XXII, R = C_6H_5), the latter is cleaved at one end, so that the product is a carboxylic acid. If there are methyl groups at the ends of the bridge, reduction to a carbinol takes place. If there are methyl groups or hydrogen at one or both ends of the bridge, *and* a side chain containing an unsaturated linkage of such a nature that upon enolization a double bond can be formed between the ring and the side chain (XXIII, R, R′ = CH_3, H), all possible types of reaction can be expected. The keto group in the side chain may be reduced to give a carbinol.



XXII XXIII

EXPERIMENTAL

I. *The bimolecular product*, I, (4, 10), distilled very smoothly at 200–204°/3 mm.; the vapor and condensate were orange-yellow. The latter crystallized when triturated with ethanol, and had the same melting point as the starting material when recrystallized from acetic acid. The yield was 66%; there was some residue which was not investigated.

II. *The 4,7-dimethyl-5,6-diphenyl-8-oxo-4,7-methano-3a,4,7,7a-tetrahydroindene*, X, was obtained in a practically quantitative yield by four hours' refluxing of 13 g. of the bimolecular product, I, 7.5 cc. of cyclopentadiene, and 35 cc. of benzene, evaporating the mixture to dryness and recrystallizing it from methanol or propanol-1; m.p. 139°. The 2,4-dinitrophenylhydrazone, prepared in the usual manner, formed orange rods, m.p. 204°.

III. *Action of alkaline reagents.* The general procedure was the same as that described

in the earlier paper (3). The rate of cleavage of the bridge by alkaline reagents can be determined by titrating samples taken at intervals. The details of the reduction reaction will be given here.

A. *1,4-Dimethyl-2,5,6-triphenyl-7-hydroxy-1,4-methano-1,2,3,4-tetrahydrobenzene*, IV. A suspension of 65 g. of the ketone, III, in 1 l. of absolute ethanol was refluxed during the addition of 25 g. of sodium, cut in large pieces. After the metal had disappeared, the solution was refluxed for four hours and then filtered from 4.1 g. of resinous material. Water (2 l.), was added, and the product (62.5 g.) slowly crystallized. It was finely ground and extracted with 700 cc. of hot ligroin (b.p. 90–120°), filtered from 2 g. of red resinous material, and treated with Norit. After standing, 50 g. of the carbinol, IV, separated from the red solution in prisms, m.p. 140–141°. The yield of recrystallized product was 83%. When acetic acid was used as a solvent for purification, the product retained a molecule as solvent of crystallization, and melted at about 108–110°, dependent on the rate of heating; a single recrystallization of this from ligroin (b.p. 90–120°) raised the melting point to 140–141°. Methanol was likewise retained, the crystals melting at 90–92°.

The same carbinol resulted from the use of sodium ethoxide on the ketone, III, but piperidine was found to have no action. Data for all analyses are collected in Table I. The most suitable solvent for many of these compounds is a petroleum fraction. Traces of solvent are held tenaciously so that correct analytical results are difficult to obtain; most samples had to be "dried" *in vacuo* at about 100°.

The acetate, V, was obtained by refluxing for one hour a solution of 2 g. of the carbinol in 15 cc. of acetyl chloride, removing the excess halide, and recrystallizing from ligroin (b.p. 90–120°); it melted at 110°.

The chloride, VI, was obtained practically quantitatively by refluxing the carbinol with thionyl chloride, removing the excess *in vacuo*, and recrystallizing from ligroin (b.p. 90–120°); it melted at 108°.

B. *4,7-Dimethyl-5,6-diphenyl-8-hydroxy-4,7-methano-3a,4,7,7a-tetrahydroindene*, XI, was prepared in a similar manner by reduction of the corresponding endocarbonyl compound, X; it melted at 126°.

Upon reduction with hydrogen in the presence of a palladium charcoal catalyst, the corresponding hydrindene, XII, m.p. 106°, resulted. It gave a yellow 2,4-dinitrophenylhydrazone, m.p. 264°.

C. *Anhydride of 1,4-dimethyl-5,6-diphenyl-1,2,3,4-tetrahydrobenzene-1,2,3-tricarboxylic acid*, XIV. The preparation of this substance required 9.5 hours' refluxing of XIII with 0.5 *N* alcoholic potassium hydroxide. The anhydride was isolated in a yield of 95%; it melted at 207–210°.

Decomposition of the carbinol, IV. The carbinol (15 g.) was heated in an all-glass apparatus using a metal-bath; a fraction slowly distilled when the bath temperature was 310–320°. This was found to be styrene, b.p. 144–146°; its dibromide, m.p. 71°, was identical with an authentic sample. The yield of styrene was 4 g. (94%). The temperature was then raised to 340° to ensure complete removal of styrene, the flask and contents were allowed to cool to about 100°, and the residue was distilled *in vacuo*. The distillate (b.p. 210–215°/15 mm.; 8.7 g., 81%) proved to be the known (6) 2,5-dimethyl-3,4-diphenyl-3-cyclopentenone, VII, m.p. 120–121°; a mixed melting point with an authentic sample was not depressed. The tetrabromides, m.p. 180°, were also identical. The 2,4-dinitrophenylhydrazone formed bright red plates, m.p. 208–211°.

This same ketone, VII, was obtained in a yield of 11% by the action of 10% alcoholic potassium hydroxide on the bimolecular product, I.

D. *Benzoylated series.* The ketone, XV, did not go into solution as fast as the other bridged compounds when heated with alcoholic alkaline reagents; consequently, side reactions gave rise to intractable materials, rendering isolation of homogeneous products tedious and purification difficult.

After 15 g. of the ketone, XV, had been refluxed with 9 g. of potassium hydroxide in 120 cc. of ethanol for 18 hours, the deep red solution was diluted with water and worked up by

suitable manipulation. An ethereal extract was distilled *in vacuo*, and the 5-g. fraction, b.p. 200–280°/2 mm., was collected; this proved to be Japp's ketone, VII. Acidification of the aqueous layer gave the acid, XVIII, m.p. 248–252°. There was also about 10% of a red polymeric material, which began to form as soon as the ketone was added to the hot alkaline solution; this behavior was never observed when methanol was used. When these same

TABLE I

PRODUCTS FROM CARBONYL BRIDGE COMPOUNDS

NO.	SUBSTANCE	M.P., °C.	EMPIRICAL FORMULA	ANALYSES					
				Calc'd, %			Found, %		
				C	H	N	C	H	N
IV	Carbinol	140–141	$C_{27}H_{26}O$						
	Carbinol·$C_2H_4O_2$	108–110	$C_{29}H_{30}O_3$	81.7	7.1	—	81.5	7.2	—
V	Acetate	110	$C_{29}H_{28}O_2$	85.0	6.9	—	85.1	7.0	—
VI	Chloride	108	$C_{27}H_{25}Cl$	—	—	9.2[a]	—	—	9.5[a]
VII	Japp's Ketone	121	$C_{19}H_{18}O$	87.1	6.9	262[b]	87.1	6.8	260[b]
	DNPH of VII	211	$C_{25}H_{22}N_4O_4$	—	—	12.7	—	—	—
X	Addition Product	139	$C_{24}H_{22}O$	88.4	6.7	—	88.2	6.7	—
	DNPH of X	204	$C_{30}H_{26}N_4O_4$	—	—	11.1	—	—	11.1
XII	Hydrindene	106	$C_{24}H_{24}O$	87.8	7.3	—	88.0	7.4	—
	DNPH of XII	264	$C_{30}H_{28}N_4O_4$	—	—	11.0	—	—	11.0
XI	Carbinol	126	$C_{24}H_{24}O$	87.8	7.3	—	88.0	7.5	—
XIII	Acid	207–210	$C_{21}H_{20}O_5$	73.4	5.3	—	73.4	5.4	—
XVI	Diol	173	$C_{28}H_{28}O_2$	84.8	7.1	—	84.5	7.3	—
XVII	Carbinol	173	$C_{28}H_{26}O_2$	85.3	6.6	—	85.6	6.9	—
XVIII	Acid	248–252	$C_{28}H_{26}O_3$	81.9	6.3	—	82.0	6.3	—
XX	Cyclopentadiene	161	$C_{17}H_{14}$	93.6	6.4	218[c]	93.7	6.4	214[c]
XXI	Methyl ester	115	$C_{23}H_{20}O_4$	76.7	5.6	—	76.5	5.4	—
XXIV	Monoacetate	65–67	$C_{30}H_{28}O_3$	82.6	6.4	—	82.6	7.1	—
XXV	Ester	172	$C_{28}H_{28}O_3$	82.0	6.7	424[c]	81.7	6.8	—
XXVI	Diacetate	158	$C_{32}H_{32}O_4$	80.0	6.7	—	80.1	6.7	—

[a] % Chlorine; [b] mol. wt. in boiling benzene; [c] mol. wt.

reagents were allowed to stand at room temperature for three days, the only recognizable products were vinyl phenyl ketone and Japp's ketone, VII.

This acid, XVIII, was very stable, being distillable *in vacuo;* b.p. 270°/3 mm. It could not be esterified by treating first with thionyl chloride, and then with methanol, but gave the methyl ester, XXV, m.p. 172°, with diazomethane in ether.

Methanolic potassium hydroxide, after seven days, gave a 48% yield of the acid, XVIII, and the monocarbinol, XVII, in 18% yield; the latter formed an acetate, XXIV, m.p. 65°,

with acetyl chloride. After only three days a mixture resulted, from which separation of pure compounds required more than a month; from this mixture were isolated the methyl ester, XXV, m.p. 173°, the carbinol, XVII, and vinyl phenyl ketone (identified as diphenylpyrazoline, m.p. 152°).

Methanolic sodium methoxide reacted with the ketone, XV, very slowly; the only recognizable products were a little of the monocarbinol, XVII, and a small amount of the bimolecular product, I.

In one day, however, ethanolic sodium ethoxide gave the diol, XVI, m.p. 173°, in a 70% yield, as the only recognizable material. The diol can be distilled without change, b.p. 260–270°/3 mm., if traces of acid are scrupulously excluded. The diol gave a diacetate, m.p. 159°, with acetyl chloride, followed by recrystallization from ligroin, b.p. 70–90°.

The ester, XXV, behaved abnormally when a molecular-weight determination was carried out. It gave a value of 490 in boiling carbon tetrachloride, but 386 in benzene.

When treated quantitatively with methylmagnesium iodide (11), the monocarbinol, XVII, evolved 1.7 moles of gas and added 0.3 mole of reagent, totaling 2 moles of reagent consumed. One mole of the gas evolved was obviously from the carbinol hydrogen. It is known (12, 13) that the Grignard reagent can bring about enolization of many ketones; this is not always quantitative, but the total reagent used approximates one equivalent for the carbonyl group. A portion added before there was time for the enolization to become complete. Thus, in the instance just cited 0.3 mole had reacted by addition, whereas 0.7 had been decomposed by the enolic form. It may be pointed out that the parent ketone, XV, was almost completely enolic, showing 0.8 active hydrogen and 1.2 addition (4).

IV. *3,4-Diphenylcyclopentadiene*, XX. A solution of 14 g. of 3,4-diphenylcyclopentenone (9) in 100 cc. of absolute ethanol containing 8.4 g. of potassium hydroxide was refluxed for 15 hours. The initially deep red solution darkened appreciably. At the end of this time, 500 cc. of water was added, and the mixture was boiled, cooled, and extracted with ether. The extract was treated with Norit, dried, the solvent removed, and the residue was distilled, up to 250°/3 mm. being collected. The distillate was crystallized from butanol, from which 3.6 g. (28%) of the hydrocarbon, XX, m.p. 161°, separated. It dissolved in concentrated sulfuric acid with formation of a brown color and very strong, deep blue fluorescence.

Methyl 5,6-diphenyl-1,4-methano-1,4-dihydrobenzene-2,3-dicarboxylate, XXI. A mixture of 0.5 cc. of methyl acetylenedicarboxylate and 0.3 g. of 3,4-diphenylcyclopentadiene was heated at 170–180° for one-half hour; methanol was added to the cooled melt, and the ester, m.p. 115°, was recrystallized from this solvent.

V. *Hydrogenation.*[1] Attempts to hydrogenate the ketone, III, were unsuccessful. In one instance glacial acetic acid was selected as the solvent, and 95% alcohol in another. The catalysts were palladium on barium sulfate, and palladium hydroxide on calcium carbonate. There was no take-up of hydrogen at room temperature or at 60°. To be sure the catalysts were active and apparatus was functioning, a little carotene was introduced at the end of each run—it was promptly reduced.

SUMMARY

The action of alkaline reagents on certain carbonyl bridge compounds, having methyl groups at the bridgehead, is described. While they resemble the corresponding phenylated compounds in certain respects, some of them differ in two ways.

In one, the carbonyl bridge is reduced so that a compound containing a carbinol bridge is formed, while in the other, dissociation occurs, so that secondary products result.

[1] We are indebted to Dr. E. M. Shantz, of Distillation Products, Inc., for these hydrogenation results.

Neither the carbonyl group nor the double bond was reduced by hydrogen in the presence of palladium catalysts.

A diphenylcyclopentenone is reduced by alcoholic potassium hydroxide to a diphenylcyclopentadiene.

ROCHESTER 4, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ROCHESTER]

THE PREPARATION OF 8-QUINOLINESULFONIC ACID[1]

G. E. McCASLAND

Received January 31, 1946

At the time this work was started, 4-chloro-8-quinolinesulfonic acid was urgently needed as a synthetic intermediate for the preparation of a 4-dialkylaminoalkylamino-8-quinolinethiol, for test as an antimalarial. Two possible routes to the former (previously unreported) compound were the sulfonation of 4-chloroquinoline, and the chlorination of 8-quinolinesulfonic acid. Since there appeared to be no assurance that the sulfonic group would enter the 8-position of 4-chloroquinoline, we chose the second method, and planned to convert 8-quinolinesulfonic acid into the 4-chloro derivative *via* the N-oxide (1).

The preparation of 8-quinolinesulfonic acid, at first expected to be a routine matter, was soon found to be a minor research project in itself, due to the confusing and contradictory state of the literature on quinolinesulfonic acids, most of which was published in the years 1881–1889. Some of the reasons for this confusion will now be described.

When quinoline is heated with concentrated or fuming sulfuric acid, sulfonation occurs in the benzene ring in the 5- ("ana"), 6- ("para"), 7- ("meta"), or 8- ("ortho") positions, depending on the conditions. The early literature was confused by a failure to distinguish between the 5- and 7-isomers, both of which were called "meta". The prefixes "α" and "β" were also used to refer to the 8- and so-called "meta" isomers, respectively, while in current quinoline nomenclature they indicate the 2- and 3- positions. Since the isomeric sulfonic acids obtained melt unsharply above 300°, they cannot be identified, or their purity established, by means of melting points. It is therefore particularly essential that the method of preparation be exactly specified, and that a convenient means of characterizing the product be offered. But it was found that in fact each reference was lacking in one or several of the essential details: time, temperature, quantities of reactants, method of isolating product, yield, and identity and homogeneity of the product.

Lubavin (2), who first sulfonated quinoline, in 1870, said nothing about the possibility of isomerism. Bedall and Otto Fischer (3) attempted to identify Lubavin's product by fusion with sodium hydroxide to a hydroxyquinoline. The results were uncertain because not all the hydroxyquinolines were then known, because 7-hydroxyquinoline does not melt sharply, and because alkali fusion might cause rearrangement. They therefore tried conversion of the sulfonic acid to a nitrile by heating with potassium cyanide. A crystalline quinolinenitrile (now known to be the 5-isomer) was isolated, and for identification was hydrolyzed to a quinolinecarboxylic acid, for comparison with the Skraup re-

[1] The work described in this article was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

action product from *m*-aminobenzoic acid. Unfortunately, this Skraup reaction could theoretically yield either the 5- or 7-quinolinecarboxylic acid (although it is now known to yield mainly the 5-). Actually Lubavin's product probably consisted mainly of 8-quinolinesulfonic acid. In a later paper (4), Fischer reported that presumably pure 8-sulfonic acid, due to a rearrangement, yielded mainly the crystalline so-called "meta" (actually 5-) nitrile, and only a small amount of the 8-nitrile (as an oil).

Such rearrangements appear to have caused a mistaken belief that certain sulfonation products were a mixture of the 8- and so-called "meta" isomers, and that these isomers could not be separated by fractional crystallization from water. (Actually, the 8-isomer is so much less soluble than the 5- and 7- that it is probably easily separated from them by simple recrystallization.) Therefore a fractionation of the calcium salts (5) was used. Since these salts in turn have no useful melting points, identification was based on crystallographic examinations. Although it is probable that pure isomers were obtained in some cases, manipulative details are inadequately described, and the procedure is not attractive as a preparative method.

La Coste and Valeur (6) stated that the calcium salt fractionation was impractical, and reported a separation of the 8- and so-called "meta-" isomers based on solubility of the 8-mercury salt in cold water. The value of this method was questioned by Claus (7); and we now find that the 8-mercury salt is in fact quite *in*soluble in water.

Further confusion was introduced by Lellman (8), who postulated that two "ana" quinolinesulfonic acids exist, due to some vague new form of isomerism.

This brief description should suffice to indicate the difficulties which may confront anyone who attempts to extract a preparative method from the literature on quinolinesulfonic acids. Therefore we believe it will be useful at this time to submit an exact description of a method which has been found convenient for the 8-sulfonic acid.

The weight of evidence from the literature and our own observations indicates that 8-quinolinesulfonic acid is that insoluble isomer which is obtained by heating with about four parts by weight of 20–30% fuming sulfuric acid at about 100° for about 40 hours (or probably up to 170° for shorter periods), and pouring the cooled reaction mixture into about four volumes of water and that it is 8-quinolinesulfonic acid which with phosphorus pentachloride yields a sulfonchloride of m.p. 124–126°.

The identity of our product was established by conversion of a sample, in 58% yield, to this sulfonchloride. To establish the homogeneity of the product, it was desirable to find a sharp-melting derivative, which could be simply prepared in nearly quantitative yield, and from which the free sulfonic acid could readily be regenerated. [A more elegant method of establishing homogeneity might be use of the counter-current distribution technique of Craig (9).]

The *p*-toluidine and *n*-butylamine derivatives were first prepared, but did not have sharp, reproducible melting points. Diazomethane failed to give the methyl ester of this sulfonic acid, probably due to the acid's dipolar character.

This ester had been prepared by another method by Claus and Steinitz (10); the yield was not stated, but was presumably too low to be useful in this case.

A derivative meeting the above requirements was finally found in the previously unreported dipolar picrate-sodium salt. This compound is in itself of some interest in that both the basic and acidic groups of the quinolinesulfonic acid appear to be simultaneously involved in external salt formation, a type of compound which is apparently unusual. The compound is not obtained unless the solution is held within a certain *p*H range during preparation, by use of suitable proportions of sodium carbonate and acetic acid.

The results obtained indicate that the crude sulfonic acid prepared in the manner described is sufficiently pure for ordinary purposes, but a product of presumably higher purity can be obtained by regeneration from the recrystallized picrate-sodium salt.

All attempts to convert 8-quinolinesulfonic acid or its sulfonchloride to the N-oxide by use of monoperphthalic or peracetic acids were unsuccessful. In an attempt to activate the halogen atom of 4-hydroxy-8-chloroquinoline by conversion to the N-oxide, as an alternate means of preparing the intermediate 4-chloro-8-quinolinethiol, the N-oxide likewise could not be prepared. Since in the meantime Riegel and co-workers (11), working independently, had succeeded in sulfonating 4-chloroquinoline in the 8-position, no further attempts were made to chlorinate the 8-sulfonic acid.

EXPERIMENTAL

8-Quinolinesulfonic acid. To 123 ml. of fuming sulfuric acid (30% SO_3) in an ice-cooled flask was added dropwise 59 ml. of dry, colorless quinoline (b.p. 105–107°/8 mm.) at such a rate that the temperature did not exceed 90°. The resulting dark solution was heated at 90° for 40 hours with exclusion of moisture, and, after cooling, was poured cautiously into 500 ml. of water. The colorless prisms which crystallized out on cooling were filtered, washed with water, and dried; yield 67 g. (54%) of the practically pure 8-sulfonic acid. [The filtrate may presumably be used for the preparation of the more soluble 5- and 7-sulfonic acids (12). The 6-sulfonic acid is prepared (13) with concentrated instead of fuming sulfuric acid.]

8-Quinolinesulfonchloride. The method of Edinger (14) was followed, but it was found better to extract the sulfonchloride with chloroform, and to recrystallize it from benzene-petroleum ether. A sample of the sulfonic acid prepared as above described gave a 58% yield of sulfonchloride, m.p. 124–126°.

Sodium 8-quinolinesulfonate picrate. To 6.7 g. of the sulfonic acid prepared as above described was added in the order named 96 ml. of water, 8.2 g. of picric acid (10% H_2O), 3.4 g. of anhydrous sodium carbonate, and 3.7 ml. of acetic acid, and the mixture heated until a clear solution resulted. On cooling, the picrate-sodium salt separated as golden leaflets in almost quantitative yield, m.p. 225–226°, with decomposition. A sample recrystallized from water, for analysis, showed the maximum m.p. 226–227°, with decomposition.

Anal.[2] Calc'd for $C_{15}H_9N_4NaO_{10}S$ (460.3): Na, 5.00; N, 12.17.
Found: Na, 5.03; N, 12.23.

Regeneration of the sulfonic acid. A 14.8-g. portion of the picrate-sodium salt was dissolved in 70 ml. of hot water, and 35 ml. of 6 *N* sulfuric acid was added. The hot solution

[2] Analysis by Dr. Carl Tiedcke.

(containing suspended solid) was then extracted with 600 ml. of benzene (preheated to about 60°) in four portions, each portion being decanted off. The colorless aqueous phase was finally heated to boiling and allowed to cool. The sulfonic acid was collected, washed with water, and dried; colorless prisms, weight 6.0 g. (recovery 88%).

SUMMARY

A synthetic method suitable for the laboratory preparation of 8-quinolinesulfonic acid has been exactly described, and the product characterized by conversion to the sulfonchloride and a new picrate-sodium salt derivative of unusual type.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME DECAMETHYLENE AND UNDECAMETHYLENE DIAMINES[1]

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In view of the antimalarial activity of 1,11-undecane diamidine (1, 2) and the amoebicidal activity of long-chain aliphatic diamines (3), it was suggested[3] that a series of the latter type be prepared for assay as antimalarial drugs.

The symmetrical decamethylene diamines were prepared by treating the appropriate secondary amine with decamethylene dibromide.

$$Br(CH_2)_{10}Br + 2R_2NH \rightarrow R_2N(CH_2)_{10}NR_2$$

The products characterized are summarized in Table I.

The unsymmetrical decamethylene diamines, summarized in Table II, were prepared through decamethylene chlorohydrin (4).

$$Cl(CH_2)_{10}OH \xrightarrow{(CH_2)_5NH} (CH_2)_5N(CH_2)_{10}OH \xrightarrow[HCl]{SOCl_2} (CH_2)_5N(CH_2)_{10}Cl$$

$$\downarrow HBr \qquad\qquad \downarrow R_2NH$$

$$(CH_2)_5\dot{N}(CH_2)_{10}Br\ \dot{H}Br \xrightarrow{R_2NH} (CH_2)_5N(CH_2)_{10}NR_2$$

Distillation of 10-N-piperidyldecyl chloride was accompanied by partial dehydrohalogenation and some 10-N-piperidyl-1-decene was isolated from the distillate. The amino alcohol was prepared from morpholine as well as piperidine but was not further transformed to the corresponding diamines.

The preparation of undecamethylene diamines was based on undecenyl alcohol, available by sodium and alcohol reduction of ethyl undecylenate (5). The acetate of the alcohol was converted to 11-bromoundecyl acetate by addition of hydrogen bromide (6) using benzoyl peroxide catalysis. The bromo ester was isolated and characterized, apparently for the first time.

$$CH_2{=}CH(CH_2)_9OCOCH_3 \xrightarrow[(C_6H_5CO_2)_2]{HBr} Br(CH_2)_{11}OCOCH_3$$

$$\downarrow (CH_2)_5NH$$

$$(CH_2)_5N(CH_2)_{11}OH + (CH_2)_5N(CH_2)_{11}OCOCH_3$$

[1] The work reported in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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[3] This suggestion was made by the malaria research group at the National Institute of Health.

Since treatment of the bromo ester with piperidine led not only to replacement of the bromine but partial aminolysis, it was found convenient to treat the mixed amino alcohol—amino ester with hydrochloric or hydrobromic acid to prepare the chloro- or bromo-amine which was then condensed with the desired secondary

TABLE I

SYMMETRICAL DECAMETHYLENE DIAMINES

R_2N	B.P. OF AMINE °C.	SALT	M.P.°C.	ANAL.		SN[a]
				Calc'd	Found	
$O(CH_2CH_2)_2N$	(m.p. 49)[b]	di HBr	226	N.E. 237	N.E. 240	5001
$(CH_2)_5N$	205–207 (7mm.)[c]	di HBr	275	N.E. 235	N.E. 235	5000
$(n\text{-}C_3H_7)_2N$	200–205 (8 mm.)					6931
$(n\text{-}C_4H_9)_2N$	193–203 (3 mm.)					8055
$(i\text{-}C_5H_{11})_2N$	205–215 (3 mm.)					6932
C_2H_5, $n\text{-}C_4H_9$	173–183 (2 mm.)					8054
C_2H_5, C_6H_5	242–243 (2 mm.)	di P.S.[d]	188	C, 47.20 H, 4.76 N, 11.56	C, 47.44 H, 5.07 N, 11.18	8904-S_2
$n\text{-}C_4H_9$, $p\text{-}CH_3OC_6H_4$	288–292 (2 mm.)	di HBr	149	C, 58.36 H, 8.21 N, 4.25	C, 58.50 H, 8.37 N, 4.28	8882

[a] The Survey Number, designated SN, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

[b] Anderson and Pollard, [*J. Am. Chem. Soc.*, **61**, 3440 (1939)] report 51.5°.

[c] Adkins [*J. Am. Chem. Soc.*, **56**, 2419 (1934)] reports 181–183° (2 mm.).

[d] P.S. = picrylsulfonate.

amine. When this secondary amine was low-boiling it was desirable to use the bromo amine since the chloro amine was too unreactive to condense readily at the boiling point of the secondary amine. The properties of the diamines prepared are summarized in Table III.

TABLE II

10-N-PIPERIDYLDECYL AMINES

R_2N	B.P. OF AMINE, °C.	n_D^{20}	M.P. OF DIPICRYL-SULFONATE, °C.	ANAL.	
				Calc'd	Found
$(C_2H_5)_2N$	145–148 (2 mm.)	1.4681	160–161	C, 42.17 H, 5.25 N, 12.69	C, 42.52 H, 5.36 N, 12.69
$(n\text{-}C_3H_7)_2N$	168–170 (2 mm.)	1.4657	173–174	C, 43.51 H, 5.53	C, 43.84 H, 5.67
$(n\text{-}C_4H_9)_2N$	176–178 (1 mm.)	1.4659	167–170	C, 44.77 H, 5.80 N, 11.93	C, 44.83 H, 5.59 N, 11.53
$(n\text{-}C_5H_{11})_2N$[a]	198–200 (2 mm.)[b]	1.4661	166–167	C, 45.95 H, 6.05 N, 11.59	C, 46.23 H, 6.23 N, 11.32
$O(CH_2CH_2)_2N$	180–182 (2 mm.)	1.4799	188–190	C, 41.51 H, 4.94 N, 12.50	C, 41.45 H, 4.84 N, 12.90

[a] SN-8904-S_1.

[b] This product has been reported (4) to boil at 235–240° (6 mm.) and to form a dihydrochloride melting at 133°.

TABLE III

11-N-PIPERIDYLUNDECYL AMINES

R_2N	B.P. OF AMINE, °C.	n_D^{20}	M.P. OF DIPICRYL-SULFONATE, °C.	ANAL.		SN[a]
				Calc'd	Found	
$(n\text{-}C_3H_7)_2N$	190 (3 mm.)	1.4703	176–178	C, 44.15 H, 5.67 N, 12.12	C, 44.46 H, 5.94 N, 11.95	8874
$(n\text{-}C_4H_9)_2N$	210 (3.5 mm.) 200 (2.5 mm.)	1.4678 1.4682	168–171	C, 45.37 H, 5.92 N, 11.76	C, 45.46 H, 5.85 N, 11.22	8875
$(n\text{-}C_5H_{11})_2N$	215 (2.5 mm.)	1.4678	165–167	C, 46.52 H, 6.16 N, 11.42	C, 46.47 H, 6.00 N, 11.55	8876
$O(CH_2CH_2)_2N$	195 (3.5 mm.)	1.4791	186–188	C, 42.19 H, 5.09 N, 12.30	C, 42.66 H, 5.58 N, 12.05	9518

[a] The Survey Number, designated SN, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

EXPERIMENTAL[4]

Symmetrical decamethylene diamines (D. B. G.). Decamethylene glycol was converted to the dibromide by treatment with hydrobromic-sulfuric acid in 67% yield, b.p. 127–130° (4 mm.); m.p. 27° [lit. (7), b.p. 162° (9 mm.); m.p. 27.4°]. The dibromide was converted to the diamine by heating at 90–100° with the desired secondary amine for twenty-four hours. The properties of products, obtained in 55–80% yield, are summarized in Table I.

Unsymmetrical decamethylene diamines (H. F. H.). Decamethylene glycol was converted to the chlorohydrin essentially according to the directions of Bennett and Mosses (4). The product, obtained in 55% yield, boiled at 126–128° (2 mm.); m.p. 12–13°; n_D^{20} 1.4578. A forerun, b.p. 104–110° (2 mm.), m.p. 10–12°, was evidently *decamethylene dichloride*. A mixture with the chlorohydrin melted from 1° to 7°.

Treatment of the chlorohydrin with piperidine at 140–160° for twelve hours yielded the *piperidyl alcohol* in 91% yield, b.p. 159–164° (3 mm.). It crystallized from 30–60° petroleum ether as flat, white platelets, m.p. 60–61°.[5] The *hydrochloride* crystallized from chloroform-ethyl acetate as fine, white needles, m.p. 170–171°.

10-N-Morpholino-1-decanol was obtained in a similar fashion in 82% yield, b.p. 163–170° (2 mm.). On recrystallization from 30–60° petroleum ether it melted at 40–40.5°. Its *hydrobromide*, prepared in hot, dilute hydrobromic acid, recrystallized from chloroform as white needles, m.p. 164–165°.

Anal. Calc'd for $C_{14}H_{30}BrNO_2$: C, 51.85; H, 9.32; N, 4.32.
Found: C, 52.33; H, 9.60; N, 4.32.

10-N-Piperidyl-1-decyl chloride hydrochloride was prepared in 82% yield by treatment of the alcohol with thionyl chloride in benzene. After recrystallization from ethyl acetate it melted at 135–136° [lit. (3), 127–128°]. The amino chloride distilled under vacuum only with considerable dehydrohalogenation. From the forerun, b.p. 109–116° (2 mm.), *10-N-piperidyl-1-decene* was isolated and identified as its hydrochloride, which crystallized from ethyl acetate as white plates, m.p. 166.5–167°.

Anal. Calc'd for $C_{15}H_{30}ClN$: C, 69.33; H, 11.64; N, 5.39.
Found: C, 69.96; H, 11.88; N, 5.12.

Conversion of the piperidyl alcohol to the diamines was accomplished most conveniently by refluxing in 42% hydrobromic acid to form the bromo amine hydrobromide. This was not isolated but treated in solution with an excess of the desired secondary amine and boiled overnight. The properties of the diamines, obtained in 32–63% yield, are listed in Table II.

Undecamethylene diamines (E. W. P.). Undecenyl acetate was obtained in 80–92% yield by the pyridine-catalyzed reaction of the alcohol with acetic anhydride, b.p. 142–152° (18 mm.); n_D^{20} 1.4390. Addition of hydrogen bromide was accomplished in ice-cold benzene solution using benzoyl peroxide as catalyst. The *bromo ester* was obtained in 82% yield, b.p. 183–197° (16 mm.); n_D^{20} 1.4648. The position of the bromine atom on the terminal carbon was established by hydrolysis to 1,11-undecamethylene glycol, m.p. 61–61.5° [lit. (6), 61–62°].

Treatment of the bromo ester with piperidine by boiling for ten hours gave a liquid mixture, boiling at 172–186° (3 mm.), in about 80% yield. On standing, some crystals separated, which were identified as 11-N-piperidyl-1-undecanol, m.p. 63–65°.

Anal. Calc'd for $C_{16}H_{33}NO$: C, 75.23; H, 13.02; N, 5.48.
Found: C, 75.48; H, 13.20; N, 5.65.

Its *hydrochloride*, crystallized from absolute ethanol, melted at 156–158°.

Anal. Calc'd for $C_{16}H_{34}ClNO$: C, 65.83; H, 11.74.
Found: C, 65.75; H, 11.84.

11-N-Piperidyl-1-undecyl chloride was prepared from the alcohol by boiling with con-

[4] Microanalyses by Miss Theta Spoor and Miss Lillian Hruda.

[5] 10-N-Piperidyldecanol is reported (3) to melt at 55–56° and to boil at 210–211° (25 mm.).

centrated hydrochloric acid for fifty-four hours. The chloride, obtained in 56% yield, boiled at 164–168° (2.5 mm.); n_D^{20} 1.4739; m.p. −7° to −5°. The corresponding bromide, prepared similarly, was not isolated but was used directly in reactions with secondary amines. The properties of the diamines, obtained in about 70–80% yield, are summarized in Table III.

The *dipicrylsulfonates* were prepared by treating the diamines, in aqueous solution as the hydrochlorides, with an aqueous solution of sodium picrylsulfonate. The salts could be purified by recrystallization from ethanol.

SUMMARY

The preparation and properties of a number of decamethylene and undecamethylene di-tertiary amines has been reported.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF RUTGERS UNIVERSITY]

THE PREPARATION OF SOME C-ALKYLMORPHOLINES[1]

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Very few preparations of C-alkylmorpholines have been reported, although the literature on N-alkyl and arylmorpholines is large. Morpholine itself was first prepared in 1889 by Knorr (1) by dehydration of diethanolamine with 70% sulfuric acid. Médard (2) studied this dehydration more thoroughly, and obtained morpholine in 90–95% yield by heating diethanolamine with 95% sulfuric acid for 7–8 hours at 175–180°. Krasuskii (3) applied this dehydration method to di-isopropanolamine but obtained only 22% yield of 2,6-dimethylmorpholine by heating di-isopropanolamine with 70% sulfuric acid in a sealed tube at 160–170° for 8 hours. Payman and Piggott's (4) method involved the condensation of alkylene or arylalkylene halohydrins with aromatic sulfonamides to form N-di-(β-hydroxyalkyl)arylsulfonamides which when treated with sulfuric acid yielded a morpholine and an arylsulfonic acid. The preparation of 2,6-dimethylmorpholine from 1-chloro-2-propanol and *p*-toluenesulfonamide is recorded by these workers. 3,5-Diphenylmorpholine-2,6-dicarboxylic acid was also prepared, by treating β-chloro-β-phenyl-α-hydroxypropionic acid (obtained from phenylglycidic acid and hydrochloric acid) with a sulfonamide and subsequently heating with sulfuric acid. Adams and Cairns (5) prepared the N-arylsulfonamide of 2,2,6,6- or 2,2,5,5-tetramethylmorpholine as a by-product of the dehydration of 1-(*p*-bromobenzenesulfonamide)-2-methyl-2-propanol with phosphorus pentoxide.

In the present work, the preparation of 2-methylmorpholine, 3,3-dimethylmorpholine, 3-ethylmorpholine, 2-methyl-5-ethylmorpholine, and 2-ethylmorpholine are reported. The first four compounds were prepared by dehydration of the corresponding alkanolamines, which were made by addition of the appropriate amino alcohol to an olefin oxide. In the preparation of 2-methylmorpholine, the dialkanolamine, N-β-hydroxyethyl-1-amino-2-propanol, was prepared by the addition of 2-aminoethanol to propylene oxide. In the preparation of 3,3-dimethylmorpholine, the dialkanolamine, N-β-hydroxyethyl-2-amino-2-methyl-1-propanol, was prepared by the addition of 2-amino-2-methyl-1-propanol to ethylene oxide. The dialkanolamine used in the preparation of 3-ethylmorpholine, N-β-hydroxyethyl-2-amino-1-butanol, was prepared by the addition of 2-amino-1-butanol to ethylene oxide. The dialkanolamine used in

[1] The experimental work reported in this paper was done on a volunteer basis in connection with a contract between Columbia University and the Committee on Medical Research of the Office of Scientific Research and Development as a part of their Antimalarial Research program.

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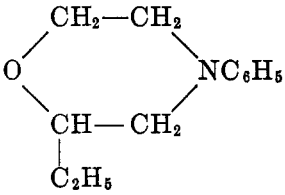
the preparation of 2-methyl-5-ethylmorpholine, N-β-hydroxy-*n*-propyl-2-amino-1-butanol, was prepared by the addition of 2-amino-1-butanol to propylene oxide. 2-Ethylmorpholine was prepared by the following series of reactions:

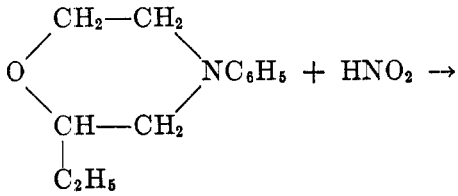
$$(CH_3CHO)_3 + HCl + ClCH_2CH_2OH \rightarrow CH_3CHCl{-}O{-}CH_2CH_2Cl + H_2O$$

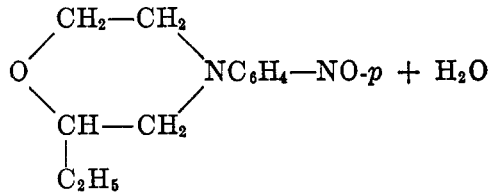
$$CH_3CHCl{-}O{-}CH_2CH_2Cl + Br_2 \rightarrow CH_2BrCHBr{-}O{-}CH_2CH_2Cl + HCl$$

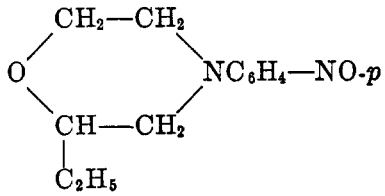
$$CH_2BrCHBr{-}O{-}CH_2CH_2Cl + C_2H_5MgBr \rightarrow CH_2BrCH(C_2H_5){-}O{-}CH_2CH_2Cl + MgBr_2$$

$$CH_2BrCH(C_2H_5){-}O{-}CH_2CH_2Cl + 3C_6H_5NH_2 \rightarrow C_6H_5NH_3Cl + C_6H_5NH_3Br +$$

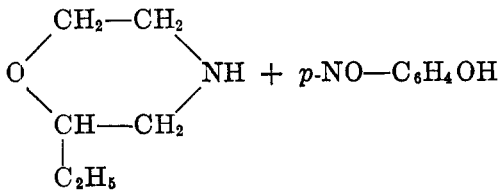








$\xrightarrow{NaHSO_3}$



EXPERIMENTAL

Reagents. The 2-aminoethanol, 2-amino-2-methyl-1-propanol, and 2-amino-1-butanol were supplied generously by The Commercial Solvents Corporation. The ethylene oxide was purified by passing it through two 4-foot towers filled with crushed sodium hydroxide. The other reagents were from common sources and were used without further purification.

Preparation of N-β-hydroxyethyl-1-amino-2-propanol. 2-Aminoethanol (1143 g. 18.7 moles) and 765 g. of water (to make a 60% solution) were chilled by ice. To the vigorously-stirred solution, 139 g. (2.4 moles) of propylene oxide was added dropwise. Water and 2-aminoethanol were removed by fractionation; the recovered 2-aminoethanol was used in subsequent runs. The dialkanolamine distilled at 160–175°/35 mm. and was refractionated through a three-bulb Snyder column to give a yield of 268 g., or 94% of a product boiling 163–166°/35 mm.; d_4^{25} 1.042; n_D^{25} 1.4670;

Anal.[5] Calc'd for $C_5H_{13}NO_2$: N, 11.76; Mol. Wt., 119.1.
Found: N, 11.75; Mol. Wt. (by titration), 120.1.

Preparation of 2-methylmorpholine. In a 3-liter 3-necked flask fitted with mercury-sealed stirrer, dropping-funnel, and condenser set for distillation was placed 1700 g. of 95% sulfuric acid. To the water-cooled, vigorously-stirred acid, 620 g. (5.2 moles) of N-β-hydroxyethyl-1-amino-2-propanol was added through the dropping-funnel. When all was added, the mixture was heated at 155–165° for ten hours, allowing the water formed to distill. After cooling, a solution of 1530 g. of sodium hydroxide in 2.5 l. of water was added carefully to the acid mixture, and the resulting alkaline solution was extracted with ether in a large continuous extractor for 48 hours. The ether extract was fractionated through a three-bulb Snyder column to obtain 297 g. or 57% yield of 2-methylmorpholine boiling 133–136°. The products from several runs were refractionated through an eight-bulb Snyder column to obtain a product boiling at 135–136°; d_4^{25} 0.939; n_D^{25} 1.4454.

Anal. Calc'd for $C_5H_{11}NO$: C, 59.40; H, 10.97; N, 13.85; Mol. Wt., 101.1.
Found: C, 59.11; H, 10.99; N, 13.42; Mol. Wt. (by titration), 101.8.

The phenylthiourea derivative and the *p*-toluenesulfonamide derivative were prepared by standard procedures (6). The phenylthiourea derivative melted at 135.5–136.5° (uncorr.).

Anal. Calc'd for $C_{12}H_{16}N_2OS$: N, 11.91; Found: N, 11.1.

The *p*-toluenesulfonamide derivative melted at 88–89° (uncorr.).

Anal. Calc'd for $C_{12}H_{17}NO_3S$: N, 5.49; Found: N, 4.99.

Preparation of N-β-hydroxyethyl-2-amino-2-methyl-1-propanol. A 60% aqueous solution of 1910 g. (24.8 moles) of 2-amino-2-methyl-1-propanol was placed in a 5-l. 3-necked flask fitted with a stirrer and wide inlet tube. To the well-cooled, vigorously-stirred solution, gaseous ethylene oxide, purified as previously described, was passed in until the gain in weight of the flask corresponded to an absorption of 136 g. (3.10 moles) of the oxide. The mixture was then fractionated through a three-bulb Snyder column; the recovered amino alcohol was used in subsequent preparations. The yield of N-β-hydroxyethyl-2-amino-2-methyl-1-propanol boiling at 143–147°/10 mm. was 396 g., or 96%. This product melted at 60–61° (uncorr.).

Anal. Calc'd for $C_6H_{15}NO_2$: C, 54.10; H, 11.35; N, 10.52; Mol. Wt., 133.2.
Found: C, 54.63; H, 11.32; N, 10.14; Mol. Wt. (by titration), 133.9.

Preparation of 3,3-dimethylmorpholine. The conditions of Médard (2) were used. Four hundred grams (3.00 moles) of N-β-hydroxyethyl-2-amino-2-methyl-1-propanol was slowly added to 540 g. of 95% sulfuric acid in a water-cooled flask fitted with mercury-sealed stirrer and condenser set for distillation. The vigorously-stirred mixture was heated for 9.5 hours at 178–180°, then cooled, made alkaline with sodium hydroxide solution and extracted with ether in a large continuous extractor. The ether extract was fractionated through a three-bulb Snyder column and 266 g., a 77% yield, of 3,3-dimethylmorpholine boiling at

[5] All microanalyses were performed by Miss Lois E. May of Columbia University, New York, New York.

143–146° was collected. The combined yields of several runs were twice fractionated through a six-bulb Snyder column to give a product boiling at 143–144°; d_{20}^{20} 0.9355; n_D^{20} 1.4472.

Anal. Calc'd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16; Mol. Wt., 115.2.
Found: C, 62.76; H, 11.64; N, 11.92; Mol. Wt. (by titration), 115.9.

Preparation of N-β-hydroxyethyl-2-amino-1-butanol. This compound was prepared by the same procedure as for N-β-hydroxyethyl-2-amino-2-methyl-1-propanol, using 2125 g. (24.0 moles) of 2-amino-1-butanol and 132 g. (3.00 moles) of ethylene oxide. The yield of product boiling at 138–140°/12 mm. was 363 g. or 91%; d_{20}^{20} 1.0153; n_D^{20} 1.4677.

Anal. Calc'd for $C_6H_{15}NO_2$: C, 54.10; H, 11.35; N, 10.52; Mol. Wt., 133.2.
Found: C, 54.90; H, 11.43; N, 10.03; Mol. Wt. (by titration), 133.2.

Preparation of 3-ethylmorpholine. This compound was prepared by the same procedure used for 3,3-dimethylmorpholine, using 400 g. (3.00 moles) of N-β-hydroxyethyl-2-amino-1-butanol and 540 g. of 95% sulfuric acid. The yield of 3-ethylmorpholine boiling at 156.5–157.5° was 248 g., or 72%. On redistillation of the combined fractions from several runs through a six-bulb Snyder column, the fraction 156.5–157.5° was collected as pure product, d_{20}^{2} 0.9556; n_D^{20} 1.4519.

Anal. Calc'd for $C_6H_{13}NO$: C, 62.57; H, 11.38; N, 12.16. Mol. Wt., 115.2.
Found: C, 62.76; H, 11.64; N, 11.92; Mol. Wt. (by titration), 116.0.

Preparation of N-β-hydroxy-n-propyl-2-amino-1-butanol. This compound was prepared by the same procedure used for N-β-hydroxyethyl-1-amino-2-propanol, using 1780 g. (20.0 moles) of 2-amino-1-butanol and 110 g. (2.50 moles) of propylene oxide. The yield of dialkanolamine boiling at 147.0–152.5°/16 mm. was 335 g., or 91%; d_{20}^{20} 1.0153; n_D^{20} 1.4677.

Anal. Calc'd for $C_7H_{17}NO_2$: C, 57.10; H, 11.65; N, 9.51; Mol. Wt., 147.3.
Found: C, 57.35; H, 12.15; N, 9.14; Mol. Wt. (by titration), 147.8.

Preparation of 2-methyl-5-ethylmorpholine. This compound was prepared by the same procedure used for 2-methylmorpholine, using 147 g. (1.0 mole) of N-β-hydroxy-*n*-propyl-2-amino-1-butanol and 330 g. of 95% sulfuric acid. The time of heating was 12 hours. The yield of 2-methyl-5-ethylmorpholine boiling at 163–164° was 110 g., or 86%; this product was refractionated through a six-bulb Snyder column to give a product boiling at 164.5–165.0°; d_{20}^{20} 0.9222; n_D^{20} 1.4471.

Anal. Calc'd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84.
Found: C, 64.53; H, 12.35; N, 10.65.

Preparation of 1-chloro-1-(β-chloroethoxy)ethane. This preparation was a modification of the ones previously applied to the same substance by Grignard and Purdy (7), who obtained it in 65% yields, and by Summerbell and Umhoefer (8), who obtained a crude yield of 79%. The yield obtained by the following procedure in five runs averaged 68% of a product distilling at 46–48°/10–11 mm. through a five-bulb Snyder column.

Dry hydrogen chloride was passed as rapidly as absorption would take place for three hours into a vigorously-stirred mixture of 350 g. (4.36 moles) of ethylene chlorohydrin and 200 g. (1.52 moles) of paraldehyde cooled to −10°. The resulting upper layer was dried overnight over calcium chloride and fractionated.

Preparation of 1,2-dibromo-1-(β-chloroethoxy)ethane. The procedure used was that of Summerbell and Umhoefer (8) except that the bromine was added at room temperature instead of at 0° because of the slowness of the reaction at the lower temperature. The yields from six preparations, each involving 2.68 to 3.11 moles of 1-chloro-1-(β-chloroethoxy)ethane averaged 82% of a product distilling at 110–113°/13 mm. through a six-bulb Snyder column. This substance was a powerful lachrymator and great care had to be exercised in handling it.

Preparation of 1-bromo-2-(β-chloroethoxy)butane. The procedure used was a modification of one described by Summerbell and Umhoefer (8). They failed to heat their reaction mixture of ethylmagnesium bromide and 1,2-dibromo-1-(β-chloroethoxy)ethane and obtained a yield of 25%. In the present work the mixtures were refluxed at 45–50° for one hour and allowed to stand 12 hours or longer before hydrolysis. The yields of seven preparations involving 1.61 to 2.60 moles of 1,2-dibromo-1-(β-chloroethoxy)ethane and approximately equivalent quantities of ethylmagnesium bromide averaged 81% of a product distilling at 91–93°/11 mm.

Preparation of 2-ethyl-4-phenylmorpholine. Although the preparation of 2-ethyl-4-phenylmorpholine had not been described previously, Cretcher, Koch, and Pittenger (9) have described various 4-arylmorpholines, and their method was adapted to this work.

1-Bromo-2-(β-chloroethoxy)butane (440 g. or 2.05 moles) and 548 g. (6.15 moles) of aniline were placed in a 3-l. flask fitted with a large Hopkins condenser and heated in an oil-bath. When the temperature reached 120–130° a vigorous reaction made removal of the oil-bath necessary. After three to four minutes the reaction subsided, the oil-bath was replaced and heating continued at 160° for four hours, at the end of which the contents of the flask were almost completely solid. After cooling, 240 g. (6.0 moles) of sodium hydroxide in 500 ml. of water was added, the organic layer removed and the water layer extracted with benzene. Distillation of the benzene removed the water, and the residue was vacuum-fractionated through a three-bulb Snyder column. The recovered aniline was used in subsequent runs. The yield of product boiling at 139–140°/9 mm. was 83%.

Anal. Calc'd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.33.
Found: C, 77.24; H, 9.23; N, 7.42.

The average yield of six similar preparations involving 1.25 to 2.11 moles of dibromoether was 78%. One preparation with 1.02 moles of dihaloether which was heated for 2 hours gave a 60% yield, and one with 2.00 moles which was heated for 9 hours gave a 56% yield.

TABLE I

THE NITROSATION OF 2-ETHYL-4-PHENYLMORPHOLINE

MOLES OF 2-ETHYL-4-PHENYLMORPHOLINE	MOLES OF HYDROCHLORIC ACID	MOLE RATIO OF ACID TO PHENYLMORPHOLINE	YIELD OF 2-ETHYLMORPHOLINE, %
0.61	4.61	7.6	23
1.00	13.0	13.0	57
1.12	10.0	8.9	36
1.50	15.0	10.0	45
1.50	15.0	10.0	54
1.50	10.0	10.0	47
1.53	10.0	9.8	33[a]
1.41	14.0	10.0	61

[a] Ratio of $NaNO_2$/phenylmorpholine was 1.5; in all other runs it was 1.05.

Preparation of 2-ethylmorpholine. (a) *Nitrosation.* The conditions given by Bennett and Bell (10) were adapted. In a typical run, 286 g. (1.50 moles) of 2-ethyl-4-phenylmorpholine was dissolved in 1250 ml. of concentrated hydrochloric acid (15 moles), diluted with 1250 ml. of water, and chilled to −6°. A solution of sodium nitrite containing 109 g. (1.58 moles) in 150 ml. of water was added dropwise to the well-stirred hydrochloride solution over a period of 2.5 hours, and stirring continued for another hour. The resulting solution was treated with 605 g. (16 moles) of sodium hydroxide in 700 ml. of water, cooled, extracted with ether, the ether removed by distillation, and the residue hydrolyzed.

Although the nitroso compound was not isolated as a pure substance, the following data on the nitrosations are of interest because the subsequent hydrolysis conditions were kept constant and the difference in yield of the 2-ethylmorpholine must be attributed to a difference in the nitrosation procedure. It will be noted that when the mole ratio of hydrochloric acid to phenylmorpholine was below 10.0, the yield of 2-ethylmorpholine suffered. Excess sodium nitrite was also found to decrease the yield of 2-ethylmorpholine.

(b) *Hydrolysis of the nitroso derivative.* The conditions for hydrolyzing the nitroso compound were those used by Mr. Munch and Miss Thannhauser of this laboratory in the preparation of some diamines (11). The nitroso compound was treated with a 27% solution of sodium bisulfite in the ratio of one mole of nitroso compound to six moles of bisulfite. The mixture was heated to 35–40° for one hour and then at 75° for one hour, with stirring

throughout. After cooling, the mixture was treated with 8 moles of concentrated hydrochloric acid per mole of phenylmorpholine nitrosated, and the volume reduced by distillation to about 1500 ml. The resulting solution was treated with 9 moles of sodium hydroxide per mole of phenylmorpholine nitrosated, during which addition much ammonia was given off. Extraction of the amine was performed with ether in a large continuous extractor, the ether solution was dried over potassium carbonate and the ether removed by distillation. The residue was fractionated through a three-bulb Snyder column, and the crude 2-ethylmorpholine distilled at 155–157°, or 38–40°/8 mm. The combined yields of several preparations were refractionated twice through a six-bulb Snyder column and the portion distilling at 154° was taken as pure product. Physical constants on this fraction were as follows: d_{20}^{20} 0.9419; n_D^{25} 1.4519.

Anal. Calc'd for $C_6H_{13}NO$: C, 62.56; H, 11.38; N, 12.17; Mol. Wt., 115.2.
Found: C, 62.44; H, 11.73; N, 11.50; Mol. Wt. (by titration), 115.5.

The phenylthiourea derivative and *p*-toluenesulfonamide derivative were prepared by standard procedures (6). The phenylthiourea derivative melted at 126.4–127.2° (uncorr.) and the *p*-toluenesulfonamide derivative melted at 116.0–116.7° (uncorr.).

SUMMARY

The preparation in quantity and in high yield of the following new compounds is reported: 2-methylmorpholine, 3,3-dimethylmorpholine, 3-ethylmorpholine, and 2-methyl-5-ethylmorpholine. These substances were made by dehydration of the dialkanolamines, N-β-hydroxyethyl-1-amino-2-propanol, N-β-hydroxyethyl-2-amino-2-methyl-1-propanol, N-β-hydroxyethyl-2-amino-1-butanol, and N-β-hydroxy-*n*-propyl-2-amino-1-butanol, which also are new substances and which were prepared by the addition of commercially available amino alcohols to olefin oxides.

The preparation of 2-ethylmorpholine, a new compound, in large quantity by a five-step synthesis starting with commercially available materials is described. This synthesis involved the preparation of 2-ethyl-4-phenylmorpholine, also a new compound, its nitrosation, and the hydrolysis of the nitroso derivative. Conditions affecting the yields of 2-ethylmorpholine from this hydrolysis are discussed.

NEW BRUNSWICK, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

NOTE ON SOME AZOMETHINES FROM *p*-DIALKYLAMINOBENZALDEHYDES

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During the course of other work, it recently became necessary to prepare some azomethines of *p*-dialkylaminobenzaldehydes. Werner (1) states that, on treatment with *p*-dimethylaminobenzaldehyde, "no reaction occurs with . . . heterocyclic amino compounds," presumably in the presence of mineral acid at room temperature. We find that, on heating, this aldehyde reacts with 2-aminopyridine and with 6-methoxy-8-aminoquinoline to give the corresponding Schiff bases.

As mentioned in the experimental section, our observations do not agree with Werner's in several particulars.

EXPERIMENTAL

p-Dimethylaminobenzylidene p'-carboxyanil. A solution of 10 g. of *p*-dimethylaminobenzaldehyde in 50 cc. of absolute ethanol was filtered into a filtered solution of 9.2 g. of *p*-aminobenzoic acid in 100 cc. of warm absolute ethanol. After 10 minutes at room temperature, separation of golden-yellow crystals commenced spontaneously. After standing overnight at room temperature, the crystals were filtered off, washed with two 25-cc. portions of absolute ethanol, and dried; wt. 14.3 g. (79.5%); m.p. 264–265° [Wayne and Cohen (2) gave m.p. 261–262°; Werner (1), m.p. 245°]. Werner (1) stated that it crystallizes as dark red rosettes and that "in ethyl alcohol . . . the reaction proceeds very slowly."

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.60; H, 6.0; N, 10.45.

Found: C, 71.91; H, 6.1; N, 10.32.

p-Diethylaminobenzylidene p'-carboxyanil. A solution of 10 g. of *p*-diethylaminobenzaldehyde in absolute ethanol was added to a solution of 7.8 g. of *p*-aminobenzoic acid in absolute ethanol as in the previous experiment. Crystallization of the product commenced after 30 minutes at room temperature; after standing overnight at room temperature, the product was filtered off and dried; wt. 11.2 g. (67%); m.p. 241–242°. It was recrystallized from chloroform (65 volumes), giving yellow crystals; m.p. 242–243°.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.93; H, 6.8; N, 9.46.

Found: C, 72.74; H, 6.6; N, 9.31.

p-Dimethylaminobenzylidene p'-sulfoanil. Sulfanilic acid (11.6 g.) was suspended in 200 cc. of absolute ethanol, a solution of 10 g. of *p*-dimethylaminobenzaldehyde in 50 cc. of absolute ethanol was added, and the mixture boiled under reflux during four hours.

After standing overnight at room temperature, the insoluble, orange-colored material was filtered off and dried; wt. 17.2 g.; m.p. above 360°. This was recrystallized from 150 volumes of water, giving 12 g. of orange-colored crystals; m.p. above 360° [Werner (1) reports m.p. 300°]. It was dried at 134° at 20 mm. for analysis.

Anal. Calc'd for $C_{15}H_{16}N_2O_3S$: N, 9.21; S, 10.54.

Found: N, 9.22; S, 10.34.

p-Diethylaminobenzylidene p'-sulfoanil. A solution of 10 g. of *p*-diethylaminobenzaldehyde in absolute ethanol was added to a suspension of sulfanilic acid (9.8 g.) in absolute ethanol and the mixture treated as in the previous experiment. After standing overnight at room temperature, the insoluble, red material was filtered off and dried; wt. 17 g.; m.p. 252–253° (decomp.). This was recrystallized from 150 volumes of water, giving 11.2 g. of red crystals; m.p. 252° (decomp.). It was dried at 134° and 20 mm. for analysis.

Anal. Calc'd for $C_{17}H_{20}N_2O_3S$: C, 61.40; H, 6.1; N, 8.43; S, 9.65.
Found: C, 61.10; H, 6.1; N, 8.83; S, 9.64.

p-Dimethylaminobenzylidene p'-dimethylaminoanil. A mixture of 9.2 g. of *p*-dimethylaminoaniline with 10 g. of *p*-dimethylaminobenzaldehyde was heated under reflux in a boiling water-bath during 15 minutes. It rapidly set to a solid, golden-yellow mass. It was stirred with absolute ethanol and filtered, giving 12.2 g. of yellow crystals; m.p. 231–232°. [Bender (3) and Moehlau (4) give m.p. 229–230°.]

Anal. Calc'd for $C_{17}H_{21}N_3$: C, 76.35; H, 7.9; N, 15.73.
Found: C, 76.43; H, 8.0; N, 16.15.

The mother liquor was evaporated to dryness, dissolved in 65 cc. of boiling chloroform, cooled, and the solution diluted with 105 cc. of heptane, giving a second crop; wt. 4.4 g. (total yield, 93%).

p-Diethylaminobenzylidene p'-diethylaminoanil. A mixture of 9.3 g. of *p*-diethylaminoaniline with 10 g. of *p*-diethylaminobenzaldehyde was heated in an open flask in a bath at 110° during 30 minutes. The brown, crystalline product was dissolved in 54 cc. of boiling 95% ethyl alcohol under reflux, and the solution cooled, yielding 14.2 g. (78%) of yellowish-brown crystals having m.p. 118–120°. It was recrystallized twice from 3 volumes of 95% ethyl alcohol, giving orange-colored crystals; m.p. 120–122°. [Doja and Mokeet (5) gave m.p. 147–149°.]

Anal. Calc'd for $C_{21}H_{29}N_3$: C, 77.96; H, 9.0; N, 13.00.
Found: C, 77.93; H, 8.8; N, 13.08.

p-Dimethylaminobenzylidene p'-amidosulfoanil. A mixture of 10 g. of *p*-dimethylaminobenzaldehyde with 11.5 g. of sulfanilamide was heated under reflux (Stark and Dean trap) at 130–135° (bath temp. 150–154°) during 45 minutes. The yellow, semi-crystalline reaction mixture was then cooled to room temperature and extracted with a boiling mixture of 160 cc. of absolute ethanol plus 30 cc. of acetone under reflux. The yellow, insoluble solid was filtered off and dried; wt. 10.6 g.; m.p. 208–210°. [According to Gray *et al.* (6), their alcohol-acetone insoluble material "consisted of the anil in a pure state, m.p. 229°."] In a repetition of the preparation, the initial product had m.p. 210–212°.

Anal. Calc'd for $C_{15}H_{17}N_3O_2S$: N, 13.86; S, 10.57.
Found: N, 13.97; S, 10.60.

On recrystallizing the anil from 80 volumes of acetone plus 40 volumes of pentane [as suggested by Kolloff and Hunter (7)] the melting point remained unchanged (208–210°). On the other hand, recrystallization of the crude anil (9.3 g.; m.p. 210–212°) from 400 volumes of absolute ethanol gave 3.1 g. of yellow crystals; m.p. 228°. [Werner (1) gives m.p. 212–214°; Kolloff and Hunter (7), m.p. 226–227°; Gray *et al.* (6), m.p. 228°.]

Anal. Calc'd for $C_{15}H_{17}N_3O_2S$: C, 59.36; H, 5.65; N, 13.86; S, 10.57.
Found: C, 59.71; H, 5.61; N, 14.20; S, 10.54.

p-Diethylaminobenzylidene p'-amidosulfoanil. A mixture of 10 g. of *p*-diethylaminobenzaldehyde with 9.7 g. of sulfanilamide was treated as in the previous experiment, the semi-crystalline reaction mixture dissolved in 70 volumes of boiling chloroform, filtered hot and the filtrate cooled, giving 0.8 g. of yellow crystals, m.p. 164–166°, which had an analysis agreeing with that calculated for sulfanilamide. The mother liquor was diluted with 70 volumes of pentane, giving 6.6 g. of yellow crystals; m.p. 154–156°. On recrystallization from 70 volumes of chloroform plus 70 volumes of pentane, it had m.p. 156°.

Anal. Calc'd for $C_{17}H_{21}N_3O_2S$: N, 12.69; S, 9.68.
Found: N, 12.87; S, 9.45.

2-(p-Dimethylaminobenzylidene)aminopyridine. A mixture of 25 g. of *p*-dimethylaminobenzaldehyde with 15.8 g. of 2-aminopyridine was heated under reflux (Stark and Dean trap), the bath temperature being gradually raised from 182° to 240° during 1 hour; 2 cc. of water collected in the trap. The mixture was then cooled to room temperature, treated with 125 cc. of absolute ethanol, and filtered, giving 10.5 g. of pale brown crystals; m.p. 118–120°. This was recrystallized from 5 volumes of absolute ethanol, yielding 6.8 g. of pale brown crystals; m.p. 122–124°.

Anal. Calc'd for $C_{14}H_{15}N_3$: C, 74.62; H, 6.7; N, 18.67.
Found: C, 74.71; H, 6.6; N, 19.08.

6-Methoxy-8-aminoquinoline. A suspension of 10 g. of recrystallized 6-methoxy-8-nitroquinoline (m.p. 162–163°) plus 0.2 g. of Adams' platinum catalyst in 100 cc. of absolute methanol was reduced with hydrogen at room temperature in the Burgess-Parr apparatus. The initial pressure was approximately 40 lb. per sq. inch; as hydrogenation proceeded the nitro derivative dissolved. After absorption was complete (45 minutes), the catalyst was filtered off, washed with methanol, and the filtrate plus washings evaporated to dryness (yield, quantitative). The product was purified by distillation under high vacuum; it boiled at 115–121° at 0.05 mm. (bath temp. 130–135°) and had m.p. 50–51° (colorless crystals). Schulemann *et al.* (8) gave b.p. 137–138° at 1 mm., m.p. 41°; Magidson *et al.* (9), b.p. 160–161° at 4 mm., m.p. 51°; Crum and Robinson (10), b.p 162° at 0.2 mm., m.p. 41°; Misani and Bogert (11), b.p. 165° at 6 mm., m.p. 50°.

6-Methoxy-8-(p-dimethylaminobenzylidene)aminoquinoline. A mixture of 10 g. of distilled, crystalline 6-methoxy-8-aminoquinoline (m.p. 50–51°) with 8.6 g. of *p*-dimethylaminobenzaldehyde plus 10 drops of piperidine in 25 cc. of toluene was boiled gently under reflux (Stark and Dean trap full of toluene) for 10 hours. A total of 0.8 cc. of water (80% of theoretical) was collected in the trap (bath temperature 141–149°; reaction temperature 119–122°). The brown reaction solution was chilled and scratched, with spontaneous crystallization into an almost solid mass. The crop of yellow crystals was filtered off, washed on the filter with two 10-cc. portions of ether, and dried in the vacuum desiccator over P_2O_5; wt. 11 g. (63%); m.p. 184–189°. It was recrystallized from 5 volumes of chloroform diluted with 10 volumes of hexane, giving yellow crystals, m.p. 189–191°. These crystals were recrystallized from 15 volumes of toluene, giving 5.8 g. of yellow crystals; m.p. 192–194°.

Anal. Calc'd for $C_{19}H_{19}N_3O$: C, 74.71; H, 6.3; N, 13.77.
Found: C, 74.52; H, 6.3; N, 13.49.

The residue from the combined mother liquors of the crude, crystalline product (from three such preparations) was reheated with piperidine plus toluene, as described above, yielding a further 9.5 g. of crude, crystalline product.

6-Methoxy-8-(p-dimethylaminobenzyl)aminoquinoline. A suspension of 5 g. of recrystallized 6-methoxy-8-(*p*-dimethylaminobenzylidene)aminoquinoline (m.p. 192–194°) plus 0.2 g. of Adams' platinum catalyst in 150 cc. of absolute methanol was reduced with hydrogen as described for 6-methoxy-8-aminoquinoline. After absorption was complete (25 minutes), the reaction mixture was diluted with 50 cc. of chloroform (with the dissolution of the yellow solid present), the catalyst was filtered off, washed with chloroform and methanol, and the filtrate plus washings evaporated to dryness. The brown-green, semi-crystalline residue was suspended in 5 volumes of cold absolute methanol and kept overnight at room temperature. The insoluble, brown-green crystals were filtered off and dried in the vacuum desiccator; wt. 2.1 g. (42%); m.p. 127–129°). This solid was dissolved in boiling absolute ethanol (15 volumes) and filtered hot through a fluted filter with spontaneous crystallization. The yellow-tan crystals were filtered off and dried; wt. 1.3 g.; m.p. 123–125°. The yellow-tan crystals were recrystallized from 150 volumes of hexane giving yellow crystals melting at 125–126°. On mixture of a sample with pure starting material, it gave a partial melt at 125–128° and a complete melt at 142–144°.

Anal. Calc'd for $C_{19}H_{21}N_3O$: C, 74.22; H, 6.9; N, 13.68.
Found: C, 74.24; H, 6.7; N, 13.74.

SUMMARY

A number of new azomethines of *p*-dialkylaminobenzaldehydes are described, and several previously reported in the literature have been reinvestigated.

PITTSBURGH 13, PA.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. VII.[1,2] AMINO ALCOHOLS OF THE TYPE $-CHOHCH(CH_3)NR_2$ DERIVED FROM TETRAHYDROPHENANTHRENE

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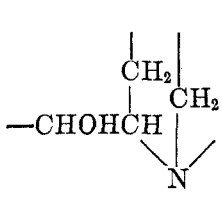
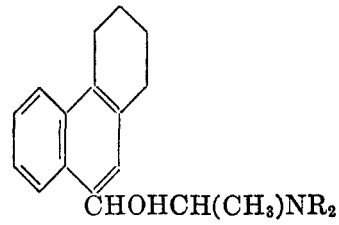
Previous communications of this series dealt with ethanolamines of the type $-CHOHCH_2NR_2$ (1, 2) and propanolamines of the type $-CHOHCH_2CH_2NR_2$ (3), the side chains being attached to position 9 of phenanthrene, tetrahydrophenanthrene, and 3-methoxyphenanthrene (4). In analyzing the structural formula of quinine one notes the presence of a carbinolamine chain (I) containing two asymmetric carbon atoms, similar to that in the ephedrines. With this point in view we undertook the synthesis of compounds represented by formula II.



I



II

9-Propionyltetrahydrophenanthrene,[3] the starting material for the synthesis of type II was prepared by the Friedel-Crafts reaction. Its structure was proved by converting it to the tetrahydro-9-phenanthroic acid. We obtained the latter by oxidation of 9-acetyltetrahydrophenanthrene with sodium hypochlorite. This ketone was prepared and elucidated in its structure by Bachmann and Struve (6). As a by-product in the preparation of 9-propionyltetrahydrophenanthrene we isolated the 7-propionyltetrahydrophenanthrene in a yield of about 15%, and proved its structure by dehydrogenation to 2-propionylphenanthrene (7). The synthesis of the propanolamines II was accomplished by brominating 9-propionyltetrahydrophenanthrene, exchanging the bromine with the amino group, and reducing the resulting amino ketones to the amino alcohols, either catalytically or with aluminum isopropoxide.

The tolerated doses (chicks) of the amino alcohols of this series do not show a consistent variation from those of the lower homologs—$CHOHCH_2NR_2$ (Dr.

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXX.

[3] The preparation of 9- and 7-propionyltetrahydrophenanthrene and the structural proof of these compounds were accomplished in the time from November 1942 to February 1943. The publication of the data pertaining to the 9-isomer was anticipated by Bachmann and Cronyn (5).

Nathan B. Eddy) (8). There is an indication that the therapeutic value is decreased by the methyl group on the carbon adjacent to the secondary alcoholic group (Dr. G. Robert Coatney and Dr. W. Clark Cooper) (9). None of these drugs showed any activity towards sporozoite-induced gallinaceum malaria except the diethylamino derivative (SN 2664),[4] which does not prevent, but consistently delays infection when given at the tolerated dose (9).

Acknowledgment. We are indebted to Mr. Edward A. Garlock, Jr. for carrying out the microanalyses.

EXPERIMENTAL[5]

Propionylation of 1,2,3,4-tetrahydrophenanthrene. To a well-stirred mixture of 93 g. of aluminum chloride, 300 cc. of nitrobenzene, and 35.5 g. of propionyl chloride was added slowly at −5° to 0°, 68 g. of 1,2,3,4-tetrahydrophenanthrene. The reaction mixture was allowed to stand for twenty-four hours at 6°, and poured into an ice-hydrochloric acid mixture. After distilling the nitrobenzene with steam, the dark oil remaining was shaken into ether, the ether solution dried, and solvent evaporated. The residue, on distillation, yielded 68 g. of straw-colored liquid boiling at 212–217° (5 mm.). From this distillate a few crystals separated after standing for several days. To further the separation 325 cc. of ligroin was added, the solution was cooled slowly, and finally allowed to stand in the ice-box for twenty-four hours. The crystalline material, consisting of the pure 7-isomer, weighed 6.3 g. and melted at 95–96°.

7-Propionyl-1,2,3,4-tetrahydrophenanthrene crystallized from 95% ethanol as hexagonal plates melting at 96–96.5°.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.69; H, 7.61; M.W., 238.
Found: C, 85.69; H, 7.80; M.W., 238.

The *semicarbazone*, prepared in alcohol, crystallized from dioxane in well-formed prisms and melted at 222.5–223.5°.

Anal. Calc'd for $C_{18}H_{21}N_3O$: N, 14.22. Found: N, 13.98.

The picrate crystallized from 70% ethanol in rectangular plates of m.p. 121.5–122.5°.

Dehydrogenation (6). A mixture of 0.5 g. of the material of m.p. 96–96.5° and 0.17 g. of sulfur was heated at 210–220° for three hours. A small amount of copper-bronze was added and heating continued for ten minutes. The mixture was extracted with benzene and the residue from this extract evaporatively distilled at 160–175° (0.5 mm.). The yield of solid melting at 98–103° was 0.4 g. After a recrystallization from ethanol-acetone the m.p. was 103–104° alone or when mixed with an authentic sample of 2-propionylphenanthrene. Further, the picrate melted at 105–106.5° and gave no depression in a mixture m.p. with authentic 2-propionylphenanthrene picrate.

9-Propionyl-1,2,3,4-tetrahydrophenanthrene (5). The ligroin filtrate of the 7-isomer (see above) was evaporated to dryness leaving an oil consisting mainly of 9-propionyl-1,2,3,4-tetrahydrophenanthrene but still containing about 6% of the 7-isomer. (This estimate was based on a separation of the semicarbazones.) This oily ketone was, however, sufficiently pure for the subsequent reactions. For complete separation from the 7-isomer it was purified through the picrate which crystallized from 95% ethanol in yellow needles of m.p. 127.5–128°.

Anal. Calc'd for $C_{23}H_{21}N_3O_8$: C, 59.10; H, 4.53.
Found: C, 58.90; H, 4.63.

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[4] SN signifies the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The SN for the drugs which have been submitted to testing, are given in the Experimental.

[5] All melting points are uncorrected.

The semicarbazone, prepared from ketone which had been purified through the picrate, crystallized from 70% ethanol as white prisms of m.p. 161–163°. It was a great deal more soluble than that of the 7-isomer.

Anal. Calc'd for $C_{18}H_{21}N_3O \cdot \frac{1}{2}H_2O$: C, 71.03; H, 7.29.
Found: C, 71.44; H, 7.38.

The sample was dried at 97° for five hours *in vacuo*, m.p. 165–168°.

Anal. Calc'd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17.
Found: C, 73.06; H, 7.30.

Oxidation. 9-Propionyl-1,2,3,4-tetrahydrophenanthrene was oxidized to the acid (5) by refluxing it for 1.5 hours with 3% potassium hypochlorite solution. It crystallized from 80% ethanol or glacial acetic acid in white blades of m.p. 213–215°. 9-Acetyl-1,2,3,4-tetrahydrophenanthrene (6) was also oxidized to the acid with hypochlorite. It likewise melted at 213–215°; mixed m.p. 213–215°. Bachmann and Cronyn (5) reported 215–216°.

The methyl ester, prepared by boiling the acid with methanolic hydrogen chloride crystallized from 80% methanol in white prisms of m.p. 71.5–72°. Bachmann and Cronyn (5) reported 70.5–71°.

Amino ketones and amino alcohols. To a stirred solution of 20 g. of the oily 9-propionyl-tetrahydrophenanthrene in 100 cc. of dry ether (cooled in ice-water) was added during a forty-minute period, 4.5 cc. of bromine. After stirring an additional thirty-five minutes without external cooling, the clear solution was shaken successively with water, 2% sodium carbonate solution, and water, dried over sodium sulfate, concentrated to 75 cc., and stored in the cold-room. This bromo ketone could not be obtained crystalline even when crystalline 9-propionyl-1,2,3,4-tetrahydrophenanthrene (m.p. 43–45°) (5) was used in the bromination.

9-(2-Dimethylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 6814). A 38-cc. portion of the ether solution of the bromo ketone equivalent to 11.4 g. of the latter was treated with 5.6 g. (3.5 moles) of dry gaseous dimethylamine during a ten-minute period (ice cooling). The reaction mixture was allowed to stand in ice-water for one-half hour, at room temperature for five hours, and finally in the ice-box for five hours. The dimethylamine hydrobromide (4.4 g.) was collected, and the filtrate extracted twice with dilute hydrochloric acid. The acid extracts were combined, made ammoniacal, and the liberated base was shaken into ether. The ether solution, after drying and evaporation, yielded 10.5 g. of oily amino ketone. This, in 50 cc. of absolute ethanol, absorbed 0.9 mole of hydrogen in 25 to 35 hours (platinum oxide, 0.3 g.). The clear solution was filtered from catalyst and concentrated until the amino alcohol base began to separate. After cooling in ice, 5.2 g. (m.p. 158.5–159.5°) was collected. On evaporating the filtrate to dryness, dissolving the residue in acetone and adding 3.5 cc. of 20% alcoholic hydrogen chloride, an additional 0.7 g. of amino alcohol (as hydrochloride) was obtained. The base crystallized from absolute ethanol in white prismatic rods of m.p. 159.5–160°.

Anal. Calc'd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89.
Found: C, 80.21; H, 9.28.

The hydrochloride crystallized from absolute ethanol-ether as clusters of white plates of m.p. 221–222°.

Anal. Calc'd for $C_{19}H_{26}ClNO$: C, 71.33; H, 8.19.
Found: C, 71.45; H, 8.24.

There was no indication of the presence of a diastereoisomer.

9-(2-Diethylamino-1-oxopropyl)-1,2,3,4-tetrahydrophenanthrene picrate. A portion of the ether solution of bromo ketone equivalent to 9 g. of the latter was concentrated to 15 cc. and 8 cc. of diethylamine was added. After allowing this mixture to stand for twenty-four hours at room temperature and for fifteen hours in the ice-box, 3.4 g. of diethylamine hydrobromide was collected. The filtrate was shaken with three portions of dilute hydrochloric acid. The combined acid extracts were then made alkaline, the liberated base was shaken into ether, and the ether washed four times with water. After drying the ether over sodium sulfate, 100 cc. of warm 7% alcoholic picric acid solution was added. After two hours at

room temperature 7.2 g. (47%) of pure amino ketone picrate of m.p. 163–164° was obtained. A recrystallization from 95% ethanol did not change the melting point; yellow plates.

Anal. Calc'd for $C_{27}H_{30}N_4O_8$: C, 60.22; H, 5.62.
Found: C, 60.14; H, 6.02.

The hydrochloride could not be obtained crystalline. Attempts to improve the yield by varying conditions, such as elevating the temperature, and using different solvents, were without success.

9-(2-Diethylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 2664). A mixture of 3.8 g. of the amino ketone obtained from the picrate above, 0.35 g. of platinum oxide, and 60 cc. of methanol absorbed 0.9 mole of hydrogen in forty hours. After filtration of catalyst and evaporation of solvent *in vacuo*, the amino alcohol base was dissolved in acetone and acidified with dry gaseous hydrogen chloride. The hydrochloride separated in a yield of 2.9 g., m.p. 218–219°. From absolute ethanol-acetone-ether it crystallized as white blades of m.p. 219–220° (decomp.).

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69.
Found: C, 72.30; H, 8.95.

There was no indication of the presence of a second isomer.

9-(2-Dipropylamino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 6820). A mixture of 25 cc. of an ether solution of bromo ketone equivalent to 12.5 g. of the latter and 10 g. of dipropylamine was kept at room temperature for 48 hours and in the ice-box for 24 hours. Dipropylamine hydrobromide was collected (4.9 g.) and the filtrate freed of excess dipropylamine by partial neutralization with 20% alcoholic hydrogen chloride and filtration of the resulting dipropylamine hydrochloride. The filtrate was then made slightly acidic with dry gaseous hydrogen chloride, whereupon 8.6 g. of the dipropylamino ketone salt crystallized out. This was reduced with 50 cc. of 3 *N* aluminum isopropoxide solution as described previously (1). The time required was 2.5 hours. After distillation (*in vacuo*) of most of the isopropanol, the residue was partitioned between an excess of 10% sodium hydroxide solution and ether. The ether layer was washed twice with water, dried, and treated with a slight excess of 20% alcoholic hydrogen chloride. The hydrochloride of the amino alcohol crystallized in a yield of 3.0 g., m.p. 190–193°. A second fraction of less pure material weighed 1.6 g. and melted at 160–180°. Two recrystallizations from absolute ethanol-ether gave the constant melting point 195.5–197°; white oblong plates.

Anal. Calc'd for $C_{23}H_{34}ClNO$: C, 73.46; H, 9.12.
Found: C, 73.17; H, 9.19.

The filtrate contained a large amount of oily hydrochloride which may be the diastereoisomeric form of the above compound. It could not be crystallized.

When the amino ketone base was used in this reduction the yields were somewhat lower and the material was more difficult to purify.

9-(2-Morpholino-1-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 6904).[6] 9-(α-Bromopropionyl)-1,2,3,4-tetrahydrophenanthrene was condensed with morpholine by the same procedure as that described for the condensation with 1,2,3,4-tetrahydroisoquinoline by Wright and Elderfield (10). After separation of the crude amino ketone hydrochloride and reduction of the amino ketone hydrochloride a 35% yield of amino alcohol hydrochloride was obtained. The product separated from methanol-ether as clusters of colorless needles which melted at 234–235° dec. (corr.)

Anal. Calc'd for $C_{21}H_{28}ClNO_2$: C, 69.7; H, 7.8.
Found: C, 69.2; H, 8.0.

SUMMARY

A series of amino alcohols derived from tetrahydrophenanthrene, and carrying the side chain $-CHOHCH(CH_3)NR_2$ in position 9 has been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

[6] This compound was prepared by Dr. S. Morris Kupchan, Columbia University.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

ATTEMPTS TO FIND NEW ANTIMALARIALS. VIII.[1] PHENYL β-D-GLUCOTHIOSIDES, DIPHENYL DISULFIDES, PHENYL THIOCYANATES, AND RELATED COMPOUNDS

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During the course of our investigations on the action of alkali on phenyl glycosides (1) an opportunity arose to have several of these compounds subjected to the screening tests for antimalarial activity. Although none of the O-glucosides was found to possess any appreciable activity, an S-glucoside, namely, phenyl β-D-glucothioside (SN 5,859),[2] was of relatively low toxicity in chicks (Dr. Nathan B. Eddy, 2) and had a slight effectiveness toward *Plasmodium gallinaceum* (Dr. G. Robert Coatney and Dr. W. Clark Cooper, 3). In order to explore this series, thirteen new glucothiosides were prepared for similar tests. Because the phenyl glucothiosides are hydrolyzable to thiophenols which in turn are readily oxidizable to diphenyl disulfides, and such transformations might occur in the chick, any antimalarial activity attributed to the phenyl glucothiosides might also be shown by the diphenyl disulfides. Some new data on these related disulfides, and descriptions of new phenyl thiocyanates which were prepared as intermediates in the syntheses of thiophenols containing substituted amino groups, are presented in the Experimental Part.

None of the fourteen phenyl β-D-glucothiosides, twelve diphenyl disulfides, six phenyl thiocyanates, or seven related sulfur compounds which we have submitted for testing seems to possess sufficient antimalarial activity, either as a therapeutic or prophylactic agent, to warrant further investigation of these classes of compounds.

EXPERIMENTAL PART

THIOCYANATES

p-Thiocyanodimethylaniline (SN 6,782), of m.p. 72–73°, was prepared from dimethylaniline, ammonium thiocyanate, and bromine in glacial acetic acid by the general method of Kaufmann and Oehring (4), as described by Brewster and Schroeder (5). Diethylaniline was thiocyanated similarly, and the product was isolated by pouring the reaction mixture into water, neutralizing with sodium bicarbonate, and extracting with 40–60° petroleum ether. The extract was washed with water, dried with Drierite, and concentrated to a pale yellow oil. The yield appeared to be practically quantitative. Fichter and Schönmann (6) have described the same product, prepared by an electrochemical method, as a yellow oil boiling at 138° at 1 mm.; its picrate melted at 134°. By the addition of ethyl alcoholic hydrochloric acid to a solution of the free base in anhydrous ether, *p-thiocyanodiethylaniline hydrochloride* (SN 9,148) was obtained; it was recrystallized from a mixture of absolute alcohol and anhydrous ether as plate-like prisms which melted *ca.* 172° to a yellow liquid. The hydrochloride is readily soluble in water, with hydrolysis to oily drops.

[1] For the seventh paper of this series see May and Mosettig, *J. Org. Chem.*, **11**, 296 (1946).

[2] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

Anal. Calc'd for $C_{11}H_{14}N_2S \cdot HCl$: C, 54.42; H, 6.23; N, 11.54.
Found: C, 54.55; H, 6.18; N, 11.46.

p-Thiocyanodi-n-propylaniline hydrochloride (SN 9,522) was prepared in the same manner. It separated from alcohol-ether as prismatic crystals, m.p. *ca.* 174° to a brownish yellow liquid.

Anal. Calc'd for $C_{13}H_{18}N_2S \cdot HCl$: C, 57.65; H, 7.07; N, 10.35.
Found: C, 57.70; H, 6.97; N, 10.27.

p-Thiocyanodi-n-propylaniline was obtained in crystalline form by stirring the hydrochloride into water, and cooling the liberated oily base. It was recrystallized from alcohol by the cautious addition of water. The small flakes melted at 32–33°.

Anal. Calc'd for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.96.
Found: C, 66.71; H, 7.66; N, 11.95.

Although Cherkasova, Sklyarenko, and Mel'nikov (7) were unable to prepare a thiocyanate derivative of dibutylaniline by their electrochemical method, the substance may be obtained readily by the method used above.

p-Thiocyanodi-n-butylaniline hydrochloride (SN 9,149) crystallized from alcohol-ether as acicular prisms which melted *ca.* 143° to a yellow liquid. The crystals are somewhat hygroscopic, become yellow-brown on continued exposure to the light, and hydrolyze in water to oily drops.

Anal. Calc'd for $C_{15}H_{22}N_2S \cdot HCl$: C, 60.28; H, 7.76; N, 9.38.
Found: C, 60.45; H, 7.65; N, 9.22.

p-Thiocyano-N-methyl-N-benzylaniline (SN 10,897) was prepared as above except that the product was extracted with ether instead of petroleum ether. It crystallized from alcohol in colorless plates which were often diamond-shaped, and melted at 68–69°. Kaufmann and Ritter (8) reported it as long, white needles from alcohol, melting at 63°. *p-Thiocyano-N-ethyl-N-benzylaniline* (SN 10,454) separated from alcohol as elongated, fibrous prisms, m.p. 52–53°; Kaufmann and Ritter (8) reported white needles, m.p. 54°. The yields were 75–80%.

1-Amino-2,4-dithiocyanonaphthalene (SN 7,477), m.p. *ca.* 200° (decomp.), was the only product isolated from the thiocyanation of α-naphthylamine, in agreement with the experiences of Kaufmann and Oehring (4). The assignment of the thiocyano groups to the 2 and 4 positions by those authors, and by Likhosherstov and Petrov (9), who prepared the same compound with the aid of dichlorourea and ammonium thiocyanate, appears to be based upon analogy only.

THIOPHENOLS

The *thiophenol*, *p-thiocresol*, and *2-amino-4-chlorothiophenol hydrochloride* were purchased from Eastman Kodak Co. The *4-bromo-*, *4-chloro-*, *2,5-dichloro-*, and *3-chloro-4-methyl-thiophenols* were prepared readily by reduction of the corresponding sulfonyl chloride with excess zinc dust and warm 1:1 aqueous hydrochloric acid, followed by extraction of the product with ether (10); the sulfonyl chlorides were obtained conveniently from the dry sodium sulfonates according to the directions of Baxter and Chattaway (11). The *4-methoxy-*, *4-ethoxy-*, and *4-acetyl-thiophenols* and the *1-thionaphthol* were prepared by the method of Leuckart (12), which consists in adding the appropriate diazotized amino compound to an excess of aqueous potassium ethyl xanthate at 80°, and decomposing the resulting oily xanthate with hot alkali.

The *4-dimethylamino-*, *4-diethylamino-*, *4-dipropylamino-*, and *4-methylbenzylamino-thiophenols* were prepared by reduction of the corresponding thiocyano compounds with metal and acid combinations (13). For the first two, tin and hydrochloric acid were used; the resulting mixture was made just neutral with sodium hydroxide, and the liberated thiophenol was separated by distillation with steam (14). The other two thiocyano compounds were reduced with zinc and hydrochloric acid as illustrated in the following example. To 20 g. of *p*-thiocyano-N-methyl-N-benzylaniline and 200 ml. of 1:1 aqueous hydrochloric acid was added 5 g. of zinc dust, and the mixture warmed to dissolve the zinc. Considerable

yellow material, presumably the disulfide, appeared. Two additional 5-g. portions of zinc dust were added and dissolved before the reduction was judged to be complete. The mixture was cooled, and the colorless solution was decanted from the grayish cake of the zinc and thiophenol compound on the bottom of the flask. This solid was then dissolved by shaking with a mixture of 300 ml. of 30% aqueous sodium hydroxide and 100 ml. of ether. The yellowish ether layer was separated, and the zinc was precipitated by bubbling hydrogen sulfide through the aqueous alkaline solution; the zinc sulfide was removed by centrifuging. The clear, colorless, supernatant liquid was decanted and made barely acid with hydrochloric acid. The liberated pale yellow oil was extracted with ether, the ethereal solution washed with water, dried with Drierite, and concentrated. The yield was 10.8 g.

Although several of the above group of thiophenols have not been described previously, no effort was made to purify or characterize any of them further in view of their generally unpleasant odor and ease of oxidation.

DISULFIDES

Most of the disulfides were prepared readily by oxidizing an alkaline solution of the thiophenol with air, or more rapidly with a slight excess of iodine. The *bis-(4-N-methyl-N-benzylaminophenyl) disulfide* (SN 10,544), however, was obtained directly from the thiocyano compound in 45% yield by the action of alcoholic potassium hydroxide according to Kaufmann and Ritter (8); the product (m.p. 85–86°) crystallized from chloroform-ethyl alcohol as mustard-yellow, chunky prisms rather than in needles as described by those authors. *Bis-(p-dimethylaminophenyl) disulfide* (SN 5,986) was prepared in 30% yield by the interaction of dimethylaniline and sulfur chloride in petroleum ether according to Merz and Weith (15). *Bis-(p-bromophenyl) disulfide* (SN 7,533) was isolated as an intermediate product in the reduction of *p*-bromobenzenesulfonyl chloride by tin and hydrochloric acid. *Bis-(2,5-dichlorophenyl) disulfide* (SN 10,902) was found to melt at 81–82° in agreement with Stewart (16), and not at 129° as reported by de Crauw (17). The *bis-(3-chloro-4-methylphenyl) disulfide* (SN 10,903) appears to be a new substance. Prepared from the thiophenol by oxidation, and recrystallized thrice from methyl alcohol, it formed very pale yellow flakes, m.p. 77–78°.

Anal. Calc'd for $C_{14}H_{12}Cl_2S_2$: C, 53.33; H, 3.84; S, 20.34.
Found: C, 53.39; H, 4.02; S, 20.23.

GLUCOTHIOSIDES

Acetobromoglucose and the desired thiophenol were condensed by alcoholic potassium hydroxide in the presence of an excess of the thiophenol, according to the directions of Purves (18). The yields averaged about 50%, the values depending upon the purity of the thiophenol. Deacetylation of the tetraacetate thus formed was effected catalytically with sodium or barium methoxide. These glucothiosides and their tetraacetyl derivatives are believed to have β-configurations and pyranoid rings because of their method of synthesis from acetobromo-α-D-glucose, and because of their negative rotations; the alkaline degradation of the phenyl- and *p*-dimethylaminophenyl-β-D-glucothiosides to levoglucosan (1b) appears to be strictly analogous to that of the phenyl β-D-glucosides (1a). Because of the low solubility of some of the glucothiosides in water, all specific rotations were determined in pyridine solution. Brief descriptions and analytical data follow.

4-Methylphenyl tetraacetyl-β-D-glucothioside, needles from absolute alcohol; m.p. 118°; $[\alpha]_D^{20}$ −21.0° in chloroform (*c*, 2).

Anal. Calc'd for $C_{21}H_{26}O_9S$: C, 55.50; H, 5.77.
Found: C, 55.46; H, 5.76.

4-Methylphenyl β-D-glucothioside monohydrate (SN 9,159), plates from water; when heated rapidly the compound softens about 95°, and when heated slowly the m.p. 149° refers to the anhydrous form; $[\alpha]_D^{20}$, for the hydrate, −57.0° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{13}H_{18}O_5S \cdot H_2O$: C, 51.30; H, 6.62; H_2O, 5.92.
Found: C, 51.46; H, 6.55; H_2O, 6.02.
Calc'd for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.34.
Found (on sample dried at 70° *in vacuo*): C, 54.48; H, 6.35.

4-Methoxyphenyl tetraacetyl-β-D-glucothioside, prismatic needles from ethyl alcohol; m.p. 101–102°; $[\alpha]_D^{20}$ −28.1° in chloroform (*c*, 1.6).

Anal. Calc'd for $C_{21}H_{26}O_{10}S$: C, 53.61; H, 5.57.
Found: C, 53.64; H, 5.50.

4-Methoxyphenyl β-D-glucothioside monohydrate (SN 10,223), clusters of plates from ethyl alcohol; m.p. 77° when heated rapidly; $[\alpha]_D^{20}$ −51.3° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{13}H_{18}O_6S \cdot H_2O$: C, 48.74; H, 6.29; H_2O, 5.63.
Found: C, 48.70; H, 6.20; H_2O, 5.59.

4-Ethoxyphenyl tetraacetyl-β-D-glucothioside, acicular prisms from absolute alcohol; m.p. 109–111°; $[\alpha]_D^{20}$ −33.1° in chloroform (*c*, 2).

Anal. Calc'd for $C_{22}H_{28}O_{10}S$: C, 54.53; H, 5.82.
Found: C, 54.35; H, 5.94.

4-Ethoxyphenyl β-D-glucothioside monohydrate (SN 10,073), needles from acetone-petroleum ether. The m.p. was 110° when heated rapidly, and 137° when heated slowly; $[\alpha]_D^{20}$ −50.2° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{14}H_{20}O_6S \cdot H_2O$: C, 50.28; H, 6.63; H_2O, 5.39.
Found: C, 50.38; H, 6.64; H_2O, 5.36.

4-Acetylphenyl tetraacetyl-β-D-glucothioside, prismatic needles from absolute alcohol; m.p. 132–133°; $[\alpha]_D^{20}$ −25.6° in chloroform (*c*, 2).

Anal. Calc'd for $C_{22}H_{26}O_{10}S$: C, 54.76; H, 5.43.
Found: C, 54.70; H, 5.44.

4-Acetylphenyl β-D-glucothioside (SN 10,074), fine, short needles from alcohol; m.p. 199°, sintering a few degrees lower; $[\alpha]_D^{20}$ −88.3° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77.
Found: C, 53.39; H, 5.83.

1-Naphthyl tetraacetyl-β-D-glucothioside, needles from absolute alcohol; m.p. 147–148°; $[\alpha]_D^{20}$ −39.7° in chloroform (*c*, 2).

Anal. Calc'd for $C_{24}H_{26}O_9S$: C, 58.76; H, 5.34.
Found: C, 58.90; H, 5.40.

1-Naphthyl β-D-glucothioside (SN 10,222), needles from absolute alcohol; m.p. 197°, sintering from 192°; $[\alpha]_D^{20}$ −76.2° in pyridine (*c*, 2).

Anal. Calc'd for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63.
Found: C, 59.50; H, 5.76.

4-Bromophenyl tetraacetyl-β-D-glucothioside, elongated prisms from absolute alcohol; m.p. 128°; $[\alpha]_D^{20}$ −24.6° in chloroform (*c*, 2).

Anal. Calc'd for $C_{20}H_{23}BrO_9S$: C, 46.25; H, 4.46.
Found: C, 46.17; H, 4.48.

4-Bromophenyl β-D-glucothioside (SN 9,158), acicular prisms from absolute alcohol; m.p. 174–176°; $[\alpha]_D^{20}$ −59.7° in pyridine (*c*, 2).

Anal. Calc'd for $C_{12}H_{15}BrO_5S$: C, 41.03; H, 4.30.
Found: C, 41.14; H, 4.34.

4-Chlorophenyl tetraacetyl-β-D-glucothioside, slender prisms from ethyl alcohol; m.p. 113°; $[\alpha]_D^{20}$ −25.0° in chloroform (*c*, 2).

Anal. Calc'd for $C_{20}H_{23}ClO_9S$: C, 50.58; H, 4.88.
Found: C, 50.56; H, 5.03.

4-Chlorophenyl β-D-glucothioside (SN 9,157), small prisms from alcohol; m.p. 172–175°; $[\alpha]_D^{20}$ −64.7° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{12}H_{15}ClO_5S$: C, 46.98; H, 4.93.
Found: C, 46.84; H, 5.01.

2,5-Dichlorophenyl tetraacetyl-β-D-glucothioside, acicular prisms from absolute alcohol; m.p. 124°; $[\alpha]_D^{20}$ −30.2° in chloroform (*c*, 1.5).

Anal. Calc'd for $C_{20}H_{22}Cl_2O_9S$: C, 47.16; H, 4.35.
Found: C, 47.17; H, 4.36.

2,5-Dichlorophenyl β-D-glucothioside hemihydrate (SN 10,542), needles from ethyl alcohol. The m.p. was 172° when heated not too rapidly; put in the bath at 120°, the compound melted only partially; $[\alpha]_D^{20}$ −96.5° in pyridine (*c*, 2).

Anal. Calc'd for $C_{12}H_{14}Cl_2O_5S \cdot \frac{1}{2} H_2O$: C, 41.15; H, 4.32; H_2O, 2.57.
Found: C, 41.29; H, 4.29; H_2O, 2.59.

3-Chloro-4-methylphenyl tetraacetyl-β-D-glucothioside, elongated prisms from absolute alcohol; m.p. 116°; $[\alpha]_D^{20}$ − 29.6° in chloroform (*c*, 1.7).

Anal. Calc'd for $C_{21}H_{25}ClO_9S$: C, 51.58; H, 5.15.
Found: C, 51.71; H, 5.17.

3-Chloro-4-methylphenyl β-D-glucothioside hemihydrate (SN 10,899), needles from ethyl acetate; m.p. 115°; $[\alpha]_D^{20}$ −59.8° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{13}H_{17}ClO_5S \cdot \frac{1}{2} H_2O$: C, 47.34; H, 5.50; H_2O, 2.73.
Found: C, 47.51; H, 5.57; H_2O, 2.78.
Calc'd for $C_{13}H_{17}ClO_5S$: C, 48.67; H, 5.34.
Found (on sample dried at 80° *in vacuo*): C, 48.67; H, 5.31.

2-Amino-4-chlorophenyl tetraacetyl-β-D-glucothioside, prismatic needles from absolute alcohol; m.p. 169–170°; $[\alpha]_D^{20}$ −24.3° in chloroform (*c*, 3).

Anal. Calc'd for $C_{20}H_{24}ClNO_9S$: C, 49.03; H, 4.94; N, 2.86.
Found: C, 49.09; H, 4.92; N, 2.90.

2-Amino-4-chlorophenyl β-D-glucothioside (SN 10,904), small needles from alcohol; m.p. 170–172; $[\alpha]_D^{20}$ −72.2° in pyridine (*c*, 1.2).

Anal. Calc'd for $C_{12}H_{16}ClNO_5S$: C, 44.79; H, 5.01; N, 4.35.
Found: C, 44.68; H, 5.03; N, 4.42.

2-Acetamino-4-chlorophenyl tetraacetyl-β-D-glucothioside, by acetylation of either of the 2-amino compounds just described, with acetic anhydride and pyridine. Needles from absolute alcohol; m.p. 162–163°; $[\alpha]_D^{20}$ −18.7° in chloroform (*c*, 4).

Anal. Calc'd for $C_{22}H_{26}ClNO_{10}S$: C, 49.67; H, 4.93; N, 2.63.
Found: C, 49.62; H, 4.87; N, 2.81.

4-Dimethylaminophenyl tetraacetyl-β-D-glucothioside, long, slender prisms from alcohol; m.p. 150–151°; $[\alpha]_D^{20}$ −47.0° in chloroform (*c*, 1.2).

Anal. Calc'd for $C_{22}H_{29}NO_9S$: C, 54.64; H, 6.05; N, 2.90.
Found: C, 54.48; H, 5.88; N, 2.89.

4-Dimethylaminophenyl β-D-glucothioside monohydrate (SN 6,773), small plates from alcohol; m.p. 116° when heated rapidly, and as high as 140° when heated slowly; $[\alpha]_D^{20}$ −52.0° in pyridine (*c*, 1.2).

Anal. Calc'd for $C_{14}H_{21}NO_5S \cdot H_2O$: C, 50.43; H, 6.95; N, 4.20; H_2O, 5.40.
Found: C, 50.47; H, 7.10; N, 4.16, 4.27; H_2O, 5.44.

4-Diethylaminophenyl tetraacetyl-β-D-glucothioside, many-sided prisms from absolute alcohol; m.p. 141–142°; $[\alpha]_D^{20}$ −43.7° in chloroform (*c*, 2).

Anal. Calc'd for $C_{24}H_{33}NO_9S$: C, 56.34; H, 6.50; N, 2.74.
Found: C, 56.23; H, 6.51; N, 2.70.

4-Diethylaminophenyl β-D-glucothioside monohydrate (SN 7,479), small prisms from alcohol; m.p. 162–163° when heated slowly; $[\alpha]_D^{20}$ −51.5° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{16}H_{25}NO_5S \cdot H_2O$: C, 53.16; H, 7.53; N, 3.88; H_2O, 4.99.
Found: C, 53.31; H, 7.43; N, 3.91; H_2O, 4.93.
Calc'd for $C_{16}H_{25}NO_5S$: C, 55.95; H, 7.34; N, 4.08.
Found (on sample dried at 80° *in vacuo*): C, 55.87; H, 7.22; N, 4.14.

4-Di-n-propylaminophenyl tetraacetyl-β-D-glucothioside, small needles from alcohol; m.p. 121–122°; $[\alpha]_D^{20}$ −43.7° in chloroform (*c*, 2).

Anal. Calc'd for $C_{26}H_{37}NO_9S$: C, 57.87; H, 6.91; N, 2.60.
Found: C, 58.04; H, 6.84; N, 2.66.

4-Di-n-propylaminophenyl β-D-glucothioside monohydrate (SN 11,578), plates from water; m.p. 58° when heated rapidly, higher when heated more slowly; $[\alpha]_D^{20}$ −47.9° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{18}H_{29}NO_5S \cdot H_2O$: C, 55.50; H, 8.02; N, 3.60; H_2O, 4.63.
Found: C, 55.56; H, 7.95; N, 3.65; H_2O, 4.60.
Calc'd for $C_{18}H_{29}NO_5S$: C, 58.19; H, 7.87.
Found (on sample dried at 65° *in vacuo*): C, 58.43; H, 7.80.

4-(N-Methyl-N-benzylamino)phenyl tetraacetyl-β-D-glucothioside, needles from alcohol; m.p. 120–121°; $[\alpha]_D^{20}$ −43.3° in chloroform (*c*, 2).

Anal. Calc'd for $C_{28}H_{33}NO_9S$: C, 60.09; H, 5.94; N, 2.50.
Found: C, 60.08; H, 6.10; N, 2.49.

4-(N-Methyl-N-benzylamino)phenyl β-D-glucothioside (SN 10,905), aggregates of prisms from alcohol; m.p. 133–134°; $[\alpha]_D^{20}$ −66.3° in pyridine (*c*, 1.2).

Anal. Calc'd for $C_{20}H_{25}NO_5S$: C, 61.35; H, 6.44; N, 3.58.
Found: C, 61.40; H, 6.37; N, 3.41.

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SUMMARY

Fourteen new aromatic β-D-glucothiosides and their tetraacetates, three new phenyl thiocyanates, and one new diphenyl disulfide have been described. Thirty-nine members of these and closely related types of sulfur compounds have been submitted to screening tests for antimalarial activity. While many of these substances have an appreciable effect upon *Plasmodium gallinaceum*, none is of sufficiently high activity to warrant further study, either as a therapeutic or prophylactic agent.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF LADY ESTHER, LTD.]

ATTEMPTS TO FIND NEW ANTIMALARIALS IX DERIVATIVES OF PHENANTHRENE, I. AMINO ALCOHOLS OF THE TYPE —CHOHCH$_2$NR$_2$, DERIVED FROM 9-BROMOPHENANTHRENE

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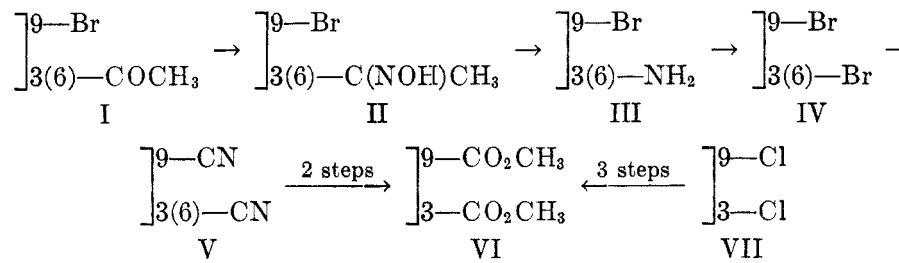
The synthesis of this and the following series of phenanthrylamino alcohols was carried out as part of a program outlined at the National Institute of Health, Bethesda, Md. Studies by May and Mosettig (1) have shown that the antimalarial activity of various phenanthrylamino alcohols is enhanced by the introduction of a chlorine atom into the phenanthrene nucleus.

9-Bromo-3- (or -6-) acetylphenanthrene, prepared first by Mosettig and van de Kamp (2), appeared to be a convenient starting material for the synthesis of halogenated amino alcohols different from those to be described by May and Mosettig. In the course of our investigations we succeeded in differentiating between positions 3 and 6 as the location of the acetyl group and assign to this compound the structure of 9-bromo-3-acetylphenanthrene (I) on the basis of the reactions indicated in the scheme below:



The amine (III) obtained by Beckmann rearrangement of oxime (II) was diazotized and converted to dibromophenanthrene (IV) and the latter transformed, *via* the dicyano derivative (V), to the diester (VI). The structure of the latter is established by its formation from 3,9-dichlorophenanthrene. This compound was prepared by reactions completely analogous to those used to prepare the dibromophenanthrene (IV) (3). It corresponded to the 3,9-dichlorophenanthrene prepared by Sandquist (4). Further conclusive proof was later obtained by total synthesis of 3,9-dicyanophenanthrene (3).

In this communication we describe the synthesis of a complete series of amino alcohols of type VIII. In the preparation of these amino alcohols we employed essentially the procedures of Mosettig and van de Kamp (5) and the Malaria Research Group at the National Institute of Health. Since elimination of the

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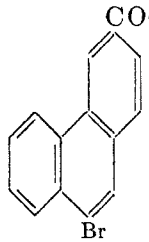
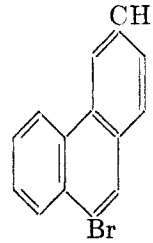
nuclear bromine can be expected in the catalytic reduction of the amino ketones to amino alcohols, the aluminum isopropoxide reduction method of Meerwein-Ponndorf-Verley as modified by Lund (6) was used in this step:



$\rightarrow$ —$COCH_2Br$ $\rightarrow$ —$COCH_2NR_2$ $\rightarrow$

I



VIII

TABLE I[5]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

SN	$C_{14}H_8$ {9-Br, 3-$CHOHCH_2$—}	Q
9464	$N(CH_3)_2$	$\frac{1}{8}$
8953	$N(C_2H_5)_2$	$\frac{1}{8}$
9821	$N(C_3H_7)_2$	$\frac{1}{4}$
8954	$N(C_4H_9)_2$	$\frac{1}{2}$
9467	$N(C_5H_{11})_2$	$\frac{1}{2}$
9468	$N(C_6H_{13})_2$	$\frac{1}{4}$
9469	$N(C_7H_{15})_2$	$\frac{1}{2}$
8952	$N(C_8H_{17})_2$	$\frac{1}{16}$
8951	$N(C_9H_{19})_2$	—
8950	$N(C_{10}H_{21})_2$	—

The amino alcohols of this group, when compared with the analogous bromine-free derivatives, the phenanthryl-3-amino alcohols (7), are more toxic (8). In regard to effectiveness against *Plasmodium gallinaceum*, they are superior to the bromine-free analogs (9). The corresponding amino ketones[6] are devoid of thera-

[5] In Table I are listed the compounds which were submitted for biological investigation. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "Quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine. A dash indicates that the equivalent is less than $\frac{1}{16}$. All compounds listed in the table were administered as hydrochlorides.

[6] The Survey Numbers (SN) of these drugs may be found in Table II.

peutic effect. None of the drugs showed any activity towards sporozoite-induced *gallinaceum* malaria (9).

EXPERIMENTAL[7]

9-Bromophenanthrene. This was prepared according to the directions of May and Mosettig (10). In the recrystallization, isopropanol was employed. The phenanthrene used was purified by partial oxidation with chromic acid followed by vacuum distillation and crystallization from alcohol (11, 12). Material so treated had the melting point 97–99°.

3-Acetyl-9-bromophenanthrene (2). To a mixture of 350 g. of 9-bromophenanthrene and 2620 cc. of carbon disulfide cooled to 5° in a 5-liter three-necked flask equipped with a liquid-sealed stirrer and vented through a calcium chloride tube, was added 128 cc. of acetyl chloride. Five hundred twenty-six grams of anhydrous aluminum chloride was added gradually with stirring and cooling, maintaining the temperature at 5°. The temperature was then allowed to rise slowly to room temperature (never above 30°) over a period of 2–3 hours. The reaction mixture, at first dark green, slowly turned to light brown. Stirring was continued another 2–4 hours (total reaction time about 6 hours) after which the evolution of hydrogen chloride had practically ceased.

The precipitate was filtered and washed several times with carbon disulfide. The separated addition product was combined with that from a second preparation (also using 350 g. of 9-bromophenanthrene).

The decomposition of the addition product from the acetylation of 700 g. of 9-bromophenanthrene (in two runs) was carried out in a 20-liter Pyrex crock equipped with a stirrer. In it was placed 3000 cc. of chloroform, 450 cc. of conc'd hydrochloric acid, and 2000 g. of ice. The addition complex was added in small portions with vigorous stirring, more ice being added as needed to keep the reaction under control. After decomposition was complete, the chloroform layer was syphoned off and the aqueous layer extracted twice with chloroform. The combined chloroformic solutions were washed once with dilute hydrochloric acid and twice with water, clarified by boiling with carbon, filtered, and evaporated to dryness.

The residual brownish crystalline mass was crystallized from acetone (1450 cc. for each 100 g. of crude material) using charcoal. In this way 305 g. of colorless needles, m.p. 150–151° was obtained. On concentration, the mother liquors yielded 101 g. of less pure material, m.p. 141–149°, and a third crop of 90 g., m.p. 128–148°. Recrystallization of the second and third crop material yielded a further 140 g. of pure 3-acetyl-9-bromophenanthrene, m.p. 150–151° [reported (2) m.p. 150–151°].

3-Acetyl-9-cyanophenanthrene. An intimate mixture of 3 g. of the acetyl compound with 1 g. (1.1 mole) of cuprous cyanide was placed in an oven at 110°. The temperature was allowed to rise to 200–205° over a period of one-half hour with occasional mixing. This temperature was maintained for 1.25 hours and then raised to 250° over a period of one-half hour. After being held at 250° for 40 minutes, the black mass was cooled, pulverized, and extracted with chloroform. The extract was evaporated to dryness and the residue crystallized twice from acetone. Light yellow, halogen-free crystals were obtained, m.p. 220–221°.

Anal. Calc'd for $C_{17}H_{11}NO$: N, 5.71. Found: N, 5.71.

3-Acetyl-9-bromophenanthrene oxime (2). To a solution of 100 g. of 3-acetyl-9-bromophenanthrene in hot dioxane was added a solution of 55 g. of hydroxylamine hydrochloride in 220 cc. of 10% aqueous sodium hydroxide. Three hundred and seventy-five cubic centimeters of hot 25% alcohol was added and the resulting clear solution heated on the steam-bath for four hours. Hot water was then added to incipient turbidity and the solution

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[7] All analyses except ionizable halogens reported in this paper and in subsequent papers of this series were done by Dr. T. S. Ma.

allowed to cool to room temperature overnight while the oxime crystallized as colorless needles. The yield was 101 g. (96%), m.p. 212–213.5°.[8]

Anal. Calc'd for $C_{16}H_{12}BrNO$: N, 4.46. Found: N, 4.25.

3-Amino-9-bromophenanthrene. The procedure of Bachmann and Boatner (13) was followed for the rearrangement of the oxime and subsequent hydrolysis. The hydrochloride of the 3-amino-9-bromophenanthrene was not very soluble in water, however, and the method of isolation was modified accordingly.

To a suspension of 90 g. of 3-acetyl-9-bromophenanthrene oxime in 1450 cc. of dry benzene was added 90 g. of phosphorus pentachloride. The mixture was then refluxed for 20 minutes, after which evolution of hydrogen chloride had ceased and a clear solution remained.

The solution was cooled, hydrolyzed by shaking with 1000 cc. of water, and the precipitated product filtered off and washed with water. The benzene layer of the filtrate was washed with water, evaporated to dryness, and the residue added to the precipitate of crude acetylamino-9-bromophenanthrene.

The crude acetylamino compound was hydrolyzed by refluxing with 3600 cc. of alcohol and 126 cc. of concentrated hydrochloric acid (mechanical stirring was employed to avoid lumping). After refluxing for 24 hours, the suspension was cooled and the amine hydrochloride filtered off. The filtrate was concentrated and a second crop of amine hydrochloride obtained, which was added to the first.

The crude amine hydrochloride was suspended in 1000 cc. of water and 1000 cc. of ether. Sufficient 25% aqueous sodium hydroxide was added to make the aqueous layer alkaline to phenol red, and the suspension shaken mechanically for 30 minutes, adding sodium hydroxide solution as necessary to maintain a slight excess.

The remaining insoluble material was filtered off and discarded. The ether layer of the filtrate was separated and the aqueous layer extracted again with ether. The combined ethereal solutions were washed with water, dried over sodium sulfate, and acidified with alcoholic hydrogen chloride. The precipitated amine hydrochloride was filtered, washed with ether, and dried.

The 3-amino-9-bromophenanthrene obtained from the hydrochloride was crystallized from benzene-hexane as buff-colored needles; yield 61.5 g. (71%); m.p. 112.5–113°.

Anal. Calc'd for $C_{14}H_{10}BrN$: N, 5.15. Found: N, 5.37.

3-Acetylamino-9-bromophenanthrene. The 3-amino-9-bromophenanthrene was acetylated with acetyl chloride in benzene in the presence of pyridine. On recrystallization from alcohol, the acetyl derivative was obtained as colorless prisms, m.p. 220.5–221.5°.

Anal. Calc'd for $C_{16}H_{12}BrNO$: N, 4.46. Found: N, 4.37.

3,9-Dibromophenanthrene. The 3-amino-9-bromophenanthrene was diazotized by a modification of the method of Misslin (14) and the diazonium salt converted to dibromophenanthrene by Schwechten's modification of the Sandmeyer reaction (15). To a solution of 5 g. of 3-amino-9-bromophenanthrene in 50 cc. of concentrated sulfuric acid cooled to 10° was added a solution of 3.5 g. of sodium nitrite in 35 cc. of concentrated sulfuric acid. The temperature was maintained at 8–10° while 250 cc. of glacial acetic acid was added slowly with stirring. The solution was maintained at 10° for one-half hour after all the acetic acid had been added and then diluted to *ca.* 600 cc. with ice and water, still holding the temperature at 10°. Five grams of urea was added and stirring continued for an additional half hour. A solution of 27.5 g. of mercuric bromide and 27.5 g. of potassium bromide in 100 cc. of water was added and stirring continued for another half hour. The suspension was held at *ca.* 5° in the refrigerator overnight, the precipitate filtered off, washed with cold water, and dried in a vacuum desiccator.

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[8] Mosettig and van de Kamp (2) report for this oxime m.p. 142.5–143° (uncorr.) while we find the oxime to melt at 212–213.5°. Dr. Mosettig informs us (private communication) that their oxime was prepared in methanolic solution. In repeating this preparation he is able to obtain either oxime depending on whether methanol or dioxane is used as solvent. He suggests that cis-trans isomerism accounts for this discrepancy. The semicarbazone was prepared and found to have the melting point recorded.

The dried double salt was intimately mixed with twice its weight of potassium bromide and decomposed in a beaker heated over a low flame. The residue was extracted with hot water and taken up in warm benzene and the benzene solution filtered. The solvent was evaporated and the residue distilled *in vacuo*, b.p. 220–230° at 6–7 mm. The distillate was crystallized from benzene-alcohol, yielding 3.5 g. (57%) of colorless needles, m.p. 144–145°. Sandquist reported 143–143.5° (4).

3,9-Dicyanophenanthrene. An intimate mixture of 1 g. of 3,9-dibromophenanthrene with 1 g. of cuprous cyanide was heated for 3 hours at 295–300° in a sealed tube. The reaction product was cooled, pulverized, and shaken with a mixture of ammonium hydroxide and chloroform. The chloroformic solution was treated with charcoal, filtered, and evaporated to dryness. The residue was recrystallized three times from toluene to yield 0.54 g. (79%) of colorless needles, m.p. 285–286°.

Anal. Calc'd for $C_{16}H_8N_2$: C, 84.3; H, 3.51; N, 12.2.
Found: C, 84.35; H, 3.21; N, 12.39.

Phenanthrene-3,9-dicarboxylic acid. A suspension of 0.2 g. of 3,9-dicyanophenanthrene in 20 cc. of a 25% methanolic potassium hydroxide solution was refluxed for 10 hours, during which ammonia was evolved and a clear solution was obtained. The solution was diluted with water, acidified, and the precipitate filtered off and washed with water. The crude 3,9-dicarboxylic acid was converted to the dipotassium salt which was crystallized from methanol-acetone, then reconverted to the free acid. After drying in a vacuum desiccator, the purified acid remained as a light yellow powder, m.p. above 330°.

Anal. Calc'd for $C_{16}H_{10}O_4$: Neut. Equiv., 133. Found: Neut. Equiv., 136.7.

Phenanthrene-3,9-dicarboxylic acid dimethyl ester. A suspension of 0.1 g. of the dicarboxylic acid in 10 cc. of methanol containing 0.18 g. of concentrated sulfuric acid was refluxed for 8 hours, when a clear solution was obtained. On cooling, the ester separated in the form of colorless needles. Two recrystallizations from methanol yielded 0.05 g. of colorless needles, m.p. 126.6–127.5°.

Anal. Calc'd for $C_{18}H_{14}O_4$: C, 73.5; H, 4.76.
Found: C, 73.47; H, 4.56.

3-Bromoacetyl-9-bromophenanthrene. To a well-stirred suspension of 60 g. of 3-acetyl-9-bromophenanthrene in 225 cc. of anhydrous ether at 30° was added a few drops of bromine in chloroform. After the bromine was consumed, the temperature was gradually lowered to 12° while adding bromine in chloroform. The bromination was completed at 12°, a total of 33 g. of bromine in 150 cc. of chloroform being added. The stirring was continued for 15 minutes after all the bromine had been added, and the reaction mixture was chilled for one hour. The sludge was filtered off, and washed with cold ether. The mother liquor and washings were combined, washed with water to remove hydrogen bromide, dried over sodium sulfate, and concentrated to about 75 cc. An equal volume of petroleum ether (35–60°) was added, the mixture chilled, and a second crop of crude product obtained. This was combined with the original precipitate and the whole recrystallized from dioxane-methanol. The crystals obtained melted at 131–133°. Further crystallization yielded colorless needles, m.p. 133–134°. The total yield from the bromination of 276 g. of 3-acetyl-9-bromophenanthrene was 282 g. (80.8%).

Anal. Calc'd for $C_{16}H_{10}BrO$: Br, 42.29. Found: Br, 42.29.

3-(2-Dialkylamino-1-oxoethyl)-9-bromophenanthrene hydrochlorides. A mixture of 53 g. (0.14 mole) of 3-α-bromoacetyl-9-bromophenanthrene, 0.28 mole of dialkylamine,[9] and 150 cc. of benzene was shaken for 30 minutes, 200 cc. of dry ether was added, the mixture shaken again for 10 minutes, and chilled for two hours. Filtration yielded about 0.135 mole of dialkylammonium bromide (96%). The filtrate was acidified with alcoholic hydrogen chloride and chilled, whereby the crude amino ketone hydrochloride precipitated. Recrystallization from the appropriate solvent (see Table II) yielded the pure compound in the form of colorless needles.

[9] We are indebted to Dr. R. C. Elderfield, Columbia University, for the amines used in the work reported here, and in the subsequent papers of this series.

3-(2-Dialkylamino-1-hydroxyethyl)-9-bromophenanthrene hydrochloride. A mixture of 0.0366 mole of 3-(2-dialkylamino-1-oxoethyl)-9-bromophenanthrene hydrochloride, 22.5 g.

TABLE II

3-(2-DIALKYLAMINO-1-OXO-ETHYL)-9-BROMOPHENANTHRENE HYDROCHLORIDES[a]

SN	ALKYL GROUP	SOLVENT	M.P., °C.	FORMULA	YIELD, %	IONIZABLE Cl, %		N, %	
						Calc'd	Found	Calc'd	Found
13307	CH_3	Methanol-dioxane ether	226–229	$C_{18}H_{17}BrClNO$	55	9.38	9.35	3.70	3.66
9061	C_2H_5	Methanol-dioxane ether	220–221	$C_{20}H_{21}BrClNO$	70	8.72	8.75	3.46	3.42
10403	C_3H_7	Methanol-ether	223–225	$C_{22}H_{25}BrClNO$	68	8.18	8.34	3.23	3.20
9471	C_4H_9	Methanol-acetone ether	195–198	$C_{24}H_{29}BrClNO$	65	7.67	7.59	3.03	3.15
10125	C_5H_{11}	Isopropanol	185–187	$C_{26}H_{33}BrClNO$	63	7.24	7.27	2.85	3.01
14448	C_6H_{13}	Isopropanol	153–157	$C_{28}H_{37}BrClNO$	45	6.85	6.93	2.69	2.57
	C_7H_{15}	Acetone-methanol ether	142–144	$C_{30}H_{41}BrClNO$	35	6.49	6.55	2.56	2.76
9060	C_8H_{17}	Acetone	129–130.5	$C_{32}H_{45}BrClNO$	65	6.21	6.31	2.45	2.46
9477	C_9H_{19}	Acetone	128–133.5	$C_{34}H_{49}BrClNO$	60	5.89	6.00	2.32	2.29
9476	$C_{10}H_{21}$	Acetone	122–126	$C_{36}H_{53}BrClNO$	65	5.63	5.58	2.22	2.25

[a] All compounds colorless needles.

TABLE III

3-(2-DIALKYLAMINO-1-HYDROXY-ETHYL)-9-BROMOPHENANTHRENE HYDROCHLORIDES[a]

ALKYL GROUP	SOLVENT	M.P., °C.	FORMULA	YIELD %	IONIZABLE Cl, %		N, %	
					Calc'd	Found	Calc'd	Found
CH_3	Absolute alcohol	227–230	$C_{18}H_{19}BrClNO$	83	9.34	9.53	3.68	3.29
C_2H_5	Methanol-dioxane-ether	195–195.5	$C_{20}H_{23}BrClNO$	70	8.70	8.75	3.46	3.42
C_3H_7	Methanol-acetone-ether	210–211	$C_{22}H_{27}BrClNO$	88	8.21	8.24	3.24	3.14
C_4H_9	Alcohol-ether	198–198.5	$C_{24}H_{31}BrClNO$	85	7.70	7.59	3.04	2.87
C_5H_{11}	Isopropanol	198–199	$C_{26}H_{35}BrClNO$	68	7.21	7.16	2.84	2.83
C_6H_{13}	Isopropanol	156–157.5	$C_{28}H_{39}BrClNO$	84	6.81	6.84	2.69	2.93
C_7H_{15}	Acetone	131.5–133	$C_{30}H_{43}BrClNO$	80	6.47	6.45	2.55	2.60
C_8H_{17}	Acetone	131–132.5	$C_{32}H_{47}BrClNO$	85	6.21	6.13	2.45	2.56
C_9H_{19}	Acetone	127.5–128.5	$C_{34}H_{51}BrClNO$	86	5.87	5.90	2.31	2.29
$C_{10}H_{21}$	Ethyl - acetate or isopropanol-ether	126.5–128	$C_{36}H_{55}BrClNO$	65	5.62	5.52	2.21	2.27

[a] All compounds colorless needles.

(0.11 mole) of aluminum isopropoxide, and 450 cc. of isopropanol was distilled slowly through a 10-ball Snyder column. Acetone was detected in the distillate only for the first

2 hours, but the distillation of the isopropanol was continued for 3.25 hours. The remaining isopropanol was then removed by distillation *in vacuo* from a water-bath at 50–55°. The residue was diluted with ether, a solution of 45 g. of citric acid in about 100 cc. of water was added, and the solution made alkaline to phenol red with 25% sodium hydroxide solution. The ether was separated, the aqueous portion extracted with ether and discarded. The combined ether extracts were washed with water, dried over sodium sulfate, acidified with alcoholic hydrogen chloride, and chilled to complete precipitation. The yield of crude carbinol was almost quantitative. Purification was effected by crystallization from the appropriate solvent (see Table III).

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SUMMARY

1. A homologous series of 3-(2-dialkylamino-1-oxoethyl)-9-bromophenanthrenes has been synthesized.

2. Each of these amino ketones has been reduced to the corresponding amino carbinol.

3. The evaluation as antimalarials of the amino alcohols and amino ketones described herein is discussed.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF LADY ESTHER, LTD.]

ATTEMPTS TO FIND NEW ANTIMALARIALS. X. DERIVATIVES OF —PHENANTHRENE, II. AMINO ALCOHOLS OF THE TYPE —CHOHCH(CH_3)NR_2 AND AMINO KETONES OF THE TYPE $COCH_2CH_2NR_2$ DERIVED FROM 9-BROMOPHENANTHRENE

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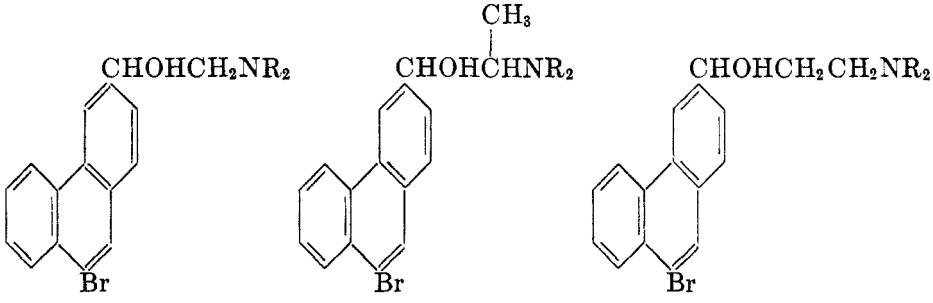
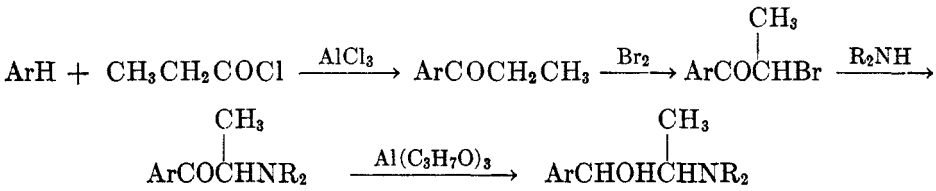
In the extension of the series of 9-bromophenanthryl amino alcohols of type I (1), we decided to synthesize the corresponding compounds of type II and III.



I II III

The synthesis of the propanolamines of type II offered no difficulties and proceeded according to the scheme:



where Ar = 9-bromophenanthryl. As was expected, the exchange of bromine in the α-bromopropionyl-9-bromophenanthrene with aliphatic amine proved to be considerably more sluggish than in the case of the corresponding α-bromoacetyl compound (1). It was necessary to reflux the reaction mixture with excess amine for some time to complete the conversion. The removal of the excess aliphatic amine from the amino ketone was effected by fractional precipitation of the hydrochlorides from ether.

The structure of the propionyl-9-bromophenanthrene was proved by oxidation of the propionyl group to yield the same carboxylic acid as 3-acetyl-9-bromophenanthrene, the structural proof of which is reported in other papers of this series

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(1, 2). Oxidation of the 3-propionyl-9-bromophenanthrene with sodium hypochlorite was unsuccessful but proceeded with 3-α-bromopropionyl-9-bromophenanthrene.[5] The 9-bromo-3-phenanthroic acid obtained was identified by conversion to the methyl ester, which was shown by direct comparison to be identical with that prepared by Mosettig and van de Kamp (3).

As in the foregoing communication, reduction of the amino ketones was effected with aluminum isopropoxide to prevent loss of bromine. In this series, two diastereoisomeric amino alcohols can be expected. We isolated both forms of the 3-(2-dimethylamino-1-hydroxypropyl)-9-bromophenanthrene in crystalline form. However, only one form of the other members of the series was found.

We intended to prepare the amino alcohols of type III by reduction of the corresponding amino ketones. The latter were prepared by the Mannich reaction (4) from 9-bromo-3-acetylphenanthrene (1). Preliminary trials were unsuccessful. Using isoamyl alcohol as solvent, as suggested by van de Kamp and Mosettig (5), gave no results. The desired compounds, however, were obtained in satisfactory yields when benzene was employed, according to the modification of Fry (6). Unfortunately, we were not able to find the conditions under which these ketones could be reduced. In hydrogenation, using noble catalysts, the nuclear bromine atom is attacked and the amino group is split off to some extent. This result could not be obviated by reduction in the presence of hydrogen bromide, the addition of which appeared to poison the catalyst. In the aluminum isopropoxide reduction, splitting and other decomposition processes were found to take place, aliphatic amine being removed.

The toxicity of the propanolamines is somewhat lower than that of the corresponding ethanolamines (7). Their effectiveness towards *Plasmodium gallinaceum*, throughout the series [from $-N(C_2H_5)_2$ to $-N(C_{10}H_{21})_2$], is decidedly lower (8). Only the dibutylamino alcohol (SN 10226), the diamylamino alcohol (SN 10893), and the dihexylamino alcohol (SN 10892) show weak activity ($Q\frac{1}{8}$, $\frac{1}{8}$, $\frac{1}{16}$). All amino ketones are therapeutically inactive. None of the drugs showed any activity towards sporozoite-induced *gallinaceum* malaria (8).[6]

EXPERIMENTAL

3-Propionyl-9-bromophenanthrene. To a mixture of 450 g. of 9-bromophenanthrene and 3800 cc. of carbon disulfide cooled to 5° in a 5-liter three-necked flask equipped with a liquid-sealed stirrer and vented through a calcium chloride tube, was added 208 cc. of propionyl chloride. Six hundred seventy-five grams of anhydrous aluminum chloride was then added slowly with stirring and cooling, maintaining the temperature at 5°. After all the aluminum chloride had been added, the temperature was allowed to rise slowly to room temperature (never above 30°) over a period of 2–3 hours. The reaction mixture, at first dark green, slowly turned light brown. Stirring was continued another 3–4 hours (total reaction time about 6 hours) after which the evolution of hydrogen chloride had practically ceased. The precipitate was filtered and washed several times with carbon disulfide.

The decomposition of the addition product from the propionylation of 900 g. of 9-bromo-

[5] Subsequently it was found that the hypochlorite oxidation of acylphenanthrenes proceeds smoothly in the presence of pyridine (2).

[6] The Survey Numbers (SN) of all the drugs which have been submitted to biological tests are given in the Experimental Part (Tables I, II, and III).

phenanthrene (in two runs) was carried out in a 20-liter Pyrex crock equipped with a stirrer. In it was placed 3000 cc. of chloroform, 150 cc. of conc'd hydrochloric acid, and 2000 g. of ice. The addition complex was added in small portions with vigorous stirring, more ice being added as needed to keep the reaction under control. After decomposition was complete, the chloroform layer was removed and the aqueous layer extracted twice with chloroform. The combined chloroformic solutions were washed once with dilute hydrochloric acid and twice with water, clarified by boiling with carbon, filtered, and evaporated to dryness. The residual brownish crystalline mass was crystallized twice from acetone to yield 550 g. (50%) of colorless needles, m.p. 116–117°.

Anal. Calc'd for $C_{17}H_{14}BrO$: C, 65.15; H, 4.15.
Found: C, 65.58; H, 4.54.

Oxime of 3-propionyl-9-bromophenanthrene. The oxime was prepared by reaction with hydroxylamine hydrochloride in dilute alcohol in the presence of sodium acetate. Colorless needles were obtained by recrystallization from alcohol, m.p. 166.5–167°.

TABLE I

3-(2-DIALKYLAMINO-1-OXOPROPYL)-9-BROMOPHENANTHRENE HYDROCHLORIDES[a]

SN	ALKYL GROUP	SOLVENT	M.P., °C.	FORMULA	YIELD, %	IONIZABLE Cl, %		N, %	
						Calc'd	Found	Calc'd	Found
	CH_3	Methanol-dioxane-ether	227–227.5	$C_{19}H_{19}BrClNO$	94	9.04	9.16	3.56	3.47
10445	C_2H_5	Methanol-acetone-ether	209–210.5	$C_{21}H_{23}BrClNO$	67	8.44	8.42	3.33	3.15
	C_3H_7	Methanol-acetone-ether	209–212	$C_{23}H_{27}BrClNO$	67	7.93	7.99	3.12	2.96
10444	C_4H_9	Methanol-acetone-ether	214.5–216.5	$C_{25}H_{31}BrClNO$	68	7.40	7.50	2.94	2.78
	C_5H_{11}	Acetone	155–156	$C_{27}H_{35}BrClNO$	59	7.05	7.14	2.78	2.92
	C_6H_{13}	Methanol-acetone-ether	164–165.5	$C_{29}H_{39}BrClNO$	53	6.65	6.71	2.63	2.64
	C_7H_{15}	Acetone	149.5–151.5	$C_{31}H_{43}BrClNO$	30	6.30	6.33	2.50	2.67
	C_8H_{17}	Acetone	134.0–137.0	$C_{33}H_{47}BrClNO$	82	6.03	5.88	2.37	2.38
10443	C_9H_{19}	Acetone	125.0–126.0	$C_{35}H_{51}BrClNO$	61	5.75	5.83	2.27	2.46
	$C_{10}H_{21}$	Acetone	116–118.5	$C_{37}H_{55}BrClNO$	70	5.50	5.63	2.16	2.17

[a] All compounds colorless needles.

Anal. Calc'd for $C_{17}H_{14}BrNO$: N, 4.27. Found: N, 4.09.

3-α-Bromopropionyl-9-bromophenanthrene. To a well-stirred suspension of 40 g. of 3-propionyl-9-bromophenanthrene in 600 cc. of absolute ether at 30° was added a few drops of a solution of bromine in chloroform. When decolorization had taken place, the mixture was cooled to 12° and 20.4 g. of bromine dissolved in 60 cc. of chloroform added as rapidly as it was taken up. Stirring was continued for 15 minutes after all the bromine had been added. The mixture was chilled to 0° for one hour and the precipitated bromo ketone filtered and washed with cold ether. The crude 3-α-bromopropionyl-9-bromophenanthrene was obtained as pale pink needles; yield 45 g. (90%), m.p. 166–168°.

Anal. Calc'd for $C_{17}H_{12}Br_2O$: Br, 40.8. Found: Br, 40.54.

3-(2-Dialkylamino-1-oxopropyl)-9-bromophenanthrene hydrochlorides. A mixture of 20 g

(0.051 mole) of 3-α-bromopropionyl-9-bromophenanthrene, 0.153 mole of dialkylamine, and 120 cc. of benzene was refluxed for 3.5 hours. After cooling to room temperature, the reaction mixture was filtered to remove precipitated dialkylammonium bromide. The filtrate was washed with dilute sodium carbonate solution, then with water. The benzene was removed by steam distillation *in vacuo*, the temperature being held below 45°. The residue was taken up in ether, and the ethereal solution dried over sodium sulfate and filtered. The solution at this point had a volume of about 500 cc. Alcoholic hydrogen chloride (10 *N*) was added slowly from a burette until the *p*H, indicated by a drop of solution on "Hydrion A" test paper, changed from about 9 to about 6. This change is quite sharp and appears to correspond to neutralization of the dialkylamine. The mixture was allowed to stand at room temperature for one-half hour with frequent shaking, then chilled for three hours. The precipitated dialkyalmine hydrochloride was filtered off, leaving fairly pure amino ketone in solution.

TABLE II

3-(2-DIALKYLAMINO-1-HYDROXYPROPYL)-9-BROMOPHENANTHRENE HYDROCHLORIDES[a]

SN	ALKYL GROUP	SOLVENT	M.P., °C.	FORMULA	YIELD, %	IONIZABLE Cl, %		N %	
						Calc'd	Found	Calc'd	Found
	CH_3	Methanol	261–262.5	$C_{19}H_{21}BrClNO$	23.5	8.99	8.97	3.55	3.74
			249–250		53.5	8.99	8.94	3.55	3.46
10438	C_2H_5	Methanol acetone-ether	204–205.5	$C_{21}H_{25}BrClNO$	69	8.40	8.21	3.32	3.63
10439	C_3H_7	Methanol acetone-ether	228–229	$C_{23}H_{29}BrClNO$	71	7.92	7.88	3.11	2.74
10226	C_4H_9	Methanol acetone-ether	186.5–188.0	$C_{25}H_{33}BrClNO$	65	7.43	7.59	2.93	2.70
10893	C_5H_{11}	Methanol acetone-ether	189–190.	$C_{27}H_{37}BrClNO$	83	7.00	7.03	2.76	2.66
10892	C_6H_{13}	Acetone	136.5–137.5	$C_{29}H_{41}BrClNO$	74	6.64	6.64	2.62	2.63
10894	C_7H_{15}	Acetone	147.0–148.0	$C_{31}H_{45}BrClNO$	71	6.30	6.33	2.49	2.55
10440	C_8H_{17}	Acetone-ether	143.5–144.0	$C_{33}H_{49}BrClNO$	77	6.01	6.02	2.37	2.39
10441	C_9H_{19}	Acetone	144.0–145.0	$C_{35}H_{53}BrClNO$	72	5.74	5.79	2.27	2.35
10442	$C_{10}H_{21}$	Acetone	136.0–136.8	$C_{37}H_{57}BrClNO$	76	5.49	5.54	2.11	2.16

[a] All compounds colorless needles.

The solution was acified strongly (Hydrion test paper showed *p*H about 1) and the amino ketone hydrochloride allowed to separate at room temperature for about two hours, then chilled overnight. The crude product was filtered off and purified by crystallization from the appropriate solvent (see Table I).

3-(2-Dialkylamino-1-hydroxypropyl)-9-bromophenanthrene hydrochlorides. The 3-(2-dialkylamino-1-oxopropyl)-9-bromophenanthrene hydrochloride was reduced with aluminum isopropoxide using the technique described for 3-(2-dialkylamino-1-hydroxyethyl)-9-bromophenanthrene (1). The yield of crude carbinol was almost quantitative. Purification was readily effected by recrystallization from the appropriate solvent (see Table II).

3-(3-Dialkylamino-1-oxopropyl)-9-bromophenanthrene hydrochloride. In a 2-necked, 300-cc. flask fitted with a stirrer and reflux condenser were placed 29.7 g. (0.1 mole) of 3-acetyl-9-bromophenanthrene, 0.122 mole of dialkylamine hydrochloride, 3.28 g. of paraformaldehyde, 0.17 cc. of concentrated hydrochloric acid, and 120 cc. of benzene. The mixture was brought to boiling in 15 minutes with vigorous stirring. After refluxing for

10 minutes considerable foaming occurred. After 30 minutes the foam disappeared and a clear yellow solution was formed. After boiling for an additional 45 minutes the reaction mixture was chilled for one hour and some dialkylamine hydrochloride filtered off. Dry ether was added to the filtrate to a volume of about 550 cc. and the mixture chilled overnight. The crude amino ketone hydrochloride was filtered off, washed with ether, and crystallized from the appropriate solvent (see Table III).

9-Bromophenanthrene-3-carboxylic acid. A mixture of 0.5 g. of 3-α-bromopropionyl-9-bromophenanthrene, 10 cc. of 5.5 *N* sodium hypochlorite, and 2 cc. of chloroform was refluxed gently for three and one-half hours. About 10 cc. of chloroform was then added, and the mixture extracted several times with water. The aqueous solution was filtered hot (the sodium salt tends to crystallize on cooling), acidified, and extracted with ether. On evaporation of the ether extract, a residue of 70 mg. remained. Crystallization from glacial acetic acid gave 50 mg. of the carboxylic acid as colorless needles, m.p. 279–280°. The melting point was not depressed by admixture of a sample of the acid described by Mosettig and van de Kamp (3).[7]

TABLE III

3-(3-DIALKYLAMINO-1-OXOPROPYL)-9-BROMOPHENANTHRENE HYDROCHLORIDES[a]

SN	ALKYL GROUP	SOLVENT	M.P., °C.	FORMULA	YIELD, %	IONIZABLE Cl, %		N, %	
						Calc'd	Found	Calc'd	Found
	CH_3	Ethanol	197–199	$C_{19}H_{19}BrClNO$	72	9.04	8.88	3.56	3.42[b]
	C_2H_5	Ethanol	158.5–159.5	$C_{21}H_{23}BrClNO$	62	8.44	8.35	3.33	2.83
	C_3H_7	Methanol-ether	172–175 dec.	$C_{23}H_{27}BrClNO$	56	7.93	7.92	3.12	2.67
9472	C_4H_9	Methanol-ether	156–158	$C_{25}H_{31}BrClNO$	51	7.40	7.62	2.94	2.80
9473	C_5H_{11}	Methanol-ether	148–150	$C_{27}H_{35}BrClNO$	45	7.05	7.04	2.78	2.75
	C_6H_{13}	Ethanol-ether	112–115	$C_{29}H_{39}BrClNO$	54	6.79	6.72	2.63	2.64
	C_7H_{15}	Methanol-acetone-ether	101–101.5	$C_{31}H_{43}BrClNO$	47	6.30	6.63	2.49	2.28
9474	C_8H_{17}	Benzene-hexane	111.5–113.5	$C_{33}H_{47}BrClNO$	45	6.03	6.28	2.38	2.17
9475	C_9H_{19}	Benzene-hexane	110–111.5	$C_{35}H_{51}BrClNO$	34	5.75	5.90	2.27	2.46
	$C_{10}H_{21}$	Benzene-ether	110–112.5	$C_{37}H_{55}BrClNO$	35	5.50	5.65	2.17	2.14

[a] All compounds colorless needles.

[b] See ref. (6).

9-Bromophenanthrene-3-carboxylic acid methyl ester. The carboxylic acid obtained was esterified with methanol. The methyl ester had the melting point 154–155.5° and the melting point was not depressed by admixture of a sample of the ester prepared by Mosettig and van de Kamp (3).[7]

SUMMARY

A homologous series of 3-(2-dialkylamino-1-oxopropyl)-9-bromophenanthrenes has been prepared.

Each of these amino ketones has been reduced to the corresponding amino carbinol.

A homologous series of 3-(3-dialkylamino-1-oxopropyl)-9-bromophenanthrenes has been synthesized.

[7] Sample furnished by Dr. Mosettig.

The evaluation as antimalarials of the amino alcohols and amino ketones described herein is discussed.

CHICAGO, ILL.

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(5) VAN DE KAMP AND MOSETTIG, *J. Am. Chem. Soc.*, **58**, 1568 (1936).
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(7) N. B. EDDY, Unpublished results.
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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF LADY ESTHER, LTD.]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XI. DERIVATIVES OF PHENANTHRENE, III. AMINO ALCOHOLS DERIVED FROM 9-CHLOROPHENANTHRENE

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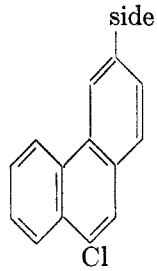
It appeared to be of interest, from a biological point of view to prepare halogenated phenanthryl amino alcohols of the types described by us previously (1, 2), but having a chlorine atom in place of the bromine atom. The following amino alcohols and amino ketones were prepared:



Side chain:

II $CHOHCH_2NR_2$

III $COCH(CH_3)NR_2$

IV $CHOHCH(CH_3)NR_2$

V $COCH_2CH_2NR_2$

The requisite starting materials, 9-chloro-3-acetyl- and 9-chloro-3-propionylphenanthrene were obtained in satisfactory yields in the Friedel-Crafts reaction on 9-chlorophenanthrene. The structural proof for these two key substances was accomplished in the following manner. The acetyl derivative was oxidized to the known 3-acetyl-9,10 quinone (3). The acetyl- and propionyl-9-chlorophenanthrene were oxidized with sodium hypochlorite to the same 9-chlorophenanthroic acid. The acetyl-9-chlorophenanthrene was converted *via* the oxime to the amino-9-chlorophenanthrene, and the latter by diazotization to the corresponding dichlorophenanthrene which melted at 125–125.5°. In this dichlorophenanthrene one chlorine atom occupies position 9, the other one must occupy position 3 or 6. Nylén (4) prepared in 1920 by the Pschorr method 3,10-dichlorophenanthrene which melts at 117-117.5°. On this basis Sandquist (5) could assign to the dichlorophenanthrene of m.p. 125–125.5°, obtained by sulfonation of 9-chlorophenanthrene and the subsequent conversion of the sulfonic group to a chlorine (6), the structure of 3,9-dichlorophenanthrene. Thus, the melting point *per se* of our dichlorophenanthrene, and the general analogy of substitution in the sulfonation process and the Friedel-Crafts reaction is a very strong indication that this compound is 3,9-dichlorophenanthrene and consequently the acyl compounds are 3-acetyl-9-chlorophenanthrene and 3-propionyl-9-chlorophenanthrene. Moreover, we have established (1, 2) the consti-

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tution of the 3-acyl-9-bromophenanthrenes by conversion to the diphenanthroic acid, which was also obtained from the above 3,9-dichlorophenanthrene *via* the corresponding dicyano compound. Since the structural proof of all these acylhalo phenanthrenes hinges on this one melting point and since dimorphism in the phenanthrene series occurs frequently, it appeared advisable to prepare 3,9-dicyanophenanthrene by an unambiguous synthesis. Recently May and Mosettig (7) synthesized by the Pschorr method 3-chloro-9-phenanthroyl chloride. We converted this derivative to 3,9-dicyanophenanthrene and to 3,9-dicarboxyphenanthrene dimethyl ester. The last two proved, by melting point and mixed melting point, to be identical with the dicyanophenanthrene and with the dicar-

TABLE I[a]

ANTIMALARIAL ACTIVITY OF AMINO ALCOHOLS

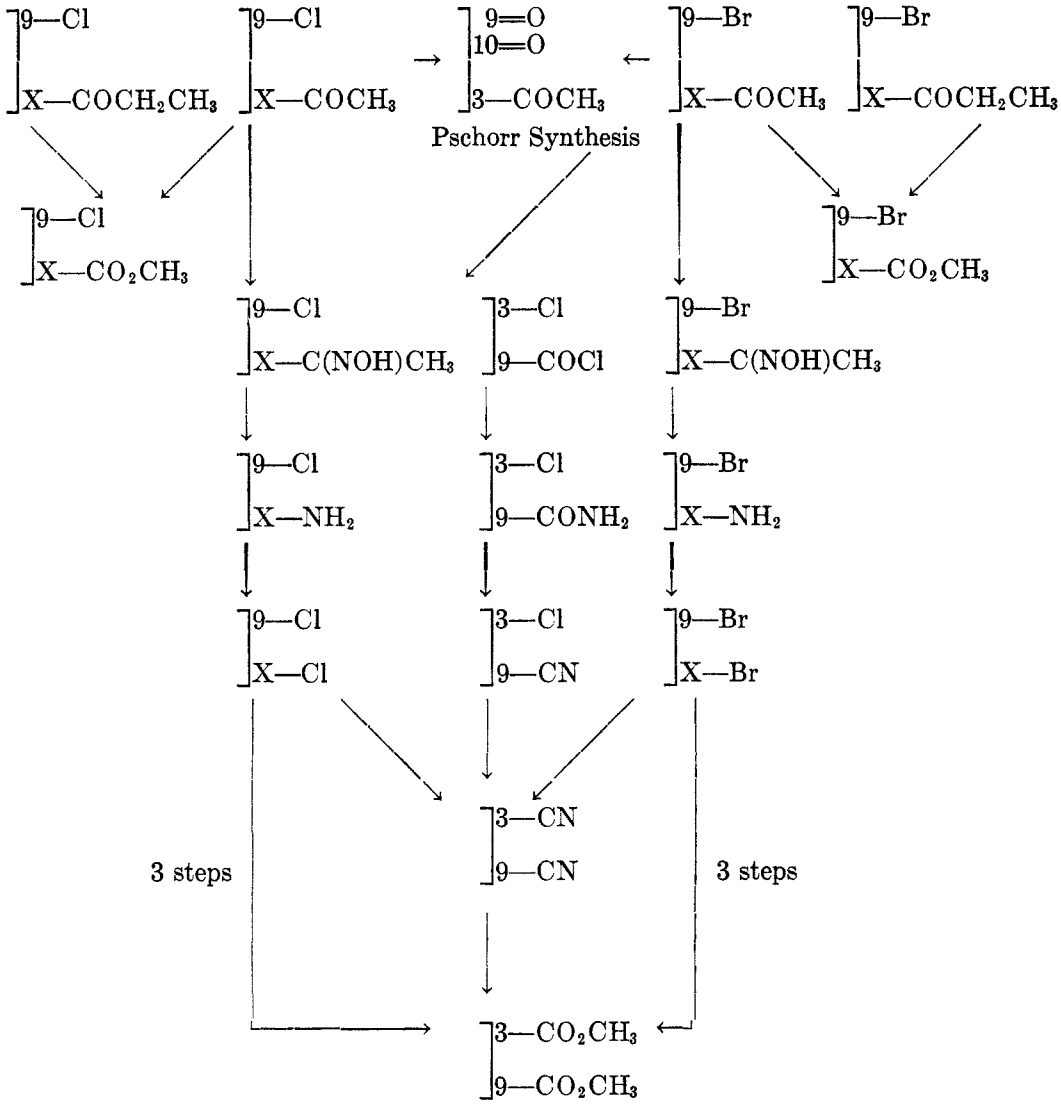
SN	$C_{14}H_8$ 9-Cl 3-$CHOHCH_2$-	Q
10228	$N(C_2H_5)_2$	$\frac{1}{8}$
10229	$N(C_3H_7)_2$	$\frac{1}{4}$
10163	$N(C_4H_9)_2$	$\frac{1}{4}$
10123	$N(C_5H_{11})_2$	$\frac{1}{2}$
13454	$N(C_6H_{13})_2$	$\frac{1}{2}$
10230	$N(C_7H_{15})_2$	$\frac{1}{4}$
10225	$N(C_8H_{17})_2$	$\frac{1}{8}$
10124	$N(C_9H_{19})_2$	—
10227	$N(C_{10}H_{21})_2$	—
	$C_{14}H_8$ 9-Cl 3-$CHOHCH(CH_3)$-	
7266	$N(C_5H_{11})_2$	—

[a] In the table are listed the compounds which were submitted for biological investigation. In the first column are given the identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council. The third column shows the approximate "quinine equivalents" expressing the effectiveness of the drugs towards *Plasmodium gallinaceum*, compared with that of quinine. A dash indicates that the equivalent is less than $\frac{1}{16}$. All compounds listed in the table were administered as hydrochlorides.

boxyphenanthrene dimethyl ester obtained from our acylated 9-halo-phenanthrenes. The flow sheet depicts the structural proof of the 3-halo-9-acylphenanthrenes.

The compounds of types I–V were synthesized as described in the two previous communications (1, 2). Also in this series we did not succeed in preparing the amino alcohol corresponding to V.

There is no significant difference either in toxicity or in effectiveness towards *Plasmodium gallinaceum* between the amino alcohols listed above and their bromo analogs (1, 2) [Dr. Nathan B. Eddy (8); Dr. G. Robert Coatney and Dr. N. Clark Cooper (9)]. None of the drugs showed any activity towards sporozoite-induced *gallinaceum* malaria (9).



EXPERIMENTAL

9-Chlorophenanthrene. In a 5-liter, 3-necked flask fitted with a stirrer was placed 1000 g. of purified phenanthrene (1) and 3000 cc. of carbon disulfide. After cooling the solution to 2–5°, a stream of chlorine was introduced while stirring. The chlorine was passed in for five hours at the rate of 88 g. per hour. At the end of the reaction, the carbon disulfide was removed by distillation. The residue, mainly phenanthrene dichloride, was then distilled in portions of 200–300 g. After a small amount of solvent and volatile matter was distilled *in vacuo*, the bulk of the product passed over at 360–370° at atmospheric pressure with the liberation of large quantities of hydrogen chloride. Distillation of the dichloride *in vacuo* was not advantageous. This crude 9-chlorophenanthrene was a light yellow oil which solidified on standing. The combined yield from two runs of 1000 g. of phenanthrene each was 2036 g. (85%), m.p. 43.5–46.5°.

The crude material was crystallized from isopropanol to yield 910 g., m.p. 51–51.5° and a second crop of 610 g., m.p. 48.5–50.0°. The yield at this point was 68%. Sandquist and Hagelin reported the melting point 52.5–53° (6).

3-Acetyl-9-chlorophenanthrene. In a 5-liter, 3-necked flask fitted with a stirrer was placed 400 g. of 9-chlorophenanthrene and 3200 cc. of carbon disulfide. The mixture was cooled to 5° and 140 cc. of acetyl chloride added. Six hundred grams of anhydrous aluminum chloride was then added in small portions over a period of about one hour. When all the aluminum chloride had been added, the mixture was allowed to warm up to room temperature (never above 30°) with continued stirring. The reaction mixture, at first dark green gradually became light brown. After stirring for a total of six hours, evolution of hydrogen chloride had practically ceased and the precipitated addition complex was filtered off and washed several times with carbon disulfide.

The combined addition complex from two such runs (total of 800 g. of 9-chlorophenanthrene) was decomposed with 1600 cc. of dilute hydrochloric acid, 6000 cc. of chloroform, and about 4000 g. of ice. After washing the chloroformic solution with water, it was dried over sodium sulfate and evaporated to dryness. The crude residue (955 g.) was crystallized from isopropanol (using carbon) to yield 620 g. (65%) of colorless needles, m.p. 154–155°.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.5; H, 4.69.
Found: C, 74.97; H, 4.53.

3-Acetyl-9-chlorophenanthrene oxime. The oxime of 3-acetyl-9-chlorophenanthrene was prepared from the ketone and hydroxylamine hydrochloride in dioxane-alcohol-water solution in the presence of an equivalent amount of sodium hydroxide. The oxime, when recrystallized from methanol, was obtained as colorless needles, m.p. 187–188°.

Anal. Calc'd for $C_{16}H_{21}ClNO$: N, 5.19. Found: N, 5.16.

3-Acetyl-9-chlorophenanthrene semicarbazone. The semicarbazone was prepared in the usual way. After crystallization from ethyl alcohol, in which it is very sparingly soluble, it was obtained as light yellow needles, m.p. 251–252°.

Anal. Calc'd for $C_{17}H_{14}ClNO$: N, 13.4. Found: N, 13.0.

3-Amino-9-chlorophenanthrene. The procedure was exactly the same as used for the preparation of 3-amino-9-bromophenanthrene (1) which follows, for most part, the method of Bachmann and Boatner (10). The yield from 101 g. of oxime was 66 g. (71%) of buff-colored needles, m.p. 112.5–113°.

Anal. Calc'd for $C_{14}H_{10}ClN$: N, 5.15. Found: N, 5.37.

3-Acetylamino-9-chlorophenanthrene. The 3-amino-9-chlorophenanthrene was acetylated with acetyl chloride in benzene in the presence of pyridine. On recrystallization from alcohol, the acetyl derivative was obtained as colorless prisms, m.p. 220.5–221.5°.

3,9-Dichlorophenanthrene. The 3-amino-9-chlorophenanthrene was diazotized by a modification of the method of Misslin (11) and the diazonium salt converted to dichlorophenanthrene by Schwechten's modification of the Sandmeyer reaction (12). To a solution of 5 g. of 3-amino-9-chlorophenanthrene in 50 cc. of concentrated sulfuric at 10° was added a solution of 3.5 g. of sodium nitrite in 35 cc. of concentrated sulfuric acid. The temperature was maintained at 8–10° while 250 cc. of glacial acetic acid was added slowly with stirring. The solution was maintained at 10° for one-half hour after all the acetic acid had been added and then diluted to *ca.* 600 cc. with ice and water, still maintaining the temperature at 10°. Five grams of urea was then added and stirring continued for another half hour. A solution of 27.5 g. of mercuric chloride and 27.5 g. of potassium chloride in 100 cc. of water was added and gentle stirring continued for an additional half hour. The suspension was held at *ca.* 5° in the refrigerator overnight, the precipitate filtered off, washed with cold water, and dried in a vacuum desiccator.

The dried double salt was intimately mixed with twice its weight of potassium chloride and decomposed in a beaker heated over a low flame. The residue was extracted with hot water and taken up in warm benzene and the benzene solution filtered. The solvent was

evaporated and the residue distilled *in vacuo*, b.p. 220–230° at 6–7 mm. The distillate was crystallized from dioxane-methanol, yielding 1.8 g. (33%) of colorless needles, m.p. 125–125.5°.

3,9-Dicyanophenanthrene. (A) *From dichlorophenanthrene obtained from 3-acetyl-9-chlorophenanthrene.* An intimate mixture of 1 g. of 3,9-dichlorophenanthrene with 1 g. of cuprous cyanide was heated for 3 hours at 295–300° in a sealed tube. The reaction product was cooled, pulverized, and shaken with a mixture of ammonium hydroxide solution and chloroform. The chloroform solution was treated with charcoal, filtered, and evaporated to dryness. The residue was recrystallized three times from toluene to yield 0.5 g. (54%) of colorless needles, m.p. 285–286°. The melting point was not depressed by mixture with the dicyanophenanthrene obtained from 3-acetyl-9-bromophenanthrene (1).

(B) *By total synthesis. 3-Chloro-9-phenanthramide.* To 75 cc. of concentrated ammonium hydroxide was added with vigorous stirring a solution of 3.0 g. of 3-chloro-9-phenanthroyl chloride (7) in 35 cc. of dry dioxane. After stirring for an additional 15 minutes, the suspension was diluted to 400 cc. with water and the precipitated amide filtered off, washed, and dried. The crude amide was recrystallized from dioxane-water to yield 2.36 g. (83.5%) of colorless needles, m.p. 253.5–254°.

Anal. Calc'd for $C_{15}H_{10}ClNO$: N, 5.52. Found: N, 5.39.

3-Chloro-9-cyanophenanthrene. A mixture of 1.5 g. of 3-chloro-9-phenanthramide, 35 cc. of phosphorus oxychloride, and 1.0 g. of phosphorus pentoxide was refluxed for one-half hour, poured on ice, and the product filtered off, washed with water, and dried. The product weighed 1.38 g. (99%) and melted at 177.9°. Recrystallization from alcohol-benzene yielded colorless crystals, m.p. 178.5–179°.

Anal. Calc'd for $C_{15}H_8ClN$: N, 5.87. Found: N, 6.16.

3,9-Dicyanophenanthrene. An intimate mixture of 0.18 g. of 3-chloro-9-cyanophenanthrene with 0.075 g. (10% excess) of cuprous cyanide was heated at 270–285° for 3 hours. The fused mass was sublimed at 1.5 mm. pressure and the sublimate crystallized from toluene. The dicyanophenanthrene separated as fine needles and the yield was 0.065 g. (38%), m.p. 284–285°. The melting point was not depressed by admixture of the dicyanophenanthrene obtained from 3-acetyl-9-chlorophenanthrene, nor by that obtained from 3-acetyl-9-bromophenanthrene(1).

Phenanthrene-3,9-dicarboxylic acid dimethyl ester. (A) *From 3-acetyl-9-chlorophenanthrene. Phenanthrene-3,9-dicarboxylic acid.* A suspension of 0.2 g. of 3,9-dicyanophenanthrene (derived from 3-acetyl-9-chlorophenanthrene) in 20 cc. of a 25% potassium hydroxide solution in methanol was refluxed for 10 hours during which ammonia was evolved and a clear solution was obtained. The solution was then diluted with water, acidified, and the precipitate filtered off and washed with water. The crude 3,9-dicarboxylic acid was converted to the dipotassium salt, which was crystallized from methanol-acetone, then reconverted to the free acid by precipitation from methanolic solution by dilute hydrochloric acid. After drying in a vacuum desiccator, the purified acid remained as a light yellow powder, m.p. above 330°.

Phenanthrene-3,9-dicarboxylic acid dimethyl ester. A suspension of 0.1 g. of the dicarboxylic acid in 10 cc. of methanol containing 0.18 g. of concentrated sulfuric acid was refluxed for eight hours during which a clear solution was obtained. On cooling, the ester separated in the form of colorless needles. Two recrystallizations from methanol yielded 0.05 g. of colorless needles, m.p. 126.5–127.5°. The melting point was not depressed by admixture of the diester obtained from 3-acetyl-9-bromophenanthrene (1).

(B) *By total synthesis.* A sample of 3,9-dicyanophenanthrene prepared by total synthesis was hydrolyzed to the dicarboxylic acid and then esterified to the dimethyl ester by the procedure indicated above. The dimethyl ester had the melting point 126.5–127.5° which was not depressed by admixture of the diester obtained from the 3-acetyl-9-chlorophenanthrene (*v.s.*) nor by that obtained from 3-acetyl-9-bromophenanthrene (1).

3-α-Bromoacetyl-9-chlorophenanthrene. A suspension of 60 g. of acetyl-9-chlorophenan-

threne in 600 cc. of absolute ether was brominated with 39 g. of bromine in 150 cc. of chloroform. The reaction was similar to the bromination of acetyl-9-bromophenanthrene (1) but was carried out at 3° after initiating the reaction at 33°. Recrystallization of the product from two runs (120 g. of starting material) from benzene-hexane gave 105 g. (67%) of greenish yellow needles, m.p. 135–135.5°. A second crop of less pure material (m.p. 128.5–130°) amounted to 28.3 g. Including the second crop material, the total yield was 84.5%.

Anal. Calc'd for $C_{16}H_{10}BrClO$: Br, Cl, 34.6. Found: Br, Cl, 34.6.

3-(2-Dialkylamino-1-oxoethyl)-9-chlorophenanthrene hydrochloride. The procedure here was essentially the same as that used for the corresponding 9-bromophenanthrene(1) series. A mixture of 15.7 g. (0.047 mole) of 3-bromoacetyl-9-chlorophenanthrene and 0.094 mole of dialkylamine in 50 cc. of benzene was shaken for 20 minutes. During this time the reaction mixture became quite warm and rather thick. An additional 25 cc. of benzene was added and the shaking continued for a total of 50 minutes. One hundred cubic centimeters of absolute ether was then added and the mixture was chilled to 0° for one hour. Filtration

TABLE II

3-(2-DIALKYLAMINO-1-OXO-ETHYL)-9-CHLOROPHENANTHRENE HYDROCHLORIDES[a]

ALKYL GROUP	SOLVENT	M.P. °C	FORMULA	YIELD %	IONIZABLE C., %		NITROGEN, %	
					Calc'd	Found	Calc'd	Found
CH_3	Methanol-isopropanol	232–233	$C_{18}H_{17}Cl_2NO$	89	10.61	10.72	4.19	3.82
C_2H_5	Ethanol-acetone	212–213.5	$C_{20}H_{21}Cl_2NO$	85	9.79	9.83	3.87	3.76
C_3H_7	Methanol-acetone	236–238	$C_{22}H_{25}Cl_2NO$	80	9.09	9.10	3.59	3.52
C_4H_9	Methanol-acetone-ether	192–193.5	$C_{24}H_{29}Cl_2NO$	65	8.48	8.65	3.35	3.22
C_5H_{11}	Methanol-acetone-ether	176.5–178	$C_{26}H_{33}Cl_2NO$	49	7.94	7.99	3.14	3.02
C_6H_{13}	Acetone	147–148	$C_{28}H_{37}Cl_2NO$	56	7.48	7.69	2.96	2.89
C_7H_{15}	Acetone	153.5–154.5	$C_{30}H_{41}Cl_2NO$	42	7.05	6.86	2.79	2.44
C_8H_{17}	Acetone	122–123	$C_{32}H_{45}Cl_2NO$	76	6.68	6.70	2.64	2.72
C_9H_{19}	Acetone-ether	108–111	$C_{54}H_{49}Cl_2NO$	45	6.35	6.45	2.51	2.46
$C_{10}H_{21}$	Acetone	106–108	$C_{36}H_{53}Cl_2NO$	64	6.04	6.31	2.39	2.30

[a] All compounds colorless needles.

yielded 0.045–0.047 mole of dialkylamine hydrobromide. The filtrate was acidified with alcoholic hydrogen chloride and chilled. Light yellow to colorless needles of the dialkyl amino ketone hydrochloride were obtained and washed with dry ether. Crystallization from the appropriate solvent (see Table II) gave practically colorless needles.

3-(2-Dialkylamino-1-hydroxyethyl)-9-chlorophenanthrene hydrochloride. A mixture of 0.028 mole of purified 3-(2-dialkylamino-1-oxoethyl)-9-chlorophenanthrene hydrochloride, 17.4 g. (0.085 mole) of aluminum isopropoxide, and 300 cc. of isopropanol was distilled through a Snyder column by the same method used for the analogous compounds in the 9-bromophenanthrene series (1). The remaining isopropanol was removed by distillation under diminished pressure and the residual complex decomposed with citric acid, sodium hydroxide, and water. The amino alcohol was extracted with ether. After drying the ethereal solution with anhydrous sodium sulfate, the amino alcohol hydrochloride was precipitated by alcoholic hydrogen chloride and purified by recrystallization (Table III).

3-Propionyl-9-chlorophenanthrene. To a well-stirred suspension of 170 g. of 9-chloro-

phenanthrene in 1600 cc. of carbon disulfide cooled to 5°, was added 67 g. of propionyl chloride and then 255 g. of anhydrous aluminum chloride in small portions over a period of one hour. The mixture was allowed to warm up to room temperature and stirring was continued until the evolution of hydrogen chloride was practically at an end. The precipitate was filtered off, washed with carbon disulfide and decomposed with 100 cc. of conc'd hydrochloric acid, 300 cc. of chloroform, and about 250 g. of ice. The chloroformic solution was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in about 1700 cc. of isopropanol, treated with carbon, filtered with the aid of a few grams of Filter-cel, and allowed to crystallize. Recrystallization from isopropanol yielded 88 g. (41%) of yellow crystals, m.p. 111.5–112.5°.

Anal. Calc'd for $C_{17}H_{13}ClO$: C, 76.0; H, 4.88.
Found: C, 76.47; H, 4.90.

3-Propionyl-9-chlorophenanthrene oxime. 3-Propionyl-9-chlorophenanthrene was treated with hydroxylamine hydrochloride in the usual manner. The product when recrystallized from methanol yielded colorless needles, m.p. 160.5–161.5°.

TABLE III

3-(2-DIALKYLAMINO-1-HYDROXYETHYL)-9-CHLOROPHENANTHRENE HYDROCHLORIDES[a]

ALKYL GROUP	SOLVENT	M.P. °C.	FORMULA	YIELD %	IONIZABLE Cl, %		NITROGEN %	
					Calc'd	Found	Calc'd	Found
C_2H_5	Methanol-acetone	194.5–196	$C_{20}H_{23}Cl_2NO$	80	9.75	9.74	3.84	3.91
C_3H_7	Methanol-acetone-ether	198.5–199	$C_{22}H_{27}Cl_2NO$	86	9.05	9.13	3.57	3.31
C_4H_9	Isopropanol	198–199	$C_{24}H_{31}Cl_2NO$	83	8.45	8.50	3.33	3.20
C_5H_{11}	Methanol-acetone-ether	197–198	$C_{26}H_{35}Cl_2NO$	85	7.91	7.92	3.12	2.89
C_6H_{13}	Methanol-acetone-ether	131–131.5	$C_{28}H_{39}Cl_2NO$	69	7.45	7.47	2.94	3.03
C_7H_{15}	Isopropanol	132–133	$C_{30}H_{43}Cl_2NO$	50	7.03	7.14	2.78	2.93
C_8H_{17}	Acetone	132.5–134	$C_{32}H_{47}Cl_2NO$	68	6.66	6.71	2.63	2.40
C_9H_{19}	Isopropanol	126.5–128	$C_{34}H_{51}Cl_2NO$	62	6.33	6.39	2.50	2.51
$C_{10}H_{21}$	Acetone	121–122.5	$C_{36}H_{55}Cl_2NO$	81	6.03	6.17	2.38	2.39

[a] All compounds colorless needles.

Anal. Calc'd for $C_{17}H_{14}ClNO$: N, 4.93. Found: N, 4.84.

3-α-Bromopropionyl-9-chlorophenanthrene. A suspension of 60 g. of 3-propionyl-9-chlorophenanthrene in 500 cc. of absolute ether was brominated with 35.7 g. of bromine in 150 cc. of chloroform. The procedure was exactly the same as for the bromination of 3-acetyl-9-chlorophenanthrene. The yield of α-bromo ketone (not quite pure) after crystallization from dioxane-petroleum ether (35–60°) was 35 g. (45%), m.p. 163.5–164°.

Anal. Calc'd for $C_{17}H_{12}BrClO$: C, 55.6; H, 3.71.
Found: C, 57.4; H, 3.60.

3-(2-Diamylamino-1-oxopropyl)-9-chlorophenanthrene hydrochloride. This substance was prepared by the same method used for the preparation of 3-(2-dialkylamino-1-oxopropyl)-9-bromophenanthrene hydrochlorides (2). A solution of 18.9 g. of 3-α-bromopropionyl-9-chlorophenanthrene and 25.6 g. of diamylamine in 125 cc. of benzene was refluxed for six hours. The diamylamine hydrobromide which was formed was filtered off and after neutralization with alcoholic hydrogen chloride the remaining secondary amine was separated as hydrochloride. The filtrate was acidified with alcoholic hydrogen chloride and the solution cooled until precipitation was complete. The product, amounting to

18.5 g., was filtered off, washed with ether, and dried, m.p. 157–160°. After recrystallization from methanol-acetone-ether, colorless needles were obtained, m.p. 160–161°.

Anal. Calc'd for $C_{27}H_{35}Cl_2NO$: N, 3.14. Found: N, 2.84.

3-(2-Diamylamino-1-hydroxypropyl)-9-chlorophenanthrene hydrochloride. This substance was prepared from the ketone by reduction with aluminum isopropoxide in isopropanol. From 9 g. of 3-(2-diamylamino-1-oxopropyl)-9-chlorophenanthrene hydrochloride and 12 g. of aluminum isopropoxide, 8 g. of the carbinol was obtained, m.p. 186–188°. Recrystallized from methanol-acetone-ether, m.p. 184–185°.

Anal. Calc'd for $C_{27}H_{37}Cl_2NO$: Cl, 7.71; N, 3.13.
Found: Cl, 7.72; N, 2.88.

3-(3-Dihexylamino-1-oxopropyl)-9-chlorophenanthrene hydrochloride. This ketone was prepared by the same method as that used for the analogous bromo derivatives (2). From 5.6 g. of starting material, 6.6 g. (66%) of the amino ketone hydrochloride was obtained, m.p. 123.5–126° with decomposition.

Anal. Calc'd for $C_{29}H_{39}Cl_2NO$: Cl, 7.69. Found: Cl, 7.72.

Conversion of 9-chlorophenanthrene to 9-cyanophenanthrene. This reaction was effected using essentially the procedure described by Mosettig and van de Kamp (13). A mixture of 4.25 g. of 9-chlorophenanthrene and 1.96 g. of cuprous cyanide was heated at 275–285 for three hours. The cooled black mass was pulverized, extracted with chloroform, and after evaporation of the solvent the residue was recrystallized three times from ethyl alcohol. The cyanophenanthrene showed no depression in melting point when mixed with material prepared from 9-bromophenanthrene.

Oxidation of 3-acetyl-9-chlorophenanthrene with chromic acid. One gram of 3-acetyl-9-chlorophenanthrene was oxidized with chromic acid by the method of Mosettig and van de Kamp (3). The product, 3-acetylphenanthrene-9,10-quinone was shown by mixed melting point to be identical with the quinone made by oxidizing 3-acetyl-9-bromophenanthrene (13).

Oxidation of 3-acetyl-9-chlorophenanthrene with sodium hypochlorite. One and one-half grams of the ketone was dissolved in 15 cc. of pyridine. To this was added 5.0 cc. of 5.5 *N* sodium hypochlorite and 3.0 cc. of water. The mixture which separated into layers was refluxed for 30 minutes, then poured into 150 cc. of 5% hydrochloric acid. The solid which separated was filtered off, washed with a little dilute hydrochloric acid and water, and heated to boiling with 300 cc. of 2% sodium hydroxide solution. The alkaline mixture was treated with carbon, and the filtrate after acidification with 6 *N* hydrochloric acid gave a white gelatinous precipitate. The dried 9-chlorophenanthrene-3-carboxylic acid on recrystallization from glacial acetic acid yielded colorless needles which melted at 276.5–277.5°.

Anal. Calc'd for $C_{15}H_9ClO_2$: Neut. equiv., 256.5. Found: 249.

Oxidation of 3-propionyl-9-chlorophenanthrene with sodium hypochlorite. This oxidation was done in the same manner as that described above for the acetyl derivative. The 9-chlorophenanthrene-3-carboxylic acid melted at 277–277.5°. A mixed melting point with the acid obtained from 3-acetyl-9-chlorophenanthrene showed no depression.

9-Chlorophenanthrene-3-carboxylic acid methyl ester. The 9-chlorophenanthrene-3-carboxylic acid was esterified with methanol in the presence of sulfuric acid. The ester was recrystallized from methanol, yielding colorless needles which melted at 155.5–156°. A mixture of the esters derived from 3-acetyl-9-chlorophenanthrene and from 3-propionyl-9-chlorophenanthrene also melted at 155.5–156°.

Anal. Calc'd for $C_{16}H_{11}ClO_2$: C, 71.0; H, 4.07.
Found: C, 71.18; H, 3.94.

SUMMARY

1. A homologous series of 3-(2-dialkylamino-1-oxoethyl)-9-chlorophenanthrenes has been synthesized.

2. 3-(2-Diamylamino-1-oxopropyl)-9-chlorophenanthrene has been synthesized.

3. Each of the above amino ketones has been reduced to the corresponding amino carbinol.

4. 3-(3-Dihexylamino-1-oxopropyl)-9-chlorophenanthrene has been synthesized.

5. The structure of the compounds described in this paper has been elucidated.

6. The evaluation of the amino alcohols described herein as antimalarials is discussed.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF LADY ESTHER, INC.]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XII. DERIVATIVES OF PHENANTHRENE, IV. 1 (OR 8)-ACETYL-9-HALOPHENANTHRENE

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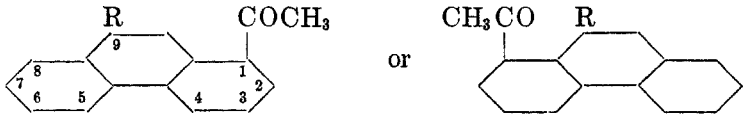
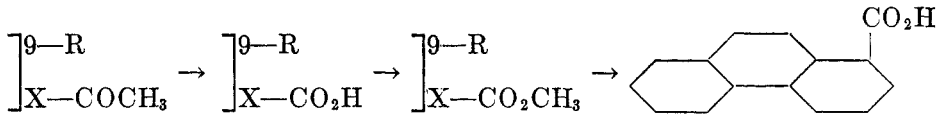
The acetylation of 9-bromo- and 9-chloro-phenanthrenes with acetyl chloride in the presence of aluminum chloride yields principally 3-acetyl derivatives (1, 2, 3,). We have succeeded, however, in isolating from these reaction mixtures smaller amounts of another isomer which we have identified as 1 (or 8)-acetyl-9-halophenanthrene:



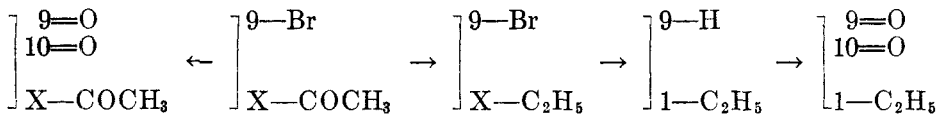
(R = Cl or Br)

The structure of these 1 (or 8)-ketones was elucidated in the following manner:



Oxidation with hypochlorite yielded the carboxylic acids which were esterified with methanol. The esters were then dehalogenated with hydrogen in the presence of palladium charcoal and the dehalogenated products saponified to the known 1-phenanthroic acid.

For 1 (or 8)-acetyl-9-bromophenanthrene, further proof of structure was obtained by the following reactions:



V I II III IV

The ketone (I) was converted to 9-bromo-1 (or 8)-ethylphenanthrene (II) by Clemmensen reduction. Debromination of (II) by hydrogen in the presence of palladium yielded the known 1-ethylphenanthrene (III) which was further identified by formation of its known picrate and by chromic acid oxidation to the previously described quinone (IV) (4). Ketone (I) was also oxidized by chromic acid to the bromine-free acetyl quinone (V).

From 1 (or 8)-acetyl-9-bromophenanthrene was prepared by methods de-

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scribed previously (2, 3) 1 (or 8)-(2-diamylamino-1-oxoethyl)-9-bromophenanthrene and the corresponding amino alcohol. The latter, SN 13456, showed a relatively low toxicity (5) and a high effectiveness towards *Plasmodium gallinaceum* (Q 1). The compound is inactive towards sporozoite-induced *gallinaceum* malaria (6).

EXPERIMENTAL

1(or 8)-Acetyl-9-bromophenanthrene. The mother liquors from the recrystallization of the crude 3-acetyl-9-bromophenanthrene (2) (three successive crops of 3-acetyl derivative had been removed) were concentrated to a thin syrup. After standing for several weeks a further quantity of crystalline material separated and was filtered off and washed with methanol. This material was dissolved in chloroform and allowed to crystallize very slowly. A small quantity of a new ketone, 1 (or 8)-acetyl-9-bromophenanthrene separated in the form of large colorless cubes. On repeated crystallization from chloroform the melting point became constant at 185.6°. This ketone is extremely insoluble in methanol and in ethanol, somewhat more soluble in benzene and toluene, and fairly soluble in hot dioxane and chloroform.

Anal. Calc'd for $C_{16}H_{11}BrO$: C, 64.2; H, 3.68.
Found: C, 63.8; H, 3.72.

1 (or 8)-Acetyl-9-bromophenanthrene oxime. The oxime was prepared in dioxane-alcohol-water and recrystallized from methanol; colorless needles, m.p. 183–184°.

Anal. Calc'd for $C_{16}H_{12}BrNO$: N, 4.46. Found: N, 4.43.

1 (or 8)-Acetyl-9-bromophenanthrene semicarbazone. The semicarbazone was prepared by treatment with semicarbazide hydrochloride in pyridine. Fine, colorless needles were obtained by recrystallization from alcohol; m.p. 220–221°.

Anal. Calc'd for $C_{17}H_{14}BrN_3O$: N, 11.8. Found: N, 12.1.

1-Acetyl-9,10-phenanthrenequinone. The 1 (or 8)-acetyl-9-bromophenanthrene was oxidized in the usual way with chromic acid (7). Recrystallization from glacial acetic acid yielded deep orange needles which did not melt but decomposed over a wide temperature range. A qualitative test (sodium fusion) showed no halogen.

Anal. Calc'd for $C_{16}H_{10}O_3 \cdot H_2O$: C, 71.6; H, 4.48.
Found: C, 71.54; H, 4.52.

9-Bromophenanthrene-(1 or 8)-carboxylic acid. To a solution of 2 g. of 1 (or 8)-acetyl-9-bromophenanthrene in 20 cc. of pyridine was added 7.5 cc. of 5.5 *N* sodium hypochlorite solution and 3 cc. of water. The mixture was refluxed for 30 minutes, poured into a large volume of water, and acidified with hydrochloric acid. The precipitate was filtered and washed with water, extracted with 300 cc. of 1% sodium hydroxide solution by heating to boiling. The solution of crude acid, which contained some insoluble material in suspension, was treated with carbon, filtered, and the acid precipitated with hydrochloric acid. The precipitated acid weighed 1.1 g. (55%). After crystallization from glacial acetic acid, it melted at 291–292°.

Anal. Calc'd for $C_{15}H_9BrO$: C, 59.8; H, 3.01.
Found: C, 59.51; H, 3.34.

9-Bromophenanthrene-1 (or 8)-carboxylic acid methyl ester. The 9-bromophenanthrene-1 (or 8)-carboxylic acid was esterified in the usual way with methanol in the presence of sulfuric acid. The ester was isolated by allowing the reaction mixture to cool and filtering off the crystallized product. The yield was almost quantitative. By recrystallization from methanol, colorless needles were obtained, m.p. 135.5–136°.

Anal. Calc'd for $C_{16}H_{11}BrO_2$: C, 61.00; H, 3.50.
Found: C, 61.02; H, 3.85.

Debromination of 9-bromophenanthrene-1 (or 8)-carboxylic acid methyl ester. To a solution of 0.1 g. of 9-bromophenanthrene-1 (or 8)-carboxylic acid methyl ester in 20 cc. of

methanol was added 50 mg. of 1% palladium on activated charcoal. A stream of hydrogen was passed through the suspension for 20 minutes at 50°. The catalyst was filtered off and the solution poured into a large volume of water. The ester was extracted with ether and the extract evaporated to dryness. The ester which remained was obtained as an oil and was saponified with methanolic potassium hydroxide. The saponification was complete in 15 minutes and the product was isolated by diluting the reaction mixture with water and acidifying with hydrochloric acid. After crystallization from glacial acetic acid, the acid was obtained as colorless crystals, m.p. 228.5–229.5°.

Calc'd for $C_{15}H_{10}O_2$: Neut. equiv., 222. Found: 225.

This acid when mixed with an authentic sample of 1-phenanthroic acid[5] showed no depresssion in melting point.

1 (or 8)-Ethyl-9-bromophenanthrene. A mixture of 1.0 g. of 1 (or 8)-acetyl-9-bromophenanthrene, 5 g. of amalgamated zinc, 10 cc. of glacial acetic acid, 10 cc. of concentrated hydrochloric acid, and 4 cc. of toluene was refluxed for 24 hours during which an additional 6 cc. of concentrated hydrochloric acid was added in small portions. The toluene layer was separated, evaporated to dryness, and the residue recrystallized from acetone-methanol. Colorless crystals, m.p. 72.5–73.5° were obtained.

Anal. Calc'd for $C_{16}H_{13}Br$: Br, 28.1. Found: Br, 27.8.

1-Ethylphenanthrene. To a solution of 0.5 g. of 1 (or 8)-ethyl-9-bromophenanthrene in 5 cc. of pyridine and 15 cc. of methanol was added 0.1 g. of palladium charcoal. A stream of hydrogen was passed through the solution at the boiling point for 30 minutes. The catalyst was then filtered off and the solution poured into water and acidified with hydrochloric acid. The debrominated product was extracted with ether and the ethereal solution evaporated to dryness. The residual ethylphenanthrene was crystallized from alcohol in the form of colorless needles, m.p. 61.5–63°; picrate, light orange, m.p. 109–110° [lit. (4), 62.5°; picrate, 108–109°].

1-Ethylphenanthrene-9,10-quinone. To a solution of 0.1 g. of 1-ethylphenanthrene in 2 cc. of glacial acetic acid was added a solution of 0.1 g. of chromic anhydride in 0.2 cc. of water and 0.5 cc. of glacial acetic acid. The solution was warmed to 70–80° for ten minutes and the quinone precipitated by the addition of water. Recrystallization from acetic acid yielded orange-red needles, m.p. 153–154° [lit. (4), 155°].

1 (or 8)-Acetyl-9-chlorophenanthrene. The mother liquors from the acetylation of 9-chlorophenanthrene (3) contained principally a mixture of the 3-acetyl- with 1 (or 8)-acetyl-9-chlorophenanthrene. By fractional crystallization from isopropanol and then chloroform, a small quantity of crystalline material was isolated, m.p. 159–160°.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.5; H, 4.36.
Found: C, 75.6; H, 4.57.

1 (or 8)-Acetyl-9-chlorophenanthrene oxime. The oxime was prepared by the method employed for 1 (or 8)-acetyl-9-bromophenanthrene oxime. After recrystallization from methanol it melted at 171–173°.

Anal. Calc'd for $C_{16}H_{12}ClNO$: N, 5.20. Found: N, 5.58.

9-Chlorophenanthrene-1 (or 8)-carboxylic acid. This acid was prepared by oxidation of the 1 (or 8)-acetyl-9-chlorophenanthrene with hypochlorite in exactly the same way as was used for the corresponding bromo derivative. After recrystallization from glacial acetic acid it was obtained in the form of colorless needles, m.p. 293–294°.

Calc'd for $C_{15}H_9ClO_2$: Neut. equiv. 256.5. Found: 258.

9-Chlorophenanthrene-1 (or 8)-carboxylic acid methyl ester. The methyl ester was prepared in the usual way with methanol in the presence of sulfuric acid. Recrystallization from methanol gave colorless crystals, m.p. 129.5–130°.

Anal. Calc'd for $C_{16}H_{11}ClO_2$: C, 70.9; H, 4.09.
Found: C, 70.8; H, 4.11.

Dechlorination of 9-chlorophenanthrene-1 (or 8)-carboxylic acid methyl ester. The ester

[5] The authentic 1-phenanthroic acid was furnished by Dr. Erich Mosettig.

was dehalogenated with hydrogen in the presence of palladium charcoal using the same procedure employed for the corresponding bromo compound. The dehalogenated product was isolated as 1-phenanthroic acid which did not depress the melting point of 1-phenanthroic acid obtained from the corresponding bromo compound.

1 (or 8)-(α-Bromoacetyl)-9-bromophenanthrene. To a suspension of 30 g. of 1 (or 8)-acetyl-9-bromophenanthrene in 400 cc. of absolute ether at 35° was added a few drops of bromine in chloroform. After decolorization was complete the temperature was lowered to 5–8° and 16 g. of bromine in 75 cc. of chloroform added slowly with stirring. After all the bromine had been absorbed, 200 cc. of hexane was added and the mixture chilled. The precipitate was filtered off and washed with hexane, then with petroleum ether. After one recrystallization from benzene-hexane the yield was 32.4 g., m.p. 117–128°. Recrystallization from dioxane-methanol gave colorless needles, m.p. 126–127°.

Anal. Calc'd for $C_{16}H_{10}Br_2O$: Br, 42.3. Found: Br, 42.1.

1 (or 8)-(2-Diamylamino-1-oxoethyl)-9-bromophenanthrene hydrochloride. To a solution of 16 g. (0.1 m.) of diamylamine in 70 cc. of benzene was added 19.7 g. (0.05 m.) of 1 (or 8)-α-bromoacetyl-9-bromophenanthrene. The mixture was shaken mechanically for one hour, 125 cc. of dry ether was added and the whole chilled overnight. The diamylamine hydrochloride which separated was filtered off and the filtrate evaporated to dryness. The residue was shaken with a mixture of dilute sodium carbonate solution and ether, the ethereal extract separated, washed with water, and dried over sodium sulfate. The remaining diamylamine was precipitated by adding alcoholic hydrogen chloride until *p*H 6 was indicated by a drop of the solution on "Hydrion A" paper. The precipitated amine hydrochloride was filtered off and the filtrate made strongly acid with alcoholic hydrogen chloride.

The amino ketone hydrochloride separated as long colorless needles, m.p. 154–156°. The yield was 16.0 g. (64%). After recrystallization from methanol-acetone-ether, the melting point became constant at 156–157.5°.

Anal. Calc'd for $C_{26}H_{43}BrClNO$: N, 2.85; Cl, 7.23.
Found: N, 2.71; Cl, 7.15.

1 (or 8)-(2-Diamylamino-1-hydroxyethyl)-9-bromophenanthrene hydrochloride, (SN-13456). To a solution of 14.9 g. (0.073 m.) of aluminum isopropoxide in 450 cc. of isopropanol was added 12 g. (0.0245 m.) of 1 (or 8)-(2-diamylamino-1-oxoethyl)-9-bromophenanthrene. Isopropanol containing acetone was slowly distilled from the solution through a 10-ball Snyder column. After 3.5 hours of distillation, the remaining isopropanol was evaporated *in vacuo*. The residue was diluted with ether, an aqueous solution of citric acid added and made alkaline to Phenol Red with sodium hydroxide solution. The ethereal phase was separated, dried over sodium sulfate, and acidified with alcoholic hydrogen chloride. After standing overnight, the separated crude amino carbinol hydrochloride was filtered and washed with ether. The yield was 7.3 g. (61%), m.p. 178–180°. After recrystallization from methanol-acetone-ether, the pure amino carbinol hydrochloride was obtained as colorless needles, m.p. 178.5–179°.

Anal. Calc'd for $C_{26}H_{45}BrClNO$: Cl, 7.20. Found: Cl, 7.19.

SUMMARY

1. 1(or 8)-Acetyl-9-bromophenanthrene and 1 (or 8)-acetyl-9-chlorophenanthrene have been prepared.

2. The structure of these ketones has been elucidated.

3. 1(or 8)-(2-Diamylamino-1-oxoethyl)-9-bromophenanthrene has been prepared and reduced to the corresponding carbinol.

4. The evaluation of this amino alcohol as an antimalarial is discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY]

THE ACTION OF BASES ON ORGANIC HALOGEN COMPOUNDS. V. THE ACTION OF POTASSIUM AMIDE ON SOME AROMATIC HALIDES (1)

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Earlier work (2, 3, 4) from these laboratories has shown that the alkali metal amides react with aryl halides in liquid ammonia to give aromatic amines. It has recently been found (5) that solutions of the alkali amides in liquid ammonia react with 4-bromo- and 4-iodo-dibenzofuran to give 3-aminodibenzofuran, although the expected (not rearranged) products are obtained from 2-bromo- and 2-iodo-dibenzofuran. *m*-Anisidine is formed from *o*-chloro- or *o*-iodo-anisole, and 3-aminodiphenyl ether may be prepared from 2-iododiphenyl ether. Urner and Bergstrom (4) found that 2-naphthylamine is the chief product of the action of potassium amide on both the α- and the β-naphthyl halides, with the exception of α-fluoronaphthalene. Meharg and Allen, Jr. (6) many years ago hydrolyzed *o*- and *p*-chlorotoluenes with aqueous sodium hydroxide at temperatures above 300°, and in each case found *m*-cresol in addition to the expected isomer.

In continuation of this work, it was found that the *o*-, *m*-, and *p*-tolyl halides, with the exception of the fluoride, react readily with a liquid ammonia solution of potassium amide to give mixtures which contain some of the amine corresponding to the halide used. *p*-Chlorophenetole and potassium amide react to give a *p*-phenetidine which probably contains an isomer. 9-Phenanthrylamine is formed from 9-bromophenanthrene and potassium amide. 2-Chloroquinoline is converted rapidly to a tar, by reaction with a strong base such as potassium amide, but it is not appreciably attacked by the ammonia-insoluble calcium amide at −33°. 2-Bromopyridine, 3-bromopyridine, 6-chloroquinoline, 4-bromoisoquinoline, and *p*-chloronitrobenzene react vigorously with potassium amide without the formation of definite products. Because of its very low solubility in liquid ammonia, sodium *p*-bromobenzenesulfonate is not appreciably attacked by the alkali amides at room temperatures.

Secondary amine fractions of low basicity were obtained in working up the products of the action of potassium amide on *o*- and *m*-chlorotoluene, *o*-iodotoluene, *p*-bromotoluene, and *p*-chlorophenetole, but they were unquestionably mixtures. It is evident that potassium amide "catalyzes" the reaction of a tolyl halide with the potassium salt of a toluidine to form ditolylamines (or isomers), in the same manner that the alkali amides catalyze the reaction between an alkali anilide and the phenyl halides to give diphenylamine, triphenylamine, and *p*-aminobiphenyl (3). An attempt to prepare pure di- or tri-*p*-tolylamines by adding potassium amide to a solution of potassium *p*-toluide and *p*-bromotoluene in liquid ammonia resulted in forming a mixture, from which

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was separated a solid, melting at 145°, and isomeric with the tri-*p*-tolylamine of Wieland (7) (m.p. 117°). The reaction between potassium amide and 1.5–2 molar proportions of a tolyl halide gives somewhat more than the quantity of potassium halide calculated from the equation,

$$C_7H_7X + 2KNH_2 \rightarrow C_7H_7NHK + KX + NH_3$$

indicating a further reaction of the type,

$$C_7H_7NHK + C_7H_7X \xrightarrow{KNH_2} (C_7H_7)_2NK + KX + NH_3$$

A tolylquinaldine of unknown orientation is obtained in 11% yield by the action of potassium amide on quinaldylpotassium and *p*-chlorotoluene in liquid ammonia.

In view of the rearrangements observed by Meharg and Allen, by Gilman, and by workers in these laboratories, it is suggested that similar rearrangements may occur in the Ullmann-Goldberg (8) syntheses of di- and tri-arylamines by heating an aryl halide other than a phenyl halide with primary or secondary arylamines in the presence of potassium carbonate or other alkali and metallic copper.

The preparation of a primary arylamine is generally best carried out by adding the phenyl halide—alone, or dissolved in ether or ligroin—to a well stirred solution of the alkali amide in liquid ammonia. The reverse addition of the amide to the halide may decrease tar formation, but it often increases the amount of the secondary amine fraction, and complicates the separation of the products. Operation at −78° appears to increase the yield of toluidine from *p*-chlorotoluene, but the speed of the reaction is noticeably slower.

The solubility of sodium amide in liquid ammonia at −33° is of the order of one gram per liter, while potassium amide is very readily soluble. Furthermore, the conductance of a solution of sodium amide is much less than that of a solution of potassium amide of the same concentration (9), indicating the possible presence of complex ions in the former (10). Accordingly, an otherwise too vigorous reaction may be somewhat moderated and controlled by the use of sodium amide.

By means of competition reactions (3), the relative ease of removal of halogen from the *m*-tolyl halides has been found to be the following: *m*-C_7H_7Cl, 1.0; *m*-C_7H_7Br, 13.4; *m*-C_7H_7I, 5.2. If the reactivity of C_6H_5Cl = 1.0, these figures become, respectively, 0.6, 8.2, and 3.4. The methyl group accordingly slightly decreases the rate of removal of the halogen from a tolyl halide, but it should be pointed out that the results are of qualitative significance only because the mechanism of replacement of the halogen may not be identical in the three cases. The order of decreasing reactivity, Br > I > Cl, is the same as observed with the phenyl halides (3).

EXPERIMENTAL

Method 1. Potassium amide solution, made in vessel 1 of Fig. 1 of a previous article (2), was slowly forced over with stirring into a solution of the aryl halide in vessel 2. A small amount of ammonia was condensed in vessel 1, and the residual potassium amide washed over into the other vessel. Halides of low solubility in liquid ammonia at −33°

were generally dissolved in a mixture of ether and liquid ammonia. At the end of a period of time that varied from about half an hour to four or five hours, C.P. ammonium nitrate equivalent to the alkali metal used in forming the amide was added to destroy reactive potassium salts. Since no nitrogen or hydrogen was formed in the first few experiments with the tolyl halides, subsequent gas collection was omitted. The residue left after evaporating the ammonia was treated with water to dissolve inorganic salts, and then extracted several times with benzene to remove amines. The extracts were distilled from a small flask with a sealed-on fractionating column, first at atmospheric pressure to remove solvent, unchanged aryl halide, and primary aromatic amine, and then *in vacuo* to obtain the secondary amine fraction. No attempts were made to separate tertiary amines from the residual tar. The primary amines were often extracted from the benzene solution with dilute hydrochloric acid. The aqueous solution of the benzene-insoluble material was occasionally analyzed for halide ion.

Method 2. Two three-necked round-bottomed flasks were so arranged that potassium amide, prepared in one of them, could be transferred by ammonia pressure to the other, which contained the aryl halide (11, 12).

Method 3. A 1000-cc. three-necked round-bottomed flask was fitted with a mechanical stirrer and with a separatory funnel containing the aryl halide or its solution in ether or in ligroin. A liquid ammonia solution of potassium amide was prepared in the flask (which was about half filled with solvent) by adding ferric oxide (0.05 g.) to a solution of metallic potassium. The aryl halide was slowly introduced with good stirring, and the reaction was stopped at the desired time by adding ammonium chloride or ammonium nitrate equivalent to the potassium. The working up of the reaction products is described under method 1.

TABLE I

THE ACTION OF POTASSIUM AMIDE ON ARYL HALIDES

	KNH_2 MOLES	ARYL HALIDE MOLES	METHOD	REACTION TIME, HRS.	(a)		(a)	
					$ArNH_2$ MOLES	%	Ar_2NH MOLES	NOTES
(1)	0.26	*o*-C_7H_7Cl, 0.080	1	5	0.018	22		(b, h)
(2)	.10	*o*-C_7H_7Cl, .080	1	5	.023	39		(b)
(3)	.313	*o*-C_7H_7Cl, .150	3	1.5	.0580	39	0.022	(b)
(4)	.205	*o*-C_7H_7I, .151	2	1	.028	18		(b)
(5)	.10	*m*-C_7H_7Cl, .080	3	5	.012	22		(c)
(6)	.215	*m*-C_7H_7Cl, .100	3	1	.029	29	.010	(c)
(7)	.307	*m*-C_7H_7Cl, .150	2	4.5	.011	7.5	.014	(c)
(8)	.151	*m*-C_7H_7Cl, .158	2	1	.020	26	.013	(c)
(9)	.128	*p*-C_7H_7Cl, .080	1	0.5	.026	33		(d)
(10)	0.26	*p*-C_7H_7Cl, .16	2	5	.033	24		(d, h)
(11)	.25	*p*-C_7H_7Cl, .12	3	5	.053	44		(d)
(12)	.25	*p*-C_7H_7Cl, .10	3	6 (−78°)	.052	52		(d, f)
(13)	.319	*p*-C_7H_7Cl, .150	3	1.5	.043	29	.011	(d)
(14)	.306	*p*-C_7H_7Br, .151	3	1.5	.048	32	.018	(d)
(15)	.243	*p*-C_8H_9OCl, .115	3	0.5	.0475	41	.011	(e)
(16)	.201	*p*-C_8H_9OCl, .150	2	2.2	.0262	23	.018	(e)
(17)	.020	9-$C_{14}H_9Br$, .010	3	5	.088	88		(g)
(18)	$NaNH_2$ 0.33	*p*-C_7H_7Cl, .11	3	2	.024	22		(i)

Notes to Table I

(a) The yield of primary amine was calculated on the basis of the proper limiting factor in the equation, $ArX + 2KNH_2 \rightarrow ArNHK + KX + NH_3$. In experiments designated by note (h), a small amount of aryl halide was recovered; the yields are here calculated on the basis of the halide actually consumed. The higher-boiling fractions have been designated as "Ar_2NH" for comparative purposes only, without implication as to complete identity with this formula.

(b) *Products from the o-tolyl halides.* In this and the following, all melting points are uncorrected. All organic halides were white label preparations of the Eastman Kodak Co., refractionated before use.

The fraction boiling at about 195–205° (760 mm.) was heated with acetic anhydride and glacial acetic acid to form an acetyl derivative which melted at 108–109° after crystallizations from dilute alcohol, and at the same temperature when mixed with authentic aceto-*o*-toluide (run no. 1). The m.p. of the acetyl derivative from run 4 is 108.7–109.8°; several crystallizations were required to attain this purity, suggesting that the original material (n_D^{23} 1.5686) was a mixture.

In run 3, a somewhat viscous liquid fraction boiling at 198–210° (46 mm.) (n_D^{23} 1.6097) was readily converted to a solid hydrochloride by passing dry hydrochloric acid gas through its solution in absolute ether (yield, 0.42 g. from 1.1 g. of liquid. The melting point was about 140–165°, indicating a mixture). It is partly decomposed by heating near its melting point, and it is easily hydrolyzed by water.

(c) *Products from the m-tolyl halides.* The tolylamine fractions boiled (760 mm.) at 190–207° (no. 6, table I); 195–215° (no. 7); and at 190–210° (no. 8). The tolylamine from run 8 had n_D^{23} 1.5689, as compared with n_D^{20} 1.5686 for *m*-toluidine and n_D^{20} 1.5688 for *o*-toluidine. The acetyl derivatives of the above fractions were uncrystallizable oils, and were accordingly mixtures. The benzoyl derivative of the tolylamine fraction from run 8 melted at 136.5–139° after many crystallizations; Benz-*o*-toluidine melts at 146°, benz-*m*-toluide at 125°, and benz-*p*-toluide at 158° (13, 14, 15). The toluidine from run 5, when refractionated, boiled at 203–204° and gave an acetyl derivative melting at 64–65°, in agreement with the literature (16).

The oily ditolylamine fraction from run no. 7 boiled at 195–205° (24 mm.) and that from run 8 at 184–210° (26 mm.). Concentrated aqueous hydrochloric acid slowly converts this material to a pasty hydrochloride, which is readily hydrolyzed to the original oil. The m.p. of the hydrochloride, washed with hot benzene and dried, was 201–229°, indicating a mixture. No solid benzoyl derivative could be made.

(d) *Products from the p-tolyl halides.* In many of the reported runs, as well as in several that are not listed, the tolylamine fraction boiling about 195–205° at 760 mm. was converted to an acetyl derivative, m.p. 152–153° alone or when mixed with authentic aceto-*p*-toluide. However, the benzoyl derivative of the tolylamine fraction in run 14 could not be obtained in a pure condition (m.p. 110–128° after several crystallizations). The tolylamine from run 13 had $n_D^{23.5}$ 1.5663, indicating contamination with an isomer, since *p*-toluidine has $n_D^{59.1}$ 1.5532.

The oily ditolylamine fraction in expt. 13 boiled at 198–215° at 24 mm.; $n_D^{24.5}$ 1.6210. An easily hydrolyzed hydrochloride was precipitated from dried ethereal solution by dry hydrochloric acid gas. The fraction from run 14 boiled at 198–212° at 24.5 mm.; $n_D^{23.5}$ 1.6197.

(e) *Products from p-chlorophenetole.* In an unreported run, a fraction boiling at 253–259° (760 mm.) gave an acetyl derivative, m.p. 136°, in agreement with the literature (17). The acetyl derivatives from runs 15 and 16 could not be purified to this melting point, though a benzoyl derivative melting at 170–171° was readily obtained [benz-*p*-phenetidide melts at 173° (18)]. A hydrochloride, prepared by the action of concentrated hydrochloric acid on the base, melted at 233–234°, in agreement with the literature (19). The lower-boiling fraction of these runs appears therefore to be chiefly *p*-phenetidine.

Viscous liquid secondary amine fractions of low basicity were obtained at 250–290° (27 mm.; run 16) and at 250–260° (24 mm.; run 15). These are undoubtedly mixtures, since di-*p*-phenetylamine is probably a solid.

(f) The flask containing the potassium amide was cooled approximately to −78° by a bath of solid carbon dioxide in alcohol. A duplicate of this experiment with a shorter time of reaction (2 hrs.) gave a 32% yield of toluidine.

(g) The benzene solution of the reaction product was evaporated to give crude 9-aminophenanthrene, m.p. 127–129°. The m.p. after several crystallizations from absolute alcohol was 136–137.5° [literature, 135–136° (20)]. The oxalate, prepared in alcohol and crystallized from the same solvent, melted at 215° in agreement with the value of Schmidt and Strobel (21).

(h) The tolyl halide not consumed in the reaction was recovered; yields were calculated on the basis of the tolyl halide actually used.

(i) The *p*-toluidine was obtained as a solid at room temperatures.

Catalytic tolylation of p-toluidine. In accordance with method 2, the potassium amide, prepared from 4.05 g. of potassium, was siphoned over into 500 cc. of a solution of potassium *p*-toluidine [made by adding 11.5 g. of *p*-toluidine to the potassium amide from 4.11 g. of potassium (1000-cc. flask)] and 18.0 g. of *p*-bromotoluene, with good stirring. The reaction was stopped at the end of 1.5 hours by adding 10 g. of ammonium chloride. After evaporation of the ammonia, water was introduced to dissolve inorganic salts, and the oil remaining extracted several times with benzene. All material (benzene, *p*-bromotoluene, *p*-toluidine) boiling under 215° at 760 mm. was discarded. A weakly basic secondary amine fraction distilled at 198–215° (24 mm.) (4.6 g.; n_D^{24} 1.6213); it was, as expected, somewhat larger than would have been obtained by the action of the potassium amide upon *p*-bromotoluene alone (*cf.* run 14). No definite compounds were isolated from this material. A fraction boiling at 245–275° (24 mm.) partly solidified in the receiver (4.6 g.); when crystallized several times from alcohol, it melted at 144–154° (the yield of purified material was small).

Anal. Calc'd for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.88.
Found: C, 87.77; H, 6.89; N, 5.00.

This is accordingly tritolylamine or an isomer; tri-*p*-tolylamine melts at 117°, according to Wieland (7). Material approximating this m.p. (m.p. 110–111°) was obtained from the filtrate of the analyzed precipitate, but was thought to be a solid solution.

2-Tolylquinaldine. Quinaldine (0.09 mole) was added to the potassium amide from 0.10 atom of potassium dissolved in 200 cc. of liquid ammonia (method 2); after the formation of the red quinaldylpotassium, 0.09 mole of *p*-chlorotoluene was introduced, followed by 0.025 mole of potassium amide in 70 cc. of liquid ammonia contained in the second flask. After two hours, an excess of ammonium chloride was added, the solvent evaporated and the residue extracted with benzene. The benzene was extracted with dil. hydrochloric acid and excess alkali added to precipitate the organic bases, which were in turn extracted with benzene. Distillation of this extract gave a fraction boiling at 250–263° (52 mm.), which formed 4.4 g. (11%) of a picrate, m.p. 167–167.5°, after several crystallizations from methyl isobutyl ketone (picrate of a tolylquinaldine).

Anal. Calc'd for $C_{23}H_{18}N_4O_7$: C, 59.74; H, 3.92; N, 12.12.
Found: C, 59.96; H, 3.74; N, 12.30.

Competition reactions. The method has been described in a previous article (3). Potassium amide, prepared in about 50 cc. of liquid ammonia from oxide-free potassium (22) and an iron wire catalyst, was siphoned over into a stirred solution of a mixture of two aryl halides in 50 cc. of ether and 50 cc. of liquid ammonia. Calculations are essentially as already given (3), and the reactivities have been corrected for the change in concentration of one halide with respect to the other during the reaction.

m-Chlorotoluene and m-bromotoluene. Potassium amide, 0.0229 mole; *m*-chlorotoluene, 0.0421 mole; *m*-bromotoluene, 0.0418 mole. Wt. of silver halide, 0.2315 g. from one-tenth

aliquot. Moles silver halide from 0.1 aliquot, 0.001256. Calculated average mol. wt. of the silver halide, 184.3. Mole per cent, AgBr, 92.1; mole per cent AgCl, 7.9. Ratio, Br/Cl, 11.6; corrected ratio, 13.4.

m-Chlorotoluene and m-iodotoluene. Potassium amide, 0.0218 mole; *m*-chlorotoluene, 0.0450 mole; *m*-iodotoluene, 0.0451 mole. Wt. silver halide (0.1 aliquot), 0.2595 g. Moles of silver halide, 0.001178 in 0.1 aliquot. Average mol. wt. of the silver halide, 220.0. Mole per cent AgI, 83.8; mole per cent AgCl, 16.2. Ratio I/Cl, 5.2; corrected ratio, 6.5.

M-Bromotoluene and m-iodotoluene. Potassium amide, 0.151 mole; *m*-bromotoluene, 0.0311 mole; *m*-iodotoluene, 0.0311 mole. Wt. of silver halide in 0.1 aliquot, 0.1670 g. Moles of silver halide, 0.00827. Average mol. wt. silver halide, 202.0. Mole per cent AgBr, 69.8; mole per cent AgI, 30.2. Ratio, Br/I, 2.3; corrected ratio, 2.4.

Chlorobenzene and m-bromotoluene. Potassium amide, 0.0254 mole; chlorobenzene, 0.0500 mole; *m*-bromotoluene, 0.0503 mole. Wt. of silver halide in 0.1 aliquot, 0.2551 g. Moles of halide, 0.001398. Ave. mol. wt. of silver halide, 182.5. Mole per cent AgBr, 88.0; mole per cent AgCl, 12.0. Ratio, Br/Cl, 7.3, or 8.2, when corrected.

The same qualitative order of reactivity was found for the *o*- and *p*-tolyl halides, that is to say, the bromides were in all cases the most reactive, and the chlorides the least.

Yields of potassium halide in the reaction between potassium amide and an excess of a tolyl halide. Potassium amide, prepared from potassium metal in weighed capsules (22) was added to an excess (generally 1.5–2 moles per atom of potassium) of a tolyl halide dissolved in liquid ammonia, in accordance with method 1. After evaporation of the ammonia, the residue was taken up in water and extracted with benzene to remove amines. The aqueous solution was then analyzed for halide ion in the usual manner, taking a tenth aliquot of a 1000 cc. solution. The figures below, each referring to a separate determination, represent the per cent of the halide ion, as determined by analysis and calculated in accordance with the equation, $C_7H_7X + KNH_2 \rightarrow C_7H_7NH_2 + KX$.

p-C_7H_7Cl: 57.0, 56.7, 53.9, 56.6.
o-C_7H_7Cl: 56.6, 55.9, 57.0.
m-C_7H_7Cl: 57.0, 53.1, 58.1.
p-C_7H_7Br: 61.4, 54.0, 54.0.
o-C_7H_7Br: 58.0, 54.5.
m-C_7H_7Br: 49.4, 53.1, 52.6.
p-C_7H_7I: 61.1, 58.4.
o-C_7H_7I: 57.0, 55.5.
m-C_7H_7I: 60.2, 61.2.

SUMMARY

1. The tolyl halides react with a solution of potassium amide in liquid ammonia to give in every case a mixture of toluidines, which contains some of the expected (not rearranged) isomer. *p*-Phenetidine, mixed possibly with an isomer, is prepared by the action of potassium amide on *p*-chlorophenetole, and 9-aminophenanthrene is similarly obtained from 9-bromophenanthrene.

2. Liquid secondary amine fractions of low basicity were isolated from the products of the reaction of potassium amide with the tolyl halides, or with *p*-chlorophenetole. In all cases, these were mixtures of unknown composition.

3. The formation of these secondary amines is doubtless due to an activation of the halogen in the tolyl halides or in *p*-chlorophenetole by the potassium amide, in the manner previously described for the phenyl halides (3). This activation has been demonstrated in the reaction between *p*-bromotoluene and potassium *p*-toluidine, and in the reaction between *p*-chlorotoluene and quin-

aldylpotassium; in the former case, an isomer of tritolylamine, m.p. 145°, was obtained; in the latter case, a tolylquinaldine of unknown orientation.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME NOVEL REACTIONS OF 4-QUINAZOLONE[1,2]

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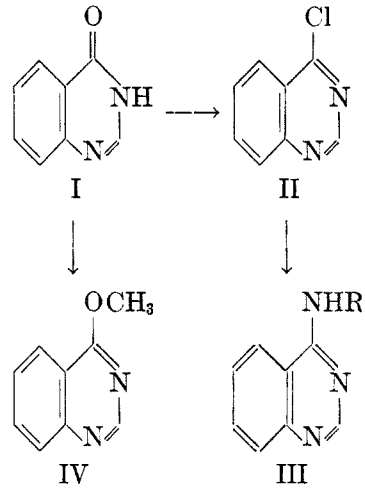
The usual method of synthesis of 4-aminoquinazolines (III) involves the conversion of 4-quinazolone (I) to 4-choloroquinazoline (II) and the treatment of II with the desired amine (1). Preliminary work with heterocyclic compounds closely related to quinazoline made it appear necessary to circumvent the chloro intermediate corresponding to II. Accordingly, model experiments have been carried out in the quinazoline series in an attempt to bring about the conversion of I to III by some other route. This paper describes the methylation of 4-



quinazolone (I) to 4-methoxyquinazoline (IV) and the reactions of these two compounds with ammonia and certain amines.

The utilization of the methyl ether (IV) was suggested by the researches of Magidson and Grigorowsky (2), who proposed that the phenyl ether (VI) is an intermediate in the preparation of Atabrine (VII) by the treatment of 6,9-dichloro-2-methoxyacridine (V) with 4-amino-1-diethylaminopentane in phenol. In support of this hypothesis, these workers prepared 6-chloro-2-methoxy-9-phenoxyacridine (VI) and treated it with the diamine. In this reaction, the yields of

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

[2] A recent paper by Tomisek and Christensen (14) appeared after preparation of this manuscript, submission of which was delayed by the absence of the senior author on an overseas mission.

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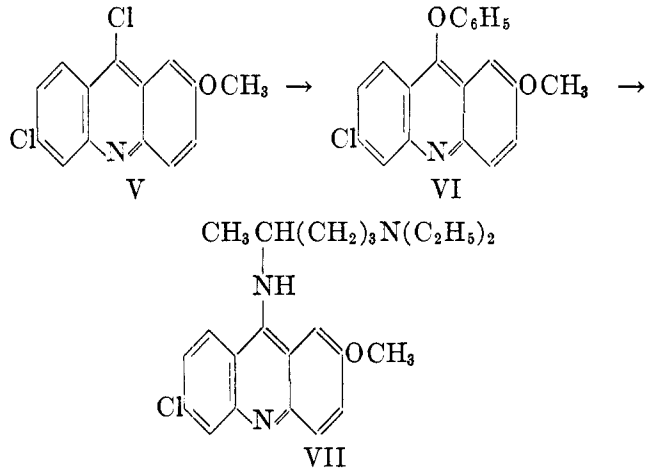
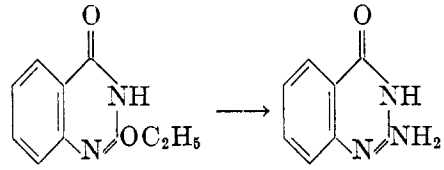


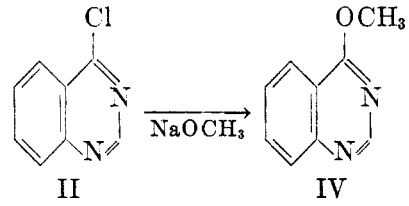
Atabrine were as good as those which had been obtained from the chloro compound (V) and the diamine. In the quinoline series, 4-alkoxyquinolines have been found to react with ammonium salts, either alone or in the presence of ammonia or alkyl amines, to give 4-aminoquinoline (3). In the quinazoline series, an example of an analogous replacement is found in the conversion of 2-ethoxy-4-quinazolone (VIII) to 2-amino-4-quinazolone (IX) by means of ethanolic ammonia at 100° (4).



4-Quinazolone can be obtained readily by heating anthranilic acid with formamide, according to the method of Niementowsky (5). Alkylation of 4-quinazolone with methyl and ethyl iodide and methyl sulfate has been discussed by Bogert and Seil (6). They concluded that alkylation with methyl iodide and ethanolic alkali gave only the 3-methyl-4-quinazolone and that methyl sulfate behaved similarly. When ethyl iodide was used, the probability of obtaining the O-ethyl compound appeared greater. The action of methyl iodide on the silver salt gave both the O-methyl and N-methyl derivatives. In this case, also, with the ethyl iodide the O-ethyl derivative was more likely to be formed. Methylation of 2- and 4-pyridones and -quinolones with diazomethane has been found, in general, to give the O-methyl product (7). Diazomethane, therefore, seemed to be the most promising methylating agent for 4-quinazolone.

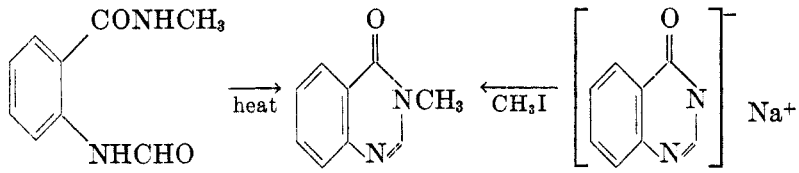
All of the possible methylation products of 4-quinazolone have been reported in the literature. 4-Methoxyquinazoline (IV), m.p. 35.4°, has been prepared by Bogert and May (8) by the treatment of 4-chloroquinazoline (II) with sodium methoxide. 3-Methyl-4-quinazolone (XI), m.p. 71°, was prepared by Knape (9)

both by the action of methyl iodide on the sodium salt of 4-quinazolone and by the ring closure of X. 2-Methyl-4-quinazolone melts at 238–239° (10). 1-Methyl-4-quinazolone (XIII), m.p. 123–124°, was obtained by Knape but, unfortunately, in amount insufficient for analysis.



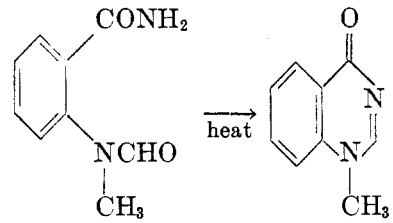
II IV

M.p. 35°



X XI

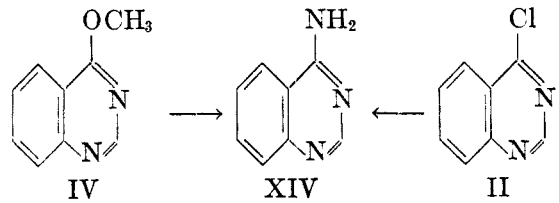
M.p. 71°



XII XIII

M.p. 123–124°

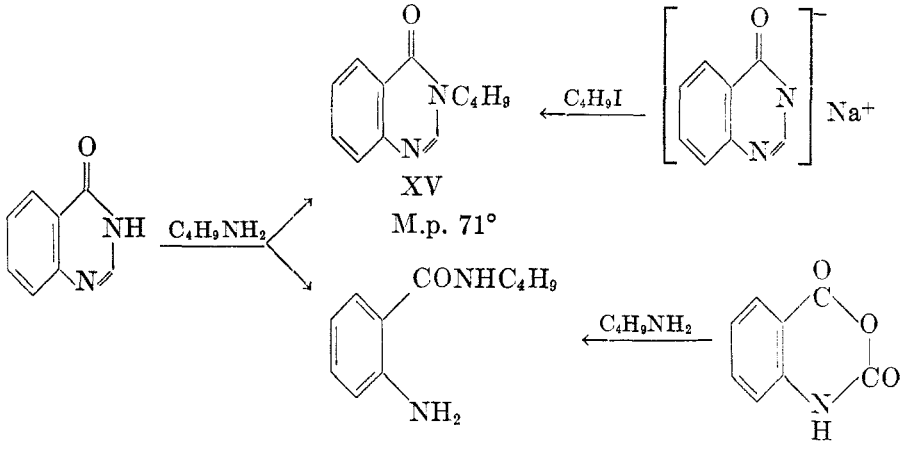
4-Quinazolone was treated with diazomethane. 4-Methoxyquinazoline was isolated by vacuum distillation in 20% yield and the only other product obtained was a crystalline solid, m.p. 103.5–105.5°, which was shown by analysis to be isomeric with 4-methoxyquinazoline. The melting point of this compound is not in agreement with that of any of the three most probable products, but its structure was not investigated further. The crude 4-methoxyquinazoline reacted with methanolic ammonia in a bomb to give 4-aminoquinazoline (XIV) which has recently been prepared by Dewar (11) from 4-chloroquinazoline and ammonia.



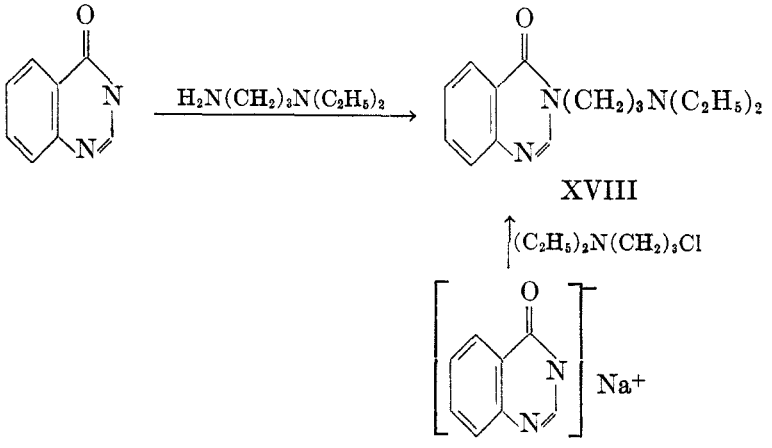
IV XIV II

The difficulty of obtaining the intermediate 4-methoxyquinazoline from 4-quinazolone (I) led to an investigation of the direct amination of I. Such amination could be effected in at least 20% yield by the use of methanolic ammonia at 200°.

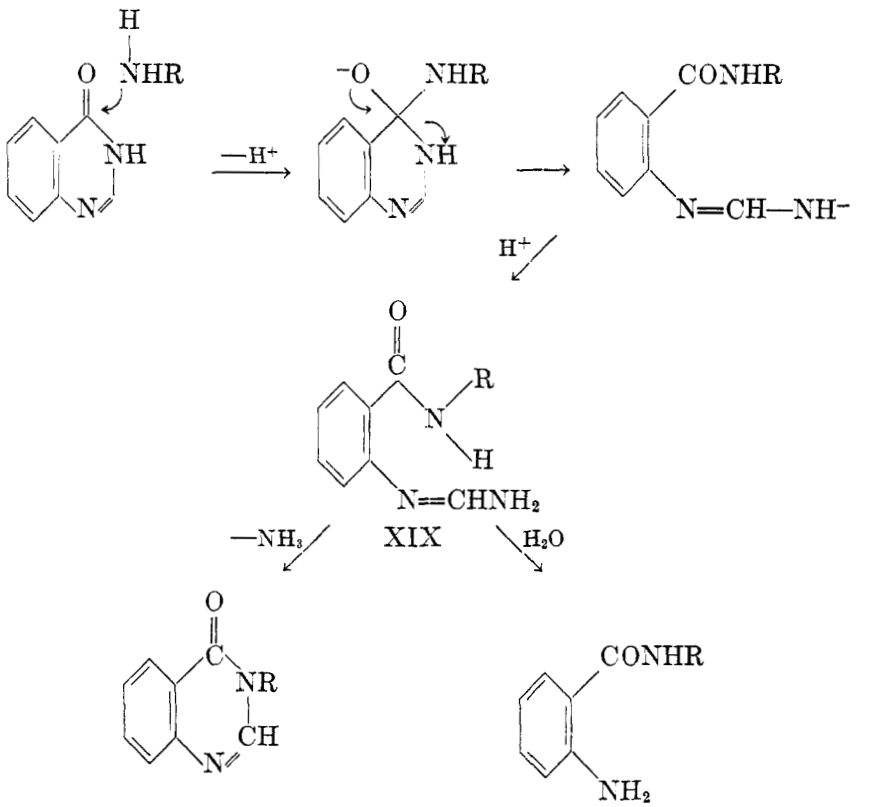
When 4-quinazolone was heated at 140° with *n*-butylamine, the product was 3-butyl-4-quinazolone (XV) rather than 4-butylaminoquinazoline. A small amount of *o*-amino-N-butylbenzamide (XVI) was also isolated. Compound XV has been prepared by Bogert and May (8) from the sodium salt of 4-quinazolone and butyl iodide, while XVI has been prepared by Clark and Wagner (12) by the action of butylamine on isatoic anhydride (XVII).



Similarly, γ-diethylaminopropylamine reacted with 4-quinazolone to give 3-(γ-diethylaminopropyl)-4-quinazolone (XVIII) which was isolated as the picrate. The same compound was obtained from the reaction of γ-diethylaminopropyl chloride with the sodium salt of 4-quinazolone.



A satisfactory mechanism for the reaction of *n*-butylamine with 4-quinazolone should account for the formation of both *o*-amino-N-butylbenzamide and 3-butyl-4-quinazolone. Such a mechanism requires that ring-opening occur. The following series of intermediates would appear to constitute a logical explanation of the course of the reaction. The formamidine XIX would be expected



to be the first stable intermediate. Ring closure of XIX by internal addition, followed by the elimination of ammonia, would provide 3-butyl-4-quinazolone. Although no water was present during the reaction to hydrolyze the amidine (XIX), that which had failed to undergo cyclization would be expected to be converted readily to *o*-amino-N-butylbenzamide when the crude reaction product was later treated with water.

EXPERIMENTAL[4]

4-Quinazolone was prepared from anthranilic acid and formamide by the method of Niementowski (5).

Reaction of 4-quinazolone with diazomethane. 4-Methoxyquinazoline. A solution of diazomethane (4.2 g., 0.10 mole) in 150 cc. of ether was prepared by the directions of Arndt

[4] All melting points are corrected. Microanalyses by Miss Theta Spoor and Miss Lillian Hruda.

(13) by adding 15 g. of nitrosomethylurea to 50 cc. of 40% potassium hydroxide and 150 cc. of diethyl ether at 5° with mechanical stirring. When the solid had dissolved, the ether layer was separated and dried over 10 g. of potassium hydroxide pellets. It was then filtered and added without distillation to a suspension of 5.0 g. (0.034 mole) of 4-quinazolone in 10 cc. of methanol. Nitrogen was evolved immediately and the suspension was stirred mechanically at room temperature. The quinazolone dissolved completely in about four hours. The solution was filtered, 50 cc. of distilled water was added, and the mixture was shaken until the excess diazomethane was decomposed. The ether layer was separated and dried over 10 g. of magnesium sulfate and the ether removed. The residue was distilled under reduced pressure over an oil-bath at 200°. The fraction boiling at 141–164° at 18 mm. (1.1 g.) was collected. It melted at 15–20° and was impure *4-methoxyquinazoline* which had been reported previously by Bogert and May (8) to melt at 35.4°. The crude product was used in the next reaction without further purification.

The residue from the vacuum distillation (1.9 g.) solidified on cooling and melted at 103.5–105.5° after recrystallization from petroleum ether (b.p. 90–110°). Its composition was shown by analysis to be that of an isomer of 4-methoxyquinazoline. 3-Methyl-4-quinazolone has been reported by Knape (9) to melt at 71° when recrystallized from petroleum ether. 1-Methyl-4-quinazolone was also prepared by Knape (9) and was reported to melt at 123–124°, although insufficient material was available for an analysis. The structure of the compound melting at 103–105° is therefore uncertain. It was soluble in acid and insoluble in alkali.

Anal. Calc'd for $C_9H_8N_2O$: C, 67.47; H, 5.03; N, 17.49.
Found: C, 67.64; H, 5.21; N, 17.40.

Reaction of 4-methoxyquinazoline with ammonia. 4-Aminoquinazoline. The impure 4-methoxyquinazoline (1.1 g.) obtained above was heated in a bomb with 10 cc. of liquid ammonia and 10 cc. of methanol at 140° for sixteen hours. The yellowish crystals which had precipitated were collected (0.3 g.) and recrystallized from an ethanol-water mixture; m.p. 268.5–269.5°. The melting point reported by Dewar (11) for 4-aminoquinazoline was 260°.

Since Dewar failed to report any derivative of 4-aminoquinazoline the *picrate* was prepared in ethanol, in which it was extremely insoluble, and was recrystallized from dilute aqueous acetic acid. It melted with decomposition at 288–290°.

Anal. Calc'd for $C_8H_7N_3 \cdot C_6H_3N_3O_7$: C, 44.92; H, 2.69; N, 22.46.
Found: C, 44.90; H, 2.72; N, 21.86.

Reaction of 4-quinazolone with ammonia. 4-Aminoquinazoline. 4-Quinazolone (1.0 g.) was heated in a bomb with 10 cc. of liquid ammonia and 10 cc. of methanol at 200° for twenty-four hours. The solvent was removed, a few cubic centimeters of 15 *N* ammonia was added, and the solution filtered. 4-Aminoquinazoline (0.2 g., 20% yield) was obtained, as shown by the melting point and mixed melting point with the sample obtained above, and also by the melting point of the picrate.

Reaction of 4-quinazolone with butylamine. 3-Butyl-4-quinazolone and o-amino-N-butylbenzamide. 4-Quinazolone (5.0 g., 0.034 mole) was heated in a bomb at 150° for twenty-four hours with 13 cc. (9.5 g., 0.13 mole) of freshly distilled *n*-butylamine. After the removal by distillation of excess butylamine the product was shaken with 20 cc. of 10% aqueous sodium hydroxide and 50 cc. of ether. The alkali layer was extracted with an additional 25-cc. portion of ether. The ether extracts were combined and dried over magnesium sulfate. The ether was distilled and the last of the volatile solvent removed under reduced pressure. The oil remaining was boiled for 10 minutes with 14 cc. of 85% sulfuric acid in order to remove impurities susceptible to hydrolysis. The solution was diluted and made basic to litmus with sodium hydroxide solution. The crude insoluble compound which separated was collected on a filter, washed with water, and dried. The yield was 2.5 g. (36% of the theoretical), m.p. 64–70°. It was purified by reprecipitation from warm dilute hydrochloric acid containing activated charcoal and recrystallization from an ethanol-

water mixture. The purified solid melted at 71–72°, the melting point reported by Bogert and May (8) for 3-butyl-4-quinazolone.

Since no derivative is reported in the literature the *picrate* was prepared and recrystallized from ethanol. It sintered at 151° and melted at 154–155° to a light yellow liquid.

Anal. Calc'd for $C_{18}H_{17}N_5O_8$: C, 50.11; H, 3.97.
Found: C, 50.05; H, 3.86.

In a second experiment, 4-quinazolone (5.0 g., 0.034 mole) was heated at 150° with 13 cc. (9.5 g., 0.13 mole) of *n*-butylamine. After addition of ether, extraction with alkali and removal of ether and butylamine, two grams of oil remained which solidified on cooling (m.p. 30–40°). On repeated recrystallization from petroleum ether (b.p. 90–110°) a very small amount of waxy solid, m.p. 83–85° remained. This melting point is in agreement with that reported by Clark and Wagner (83–84°) (12) for *o-amino-N-butylbenzamide*. The identity of the solid was further confirmed by analysis.

Anal. Calc'd for $C_{11}H_{16}N_2O$: C, 68.73; H, 8.93; N, 14.58.
Found: C, 68.55; H, 8.38; N, 14.72.

The presence of 3-butyl-4-quinazolone in the mixture was shown by evaporation to dryness of the filtrates obtained in the preparation of the analytical sample. The solid (0.3 g.) obtained was refluxed ten minutes with 5 cc. of 85% sulfuric acid. The solution was diluted and made alkaline with aqueous sodium hydroxide. The insoluble white solid (0.1–0.2 g.) which remained was washed with water and recrystallized from water-ethanol solution. It was shown by melting point and mixed melting point to be identical with the 3-butyl-4-quinazolone obtained above.

Reaction of 4-quinazolone with γ-diethylaminopropylamine. 3-(γ-Diethylaminopropyl)-4-quinazolone. Five grams (0.034 mole) of 4-hydroxyquinazoline was heated in a bomb for twenty-four hours at 150° with 13 cc. (10 g., 0.072 mole) of γ-diethylaminopropylamine. When the bomb was cooled and opened, a gas with an ammoniacal odor escaped. The solution was evaporated on a steam-cone under reduced pressure. The oil remaining was added to 20 cc. of benzene and the solution was extracted with 10 cc. of aqueous 20% sodium hydroxide. The water solution was separated and extracted with 10 cc. of benzene. The combined benzene extracts were dried over magnesium sulfate and filtered.

Carbon disulfide (10 cc.) was added to the solution in order to remove the excess γ-diethylaminopropylamine. The dithiocarbamate of the latter separated as an oil. Acetone (30 cc.) was added to cause it to solidify. The solid was removed and rinsed with benzene. The filtrate was evaporated, dissolved in 50 cc. of ethanol, and the solution added to 16 g. (0.070 mole) of picric acid dissolved in 500 cc. of hot ethanol. The solution was allowed to cool slowly and was decanted from a small amount of dark oil which first separated. The crystalline picrate which then precipitated was collected and washed with cold dilute ethanol. Eighteen grams (74%), m.p. 146–153°, was obtained. The *3-(γ-diethylaminopropyl)-4-quinazolone dipicrate* was purified for analysis by recrystallization from ethanol and methyl cellosolve. It then melted at 160–161° to a pale liquid.

Anal. Calc'd for $C_{15}H_{21}N_3O \cdot 2C_6H_3N_3O_7$: C, 45.19; H, 3.79; N, 17.57.
Found: C, 45.38; H, 4.18; N, 17.67.

When the above reaction was carried out at 200° for twenty-four hours the product was quite dark and the picrate was induced to crystallize only with considerable difficulty.

3-(γ-Diethylaminopropyl)-4-quinazolone was also prepared by refluxing a suspension of 3.0 g. (0.020 mole) of 4-quinazolone, 9.0 g. (0.060 mole) of γ-diethylaminopropyl chloride, and 1.2 g. (0.020 mole) of potassium hydroxide for fourteen hours. The residual oil was added to a hot solution of 9.2 g. (0.040 mole) of picric acid in 200 cc. of ethanol. The picrate separated almost immediately as an oil but solidified on cooling to a light yellow solid. It was collected and washed thoroughly with 95% ethanol and melted at 152–155° (1.8 g.). On further recrystallization, the melting point was raised to 158–160° and a mixed melting point with the compound prepared above showed no depression.

SUMMARY

1. 4-Quinazolone has been found to react with diazomethane to give 4-methoxyquinazoline and a considerable amount of an unidentified monomethylation product.

2. 4-Methoxyquinazoline and 4-quinazolone were converted to 4-aminoquinazoline by treatment with methanolic ammonia under pressure.

3. Treatment of 4-quinazolone with *n*-butylamine or γ-diethylaminopropylamine yielded the 3-alkyl-4-quinazolone. A possible course for this reaction has been proposed.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

PREPARATION OF 4-MERCAPTO AND 4-AMINO QUINAZOLINES[1]

NELSON J. LEONARD AND DAVID Y. CURTIN[2]

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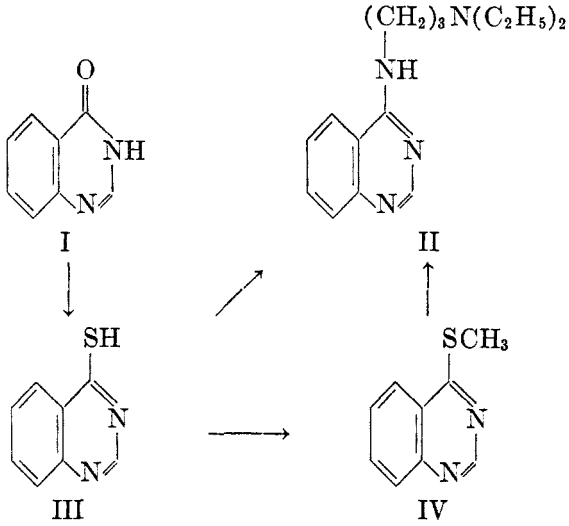
In a previous communication (1) attempts to convert 4-quinazolone (I) to 4-(γ-diethylaminopropylamino)quinazoline (II) without proceeding through 4-chloroquinazoline were described and it was shown that, while 4-quinazolone reacted with ammonia in a bomb to give 4-aminoquinazoline, it reacted with γ-diethylaminopropylamine to give 3-(γ-diethylaminopropyl)-4-quinazolone. Although 4-methoxyquinazoline was converted to 4-aminoquinazoline by treatment with ammonia and might give the desired product with γ-diethylaminopropylamine, the difficulties in its preparation by O-methylation of 4-quinazolone made this route look unpromising.

In this paper a method of converting 4-quinazolone to 4-(γ-diethylaminopropylamino)quinazoline by using 4-mercaptoquinazoline (III) and 4-methylmercaptoquinazoline (IV) as intermediates is described.



A synthesis of 4-mercaptoquinazoline (III) has been reported in a British patent by Kendall (2), who prepared it by the reaction of 4-chloroquinazoline with sodium hydrosulfide. He found that it reacted with dimethyl sulfate in the presence of alkali to give 4-methylmercaptoquinazoline (IV). This reaction is not surprising in view of the S-alkylation of thioamides by alkyl halides (3).

Since the purpose of this research was to avoid the use of 4-chloroquinazoline

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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as an intermediate, it was necessary to find a different method of converting I to III. Although there seems to be no report in the chemical literature of the reaction of phosphorus pentasulfide with 2- or 4-quinazolones, quinolones, pyrimidones, or pyridones, it is well known that amides are readily converted to thioamides by treatment with this reagent (3). Investigation disclosed that 4-quinazolone (I) was converted to 4-mercaptoquinazoline (III) in 59% yield by treatment with phosphorus pentasulfide in refluxing xylene.

Since it is easy to replace a 2- or 4-methylmercapto group on the pyrimidine ring by the action of ammonia and amines (4), 4-methylmercaptoquinazoline (IV) was prepared from 4-mercaptoquinazoline (III) and dimethyl sulfate. On treatment with γ-diethylaminopropylamine it was converted smoothly to the desired product (II). The over-all yield from I was 27%.

It is well known that thioamides react with amines to give amidines (3). It was hoped therefore that 4-mercaptoquinazoline might react directly with γ-diethylaminopropylamine to give II. This has actually proved to be a superior for converting I to II, giving an over-all yield of 47%.

TABLE I

REACTION OF 4-MERCAPTOQUINAZOLINE WITH AMINES

AMINE	TEMP. °C.	TIME	YIELD OF THE 4-AMINOQUINAZOLINE, %
γ-Diethylaminopropylamine	90–110	20 min.	80
n-Butylamine	Reflux	2 hours	70
Aniline	130–160	4½ hours	14
	Reflux	3 hours	23
Morpholine	105–110	3½ hours	27
Diethylamine	Reflux	72 hours	0

A few other amines have been found to react similarly, yielding 4-alkylaminoquinazolines. In table I, the amines used, reaction conditions, and yields are given.

EXPERIMENTAL[3]

Reaction of 4-quinazolone with phosphorus pentasulfide. 4-Mercaptoquinazoline. 4-Quinazolone (15.0 g., 0.10 mole) was heated with 21.6 g. (0.10 mole) of phosphorus pentasulfide in 100 cc. of refluxing xylene with mechanical stirring for two hours. Aqueous sodium hydroxide (70 cc., 20%) was added. The mixture was filtered and the xylene distilled. The filtrate was made slightly acid with glacial acetic acid and the yellow solid which precipitated was collected and washed with water. It was reprecipitated from 50 cc. of 20% sodium hydroxide and then digested in 100 cc. of refluxing glacial acetic acid for one-half hour. The yield of yellow solid melting at 324–325° (311–312°, uncorr., darkened at 300°) was 9.5 g. (59%). The melting point reported in the literature is 312° (2).

Methylation of 4-mercaptoquinazoline. 4-Methylmercaptoquinazoline. To 10 cc. of water containing 0.4 g. (0.01 mole) of sodium hydroxide was added 1.6 g. (0.010 mole) of 4-mercaptoquinazoline and then 1.0 cc. (1.3 g., 0.010 mole) of dimethyl sulfate. After a minute or two of stirring, heat was evolved and an oil began to separate. The suspension was allowed to stand overnight. A few cubic centimeters of ammonium hydroxide was added

[3] Analyses by Misses Theta Spoor and Lillian Hruda. All melting points corrected.

and, after several hours, the oil solidified. The solid was collected and washed with water. The yellowish solid obtained (1.5 g., 85%) melted at 50–57° and was used without further purification in the reaction described below. The melting point previously reported was 68° (2).

Reaction of 4-methylmercaptoquinazoline with γ-diethylaminopropylamine. 4-(γ-Diethylaminopropylamino)quinazoline. The crude methylmercapto compound obtained above (1.5 g., 0.0085 mole) was heated with 1.4 cc. (1.1 g., 0.0085 mole) of γ-diethylaminopropylamine at 90–110°. Methylmercaptan was evolved and the heating was continued until its evolution ceased. Ethanol (2 cc.), benzene (4 cc.), and carbon disulfide (2 cc.) were added in order to precipitate unreacted γ-diethylaminopropylamine as the dithiocarbamate. The solution was seeded with a small amount of authentic dithiocarbamate, cooled, and filtered. The filtrate was added to 4.0 g. (0.18 mole) of picric acid in 75 cc. of 95% ethanol. The dipicrate of 4-(γ-diethylaminopropylamino)quinazoline precipitated as an oil which later solidified to a yellow solid, m.p. 195–199°. The melting point previously reported was 199–200° (5). The yield was 3.4 g. (56%). The identity of the picrate was further established by a mixed melting point with an authentic sample of 4-(γ-diethylaminopropylamino)quinazoline dipicrate, and by adding the picrate obtained above to 40 cc. of 6 *N* hydrochloric acid and extracting the picric acid with benzene. The acid solution was then made strongly alkaline with potassium hydroxide (50% solution at first, then solid) and the amine was extracted with four 20-cc. portions of benzene. The benzene extracts were combined and dried over magnesium sulfate. The benzene was evaporated on a steam-bath. The residue solidified on standing in a desiccator under reduced pressure overnight. On recrystallization from petroleum ether it melted at 58–63°. The melting point reported in the literature (5), was 69–70°.

Reaction of 4-mercaptoquinazoline with γ-diethylaminopropylamine. 4-(γ-Diethylaminopropylamino)quinazoline. 4-Mercaptoquinazoline (1.6 g., 0.010 mole) was heated with 3.2 cc. (2.6 g., 0.02 mole) of γ-diethylaminopropylamine at 90–110° for twenty minutes. The mercaptoquinazoline quickly dissolved with the evolution of hydrogen sulfide. To the solution was added 4.6 g. (0.020 mole) of picric acid in 75 cc. of ethanol. The picrate separated as an oil but solidified when the solution was heated to boiling. It was purified by recrystallization from 50 cc. of ethanol and 75 cc. of methyl cellosolve. The yield was 5.7 g. (80%), m.p. 197–200°. The melting point recorded in the literature is 199–200° (5). There was no depression in melting point when the compound was mixed with an authentic sample of 4-(γ-diethylaminopropylamino)quinazoline dipicrate.

Reaction of 4-mercaptoquinazoline with n-butylamine. 4-Butylaminoquinazoline. 4-Mercaptoquinazoline (1.6 g., 0.010 mole) was heated with 5 cc. of refluxing *n*-butylamine for two hours. The butylamine was then removed under reduced pressure. The solid residue was added to 10 cc. of warm 10% sodium hydroxide solution. Although it melted to an oil in the warm solution, it solidified again on cooling. It was purified by solution in 10 cc. of warm dilute hydrochloric acid and decolorization with activated charcoal, followed by recrystallization from an ethanol-water mixture. The yield was 1.4 g. (70%) of product melting at 114–117°. The compound was purified for analysis by recrystallization from petroleum ether (b.p. 90–110°), which was a far more satisfactory solvent than ethanol-water. It recrystallized as long white needles melting at 116–117°.

Anal. Calc'd for $C_{12}H_{15}N_3$: C, 71.60; H, 7.51; N, 20.87.
Found: C, 71.87; H, 7.48; N, 20.87.

The *picrate*, m.p. 189.5–190.5° was prepared in, and recrystallized from ethanol.

Anal. Calc'd for $C_{12}H_{15}N_3 \cdot C_6H_3N_3O_7$: C, 50.23; H, 4.22.
Found: C, 50.09; H, 4.14.

Reaction of 4-mercaptoquinazoline with aniline. 4-Anilinoquinazoline. 4-Mercaptoquinazoline (1.6 g., 0.010 mole) was heated with 5 cc. of aniline for four and one-half hours at 130–160°. The solid had completely dissolved at the end of that time. Brownish needles separated on cooling. Excess aniline was removed, and 10 cc. of 10% sodium hydroxide was added. The solid was collected and washed. Only 0.5 g. of solid melting at 187–206° was obtained. On decolorization with activated charcoal and zinc dust and recrystalliza-

tion from an ethanol-water mixture 0.3 g. (14%) of product melting at 210–216° was obtained. After further recrystallization from the same solvent it melted at 216–217°. The melting point has been reported to be 221–222° (6). The filtrate from the first recrystallization above was made acid with glacial acetic acid. The solid which precipitated was recovered starting material and amounted to 1.2 g.

The identity of the 4-anilinoquinazoline above was further established by conversion to the picrate, which melted at 230–231° on recrystallization from ethanol. The melting point reported in the literature is 233° (6).

When an experiment was carried out which differed from that above only in that the aniline solution of 4-mercaptoquinazoline was refluxed for three hours, 0.9 g. of alkali-insoluble solid was obtained which on recrystallization from petroleum ether-benzene-ethanol solution melted at 217–220° (0.5 g., 23%). Only 0.8 g. of starting material was recovered.

Reaction of 4-mercaptoquinazoline with morpholine. 4-Mercaptoquinazoline (1.6 g., 0.010 mole) was heated at 105–110° with 8 cc. of morpholine for three and one-half hours. The morpholine was evaporated under reduced pressure and the residue was warmed with 10 cc. of 10% sodium hydroxide. It melted but solidified again on cooling, and was collected and washed with water. The white solid obtained (0.6 g., 27%) melted at 90–93°. It was recrystallized from petroleum ether (b.p. 90–110°) from which it precipitated in chunky snow-white crystals, m.p. 93.5–94.5°. 4-Mercaptoquinazoline (0.4 g.) was recovered from the first filtrate above by acidification with acetic acid.

Anal. Calc'd for $C_{12}H_{13}N_3O$: C, 66.97; H, 6.09; N, 19.53.
Found: C, 66.78; H, 6.05; N, 19.48.

The *picrate* was prepared in ethanol in which it was sparingly soluble. It was purified by recrystallization from an ethanol-methyl cellosolve mixture and melted at 204–205°.

Anal. Calc'd for $C_{12}H_{13}N_3O, C_6H_3N_3O_7$: C, 48.65; H, 3.63.
Found: C, 48.83; H, 3.82.

Attempted reaction of 4-mercaptoquinazoline with diethylamine. 4-Mercaptoquinazoline (1.6 g., 0.010 mole) was refluxed with 10 cc. of diethylamine for seventy-two hours. A large amount of solid was still undissolved at the end of that time. The diethylamine was removed and 10 cc. of 10% sodium hydroxide was added. The solution which resulted was filtered. There was no significant amount of insoluble material. The filtrate was acidified with acetic acid; the solid which precipitated was recovered 4-mercaptoquinazoline (1.2 g.).

SUMMARY

4-Quinazolone reacted with phosphorus pentasulfide to form 4-mercaptoquinazoline, which, in turn, reacted with γ-diethylaminopropylamine, *n*-butylamine, aniline, or morpholine to give the corresponding 4-aminoquinazoline. The reaction proceeded most satisfactorily for the two aliphatic primary amines and failed with diethylamine under the conditions employed.

4-Methylmercaptoquinazoline reacted in a similar fashion with γ-diethylaminopropyl amine.

URBANA, ILL.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

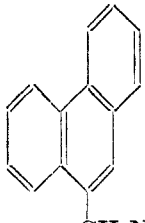
ATTEMPTS TO FIND NEW ANTIMALARIALS. XIII. ALKANOLAMINES DERIVED FROM PHENANTHRENE AND ANTHRACENE[1]

EVERETTE L. MAY

Received February 14, 1945

Earlier investigations (1) in this Laboratory have shown that a large number of phenanthryl-9 and tetrahydrophenanthryl-9 amino alcohols possess strong antimalarial activity. More recent communications (2) deal with compounds of this type in which slight modifications of the side chain have been made without producing a marked change in activity. In order to study the effect of a more radical variation of the carbinolamine chain, representatives of types I and II have been synthesized.

Recent researches by Hass and co-workers (3), Sprang and Degering (4), and Gakenheimer and Hartung (5) have served to improve hitherto unsatisfactory procedures for the preparation of alkamines of the type NH_2CH_2CHOHR (R = alkyl). By condensing these alkamines with an aromatic aldehyde and hydrogenating the resulting aldimines, one should arrive at amino alcohols of the general formula $ArCH_2NHCH_2CHOHR$. The two requisite 9-aldehydes for I and II can be easily obtained in large amounts and offered, therefore, convenient



$CH_2NHCH_2CHOHC_nH_{2n+1}$

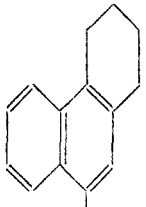
I

$C_{14}H_9—9—CHOHCH_2N(C_nH_{2n+1})_2$

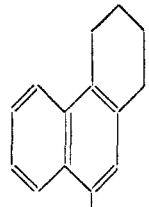
III

$C_{14}H_{13}—9—CHOHCH_2N(C_nH_{2n+1})_2$

IV



$\frac{CH_2O}{HCOOH}$



$CH_2NHCH_2CHOHC_nH_{2n+1}$

II

$CH_2N(CH_3)CH_2CHOHC_nH_{2n+1}$

V

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

TABLE I

AMINO ALCOHOLS

PHENANTHRENE-9-	SN	M.P., °C.	SOLVENT	APPEARANCE[a]	FORMULA	CALC'D		FOUND	
						C %	H %	C %	H %
1. $CH_2NHCH_2CHOHCH_3 \cdot HCl$	5926	216–217	Abs. EtOH-ether	Rect. plates	$C_{18}H_{20}ClNO$	71.63	6.68	71.36	6.62
2. $CH_2NHCH_2CHOHCH_2CH_3 \cdot HCl$	11893	195–198	Abs. EtOH-ether	Needles	$C_{19}H_{22}ClNO$	72.24	7.02	72.10	7.24
3. $CH_2NHCH_2CHOH(CH_2)_2CH_3 \cdot HCl$	5848	217–218.5	Abs. EtOH-ether	Needles or plates	$C_{20}H_{24}ClNO$	72.81	7.33	72.55	7.53
4. $CH_2NHCH_2CHOH(CH_2)_5CH_3 \cdot HCl$	8866	180–182.5	Abs. EtOH	Fine needles	$C_{25}H_{30}ClNO \cdot 0.5\ H_2O$	72.49	8.20	72.30	8.39
					$C_{23}H_{30}ClNO$[b]	74.28	8.13	73.95	8.25
1,2,3,4-TETRAHYDROPHENANTHRENE-9-									
5. $CH_2NHCH_2CHOHCH_3 \cdot HCl$	6810	198.5–200	Abs. EtOH-ether	Prisms	$C_{18}H_{24}ClNO$	70.67	7.91	70.47	7.89
6. $CH_2NHCH_2CHOHCH_2CH_3 \cdot HCl$	6813	157–159	Abs. EtOH-ether	Rods	$C_{19}H_{26}ClNO \cdot C_2H_5OH$[c]	68.91	8.82	69.07	8.76
7. $CH_2NHCH_2CHOH(CH_2)_2CH_3 \cdot HCl$	6815	188.5–190.5	Abs. EtOH	Plates	$C_{20}H_{28}ClNO$	71.94	8.46	71.87	8.61
8. $CH_2N(CH_3)CH_2CHOHCH_3 \cdot HCl$	9462	161–165	Abs. EtOH-acetone	Prisms	$C_{19}H_{26}ClNO$	71.33	8.19	71.13	8.85
9. $CH_2N(CH_3)CH_2CHOHCH_3 \cdot$ Picrate		87–89	95% EtOH	Yellow rods	$C_{25}H_{28}N_4O_8$	58.59	5.51	58.46	5.70
10. $CH_2N(CH_3)CH_2CHOHCH_2CH_3 \cdot HCl$	9461	188–190	Abs. EtOH-ether	Clusters of rods	$C_{20}H_{28}ClNO$	71.93	8.45	72.01	8.26
11. $CH_2N(CH_3)CH_2CHOH(CH_2)_2CH_3 \cdot HCl$	9463	162.5–164.5	Abs. EtOH-acetone	Hexagonal plates	$C_{21}H_{30}ClNO$	72.45	8.70	72.62	9.14
ANTHRACENE-9-									
12. $CH_2NHCH_2CHOHCH_3$		93–94	95% EtOH	Rect. plates	$C_{18}H_{19}NO$	81.49	7.22	81.18	7.49
13. $CH_2NHCH_2CHOHCH_3 \cdot HCl$	5851	198–199	Abs. EtOH	Yellow needles	$C_{18}H_{20}ClNO$	71.63	6.68	71.62	6.93

14. $CH_2NHCH_2CHOHCH_2CH_3 \cdot HCl$	6829	211–212.5	97% EtOH-ether	Large needles	$C_{19}H_{22}ClNO$	72.24	7.02	72.32	7.49
15. $CH_2NHCH_2CHOH(CH_2)_2CH_3 \cdot HCl$	6830	214–215	98% EtOH-ether	Rods	$C_{20}H_{24}ClNO$	72.81	7.33	72.48	7.41
9,10-DIHYDROANTHRACENE-9-(?)									
16. $CH_2NHCH_2CHOH(CH_2)_2CH_3 \cdot HCl$[d]		201–202.5	Abs. EtOH	Hexagonal plates	$C_{20}H_{26}ClNO$	72.36	7.90	72.09	8.10

[a] Compounds are white unless otherwise specified.

[b] Compound 4 dried *in vacuo* at 110° for three to five hours, m.p. 182–184°.

[c] Solvate ethanol determined by weight loss on heating. Calc'd for C_2H_5OH, 12.6. Found: 13.1.

[d] Isolated from the mother liquors of compound 15. There was not enough material for testing.

starting points. For biological comparison, analogous anthracylamino alcohols[2] also seemed of interest, the starting material in this instance being anthracene-9-aldehyde.

A structural comparison of these new types (I and II) with III and IV (1) reveals that in I and II the parent compound of the amino alcohol is the aliphatic chain C_nH_{2n+1}, and phenanthrene is a part of the amino group, while in III and IV this condition is reversed. On the other hand, the hydroxyl and amino groups occupy adjacent carbon atoms in each instance.

From phenanthrene-9-aldehyde, 1,2,3,4-tetrahydrophenanthrene-9-aldehyde, and anthracene-9-aldehyde, a total of ten alkanolamines were prepared. No difficulties were encountered in condensing the aldehydes with the aliphatic alkamines to aldimines. Hydrogenation of the latter likewise proceeded smoothly.

The compounds thus obtained proved to be greatly inferior, therapeutically, to those of types III and IV. On the assumption that their low activity might be accounted for in part by the secondary character of the amino group, the three representatives of II were methylated with formaldehyde and formic acid and were thereby converted into V. The structure of V was proved by synthesizing the lowest homolog from 9-chloromethyl-1,2,3,4-tetrahydrophenanthrene, propylene oxide, and methylamine. This synthesis is at the same time a confirmation of the structures of I and II, which were assigned to these compounds on the basis of reactions involved in their preparation.

The amino alcohols[3] listed in Table I were ineffective against *Plasmodium gallinaceum* in chicks, except SN 5848 which showed a weak activity.

Acknowledgment. The microanalyses were carried out by Mr. Edward A. Garlock, Jr. The 1-amino-2-butanol and 1-amino-2-pentanol were kindly supplied by Commercial Solvents Corporation.

EXPERIMENTAL[4]

The isopropanolamine used was an Eastman Kodak product.

1-Amino-2-butanol and 1-amino-2-pentanol (b.p. 183–185°; α_D^{20} 1.4500; d_{20}^{20} 0.9219)[5] were supplied by Commercial Solvents Corporation.

1-Amino-2-octanol was prepared by hydrogenating 1-nitro-2-octanol (4) according to the procedure of Gakenheimer and Hartung (5).

Phenanthrene-9-aldehyde was prepared according to Mosettig and van de Kamp (6).

Anthracene-9-aldehyde was obtained by the "methylformanilide" method according to Fieser and Hartwell (7). It melted at 104–104.5° (8).

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[2] The preparation of anthracyl-9-amino alcohols analogous to III was undertaken simultaneously with the synthesis of the phenanthrene alkamines. Considerable difficulty was encountered but the work is being continued.

[3] The identification numbers assigned to the drugs by the Malaria Survey Office of the National Research Council are given in the second column of Table I. The drugs were administered as hydrochlorides.

[4] All melting points are uncorrected.

[5] The physical constants of the amino pentanol were supplied by Dr. Jerome Martin, Director of Research of Commercial Solvents Corporation.

1,2,3,4-Tetrahydrophenanthrene-9-aldehyde. Bachmann and Cronyn (9) obtained this aldehyde by the method of Sonn and Müller, but it was found advantageous to prepare it by the action of hexamethylenetetramine (10) on 9-chloromethyl-1,2,3,4-tetrahydrophenanthrene (9). A mixture of 10 g. of the latter, 6 g. of hexamethylenetetramine and 45 cc. of 95% ethanol was warmed on the steam-bath to homogeneity. After addition of 2 cc. of water and 15 cc. of 95% ethanol, the clear reaction mixture was refluxed for eighteen hours. The aldehyde separated in a yield of 5.3 g. (about 60%), m.p. 124–127°, upon cooling in the ice-box. Bachmann and Struve report the melting point 128.5–129° for the pure aldehyde.

Amino alcohols. A mixture of 10 g. of the aromatic aldehyde, one molecular equivalent of the appropriate aliphatic amino alcohol and 50 cc. of absolute ethanol was boiled under reflux for one hour (two to three hours when anthracene-9-aldehyde was employed). The solution was hydrogenated (0.1 to 0.2 g. platinum oxide) and 0.9 to 1.05 molecular equivalents of hydrogen was absorbed in four to twenty-four hours. After filtration from catalyst and evaporation of solvent *in vacuo*, the residue was dissolved in acetone and the solution made slightly acidic with alcoholic HCl. The hydrochloride of the secondary amino alcohol separated crystalline, and was purified by recrystallization. The yields (based on the aldehydes) varied from 40% to 80%.

Methylation (11) of compounds 5, 6, 7 of Table I. One mole of the base of 5, 6, or 7, 1.2 moles of formaldehyde as a 40% aqueous solution, and 2.5 moles of formic acid (90% solution) were heated together on the steam-bath for one to two hours. The reaction mixture was partitioned between ether and an excess of dilute sodium hydroxide solution. The ether layer was dried over sodium sulfate and made slightly acidic with 20% alcoholic HCl. The oil which separated was dissolved by addition of acetone, whereupon the hydrochloride gradually crystallized. The average yield was 75%.

Synthesis of 9-[(2-hydroxypropylmethylamino)methyl]-1,2,3,4-tetrahydrophenanthrene or compound 8 of Table I. To 1.0 g. of propylene oxide cooled in ice, was added 0.5 g. of methylamine in 5 cc. of absolute ethanol. After twenty-four hours at room temperature, 1.0 g. of 9-chloromethyl-1,2,3,4-tetrahydrophenanthrene was added and the mixture refluxed for forty-eight hours. It was then made alkaline with dilute sodium carbonate solution and extracted with ether. The light oil (0.9 g.) obtained after evaporatively distilling (150° at 0.2 mm.) the residue from the dried ether extracts, was dissolved in ether and acidified with 1 cc. of 15% alcoholic HCl. The resulting oil was just dissolved with acetone and the solution seeded. After twenty-four hours, a hydrochloride had crystallized (prisms) in a yield of 0.15 g., m.p. 161–165°. A mixture with compound 8 of Table I (prepared from 5) melted at 161–164.5°. The picrate, prepared from either sample, as well as a mixture of the two, melted at 87–89°.

SUMMARY

Amino alcohols in which the side chain $—CH_2NHCH_2CHOHC_nH_{2n+1}$ is attached to position 9 of phenanthrene, tetrahydrophenanthrene, and anthracene are described. The N-methyl derivatives of three of these have been prepared and their structure proved by alternative synthesis.

The antimalarial activity of these compounds is discussed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XIV. STUDIES IN THE ACRIDINE SERIES II. DIALKYLAMINOALKYLAMINES DERIVED FROM 9-CHLORO-1,2,3,4-TETRAHYDROACRIDINE[1]

LEWIS J SARGENT AND LYNDON SMALL

Received February 18, 1946

In our search for compounds which might prove useful in the prophylaxis of malaria, we considered the feasibility of preparing Atabrine analogs in the tetrahydroacridine series in the hope that such compounds, while retaining plasmodicidal activity, would be less toxic than Atabrine. A survey of the literature revealed that experiments along these lines had been twice attempted in recent years with indefinite results. Magidson (1) described experiments in which substituted 9-chlorotetrahydroacridines were condensed with certain dialkylaminoalkylamines in phenol solution at temperatures ranging from 180–210°. With the exception of two meconic acid salts (of dubious composition) isolated in the experiments, no definite products were obtained or characterized. The meconates were not only found to be devoid of antimalarial activity but also more toxic than the unhydrogenated acridine analogs. Basu and Das-Gupta (2), employing somewhat more carefully controlled conditions, condensed both 9-chlorotetrahydroacridine and 7-methoxy-9-chlorotetrahydroacridine with dialkylaminoalkylamines in sealed tubes at 150-160°. In the first case failing to isolate a hydrochloride of the product, the authors prepared the methylenedioxynapthoic acid salt. In the second instance (methoxy analog) they succeeded in preparing the expected dihydrochloride. In neither case, however, were the yields reported nor mention made of the activity of the compounds toward malaria infections. In view of the paucity of information concerning the chemistry of these substances as well as the lack of clear-cut, related pharmacological data, a re-examination of this series of compounds was undertaken.

von Braun (3) early recognized the fact that the chlorine atom in 9-chlorotetrahydroacridine is less reactive than that in 9-chloroacridine. Whereas the halogen atom in the latter compound reacts readily with primary and secondary amines in phenol solution at temperatures below 100° (*e.g.*, Atabrine synthesis), the replacement of the chlorine atom in 9-chlorotetrahydroacridine (3) by primary and secondary amines requires temperatures of the order of 160° or above, preferably carried out in sealed tubes. In this respect then, it is probably more logical to compare 9-chlorotetrahydroacridine with 4-chloroquinoline or the alkyl-substituted 4-chloroquinolines. With both of these quinoline derivatives, condensation with primary and secondary amines is feasible only at elevated temperatures. Holcomb and Hamilton (4) recently described the condensation of 4-chloro-6-methoxyquinaldine with certain amines at tempera-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health.

TABLE I

DIALKYLAMINOALKYLAMINOTETRAHYDROACRIDINES

S.N.*	COMPOUND	YIELD %	APPEARANCE	FORMULA	M.P., C°.	ANALYSES			
						Calc'd		Found	
						C	H	C	H
	9-(γ-Dimethylaminopropylamino) dipicrate	72	Yellow prisms[a]	$C_{30}H_{31}N_9O_{14}$	199–200.5	48.60	4.21	48.96	4.32
12079	9-(γ-Diethylaminopropylamino) dihydrochloride	80	Flat prisms[b]	$C_{20}H_{31}Cl_2N_3$	194.5–196	62.19	8.13	62.19	7.87
	9-(γ-Diethylaminopropylamino) diperchlorate		Needles[b]	$C_{20}H_{31}Cl_2N_3O_8$	174.5–176	46.88	6.10	47.04	5.78
	9-(γ-Di-*n*-butylaminopropylamino) dipicrate	88	Yellow plates[a]	$C_{36}H_{43}N_9O_{14}$	161–163	52.36	5.25	52.15	5.27
	9-(γ-Di-*n*-butylaminopropylamino) diperchlorate		Needles[a]	$C_{24}H_{39}Cl_2N_3O_8$	173–175	50.70	6.92	50.67	6.80
12081	9-(γ-Di-*n*-amylaminopropylamino) diperchlorate	81	Stout prisms[b]	$C_{26}H_{43}Cl_2N_3O_8$	157.5–159	52.35	7.27	52.29	6.85
	9-(γ-Diisoamylaminopropylamino) dipicrate	64	Yellow plates[a]	$C_{38}H_{47}N_9O_{14}$	191–192.5	53.45	5.55	53.77	5.62
12487	9-(δ-Diethylamino-α-methylbutylamino) diperchlorate	62	Stout prisms[a]	$C_{22}H_{35}Cl_2N_3O_8$	147–148.5	48.89	6.53	48.99	6.34
	9-(Methyl-γ-diethylaminopropylamino) diperchlorate	71	Yellow prisms[a]	$C_{21}H_{33}Cl_2N_3O_8$	166.5–168	47.91	6.32	48.24	6.22
12078	9-(Morpholino) hydrochloride	60	Yellow prisms[d]	$C_{17}H_{21}ClN_2O$	282–284 d.	66.98	6.94	67.16	6.82
	9-(Morpholino) free base		Prisms[c]	$C_{17}H_{20}N_2O$	145–146.5	76.08	7.51	76.40	7.14

* The Survey Numbers (SN) are the identification numbers assigned by the Malaria Survey Office of the National Research Council. S.N. 12081 was tested in the form of its sulfate (B.H_2SO_4), m.p. 80° (foams); S.N. 12487 was tested as the phosphate (B.2/3 H_3PO_4), m.p. 106–8° (foams).

[a] Acetone + Ether

[b] Absol. Alc. + Ether

[c] 50% Ethanol

[d] Absol. Ethanol

tures ranging from 140° to 225°, the yields varying from 26–80%. Similarly, Gilman and Spatz (5) condensed several 2-chlorophenyl-4-chloro-6-methoxyquinolines with secondary amines at temperatures of 170° to 205° in yields of 60–70%.

In our hands, 9-chlorotetrahydroacridine condensed smoothly with various amines (see Table I) in the presence of a trace of copper-bronze powder by heating in sealed tubes at 180° for 20–24 hours, the yields varying between 60–88%. However, with 4-diethylamino-1-methylbutylamine, it was necessary to heat the reactants to 220° (72 hours) in order to obtain the desired product (60%). With the exception of the morpholine-substituted tetrahydroacridine, which was obtained in crystalline form, all of the reaction products were viscous, amber syrups. In a few cases it was possible to prepare crystalline dihydrochlorides; in others the products were converted to crystalline phosphates (solvated). Both of these salts were suitable for the pharmacological tests. For analytical specimens, the perchlorates and picrates proved superior. The corresponding ar-substituted chloro- and methoxy-tetrahydroacridines have also been prepared and these will be reported shortly.

Acknowledgment. We wish to thank Dr. R. C. Elderfield (Columbia Univ.) as well as Dr. Nathan Drake (Univ. of Maryland) for generously supplying us with the amines used in this investigation. Grateful acknowledgment is due to Mr. E. A. Garlock, Jr., for the analytical data.

Melting points are uncorrected. The following experimental details are typical of the techniques employed in preparing the compounds described below.

EXPERIMENTAL

9-Chloro-1,2,3,4-tetrahydroacridine. 1,2,3,4-Tetrahydroacridone was prepared according to Tiedtke (6), using a water-collector. From 100 g. of cyclohexanone and 100 g. of anthranilic acid, 66 g. of tetrahydroacridone was obtained (45.5%); water, 18 ml.

To 40 ml. of phosphorus oxychloride was added portionwise, with good swirling, 25 g. of tetrahydroacridone. If the acridone was allowed to clump together it blackened rapidly. Before addition was completed, crystallization usually took place. The solid was warmed into solution and refluxed for 15 min., cooled with stirring, and the crystalline mush scraped onto 0.5 liter of ice. After an hour at room temperature to decompose phosphorus compounds, the crystalline hydrochloride was filtered and dissolved in 800 ml. of warm water, and stirred at 80° with Norit for 30 min. From the cold filtrate the base precipitated crystalline with ammonia; yield 25.8 g. (96%); from 70 ml. of acetone, 18.5 g. (69%), m.p. 66–68°.

Anal. Calc'd for $C_{13}H_{12}ClN$: C, 71.7; H, 5.56.
Found: C, 71.4; H, 5.32.

9-Bromo-1,2,3,4-tetrahydroacridine. Ten grams of tetrahydroacridone in 45 g. of phosphorus tribromide was heated at bath temp. 125° for 20 min. The hard red cake was brought onto ice, and the suspension of pink powder bubbled out with CO_2 (explosion danger otherwise). The powder was suspended in dil. ammonia and extracted into ether; the residue from the ether was recrystallized from methanol or acetone; 4.5 g. (34%), m.p. 76–77°. Analytical sample, sublimed in a high vacuum, m.p. 78–80°.

Anal. Calc'd for $C_{13}H_{12}BrN$: C, 59.56; H, 4.61.
Found: C, 59.70; H, 4.65.

9-(3-Diethylaminopropylamino)-1,2,3,4-tetrahydroacridine. Eight grams of 9-chloro-1,2,3,4-tetrahydroacridine, 9.6 g. (2 moles) of 3-diethylaminopropylamine, and a few milli-

grams of copper-bronze powder were heated together in a sealed tube at 180° for 24 hours. The light amber, jelly-like reaction product was transferred to a separatory funnel with water and the insoluble basic material taken up in ether. The ethereal solution was washed with water several times to remove diethylaminopropylamine hydrochloride. Any unreacted diethylaminopropylamine was removed by fractional extraction with dilute acid in the following manner: The calculated amount of 2 *N* acetic acid (based on 100% conversion) was diluted to 200 ml. with water and this solution divided into 8–10 equal portions. The ethereal solution was then extracted with each portion of dilute acetic acid. The first two extracts, containing small amounts of diethylaminopropylamine, were discarded; the remainder were combined, cooled, basified with 10 *N* sodium hydroxide and extracted with ether. After drying over sodium sulfate and concentrating *in vacuo*, there remained 9 g. (75%) of a clear, amber syrup. The dihydrochloride was prepared in a cooled acetone solution with anhydrous hydrogen chloride and was recrystallized from a mixture of absolute ethanol-ether.

With those compounds not forming dihydrochlorides, the phosphates were generally prepared by treating the cooled, syrupy bases with alcoholic phosphoric acid (25%) to Congo acidity and recrystallizing the resulting salts from methanol-ether. The perchlorates prepared with alcoholic perchloric acid (25%) were recrystallized either from absolute alcohol-ether, or from acetone-ether, while the picrates, prepared with alcoholic picric acid (5%), were recrystallized from acetone-ether.

SUMMARY

The synthesis of a series of 9-dialkylaminoalkylaminotetrahydroacridines is described. None of the members of this group showed antimalarial activity towards *P. gallinaceum* (chick infection).

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE EFFECT OF ACID AND ALKALI ON THE ROTATION OF *l*(+)-ARGININE[1]

ROBERT M. HERBST[2] AND HENRY M. GROTTA

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The influence of optically inactive electrolytes upon the rotatory power of optically active organic compounds has long attracted attention. As long ago as 1880 Landolt (1) studied the effect of various acids upon the rotation of solutions of asparagine and aspartic acid and observed that acetic acid caused a large change in their rotation, and that sulfuric acid in equivalent amount exerted a still greater effect. In the following year, Becker (2) studied the effect of increasing molecular ratios of hydrochloric acid and sodium hydroxide on the same compounds. He observed that asparagine in the presence of one equivalent of base exhibited the specific rotation $-8.64°$ while in the presence of an equivalent of hydrochloric acid the specific rotation changed to $+26.42°$. These results were regarded merely as solvent effects and no attempt was made to relate the changes to the effects of alkali and acid upon the substrate. At a later date, Marshall (3) reinvestigated the rotation of aspartic acid with similar results but advanced no further explanation of the observed effects.

More recent investigators (4, 5, 6) have distinguished between the effects produced by the addition of electrolytes which might be expected to react with the substrates, as in the case of acids or bases and an amino acid, and neutral salts which would not enter into any apparent chemical reaction with the substrate. An attempt to determine the dissociation constants of a number of amino acids was made by Wood (7) from measurements of their optical rotatory power in the presence of various concentrations of hydrochloric acid and sodium hydroxide. The specific rotations of leucine, aspartic acid, and glutamic acid in the presence of varying amounts of hydrochloric acid were plotted as a function of the number of equivalents of acid added. Similar curves were drawn for the influence of base, but the two segments were not plotted as a single curve. Leucine exhibited the minimum rotation as the free amino acid, the rotation becoming more positive as either acid or base was added. Aspartic acid and glutamic acid had qualitatively almost identical curves, both showing the minimum value of the rotation in the presence of one equivalent of base and becoming more positive upon the addition of either acid or more base.

It remained for Lutz and Jirgensons (8) to demonstrate that all of the naturally occurring amino acids exhibited similar behavior. In every case the qualitative form of the curve representing change of rotation upon addition of acid or base was the same. The most highly ionized form of the natural amino acids always

[1] Abstacted from a thesis submitted by Henry M. Grotta to the University College of Arts and Sciences at New York University in partial fulfillment of the requirements for the degree of Bachelor of Arts with Honors in Chemistry.

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exhibited the least positive or most negative rotation. Addition of either alkali or acid to this form caused the rotation to become more positive, or less negative. The enantiomorphs of several amino acids were studied, and showed curves of identical shape, but the changes in rotation evoked by acid or alkali were in the opposite sense, and the most highly ionized form showed the most positive rotation. Since a number of the natural amino acids had previously been related to the optically active lactic acid to which the *l*-configuration has been assigned

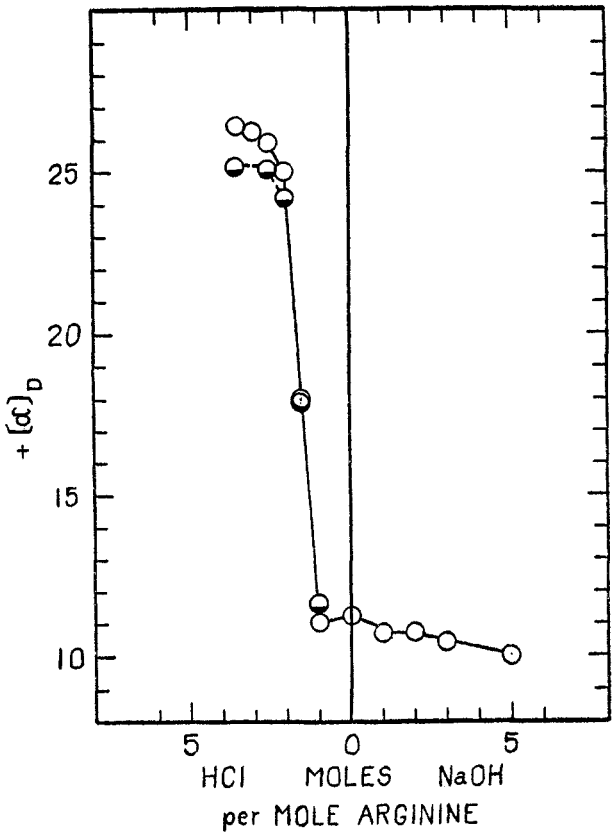

FIG. 1. ○ Specific rotation of *l*(+)-arginine in molar aqueous sodium chloride solution in the presence of varying amounts of hydrochloric acid and sodium hydroxide. ◒ Specific rotation of *l*(+)-arginine in aqueous solution in the presence of varying amounts of hydrochloric acid without addition of sodium chloride.

(9, 10, 11, 12), the conclusion seemed justified that all the natural amino acids were members of the *l*-configurational series.

In connection with another study in progress in our laboratory it was desirable to compare the effect of alkali and acid upon the rotation of certain *l*(+)-arginine derivatives with that produced upon *l*(+)-arginine itself. The curve recorded by Lutz and Jirgensons did not appear to be adequate for our purposes since it was carried out in relatively dilute solutions (0.05 M), at which concentration free

arginine and its sodium salt would exhibit actual rotations of the order of 0.25° in a two-decimeter tube. Since an error of ±0.02° is not unlikely in making these readings, the specific rotations in this part of the curve (+12° to +13°) are subject to a ten per cent error (±1°). The points covering the range from arginine monohydrochloride to free arginine to the sodium salt vary between +12.2° and +13.7°. On the basis of these readings, Lutz and Jirgensons indicate that free arginine exhibits the least positive rotation, although on the basis of their observations with other amino acids, arginine monohydrochloride, the most highly ionized form, should exhibit lowest positive rotation.

For this reason the effect of acid and base upon the rotatory power of $l(+)$-arginine was reinvestigated. Concentrations of arginine (1 M) were chosen, so that at the minimum point on the curve the observed rotation was at least 1.75°,

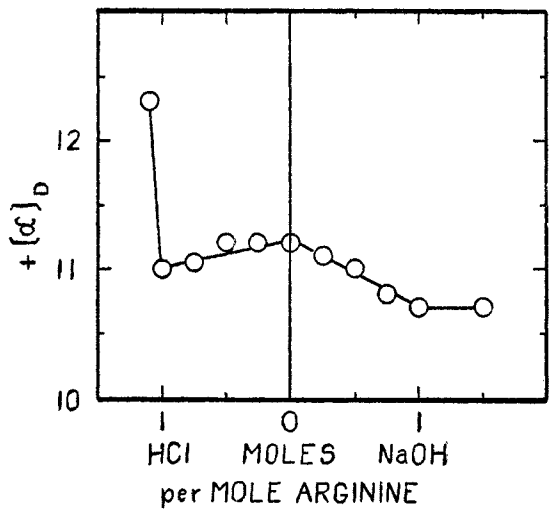

FIG. 2. Specific rotation of $l(+)$-arginine in molar aqueous sodium chloride solution containing varying proportions of the monohydrochloride, free arginine and the sodium salt.

corresponding to a specific rotation of 10°. The results shown in Figure 1 indicate that the rotation of arginine monohydrochloride actually represents a point of minimum rotation. However, the curve is more complex than that of other poly-functional amino acids. On going from arginine monohydrochloride to free arginine there is a slight increase in rotation, while thereafter addition of alkali causes a continuous decrease in the positive rotation of the compound. In Figure 2, these changes are illustrated in greater detail by data showing the effect of stepwise conversion of arginine monohydrochloride to free arginine and the sodium salt. The magnitude of the changes is well outside the limits of experimental error.

For purposes of simplicity in purifying and handling the amino acid, $l(+)$-arginine monohydrochloride was employed. Under these conditions, the points for free arginine and all more alkaline solutions were determined in a molar so-

dium chloride solution. For this reason the entire curve was determined in molar sodium chloride solution. In Figure 1 the rotation of arginine monohydrochloride and the more acid points in aqueous solution or hydrochloric acid solution of appropriate concentration are recorded for purposes of comparison. It appears unlikely that the presence of sodium chloride would have any effect other than to displace some of the points without qualitatively altering the form of the curve, since its effect upon the rotation is not very marked at any point.

EXPERIMENTAL

Arginine was isolated from a gelatin hydrolysate (13) and carefully purified as the monohydrochloride by the methods of Cox (14) and Hunter (15).

Anal. Calc'd for $C_6H_{15}ClN_4O_2$: N, 26.6. Found: N, 26.5, 26.4 (Kjeldahl).

$[\alpha]_D^{25}$ +25.2° for arginine monohydrochloride dissolved in 3.5 normal hydrochloric acid ($c = 21$; $l = 1$ dm.).

Solutions for the determination of rotations in the presence of varying amounts of hydrochloric acid or sodium hydroxide were prepared by weighing the desired amount of arginine monohydrochloride into a calibrated 2 ml. volumetric flask. Thirty-one individual samples were weighed within the limits of 0.4211 and 0.4218 grams, providing finally a molar solution of arginine. Each sample was treated with the calculated quantity of standard hydrochloric acid or sodium hydroxide solution and diluted to volume with distilled water. Sufficient standard sodium chloride solution was added to all solutions, prior to dilution to make the resulting solvent a molar sodium chloride solution. When the arginine monohydrochloride was treated with one equivalent of sodium hydroxide or more, addition of sodium chloride was unnecessary. For comparison purposes the rotation of arginine monohydrochloride and several points in the more acidic range were determined without addition of sodium chloride as indicated in Figure 1.

All rotations were taken in the same one-decimeter semi-micro tube in a Schmidt and Haensch half-shadow polarimeter using a sodium vapor lamp as the source of monochromatic light. Rotations were all determined during a period when the room temperature was within the limits 23–28°. The actual rotation for each point represents the average of ten successive readings none of which deviated more than ±0.02° from the average. Since at the concentration of arginine chosen (one molar), the smallest actual reading of rotation was +1.75°, the maximum error in reading the polarimeter is about ±1%. Consequently the specific rotations are in error to the same degree in the lower portions of the curve. With larger values of the rotation the error decreases to about ±0.5%.

SUMMARY

Reinvestigation of the effect of acid and alkali on the rotation of *l*(+)-arginine has shown that this amino acid exhibits the characteristics ascribed to the other amino acids of the *l*-configurational series. The minimum positive value of the specific rotation is associated with the most highly ionized form of the amino acid, namely the monohydrochloride. The strongly alkaline solutions of the sodium salt exhibit a second minimum point in the curve. The changes in rotation are recorded graphically.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE SYNTHESIS AND PROPERTIES OF OCTOPINE AND ITS DIASTEREOISOMER, ISO-OCTOPINE[1]

ROBERT M. HERBST[2] AND E. AUGUSTUS SWART[3]

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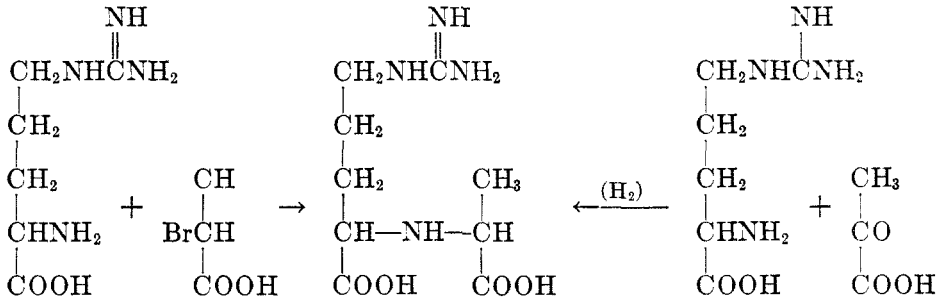
The asymmetric influence of an optically active grouping upon the configuration of a second optically active grouping entering a molecule has long been recognized. However, the effect of external conditions in modifying this influence has not received much attention. In most instances where a second asymmetric group has been introduced into an optically active compound, the conditions favoring the synthesis have not been amenable to wide variation. At other times, it has not been feasible to work with an optically active form so that the resulting product was a mixture of racemates. An interesting modification of the latter type was the synthesis developed by Manske and Johnson for ephedrine (1, 2) and certain of its analogs, wherein both asymmetric groups were introduced during a single catalytic hydrogenation.

A number of years ago an amino acid derivative, octopine (I), was isolated from various marine organisms (3, 4). On the basis of subsequent investigations by Akasi (5, 6) and Wilson and his co-workers (4, 7) octopine (I) was assigned the structure of an arginine-α-propionic acid derivative. Its synthesis from $l(+)$-arginine and α-bromopropionic acid was described by Akasi (6) and Ackermann and Mohr (8) and again by Irvin and Wilson (7) who used the esters of arginine and α-bromopropionic acid. Soon thereafter Knoop and Martius (9) described he synthesis of an octopine by the catalytic hydrogenation of a mixture of $l(+)$-arginine and pyruvic acid in aqueous solution.



(I)

During the synthesis of octopine by the method of Knoop and Martius it seemed likely that a second product, diastereoisomeric with octopine should be formed, although the authors had reported the isolation of only a single product.

[1] Abstracted from a thesis presented by E. Augustus Swart to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Akasi (10) had already reported the synthesis of both octopine and its diastereoisomer, iso-octopine, by interaction of *l*(+)-arginine and α-bromopropionic acid, both as the racemate and as the optically active forms. The separation of the diastereoisomers was simple since octopine formed a very insoluble picrate while iso-octopine picrate was rather soluble in water.

The procedure of Knoop and Martius was of particular interest to us, since it offered an opportunity to investigate the influence of an external factor such as the *p*H of the medium upon the proportions of octopine and iso-octopine formed by hydrogenation of a mixture of *l*(+)-arginine and pyruvic acid. However, certain difficulties were immediately encountered. No octopine picrate could be isolated from the reaction mixture. On the other hand, a product forming a very soluble picrate was present. This product was eventually isolated by means of its sparingly soluble salt with flavianic acid.

In the face of this difficulty, it became desirable to repeat the synthesis of octopine and iso-octopine by Akasi's procedure. In order to avoid the tedious precipitation of these products with phosphotungstic acid to free them from inorganic ions, Akasi's procedure was modified to the extent of substituting barium hydroxide for sodium hydroxide to maintain an alkaline environment during the interaction of *l*(+)-arginine and *dl*-α-bromopropionic acid. Both octopine and iso-octopine were isolated from the reaction mixture, the former by means of its insoluble picrate, and the latter by means of its sparingly soluble flavianate. The octopine so obtained was in every way identical with the product obtained from natural sources, a sample of which was made available to us through the kindness of Dr. D. W. Wilson. On the other hand, the properties of the iso-octopine isolated from the reaction mixture failed to correspond with the description given in the literature (10) for this product. It was, however, identical with the material synthesized by the Knoop and Martius procedure.

In view of these developments, it became imperative to determine whether the compound isolated by us was iso-octopine and to verify the properties ascribed to it in the literature. Efforts to study the effect of *p*H upon the proportions of octopine and iso-octopine formed in the Knoop and Martius synthesis were therefore temporarily abandoned.

Akasi (10) has described iso-octopine as a colorless product crystallizing from aqueous alcohol with two molecules of water of crystallization and melting at 158–159°. Its specific rotation in water was reported as +25.77°. The picrate was described as fine yellow needles, melting at 198°, and showing moderate water-solubility. Our iso-octopine contained no water of crystallization, melted with decomposition at 258–259°, and gave a rather soluble picrate melting with decomposition between 190° and 195° depending on the rate of heating. The specific rotation of our product in water was +25°. As claimed by Akasi, both octopine and iso-octopine give a positive Sakaguchi test, the color being purple rather than orange-red as in the case of arginine. Both products fail to liberate nitrogen in the van Slyke amino-nitrogen determination. It is interesting to note that octopine, m.p. 270–271° with decomposition, does not depress the melting point of iso-octopine. The melting point of the mixture is generally the same

or just slightly higher than that of iso-octopine. The melting points of both compounds may vary considerably depending on the rate of heating, due to the accompanying decomposition. Therefore, comparisons should always be made by simultaneous observation of the melting points in the same bath. Similar behavior was observed with derivatives of both compounds, so that melting point comparisons should be interpreted with caution.

It had been shown that octopine, on oxidation with barium permanganate by the technique applied to arginine by Kutscher (11), gave as products carbon dioxide, acetaldehyde, and γ-guanidinobutyric acid. Our iso-octopine prepared either by the modified Akasi method or by the Knoop and Martius method when oxidized in this manner was broken up into carbon dioxide, acetaldehyde, and

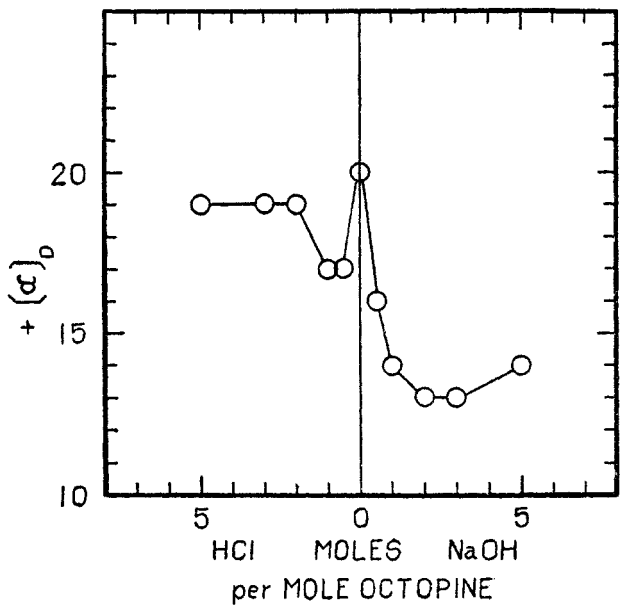


FIG. 1. THE EFFECT OF HYDROCHLORIC ACID AND SODIUM HYDROXIDE ON THE SPECIFIC ROTATION OF NATURAL OCTOPINE (WILSON)

γ-guanidinobutyric acid. The latter product was identical with a sample prepared by the oxidation of arginine.

Apparently the material isolated by Knoop and Martius for which they give the melting point as 261° and described by them as octopine was actually iso-octopine. Their error in identification can be attributed to Akasi's incorrect description of the characteristic properties of iso-octopine.

Akasi had further attempted to characterize octopine and iso-octopine by the effect of alkali and acid upon their rotations in aqueous solutions following the technique of Lutz and Jirgensons (12). The curves for the changes in rotation exhibited by these compounds upon addition of acid and alkali are rather incongruous as represented by Akasi. Reinvestigation of these effects gave entirely

different results in our hands. The curves for both compounds (Figures 2 and 3) are qualitatively very similar but show pronounced quantitative differences. Both compounds show two points of maximum rotation and two points of minimum rotation, the changes in rotation being markedly greater for iso-octopine than for octopine. A similar curve for natural octopine (Figure 1) agreed in every respect with the curve for synthetic octopine. The curves for changes in rotation of iso-octopine prepared by the Knoop method or the modified Akasi method were identical.

Both Akasi and later Karrer and his co-workers (13) have speculated on the configuration of the propionic acid portion of octopine. The latter authors have retracted their conclusions, while those of the former are open to criticism on the

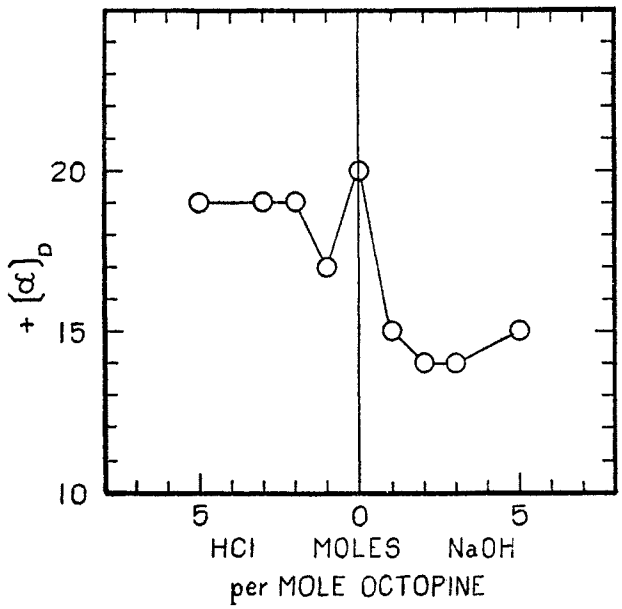


FIG. 2. THE EFFECT OF HYDROCHLORIC ACID AND SODIUM HYDROXIDE ON THE SPECIFIC ROTATION OF SYNTHETIC OCTOPINE (METHOD B)

grounds of failure to take into consideration the probable occurrence of Walden inversions. Akasi found that octopine was formed by interaction of *l*(+)-arginine and *l*(−)-α-bromopropionic acid, while iso-octopine resulted from *l*(+)-arginine and *d*(+)-α-bromopropionic acid. From this he concluded that octopine had *ll* configuration while iso-octopine possessed the *ld* configuration although Fischer (14) had demonstrated that the α-bromopropionic acids undergo a Walden inversion upon reacting with ammonia, and Abderhalden and Haase (15) had shown the same to be true during imino-dicarboxylic acid formation with glycine.

Although it is tempting to speculate on the basis of Akasi's synthetic work and the new rotation curves as to the configuration of the octopines, the question must

remain unsettled for the present. Both compounds contain asymmetric carbon atoms comparable to those of arginine and alanine. The configuration of the arginine moiety is established by the synthesis of both compounds from *l*(+)-arginine without involvement of the asymmetric carbon atom. Only the configuration of the alanine carbon atom remains in question. It appears likely from a consideration of the rotation curves and the van't Hoff principle of optical super-position that octopine has the *ld* configuration while iso-octopine has the *ll* configuration, although unequivocal proof is lacking. The natural occurrence of certain amino acids in the *d*-configurational form, although not common, is not

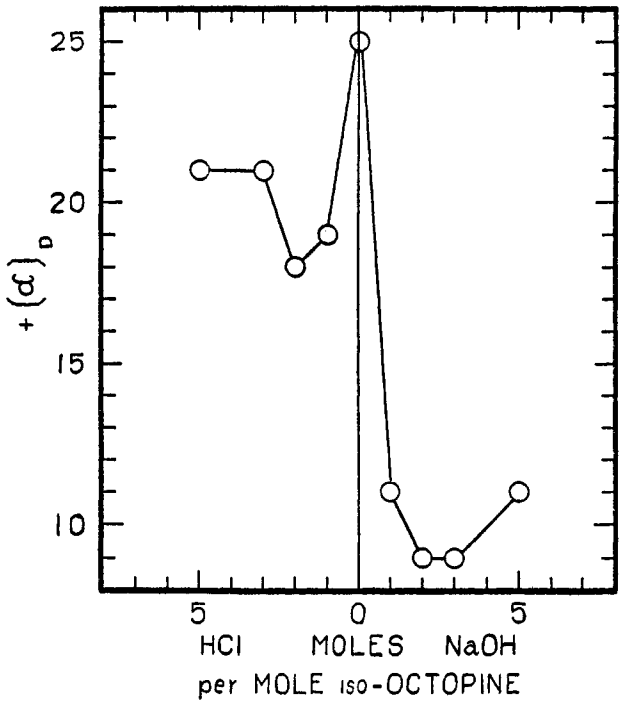


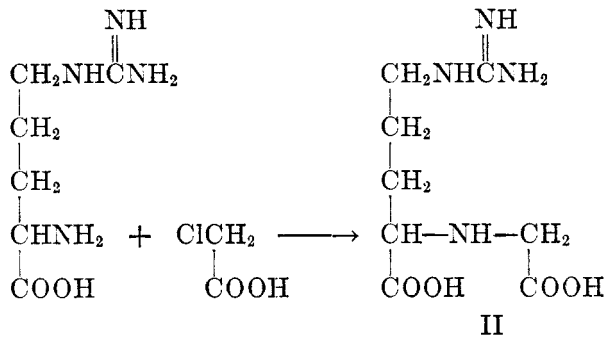
FIG. 3. THE EFFECT OF HYDROCHLORIC ACID AND SODIUM HYDROXIDE ON THE SPECIFIC ROTATION OF ISO-OCTOPINE (METHOD A)

unusual, hence the *d* configuration of the alanine moiety of octopine cannot be ruled out on the basis of the natural occurrence of this compound.

Of interest was the isomer designated as β-octopine by Akasi in view of its reputed synthesis from *l*(+)-arginine and β-bromopropionic acid. Such a compound would exhibit all the functional groups of the octopines but contain only one asymmetric carbon atom, thus making its rotation curve particularly interesting. From Akasi's description of this compound, it possesses many of the characteristics of octopine, and even the curve representing changes in rotation effected by acids and bases as observed by Akasi bears great similarity to our curve for octopine. We were unable to synthesize this compound. Mixtures of arginine and β-bromopropionic acid showed no inclination to react under the

conditions used for synthesis of the octopines, as evidenced by unchanged van Slyke amino-nitrogen content of the reaction mixtures. One is tempted to wonder whether Akasi's β-bromopropionic acid may not have been contaminated with the alpha isomer.

In order to obtain a compound carrying all of the functional groups of the octopines but having only a single asymmetric carbon atom, *l*(+)-arginine was condensed with chloroacetic acid under the conditions employed in the octopine synthesis.



II

The product, for which the name desmethyloctopine (II) is suggested, is a colorless, crystalline solid melting at 281–282° with decomposition and bearing great similarity to the octopines. Like the octopines, it gives a purple color in the Sakaguchi test and fails to liberate nitrogen in the van Slyke amino-nitrogen determination. The effect of the addition of acid or base to its aqueous solutions upon its rotation (Figure 4) is, however, qualitatively quite different from that observed with the octopines. In this respect it is also interesting to note that the rotation curve differs quite markedly from that of *l*(+)-arginine (16). The effect of addition of the acetic acid residue and the new functional group it carries places the rotation curve rather midway between that of arginine and the octopines.

The authors wish to acknowledge gratefully the gift of a generous sample of natural octopine by Dr. D. W. Wilson of the University of Pennsylvania.

EXPERIMENTAL

l(+)-*Arginine monohydrochloride* was isolated from a gelatin hydrolysate as the insoluble flavianate (17). The flavinate was decomposed by continuous extraction of its suspension in warm dilute hydrochloric acid with *n*-butyl alcohol. Arginine remained in the aqueous acid solution from which it was isolated as the monohydrochloride by precipitation with pyridine after decolorization, concentration, and dilution with ethanol. Hunter's (18) method of purification was followed.

Anal. Calc'd for $C_6H_{15}ClN_4O_2$: N, 26.6. Found: N, 26.7, 26.5 (Micro Kjeldahl).

$[\alpha]_D^{28}$ +25.2° for arginine monohydrochloride in 3.5 normal hydrochloric acid (c = 21; l = 1 dm.).

l(+)-*Arginine carbonate* was isolated by the method of Kossel and Gross (19) after decomposition of arginine flavianate according to Felix and Dirr (20).

Flavianic acid was prepared from Naphthol Yellow S (17).

Pyruvic acid was redistilled under reduced pressure frequently, and stored in the ice-chest.

Iso-octopine (*A*) [Knoop and Martius Method (9)]. A solution of 4.2 g. of *l*(+)-arginine monohydrochloride and 1.36 ml. of pyruvic acid in 25 ml. of water was neutralized to litmus by addition of saturated barium hydroxide solution, after which a second equivalent of pyruvic acid (1.36 ml.) was added. The solution was hydrogenated with palladium oxide catalyst (21) at a hydrogen pressure slightly over atmospheric. After about thirty hours, hydrogen absorption was negligible and van Slyke determinations indicated that 85–90% of the arginine amino nitrogen had disappeared. After acidification with a slight excess of sulfuric acid and removal of the barium sulfate, unreacted arginine was removed by the addition of a slight excess of flavianic acid. After concentrating the filtrate from the arginine flavianate to about 75 ml., iso-octopine flavianate was isolated upon addition of excess flavianic acid and chilling. After recrystallization from water, iso-octopine flavianate melted at 206–207° with decomposition.

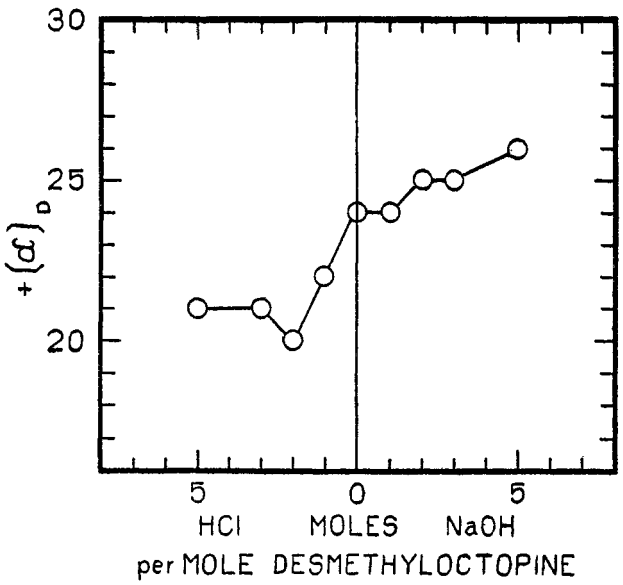


FIG. 4. THE EFFECT OF HYDROCHLORIC ACID AND SODIUM HYDROXIDE ON THE SPECIFIC ROTATION OF DESMETHYLOCTOPINE

The flavianate was decomposed by suspension in a small amount of hot water and grinding with hot saturated aqueous barium hydroxide solution and filtering. After repeating this treatment with the insoluble material, barium ion was quantitatively removed from the combined filtrates by careful addition of sulfuric acid. The resulting solution of iso-octopine was decolorized with charcoal, concentrated to a syrup under reduced pressure and treated with 40–50 ml. of ethanol. The iso-octopine separated as a colorless solid which crystallized from 70% ethanol as clusters of fine, glistening needles, m.p. 258–259° with decomposition. (Natural octopine, simultaneously in the same bath, melted at 270–271°, with decomposition.)

Anal. Calc'd for $C_9H_{18}N_4O_4$: N, 22.75. Found: N, 22.5, 22.5 (Micro Kjeldahl).

$[\alpha]_D^{24.5}$ +25° in 2.5% aqueous solution in a semi-micro 1 dm. tube.

The same product resulted when *l*(+)-arginine carbonate, as directed by Knoop and Martius, was used in place of the monohydrochloride.

Oxidation of iso-octopine. An aqueous solution of 1 g. of iso-octopine was treated with a solution of a slight excess of barium permanganate. The reaction mixture was aerated for

two hours at 40°, the exhaust air passing through sodium bisulfite solution. Barium ion was removed quantitatively by careful addition of sulfuric acid after filtering off the precipitated manganese dioxide. The resulting solution was evaporated to a small volume under reduced pressure, treated with 15 ml. of concentrated hydrochloric acid, and the volume again reduced to about 2–3 ml. On chilling, γ-guanidinobutyric acid hydrochloride crystallized. After recrystallization from a small volume of dilute hydrochloric acid, the material melted at 184–185°, and showed no depression when mixed with γ-guanidinobutyric acid hydrochloride obtained by oxidation of arginine (11).

The sodium bisulfite solution was distilled after addition of excess sodium carbonate. From the distillate, acetaldehyde was isolated as the dimedon derivative, m.p. 141–142°, showing no depression when mixed with an authentic sample.

Octopine and iso-octopine (*B*) [Akasi Method (10)]. Two modifications of the procedure were introduced, the volume of the solution was reduced to about 25% of that specified by Akasi, and barium hydroxide replaced sodium hydroxide to maintain an alkaline reaction in the solution.

A solution of 11.4 g. of *l*(+)-arginine monohydrochloride and 7.6 g. of *dl*-α-bromopropionic acid in 200 cc. of water was made alkaline by the addition of 31.5 g. of crystalline barium hydroxide. After keeping at 37° for 72 hours the amino-nitrogen content of the solution indicated that 80% of the arginine had reacted. Barium ion and unreacted arginine were removed as described above, while excess flavianic acid was removed by extraction with butyl alcohol.

The arginine-free filtrate was treated with a hot saturated aqueous solution of picric acid equivalent to the octopines present. On concentrating the solution under reduced pressure the red picrate of octopine crystallized. After two recrystallizations from water it melted at 222–222.5° with decomposition. Octopine was liberated from the picrate by treating its hot aqueous solution with an excess of 6 *N* sulfuric acid and extracting the picric acid with ether. After quantitative removal of the sulfate ion with barium hydroxide, the solution was evaporated to a thin syrup. Addition of ethanol precipitated the octopine as a colorless solid, which after two recrystallizations from 70% ethanol melted at 262–263° with decomposition. (Simultaneously in the same bath natural octopine melted at 262–263° with decomposition.)

Anal. Calc'd for $C_9H_{18}N_4O_4$: N, 22.75. Found: N, 22.9 (Micro Kjeldahl).

$[\alpha]_D^{25}$ +20° in 2.5% aqueous solution in a semi-micro 1 dm. tube.

The filtrate from the precipitation of crude octopine picrate was acidified with sulfuric acid, and extracted with ether to remove picric acid. After quantitative removal of sulfate ion from the solution, iso-octopine was isolated as the flavianate as described above. The product obtained by decomposition of the flavianate crystallized from 70% ethanol as clusters of fine, glistening needles, m.p. 258–259° with decomposition. (Simultaneously in the same bath iso-octopine (A) melted at 258–259° with decomposition.)

The air-dried product failed to lose weight on drying at elevated temperatures or in vacuum, and no other evidence of water of crystallization could be obtained.

Anal. Calc'd for $C_9H_{18}N_4O_4$: N, 22.75. Found: N, 22.6 (Micro Kjeldahl).

$[\alpha]_D^{25}$ +25° in 2.5% aqueous solution in a semi-micro 1 dm. tube.

β-Octopine. An attempt was made to condense *l*(+)-arginine with β-bromopropionic acid following closely the conditions described by Akasi (10) in one experiment, and our own in a second. In both cases van Slyke amino-nitrogen determinations failed to indicate the disappearance of arginine and this reactant could be recovered quantitatively as the flavianate.

Desmethyloctopine (*II*). A solution of 4.2 g. of *l*(+)-arginine monohydrochloride and 3.8 g. of monochloroacetic acid in water was treated with 30 ml. of 0.1 *M* sodium carbonate solution and diluted to 330 ml., after which it was boiled under reflux for four hours, when 90% of the amino nitrogen (van Slyke) had disappeared. As the reaction proceeded, the color given in the Sakaguchi test changed from the orange characteristic of arginine to a purple similar to that given by octopine. After acidification of the reaction mixture to

Congo Red with hydrochloric acid and removal of unreacted arginine as the flavianate, the solution was evaporated to a thin syrup under reduced pressure. Addition of ethanol precipitated the product, which was redissolved in 70% ethanol acidified with hydrochloric acid, and reprecipitated by addition of pyridine. After two recrystallizations from 70% ethanol, the product melted at 281–282° with decomposition. It gave a purple color in the Sakaguchi test and was only moderately soluble in cold water.

Anal. Calc'd for $C_8H_{16}N_4O_4$: N, 24.14. Found: N, 23.9, 23.9 (Micro Kjeldahl).

$[\alpha]_D^{24}$ +24° in 2.5% aqueous solution in a semi-micro 1 dm. tube.

Rotation curves. All solutions for determination of specific rotations were freshly prepared by weighing amounts of each compound sufficient to prepare a tenth molar solution into calibrated 2 ml. volumetric flasks, adding the calculated amount of standard hydrochloric acid or sodium hydroxide solution and diluting to the mark. Rotations were determined in a 1 dm. semi-micro tube in a Schmidt and Haensch half-shadow polarimeter, using a sodium vapor lamp as a source of monochromatic light. Each rotation was the average of ten consecutive readings and the average deviation was ±0.02°. Since the observed rotations were all less than unity, specific rotations are not significant beyond the nearest whole degree as reported in the table. The pertinent data are recorded in Table I.

TABLE I

CHANGE OF ROTATION ON ADDITION OF ACID OR ALKALI TO NATURAL AND SYNTHETIC OCTOPINE, ISO-OCTOPINE AND DESMETHYLOCTOPINE

	OCTOPINE					ISO-OCTOPINE				DESMETHYL OCTOPINE t = 24		
	Natural t = 28			Synthetic Method B c = 2.5 t = 25		Method A c = 2.5 t = 24.5		Method B c = 2.5 t = 25				
	c	α	$[\alpha]_D$	α	$[\alpha]_D$	α	$[\alpha]_D$	α	$[\alpha]_D$	c	α	$[\alpha]_D$
Approx. 0.1 M solution	2.4	+0.47	+20	+0.49	+20	+0.63	+25	+0.62	+25	2.5	+0.61	+24
Moles HCl:mole substance												
0.5:1	2.4	+0.41	+17									
1:1	2.5	+0.43	+17	+0.42	+17	+0.48	+19	+0.48	+19	2.6	+0.56	+22
2:1	2.4	+0.45	+19	+0.47	+19	+0.46	+18	+0.45	+18	2.5	+0.49	+20
3:1	2.5	+0.47	+19	+0.47	+19	+0.53	+21	+0.50	+20	2.5	+0.52	+21
5:1	2.5	+0.48	+19	+0.48	+19	+0.52	+21	+0.52	+21	2.5	+0.52	+21
10:1	2.5	+0.49	+20	+0.48	+19	+0.53	+21					
Moles NaOH:mole substance												
0.5:1	2.5	+0.41	+16									
1:1	2.4	+0.33	+14	+0.37	+15	+0.28	+11	+0.26	+10	2.5	+0.59	+24
2:1	2.4	+0.32	+13	+0.36	+14	+0.22	+9	+0.23	+9	2.5	+0.63	+25
3:1	2.4	+0.32	+13	+0.34	+14	+0.23	+9	+0.23	+9	2.6	+0.65	+25
5:1	2.4	+0.34	+14	+0.38	+15	+0.27	+11	+0.24	+10	2.5	+0.66	+26

c = grams of solute per 100 ml. of solution
t = temperature in degrees centigrade
α = observed rotation in degrees
$[\alpha]_D$, = specific rotation, in degrees, at the given temperature

SUMMARY

1. The catalytic hydrogenation of a mixture of *l*(+)-arginine and pyruvic acid in aqueous solution proceeds asymmetrically with the formation of iso-octopine, a diastereoisomer of octopine.

2. The characteristic properties of iso-octopine have been described and its structure has been established by its oxidative degradation to γ-guanidinobutyric acid and acetaldehyde and by its synthesis together with octopine from $l(+)$-arginine and *dl*-α-bromopropionic acid.

3. The synthesis of desmethyloctopine from $l(+)$-arginine and monochloroacetic acid has been described.

4. The effect of acid and alkali upon the specific rotation of natural and synthetic octopine, iso-octopine, and desmethyloctopine has been determined.

5. It is suggested that the α-propionic acid residue has the *d* configuration in octopine and the *l* configuration in iso-octopine.

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THE SYNTHESIS OF POTENTIAL ANTIMALARIALS. SOME SUBSTITUTED N-PHENYLSULFONAMIDES[1]

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Drugs of the sulfonamide type have recently been extensively investigated as antimalarials. As part of this general program the compounds in Table I were prepared.[3]

As intermediates, several unreported aniline derivatives were required and their preparation is also described.

These compounds were prepared by coupling an appropriate sulfonyl chloride with the required aniline derivative and hydrolyzing or reducing the product to the final compound. The method of coupling and hydrolysis employed was essentially that of Long and Burger (1), but it was found that variations in the experimental details were of great importance in obtaining satisfactory yields of the products.

Two methods are described for the preparation of III. The coupling with 2,6-dibromo-4-aminoacetanilide was employed, since it was thought that the blocking of one amino group would be necessary to prevent formation of two products. When the removal of the blocking group gave difficulty, the alternate method with 2,6-dibromo-*p*-phenylenediamine was used, which gave satisfactory yields.

The preparation of 4-dimethylamino-3,5-dibromonitrobenzene presented some difficulty. Bromination of *p*-nitro-N,N-dimethylaniline, as described below, led to a monomethyl derivative, a result similar to that reported by Fries (2) in the bromination of dimethylaniline. Only starting material was recovered when an attempt was made to methylate 4-nitro-2,6-dibromoaniline with dimethyl sulfate as described by Evans and Williams (3) for the methylation of *p*-nitroaniline. The formaldehyde-formic acid method described by Clarke *et al* (4) for the methylation of 2,4,6-trisubstituted anilines gave similar results. The preparation was finally accomplished by the reaction of dimethylamine with 4-iodo-3,5-dibromonitrobenzene.

An attempt was made to prepare 4-cyano-3′,5′-dibromobenzenesulfonanilide from II following the procedure used by Miller *et al* (5) to prepare *p*-cyanoben-

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Instatute of Technology.

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[3] At the time this work was started compound II and the acetyl derivative of I were described in the patent literature (6), but they were not available for testing. Since the completion of this work compounds II and VIII have been briefly described by Kaplan and Leubner (10), while compound VI has been prepared by a different method by Cook *et al* (20).

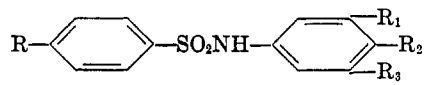
zenesulfonamide from sulfanilamide. The method failed because of the insolubility of both II and its diazonium salt. The required compound was then obtained by the reaction of *p*-cyanobenzenesulfonyl chloride with 3,5-dibromoaniline.

EXPERIMENTAL[4,5]

N^4-Acetyl-N^1-(3,5-dinitrophenyl)sulfanilamide (6). Twenty-eight grams of 3,5-dinitroaniline (7) was dissolved in 200 ml. of reagent pyridine, and 55 g. of acetylsulfanilyl chloride[6] was added in small portions while the solution was cooled and shaken. After standing at room temperature for one hour the solution was heated on a steam-bath for fifteen hours. It was then poured into a mixture of hydrochloric acid and ice, and the precipitated solid filtered and washed with dilute acid and water. For purification it was dissolved in 200 ml. of hot 2 *N* sodium carbonate solution, filtered, and precipitated with 2 *N* hydrochloric acid. After filtration, washing, and drying, the product weighed 55 g. (93%) and melted with decomposition at 280–281°.

N^1-(3,5-Dinitrophenyl)sulfanilamide (I), (SN 3863).[7] The acetyl group was removed by refluxing a solution of 55 g. of the amide in a mixture of 750 ml. of ethanol and 220 ml. of

TABLE I



	R	R_1	R_2	R_3
I	$-NH_2$	$-NO_2$	—H	$-NO_2$
II	$-NH_2$	—Br	—H	—Br
III	$-NH_2$	—Br	$-NH_2$	—Br
IV	$-NH_2$	—Br	$-NHCH_3$	—Br
V	$-NH_2$	—Br	$-N(CH_3)_2$	—Br
VI	$-NH_2$	—CN	—H	—H
VII	$-NH_2$	—CN	—H	—CN
VIII	$-CH_2NH_2$	—Br	—H	—Br

concentrated hydrochloric acid. After two hours the solution was poured into five volumes of water and made basic with ammonia. The amine after filtration, washing, and drying weighed 45 g. (90%). It melted at 214–215° after crystallization from ethanol.

Anal. Calc'd for $C_{12}H_{10}N_4O_6S$: C, 42.6; H, 3.0; N, 16.6.
Found: C, 42.7; H, 3.1; N, 16.5.

3,5-Dibromoaniline. 3,5-Dibromonitrobenzene (8) was reduced catalytically with Raney nickel at 50° and 50 lbs. pressure.[8] The catalyst was removed by filtration and the solution evaporated to dryness. The residue, after purification through the hydrochloride,

[4] All melting points reported have been corrected for exposed stem.

[5] The microanalyses reported have been carried out by Dr. Gertrude Oppenheimer and Mr. Alan Swinhart.

[6] We wish to thank Merck and Company for a generous gift of this compound.

[7] The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of the compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

[8] This method of reducing halogenated nitrobenzenes was suggested by Dr. N. L. Drake of the University of Maryland in a private communication.

was obtained in an 86% yield and had the m.p. 47.5–50.5° in agreement with the literature (9).

N^4-Acetyl-N^1-(3,5-dibromophenyl)sulfanilamide (*6*). This compound was prepared from 3,5-dibromoaniline and acetylsulfanilyl chloride in the manner described above. After purification, the product was obtained in 93% yield and melted at 242–244°.

N^1-(3,5-Dibromophenyl)sulfanilamide (*II*) (*6*, *10*), (*SN 187*). The acetyl compound was hydrolyzed as described above. The crystalline precipitate of the product was obtained in 79% yield and melted at 149.5–152°. A sample recrystallized from ethanol melted at 154–155°.

Anal. Calc'd for $C_{12}H_{10}Br_2N_2O_2S$: C, 35.5; H, 2.5; N, 6.9.
Found: C, 35.3; H, 2.4; N, 6.9.

2,6-Dibromo-4-aminoacetanilide. 2,6-Dibromo-4-nitroaniline prepared in 96% yield from *p*-nitroaniline under the conditions employed by Hartman and Dickey (11) for the bromination of *p*-nitrophenol was acetylated by the method of Smith and Orton (12, 13) and the nitro group reduced catalytically (64% yield) as described above for 3,5-dibromonitrobenzene. The product was crystallized from ethanol to give colorless crystals melting at 246.5–248.5°.

Anal. Calc'd for $C_8H_8Br_2N_2O$: C, 31.2; H, 2.6; N, 9.1.
Found: C, 31.5; H, 2.8; N, 8.9.

N^4-Acetyl-N^1-(3,5-dibromo-4-acetaminophenyl)sulfanilamide. The reaction was carried out in the usual fashion, with two and one-half hours' warming on a steam-bath. A yield of 81% of crude material was obtained. A sample crystallized from aqueous ethanol melted at 236–238°.

N^1-(3,5-Dibromophenyl-4-acetaminophenyl)sulfanilamide. The hydrolysis was carried out as described above. After one and one-half hours of refluxing, a compound melting at 210–213° was obtained in 76% yield.

Anal. Calc'd for $C_{14}H_{13}Br_2N_3O_3S$: C, 36.3; H, 2.8.
Found: C, 36.5; H, 3.1.

N^4-Acetyl-N^1-(3,5-dibromo-4-aminophenyl)sulfanilamide. Twenty grams of 2,6-dibromo-*p*-phenylenediamine (14) and 18.5 g. of acetylsulfanilyl chloride were coupled using one hour of heating. A sample crystallized from aqueous ethanol melted at 232–233.5°.

Anal. Calc'd for $C_{14}H_{13}Br_2N_3O_3S$: N, 9.1. Found: N, 9.5.

N^1-(3,5-Dibromo-4-aminophenyl)sulfanilamide (*III*), (*SN 3864*). The hydrolysis of N^1-(3,5-dibromo-4-acetaminophenyl)sulfanilamide required eight hours of additional refluxing. A product melting at 176–177° was obtained in 60% yield.

Anal. Calc'd for $C_{12}H_{11}Br_2N_3O_2S$: C, 34.2; H, 2.6; N, 9.8.
Found: C, 34.5; H, 2.7; N, 10.3.

The crude N^4-acetyl-N^1-(3,5-dibromo-4-aminophenyl)sulfanilamide was hydrolyzed by one hour of refluxing. Recrystallization from aqueous ethanol gave a yield of 85% of a compound identical with that reported above.

p-Nitro-N,N-dimethylaniline. A solution of 44.8 g. of *p*-nitrochlorobenzene, 40 ml. of dimethylamine, and 200 ml. of ethanol was heated for four hours at 160° in bomb tubes. On cooling, the product crystallized out and was collected by filtration. After recrystallization from ethanol 41.6 g. (88%) of *p*-nitro-N,N-dimethylaniline was obtained melting at 163–166° in agreement with the literature (15).

N-Methyl-2,6-dibromo-4-nitroaniline. The bromination of *p*-nitro-N,N-dimethylaniline was carried out as was the bromination of *p*-nitroaniline. On recrystallization of the crude product from ethanol, 30% of yellow crystals was obtained, m.p. 111–113° in agreement with the literature (16).

N^1-Methyl-2,6-dibromo-p-phenylenediamine. The nitro compound was reduced as usual, in 54% yield. An analytical sample of the amine crystallized from benzene melted at 103–104°.

Anal. Calc'd for $C_7H_8Br_2N_2$: C, 30.0; H, 2.9; N, 10.0.
Found: C, 29.9; H, 2.9; N, 10.0.

N^4-Acetyl-N^1-(3,5-dibromo-4-methylaminophenyl)sulfanilamide. The reaction between the amine and acetylsulfanilyl chloride required one hour of heating. The crude product was obtained in 92% yield. A sample recrystallized from aqueous ethanol melted at 220–221.5°.

Anal. Calc'd for $C_{15}H_{15}Br_2N_3O_3S$: C, 37.8; H, 3.2; N, 8.8.
Found: C, 38.4; H, 3.2; N, 8.3.

N^1-(3,5-Dibromo-4-methylaminophenyl)sulfanilamide (IV), (SN 3865). The hydrolysis and isolation were carried out in the usual manner. There was obtained an 80% yield of a product which melted at 147–148.5° after recrystallization from a chloroform-ligroin mixture.

Anal. Calc'd for $C_{13}H_{13}Br_2N_3O_2S$: C, 35.9; H, 3.0; N, 9.7.
Found: C, 36.3; H, 3.3; N, 9.8.

3,5-Dibromo-4-iodonitrobenzene. This compound was prepared from 2,6-dibromo-4-nitroaniline in the manner employed by Niemann and Redemann (17) to obtain 3,4,5-triiodonitrobenzene. After recrystallization from an ethanol-Cellosolve (2:1) mixture 75% of product melting at 150.5–152.5° was obtained. The previously reported melting point 135.5° (18) seems to be in error.

Anal. Calc'd for $C_6H_2Br_2INO_2$: C, 17.7; H, 0.5.
Found: C, 18.0; H, 0.9. 7.460 mg. compound gives 11.21 mg. AgX. Calculated 11.19 mg. AgX.

3,5-Dibromo-4-dimethylaminonitrobenzene. A mixture of 40.7 g. of 3,5-dibromo-4-iodonitrobenzene, 80 ml. of butanol, and 15 ml. of dimethylamine was heated in a sealed tube at 120–130° for seven hours. A homogeneous solution was obtained. On cooling, the product crystallized out and was filtered and washed with methanol. Recrystallization from ethanol yielded 25.3 g. of golden plates melting at 102–103.5°. A second crop was obtained from the mother liquors. The total yield was 27.5 g. (85%).

Anal. Calc'd for $C_8H_8Br_2N_2O_2$: C, 29.7; H, 2.5; N, 8.7.
Found: C, 29.8; H, 2.5; N, 8.5.

3,5-Dibromo-4-dimethylaminoaniline. The catalytic reduction of 4-dimethylamino-3,5-dibromonitrobenzene in the usual manner gave a quantitative yield. The free amine appeared to be unstable and was therefore immediately coupled with acetylsulfanilyl chloride.

N^4-Acetyl-N^1-(3,5-dibromo-4-dimethylaminophenyl)sulfanilamide. The crude amine from the reduction of 15 g. of the nitro compound was dissolved in 25 ml. of pyridine and coupled with acetylsulfanilyl chloride in the usual manner. The product weighed 21.7 g. (95% from the nitro compound), m.p. 248.5–250.5°. An analytical sample from aqueous ethanol melted at 252–253°.

Anal. Calc'd for $C_{16}H_{17}Br_2N_3O_3S$: C, 39.1; H, 3.5; N, 8.6.
Found: C, 39.5; H, 3.7; N, 8.6.

N^1-(3,5-Dibromo-4-dimethylaminophenyl)sulfanilamide (V), (SN 3866). The acetyl compound was hydrolyzed as usual, yielding 79% of colorless platelets, m.p. 194.5–196°, after crystallization from aqueous ethanol.

Anal. Calc'd for $C_{14}H_{15}Br_2N_3O_2S$: C, 37.4; H, 3.4; N, 9.4.
Found: C, 37.3; H, 3.3; N, 9.4.

p-Nitrobenzenesulfonyl-m-cyanoanilide. The reaction of *m*-cyanoaniline (19) with *p*-nitrobenzenesulfonylchloride was carried out in the same fashion as the couplings previously described. Two hours' heating were required. After crystallization from acetic acid 77% of colorless prisms, m.p. 198.5–199.5° was obtained.

Anal. Calc'd for $C_{13}H_9N_3O_4S$: C, 51.5; H, 3.0; N, 13.9.
Found: C, 51.5; H, 3.1; N, 13.3.

N^1-(3-Cyanophenyl)sulfanilamide (VI) (20), (SN 6947). To a suspension of 45 g. of iron powder in 150 ml. of 96% ethanol containing 1.5 ml. of dilute hydrochloric acid was added 14 g. of *p*-nitrobenzenesulfonyl-*m*-cyanoanilide, and the mixture was stirred and heated on the steam-bath for six hours. At the end of this period the suspension was filtered hot, and

the residue was washed with hot ethanol. The solution thus obtained was poured into about five volumes of water whereupon a colorless crystalline precipitate slowly appeared. It was filtered, washed, and dried to give 11.4 g. (90%) of product, m.p. 188–191°. After several recrystallizations from 30% ethanol the product melted at 191–192°.

Anal. Calc'd for $C_{13}H_{11}N_3O_2S$: C, 57.1; H, 4.1; N, 15.4.
Found: C, 57.3; H, 4.2; N, 15.6.

5-Nitroisophthalic acid. When 120 g. of isophthalic acid was heated with 600 ml. of fuming nitric acid, density 1.59–1.60, the solid went into solution in about eight hours. Evaporation of the solution and recrystallization of the product from water gave yields of 70–75% of 5-nitroisophthalic acid,[9] m.p. 254–258°.

3,5-Dicyanonitrobenzene. The preparation of the dicyano compound was carried out in ten-gram batches as larger runs tended to decrease the yield. An intimate mixture of 10 g. of 5-nitroisophthalamide (21) and 13 g. of phosphorus pentoxide was heated at 240–250° for eight hours. The residue was treated with water until it softened and was then filtered and dried. This material was extracted with a 50-ml. portion of boiling acetic acid. The filtrate on standing deposited yellow crystals which were filtered and dried. The solid residue from the first extraction was extracted twice more with the same portion of acetic acid, the yields thus obtained being combined. There was obtained 3.9 g. (46%) of yellow prisms, m.p. 203.5–205.5°.

3,5-Dicyanoaniline. To 3.5 g. of 3,5-dicyanonitrobenzene dissolved in 40 ml. of hot acetic acid was added 13 g. of stannous chloride dihydrate. Dry hydrogen chloride was passed into the hot suspension until a clear orange solution was obtained (about ten minutes). The solution was allowed to cool and then poured into 250 ml. of ether. Water was added and the mixture was shaken until two clear phases were obtained; then, with constant shaking, 40% sodium hydroxide solution was gradually added until the aqueous phase was strongly basic. The ethereal phase was washed and dried. Evaporation of the ether and crystallization of the residue from 30% ethanol gave 1.2 g. (41%) of colorless needles, m.p. 192–193°.

Anal. Calc'd for $C_8H_5N_3$: C, 67.1; H, 3.5; N, 29.4.
Found: C, 67.3; H, 3.5; N, 29.2.

p-Nitrobenzenesulfonyl-3,5-dicyanoanilide. The coupling of 3,5-dicyanoaniline with *p*-nitrobenzenesulfonyl chloride was effected in the manner employed for the monocyano compound. A yield of 91% of product melting above 300° was obtained. An analytical sample was prepared by crystallization from ethanol.

Anal. Calc'd for $C_{14}H_8N_4O_4S$: C, 51.2; H, 2.5; N, 17.1.
Found: C, 51.4; H, 2.9; N, 17.5.

N^1-(3,5-Dicyanophenyl)sulfanilamide (VII), (SN 6946). The nitro compound was reduced using iron powder and hydrochloric acid as described above for the monocyano compound. A yield of 76% of product, m.p. 222–224°, was obtained. After crystallization from aqueous ethanol it was recovered as light greenish-yellow prisms, m.p. 227.5–228.5°.

Anal. Calc'd for $C_{14}H_{10}N_4O_2S$: C, 56.4; H, 3.4; N, 18.8.
Found: C, 56.3; H, 3.8; N, 18.8.

4-Cyano-3',5'-dibromobenzenesulfonanilide. To a solution of 24.0 g. of 3,5-dibromoaniline in 48 ml. of dry pyridine was added 19.6 g. of *p*-cyanobenzenesulfonyl chloride (22, 23) in small portions. After standing at room temperature for 45 minutes the mixture was heated on a steam-bath for three hours. The product was then isolated in the usual fashion. The crude material was crystallized from 500 ml. of boiling ethanol by adding hot water (500 ml.) until crystallization began. After cooling, the product was filtered, washed, and dried, yielding 36.9 g. (93%) of colorless plates and flat prisms melting at 196.5–197.5°.

Anal. Calc'd for $C_{13}H_8Br_2N_2O_2S$: C, 37.5; H, 1.9; N, 6.7.
Found: C, 37.3; H, 2.0; N, 6.7.

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[9] Under the conditions described by Meyer and Wesche (24) and Storrs and Fittig (25) no reaction could be made to occur even when the reactants were refluxed together for seventy-two hours.

4-Aminomethyl-3',5'-dibromobenzenesulfonanilide (*VIII*), (*SN 8828*), (*10*). A suspension of 37.5 g. of 4-cyano-3',5'-dibromobenzenesulfonanilide in 920 ml. of absolute ethanol containing 0.112 mole of hydrochloric acid was catalytically reduced by shaking with 3.0 g. of platinum oxide under one atmosphere of hydrogen (5). The theoretical quantity of hydrogen was adsorbed in five hours. After the catalyst was filtered, the solvent was removed under reduced pressure. The residue was extracted with 1200 ml. of boiling water, and, on cooling, large, colorless, flat prisms were deposited weighing 30.4 g., m.p. 271–272° with decomposition and effervescence. A second crop of 2.7 g. was obtained from the mother liquors making a total yield of 78%. An analytical sample from water melted at 273–274°.

Anal. Calc'd for $C_{13}H_{13}Br_2ClN_2O_2S \cdot H_2O$: C, 32.9; H, 3.2; N, 5.9.
Found: C, 32.8; H, 3.4; N, 5.9.

The free base was obtained by neutralization of a hot solution of the hydrochloride with saturated potassium bicarbonate solution. Recrystallization from absolute ethanol resulted in colorless prisms melting at 214.5–215.5°.

Anal. Calc'd for $C_{13}H_{12}Br_2N_2O_2S$: C, 37.2; H, 2.9; N, 6.7.
Found: C, 37.0; H, 3.1; N, 6.6.

SUMMARY

The preparation of several new derivatives of aniline and of nitrobenzene is described and the synthesis of a group of substituted sulfonanilides is reported.

PASADENA, CALIF.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF SOUTHERN CALIFORNIA]

SYNTHESIS OF α-DIALKYLAMINOMETHYL-4-BENZYLOXY-1-NAPHTHALENEMETHANOLS[1]

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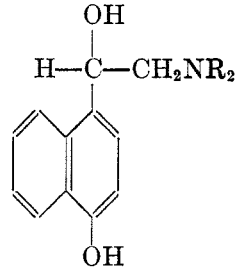
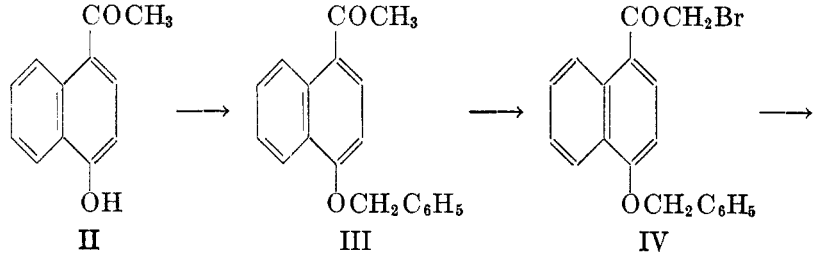
At the suggestion of Dr. Lyondon F. Small of the National Institute of Health, an attempt was made to synthesize potential antimalarial substances in the α-dialkylaminomethyl-4-hydroxy-1-naphthalenemethanol series (I).



I

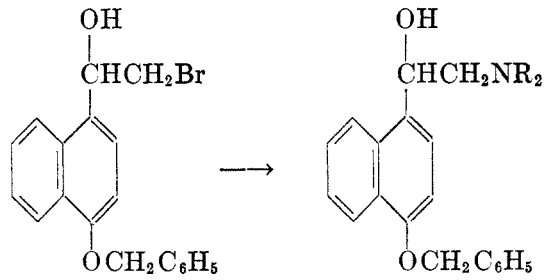
The most apparent route to compounds of this type, involving condensation of 1-chloroaceto-4-hydroxynaphthalene (1) and a secondary amine, proved not to be feasible. Reaction of 1-chloroaceto-4-hydroxynaphthalene with dibutylamine, for example, produced only amorphous red tars. The failure of a similar amino ketone synthesis has been reported by Tutin, Caton, and Hann (2) who isolated only red tarry material from the reaction of *p*-hydroxyphenacyl chloride with ammonia.

Proceeding on the hypothesis that the free phenolic group of 1-chloroaceto-4-hydroxynaphthalene interferes with the anticipated amine condensation, an attempt was made to protect the hydroxyl group by benzylation (3), complete the synthesis, and, as the final step, to remove the protecting group by catalytic hydrogenolysis.



II III IV

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Southern California. The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such a number has been assigned will be tabulated in a forthcoming monograph.



V VI; R = *n*-Propyl
VII; R = *n*-Butyl

1-Aceto-4-hydroxynaphthalene (II), prepared by the method of Akram and Desai (4), was benzylated in 60% yield by means of benzyldimethylphenylammonium chloride in boiling 20% sodium carbonate solution. The resulting benzyloxyketone (III) was then brominated in boiling anhydrous ether to give IV in 75% yield, along with a small quantity of a dibromo ketone. Reduction of IV to the bromohydrin V was effected in 70% yield by means of aluminum isopropoxide. Amino alcohols VI and VII were obtained by treatment of the bromohydrin with the appropriate secondary amine in a sealed tube at 100–130°. Unfortunately, attempted catalytic hydrogenolysis of VI yielded a dihydronaphthalene derivative instead of the desired α-dipropylaminomethyl-4-hydroxy-1-naphthalenemethanol.

EXPERIMENTAL[2]

1-Aceto-4-benzyloxynaphthalene (III). In a five-liter three-neck flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping-funnel, was placed a solution of 319 g. (2.10 moles) of 1-aceto-4-hydroxynaphthalene (3) dissolved in 2700 cc. of 20% sodium carbonate solution. During the course of three hours, 573 g. (2.31 moles) of benzyldimethylphenylammonium chloride dissolved in 1000 cc. of water was added dropwise to the stirred refluxing solution. The mixture was allowed to cool and 1000 cc. of benzene was added. The benzene solution was washed with 5% sodium hydroxide, then with 6 *N* hydrochloric acid, and finally with water. The crude product, which separated from the solution after most of the solvent had been removed by distillation, was filtered off, washed with a little cold benzene, and leached with 800 cc. of 95% ethanol under reflux for four hours. The leaching flask and its contents were cooled to room temperature and the 1-aceto-4-benzyloxynaphthalene was filtered off and dried; yield 325 g. (64.3%); m.p. 116–117°.

4-Benzyloxy-1-bromoacetonaphthalene (IV). Eighty-five grams (0.308 mole) of 1-aceto-4-benzyloxynaphthalene was placed in a five-liter three-necked flask equipped with a mercury-sealed stirrer, a dropping-funnel, and a reflux condenser and dissolved in 4000 cc. of anhydrous ether under gentle reflux. One hundred cc. of a saturated solution of anhydrous hydrogen chloride in ether was added. The ether solution was maintained at reflux temperature while 51.6 g. (0.324 mole) of dry bromine dissolved in 400 cc. of dry carbon tetrachloride was added dropwise in the course of two hours. The reaction mixture was then concentrated to a volume of 200 cc. by distillation of the solvents. The crude bromo ketone which crystallized when the solution was cooled to room temperature was filtered off and recrystallized from 200 cc. of carbon tetrachloride; yield, 82 g. (75%) of 4-benzyloxy-1-bromoacetonaphthalene; m.p. 105–107°.

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[2] All melting points are corrected. Analyses by Bruce Day and Richard Nevé, The University of California at Los Angeles.

Anal. Calc'd for $C_{19}H_{15}BrO_2$: C, 64.24; H, 4.26.
Found: C, 64.68; H, 4.40.

If undiluted bromine was used or if the solution of bromine in carbon tetrachloride was added too rapidly, the formation of dibromo ketone increased to such an extent that it became possible to separate manually rectangular plates of this compound from the needle-like crystals of the monobromo ketone in the crude reaction product. The preparation of the dibromo ketone is described below.

4-Benzyloxy-1-dibromoacetonaphthalene. To a solution of 2.43 g. of 1-aceto-4-benzyloxynaphthalene dissolved in 150 cc. of anhydrous ether was added 5 cc. of a saturated solution of anhydrous hydrogen chloride in ether. Bromine (0.9 cc.) was added to the ether solution during two hours. The color faded rapidly after each drop of bromine had been added until 0.45 cc. had been consumed but disappeared slowly during the addition of the remaining 0.45 cc. The ether solution was washed consecutively with water, sodium thiosulfate solution, and 5% sodium bicarbonate solution. After a final washing with water it was dried with anhydrous sodium sulfate and concentrated to a volume of 100 cc. The first crop of crystals (2.34 g.) had the m.p. 130.8–131°; a second crop (0.52 g.) had the m.p. 129.8–130.8°; total yield, 75%. One recrystallization from 95% ethanol raised the m.p. of the first fraction to 131.6–132°.

Anal. Calc'd for $C_{19}H_{14}Br_2O_2$: C, 52.56; H, 3.25.
Found: C, 53.14; H, 3.30.

4-Benzyloxy-α-bromomethyl-1-naphthalenemethanol (*V*). To 28.13 g. of 4-benzyloxy-1-bromoacetonaphthalene contained in a one-liter conical flask was added 400 cc. of hot 3 *N* aluminum isopropoxide in isopropyl alcohol. The reaction mixture was heated to reflux for twenty minutes and 150 cc. of isopropyl alcohol was distilled through a take-off condenser. The reaction flask was then cooled for three minutes under the water tap and its contents were then poured into a mixture of 200 cc. of 12 *N* hydrochloric acid and 400 g. of ice. After thirty minutes, the supernatant liquid was decanted from the solid residue and extracted twice with ether. The combined ether extract was used to dissolve the solid residue. The ether solution was washed with 5% sodium bicarbonate and with water. The dried solution was concentrated to a volume of 100 cc. and 50 cc. of carbon tetrachloride was added. After the volume of the solution had been reduced to 50 cc. by distillation, 25 cc. of petroleum ether (30–60°) was added in small amounts with intermittent heating. The 4-benzyloxy-α-bromomethyl-1-naphthalenemethanol which crystallized from the solution weighed 20.14 g. (71%); m.p. 84–85°.

Anal. Calc'd for $C_{19}H_{17}BrO_2$: Br, 22.4. Found: Br, 22.4.

4-Benzyloxy-α-dipropylaminomethyl-1-naphthalenemethanol (*SN-11,448*; *VI*). A solution of 15.58 g. of 4-benzyloxy-α-bromomethyl-1-naphthalenemethanol in 30 cc. of dipropylamine was heated in a sealed tube at 100° for twelve hours. The dipropylamine hydrochloride which was filtered off from the reaction mixture weighed 8.01 g. (100%). The filtrate was steam distilled in the presence of 25% sodium hydroxide solution for two hours in order to remove unreacted dipropylamine, and the gummy yellow residue was then dissolved in ether. The addition of a few cc. of petroleum ether to the dry ethereal solution caused the separation of a small amount of tan solid which was filtered off and discarded. The only hydrochloride, which was formed when sufficient anhydrous hydrogen chloride in anhydrous ether was added to the filtrate, was dissolved in the minimum amount of absolute ethanol at the boiling point of the solution and anhydrous ether was slowly added to the point of incipient crystallization. After standing overnight at 0°, the solution deposited 8.34 g. (47.5%) of 4-benzyloxy-α-dipropylaminomethyl-1-naphthalenemethanol hydrochloride; m.p. 130–132°.

Anal. Calc'd for $C_{26}H_{32}ClNO_2$: C, 72.50; H, 7.79.
Found: C, 72.31; H, 7.93.

4-Benzyloxy-α-dibutylaminomethyl-1-naphthalenemethanol (*SN-10,201*; *VII*). Upon being heated to 130° for fourteen hours, a mixture of 7.82 g. of 4-benzyloxy-α-bromomethyl-1-

naphthalenemethanol and 14.2 g. of dibutylamine yielded 4.45 g. (60%) of 4-benzyloxy-α-dibutylaminomethyl-1-naphthalenemethanol isolated as the hydrochloride; m.p. 140–142°.

Anal. Calc'd for $C_{27}H_{36}ClNO_2$: C, 73.36; H, 8.21.
Found: C, 73.74; H, 8.42.

4-Benzyloxy-α-dibutylaminomethyl-1-dihydronaphthalenemethanol. 4-Benzyloxy-α-dibutylaminomethyl-1-naphthalenemethanol hydrochloride (17.68 g.) was hydrogenated at 40 lbs./in.^{2} with 0.5 g. of platinum oxide as catalyst. The crystalline material obtained after the removal of solvent *in vacuo* was leached with distilled water at room temperature overnight and recrystallized from absolute ethanol. There was obtained 8.49 g. of a substance which melted at 140–142°. A mixture of this material with VII melted at 119–126°. The reduction product did not give a positive test for a phenolic group with 10% aqueous ferric chloride although the aqueous extract of the crude reduction product produced a brilliant violet color with this reagent.

Anal. Calc'd for $C_{27}H_{38}ClNO_2$: C, 73.03, H, 8.63.
Found: C, 73.18; H, 8.57.

SUMMARY

Synthesis of the potential antimalarials α-dipropylaminomethyl-4-benzyloxy-1-naphthalenemethanol and α-dibutylaminomethyl-4-benzyloxy-1-naphthalenemethanol, from 1-aceto-4-hydroxynaphthalene, has been described.

LOS ANGELES 7, CALIF.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF SOUTHERN CALIFORNIA]

POTENTIAL ANTIMALARIALS IN THE 4-DIALKYLAMINOMETHYL-2-METHYL-3-PYRIDOL SERIES[1]

RONALD F. BROWN AND STANLEY J. MILLER

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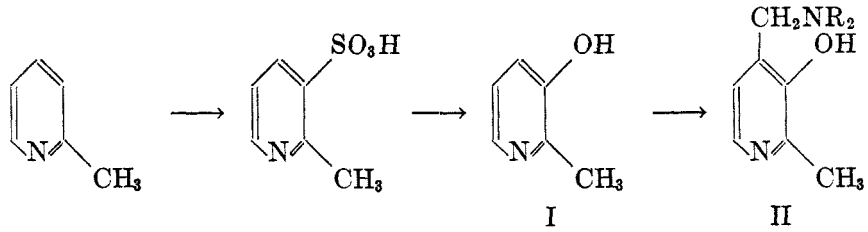
The activity of the minimal effective dose of quinine and of Atabrine against *P. lophurae* infection in Pekin ducklings has been shown by Seeler (1) to be inhibited by the administration of pyridoxine in quantities three thousand times the basic nutritive requirements of the host. It appeared, therefore, that pyridoxine might be an essential metabolite for the malaria organisms, and it seemed a reasonable expectation that similar compounds might interfere with this metabolism.

In order to investigate this possibility, several compounds of type II, which contain structural features of pyridoxine as well as the dialkylaminoalkyl side chain found in active antimalarials, were synthesized from picolinol I by means of Mannich reactions.



Sulfonation of 2-picoline and the subsequent alkaline fusion to yield I were carried out according to the methods of Wulff (2), except that sulfonation with fuming sulfuric acid was found to be expedient. The crude 2-picolin-3-ol (I) was recrystallized from ethyl acetate in order to remove inorganic salts.

The usual procedure for the Mannich reaction with phenols (3) was found to be applicable to picolinol I. Participation of the methyl group of I in a Mannich reaction requires relatively rigorous conditions (4) and no interference from that source was observed.

The aminopyridols which were prepared in the aforedescribed manner are shown in Table I.

EXPERIMENTAL

4-Diethylaminomethyl-2-methyl-3-pyridol (II, R = ethyl). To a solution of 16.35 g. (0.15 mole) of 2-picoline-3-ol and 11 g. (0.15 mole) of diethylamine in 50 cc. of water was added

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Southern California. The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such a number has been assigned will be tabulated in a forthcoming monograph.

over a period of one hour 13.5 g. of 40% formalin. After standing at room temperature for several hours, the reaction mixture was heated to boiling, was saturated with salt, and the oily layer (27 g.) was separated. Distillation of the crude oil yielded 19 g. (65%) of light yellow oil; b.p. 100–100.5° at 3 mm.

The free base was dissolved in absolute ethanol and hydrogen chloride gas was bubbled in until precipitation of the solid *dihydrochloride* was complete; yield, quantitative.

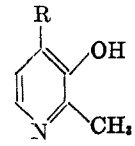
See Table I for analyses of free base and hydrochloride.

4-Piperidinomethyl-2-methyl-3-pyridol was prepared in the aforedescribed manner from 10.9 g. (0.1 mole) of 2-picoline-3-ol and 8.5 g. (0.1 mole) of piperidine in 40 cc. of water; yield, 13 g. (62%) of light yellow oil; b.p. 145–147° at 7 mm.

The *dihydrochloride*, prepared as before, melted at 250–252° dec. (see Table I for analysis).

4-Dibutylaminomethyl-2-methyl-3-pyridol (*II*, *R* = *n-butyl*). To a mixture of 10.9 g. (0.1 mole) of 2-picoline-3-ol, 13 g. (0.1 mole) of dibutylamine and 40 cc. of water was added sufficient ethanol to produce a homogeneous solution. Four grams of trioxymethylene was

TABLE I



SN	R	M.P., °C. (CORR.)	ANALYSES[2]			
			Calc'd		Found	
			% C	% H	% C	% H
13,484	$-CH_2N(C_2H_5)_2$	B.p. 100–100.5/3 mm.	68.05	9.34	67.34	9.29
	$-CH_2N(C_2H_5)_2$ (HCl)	210–211.5	49.03	7.55	49.03	7.56
13,636	$-CH_2N<^{CH_2CH_2}_{CH_2CH_2}>CH_2$ (2 HCl)	250–252 dec.	51.56	7.22	51.68	7.12
14,069	$-CH_2N(CH_2CH_2CH_2CH_3)_2$	B.p. 134–136/3 mm.	71.95	10.47	71.68	10.52

then added, and the solution was allowed to stand at room temperature overnight. The solution was heated to boiling and formalin added until no further cloudiness resulted. Water was added, and the ethanol boiled off. Saturation of the solution with salt yielded the oily amine. Distillation at 134–136° at 3 mm. yielded 7 g. (28%) of 4-dibutylaminomethyl-2-methyl-3-pyridol as a light yellow oil. See Table I for analysis.

LOS ANGELES 7, CALIF.

SUMMARY

The synthesis of three potential antimalarials in the 4-dialkylaminomethyl-2-methyl-3-pyridol series has been described.

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[2] Analyses by Bruce Day and Richard Nevé, The University of California at Los Angeles.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

POTENTIAL ANTIMALARIAL COMPOUNDS IN THE α-(1-DIALKYLAMINOETHYL)-1-NAPHTHALENE-METHANOL SERIES[1]

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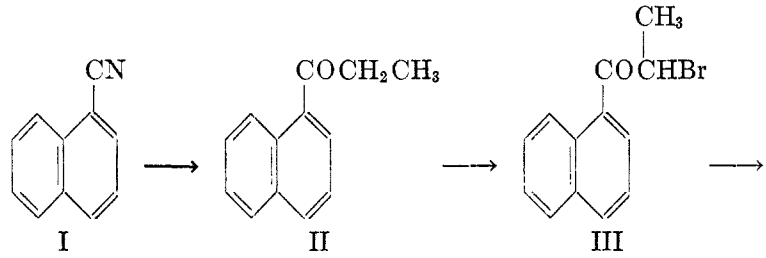
The preparation of potential antimalarial substances of type V was undertaken, at the suggestion of the malaria unit at the National Institute of Health, as part of a program of synthesis of amino alcohols containing the naphthalene nucleus.

1-Naphthonitrile served as a convenient starting material for the proposed synthesis. By reaction with ethylmagnesium bromide this nitrile (I) gave 1-propionylnaphthalene (II) in 85–90% yields. Bromination of 1-propionylnaphthalene in anhydrous ether solution at 10° afforded a solid bromo ketone (79–85% yields of pure material) which yielded 1-naphthoic acid upon oxidation with sodium hypochlorite. Since the identical bromo ketone was obtained from the reaction of naphthalene with α-bromopropionyl bromide, its structure was established as III.

1-(α-Bromopropionyl)naphthalene (III) in ether solution reacted slowly at room temperature with piperidine, dimethylamine, diethylamine, di-*n*-propylamine, and di-*n*-butylamine to yield amino ketones of type IV. In two instances (NR_2 = piperidino and dimethylamino) the amino ketones were isolated as crystalline hydrochlorides. Usually, however, the crude, relatively unstable, liquid amino ketone was reduced directly with aluminum isopropoxide in a nitrogen atmosphere. The amino alcohols (V) obtained in this manner were isolated as crystalline hydrochlorides in over-all yields of 25–68% from bromo ketone III. α-(1-Piperidinoethyl)-1-naphthalenemethanol (V, NR_2 = piperidino) was also isolated as the crystalline free base.



I II III

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and DePauw University. The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such a number has been assigned will be tabulated in a forthcoming monograph.

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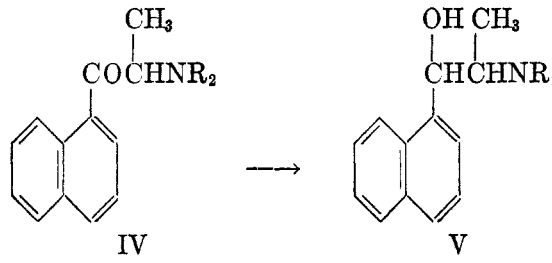

IV V

EXPERIMENTAL

1-Propionylnaphthalene (II)[3]. To the Grignard reagent prepared from 16.2 g. of magnesium, 80 g. of ethyl bromide, and 200 cc. of ether was added with constant swirling 86.4 g. of 1-naphthonitrile in 200 cc. of ether. The clear brown solution was refluxed gently for eighteen hours (precipitation of solid yellow complex) and was then hydrolyzed with ice and hydrochloric acid. The ethereal layer was separately refluxed with 100 cc. of 10% hydrochloric acid, while the original aqueous layer was heated on the steam-bath for one-half hour. The combined hydrolysis mixtures were separated and the aqueous layer extracted with ether. Upon evaporation, the combined ether extracts yielded a dark oil which was distilled in vacuum; yield, 90 g. (89%) of colorless 1-propionylnaphthalene; b.p. 144–146° at 1 mm. Hartung, Munch, and Crossley (1) reported a 68% yield of 1-propionylnaphthalene from the reaction of ethylmagnesium bromide and 1-naphthonitrile. This ketone has also been obtained, along with the 2-isomer, from the reaction of propionyl chloride with naphthalene (2).

1-Propionylnaphthalene yielded a picrate, m.p. 78–79°. Rousset (2) reported the m.p. 77–78° for this picrate.

1-(α-Bromopropionyl)naphthalene (III). (*a*) *From 1-propionylnaphthalene.*[3] To a stirred solution of 92 g. of 1-propionylnaphthalene in 500 cc. of anhydrous ether was added dropwise 80 g. of bromine. The bromination was begun at room temperature, but was carried out at 10° for the major portion of the addition. The bromo ketone which had crystallized during the bromination was brought back into solution by the addition of benzene and the reaction mixture was then washed with 10% sodium bisulfite and with water. The dried organic layer was evaporated to a volume of about 300 cc., 200 cc. of hot petroleum ether (b.p. 60–75°) was added, and the solution was allowed to cool. Pure bromo ketone crystallized (88 g.); m.p. 88–89°. By working up the mother liquor, an additional quantity (21 g.) of the same purity was obtained; total yield, 109 g. (83%).

(*b*) *From naphthalene and α-bromopropionyl bromide.* To a mechanically-stirred mixture of α-bromopropionyl bromide (24.6 g., freshly-distilled), naphthalene (14.6 g.), and carbon disulfide (150 cc.) which was cooled in an ice-salt bath, was added anhydrous aluminum chloride (18.3 g., finely powdered) over a period of twenty minutes. The reaction mixture was then allowed to stand at 0° for four hours and at room temperature for twenty-four hours, and was finally hydrolyzed with ice and hydrochloric acid. Two hundred cc. of ether was added to the hydrolyzed mixture, the layers were separated and the organic layer was washed with water and dried. Upon concentrating and cooling the ethereal solution, crude *1-(α-bromopropionyl)naphthalene* crystallized, and was purified by crystallization from ether; yield, 8–10 g. (27–33%) melting at 88–89° alone and also when mixed with a sample of bromo ketone prepared from 1-propionylnaphthalene.

Anal. Calc'd for $C_{13}H_{11}BrO$: C, 59.33, H, 4.21.

Found: C, 59.00; H, 4.16.

A mixture of 2 g. of 1-(α-bromopropionyl)naphthalene, 12 cc. of 5% sodium hypochlorite solution and 0.4 g. of potassium hydroxide was refluxed for three hours, and was then distilled as long as water-insoluble material came over. When the residual solution was treated with charcoal, filtered, and acidified with hydrochloric acid, there was precipitated

[3] Prepared by Emma Ruth Hornor.

1.0 g. of *1-naphthoic acid*, m.p. 157–159°. One recrystallization of this material from ethanol yielded colorless needles, m.p. 160–161°, which were identified as 1-naphthoic acid by mixed m.p. determination.

Synthesis of α-(1-piperidinoethyl)-1-naphthalenemethanol. (*a*) *1-(α-Piperidinopropionyl)naphthalene* (*IV*, NR_2 = *piperidino*). When a solution of 10 g. of 1-(α-bromopropionyl)naphthalene in 100 cc. of anhydrous ether was added to a solution of 6.5 g. (2 moles) of piperidine in 25 cc. of anhydrous ether, the mixture soon became cloudy due to precipitation of piperidine hydrobromide. The solution was allowed to stand in the dark in a stoppered flask at room temperature for four days before being filtered from piperidine hydrobromide (5.1 g. or 80%). The ethereal solution was then washed with 50 cc. of 10% sodium hydroxide, then with water, and was finally extracted with two 100-cc. portions of 10% hydrochloric acid. The combined acid extracts were neutralized with sodium hydroxide and the precipitated keto amine was extracted with ether. To the dried ethereal extract was added dropwise a solution of anhydrous hydrogen chloride in anhydrous ether until no further precipitation resulted. The precipitated *1-(α-piperidinopropionyl)naphthalene hydrochloride* weighed 7.7 g. (67% yield); m.p. 213–215°. One recrystallization of this material from anhydrous ethanol-ether yielded 5.5 g. of colorless needles, m.p. 218–219°.

(*b*) *α-(1-Piperidinoethyl)-1-naphthalenemethanol* (*V*, NR_2 = *piperidino*). The amino ketone regenerated from 5.5 g. of the aforementioned hydrochloride by means of sodium hydroxide was reduced in an atmosphere of nitrogen by refluxing with 3.7 g. of aluminum isopropoxide (vacuum-distilled) and 20 cc. of anhydrous isopropyl alcohol, slowly distilling off the acetone and part of the isopropyl alcohol, adding fresh alcohol, and repeating the process until no more acetone could be detected in the distillate with 2,4-dinitrophenylhydrazine test solution (about three hours). To the cooled reduction mixture, from which the bulk of the isopropyl alcohol had been distilled, was added 6 cc. of 10 *N* sodium hydroxide solution to decompose the complex, followed by ether to dissolve the free amino alcohol. The layers were separated and the aqueous layer was extracted a second time with ether. The combined ethereal extracts were extracted twice with 15-cc. portions of 10% hydrochloric acid and the acid extracts were decolorized with charcoal. Upon evaporation of the acidic solution to a small volume there was obtained 3.84 g. (70% yield) of *α-(1-piperidinoethyl)-1-naphthalenemethanol hydrochloride*, m.p. 226–231°. One crystallization of this material from anhydrous ethanol-ether yielded colorless needles, m.p. 244–245°.

Anal. Calc'd for $C_{18}H_{23}NO \cdot HCl$: C, 70.68; H, 7.91.
Found: C, 70.24; H, 7.91.

When an aqueous solution of the aforementioned hydrochloride was neutralized with sodium hydroxide, the free amino alcohol was precipitated as a colorless solid. *α-(1-Piperidinoethyl)-1-naphthalenemethanol* crystallizes from ethanol-water in colorless needles, m.p. 108–109°.

Anal. Calc'd for $C_{18}H_{23}NO$: C, 80.25; H, 8.60.
Found: C, 80.03; H, 8.30.

1-(α-Dimethylaminopropionyl)naphthalene (*IV*, *R* = *methyl*). When a solution of 10 g. of 1-(α-bromopropionyl)naphthalene in 100 cc. of anhydrous ether was added to a solution of 6.8 g. (4 moles) of anhydrous dimethylamine in 15 cc. of anhydrous ether, crystallization of dimethylamine hydrobromide began almost immediately, but no heat of reaction was evolved. The mixture was allowed to stand in the dark in a nitrogen atmosphere at room temperature for twenty hours, and the dimethylamine hydrobromide was filtered off: yield, 3.88 g., or 81%. The amino ketone solution was worked up in the manner previously described for the preparation of 1-(α-piperidinopropionyl)naphthalene hydrochloride: yield, 3.2 g. (32%) of crude hydrochloride, m.p. 200–210°. Three recrystallizations from anhydrous ethanol-ether raised the m.p. of *1-(α-dimethylaminopropionyl)naphthalene hydrochloride* to 215–216°.

Anal. Calc'd for $C_{15}H_{17}NO \cdot HCl$: C, 68.30; H, 6.88.
Found: C, 68.35; H, 6.92.

α-(1-Dimethylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *methyl*; *SN-7728*). A solution

of 52.6 g. of 1-(α-bromopropionyl)naphthalene in 500 cc. of anhydrous ether was added to a solution of 36 g. (4 moles) of anhydrous dimethylamine in 50 cc. of anhydrous ether, the mixture was allowed to stand in the dark in an atmosphere of nitrogen at room temperature for twenty hours, and the dimethylamine hydrobromide was filtered off (20.4 g. or 81%). The yellow filtrate was washed with 100 cc. of 5% sodium hydroxide and twice with 50-cc. portions of water, and was dried briefly over calcium chloride. Evaporation of the ether under reduced pressure (finally employing a vacuum of 15 mm.) yielded a yellow oil which was reduced in an atmosphere of nitrogen according to the method of Meerwein and Ponndorf. Two hundred cc. of isopropyl alcohol and 40.8 g. of vacuum-distilled aluminum isopropoxide were employed, and the distillate contained no acetone after heating the reaction mixture for a period of nine hours.

The dark, semi-solid complex (volume about 120 cc.) which remained when the bulk of the isopropyl alcohol was distilled from the reduction mixture was decomposed by adding, with cooling, 60 cc. of 10 *N* sodium hydroxide. The aqueous solution was diluted with water and extracted several times with ether. To the dried (calcium chloride) ethereal extract was added dropwise, at room temperature, a solution of anhydrous hydrogen chloride in anhydrous ether, swirling vigorously throughout the addition. When the addition of a drop of the hydrogen chloride solution no longer caused any precipitation, the crude, chocolate-brown, crystalline *α-(1-dimethylaminoethyl)-1-naphthalenemethanol hydrochloride* was filtered off and air-dried; yield, 36 g. (68%). One crystallization from anhydrous methanol-ether yielded 24.7 g. (47%) of cream colored needles, m.p. 204–207° dec., and a second crystallization raised the m.p. to 207–210° dec. and removed all color.

Anal. Calc'd for $C_{15}H_{19}NO \cdot HCl$: Cl, 13.34. Found: Cl, 13.33

α-(1-Diethylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *ethyl*; *SN-7729*). The reaction between 1-(α-bromopropionyl)naphthalene (72 g.) and diethylamine (80 g.) in ether (760 cc.) took place to the extent of 81% (on the basis of the quantity of diethylamine hydrobromide precipitated; 34 g.) when carried out under the conditions previously described for the reaction with dimethylamine. The brown-red ethereal solution of the keto amine was worked up as previously described, and the Meerwein-Ponndorf reduction was carried out in a nitrogen atmosphere for six and one-half hours, employing 56.4 g. of aluminum isopropoxide.

Precipitation of the crude amino alcohol hydrochloride with anhydrous hydrogen chloride in ether was carried out as before. At first the hydrochloride was precipitated as a finely-divided solid, but as precipitation neared completion the hydrochloride became gummy. Addition of hydrogen chloride was stopped at this point, and the solid hydrochloride (52 g. or 64.5%) was filtered off. Addition of hydrogen chloride to the filtrate yielded only a dark, oily product which could not be crystallized.

Two crystallizations of the *α-(1-diethylaminoethyl)-1-naphthalenemethanol hydrochloride* from anhydrous ethanol-ether yielded 30 g. (37%) of practically colorless crystals melting at 182–185° dec. One more crystallization raised the m.p. to 185–187° dec.

Anal. Calc'd for $C_{17}H_{23}NO \cdot HCl$: C, 69.48; H, 8.23.
Found: C, 69.08, H, 7.70.

The *4,4'-methylenebis-(3-hydroxy-2-naphthoic acid) salt of α-(1-diethylaminoethyl)-1-naphthalenemethanol* was precipitated in quantitative yield as a grey solid when a solution of 1.953 g. (1.95 moles) of 4,4'-methylenebis-(3-hydroxy-2-naphthoic acid) in 104 cc. of 0.1 *N* sodium hydroxide was added dropwise, with constant swirling, to a solution of 2.672 g. (1 mole) of α-(1-diethylaminoethyl)-1-naphthalenemethanol (prepared from the aforementioned hydrochloride by neutralizing an aqueous solution with sodium hydroxide) dissolved in 104 cc. of 0.1 *N* hydrochloric acid. The salt may be recrystallized from anhydrous ether-petroleum ether or from dioxane; yellow needles, m.p. 126° dec.

Anal. Calc'd for $C_{57}H_{62}N_2O_8$: N, 3.10. Found: N, 2.50.

α-(1-Di-n-propylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *n-propyl*; *SN-8660*) was prepared from 65 g. of 1-(α-bromopropionyl)naphthalene and 99 g. of di-*n*-propylamine in the manner previously described for the dimethylamino analog. The reaction between the

bromo ketone and the di-*n*-propylamine took place to the extent of 85.5% within thirty days (38.5 g. of di-*n*-propylamine hydrobromide was filtered off). Ether and unreacted di-*n*-propylamine were then distilled in vacuum and the crude, oily, red-brown keto amine was reduced in a nitrogen atmosphere over a period of five hours, employing 50.4 g. of aluminum isopropoxide.

To the mixture of acetone and isopropyl alcohol distilled from the reduction was added 49 g. of 2,4-dinitrophenylhydrazine and 50 cc. of 36% hydrochloric acid. The mixture was heated to boiling, 200 cc. of hot water was added to the clear solution, and the solution was allowed to cool. There was obtained 48.3 g. of acetone 2,4-dinitrophenylhydrazone, m.p. 123–125°, indicating that the reduction had gone at least 82% to completion.

When anhydrous ethereal hydrogen chloride was added to the ether solution of the crude amino alcohol, *α-(1-di-n-propylaminoethyl)-1-naphthalenemethanol hydrochloride* was precipitated as an orange-brown gum. This material was dissolved in 200 cc. of water, and the solution was decolorized by first shaking several times with ether and finally treating with charcoal. Aqueous sodium hydroxide was added to precipitate the amino alcohol, which was extracted with ether. The amino alcohol hydrochloride was again precipitated from the dried ether solution by addition of ethereal hydrogen chloride. Cooling and rubbing the gummy hydrochloride with a little anhydrous methanol and ether sufficed to induce crystallization. There was finally obtained 19.7 g. (25% yield) of crystalline hydrochloride, which formed 17.9 g. of colorless prisms, m.p. 168–170°, when recrystallized from anhydrous methanol-ether.

Anal. Calc'd for $C_{19}H_{27}NO \cdot HCl$: Cl, 11.02. Found: Cl, 11.02.

α-(1-Di-n-butylaminoethyl)-1-naphthalenemethanol (*V*, *R* = *n-butyl*; *SN-8659*) was prepared from 10 g. of 1-(α-bromopropionyl)naphthalene and 20 g. of di-*n*-butylamine in the previously described manner. The bromo ketone reacted quantitatively with the di-*n*-butylamine within seventy days. Ether and unreacted di-*n*-butylamine were distilled from the crude, oily, orange-brown keto amine in vacuum. Meerwein-Ponndorf reduction in a nitrogen atmosphere was complete within four hours, employing 8.35 g. of aluminum isopropoxide, and 81% of the theoretical quantity of acetone 2,4-dinitrophenylhydrazone was recovered from the distillate in the manner previously described.

Addition of anhydrous ethereal hydrogen chloride to the ethereal solution of the crude amino alcohol precipitated *α-(1-di-n-butylaminoethyl)-1-naphthalenemethanol hydrochloride* in crystalline form; yield, 6.2 g. (47%). One crystallization from anhydrous methanol-ether yielded 5.2 g. of colorless needles, m.p. 135–137°.

Anal. Calc'd for $C_{21}H_{31}NO \cdot HCl$: Cl, 10.13. Found: Cl, 10.40.

SUMMARY

The synthesis of five α-(1-dialkylaminoethyl)-1-naphthalenemethanols has been described.

GREENCASTLE, IND.

REFERENCES

(1) HARTUNG, MUNCH, AND CROSSLEY, *J. Am. Chem. Soc.*, **57**, 1091 (1935).
(2) ROUSSET, *Bull. soc. chim.*, [3] **15**, 62 (1896).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

SYNTHESIS OF 1,2-DIETHYLNAPHTHALENE[1]

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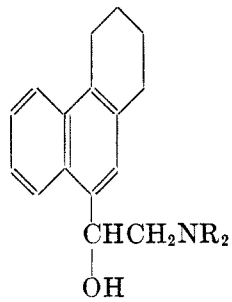
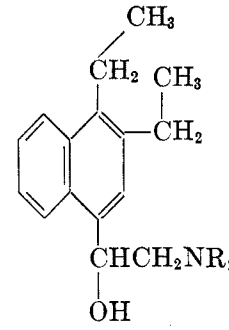
In view of the antimalarial activity exhibited by certain 9-substituted tetrahydrophenanthrenes (Type A), it has been proposed by Dr. Lyndon F. Small (1) of the National Institute of Health that structurally analogous 1,2-diethylnaphthalene derivatives (Type B) be synthesized for physiological testing.



Type A

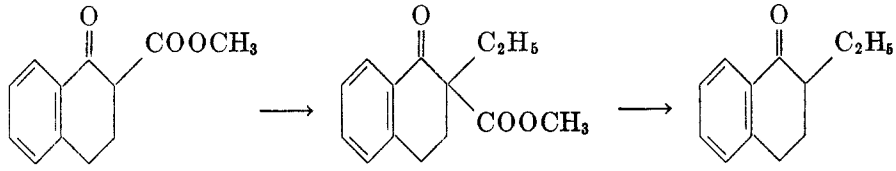


Type B

Herein is described the preparation of 1,2-diethylnaphthalene, an intermediate in the synthesis of compounds of Type B.

2-Carbomethoxy-1-tetralone (I) was prepared from 1-tetralone by the method of Bachmann and Thomas (2). The sodio derivative of I reacted with ethyl iodide to give the crystalline keto ester II in 76% yield. The attempted use of ethyl bromide to effect a similar conversion was found to produce erratic results. Hydrolysis of II with 20% sodium hydroxide, and subsequent decarboxylation of the resulting keto acid afforded a 98% yield of 2-ethyl-1-tetralone (III).

1,2-Diethylnaphthalene (VI) was prepared from 2-ethyl-1-tetralone by treatment of this cyclic ketone with ethylmagnesium bromide, followed by dehydration of the resulting tertiary carbinol (IV) with anhydrous formic acid and subsequent dehydrogenation of the 1,2-diethyl-3,4-dihydronaphthalene (V). Dehydrogenation of V was effected both catalytically and with sulfur.



I II III

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and DePauw University.

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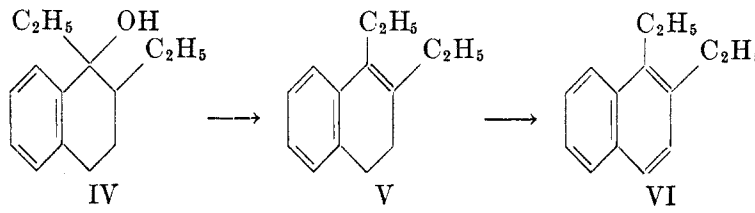

IV V VI

Acetylation of 1,2-diethylnaphthalene was effected with acetyl chloride and aluminum chloride in carbon disulfide (36% yield) and also in nitrobenzene (78% yield). The identical crystalline ketone was obtained in both instances, and is presumed to be 1-aceto-3,4-diethylnaphthalene.[3] Experiments designed to ascertain the position of the aceto group in this compound are now in progress.

EXPERIMENTAL

2-Ethyl-2-carbomethoxy-1-tetralone (II). To a solution of 17 g. of sodium in 380 cc. of anhydrous methanol contained in a three-liter flask fitted with a dropping-funnel and reflux condenser was added a solution of 76.1 g. of 2-carbomethoxy-1-tetralone (2) in a mixture of 190 cc. of anhydrous methanol and 190 cc. of anhydrous benzene. The sodio derivative precipitated and the reaction mixture was then refluxed for fifteen minutes. After cooling to room temperature, 144 g. (74 cc., 0.92 mole) of ethyl iodide was added, and the resulting red mixture was refluxed for three hours. During this period the sodio derivative dissolved completely, and the color of the solution changed to bright yellow. After cooling, the solution was neutralized with acetic acid and the solvents were distilled off under reduced pressure. The residue was taken up with water and benzene, and the aqueous layer was extracted twice with benzene. The combined benzene extracts were washed with sodium bicarbonate solution, were dried over anhydrous potassium carbonate and finally evaporated. The residual 2-ethyl-2-carbomethoxy-1-tetralone distilled at 136–140° at 1.5 mm.; yield, 82.2 g. (95%) of yellow oil. When this oil was crystallized from petroleum ether (60–70°) there was obtained 66 g. (76%) of colorless prisms, m.p. 55–57°.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 72.39; H, 6.94.
Found: C, 72.61; H, 7.20.

2-Ethyl-1-tetralone (III). 2-Ethyl-2-carbomethoxy-1-tetralone (110.8 g.) was hydrolyzed by refluxing with 780 cc. of 20% sodium hydroxide and 195 cc. of ethanol for three hours. The reaction mixture became orange but the organic layer never completely disappeared (4). Acidification of the mixture with 1:1 sulfuric acid caused a vigorous evolution of carbon dioxide, and complete decarboxylation of the liberated 2-ethyl-1-keto-1,2,3,4-tetrahydro-2-naphthoic acid was effected by warming the acidified solution on the steam-bath. The ketone was extracted with benzene, the benzene extracts were washed with dilute sodium bicarbonate solution and dried over anhydrous potassium carbonate. Vacuum distillation yielded 81.5 g. (98%) of colorless 2-ethyl-1-tetralone b.p. 112–113° at 1 mm.

2-Ethyl-1-tetralone semicarbazone, prepared by refluxing for twenty hours a mixture of 0.7 g. of the ketone, 0.7 g. of semicarbazide hydrochloride, 1.0 cc. of pyridine, and 15 cc. of absolute ethanol, and distilling the mixture nearly to dryness, melted at 194–196° after three crystallizations from ethanol-water. Levy (5), who prepared the 2-ethyl-1-tetralone by another method, reported the m.p. 207° (corr.) for the semicarbazone.

Synthesis of 1,2-diethylnaphthalene. To the cold, mechanically-stirred Grignard reagent prepared from 98 g. of ethyl bromide, 21.6 g. of magnesium, and 200 cc. of ether was added slowly 78.8 g. of 2-ethyl-1-tetralone in 200 cc. of ether. The reaction mixture was allowed

[3] Kruber and Schade (3) have shown that 1,2-dimethylnaphthalene is sulfonated in the 4-position.

to warm up to room temperature and was then refluxed for two and one-half hours. The colorless addition product precipitated during the period of reflux. Hydrolysis of the reaction mixture with ice and ammonium chloride yielded an oily product which was extracted with ether. Evaporation of the ether extracts yielded 90.5 g. (98%) of faintly yellow 1,2-diethyl-1-tetralol (IV).

The aforementioned carbinol was dehydrated by treatment with 235 cc. of anhydrous formic acid for one and one-half hours at room temperature. The hydrocarbon separated from the formic acid as an insoluble oil, and was isolated by pouring the reaction mixture into 500 cc. of water and extracting with benzene. After one vacuum distillation over sodium there was obtained 79 g. (96%) of colorless 1,2-diethyl-3,4-dihydronaphthalene (V) boiling at 103–105° at 1 mm.

Dehydrogenation of the 1,2-diethyl-3,4-dihydronaphthalene was accomplished both catalytically and with sulfur. When the unsaturated hydrocarbon was heated with one-tenth of its weight of palladium-charcoal catalyst (6) and the temperature was gradually raised to 290–300°, a smooth evolution of hydrogen took place (94–98% of the theoretical volume within two hours). The crude 1,2-diethylnaphthalene (VI) (89% yield) distilled at 102–115° at 1 mm. as a bright yellow oil. One distillation over sodium yielded 83% of the hydrocarbon as a yellow oil boiling at 115° at 1 mm.

When 1,2-diethyl-3,4-dihydronaphthalene was heated to 200° with the theoretical quantity of sulfur, hydrogen sulfide was evolved vigorously. After being heated to 200° for one-half hour, the mixture was heated at 270–275° for an additional period of one-half hour to complete the evolution of hydrogen sulfide. The vacuum-distilled product was bright yellow, but the color was removed by distilling over sodium; yield, 83% of colorless 1,2-diethylnaphthalene (VI) boiling at 114° at 1.5 mm.

Anal. Calc'd for $C_{14}H_{16}$: C, 91.25; H, 8.75.
Found: C, 91.53; H, 9.08.

1,2-Diethylnaphthalene picrate crystallized from ethanol in orange needles, m.p. 107.5–108.5°.[4]

Anal. Calc'd for $C_{20}H_{19}N_3O_7$: N, 10.17. Found: N, 10.22.

The 1,3,5-trinitrobenzene derivative of 1,2-diethylnaphthalene crystallized from anhydrous methanol in yellow needles, m.p. 112.5–113.5°.

Anal. Calc'd for $C_{20}H_{19}N_3O_6$: C, 60.44; H, 4.82.
Found: C, 60.66; H, 5.05.

Acetylation of 1,2-diethylnaphthalene. (*a*) *in Nitrobenzene.* To an ice-cold, mechanically-stirred mixture of 1,2-diethylnaphthalene (10 g.), finely-powdered anhydrous aluminum chloride (13.3 g.), and nitrobenzene (75 cc.), was added dropwise 5.1 g. of acetyl chloride. Cooling and stirring were continued for three hours, and the mixture was allowed to stand at room temperature for three hours. The reaction mixture was hydrolyzed with ice and hydrochloric acid in the customary manner and the nitrobenzene was distilled off under reduced pressure. *Acetodiethylnaphthalene* distilled at 156–162° at 1 mm.; yield, 9.6 g. (78%) of yellow oil. Crystallization of the crude product from petroleum ether (60–75°) yielded colorless prisms, m.p. 61.5–62.5°.

(*b*) *In carbon disulfide.* Acetylation was carried out as previously described, employing 10 g. of 1,2-diethylnaphthalene, 9.3 g. of aluminum chloride, 75 cc. of carbon disulfide, and 4.0 g. of acetyl chloride. There was obtained 4.4 g. (36% yield) of yellow oil boiling at 155° at 1 mm. Crystallization of this crude material from petroleum ether again gave colorless hexagonal prisms (3.6 g. or 29%), m.p. 61.5–62.5°.

Anal. Calc'd for $C_{16}H_{18}O$: C, 84.91; H, 8.02.
Found: C, 85.18, H, 8.10.

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[4] While this investigation was in progress, Arnold and Barnes (7) obtained 1,2-diethylnaphthalene by catalytic dehydrogenation of 5,6-diethyltetralin, and reported the m.p. of the picrate as 105.5–107°.

Aceto-1,2-diethylnaphthalene picrate crystallized in yellow needles from anhydrous ethanol; m.p. 88–88.5°.

Anal. Calc'd for $C_{22}H_{21}N_3O_8$: N, 9.22. Found: N, 9.09.

SUMMARY

A synthesis of 1,2-diethylnaphthalene from 1-tetralone is described.

GREENCASTLE, IND.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENE-METHANOLS. IX. α-(2-DIALKYLAMINOETHYL)-α-METHYL ARYLMETHANOLS[1]

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Because of the availability of 1-dialkylamino-3-butanones through the Mannich synthesis, compounds of the type aryl-$C(CH_3)(OH)CH_2CH_2NR_2$ should readily be prepared by a Grignard reaction as shown in the following equations:

$$CH_3COCH_3 + R_2NH_2Cl + (CH_2O) \rightarrow CH_3COCH_2CH_2NR_2$$

$$\text{Aryl—MgX} + CH_3COCH_2CH_2NR_2 \rightarrow \text{Aryl—}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}CH_2CH_2NR_2$$

These compounds were of interest as possible antimalarials.

At the time this work was started, only two references (1, 2) were found to the reaction of β-amino ketones with Grignard reagents. In 1944 Cromwell and Burch (3) reported moderate yields in a similar reaction. The reaction of the Grignard reagent with several β-amino esters and aldehydes has also been reported (4, 5, 6, 7).

We found that pure amino alcohols could be isolated in only 15–33% yields from the reaction of 1-dialkylamino-3-butanones with aryl Grignard reagents. The products were difficult to purify and often formed oily salts even when pure. The desired reaction was accompanied by a side reaction which gave dialkylamine and the product of simple hydrolysis of the Grignard reagent. Such a reaction is readily formulated as follows:

$$CH_3COCH_2CH_2NR_2 + \text{Aryl-MgX} \rightarrow CH_3COCH{=}CH_2 + \text{Aryl-H} + R_2NMgX$$

If methyl vinyl ketone were produced it would be expected to react with the Grignard reagent or polymerize. Smith and Sprung (8) observed that the reaction of methyl vinyl ketone with laurylmagnesium bromide went poorly, the ketone polymerizing, but Heilbron and co-workers (9) found that hexynylmagnesium bromide gave a 55% yield of the 1,2-addition product with that ketone. We found that the products of the reaction between phenyl- or naphthyl-magnesium bromide and 1-dialkylamino-3-butanones contained no unsaturated substances, but time did not permit a close search for other products.

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

A preliminary study of the reaction of 1-dialkylamino-3-butanones with methylmagnesium iodide in the Grignard machine (10, 11) revealed that 0.9 to 0.95 mole of methane was produced per mole of ketone. A further 0.25 to 0.35 mole of methylmagnesium iodide was used up in an addition reaction. On the basis of the above side reaction, this addition would be expected to be greater. The small amount of addition is consistent with the idea that the Grignard reagent has an enolizing action on Mannich ketones. Enolization was suggested

TABLE I

α-(2-DIALKYLAMINOETHYL)-α-METHYL ARYLMETHANOLS, ARYL-C(OH)$CH_2CH_2NR_2$ (CH_3 on the C)

SN	ARYL GROUP	R	M.P., °C.[b]	SOLUBILITY[a]	ANALYSES[b]			
					C		H	
					Calc'd	Found	Calc'd	Found
8349	Phenyl	Ethyl	141–142.5	>100	65.22	65.18	9.38	9.30
	1-Naphthyl	Ethyl	96.5–98[d]	21[d]	66.34[d]	66.32	8.66	8.68
	1-Naphthyl	*n*-Butyl	170.5–171.5	0.9	72.60	72.56	9.42	9.44
	2-Naphthyl	Ethyl	145–154[e]	>40	70.22	70.07	8.51	8.57
5903	4-Methoxy-1-naphthyl	Methyl	103–103.5[c] 195–210 dec.	Very sol.	74.69[e]	74.49	8.48	8.47
6977	4-Methoxy-1-naphthyl	Ethyl	182–182.5	7	67.54	67.36	8.35	8.38
6760	4-Methoxy-1-naphthyl	*n*-Butyl	137–138[f]	1.5	70.11	70.23	9.21	9.31
	9-Phenanthryl	Ethyl	181–186	>10	73.82	73.22 73.27	7.88	8.11 7.94
6937	9-Phenanthryl	*n*-Butyl	76.5–77[c]	8[g]	82.70[c]	83.00	9.34	9.34

[a] Solubility of hydrochloride at 25° in water; g./100 ml. of solution.
[b] Data for the hydrochloride except where indicated.
[c] Free amine.
[d] Hydrochloride monohydrate.
[e] Broad m.p. believed due to existence of 2 crystalline forms.
[f] Needles. This compound also crystallized in plates, m.p. 133–134°.
[g] Solubility of free base in 0.2 *N* hydrochloric acid.

by Wiley and Adkins (12) to explain their observation that 1-amino-2-alkyl-4-methyl-3-pentanones gave two moles of methane and no addition in the Grignard machine.

The course of the reaction between Mannich ketones and the Grignard reagent is under further investigation and will be reported later.

Table I lists the amino alcohols which were prepared for testing as antimalarials. Three of the products were not obtained as crystalline solids either as free amines or salts, and are not included in the table. These were α-(2-di-*n*-propylaminoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol, α-(2-diethyl-

aminoethyl)-α-methyl-4-chloro-1-naphthalenemethanol and the corresponding di-*n*-butylamino compound.

Several other methods for the preparation of α-(2-dialkylaminoethyl)-α-methyl arylmethanols were tried. The reaction of 1-dialkylamino-3-butanones with arylcadmium compounds gave only amorphous products, and with aryllithium compounds the yields of amino alcohol were lower than with the Grignard reagent. An unsuccessful attempt was made to obtain α-(2-dibutylaminoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol by the reaction of 2-dibutylaminoethyl 4-methoxy-1-naphthyl ketone and methylmagnesium iodide. A second synthesis was found which involved the preparation of β-bromoethyl methyl ketone, its reaction with 4-methoxy-1-naphthylmagnesium bromide and treatment of the product with dibutylamine. The resulting compound was identical with that obtained from 1-dibutylamino-3-butanone and 4-methoxy-1-naphthylmagnesium bromide. A few examples of similar syntheses have been reported (7, 13, 14).

Further work on the series was not undertaken because the results of avian testing indicated that the compounds were poor antimalarials.

EXPERIMENTAL

All melting points are corrected unless marked otherwise. Analyses were carried out by Bruce F. Day, Richard Nevé and Jack W. Ralls.

1-Dialkylamino-3-butanones. The procedure of Wilds and Shunk (15) for the Mannich reaction was used with only slight modification. It was found that 0.5 to 1.5 ml. of hydrochloric acid improved the yield and shortened the reflux time in the condensation of acetone and paraformaldehyde with dimethylamine, di-*n*-propylamine, and di-*n*-butylamine. The addition of hydrochloric acid in the Mannich condensation has been suggested before (16). With diethylamine this procedure increased the yield of 1,1-bis-(diethylaminomethyl)acetone and polymeric products at the expense of the compound desired. For the synthesis of 1-diethylamino-3-butanone we followed exactly the procedure of Wilds and Shunk and checked the data they reported.

1-Dimethylamino-3-butanone (17). Reflux time, three hours; yield, 45%; b.p., 70°/40 mm.; n_D^{25} 1.4213; d_4^{25} 0.8636; MR_D obs. 33.84, Calc'd 33.86.

Anal. Calc'd for $C_6H_{13}NO$: C, 62.62; H, 11.31.
Found: C, 62.49; H, 11.28.

1-Di-n-propylamino-3-butanone. Reflux time, four hours; yield, 66%; b.p. 116–117°/11 mm.; n_D^{25} 1.4331; d_4^{25} 0.8498; MR_D obs. 52.39, Calc'd 52.33.

Anal. Calc'd for $C_{10}H_{21}NO$: C 70.12; H, 12.36.
Found: C, 70.16; H, 12.32.

1-Di-n-butylamino-3-butanone. Reflux time, four hours; yield, 62%; b.p. 80°/2 mm.; n_D^{25} 1.4381; d_4^{25} 0.8466; MR obs. 61.82, Calc'd 61.57.

Anal. Calc'd for $C_{12}H_{25}NO$: C, 72.30; H, 12.64.
Found: C, 72.38; H, 12.68.

Grignard reagents. The use of benzene as an accessory solvent was necessary for all of the Grignard reagents except phenylmagnesium bromide. β-Bromonaphthalene was obtained from β-naphthylamine, and 9-bromophenanthrene from purified phenanthrene (18) by slight modification of known methods (19, 20). The 4-chloro-1-iodonaphthalene used in this work was prepared by the method of Beattie and Whitmore (21) although a less tedious method was found later (7). Carbonation of the Grignard reagent from this compound gave 4-chloro-1-naphthoic acid, m.p. 221–223°, neutral equivalent 208.1 (Calc'd 206.6). The acid contained no iodine and gave no melting point depression when mixed with the acid prepared by hypochlorite oxidation of 4-chloro-1-acetonaphthone (22).

4-Bromo-1-methoxynaphthalene. The bromination of 1-methoxynaphthalene was carried out with iodine monobromide by Militzer's method (23) using chloroform as the extracting solvent. The product was an oil, b.p. 147–153° 3 mm. on the second distillation, yield 75%, $n_D^{21.5}$ 1.6532. 4-Bromo-1-methoxynaphthalene has been reported three times in the literature with the following constants: b.p. 181° 18 mm. (24), b.p. 178° 15 mm. (25), and m.p. 46° (26). Our product could be induced to crystallize at −80°, but melted below room temperature. An attempt to obtain a solid product by repetition of the procedure of Underwood, Baril, and Toone (26) was unsuccessful. The structure of the 4-bromo-1-methoxynaphthalene obtained using iodine monobromide was proved by carbonation of its Grignard reagent. 4-Methoxy-1-naphthoic acid was obtained in 84% yield, m.p. 242–243° (from alcohol).

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99, neutral equivalent 202.2.
Found: C, 70.82; H, 5.01, neutral equivalent 197.

The following melting points have been reported for 4-methoxy-1-naphthoic acid: 239° (27), 232° and 230° (29). No other known 1-methoxynaphthoic acid has a melting point near this value; 1-methoxy-6-naphthoic acid has not been reported.

α-(2-Dialkylaminoethyl)-α-methyl arylmethanols. The general procedure used for the condensation of aryl Grignard reagents with 1-dialkylamino-3-butanones is illustrated by the directions for α-(2-di-*n*-butylaminoethyl)-α-methyl-1-naphthalenemethanol.

A solution of α-naphthylmagnesium bromide prepared from 41.5 g. (0.2 mole) of α-bromonaphthalene in 185 ml. of ether and 50 ml. of benzene was filtered into a 1-liter, 3-n. flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping-funnel. This solution was cooled in an ice-bath and stirred under nitrogen while a solution of 40 g. (0.2 mole) of 1-di-*n*-butylamino-3-butanone in 100 ml. of ether was added dropwise during thirty minutes. The mixture was refluxed with stirring for one hour, then cooled in ice during the addition of 100 ml. of saturated ammonium chloride solution. The aqueous layer was separated and washed twice with small portions of ether which were combined with the ether-benzene layer; the latter was extracted three times with 100 ml. portions of 2 *N* hydrochloric acid. A light colored, crystalline solid soon separated from this acid solution; it was collected after standing at 0° for several hours and washed on the filter with a little ice-water. The yield of light yellow solid, m.p. 161–166.5°, was 21 g. (29%). Recrystallization from alcohol-ether and from water gave white plates of pure α-(2-di-*n*-butylaminoethyl)-α-methyl-1-naphthalenemethanol hydrochloride (Table I).

The acid solution gave no more solid on concentration to 100 ml. under reduced pressure; it was basified with 6 *N* sodium hydroxide in an ice-bath and saturated with potassium carbonate. The oil that separated was taken up in ether, dried over potassium carbonate, and the solution concentrated at reduced pressure (residue 18 g.). This residue was held at 70° under 3 mm. pressure for seven hours and the distillate was collected in a trap cooled in dry ice. Di-*n*-butylamine was isolated from the condensate as the hydrochloride (7.8 g.; 0.047 mole), identified by reaction with phenyl isothiocyanate to give N-phenyl-N,N-di-*n*-butylthiourea, m.p. and mixed m.p. 83–84°. The basic material which did not distill could not be induced to crystallize or to yield a solid salt.

The ether-benzene solution from the original reaction mixture did not contain unsaturated compounds. From it was isolated by sublimation 14 g. (0.11 mole) of naphthalene.

A crystalline hydrochloride separated from the hydrochloric acid extract only in the case of α-(2-di-*n*-butylaminoethyl)-α-methyl-1-naphthalenemethanol. In all other cases, the free base was liberated from the hydrochloric acid solution by basifying with dil. sodium hydroxide in the cold. The amino alcohol was taken up in ether, the ether solution dried over potassium carbonate, and the hydrochloride formed by passing anhydrous hydrogen chloride over the surface of the cold solution with swirling. Excess hydrogen chloride caused oil formation and even when a solid was obtained, it often turned oily when filtered (possibly it was an etherate). Sometimes these oily hydrochlorides solidified on long standing. It was occasionally preferable to remove ether from the dried solution of amino alcohol, dissolve the residue in anhydrous ethanol, saturate the solution with anhydrous

hydrogen chloride, and precipitate the hydrochloride by adding ether. Another effective procedure was fractional extraction of the original ether-benzene solution with small portions of 0.5 *N* hydrochloric acid. An impurity (probably dialkylamine hydrochloride) was taken up first, and later fractions gave solid hydrochlorides. Hydrobromides, sulfates, oxalates, and other salts usually behaved like the hydrochlorides.

Hydrochlorides were crystallized from anh. alcohol, ethyl acetate, or chloroform by adding anh. ether or occasionally petroleum ether. The free bases were crystallized from acetone and water.

α-(2-Di-n-butylaminoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol. This compound was obtained in 27% yield by the synthesis described above. It was also prepared from β-bromoethyl methyl ketone (30) and 4-methoxy-1-bromonaphthalene by a synthesis which was tried only once. β-Bromoethyl methyl ketone was obtained from β-bromopropionyl chloride and dimethylcadmium following the general directions of Gilman and Nelson (31). The acid chloride was readily prepared from β-bromopropionic acid (32) and thionyl chloride. β-Bromoethyl methyl ketone was an unstable liquid which decomposed on attempted distillation at 3 mm. The homologous β-bromoethyl ethyl ketone is also an unstable liquid (13). The crude methyl ketone was dried in ether and added to a slight excess of 4-methoxy-1-naphthylmagnesium bromide to yield α-(2-bromoethyl)-α-methyl-4-methoxy-1-naphthalenemethanol which was isolated but not purified. It was converted to the desired amino alcohol by heating in a sealed tube at 120–130° for twenty-four hours with slightly more than two moles of di-*n*-butylamine.

SUMMARY

Nine α-(2-dialkylaminoethyl)-α-methyl arylmethanols have been prepared by the reaction of aryl Grignard reagents with 1-dialkylamino-3-butanones. Yields of only 15–33% were obtained due to side reactions and to difficulties in purification of the final products.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

CINNOLINES. I. SYNTHESIS OF AMINOACETOPHENONES AND AMINOPROPIOPHENONES[1]

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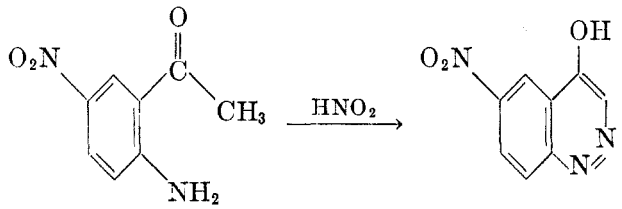
In view of the reported antimalarial activity of 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline (1) it was considered of interest to prepare some cinnoline analogs of this quinoline drug. Such cinnoline drugs could be obtained from a 4-chlorocinnoline and an appropriate diamine. The 4-chlorocinnoline could be prepared from the corresponding 4-hydroxycinnoline. A survey of the cinnoline literature revealed, however, that none of the methods which had been used for the preparation of 4-hydroxycinnolines (2, 3, 4, 5, 6) had been demonstrated to be capable of general application. The method used by Borsche and Herbert (3) for the preparation of 4-hydroxy-6-nitrocinnoline (I → II) offered most promise as a general method.



I II

The first step in the researches leading to the desired cinnoline drugs was an investigation of the preparation of various substituted *o*-aminoacetophenones. The present paper describes the preparation of *o*-aminoacetophenones and *o*-aminopropiophenones. Subsequent papers will report the synthesis of cinnolines from these ketones.

Since the completion of these studies, a paper by Waters (7) and one by Simpson, Atkinson, Schofield, and Stephenson (8) have presented the results of investigations on the preparation of substituted *o*-aminoacetophenones. In these three parallel yet independent investigations, there has been some duplication which will be indicated in the course of the discussion.

The method of Camps (9) for the nitration of acetophenone was modified to render it suitable for nitration of two- or three-mole quantities; *m*- and *o*-nitroacetophenone were the products. Reduction of nitroacetophenones has usually been accomplished by chemical reagents: tin and hydrochloric acid for *o*-nitro-

[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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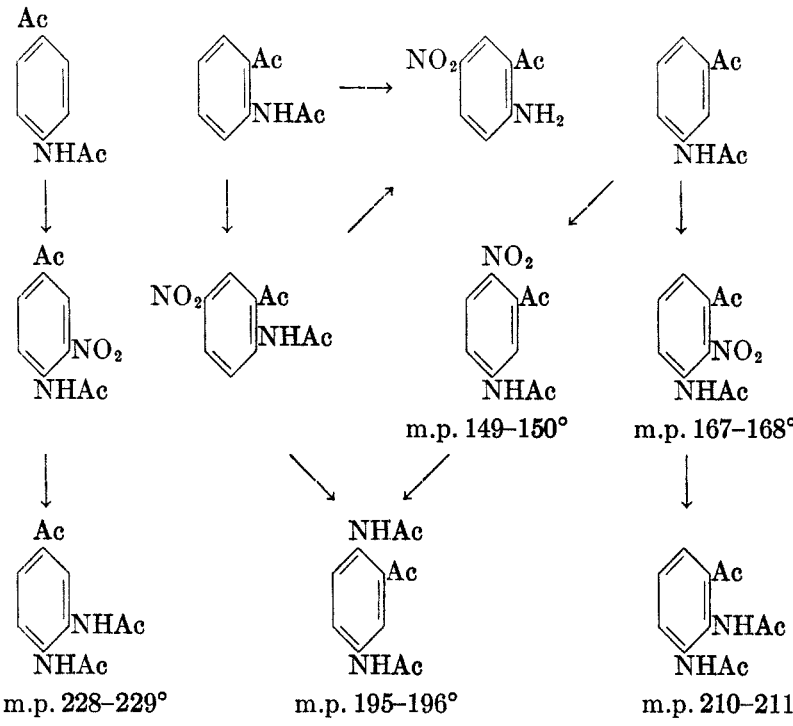
acetophenones, and iron and acetic acid for *m*-nitroacetophenones. Catalytic hydrogenation has been employed in a few instances (10, 11, 12, 13, 14). A comparison of three methods of reduction of *o*-nitroacetophenone to *o*-aminoacetophenone (tin and hydrochloric acid, hydrogen over platinum oxide, hydrogen over Raney nickel) has indicated that hydrogenation over platinum oxide is the most efficient. Reduction of *m*-nitroacetophenone by these three methods and by means of iron and acetic acid produced *m*-aminoacetophenone in equivalent yields. In the presence of Raney nickel the hydrogenation of *m*-nitroacetophenone may proceed to *m*-aminophenylmethylcarbinol. The rate of hydrogenation of the nitro group is greater than that of the carbonyl group; hence, the reduction can be interrupted readily at the *m*-aminoacetophenone stage. Marvel and Overberger (15) have recently reported the preparation of *m*-aminophenylmethylcarbinol in a forty-seven per cent yield by a two state reduction of *m*-nitroacetophenone. The direct hydrogenation over Raney nickel gave a yield of seventy-five per cent.

Nitration of *o*-acetaminoacetophenone, followed by hydrolysis of the intermediate, resulted in the formation of 2-amino-5-nitroacetophenone (3), which has also been obtained by Simpson *et al.* (8) in seventy-four per cent yield by the same procedure. 2-Amino-3,5-dibromoacetophenone and 2-acetamino-5-bromoacetophenone were obtained by the methods of Fuchs (16) and Gibson and Levin (17), respectively.

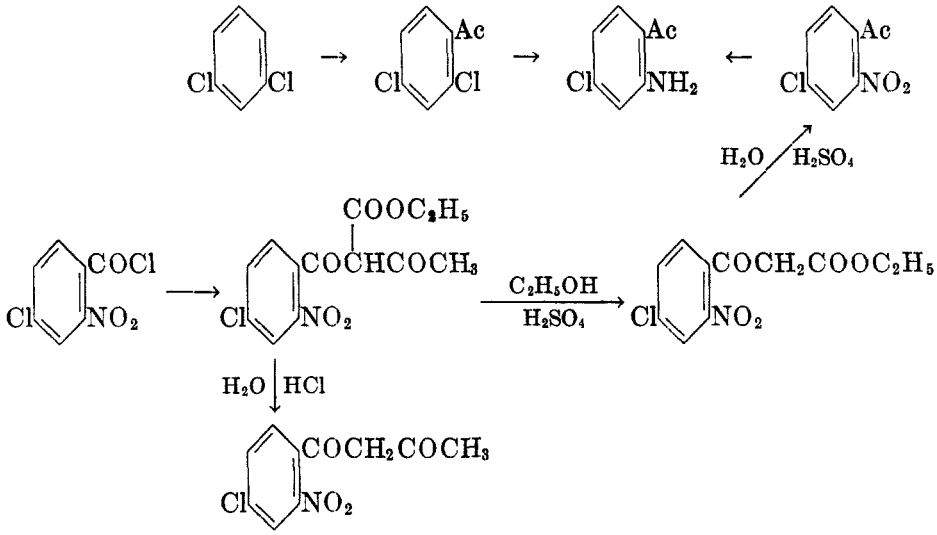
Nitration of *m*-acetaminoacetophenone afforded 3-acetamino-2-nitroacetophenone, m.p. 167–168°, and 5-acetamino-2-nitroacetophenone, m.p. 149–150°, in a yield ratio of 2.5 to 1. The same isomers were obtained by Simpson and his coworkers (8), although the proportionate yields were reversed. All three of the expected mononitration products were obtained by Waters (7) in the reaction of *m*-acetaminoaetophenone with a solution of acetic and fuming nitric acids. The structures of these isomeric nitration products have been determined adequately. The present contribution provides an independent proof of the structures of two of the mononitration isomers from *m*-acetaminoacetophenone and describes the interrelation of the nitration products of *m*- and *o*-acetaminoacetophenones by a method different from that employed by Simpson. The isomer melting at 149–150° was proved to be 5-acetamino-2-nitroacetophenone by the fact that reduction followed by acetylation gave a diacetaminoacetophenone identical with the product (m.p. 195–196°) obtained by reduction and subsequent acetylation of 2-acetamino-5-nitroacetophenone. When the isomer melting at 167–168° was reduced and the reduction product was acetylated, a diacetaminoacetophenone (m.p. 210-211°) was obtained which was not identical with that obtained (m.p. 228–229°) when 4-acetamino-3-nitroacetophenone was treated in the same manner. Yet the product obtained by acid hydrolysis of the diacetaminoacetophenone behaved chemically like an *o*-phenylenediamine type compound. It was assumed, therefore, that the isomer of m.p. 167–168° was 3-acetamino-2-nitroacetophenone. The direct structure proof by Waters (7) indicates that this assumption was valid.



m-Chloroacetophenone was obtained from *m*-aminoacetophenone by the Sandmeyer reaction. Nitration of this compound gave a mixture of isomers from which 5-chloro-2-nitroacetophenone was isolated with ease. Catalytic hydrogenation produced 2-amino-5-chloroacetophenone. Simpson (8) isolated both 5-chloro-2-nitro- and 3-chloro-2-nitro-acetophenone from the nitration of *m*-chloroacetophenone. *m*-Iodoacetophenone was also obtained from *m*-aminoacetophenone *via* the diazonium salt. From the crude nitration product of *m*-iodoacetophenone, one isomer was readily isolated and was assumed to be 5-iodo-2-nitroacetophenone by analogy with the nitration of *m*-chloro- and *m*-bromo-acetophenone. Reduction of the nitro compound was effected catalytically.

None of the recorded substitution reactions of *o*-aminoacetophenone leads to the formation of a 2-aminoacetophenone bearing a substituent in the 4-position, or the position isomer necessary for the preparation of 7-substituted cinnolines. 2-Amino-4-chloroacetophenone has been prepared by two methods. 2,4-Dichloroacetophenone was obtained by a Friedel-Crafts acetylation of *m*-dichlorobenzene and subjected to ammonolysis under pressure. The desired product was realized in low yield, along with some 2,4-diaminoacetophenone. 2-Amino-4-chloroacetophenone was prepared in a more satisfactory yield by reduction of 2-nitro-4-chloroacetophenone obtained by an acetoacetic ester condensation. 4-Chloro-2-nitrobenzoyl chloride was allowed to condense with the sodium salt of ethyl acetoacetate. The removal of the acetyl group from the condensation

product by hydrolysis in ethanolic sulfuric acid was followed by the removal of the carbethoxy group in aqueous acid. When this preliminary cleavage of the acetyl group was not effected, the carbethoxy group was removed first to give 4-chloro-2-nitrobenzoylacetone.



Kermack and Smith (18) prepared *o*-nitroacetophenone and *o*-nitrobenzoylacetone by similar reactions from *o*-nitrobenzoyl chloride.

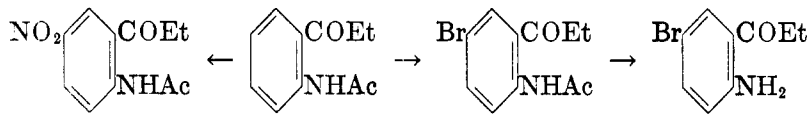
At the same time that the above two methods of preparing 2-amino-4-chloroacetophenone were being investigated, a third approach, utilizing *p*-chloroacetophenone, was studied. This compound was nitrated by the method of Le-Fèvre and LeFèvre (19). 4-Chloro-3-nitroacetophenone, upon hydrogenation over platinum oxide, gave the expected 3-amino-4-chloroacetophenone and a pale orange material of composition $C_{16}H_{12}Cl_2N_2O_3$, but of undetermined structure. When the reduction was carried out with iron and acetic acid, 3-amino-4-chloroacetophenone was the only product. 3-Acetamino-4-chloroacetophenone was nitrated to produce 5-acetamino-4-chloro-2(?)-nitroacetophenone. It was expected that deamination of this compound would yield the desired 4-chloro-2-nitroacetophenone, but the nitration product was not further investigated since the acetoacetic ester method mentioned above had been developed by this time.

3-Amino-4-chloroacetophenone was converted by means of the Sandmeyer reaction of 3,4-dichloroacetophenone. Roberts and Turner (20) prepared this compound by the acetylation of *o*-dichlorobenzene and nitrated it to obtain a compound to which they assigned the structure 3,4-dichloro-2-nitroacetophenone. An attempt to duplicate the nitration described by Roberts and Turner was not successful.

2-Amino-1-acetonaphthone was prepared by the nuclear acetylation of acet-2-naphthalide as described by Ott and Levy (21). It was believed that *p*-chloroacetanilide might undergo nuclear acetylation in the presence of aluminum chloride to produce 2-acetamino-5-chloroacetophenone. Kunckell (22, 23, 24)

had carried out acetylations of this type with a variety of substituted acetanilides. However, numerous attempts to bring about the desired reaction were without success.

In order to prepare cinnoline analogs of Santochin *via* substituted *o*-aminopropiophenones, propiophenone was nitrated by a modification of the method of Elson, Gibson, and Johnson (25). The *o*- and *m*-nitropropiophenones were separated, and the *ortho* isomer was hydrogenated and converted to the acetyl derivative. Bromination and nitration of *o*-acetaminopropiophenone gave a monobromo and a mononitro derivative. By analogy with the reactions of *o*-acetaminoacetophenone, it was assumed that substitution occurred at the 5-position.



EXPERIMENTAL[3]

Nitration of acetophenone. The method used is a modification of that of Camps (9).

Four pounds of nitric acid (sp. g. 1.50) was cooled to −20° and 300 g. (2.5 moles) of acetophenone was added dropwise over a period of 0.5 hr. The temperature was maintained between −15° and −8° during the addition. The resulting clear solution was stirred for one hour at −10° to −15° and then poured onto 4 l. of crushed ice. The crude *m*-nitroacetophenone separated as a pale yellow crystalline mush. The filtrate was rendered alkaline with sodium carbonate, and the oil which separated was removed by extraction with ether. After drying and removal of the ether, the residue was distilled under diminished pressure. A sizable forerun was collected, and then the nitroacetophenones distilled at 133–135° (4 mm.). This distillate was cooled in an ice-bath, and the *meta* isomer which separated was removed. The yield of the crude *ortho* isomer was 120 g. The two portions of *m*-nitroacetophenone were combined and recrystallized from ethanol. The yield was 197 g. of stout, pale yellow prisms melting at 78–79°. Redistillation of the above fore-run afforded 32.7 g. of acetophenone boiling at 70–71° (3 mm.); n_D^{20} 1.5328. The yield of nitroacetophenones, based on the amount of unrecovered acetophenone was 89%: that of the impure *ortho* isomer was 33.6% and that of the *meta* isomer 55.4%.

Reduction of o-nitroacetophenone

Tin and hydrochloric acid. Reduction with tin and hydrochloric acid by the method of Camps (9) gave a 67.7% yield of *o*-aminoacetophenone boiling at 130° (12 mm.).

Catalytic hydrogenation. Four samples of 33 g. and one sample of 29 g. of *o*-nitroacetophenone were hydrogenated in an Adams machine (26) at room temperature and 2–3 atm. pressure. In each case 150 cc. of absolute ethanol was used as solvent and 0.2 g. of platinum oxide as catalyst. The absorption of hydrogen was so rapid that it was necessary to interrupt the hydrogenation at intervals to prevent the temperature from becoming too high. The catalyst was removed and the ethanolic filtrates were combined and dried over anhydrous sodium sulfate. The drying agent was removed and the solvent distilled. The residue, when subjected to distillation at reduced pressure, afforded 103.4 g. (78.4%) of *o*-aminoacetophenone boiling at 113° (6 mm.).

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[3] All melting points are corrected for both emergent stem and thermometer errors. Boiling points are not corrected. Analyses were performed by Miss Theta Spoor, Miss Lillian Hruda, and Mr. Howard Clark.

When the hydrogenation was carried out over Raney nickel, using absolute ethanol as the solvent, the absorption of hydrogen proceeded at a much slower rate. A 75.3% yield of product boiling at 103–105° (1 mm.) was obtained. An attempt to carry out the hydrogenation using Raney nickel as catalyst and a 2:1 mixture of ethyl ether and absolute ethanol as the solvent resulted in incomplete reduction of the nitro group.

2-Amino-3,5-dibromoacetophenone. *o*-Aminoacetophenone was brominated in glacial acetic acid by the method of Fuchs (16). A 65% yield of material melting at 123–124° was obtained.

o-Acetaminoacetophenone. Five grams of *o*-aminoacetophenone was dissolved in 10 cc. of acetic anhydride and allowed to stand at room temperature for three hours. The clear solution was poured onto 100 cc. of crushed ice and allowed to stand until all of the excess acetic anhydride had been hydrolyzed. The white precipitate was removed and dried at room temperature. The yield was 6.3 g. (96%) of material melting at 74–75°.

When the acetic anhydride and *o*-aminoacetophenone were allowed to stand together for more than three hours the yield of the acetylated product was decreased.

2-Acetamino-5-bromoacetophenone. *o*-Acetaminoacetophenone (62.0 g., 0.35 mole) was brominated by the procedure of Gibson and Levin (17). After recrystallization from ethanol the product formed white threads melting at 158–159°. The yield was 80.4 g. (89.2%).

Nitration of o-acetaminoacetophenone. To a well-stirred mixture of 30 cc. of nitric acid (*d.* 1.42) and 30 cc. of sulfuric acid (*d.* 1.84) was added in portions 10.2 g. of *o*-acetaminoacetophenone. The temperature was maintained between 15° and 20° during the addition and for thirty minutes thereafter. The clear red-brown solution was poured onto 300 cc. of crushed ice, and the resulting light yellow precipitate was removed. Fractional crystallization from ethanol furnished a more soluble solid (A) (1.3 g.) which melted at 152–153° after two recrystallizations from benzene followed by two from benzene-petroleum ether,[4] and a less soluble solid (B) (8.0 g.) which melted likewise at 152–153° after three further recrystallizations from ethanol. A mixture of A and B melted at 115–125°; A was soluble in mineral acids, B was not. Analysis of A showed that it was 2-amino-5-nitroacetophenone (3).

Anal. Calc'd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48.
Found: C, 53.62; H, 4.58.

Compound B was 2-acetamino-5-nitroacetophenone (3), which gave A on acid hydrolysis.

When the crude nitration product was hydrolyzed by heating under reflux in 6 *N* hydrochloric acid solution, 2-amino-5-nitroacetophenone was obtained in 57% yield.

Reduction of m-nitroacetophenone

Tin and hydrochloric acid. The reduction of 127 g. (0.77 mole) of *m*-nitroacetophenone by the method of Camps (9) gave a yield of 86 g. (82.6%) of the amine melting at 97–99°.

Iron and acetic acid. Reduction of 60 g. (0.364 mole) of the nitro compound by the method of Morgan and Moss (27) gave a yield of 41 g. (83.7%) of the amine melting at 95–96°.

Hydrogenation in presence of platinum oxide. The hydrogenation was carried out on an Adams machine in the usual manner. The reaction mixture consisted of 16.5 g. (0.10 mole) of *m*-nitroacetophenone, 150 cc. of absolute ethanol, and 0.10 g. of platinum oxide. The absorption of hydrogen was very rapid. The catalyst was removed, and the filtrate was concentrated to a volume of *ca.* 30 cc. on the steam-cone. The residue was diluted with 200 cc. of water, heated to the boil, treated with charcoal, and filtered hot. The filtrate was cooled in an ice-bath and the precipitate removed. The filtrate was concentrated to a volume of *ca.* 100 cc. and again treated with charcoal and filtered. The crystals obtained by cooling the filtrate were added to the bulk of the product. The product melted at 95–

[4] The petroleum ether used throughout these studies had the boiling range 90–110°.

96°. In four runs of this type the yields were 12.6 g., 11.9 g., 12.7 g., and 11.1 g., or, respectively, 93.5%, 88.3%, 94.2%, and 82.3%.

Hydrogenation in presence of Raney nickel. The hydrogenation and isolation of the product were carried out in the manner described in the preceding section. About 5 g. of Raney nickel was used for 0.10 mole of the nitro compound. The absorption of hydrogen was very slow, about sixteen hours being required for the completion of the reduction. The yield was 11.2 g. (83%) of product melting at 98–99°.

A large scale hydrogenation of the nitro compound was carried out as follows: A mixture of 300 g. of *m*-nitroacetophenone, 700 cc. of absolute ethanol, and 30 g. of Raney nickel was placed in a high-pressure hydrogenation apparatus. The initial pressure was 1700 lb., and the temperature was 50°. The theoretical quantity of hydrogen was absorbed over a period of 4.5 hr., during which the temperature rose to 73°. The catalyst was removed and the solvent evaporated under diminished pressure. The residue was suspended in 1 liter of water and 150 cc. of concentrated hydrochloric acid. The mixture was heated to *ca.* 90°, treated with charcoal, and filtered. The filtrate was rendered alkaline with aqueous sodium hydroxide and the solid product was recrystallized from a mixture of benzene and petroleum ether containing just sufficient ethanol to effect complete solution of the amine. The fine granules had a slight brown tinge and melted at 98–99°. The yield was 180 g. (73%).

m-Aminophenylmethylcarbinol. In one attempted large scale reduction of *m*-nitroacetophenone, an Adams machine was connected directly to a large low-pressure tank of hydrogen, and the gas was admitted to the reaction mixture until no more was absorbed. The reaction mixture consisted of 165 g. (1.0 mole) of *m*-nitroacetophenone, 1 liter of 95% ethanol, and 25 g. of Raney nickel. The catalyst was removed and the solvent distilled. The residue was recrystallized from water, in which it was fairly soluble. The yield was 101 g. (75%) of a compound melting at 67°. A sample recrystallized from benzene for analysis formed small colorless plates melting at 68–69°.

Anal. Calc'd for $C_8H_{11}NO$: C, 70.04; H, 8.08.
Found: C, 70.21; H, 8.14.

m-Acetoaminoacetophenone. A solution of 60 g. (0.445 mole) of *m*-aminoacetophenone in 200 cc. of benzene was heated under reflux while 55 cc. of acetic anhydride was added dropwise. The solution was treated with charcoal and filtered hot. Cooling of the filtrate gave 71 g. (90%) of product melting at 127–128°.

Nitration of m-acetaminoacetophenone. *m*-Acetaminoacetophenone (50 g.) was added in portions to 250 cc. of nitric acid (*d.* 1.50) at temperatures below 0°. The clear solution was stirred an additional fifteen minutes at 0° and then poured onto *ca.* 800 cc. of ice. The clear yellow solution was rendered alkaline with sodium carbonate, and the precipitated product was recrystallized twice from ethanol. Twenty-five grams of 3-acetamino-2-nitroacetophenone, m.p. 168–169°, was collected. Concentration of the ethanolic filtrates furnished a second product, shown below to be 5-acetamino-2-nitroacetophenone. After three recrystallizations from benzene-ethanol solution, the weight of this product was reduced to 10 g. and the melting point was raised to 149–150°.

Anal. Calc'd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61.
Found: (3-acetamino-2-nitroacetophenone): C, 54.12; H, 4.64; N, 12.57.
Found: (5-acetamino-2-nitroacetophenone): C, 53.88; H, 4.56; N, 12.61.

Aminonitroacetophenones. The acetaminonitroacetophenones were hydrolyzed by heating in 6 *N* hydrochloric acid until a clear solution resulted. The amines were isolated by filtration after the hydrolysis solutions were rendered alkaline. *3-Amino-2-nitroacetophenone* was obtained as golden microcrystals, m.p. 93–93.5°, from benzene, and *5-amino-2-nitroacetophenone* gave light yellow needles, m.p. 152–153°, when recrystallized from benzene-ethanol.

Anal. Calc'd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55.
Found (3-amino-2-nitroacetophenone): C, 53.50; H, 4.44; N, 15.62.
Found (5-amino-2-nitroacetophenone): C, 53.18; H, 4.64; N, 15.68.

Acetaminoaminoacetophenones. The two acetaminonitroacetophenones were separately

subjected to hydrogenation over platinum oxide. *3-Acetamino-2-aminoacetophenone* formed stout needles, m.p. 169–170°. *5-Acetamino-2-aminoacetophenone* melted at 175°.

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.30.
Found (3-acetamino-2-aminoacetophenone): C, 62.45; H, 6.49.
Found (5-acetamino-2-aminoacetophenone): C, 62.52; H, 6.57.

Diacetaminoacetophenones. The acetaminoaminoacetophenones were acetylated with acetic anhydride in boiling benzene. After three recrystallizations from aqueous ethanol, *2,3-diacetaminoacetophenone* formed colorless microcrystals melting at 210–211°, *2,5-diacetaminoacetophenone,* after one recrystallization from aqueous ethanol, melted at 195–196°.

Anal. Calc'd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02.
Found (2,3-isomer): C, 61.49; H, 6.21.
Found (2,5-isomer): C, 61.73; H, 6.27.

2-Acetamino-5-aminoacetophenone. 2-Acetamino-5-nitroacetophenone was hydrogenated over platinum oxide in the usual manner. The product after three recrystallizations from ethanol-benzene formed microcrystals melting at 165–166°.

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.30; N, 14.58.
Found: C, 62.39; H, 6.34; N, 14.71.

2,5-Diacetaminoacetophenone. 2-Acetamino-5-aminoacetophenone was acetylated in benzene solution with acetic anhydride. The authentic 2,5-diacetaminoacetophenone melted at 195–196° and gave no depression of melting point when mixed with the compound of m.p. 195–196° designated above as 2,5-diacetaminoacetophenone. This definitely characterizes the compound from which it was obtained, *i.e.*, the nitration product of *m*-acetaminoacetophenone melting at 149–150°, as 5-acetamino-2-nitroacetophenone.

4-Acetamino-3-nitroacetophenone. p-Acetaminoacetophenone was prepared from *p*-aminoacetophenone by the method of Kaufmann (28). The product melted at 174–175°. The nitration was carried out by the procedure of Gibson and Levin (17). The product after recrystallization from ethanol formed yellow crystals melting at 139°.

4-Acetamino-3-aminoacetophenone. 4-Acetamino-3-nitroacetophenone (4.0 g.) was hydrogenated over platinum oxide in the usual manner. The product, after isolation from the reaction mixture and recrystallization from a mixture of ethanol and benzene, formed white threads melting at 179–180°. The yield was 2.9 g. (84%).

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.30.
Found: C, 62.32; H, 6.33.

3,4-Diacetaminoacetophenone. A small amount of the amine was dissolved in a mixture of benzene and ethyl acetate at the boil and acetylated by the addition of 5 cc. of acetic anhydride. The precipitate which appeared when the reaction mixture was cooled was recrystallized from ethanol. The compound formed fine white threads melting at 228–229°.

Anal. Calc'd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02.
Found: C, 61.91; H, 6.25.

m-Chloroacetophenone. This compound was obtained from *m*-aminoacetophenone by means of a Sandmeyer reaction. The yield was 56.6 g. (82.5%); b.p. 80° (2.5 mm.); n_D^{20} 1.5494.

5-Chloro-2-nitroacetophenone. Nitration of *m*-chloroacetophenone produced 5-chloro-2-nitroacetophenone in 49.6% yield as white needles, m.p. 62–62.5°.

Anal. Calc'd for $C_8H_6ClNO_3$: C, 48.14; H, 3.03; N, 7.02.
Found: C, 48.37; H, 3.04; N. 7.20.

2-Amino-5-chloroacetophenone. Hydrogenation of 5-chloro-2-nitroacetophenone was carried out in ethanol solution over platinum oxide. A 54% yield of 2-amino-5-chloroacetophenone, m.p. 65–66°, was obtained.

Anal. Calc'd for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26.
Found: C, 56.61; H, 4.82; N, 8.60.

m-Iodoacetophenone. This compound was prepared by the method of Evans, Morgan, and Watson (29) in a yield of 53%; b.p. 117° (4 mm.); n_D^{20} 1.6220.

5-Iodo-2-nitroacetophenone. One pound of nitric acid (sp. g. 1.49–1.50) was cooled to 0° in an ice-salt bath, and 48.0 g. (0.0195 mole) of *m*-iodoacetophenone was added at such a rate that the temperature did not exceed 0°. The solution was stirred an additional twenty minutes at 0° and was then poured onto 1 liter of crushed ice. After three recrystallizations from ethanol and one from a mixture of benzene and petroleum ether the compound formed stout needles with a green tinge. The yield was 22.5 g. (40%) of material melting at 140–141°.

Anal. Calc'd for $C_8H_6INO_3$: C, 33.01; H, 2.08; N, 4.81.
Found: C, 33.07; H, 2.10; N, 4.87.

2-Amino-5-iodoacetophenone. 5-Iodo-2-nitroacetophenone (29.1 g., 0.10 mole) was hydrogenated over platinum oxide in the usual fashion. The catalyst was removed and the filtrate cooled in an ice-bath. Addition of 150 cc. of concentrated hydrochloric acid caused the precipitation of the amine hydrochloride. This was removed and slurried with aqueous sodium carbonate to regenerate the free amine. After two recrystallizations from a mixture of benzene and petroleum ether the product melted at 98.5–99°. The yield was 16.5 g. (63.2%).

Anal. Calc'd for C_8H_8INO: C, 36.80; H, 3.09; N, 5.37.
Found: C, 36.95; H, 3.10; N, 5.41.

The amine formed an *acetyl* derivative which melted at 176–176.5°.

Anal. Calc'd for $C_{10}H_{10}INO_2$: C, 39.99; H, 3.33; N, 4.63.
Found: C, 39.75; H, 3.32; N, 4.79.

2,4-Dichloroacetophenone. The procedure employed in this preparation is a modification of that used by Roberts and Turner (20) for the preparation of 3,4-dichloroacetophenone.

To a mixture of 100 g. (0.68 mole) of *m*-dichlorobenzene (Eastman) and 100 g. of anhydrous aluminum chloride was added 50 g. of acetyl chloride over a period of an hour. The system was then heated at 100° while an additional 25 g. of acetyl chloride was added over a period of an hour. The mixture was stirred an additional two and one-half hours at 100°, allowed to cool somewhat, and poured onto 2 l. of ice. The oil which separated was removed by extraction with ether. The ether extracts were combined and washed twice with water, once with aqueous sodium hydroxide, and again with water until the washings were neutral to litmus. The ether solution was dried over magnesium sulfate, filtered, and the ether was removed. The residue was distilled under diminished pressure through an 18 in. Widmer column. The fraction boiling at 104–105° (5 mm.) was collected. The weight was 79 g. (62%); n_D^{20} 1.5640. Johnston (30) gave n_D^{20} 1.5642.

Ammonolysis of 2,4-dichloroacetophenone. The procedure used was a modification of that described in a German patent (31) for the ammonolysis of 2,4-dichlorobenzoic acid.

A mixture of 20.0 g. (0.105 mole) of 2,4-dichloroacetophenone, 90 cc. of 28% aqueous ammonia, and 0.5 g. of copper-bronze was placed in a pressure bomb and heated, with agitation, at 120° for 48 hr. The oily product was extracted with ether and the extracts filtered to remove suspended copper-bronze. Extraction of the ether solution with 4 *N* hydrochloric acid caused the separation of an oil (A) from the aqueous layer (B). The ether layer (C) was dried over magnesium sulfate. The oil (A) became partially solid upon standing in the aqueous solution, but resisted all attempts at purification. The aqueous extract (B) was cooled in an ice-bath and rendered alkaline with aqueous sodium hydroxide. An oil separated and was removed by extraction with ether. After drying over magnesium sulfate, the ether was removed, and the oily residue was dissolved in a mixture of benzene and petroleum ether. Crystals appeared in the solution after it had been allowed to stand overnight. These crystals were recrystallized three times from benzene-petroleum ether, whereupon about 1 g. of fine white needles melting at 136–137° was obtained. This material had the composition of *2,4-diaminoacetophenone.*

Anal. Calc'd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71.
Found: C, 63.94; H, 6.60.

The drying agent was removed from the ether solution (C), and the ether was removed by distillation. A residue remained which solidified upon cooling. After three recrystalli-

zations from a mixture of benzene and petroleum ether, 1.9 g. (11%) of *2-amino-4-chloroacetophenone* melting at 90° was obtained.

Anal. Calc'd for C_8H_8ClNO: C, 56.65; H, 4.75.
Found: C, 56.45; H, 4.84.

4-Chloro-2-nitrobenzoic acid. One hundred grams (0.58 mole) of 4-chloro-2-nitrotoluene (Eastman, practical grade) was dissolved in 500 cc. of pyridine and 390 cc. of water. The solution was heated on the steam-cone under reflux while six 43-g. portions of potassium permanganate were added at intervals of one hour. The heating was continued for an additional hour. The manganese dioxide was filtered and sucked as dry as possible on the filter. The water and pyridine were removed from the filtrate by evaporation under diminished pressure. The residue was treated with excess aqueous sodium hydroxide and a separatory funnel was utilized to remove the oil which was present. The oil was crystallized from alcohol and proved to be the starting chloronitrotoluene (33 g.). The alkaline aqueous solution was acidified with hydrochloric acid, and the crystalline mush was removed and dried. The yield was 56.5 g. of material melting at 138–140°. The yield based on unrecovered starting material was 62.5%.

4-Chloro-2-nitrobenzoyl chloride. A mixture of 100 g. (0.50 mole) of 4-chloro-2-nitrobenzoic acid and 110 g. of phosphorus pentachloride was gradually raised to 95° while as much as possible of the phosphorus oxychloride was removed under diminished pressure. The acid chloride was dissolved in 250 cc. of benzene, charcoal was added, and the mixture was filtered. The acid chloride was utilized as its benzene solution in subsequent reactions.

Sodium salt of ethyl 4-chloro-2-nitrobenzoylacetoacetate. A solution of sodium ethoxide was prepared by dissolving 35 g. (1.56 moles) of sodium in 600 cc. of absolute ethanol. One-half of this solution was cooled in an ice-salt bath, and 100 g. (0.77 mole) of acetoacetic ester was added. The temperature was maintained below 5° while one-half of the above benzene solution of 4-chloro-2-nitrobenzoyl chloride was added dropwise over a period of forty-five minutes. One-half of the remaining sodium ethoxide solution was added all at once, and one-half of the remaining acid chloride solution over a period of forty-five minutes. The remaining portions of the two solutions were added to the system in the same manner. A yellow solid precipitated in the reaction mixture as the addition of the acid chloride progressed. The mixture was allowed to stand at room temperature for four hours. The solid was removed by filtration and washed three times with ether. The yield was 172 g. of the crude condensation product.

4-Chloro-2-nitrobenzoylacetone. One-half of the crude condensation product from the preceding reaction was dissolved in 450 cc. of 4 *N* hydrochloric acid and heated under reflux for eight hours. The resulting brown oil was removed by extraction with ether. After drying and removal of the ether, the oily residue was dissolved in benzene, treated with charcoal, and filtered. The filtrate was cooled in an ice-bath and diluted with petroleum ether. The solid which precipitated was washed on the filter with petroleum ether. The compound dissolved completely in aqueous sodium hydroxide to give a bright red solution. This solution was acidified with acetic acid and the precipitated solid, after two recrystallizations from benzene-petroleum ether, formed small shimmering plates melting at 79°. The yield was 13.8 g. or 23% based on the quantity of 4-chloro-2-nitrobenzoic acid employed.

Anal. Calc'd for $C_{10}H_8ClNO_4$: C, 49.70; H, 3.34; N, 5.80.
Found: C, 49.70; H, 3.43; N, 5.85.

4-Chloro-2-nitroacetophenone. The hydrolytic procedure used here is a modification of that employed by Kermack and Smith (18) for the preparation of *o*-nitroacetophenone.

4-Chloro-2-nitrobenzoic acid (116 g.) was converted to the sodium salt of ethyl 4-chloro-2-nitrobenzoylacetoacetate in the manner described above. The latter compound was not isolated from the alcoholic reaction medium, but 150 cc. of concentrated sulfuric acid was added and the system heated under reflux for twelve hours. At the end of this time 1 liter of water was added and the mixture subjected to distillation until 1 liter of distillate had been collected. A large amount of oil suspended in a colorless solution remained in the distilling flask. The oil was removed by extraction with ether, and dried over magnesium

sulfate. After removal of the drying agent and ether the residue was distilled under diminished pressure. A yellow oil distilling at 157° (9 mm.) was collected. The oil solidified upon standing at room temperature and remelted at 44°. The yield was 70 g. (61% based on the chloronitrobenzoic acid used).

Anal. Calc'd for $C_8H_6ClNO_3$: C, 48.14; H, 3.03.
Found: C, 48.39; H, 3.04.

2-Amino-4-chloroacetophenone. 4-Chloro-2-nitroacetophenone (40 g., 0.20 mole) was dissolved in 100 cc. of absolute ethanol; 0.20 g. of platinum oxide was added and the hydrogenation was carried out on an Adams machine in the usual manner. The catalyst was removed by filtration, and 100 cc. of concentrated hydrochloric acid was added to the filtrate. The thick crystalline mush of the amine hydrochloride was removed and the free base regenerated by slurrying with aqueous sodium carbonate. After recrystallization from a mixture of benzene and petroleum ether the product weighed 21.7 g. (64.2% yield) and melted at 90–91°.

The amine formed an *acetyl* derivative which melted at 152–153°.

Anal. Calc'd for $C_{10}H_{10}ClNO_2$: C, 57.18; H, 4.74; N, 6.63.
Found: C, 56.70; H, 4.82; N, 6.60.

p-Chloroacetophenone. This compound was prepared by the method described in "Organic Syntheses" (32). The product boiled at 99–100° (5 mm.).

4-Chloro-3-nitroacetophenone. *p*-Chloroacetophenone was nitrated by the method of Le Fèvre and Le Fèvre (19). The product formed white needles melting at 99–100°.

Reduction of 4-chloro-3-nitroacetophenone. A mixture of 15.0 g. (0.075 mole) of the nitro compound, 150 cc. of absolute ethanol, and 0.075 g. of platinum oxide was subjected to hydrogenation. The catalyst was removed by filtration and the solvent by evaporation. The residue was slurried with excess dilute hydrochloric acid, and an insoluble substance was removed. The filtrate was rendered alkaline with sodium carbonate, and the free amine was recrystallized from a mixture of benzene and petroleum ether. The yield of *3-amino-4-chloroacetophenone* was 6.7 g. (53%) of white needles melting at 109°.

Anal. Calc'd for C_8H_8ClNO: C, 56.65; H, 4.75; N, 8.26.
Found: C, 56.66; H, 4.93; N, 8.20.

The acid-insoluble hydrogenation product after two crystallizations from ethanol formed fine flesh-colored threads which melted at 175–176°.

Anal. Calc'd for $C_{16}H_{12}Cl_2N_2O_3$: C, 54.72; H, 3.61; Cl, 20.19; N, 7.98.
Found: C, 54.98; H, 3.50; Cl, 20.43; N, 7.29.

A mixture of 39.9 g. (0.20 mole) of 4-chloro-3-nitroacetophenone, 55 g. of 100-mesh iron powder, 11 cc. of glacial acetic acid, and 220 cc. of water was heated under reflux for one hour. The system was then cooled in an ice-bath and filtered. The filter-cake was extracted with three 100-cc. portions of hot ethanol. The ethanol extracts were combined, heated to the boil, treated with charcoal, and filtered. The filtrate was concentrated to a volume of *ca.* 100 cc. and then cooled in an ice-bath. The crystals consisted of 21.2 g. (60.2%) of *3-amino-4-chloroacetophenone* melting at 108–109°.

The amine was acetylated in boiling benzene solution by the addition of acetic anhydride. After two recrystallizations from aqueous alcohol the *3-acetamino-4-chloroacetophenone* melted at 123–124°.

Anal. Calc'd for $C_{10}H_{10}ClNO_2$: C, 56.74; H, 4.79.
Found: C, 56.71; H, 4.90.

Nitration of 3-acetamino-4-chloroacetophenone. This compound (5.0 g.) was added gradually to 50 cc. of nitric acid (*d.* 1.50) at temperatures below −5°. The system was stirred for an additional 15 min. at −5 to 0° and was poured onto *ca.* 200 cc. of ice. The clear solution was rendered alkaline with sodium carbonate, and the resulting precipitate, after repeated recrystallization from benzene-petroleum ether, melted at 176–177°. The yield was 1 g. of very light yellow threads. The product has the composition of an *acetamino-chloronitroacetophenone.*

Anal. Calc'd for $C_{10}H_9ClN_2O_4$: C, 46.97; H, 3.54.
Found: C, 46.81; H, 3.84.

3,4-Dichloroacetophenone. 3-Amino-4-chloroacetophenone (21.2 g., 0.124 mole) dissolved in 100 cc. of water and 30 cc. of concentrated hydrochloric acid was diazotized at 5–10° by the addition of 25 cc. of a 5 *N* solution of sodium nitrite. A solution of cuprous chloride was prepared from 40 g. of cupric sulfate pentahydrate and this cuprous chloride solution was agitated and the diazonium chloride solution added to it over a period of five minutes. A vigorous evolution of nitrogen occurred. The reaction mixture was allowed to stand at room temperature overnight, and the orange solid was recrystallized from petroleum ether. The yield was 13.0 g. (55.6%) of material melting at 72–75°.

An attempt to nitrate this product by the procedure of Roberts and Turner (20) yielded only a small amount of a brown tar from which nothing could be isolated.

2-Amino-1-acetonaphthone. The method used here is that of Ott and Levy (21).

2-Naphthylamine (71.5 g., 0.5 mole) was heated with 250 cc. of benzene to 75° and 56 g. (0.55 mole) of acetic anhydride was added at such a rate as to maintain the system at a gentle reflux. The pink crystals were washed twice with cold benzene and twice with petroleum ether. The yield was 85 g. of *acet-2-naphthalide* melting at 132–133°.

A mixture of 18.5 g. (0.10 mole) of acet-2-naphthalide, 67 g. (0.50 mole) of anhydrous aluminum chloride and 370 cc. of carbon disulfide was cooled in an ice-bath while 9.3 g. (0.125 mole) of redistilled acetyl chloride was added over a period of 20 min. Stirring was continued for three hours, at which time the product had become too viscous to permit further stirring. The system was allowed to stand overnight and was then heated under reflux for one hour. The mixture was chilled thoroughly and the carbon disulfide removed by decantation. Ice (300 g.) was added to the mixture, and the system was allowed to stand for 1.5 hr. in the hood. Concentrated hydrochloric acid (100 cc.) was added, the mixture was heated on the steam-bath to expel any carbon disulfide, and then boiled vigorously for 1.5 hr. The resulting solution was cooled in an ice-bath, and the greenish precipitate of the amine hydrochloride was removed by filtration. The free amine was obtained by treating the salt with aqueous sodium hydroxide. After crystallization from benzene the product formed small yellow plates melting at 108–109°. The yield was 7.5 g. (41%).

Attempts to prepare 2-acetamino-5-chloroacetophenone by the Friedel-Crafts reaction. An attempt was made to carry out the nuclear acetylation of *p*-chloroacetanilide by the method of Kunckell (22, 23, 24). Acetyl bromide was employed as the acylating agent in carbon disulfide medium. The *p*-chloroacetanilide was recovered in good yield. The use of acetyl chloride in carbon disulfide, tetrachloroethane, or nitrobenzene likewise produced no acylation.

Nitration of propiophenone. The procedure followed is a modification of that of Elson, Gibson, and Johnson (25).

Two pounds of nitric acid (*d* 1.50) was cooled between −15° and −8° in an ethanol-dry ice bath while 150 g. (1.12 moles) of propiophenone (Eastman) was added dropwise over a period of one hour. The mixture was stirred an additional hour between −30° and −20°, and the temperature was allowed to rise to −10° over a period of one-half hour. The reaction mixture was poured onto ice, and the precipitated *m-nitropropiophenone* was removed by filtration and sucked as dry as possible on the filter. The filtrate was rendered alkaline with sodium carbonate and extracted with ether. The ether extracts were dried over magnesium sulfate, and the drying agent and solvent were removed. The crude *o-nitropropiophenone* remained as an oil. The *meta* isomer was recrystallized from ethanol; the yield was 121 g. of white needles melting at 100–101°. The alcoholic filtrate was evaporated under diminished pressure. The oily residue was added to the above crude *ortho* isomer. The yield of crude *o*-nitropropiophenone was 71.8 g.

o-Aminopropiophenone. A solution of 36.0 g. of the crude *o*-nitropropiophenone in 150 cc. of ethanol was slurried with 5 g. of Raney nickel and heated to the boil. Charcoal was added and the mixture filtered. Eight grams of fresh Raney nickel was added to the filtrate and the mixture was subjected to hydrogenation in the Adams machine. The catalyst was removed, concentrated hydrochloric acid (20 cc.) was added to the filtrate, and

the solvent was removed by evaporation under diminished pressure. The residue was rendered alkaline with aqueous potassium hydroxide, and the mixture was subjected to steam distillation. The amine was removed by extraction with ether, and the ether extracts were dried over magnesium sulfate. After removal of the drying agent and solvent the residue was distilled under diminished pressure. The fraction boiling at 93° (0.8 mm.) was collected. The yield was 15.5 g.

The amine was acetylated in the manner described for *o*-aminoacetophenone. The *acetyl* derivative melted at 70–71°.

2-Acetamino-5-bromopropiophenone. A solution of 8.0 g. (0.042 mole) of *o*-acetaminopropiophenone in 75 cc. of acetic acid and 75 cc. of water was stirred mechanically while a solution of 2.2 cc. of bromine in 42 cc. of acetic acid was added dropwise over a period of one hour. The mixture was stirred an additional hour, and the white precipitate was recrystallized from ethanol. The yield was 8.5 g. (75%) of fine white crystals melting at 188–189°.

Anal. Calc'd for $C_{11}H_{12}BrNO_2$: C, 48.90; H, 4.48; N, 5.19.
Found: C, 49.19; H, 4.46; N, 5.15.

A small amount of the product was heated in 6 *N* hydrochloric acid until a clear solution was obtained. The solution was treated with ammonia until alkaline and the free amine was crystallized from a mixture of benzene and petroleum ether. The *2-amino-5-bromopropiophenone* formed small light yellow prisms melting at 79–80°.

Anal. Calc'd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14.
Found: C, 47.54; H, 4.60; N, 6.02.

2-Acetamino-5-nitropropiophenone. A mixture of 40 cc. of nitric acid (*d.* 1.42) and 40 cc. of sulfuric acid (*d.* 1.84) was cooled at −30° in an ethanol-dry ice bath while 10 g. (0.052 mole) of *o*-acetaminopropiophenone was added. The temperature was allowed to rise to −10°, and the mixture was stirred between −15° and −10° for one-half hour. Since a considerable amount of solid remained undissolved in the claret-colored solution, the ethanol-dry ice bath was replaced by an ice-bath, and stirring was continued between 0° and 5° for one hour. The resulting solution was poured onto 300 cc. of ice. The precipitate was washed with aqueous sodium bicarbonate until alkaline, and then washed free of alkali with water. After recrystallization from ethanol the product formed fine white needles melting at 144–145°. The yield was 4.9 g. (40%).

Anal. Calc'd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86.
Found: C, 55.99; H, 5.19; N, 11.81.

SUMMARY

A wide variety of substituted *o*-aminoacetophenones and related compounds has been synthesized.

Two new *o*-aminopropiophenones have been synthesized.

Catalytic hydrogenation has been found to be generally applicable to the selective reduction of nitroacetophenones.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

CINNOLINES. II. SYNTHESIS OF 4-HYDROXYCINNOLINES[1]

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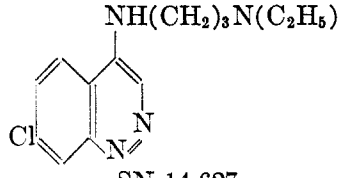
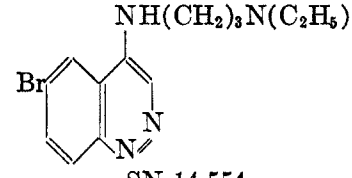
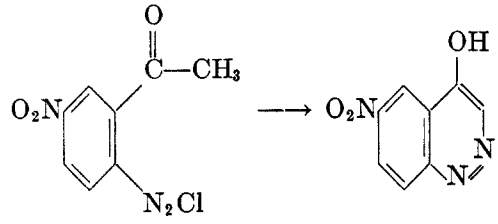
In view of the antimalarial activity of 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (1), it was considered of interest to prepare cinnoline analogs of this quinoline drug. The present paper describes the preparation of 7-chloro-4-(3-diethylaminopropylamino)cinnoline (SN-14,627)[2] and 6-bromo-4-(3-diethylaminopropylamino)cinnoline (SN-14,554). In the course of the synthesis of these potential antimalarial drugs, the corresponding 4-hydroxycinnolines were first prepared by the method of Borsche and Herbert (2). These investigators obtained 4-hydroxy-6-nitrocinnoline directly in a yield of eighty per cent when a solution of the diazonium salt from 2-amino-5-nitroacetophenone was allowed to stand overnight at room temperature and was then heated until the diazonium reaction had disappeared.



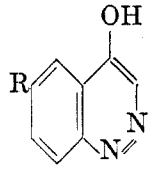
SN-14,627

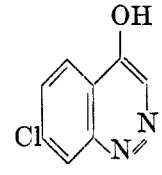


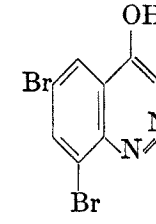
SN-14,554



The preparation of certain substituted *o*-aminoacetophenones has been described in the preceding paper (3). The following 4-hydroxycinnolines have been synthesized from these *o*-aminoacetophenones:







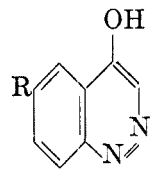
R = H, Cl, Br, I, NO_2, NH_2

[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

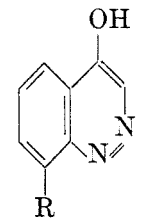
[2] The Survey Number, designated SN, refers to the number assigned to a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

In general, the aminoacetophenone was diazotized in either aqueous solution or acetic acid solution, and the solution of the diazonium salt was allowed to stand in the dark at room temperature until it no longer gave a diazo coupling reaction with β-naphthol. The time required for the completion of the cyclization under these conditions varied from a few days to two or three months. While the individual preparations were not carried out under strictly comparable conditions, the reaction time appeared to be a function of the basicity of the original amine. The yield of cinnoline obtained likewise depended upon the character of the *o*-aminoacetophenone utilized in its preparation. In general, the less basic the aminoacetophenone, the shorter the time required for the cyclization and the greater the yield of the cinnoline.

Since the completion of the work described in the present paper, two publications by Schofield and Simpson (4, 5) have appeared in the literature. The first of these papers describes the synthesis of 4-hydroxycinnolines by von Richter's method from *o*-aminophenylpropiolic acids (6). The second paper describes the synthesis of the following 4-hydroxycinnolines by the Borsche-Herbert method from *o*-aminoacetophenones:



R = H, Cl, Br, CN, NO_2



R = Cl, Br

In the preparation of 4-hydroxycinnoline and 6-bromo-, 6-chloro-, and 6-nitro-4-hydroxycinnolines, there have been some duplications in the investigations of Schofield and Simpson and those of the present authors, but there have also been sufficient variations in the procedures employed to warrant present discussion. In the 4-hydroxycinnoline preparations of Schofield and Simpson, the diazonium salt solutions were not allowed to stand at room temperature for an extended period of time but were heated to effect the cyclizations. This procedure, while requiring less time, gave smaller yields of the cinnolines than the other method. For example, Schofield and Simpson obtained only a ten per cent yield of 4-hydroxycinnoline from an aqueous acetic acid solution of diazotized *o*-aminoacetophenone; and they stated that "no hydroxycinnoline could be obtained when the reaction was carried out in dilute hydrochloric acid." The present authors, by carrying out the reaction in dilute hydrochloric acid and allowing the diazonium solution to stand at room temperature until the cyclization was complete, obtained a forty-three per cent yield of the desired cinnoline. It was also found in the course of the present work that if 2-amino-5-bromoacetophenone was diazotized and the solution heated to effect cyclization, 6-bromo-4-hydroxycinnoline was formed in a yield of 80.8%; while if the cyclization was effected at room temperature the cinnoline was formed in a yield of 95.5%. These observations

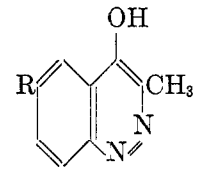
lead to the conclusion that the competing phenolic decomposition of the diazonium salt is favored to a much greater extent at the higher temperature, thereby reducing the extent to which the cyclization occurs.

Schofield and Simpson (4) reported that the reduction of 4-hydroxy-6-nitrocinnoline to 6-amino-4-hydroxycinnoline was unsuccessful. The present authors experienced no difficulty in carrying out this reduction with iron and acetic acid.

4-Chloro-, 6-bromo-4-chloro-, and 4,7-dichloro-cinnoline were prepared from the corresponding 4-hydroxycinnolines by heating with phosphorus oxychloride. 4-Chlorocinnoline was prepared also by heating 4-hydroxycinnoline with a mixture of phosphorus pentachloride and phosphorus oxychloride by the method of Busch and Klett (7). When this latter method was applied to 6-bromo-4-hydroxycinnoline, however, 6-bromo-4-chlorocinnoline was not obtained. The product apparently no longer contained bromine, and the possibility that it was 4,6-dichlorocinnoline has not been excluded.

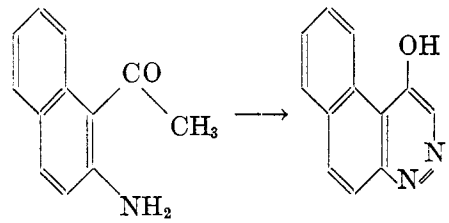
To prepare cinnoline derivatives of possible therapeutic value, 6-bromo-4-chloro- and 4,7-dichloro-cinnoline were allowed to react with 3-diethylaminopropylamine. The condensations occurred readily and yielded 6-bromo- and 7-chloro-4-(3-diethylaminopropylamino)cinnoline. The high order of reactivity of the chlorine in 4-chlorocinnolines is exemplified also by the facile preparation of 6-bromo-4-(*m*-chloroanilino)cinnoline from 6-bromo-4-chlorocinnoline and *m*-chloroaniline.

The Borsche-Herbert reaction was found to be applicable also to the preparation of 4-hydroxy-3-methylcinnolines. By following the general procedure outlined for the preparation of 4-hydroxycinnolines, the following cinnolines were prepared from the corresponding *o*-aminopropiophenones:



R = H, Br, NO_2

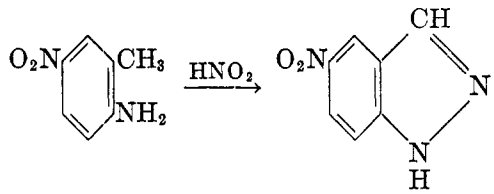
In an attempt to prepare 4-hydroxybenzo[*f*]cinnoline, 2-amino-1-acetonaphthone was diazotized and the diazonium solution was allowed to stand at room temperature.



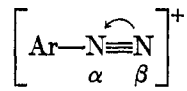
The product obtained, in contrast with the known 4-hydroxycinnolines, had a relatively low melting point (150–151°) and was soluble in the common organic solvents. Analytical data indicated that it possessed the molecular formula of a

hydroxyacetonaphthone rather than that of a hydroxybenzocinnoline. The melting point of the product does not coincide with that of any of the 2-hydroxyacetonaphthones recorded in the literature: 2-hydroxy-1-acetonaphthone, m.p. 64–65° (8); 2-hydroxy-3-acetonaphthone, m.p. 112° (9); 2-hydroxy-6-acetonaphthone, m.p. 171° (10). The 2-amino-1-acetonaphthone was prepared by the nuclear acetylation of acet-2-naphthalide (3). The structures of the aminoacetonaphthone and of its diazotization product are being investigated further.

The controlling factor in the cyclization of *o*-aminoacetophenones to cinnolines appears to be the reactivity of the diazonium cation. Schofield and Simpson (5) have pointed this out as a logical conclusion from the fact that negatively substituted *o*-aminoacetophenones form the corresponding 4-hydroxycinnolines in much greater yields than 4-hydroxycinnoline itself is formed. The same holds true for *o*-aminopropiophenones. The findings are consistent with those of Noelting (11) in the indazole series. 5-Nitroindazole was formed from diazotized 2-amino-5-nitrotoluene in yields of 82–89%. Indazole itself, however, is formed



from diazotized *o*-toluidine in yields of only 3–5%. For the successful formation of 6-substituted cinnolines, the *o*-aminoacetophenone employed contains an electronegative group (Cl, Br, I, NO_2, CN) in the position *para* to the amino group. For the formation of 8-substituted cinnolines, the *o*-aminoacetophenone has an electronegative group (Cl, Br) in the position *ortho* to the amino group. In the presently described synthesis of 7-chloro-4-hydroxycinnoline in eighty-one per cent yield, 2-amino-4-chloroacetophenone is the intermediate. Evidently, the property which promotes reactivity in the diazonium cation may result from either inductive or resonance displacement of electrons toward the benzene ring. Such displacement tends to bring about withdrawal of an electron pair from the



multiple link of the diazonium cation and to create an electron deficit on the β-nitrogen. With the cationic activity thus enhanced, the indigenous donor group will add at this seat of unsaturation to produce a cyclic molecule: a cinnoline when the group *ortho* to the amino group is acyl and an indazole when it is methyl.

EXPERIMENTAL[3]

4-Hydroxycinnoline. *o*-Aminoacetophenone (37.5 g., 0.278 mole) was dissolved in 120 cc. of water and 90 cc. of concentrated hydrochloric acid and diazotized between 0° and 7° by

[3] Unless otherwise indicated, all melting points are corrected for both emergent stem and thermometer errors. Microanalyses were performed by Miss Theta Spoor, Miss Lillian Hruda, and Mr. Howard Clark.

the dropwise addition of 59 cc. of a 5 *N* solution of sodium nitrite. The solution was then treated with charcoal and filtered. A small amount of excess nitrous acid was removed from the filtrate by the addition of urea, and the solution was stored in the dark at room temperature until a diazonium reaction was no longer obtained with an alkaline solution of the anilide of 2-hydroxy-3-naphthoic acid (44 days). The reaction mixture consisted of a dark red solution in which was suspended some needle-like crystals and several globules of a red-brown oil. There was evidence of the evolution of a considerable amount of nitrogen. The solid material was removed by filtration. An additional crop of crystals was obtained by allowing the filtrate to stand for several hours at room temperature. After recrystallization from ethanol the product formed slender white needles which melted at 232–233°. The yield was 17.4 g. (42.9%). A sample recrystallized for analysis melted at 236° (233.5–234°, Schofield and Simpson).

Anal. Calc'd for $C_8H_6N_2O$: C, 65.29; H, 4.11; N, 19.04.
Found: C, 65.41; H, 4.18; N, 18.87.

4-Hydroxycinnoline did not form a *picrate* or *picrylsulfonate*.

4-Chlorocinnoline. The method used for this preparation is a modification of that of Busch and Klett (7).

A mixture of 2.0 g. (0.014 mole) of 4-hydroxycinnoline, 2.7 g. (0.013 mole) of phosphorus pentachloride and 4 cc. of phosphorus oxychloride was heated under reflux in an oil-bath at 140° for thirty minutes. The clear solution was poured onto 100 cc. of crushed ice and rendered neutral to Congo Red by the addition of sodium acetate. The solution was extracted with ether. The extracts were washed free of acetic acid with a very dilute aqueous solution of sodium carbonate and then dried over magnesium sulfate. The ether was evaporated under diminished pressure and the residue recrystallized from petroleum ether (b.p. 90–110°); bright yellow needles melting at 75–76°; yield 2.0 g. (89%).

By the following procedure the preparation of 4-chlorocinnoline was effected without the use of phosphorus pentachloride. A mixture of 5.0 g. (0.034 mole) of 4-hydroxycinnoline and 25 cc. of phosphorus oxychloride was heated in an oil-bath at 95° for five minutes. Heating was discontinued and about 15 cc. of the phosphorus oxychloride removed from the system under diminished pressure. The residue was poured onto ice and rendered alkaline with potassium bicarbonate. The resulting solution was extracted with ether and the 4-chlorocinnoline was isolated and purified in the manner described above. The yield was 3.5 g. (62%) of a product melting at 76–77°.

The black by-product described by Busch and Klett (7) was found to accompany every attempt to prepare 4-chlorocinnoline by either of the two methods described. In some cases the formation of this black substance was so extensive that none of the desired product could be isolated. The extent to which this secondary reaction proceeds depends directly upon the *p*H of the aqueous solution which results when the reaction mixture is poured onto ice, *i.e.*, if the solution is rendered too alkaline before extraction with ether, the by-product is formed almost exclusively; if the solution is just exactly neutralized with a weak base, however, the 4-chlorocinnoline can be isolated before the secondary reaction occurs to too great an extent.

6-Bromo-4-hydroxycinnoline. A mixture of 73.9 g. (0.288 mole) of 2-acetamino-5-bromoacetophenone, 250 cc. of water and 350 cc. of concentrated hydrochloric acid was heated between 80° and 90° until complete solution was effected. The solution was agitated vigorously and cooled to 5° in an ice-salt bath. The amine was diazotized between 5° and 7° by the dropwise addition of 60 cc. of a 5 *N* solution of sodium nitrite. The resulting solution was treated with charcoal, filtered, and stored in the dark at room temperature until the diazonium reaction had completely disappeared (15 days). The yield of pale gray needles was 61.0 g. (95.5%), m.p. 283–285°. A sample recrystallized from ethanol for analysis melted at 286–287° (276–277°, Schofield and Simpson).

Anal. Calc'd for $C_8H_5BrN_2O$: C, 42.69; H, 2.24; Br, 35.51; N, 12.45.
Found: C, 42.78; H, 2.42; Br, 35.46; N, 12.33.

2-Acetamino-5-bromoacetophenone (72.0 g., 0.281 mole) was hydrolyzed and diazotized in the manner described above. The diazonium chloride solution was treated with char-

coal, filtered, and stored in the dark at room temperature for six hours. The solution was then heated at 70–80° for three hours and allowed to stand overnight at room temperature. The product was recrystallized from ethanol, yield 51.0 g. (80.8%) of material melting at 282–283°. It did not form a *picrate* or *picrylsulfonate* derivative.

6-Bromo-4-chlorocinnoline. A mixture of 4.0 g. (0.018 mole) of 6-bromo-4-hydroxycinnoline and 25 cc. of phosphorus oxychloride was heated at 100° for 15 min. The 6-bromo-4-chlorocinnoline was isolated in the manner described under the preparation of 4-chlorocinnoline. The yield was 2.5 g. (58%) of a compound melting at 124–126°. A sample purified by recrystallization for analysis melted at 127–128°. After a sample had stood for several days this melting point changed to 136–137°. When a sample melting at 136–137° was heated overnight in an Abderhalden drying pistol over refluxing ethanol the melting point reverted to 127–128°. A mixture of the two forms melted sharply at 127–128°.

Anal. Calc'd for $C_8H_4BrClN_2$: C, 39.46; H, 1.66; N, 11.51.
Found: C, 39.58; H, 1.73; N, 11.48.

Here again the preparation of the 4-chlorocinnoline resulted in the simultaneous formation of a black by-product in quantities depending on the degree of alkalinity to which the reaction mixture was exposed.

When 6-bromo-4-hydroxycinnoline was heated at 135–140° with a mixture of phosphorus pentachloride and phosphorus oxychloride in the manner described for 4-hydroxycinnoline the product was not 6-bromo-4-chlorocinnoline. It melted at 113–114°, even after exhaustive purification, and yielded the following analytical data.

C, 47.73, 47.50, 47.76; H, 1.92, 2.01, 2.07; N, 13.65; Hal., (as Cl, Br) 48.72, 48.55; (as Cl) 34.60, 34.46.

Calc'd for $C_8H_4Cl_2N_2$: C, 48.27; H, 2.03; N, 14.08; Cl, 35.63.

The color of the silver halide obtained in the analytical procedure indicated the absence of silver bromide, as did the analytical figures.

4-Hydroxy-6-nitrocinnoline. This compound was prepared from 2-amino-5-nitroacetophenone by the method of Borsche and Herbert; the diazonium salt solution was allowed to stand for ten days at room temperature and was then heated to complete the cyclization. The aminoacetophenone (19.5 g., 0.108 mole) yielded 18.0 g. (87%) of a red-brown product which did not melt sharply below 360° but sintered over a wide temperature range. A sample recrystallized from nitrobenzene melted at 338–340°. (Borsche and Herbert give m.p. 343–344°; Schofield and Simpson give m.p. 330–331°.)

6-Amino-4-hydroxycinnoline. A mixture of 9.3 g. (0.049 mole) of 4-hydroxy-6-nitrocinnoline, 60 cc. of glacial acetic acid, and 24 cc. of water was stirred vigorously while 6.4 g. of 100-mesh iron powder was added. The system was heated under reflux for an hour and then filtered hot. The filter cake was washed with 300 cc. of boiling water. The filtrate and washings were combined and cooled in an ice-bath, and yielded 3.4 g. of small yellow-brown needles which melted at 274–275°. The filtrate was evaporated to dryness. The residue was treated with aqueous potassium hydroxide and the iron compounds removed. The filtrate was acidified with acetic acid; the precipitate was removed and recrystallized from ethanol. This afforded an additional 1.4 g. of product melting at 274–275°. The total yield was 4.8 g. (61%). The product was soluble in either aqueous acid or alkali. A sample recrystallized from ethanol for analysis formed small clusters of brilliant yellow needles which melted at 275–276°.

Anal. Calc'd for $C_8H_7N_3O$: C, 59.62; H, 4.38.
Found: C, 59.67; H, 4.53.

6-Acetamino-4-hydroxycinnoline. A solution of 5.8 g. (0.03 mole) of 5-acetamino-2-aminoacetophenone in 100 cc. of hot glacial acetic acid was stirred vigorously while 5 cc. of concentrated sulfuric acid was added. The mixture was cooled in an ice-bath and 2.0 g. of finely divided sodium nitrite was added over a period of 0.5 hr. The mixture was stirred an additional 0.5 hr., treated with charcoal, and filtered. The filtrate was allowed to stand for three months in the dark at room temperature and protected from moisture. The resulting suspension was poured into 500 cc. of water, and the solid was removed. The

solid was extracted several times with boiling ethanol, and the extracts were combined and concentrated to a volume of *ca.* 200 cc. When the ethanolic solution was cooled in an ice-bath small iridescent golden plates precipitated. The yield was 2.0 g. (33%). The compound melted over a wide temperature range, and the range was variable, depending upon the rate of heating. Several recrystallizations from ethanol failed to alter this phenomenon. An instantaneous melting point was obtained for a highly purified sample and proved to be 264°.

A satisfactory analysis was not obtained for this compound, but its structure was elucidated in the following manner. One-half gram of the product was heated with 15 cc. of concentrated hydrochloric acid and 30 cc. of water until complete solution was attained. The solution was treated with charcoal and filtered. The filtrate was rendered just neutral with sodium carbonate and cooled in an ice-bath. Small yellow needles precipitated, m.p. 273°, no depression with a sample of 6-amino-4-hydroxycinnoline.

6,8-Dibromo-4-hydroxycinnoline. Fourteen grams (0.048 mole) of 2-amino-3,5-dibromoacetophenone was dissolved in 150 cc. of hot glacial acetic acid; 8.0 cc. of concentrated sulfuric acid was added, and the solution was stirred vigorously and allowed to cool to the temperature of the room. The amine was diazotized at this temperature by the gradual addition of 3.3 g. of finely powdered sodium nitrite. The diazonium solution was poured onto *ca.* 100 cc. of ice, treated with charcoal, and filtered. The filtrate was allowed to stand for 35 days. The red needles were recrystallized from ethanol, yield 9.5 g. (65%), m.p. 223–226°. Considerable difficulty was experienced in obtaining a sample of this compound sufficiently pure for analysis. After two recrystallizations from nitromethane and seven from ethanol, the fine white needles melted at 247–247.5°.

Anal. Calc'd for $C_8H_4Br_2N_2O$: C, 31.61; H, 1.33; Br, 52.58; N, 9.22.
Found: C, 32.02; H, 1.36; Br, 52.93; N, 9.36.

6-Chloro-4-hydroxycinnoline. 2-Amino-5-chloroacetophenone (2.5 g.) was dissolved in 60 cc. of hot 6 *N* hydrochloric acid. The solution was stirred vigorously while being cooled to 15°, and the amine was diazotized at this temperature by the addition of 3 cc. of a 5 *N* solution of sodium nitrite. The solution was treated with charcoal, filtered, and the filtrate allowed to stand for twelve days. The mixture was then heated on a steam-bath for one hour, and the precipitate was removed and recrystallized from ethanol. The yield was 1.67 g. (63%) of fine white needles melting at 289.5–290° (uncorr.). (Schofield and Simpson give m.p. 294–295°.)

Anal. Calc'd for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.51.
Found: C, 53.20; H, 2.90; N, 15.37.

4-Hydroxy-6-iodocinnoline. A mixture of 1.2 g. of 2-amino-5-iodoacetophenone, 20 cc. of water and 10 cc. of concentrated hydrochloric acid was stirred in an ice-bath while a 5 *N* solution of sodium nitrite was added as rapidly as it was absorbed. An excess of nitrous acid was maintained for 0.5 hr. The mixture was treated with charcoal, filtered, and the filtrate stored in the dark for three days. At the end of this period the system was heated on a steam-bath for 0.5 hr., and the crystals were recrystallized twice from ethanol; tan plates melting at 300–301° (uncorr.).

Anal. Calc'd for $C_8H_5IN_2O$: C, 35.31; H, 1.85.
Found: C, 35.28; H, 2.10.

7-Chloro-4-hydroxycinnoline. A solution of 30.5 g. (0.18 mole) of 2-amino-4-chloroacetophenone in 150 cc. of glacial acetic acid was cooled between 15° and 20° while a solution of nitrosyl sulfuric acid (14 g. of sodium nitrite in 100 cc. of concentrated sulfuric acid) was added dropwise over a period of 0.5 hr. The solution was stirred for an additional 0.5 hr. and then poured onto 800 cc. of crushed ice. The mixture was treated with charcoal, filtered, and the filtrate allowed to stand for 28 days. The system was heated at 70–80° for one hour and then cooled to room temperature. The reddish solid was recrystallized from ethanol. This gave 26.3 g. (81%) of white needles melting at 286–287°. A sample recrystallized from ethanol for analysis melted at 288°.

Anal. Calc'd for $C_8H_5ClN_2O$: C, 53.20; H, 2.79.
Found: C, 53.12; H, 3.02.

When the diazonium salt solution was allowed to stand overnight at room temperature and was then heated at 60–70° for 5 hr., an 80% yield of 7-chloro-4-hydroxycinnoline melting at 285–286° was obtained.

4,7-Dichlorocinnoline. A mixture of 5.0 g. of 7-chloro-4-hydroxycinnoline and 30 cc. of phosphorus oxychloride was heated at 90–95° until complete solution was attained. As much of the excess phosphorus oxychloride as possible was removed by distillation under diminished pressure; 30 cc. of dry toluene was added and again as much as possible of the solvent was removed by distillation. This "flushing" operation with toluene was repeated four times. The residue was poured onto ice and the product isolated in the manner described in the preparation of 4-chlorocinnoline. The 4,7-dichlorocinnoline, after recrystallization from petroleum ether (b.p. 90–110°) weighed 4.2 g. (77%) and melted at 142–143°. A sample recrystallized for analysis melted at 143–143.5°.

Anal. Calc'd for $C_8H_4Cl_2N_2$: C, 48.27; H, 2.03; N, 14.08.
Found: C, 48.57; H, 2.17; N, 13.68.

6-Bromo-4-(m-chloroanilino)cinnoline. A solution of 0.8 g. of 6-bromo-4-chlorocinnoline and 3.0 cc. of *m*-chloroaniline in 40 cc. of dry benzene was boiled gently for 10 min. The benzene was removed by evaporation, and the residue was slurried with dilute aqueous potassium hydroxide and filtered. The product was recrystallized once from ethanol and once from ethyl acetate. The compound formed small yellow plates melting at 246–247°.

Anal. Calc'd for $C_{14}H_9BrClN_3$: C, 50.25; H, 2.71; N, 12.56.
Found: C, 50.72; H, 2.79; N, 13.16.

6-Bromo-4-(3-diethylaminopropylamino)cinnoline (*SN-14,554*). A solution of 15.0 g. of 6-bromo-4-chlorocinnoline and 30 g. of 3-diethylaminopropylamine in 100 cc. of dry benzene was heated under reflux for 5 hr. A clear maroon solution resulted. The solvent was removed by evaporation, and the residue was slurried with water, filtered, and the residue washed well with water. The product was dried in a vacuum desiccator over phosphorus pentoxide and recrystallized four times from a mixture of benzene and petroleum ether (b.p. 90–110°). The yield was 13.5 g. of light tan microcrystals melting at 149–150°.

Anal. Calc'd for $C_{15}H_{21}BrN_4$: C, 53.41; H, 6.28; N, 16.61.
Found: C, 53.57; H, 6.38; N, 16.45.

The base formed a *dipicrate* from ethanol solution: m.p. 194–195°.

Anal. Calc'd for $C_{27}H_{27}BrN_{10}O_{14}$: C, 40.76; H, 3.42; N, 17.61.
Found: C, 41.08; H, 3.61; N, 16.91.

7-Chloro-4-(3-diethylaminopropylamino)cinnoline (*SN-14,627*). A solution of 17.0 g. of 4,7-dichlorocinnoline and 34.0 g. of 3-diethylaminopropylamine in 100 cc. of dry benzene was heated under reflux for 7 hr. The clear maroon solution was washed well with aqueous potassium hydroxide and then poured onto anhydrous magnesium sulfate. Carbon disulfide (50 cc.) was added to convert any excess diethylaminopropylamine to the corresponding dithiocarbamate, and the mixture was allowed to stand overnight. The solid material was removed and the solvent removed from the filtrate by evaporation. After two recrystallizations from a mixture of benzene and petroleum ether (b.p. 90–110°), the residue separated as small white plates melting at 164–165°. The yield was 10.2 g.

Anal. Calc'd for $C_{15}H_{21}ClN_4$: C, 61.52; H, 7.32; N, 19.14.
Found: C, 61.79; H, 7.31; N, 18.60.

The base formed a *dipicrate*, from ethanol solution, melting at 197–198°.

Anal. Calc'd for $C_{27}H_{27}ClN_{10}O_{14}$: C, 43.17; H, 3.62; N, 18.65.
Found: C, 43.08; H, 3.75; N, 17.82.

4-Hydroxy-3-methylcinnoline. *o*-Aminopropiophenone (9.6 g., 0.065 mole) in 70 cc. of water and 20 cc. of concentrated hydrochloric acid was diazotized at 0–5° by the addition of 13 cc. of a 5 *N* solution of sodium nitrite. The solution was treated with charcoal, filtered, and the filtrate allowed to stand for 11 days. The precipitated needles were removed by

filtration and recrystallized from ethanol. The yield was 1.8 g. (18%) of a product melting at 245–247°. A sample recrystallized from ethanol for analysis formed bright yellow needles melting at 248–249°.

Anal. Calc'd for $C_9H_8N_2O$: C, 67.48; H, 5.04; N, 17.49.
Found: C, 68.04; H, 5.34; N, 17.87.

6-Bromo-4-hydroxy-3-methylcinnoline. A suspension of 5.3 g. (0.02 mole) of 2-acetamino-5-bromopropiophenone in 90 cc. of water and 77 cc. of concentrated hydrochloric acid was heated at the boil until complete solution was attained. The solution of the amine hydrochloride was treated with charcoal and filtered. The filtrate was cooled to 0° and the amine diazotized at 0–5° by the addition of 4.1 cc. of a 5 *N* solution of sodium nitrite. The diazonium salt solution was stored in the dark for 23 days. The solid was removed from the reaction mixture by filtration and recrystallized from ethanol. This gave 3.4 g. (76% yield) of fine white needles melting at 323–326° (uncorr.). A sample recrystallized from ethanol for analysis melted at 326–327° (uncorr.).

Anal. Calc'd for $C_9H_7BrN_2O$; C, 45.21; H, 2.95; N, 11.72.
Found: C, 45.45; H, 3.11; N, 11.70.

4-Hydroxy-3-methyl-6-nitrocinnoline. A suspension of 3.7 g. (0.016 mole) of 2-acetamino-5-nitropropiophenone in 65 cc. of concentrated hydrochloric acid and 180 cc. of water was heated at the boil for 1.5 hr. Complete solution was not attained, but the color of the suspended solid turned gradually from white to yellow. The amine was diazotized at room temperature by the addition of 3.2 cc. of a 5 *N* solution of sodium nitrite. A small amount of insoluble material was removed and the filtrate was stored in the dark for 7 days. The yield was 2.1 g. (65%) of fine light yellow needles melting above 350°. It was only very slightly soluble in ethanol and insoluble in the other common solvents. Recrystallization from ethanol was used to purify the product for analysis.

Anal. Calc'd for $C_9H_7N_3O_3$: C, 52.68; H, 3.44; N, 20.48.
Found: C, 52.74; H, 3.62; N, 20.54.

Attempt to prepare 4-hydroxybenzo[f]cinnoline. 2-Amino-1-acetonaphthone (4.6 g., 0.025 mole) suspended in 15 cc. of concentrated hydrochloric acid and 80 cc. of water was diazotized at 0–5° with 5 cc. of a 5 *N* solution of sodium nitrite. The solution was stored in the dark at room temperature. At the end of 7 days the diazonium test was very faint. The mixture was heated on a steam-bath for one hour, and sufficient ethanol was added to bring about complete solution. The solution was treated with charcoal, filtered, and the solvent removed from the filtrate by evaporation. The residue, after recrystallization from a mixture of benzene and petroleum ether (b.p. 90–110°) formed pale yellow needles melting at 150–151°. This product was very soluble in ethanol, ether, and benzene. It had the composition of an hydroxyacetonaphthone.

Anal. Calc'd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41.
Found: C, 77.61; H, 5.47.

The compound did not give a color reaction with ferric chloride in ethanolic solution; it dissolved in aqueous potassium hydroxide to give a bright yellow solution.

SUMMARY

Several 4-hydroxycinnolines have been prepared by the diazotization and subsequent cyclization of *o*-aminoacetophenones. 4-Hydroxy-3-methylcinnolines have been prepared in the same manner from *o*-aminopropiophenones.

6-Amino-4-hydroxycinnoline has been prepared by the reduction with iron and acetic acid of 4-hydroxy-6-nitrocinnoline.

4-Chloro-, 6-bromo-4-chloro-, and 4,7-dichloro-cinnoline have been prepared by heating the corresponding 4-hydroxycinnoline with phosphorus oxychloride.

6-Bromo- and 7-chloro-4-(3-diethylaminopropylamino)cinnoline, compounds

of possible therapeutic interest, have been prepared from the corresponding 4-chlorocinnolines and 3-diethylaminopropylamine.

URBANA, ILL.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XV.[1,2] AMINO ALCOHOLS OF THE TYPE —CHOHCH$_2$NR$_2$ DERIVED FROM 3-CHLORO-6-ACETYLPHENANTHRENE

EVERETTE L. MAY AND ERICH MOSETTIG

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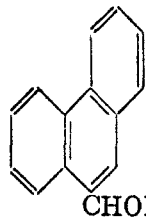
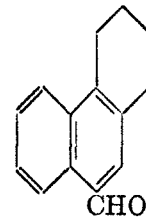
Replacement of the chlorine in Atabrine by hydrogen results in a considerable decrease in the antimalarial effectiveness of this drug (1). We have shown recently that a number of phenanthrylamino alcohols of types I and II are effective agents in *gallinaceum* malaria and human malaria (2, 3), the members of type I being somewhat more effective than those of type II.



CHOHCH$_2$NR$_2$

I



CHOHCH$_2$NR$_2$

II

We hoped that, in accordance with the findings in the acridine series, we could increase the antimalarial activity of compounds I and II by introducing a chlorine into the phenanthrene nucleus.

By analogy with the course of the Friedel-Crafts reaction on 3-hydroxy- and 3-methoxy-phenanthrenes (4), and 3-methylphenanthrene (5), we could expect that a chlorine in position 3 would direct an acyl group to position 6 or 9, the latter one being the desired location for the alkamine side chain. When acetyl chloride was allowed to react with 3-chlorophenanthrene in nitrobenzene solution[3] in the presence of aluminum chloride, 3-chloro-6-acetylphenanthrene was obtained in a yield of 60%. As by-products, 3-chloro-x-acetylphenanthrene (m.p. 95–96° and 106–107°) and 3-chloro-y-acetyl phenanthrene (m.p. 138–139°) were isolated in a yield of three and two per cent respectively. No directed efforts have been made to determine positions x and y. The total synthesis, however, of 3-chloro-9-acetylphenanthrene and 3-chloro-10-acetylphenanthrene described in the following papers (6, 7) and their non-identity with either of these by-products excludes positions 9 and 10 for either x or y.

The structure of 3-chloro-6-acetylphenanthrene (III) became evident by the

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXXI.

[3] In the following publication by May and Mosettig (6) it will be shown that the nature of the solvent has a decisive influence on the course of this reaction.

reactions depicted in Fig. 1. 3-Acetylaminophenanthrene was submitted to a Friedel-Crafts reaction. The methyl ketone IV, formed thereby in 30–40% yields, was hydrolyzed and the resulting amino compound converted by the method of de Milt and Van Zandt (8) to 3-hydroxy-6-acetylphenanthrene (4). On the other hand, ketone IV was hydrolyzed and converted by the Sandmeyer reaction, to ketone III.

Nine dialkylamino alcohols of the type —$CHOHCH_2NR_2$ were synthesized from 3-chloro-6-acetylphenanthrene (III) by methods described in foregoing papers of this series. The exchange of the ω-bromine atom in 3-chloro-6-ω-bromoacetylphenanthrene with the amino groups was effected in hot ethyl acetate or in an acetone-ether mixture. Reduction of the resulting amino

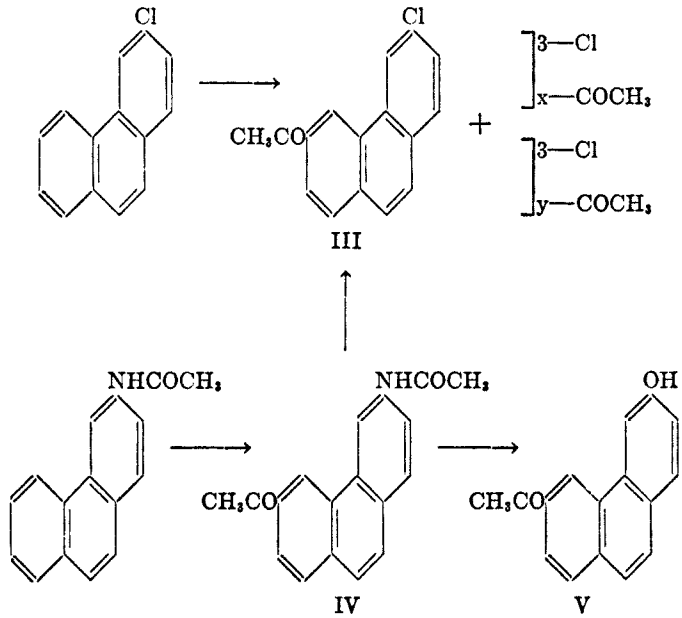


FIG. 1

ketones to the corresponding amino alcohols with aluminum isopropoxide proceeded readily and in good yields.

When comparing the biological data of the phenanthryl-3-amino alcohols (9) and the 3-chlorophenanthryl-6-amino alcohols,[4] the therapeutic superiority of the "chloro series" becomes evident. In both series the tolerated doses (chicks) lie approximately in the same range and in both series there is a general trend towards decrease in toxicity with increase in size of the dialkylamino group (Dr. Nathan B. Eddy) (10). The members of the "chloro series" are from four to eight times as effective towards *Plasmodium gallinaceum* as the corresponding chlorine-free amino alcohols (Dr. G. Robert Coatney and Dr. W. Clark Cooper)

[4] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph. These numbers are given in Table I.

(11). None of the drugs described herein showed any activity towards sporozoite-induced *gallinaceum* malaria[5] (11).

Acknowledgment. We are indebted to Mr. Edward A. Garlock, Jr. for carrying out the microanalyses.

EXPERIMENTAL[6]

Friedel-Crafts Reaction on 3-Chlorophenanthrene

3-Chloro-6-acetylphenanthrene (III). To a stirred solution of 20 g. of aluminum chloride and 16.5 g. of 3-chlorophenanthrene (12) in 110 cc. of nitrobenzene was added 9.0 g. of acetyl chloride during a five-minute period (temperature 0° to 3°). After stirring at 3° to 5° for 1.5 hours the reaction mixture was allowed to stand at +6° for twenty hours. It was poured onto ice-hydrochloric acid, the nitrobenzene removed with steam, and the residue taken up in benzene. After removal of solvent *in vacuo* the oily product was evaporatively distilled at 170–175° (0.05 mm.). The semisolid distillate (19.5 g.), upon recrystallization from about 200 cc. of methanol [ether-ligroin (30–60°) was used to wash the product], gave 3-chloro-6-acetylphenanthrene, m.p. 110.5–111.5° in a yield of 12 g. Two more recrystallizations followed by a sublimation in an oil-pump vacuum gave white rods of m.p. 111.5–112.5°.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35.
Found: C, 75.08; H, 4.45.

3-Chloro-x-acetylphenanthrene. The filtrate and washings from the 12 g. of ketone above, deposited on standing overnight 3.5 g. of a white solid melting at 75–95°. This consisted of about a 1:1 mixture of 3-chloro-6- and 3-chloro-x-acetylphenanthrenes. One gram of the ketone mixture in 25 cc. of 95% ethanol was converted to the semicarbazone. The latter was dissolved in 25 cc. of boiling nitrobenzene, the solution filtered hot, and the filtrate cooled to room temperature. The product which separated weighed 0.4 g. and did not melt below 280°. It was refluxed for twenty hours with 10 cc. of 10% hydrochloric acid, after which a benzene-soluble product weighing 0.3 g. and melting at 85–95° was obtained. It crystallized from methanol in long needles of m.p. 96–97°. After sublimation under high vacuum it melted at 106–107° and then crystallized from methanol in white prisms. The two forms were interconvertible in methanol solution.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35.
Found: C, 75.14; H, 4.65.

On dilution of the nitrobenzene filrate above with benzene-ligroin a fairly pure semicarbazone of 3-chloro-6-acetylphenanthrene separated, giving on hydrolysis, 0.3 g. of the ketone.

3-Chloro-y-acetylphenanthrene. The mother liquor from the 3.5 g. of solid melting at 75–95°, on standing for several weeks, deposited a solid along with some oil. The solid was picked out and recrystallized from methanol yielding 0.4 g. of white square plates melting at 134.5–137°. The analytical sample melted at 138–139°.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35.
Found: C, 74.96; H, 4.44.

The semicarbazone crystallized from dioxane in glittering white plates of m.p. 244–245° (decomp.).

Anal. Calc'd for $C_{17}H_{14}ClN_3O \cdot \frac{1}{2}C_2H_5OH$: C, 64.58; H, 5.12; N, 12.56.
Found: C, 64.78; H, 5.37; N, 11.68.

A determination of solvate ethanol by loss in weight was unsuccessful, and we can offer no explanation for the low N value. The semicarbazone was readily hydrolyzed to the original ketone of m.p. 138–139°.

3-Acetylamino-6-acetylphenanthrene (IV). Ten grams of 3-acetylaminophenanthrene

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[5] SN 9012 was not included in these tests because of lack of material.

[6] All melting points are uncorrected.

(13) was added all at once to a stirred solution of 12 g. of aluminum chloride in 60 cc. of nitrobenzene, at a temperature of 25–30°. To this stirred suspension, cooled to 15–20°, was added during forty-five minutes, 4.5 cc. of acetyl chloride. The mixture was stirred without external cooling for four to five hours after which 50 cc. of benzene and 50 cc. of ligroin (30–60°) were added. By filtration, 1.3 g. of 3-acetylaminophenanthrene was recovered as an aluminum chloride complex. The filtrate was stirred thoroughly with cold dilute hydrochloric acid, and the solid which separated was filtered off and triturated with cold 95% ethanol. It was collected, dried, and sublimed at 230° (0.05 mm.). The yield of 3-acetylamino-6-acetylphenanthrene was 4.6 g., m.p. 238–239°. After another sublimation the m.p. was 238.5–239.5°. It could be recrystallized from nitrobenzene or dioxane; pale yellow plates.

Anal. Calc'd for $C_{16}H_{15}NO_2$: C, 77.97; H, 5.46.
Found: C, 77.44; H, 5.51.

3-Amino-6-acetylphenanthrene. A mixture of 6.8 g. of IV, 35 cc. of glacial acetic acid, 35 cc. of concentrated hydrochloric acid, and 10 cc. of water was refluxed for one hour, cooled, and the hydrochloride collected and washed with acetone (6.5 g.). By treating it with dilute aqueous ammonia, the free base was obtained; recrystallized from methanol. The yield was 4.8 g., m.p. 140.5–142°; broad yellow needles.

Anal. Calc'd for $C_{16}H_{13}NO$: C, 81.67; H, 5.57.
Found: C, 81.29; H, 5.98.

Conversion of 3-amino-6-acetylphenanthrene to (a) 3-hydroxy-6-acetylphenanthrene and (b) 3-chloro-6-acetylphenanthrene. (a) To 15 cc. of concentrated sulfuric acid and 8 cc. of water cooled to 10° was added 1.6 g. of sodium nitrite. The mixture was warmed to effect complete solution, then cooled to 0° to 5° (stirring) while adding during forty-five minutes, 2.4 g. of 3-amino-6-acetylphenanthrene in 10 cc. of pyridine. After stirring an additional hour at 0° to 5°, the reaction mixture was diluted to 200 cc. with ice-water and stirring was continued for another hour. One-third of it was then added slowly to 70 cc. of boiling water, the suspension was boiled a few minutes, cooled, and filtered. The precipitate was digested with boiling dilute potassium hydroxide solution, the insoluble material filtered off, the filtrate acidified with hydrochloric acid, and the precipitate extracted with benzene. The solid from the benzene extract was sublimed at 170° (0.05 mm.). The sublimate weighed 0.15 g. and crystallized from methanol in slightly yellow prisms of m.p. 179.5–181°. A mixture melting point with the known 3-hydroxy-6-acetylphenanthrene (4a) was 180–181°. The methyl ether, prepared with ethereal diazomethane, crystallized from methanol, and melted at 83.5–85°. When recrystallized and seeded with an authentic specimen (4a), it melted at 107–108° and gave no depression when mixed with the authentic material.

(b) The remaining two-thirds of the diazotization mixture above was stirred with 7 g. of potassium chloride and 7 g. of mercuric chloride at 0° to 5° for one hour. The precipitated double salt was collected, air dried, and refluxed for twenty minutes (stirring) with 35 cc. of water and 20 g. of potassium chloride. The resulting red product was shaken into benzene, and evaporately distilled. The yield of 3-chloro-6-acetylphenanthrene was 0.15 g. It crystallized from methanol in clusters of white rods of m.p. 110–111.5°. A mixture m.p. with the predominant product obtained in the acetylation of 3-chlorophenanthrene was 110–112°. Mixed with 3-chloro-x-acetylphenanthrene of m.p. 106–107°, it melted at 75–98°.

3-Chloro-6-ω-bromoacetylphenanthrene. A stirred, ice-cooled suspension of 19.5 g. of 3-chloro-6-acetylphenanthrene and 40 cc. of dry ether was treated dropwise with 12.3 g. (4.2 cc.) of bromine during twenty-five minutes (the first drop or two of bromine was added at room temperature to initiate the reaction). After stirring for one hour without external cooling, the reaction mixture was thoroughly cooled in ice and the precipitate collected. It weighed 24.0 g. and melted at 197–200°. It crystallized from ethyl acetate in fine white needles of m.p. 202–203°.

Anal. Calc'd for $C_{16}H_{10}BrClO$: C, 57.61; H, 3.02.
Found: C, 57.62; H, 3.24.

TABLE I

AMINO ALCOHOLS

SN	$C_{14}H_8$(3-Cl, 6-$CHOHCH_2$—)[a]	M.P., °C	APPEARANCE	SOLVENT	FORMULA	% CARBON		% HYDROGEN	
						Calc'd	Found	Calc'd	Found
9017	$N(CH_3)_2 \cdot HCl$	197.5–199	Plates	Abs. EtOH-ether[b]	$C_{18}H_{19}Cl_2NO$	64.29	64.50	5.69	6.11
9016	$N(C_2H_5)_2 \cdot HCl$	200.5–202.5	Rods	Abs. EtOH-acetone	$C_{20}H_{23}Cl_2NO$	65.93	66.12	6.36	6.69
9015	$N(C_3H_7)_2 \cdot HCl$	210–211.5	Large needles	Abs. EtOH-acetone	$C_{22}H_{27}Cl_2NO$	67.34	67.25	6.94	6.80
9014	$N(C_4H_9)_2 \cdot HCl$	206–208	Fine long needles	Abs. EtOH-acetone	$C_{24}H_{31}Cl_2NO$	68.56	68.27	7.43	7.34
8978	$N(C_5H_{11})_2 \cdot HCl$	190–192.5	Fine needles	Acetone	$C_{26}H_{35}Cl_2NO$	69.62	69.42	7.87	7.55
9013	$N(C_6H_{13})_2 \cdot HCl$	132–134[c]	Small needles	Acetone	$C_{28}H_{39}Cl_2NO$	70.57	70.39	8.25	8.40
8911	$N(C_7H_{15})_2 \cdot HCl$	154–155.5	Fine needles	Acetone-ether	$C_{30}H_{43}Cl_2NO$	71.40	71.41	8.59	8.95
9012	$N(C_8H_{17})_2 \cdot HCl$	137–138	Needles	Acetone	$C_{32}H_{47}Cl_2NO$	72.16	72.07	8.90	8.37
9011	$N(C_9H_{19})_2 \cdot HCl$	144–145.5	Long slender needles	Acetone	$C_{34}H_{51}Cl_2NO$	72.83	72.72	9.17	9.07

[a] The yields (based on bromo ketone) varied from 55–65%.

[b] Norit was used for decolorization.

[c] If the temperature rise is slow, the compound does not melt completely until the temperature 143° is reached. When cooled and remelted the m.p. was 144–148°. After one year of storage the m.p. was 133–135° irrespective of the speed of temperature rise.

Debromination of 3-chloro-6-ω-bromoacetylphenanthrene. A mixture of 5.0 g. of bromo ketone, 3 g. of palladium-charcoal (5% Pd), and 200 cc. of absolute ethanol absorbed 0.85 mole of hydrogen in 1.5 hours. Absorption had slowed to a rate of 0.5 cc. per minute (original rate 30 cc. per minute). After filtration of catalyst and concentration of the filtrate to about 50 cc. followed by thorough cooling, 3-chloro-6-acetylphenanthrene separated in a yield of 2.0 g. (53%), m.p. 109–111°. It was identical with that obtained in the Friedel-Crafts reaction.

Amino alcohols. One mole of 3-chloro-6-ω-bromoacetylphenanthrene (m.p. 197–200°), two moles of the dialkyl amine, and 7 cc. of ethyl acetate per gram of bromo ketone were heated together on the steam-bath for five to ten minutes (frequent shaking).[7] The bromo ketone gradually gave way to a flaky precipitate of secondary amine hydrobromide. After shaking mechanically at room temperature for one to two hours, the reaction mixture was diluted with an equal volume of ether, cooled, and secondary amine hydrobromide removed. The filtrate was evaporated to dryness *in vacuo* and the residual amino ketone reduced with five molecular equivalents of 3 *N* aluminum isopropoxide in isopropanol as described previously (2). Most of the isopropanol was then evaporated *in vacuo* and the residue partitioned between ether and an excess of 10% sodium hydroxide solution. After washing the ether layer twice with water and drying over sodium sulfate it was treated with slightly more than the calculated amount of 20–25% alcoholic hydrogen chloride, whereupon the amino alcohol hydrochloride crystallized and was purified by recrystallization. Compounds 3 to 9 inclusive (Table I) were prepared in this manner. For compounds 1 and 2, three molecular equivalents of secondary amine was used. No heating was required in the reaction between dimethylamine and 3-chloro-6-ω-bromoacetylphenanthrene. The dried ether solution of the amino alcohol in these two instances was evaporated to dryness and the residue dissolved in acetone from which solution the hydrochloride was precipitated with alcoholic hydrogen chloride.

SUMMARY

Nine amino alcohols derived from 3-chlorophenanthrene, and carrying the alkamine side chain in position 6, have been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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[7] In subsequent preparations of large amounts of 3-chloro-6-(2-diheptylamino-1-oxoethyl)phenanthrene it was found advantageous to use an ether-acetone mixture (4:1) at room temperature.

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XVI.[1,2] AMINO ALCOHOLS OF THE TYPE —CHOHCH$_2$NR$_2$ DERIVED FROM 3-CHLORO-9-ACETYLPHENANTHRENE

EVERETTE L. MAY AND ERICH MOSETTIG

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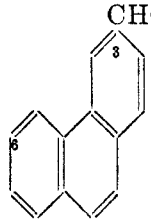
In the foregoing communication (1) we have shown that the introduction of a chlorine atom into the nucleus (position 6) of 3-phenanthrylamino alcohols (I) increases considerably the activity against *Plasmodium gallinaceum*.



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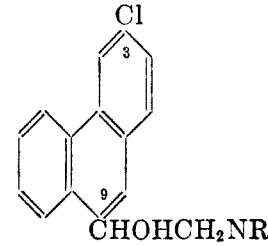


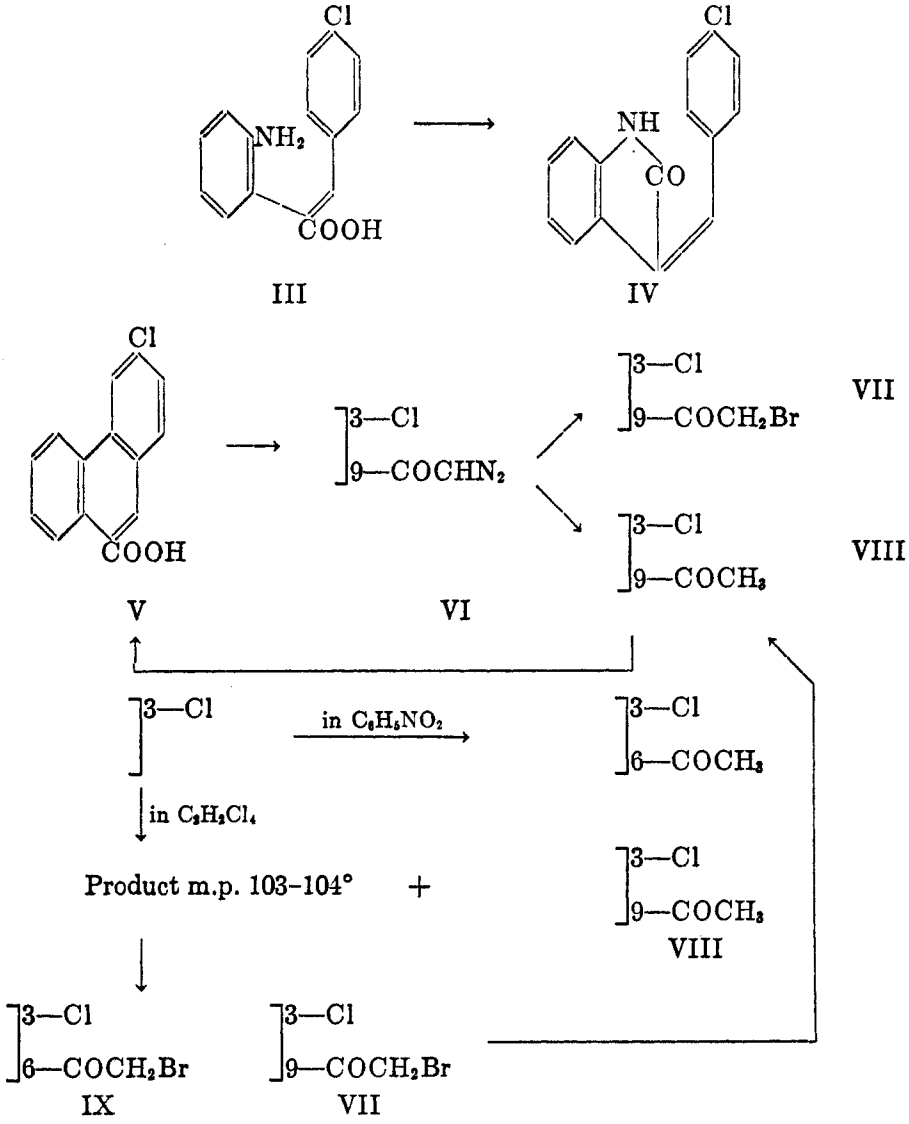
II

The synthesis of these amino alcohols (chlorine in position 6) was not planned originally. Rather, it was hoped that in the Friedel-Crafts reaction on 3-chlorophenanthrene, the acetyl group would enter position 9. Our previous investigations had shown that the phenanthrylalkamines carrying the alkamine side chain in position 9 are decidedly more active than the corresponding 3-isomers (2), and we expected that this would be true also with phenanthrylalkamines containing a nuclear chlorine. Thus, in order to arrive at compounds of formula II, it appeared necessary to prepare the starting material, the 3-chloro-9-acetylphenanthrene (VIII) by total synthesis. We prepared first 3-chloro-9-phenanthrenecarboxylic acid (V) by the Pschorr method, employing *o*-nitrophenylacetic acid and *p*-chlorobenzaldehyde. The yields of acid V were lower than generally observed in the Pschorr synthesis when the nitro group, instrumental in the ring closure, is located in the aromatic aldehyde. This corroborates the results obtained by Mayer and Balle (3) in the preparation of phenanthrene derivatives from *o*-nitrophenylacetic acid. The intermediate cinnamic acid derivative III loses water readily, even by recrystallization from ethanol, to form lactam IV which we also prepared by condensing *p*-chlorobenzaldehyde with oxindole, and which proved to be very resistant to hydrolyzing agents. Phenanthroic acid V was then converted by the method of Arndt and Eistert (4) *via* diazo ketone VI either to 3-chloro-9-ω-bromoacetylphenanthrene (VII) or according to Wolfrom and Brown (5) to 3-chloro-9-acetylphenanthrene (VIII).

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXXII.

In the foregoing communication (1) we described the formation of 3-chloro-6-acetylphenanthrene in a yield of 60% in the Friedel-Crafts reaction with



acetyl chloride and 3-chlorophenanthrene in a nitrobenzene medium. No 9-acyl derivative could be found among the by-products. We find now that by employing *s*-tetrachloroethane as reaction medium, the course of this reaction is considerably altered.[3] We obtained in a 20–25% yield 3-chloro-9-acetylphenan-

[3] In the choice of this solvent we were influenced by similar experiments of Bachmann and Cronyn (6) in the tetrahydrophenanthrene series.

threne, and in about 30% yield a seemingly isomeric ketone which had after purification by crystallization and sublimation, the constant m.p. 103–104°. By bromination of this product it became apparent, however, that it is a double compound of the two ketones. The brominated substance could be separated by fractional crystallization into approximately equal amounts of two ω-bromoacetyl derivatives which yielded on catalytic debromination 3-chloro-6-acetylphenanthrene and 3-chloro-9-acetylphenanthrene. The structure of the latter was proved by oxidizing it with sodium hypochlorite to an acid identical with 3-chloro-9-phenanthrenecarboxylic acid prepared by the Pschorr method, and by direct comparison with the methyl ketone prepared therefrom.

Two amino alcohols of type II, the dihexylamino derivative (SN 10908)[4] and the diheptylamino derivative (SN 9161) were prepared from 3-chloro-9-ω-bromoacetylphenanthrene by treatment with the appropriate amine and subsequent reduction of the resulting amino ketone with aluminum isopropoxide.

SN 10908 (Q 2) and SN 9161 (Q 1) do not differ in their effectiveness towards *P. gallinaceum* from the corresponding chlorine-free 9-alkamines (2a) as much as the analogous pairs in the phenanthryl-3-alkamine series (1). They do not differ appreciably from the corresponding 3-chlorophenanthryl-6-alkamines (1). They are, however, four times as effective as the corresponding 9-chlorophenanthryl-3-alkamines (SN 13454, SN 10230) in which the positions of the alkamine side chain and the chlorine atom are reversed (7, 8, 9). The two amino alcohols described in this paper do not show any prophylactic activity against sporozoite induced *gallinaceum* malaria (9).

Acknowledgment. We are indebted to Mr. Edward A. Garlock, Jr. for carrying out the microanalyses, and to Dr. R. C. Elderfield for the supply of large quantities of 3-chlorophenanthrene. We wish to thank Heyden Chemical Corporation for furnishing us with *p*-chlorobenzaldehyde.

EXPERIMENTAL[5]

o-Nitrophenylacetic acid. The procedure of Mayer and Balle (3) with a few modifications, was used in this preparation. To a stirred solution of 51 g. of commercial sodium methoxide and 120 cc. of ethyl oxalate in 250 cc. of absolute ethanol was added during forty-five minutes, 110 cc. of *o*-nitrotoluene. The mixture was boiled under reflux for fifteen minutes, cooled somewhat, diluted with about 100 cc. of water, and steam passed in until all volatile material was removed. The almost clear solution (volume about 1000 cc.) was treated with 60 cc. of 30% hydrogen peroxide while keeping the temperature below 30°. After gas evolution had ceased the reaction mixture was filtered, the filtrate acidified with concentrated hydrochloric acid, and the precipitated material recrystallized from about 1200 cc. of water (Norit). The yield of acid melting at 136–139° was 60 g. The reported melting point is 141°.

α-(o-Nitrophenyl)-p-chlorocinnamic acid. To an ice-cooled solution of 7.1 g. of sodium in 100 cc. of absolute ethanol was added with stirring 55 g. of *o*-nitrophenylacetic acid.

[4] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph.

[5] All melting points given are uncorrected.

After adding 250 cc. of dry ether, the sludge was stirred mechanically for one hour and left in the ice-box overnight. The sodium salt was collected, washed with absolute ethanol-ether, and dried in a vacuum desiccator (56.5 g. yield). A mixture of 28 g. of this sodium *o*-nitrophenylacetate, 19 g. of *p*-chlorobenzaldehyde, 2.5 g. of fused zinc chloride, and 100 cc. of acetic anhydride was heated on the steam-bath for fifteen to twenty hours. Excess acetic anhydride was decomposed with 100 cc. of water. Further dilution with water and cooling in ice yielded a semisolid product which, on recrystallization from glacial acetic acid, gave 14.9 g. of nitro acid melting at 196–199°. After one recrystallization from acetic acid and one from methanol, it melted at 199–200.5°; light yellow, prismatic rods.

Anal. Calc'd for $C_{15}H_{10}ClNO_4$: C, 59.32; H, 3.32.
Found: C, 59.56; H, 3.74.

p-Chlorobenzaloxindole (*IV*). A hot solution of 5.1 g. of the above nitro acid in 16 cc. of conc'd NH_4OH and 34 cc. of water was added to a mixture of 34 g. of ferrous sulfate, 102 cc. of water, and 85 cc. of conc'd NH_4OH heated to 80–90°. The mixture was then maintained at 85–90° for about ten minutes and filtered through Filter-Cel. Acidification of the filtrate with acetic acid yielded 3.4 g. (air-dried) of α-(*o*-aminophenyl)-*p*-chlorocinnamic acid (III) of m.p. 138–140° with effervescence. The melt solidified and remelted at 170–180°. The yield of III could be reproduced even in large scale runs. Upon recrystallization from ethanol, it underwent dehydration to IV of m.p. 188–190°; yellow needles.

Anal. Calc'd for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94.
Found: C, 70.30; H, 4.27.

The same compound was obtained in 60% yield when 0.5 g. of oxindole (10), 0.5 g. of *p*-chlorobenzaldehyde, two drops of piperidine, and 100 cc. of ethanol were refluxed together for fifteen hours. It melted at 185–188°. A mixture m.p. with the sample of m.p. 188–190° was 186–189°.

3-Chloro-9-phenanthrenecarboxylic acid (*V*). To 80 cc. of 5 *N* sulfuric acid, mechanically stirred, and cooled to −3° to 2°, was added a homogeneous suspension of 5 g. of III, 3 g. of sodium nitrite, 75 cc. of water, and 2 cc. of conc'd NH_4OH during twenty minutes. After an additional hour of stirring at 0° to 5°, 20–30 cc. of ethanol and 5 g. of copper-bronze were added, and the mixture was heated to 70–80° (stirring) for one-half hour. The precipitate was collected and alkali-soluble material leached from the copper with hot dilute sodium hydroxide. The alkaline filtrate yielded, on acidification, V (1.4 g. of m.p. 249–251° after one recrystallization from glacial acetic acid). Sublimation in a high vacuum followed by two recrystallizations from ethanol gave small needles of m.p. 250–252°.

Anal. Calc'd for $C_{15}H_9ClO_2$: C, 70.18; H, 3.53.
Found: C, 69.83; H, 3.95.

3-Chloro-9-phenanthroyl chloride. A mixture of 5 g. of V, 5 cc. of dry benzene, and 5 cc. of thionyl chloride was refluxed for two hours. Solvent and excess reagent were removed *in vacuo* and the residual acid chloride sublimed in a high vacuum; yield 5.1 g., m.p. 154–156°. Two recrystallizations from benzene gave the constant m.p. 153–154°; long needles.

Anal. Calc'd for $C_{15}H_8Cl_2O$: C, 65.49; H, 2.93.
Found: C, 65.34; H, 3.03.

3-Chloro-9-ω-bromoacetylphenanthrene (*VII*). To a stirred mixture (0° to 5°) of 100 cc. of an ether solution of diazomethane (from 10 g. of nitrosomethylurea) and 50 cc. of dry benzene, was added 5.0 g. of the above finely-divided acid chloride during forty-five minutes. The mixture was stirred for one hour at 0° to 5° and for five hours without cooling, and allowed to stand overnight. After cooling to 0°, the solid 3-chloro-9-phenanthroyldiazomethane (VI) was collected; 4.5 g. of m.p. 150–151.5° with gas evolution. It was stirred in suspension with 100 cc. of dioxane, while 4 cc. of 48% HBr in 4 cc. of dioxane was added during ten minutes (temperature 20–25°). After stirring for an additional one-half hour, 2.5 g. of potassium carbonate in about 5 cc. of water was added and the dioxane evaporated *in vacuo* at a bath temperature of 50–70°. The residue was partitioned between warm benzene and water, the benzene layer dried over sodium sulfate and concentrated to 15–20 cc. On addition of ligroin (30–60°), the bromo ketone separated in a yield of 4.7 g.,

m.p. 122–126°. Two recrystallizations from ethyl acetate (Norit) gave prismatic rods of m.p. 127–128°.

Anal. Calc'd for $C_{16}H_{10}BrClO$: C, 57.61; H, 3.02.
Found: C, 57.71; H, 3.42.

3-Chloro-9-acetylphenanthrene (VIII). (a) From VI and (b) from the Friedel-Crafts reaction on 3-chlorophenanthrene. (a) To a solution of 0.5 g. of VI in 15 cc. of chloroform was added dropwise with shaking, 1.5 cc. of 55% HI. After ten minutes the chloroform was washed with water, 10% sodium carbonate solution, and again with water, dried over sodium sulfate and evaporated to dryness. The residue, on sublimation in a high vacuum followed by two recrystallizations from methanol yielded 0.25 g. of ketone, m.p. 115–116°; blades.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35.
Found: C, 75.16; H, 4.50.

(b) A mixture of 16 g. of aluminum chloride, 70 cc. of *s*-tetrachloroethane, and 10 cc. of acetyl chloride was stirred at 10–15° while adding to it during twenty minutes, 12 g. of 3-chlorophenanthrene in 30 cc. of *s*-tetrachloroethane. Stirring was continued for one hour at 10° and for two hours at 0° to 5°. The complex was collected, washed with a little benzene, and decomposed in cold dilute HCl. The resulting material was dried in benzene (sodium sulfate) and the oil remaining after evaporation of solvent was dissolved in 75–100 cc. of hot methanol, yielding 4.9 g. of ketone of m.p. 110–113°. It was identical with the VIII synthesized as described above.

The methanol filtrate yielded 3.0 g. of product melting at 93–103°, which, when recrystallized had the constant m.p. 103–104°. By bromination (see below) it was found to consist of about equal quantities of 3-chloro-6- and 3-chloro-9-acetylphenanthrenes. On recrystallization or fusion of a 1:1 mixture of these ketones, a product melting at 103–104°, and giving no depression with the Friedel-Crafts product of m.p. 103–104°, was obtained. High vacuum sublimation did not alter the melting point.

The foregoing Friedel-Crafts experiment represents the best in a series of about twenty runs. The yields of VIII were quite variable and appeared to depend somewhat on the aluminum chloride used. In some runs only the fraction melting at 103–104° was obtained.

Bromination of the fraction melting at 103–104°. To 15 g. of crude double compound (m.p. 96–100°) in 125 cc. of dry ether was added 9.4 g. of bromine in about twenty minutes (stirring). After stirring an additional hour at room temperature and cooling in ice, 16 g. of precipitate was collected. It was dissolved in 300 cc. of boiling benzene and the solution allowed to stand at room temperature for five hours, then in the ice-box overnight. The product which separated (6 g. of m.p. 197–200°) was identical with 3-chloro-6-ω-bromoacetylphenanthrene (1). The benzene filtrate was concentrated to 40–50 cc., diluted with 95 cc. of ligroin (30–60°) and the mixture cooled thoroughly, yielding 7.0 g. of bromo ketone of m.p. 119–124°. After recrystallization from ethyl acetate the m.p. was 126–127° and was unchanged when mixed with 3-chloro-9-ω-bromoacetylphenanthrene, prepared by the Pschorr and Arndt-Eistert reactions. However, with 3-chloro-10-ω-bromoacetylphenanthrene (11) of m.p. 126.5–127°, it gave a 20–25° depression.

The same compound (VII) was prepared in a yield of 90% by the bromination of pure 3-chloro-9-acetylphenanthrene, isolated as the first fraction in the acetylation of 3-chlorophenanthrene above.

Debromination of 3-chloro-9-ω-bromoacetylphenanthrene. A mixture of 1.0 g. of VII, 0.5 g. of palladium-charcoal (5% Pd), and 50 cc. of absolute ethanol absorbed one mole of hydrogen in twenty-five minutes. After warming the mixture on the steam-bath, the catalyst was removed and the filtrate concentrated to about 10 cc., whereupon 0.5 g. of VIII of m.p. 114–115.5° separated. This ketone (0.5 g.) was oxidized by heating it under reflux for three hours with 35 cc. of potassium hypochlorite solution (prepared from 1.0 g. of "HTH"). The resulting 3-chloro-9-phenanthrenecarboxylic acid crystallized from acetic acid in needles of m.p. 251–253°. It was identical with a pure synthetic sample previously described.

3-Chloro-9-(2-dihexylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 10908). A mixture of 6.0 g. of VII, 7.0 g. of dihexylamine, 24 cc. of dry ether, and 6 cc. of acetone was shaken mechanically for one to two hours and left in the ice-box overnight. The precipitate of dihexylamine hydrobromide was filtered, the filtrate evaporated to dryness *in vacuo* and the residual amino ketone reduced with 25 cc. of 3 *N* aluminum isopropoxide (12). After 1.5–2 hours, the isopropanol was evaporated *in vacuo* and the reddish residue partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water, dried over sodium sulfate, and made acidic to Congo Red with dry gaseous hydrogen chloride. The amino alcohol hydrochloride eventually crystallized in a yield of 4.0 g., m.p. 152–157°. An additional 0.4 g. was recovered from the filtrate. After one recrystallization from acetone-ether and one from acetone, it appeared as clusters of rods of m.p. 164–165.5°.

Anal. Calc'd for $C_{28}H_{39}Cl_2NO$: C, 70.57; H, 8.25.
Found: C, 70.81; H, 8.47.

3-Chloro-9-(2-diheptylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 9161). This compound was prepared like the foregoing one; yield from 5.6 g. of VII, 3.7 g., m.p. 135–139°. It crystallized from acetone-ether in rectangular plates of m.p. 137–138.5°.

Anal. Calc'd for $C_{30}H_{43}Cl_2NO$: C, 71.40; H, 8.59.
Found: C, 71.41; H, 8.93.

SUMMARY

Two amino alcohols derived from 3-chlorophenanthrene, and carrying the alkamine side chain in position 9 have been described.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XVII.[1,2] AMINO ALCOHOLS OF THE TYPE —CHOHCH$_2$NR$_2$ DERIVED FROM 3-CHLORO-10-ACETYLPHENANTHRENE

EVERETTE L. MAY AND ERICH MOSETTIG

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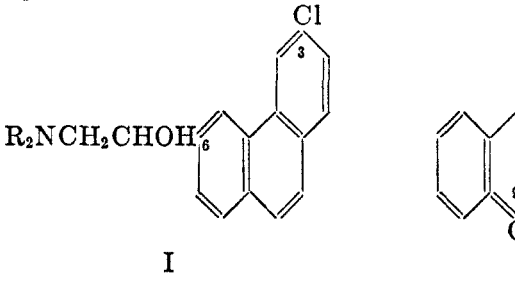
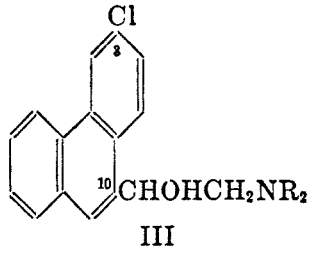
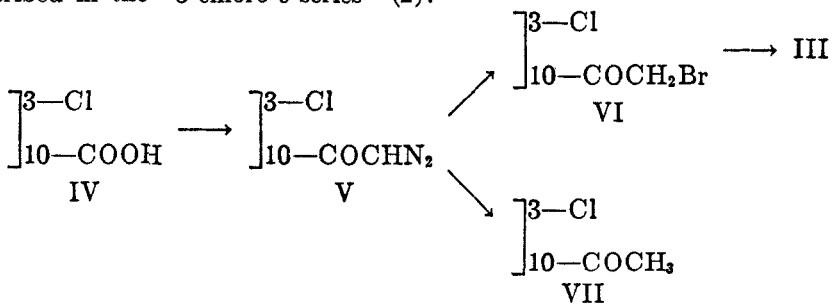
In the two foregoing communications (1, 2) we have shown that by introduction of a chlorine atom into 3-phenanthrylethanolamines and 9-phenanthrylethanolamines one arrives at alkamines I and II which exhibit a considerably stronger effectiveness against *Plasmodium gallinaceum* than the corresponding parent compounds.





The known 3-chloro-10-phenanthrenecarboxylic acid (IV) (3) lent itself to convenient preparation of the starting material for the synthesis of the alkamines of formula III. This synthesis proceeded very much in the manner described in the "3-chloro-9-series" (2):



[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXXIII.

The amino alcohols of type III (diamylamino to dinonylamino derivative inclusive)[3] appear biologically (4, 5) very similar to the 3-chlorophenanthrene-9-alkamines (2) and 3-chloro-6-alkamines (1). SN 1375, the 3-chloro-10-(2-diheptylamino-1-hydroxyethyl)phenanthrene, was investigated clinically. It is superior to quinine in *vivax* malaria.[4] The first four drugs of this series did not show any activity against sporozoite-induced *gallinaceum* malaria (5).[5]

Acknowledgment. We wish to thank Mr. E. A. Garlock, Jr. for carrying out the microanalyses.

EXPERIMENTAL[6]

3-Chloro-10-phenanthrenecarboxylic acid (IV) was prepared by the Pschorr synthesis according to the directions of Nylén (3). The crude acid (m.p. 285–287°) was used in the subsequent reaction.

3-Chloro-10-phenanthroyl chloride. A mixture of 17 g. of IV, 25 cc. of thionyl chloride, and 30 cc. of dry benzene was refluxed for two hours. Evaporation of the solvent and excess reagent *in vacuo*, followed by sublimation of the residue in a high vacuum (150–170°/0.05 mm.) gave a 16.8 g. yield of acid chloride of m.p. 154–156.5°. It crystallized from benzene in long needles, m.p. 154–156°.

TABLE I

AMINO ALCOHOLS

SN	$C_{14}H_8$ {3-Cl, 10-$CHOHCH_2$—}	M.P., °C	SOLVENT	APPEARANCE	FORMULA	CALC'D		FOUND	
						C%	H%	C%	H%
9130	$N(C_6H_{11})_2 \cdot HCl$	207 –209	Abs. EtOH-acetone	Needle clusters	$C_{28}H_{35}Cl_2NO$	69.62	7.87	69.62	8.18
10456	$N(C_8H_{13})_2 \cdot HCl$	183.5–185[a]	Abs. EtOH-acetone	Prisms	$C_{32}H_{43}Cl_2NO$	70.57	8.25	70.59	8.48
9160	$N(C_7H_{15})_2 \cdot HCl$	184 –186	Abs. EtOH-acetone	Needle clusters	$C_{36}H_{59}Cl_2NO$	71.40	8.59	71.27	8.71
10901	$N(C_8H_{17})_2 \cdot HCl$	177 –178	Acetone	Needles	$C_{32}H_{47}Cl_2NO$	72.16	8.90	72.18	8.93
9466	$N(C_9H_{19})_2 \cdot HCl$	176 –177.5	Abs. EtOH-acetone	Needle clusters	$C_{34}H_{51}Cl_2NO$	72.83	9.17	72.94	8.97

[a] Resolidified and melted again at 191–193°.

Anal. Calc'd for $C_{15}H_8Cl_2O$: C, 65.49; H, 2.93.
Found: C, 65.48; H, 3.02.

3-Chloro-10-ω-bromoacetylphenanthrene (VI). In order to obtain the 3-chloro-10-phenanthroyl chloride in more finely-divided form, 8.0 g. of the sublimed material was dissolved in hot benzene, the solution cooled quickly, and 7.0 g. of acid chloride collected. The filtrate (about 75 cc.) was added during ten minutes to 130 cc. of a stirred, ice-cooled ether solution of diazomethane (from 13 g. of nitrosomethylurea). The 7.0 g. of solid acid chloride was then added under the same conditions during forty-five minutes, after which the

[3] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph. These numbers are shown in Table I.

[4] The clinical study with this drug will be published by the several groups to whom this compound was assigned by the Board of Coordination of Malaria Studies.

[5] SN 9466 was not included in these tests because of lack of material.

[6] All melting points given are uncorrected.

mixture was stirred for five hours without cooling and left standing overnight. After thorough cooling in ice the diazo ketone (V) was collected; yield 7.0 g., m.p. 150–152° with gas evolution. This product (4.8 g.) was stirred in suspension with 50 cc. of dioxane at 15–25°, while 4 cc. of 48% HBr in 4 cc. of dioxane was added during fifteen minutes. After an additional ten minutes the turbid solution was treated dropwise with 1.1 g. of sodium carbonate in a little water, and the dioxane evaporated *in vacuo* at a bath temperature not exceeding 65°. The residue was partitioned between warm benzene and water, the benzene layer dried over sodium sulfate and concentrated to about 25 cc. On addition of an equal volume of ligroin (30–60°), the bromo ketone separated in a yield of 4.9 g., m.p. 121–123.5°. It crystallized from benzene or ethyl acetate (Norit) in large needles of m.p. 126.5–127°.

Anal. Calc'd for $C_{16}H_{10}BrClO$: C, 57.61; H, 3.02.
Found: C, 57.91; H, 3.15.

3-Chloro-10-acetylphenanthrene (VII), (a) from the diazo ketone V and (b) and from the bromo ketone VI. (a) The procedure of Wolfrom and Brown (6) was used in this preparation. A solution of 0.5 g. of V in 15 cc. of chloroform was treated with 1.5 cc. of 55% HI. After shaking for ten minutes, the chloroform was washed successively with water, dilute sodium carbonate solution and water, dried, and solvent evaporated. The residue, on high vacuum sublimation, yielded 0.25 g. of ketone. After recrystallization from methanol followed by another sublimation, it melted at 139–140°; needles.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35.
Found: C, 75.48; H, 4.59.

Upon mixing VII with 3-chloro-y-acetylphenanthrene (1) of m.p. 138–139°, the m.p. was 105–120°.

(b) A mixture of 0.5 g. of VI, 0.5 g. of palladium-charcoal (5% Pd), and 30 cc. of absolute ethanol absorbed 0.9 mole of hydrogen in one hour. The reduction mixture was warmed, filtered, and the filtrate concentrated to 8–10 cc. On cooling to room temperature, 3-chloro-10-acetylphenanthrene separated in a yield of 0.2 g., m.p. 138.5–140°.

Amino alcohols. A mixture of one mole of VI, 2 moles of secondary amine and dry ether-acetone (5 cc. of a 4:1 mixture per gram of VI) was shaken mechanically for one to two hours, cooled in ice, and filtered. The filtrate was evaporated to dryness *in vacuo* and the residual amino ketone reduced with 3 *N* aluminum isopropoxide (7) (5 cc. per gram of VI). After two hours, the isopropanol was evaporated *in vacuo* and the dark red residue partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water, dried over sodium sulfate, and acidified to Congo Red by addition of 20% alcoholic HCl. The flocculent precipitate of amino alcohol hydrochloride was collected and washed with acetone-ether. The yields, based on bromo ketone, varied from 55–65%.

SUMMARY

Five amino alcohols derived from 3-chlorophenanthrene, and carrying the alkamine side chain in position 10 have been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XVI.[1] PHENYL HALOGENATED PROPADRINES

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INTRODUCTION

The effect of nuclear substituents such as OH, CH_3, OCH_3, etc. on the sympathomimetic properties of propadrine, $C_6H_5CH(OH)CH(NH_2)CH_3$, has been studied (1, 2, 3, 4, 5, 6). However, reports of the effect of nuclear halogen substitution in this series are still meager. Only *p*-chloropropadrine has been studied and reported as possessing three times the toxicity and one twenty-fifth the pressor activity of the unsubstituted amine (2).

Reported studies of the effect of halogens in related amines are also limited (7, 8, 9, 10, 11). Consequently, adequate correlation of the effect of the presence of a halogen atom in the phenyl nucleus on physiological activity is difficult.

This investigation was undertaken to make available for pharmacological study a series of propadrines containing halogens substituted in various positions of the aromatic nucleus in order to make possible a more complete correlation of the physiological effect of halogen substitution with the effect produced by other nuclear substituents already studied in this series.

The synthesis of *o*-, *m*-, and *p*-fluoro-; *o*-, *m*-, and *p*-chloro; and *o*-, *m*-, and *p*-bromopropadrine, $XC_6H_4CH(OH)CH(NH_2)CH_3$, was undertaken. *p*-Chloropropadrine, though previously reported, was included for comparison.

The synthesis depended, first, on the preparation of the appropriately substituted propiophenones. The *p*-halogen ketones were prepared by the Friedel-Crafts reaction from the appropriate phenyl halide and propionyl chloride. The *o*- and *m*-halogen ketones were obtained by replacing the amino group of *o*- and *m*-aminopropiophenones, respectively, with the desired halogen atom.

Nitration of propiophenone produced both the *o*-and *m*-mononitro derivatives. Since large amounts of these intermediates were required, a study of the optimum conditions for their preparation was made. Their reduction to the aminopropiophenones was conveniently accomplished by catalytic hydrogenation in benzene. The water formed in the reaction was drawn off, and the amine hydrochloride was precipitated in good yield by passing hydrogen chloride into the benzene solution. This method gave improved yields over those reported using tin and hydrochloric acid (3, 12, 13), iron and acetic acid (12), or stannous chloride and hydrochloric acid (14). The ketone group was unaffected under the conditions used.

Attempts to replace the amino group with fluorine by heating the dry dia-

[1] For Amino Alcohols XV, see Hartung and Foster, *J. Am. Pharm. Assoc., Scientific Ed.*, **35**, 15 (1946).

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zonium fluoroborates, according to the procedure of Schiemann and Winkelmüller (15), gave poor yields and formed large amounts of tar. However, it was found during this investigation that if the diazonium fluoborates were dropped into a stirred inert liquid hydrocarbon (toluene for the *m*-compound or heptane for the *o*-isomer) maintained at a temperature above the decomposition point of salt, satisfactory yields of the fluoropropiophenones were obtained.

The halogenated ketones were next converted into their corresponding isonitroso derivatives by a general reaction (1, 2, 3, 16) using butyl nitrite and hydrogen chloride in ether,

$$XC_6H_4COCH_2CH_3 \xrightarrow[HCl]{CH_3(CH_2)_2CH_2ONO} XC_6H_4COCCH_3 \quad (\text{NOH above the C})$$

It has well been established that isonitroso ketones of this type can be hydrogenated in good yields to the corresponding amino alcohols with a palladium-charcoal catalyst in ethanolic hydrogen chloride (1, 2, 3, 4). However reports in the literature indicated that difficulty in preventing the loss of halogen from the ring during hydrogenation might be encountered.

Edkins and Linnell (9), in an attempt to prepare *p*-chloro- and *p*-bromopropadrine by the hydrogenation of the corresponding *p*-halogen aminopropiophenone, $XC_6H_4COCH(NH_2)CH_3$, with a palladium-charcoal catalyst in acid aqueous medium, obtained only propadrine, the halogen being removed from the ring. They further found that hydrogenation in an acidified ethanolic solution gave, instead of the desired products, the corresponding *p*-halogen benzoic acid in almost theoretical yield. The formation of these acids was explained by a hydrolysis involving a break of the carbon chain at the carbonyl group,

$$XC_6H_4CCH(NH_2)CH_3 \longrightarrow XC_6H_4C{=}C(NH_2)CH_3 \longrightarrow$$

(O above the first C; OH below the second C)

$$XC_6H_4COOH + CH_3CH_2NH_2$$

In our work no formation of halogen benzoic acids was observed.

Hartung, Munch, and Crossley (2) observed, in the hydrogenation of *p*-chloroisonitrosopropiophenone, that in the presence of water the aromatic chlorine atom was removed, but they were able to obtain the desired *p*-chloropropadrine by avoiding the use of water in the hydrogenation solvent.

In this work the isonitroso ketones were hydrogenated until three equivalents of hydrogen had been taken up. The fluorine atom did not possess the reported lability of chlorine and bromine in the presence of water, and the desired *o*-, *m*-, and *p*-fluoropropadrines were obtained as their hydrochloride salts. By the use of anhydrous conditions, it was also possible to obtain *m*- and *p*-chloropropadrine hydrochloride. However the *o*-chloro isomer was not successfully isolated in pure form; the hydrogenation product appeared to be a mixture of the hydrochlorides of the dehalogenated amino ketone, C_6H_5COCH-

$(NH_2)CH_3 \cdot HCl$, and *o*-chloropropadrine whose separation by recrystallization was not successful.

Hydrogenation of the *m*-bromoisonitroso ketone resulted in the loss of bromine from the ring, the product isolated being the dehalogenated amino ketone salt. The reduction of *o*- and *p*-bromoisonitroso ketones was not tried in this investigation.

The authors are indebted to Dr. Karl H. Beyer of Sharp and Dohme for a physiological evaluation of the halogenated propadrines. Compared to *l*-epinephrine as unity the observed potencies were: propadrine 1/185, *o*-fluoropropadrine 1/80, *m*-fluoropropadrine 1/102, *p*-fluoropropadrine 1/275, *m*-chloropropadrine 1/133, *p*-chloropropadrine 1/550. It is of particular interest to note that a fluorine atom introduced into the ortho position of the parent molecule doubles the pressor activity, but introduced into the para position it decreases the activity.

EXPERIMENTAL

All melting points recorded were taken with an Anschütz thermometer; all boiling points are uncorrected.

Synthesis of Phenyl Halogenated Propiophenones

A summary of the data for all the phenyl substituted propiophenones is given in Table I.

p-Halogen propiophenones. Propionyl chloride (92.5 g., 1 mole) was allowed to react with a stirred mixture of anhydrous aluminum chloride (147 g., 1.1 mole) and the phenyl halide (1 mole) in 400 cc. of dry carbon disulfide by the usual Friedel-Crafts procedure. After refluxing for 2 to 3 hours, the complex (surrounded by a cold water-bath) was decomposed in the presence of the solvent by the dropwise addition of water with stirring. Any suspended aluminum salts were dissolved by the addition of hydrochloric acid. The reaction mixture was filtered, the carbon disulfide layer was separated, and the aqueous layer was extracted with carbon disulfide. The combined carbon disulfide solutions were washed, dried over anhydrous calcium chloride, and the solvent was distilled off through a short column. The residue was distilled *in vacuo* in a Claisen flask.

Nitration of propiophenone. After investigating a number of nitrating mixtures, the best results were obtained by the addition of propiophenone to fuming nitric acid according to the method described by Hartung *et al.* (3, 17).

In order to determine the effect of temperature on the course of the reaction, a series of runs was carried out in which the temperature was varied. The results are summarized in Table II. At each temperature studied, two ½-mole portions of propiophenone were nitrated in two separate batches, the products of the two runs being combined and purified together. This procedure decreased the time during which the initial portions of the ketone remained in contact with the acid, thereby reducing the possibility of oxidation.

The general nitration procedure was as follows: Into 425 cc. of stirred fuming nitric acid (*d.* 1.5, straw colored), previously cooled to the desired temperature by an ice-bath, was dropped 67 g. (0.5 mole) of propiophenone. The temperature of the reaction was controlled by the rate of the addition of the ketone and by external cooling. Temperatures of $-10°$ to $-5°$ were obtained by the addition of solid carbon dioxide chips to the reaction mixture. Stirring was continued for 5 to 10 minutes after all the ketone had been added. The reaction mixture was then poured into 2 liters of ice and water and the product which separated was filtered off with suction. The filtrate was extracted with benzene and the benzene was warmed and used to dissolve the product on the filter. The benzene solution was washed with water, then with 10% sodium hydroxide until the washings were practically colorless, and finally with water. After drying over anhydrous calcium chloride, the ben-

zene was distilled off through a short column. The residue, consisting of the *o*- and *m*-nitropropiophenones, was washed with cold 95% ethanol to remove the soluble *o*-isomer. The insoluble *m*-isomer was recrystallized from 95% ethanol.

TABLE I

PHENYL SUBSTITUTED PROPIOPHENONES

$XC_6H_4COCH_2CH_3$ X =	M.P., °C.	B.P.		YIELD %	SEMICARBAZONE
		°C.	Mm.		M.P., °C.
p-F		215–217[j]	atm.	86	196–197
m-F[a]		94–96	4–5	68	187–188
o-F		87–91[k]	12–13	47	143–144
p-Cl	34–35[e]	114–118[l]	2	76	176–177[p]
m-Cl[a]	45–46			73	179–180
o-Cl[a]		105–106	12	85	172–173
p-Br	45–46[f]	137–140[m]	2	58	170–171
m-Br	37.5–40[g]			44	182–183[q]
o-Br		116–118[n]	10–11	77	178–179[r]
m-NO_2	98–99[h]			*	188–189
o-NO_2[b]		152–155[o]	2–3	*	183–184[s]
m-$NH_2 \cdot HCl$[c]	198–199[i]			83–88	
o-$NH_2 \cdot HCl$[d]	184–185			73–79	

[a] Not previously reported.

[b] Commanducci and Pescitelli (24) reported *o*-nitropropiophenone, which they claimed to have obtained by the addition of propiophenone to "136%" nitric acid at 40°, to be a crystalline compound, m.p. 85°. However subsequent workers (3, 13, 14), as well as the present work, have shown it to be an oil. From our experiments, as well as those of other colleagues, it develops that if the temperature of the nitration is allowed to rise above 25–35°, the reaction becomes vigorous and difficult to control, brown fumes are evolved, and a large amount of oxidation takes place.

[c] Melts with decomposition. Oxime, m.p. 112–113°. *p*-Toluenesulfonamide, m.p. 102–103°; reported m.p. 97° (12).

[d] Melts with decomposition. Free amine, m.p. 44–45°; reported m.p. 45–46° (13), 46–47° (14), 46° (12). Oxime, m.p. 87–88°; reported m.p. 88–89° (14). Commanducci and Pescitelli (24) reduced their purported *o*-nitropropiophenone and obtained an amine whose hydrochloride decomposed at 200°. However since they probably did not have *o*-nitropropiophenone, they probably did not have *o*-aminopropiophenone.

Reported melting points: [e]35–36° (25), 35.8° (9); [f]44–45° (25), 47° (9); [g]36° (12); [h]97° (3) 100° (26), 98–100° (12), 98° (24); [i]202.5 (3); [p]175–176° (27); [q]180° (12); [r]182° (12) [s]182–183° (14).

Reporting boiling points: [j]105–107° at 22 mm. (28); [k]95–99° at 19 mm. (29); [l]115° at 3 mm. (2), 152° at 30 mm. (9); [m]167° at 30 mm. (9); [n]125° at 12 mm. (12), 135–140° at 16 mm. (30); [o]153–160° at 7–10 mm. (3), 161° at 10–11 mm. (14), 175° at 25 mm. (13).

* See Table II.

Distillation of the solvent from the alcohol washings left the *o*-isomer as a brown oil which was placed in the refrigerator for several days to allow the separation of any dissolved *m*-isomer. On distillation *in vacuo*, *o*-nitropropiophenone was obtained as a yellow oil which darkened on standing.

Upon acidification, the sodium hydroxide washings gave a yellow crystalline precipitate which was soluble in sodium bicarbonate solution and which probably consisted of the nitrobenzoic acids, though its identity was not further investigated.

m-Aminopropiophenone hydrochloride. A solution of 53.7 g. (0.3 mole) of *m*-nitropropiophenone in 300 cc. of thiophene-free benzene was hydrogenated with 3 g. of a palladium-charcoal catalyst at room temperature and at approximately atmospheric pressure in an apparatus similar to that described by Hartung (18). The theoretical amount of hydrogen required to reduce the nitro group was absorbed in 13 hours, after which the uptake of hydrogen ceased. The catalyst was filtered off, and the benzene solution was dried over anhydrous sodium sulfate. Upon saturation of the dried solution with hydrogen chloride, the amine hydrochloride precipitated. It was filtered off, washed with benzene, and then with acetone until practically colorless. The compound was used without further purification.

When the hydrogenation was carried out in a glass container under an initial pressure of 300 pounds, the reaction required only $\frac{1}{4}$ to $\frac{1}{5}$ of the time needed under atmospheric pressure.

o-Aminopropiophenone hydrochloride. *o*-Nitropropiophenone (53.7 g., 0.3 mole) was hydrogenated in 100 cc. of benzene with 5 g. of catalyst at an initial pressure of 300 pounds, and the product was isolated as described for the *m*-isomer. It was necessary to heat the reduction mixture to start the uptake of hydrogen. The theoretical amount of hydrogen

TABLE II

EFFECT OF TEMPERATURE ON THE NITRATION OF PROPIOPHENONE

NITRATION TEMPERATURE, °C	YIELD (FROM 1 MOLE OF PROPIOPHENONE)		
	Nitropropiophenone		NaOH Extractive[a] g.
	Meta %	Ortho %	
−10 to −5	60	30	2
10	51.4	37.4	4
15	47.5	36.8	7
20	41.3	35.2	9
25	35.8	34.0	16

[a] Crude acidic material obtained upon acidification of the NaOH washings. Soluble in $NaHCO_3$ solution.

was absorbed in approximately 7 hours. *o*-Aminopropiophenone hydrochloride was obtained as a pinkish powder which darkened on standing.

m-Fluoropropiophenone. The amino group was replaced with fluorine by a modification of the method of Schiemann and Winkelmüller (15).

A mixture of 83.5 g. (0.45 mole) of *m*-aminopropiophenone hydrochloride, 45 cc. of concentrated hydrochloric acid, and 200 cc. of water was diazotized with a solution of 34.5 g. (0.5 mole) of sodium nitrite in 60 cc. of water. Then 120 cc. of cold commercial 48% fluoboric acid was rapidly added with vigorous stirring. The diazonium fluoborate which separated as a thick suspension was collected on a filter, washed with cold ethanol, then with ether, and dried in a vacuum desiccator over concentrated sulfuric acid. The diazonium fluoborate was obtained as a pinkish powder in a yield of 88%, decomposition point 97–98°. It was converted into *m*-fluoropropiophenone by the following procedure:

In a 1-liter, 3-neck flask fitted with a sealed stirrer and a reflux condenser connected to a gas absorption trap for the evolved boron trifluoride, was placed 300 cc. of dry toluene. To the stirred and boiling toluene was added in small portions 98 g. (0.39 mole) of the dry diazonium fluoborate, each portion being added after the initial evolution of gas from the previous portion had subsided. The toluene solution was decanted from a small amount of tar which separated during the reaction, cooled, and washed with water, 5% sodium

hydroxide, and again with water. After drying over calcium chloride, the toluene was distilled off and the residual oil was distilled *in vacuo*. *m*-Fluoropropiophenone was obtained as a light yellow oil which formed colorless crystals on cooling in an ice-bath.

o-Fluoropropiophenone. *o*-Aminopropiophenone hydrochloride was converted into its diazonium fluoborate by the method used for the *m*-isomer. After the addition of the fluoboric acid to the diazotized amine, it was necessary to stir the mixture in the ice-bath for about 10 minutes before the diazonium salt precipitated. After filtration, a second crop was obtained by saturating the filtrate with sodium fluoborate. The total yield was washed with cold alcohol, then with ether, and dried in a vacuum desiccator over sulfuric acid; yield 79%, decomposition point 81–82°.

The diazonium fluoborate was converted to *o*-fluoropropiophenone as described for the *m*-isomer, substituting dry heptane for the toluene. The *o*-fluoropropiophenone was obtained as a light yellow oil which did not solidify on cooling in an ice-bath.

m-Chloropropiophenone. This ketone was prepared by the Sandmeyer reaction by a procedure similar to that described by Marvel and McElvain for *o*-chlorotoluene (19).

A mixture of 92.7 g. (0.5 mole) of *m*-aminopropiophenone hydrochloride, 300 cc. of water, and 200 cc. of concentrated hydrochloric acid was diazotized at 0° to 5° by the addition of a solution of 34.5 g. (0.5 mole) of sodium nitrite in 75 cc. of water. The cold diazonium solution was then poured into a well stirred cold cuprous chloride solution previously prepared in the following manner:

An alkaline solution of sodium meta sulfite (33.3 g., 0.175 mole) and 40 g. (1 mole) of sodium hydroxide in 300 cc. of water was added over a 10-minute period to a stirred hot solution of 162.3 g. (0.65 mole) of crystallized copper sulfate and 76 g. (1.3 mole) of sodium chloride in 500 cc. of water. The mixture was allowed to cool to room temperature. The cuprous chloride which precipitated as a white powder was washed with water by decantation and dissolved in a mixture of 200 cc. of concentrated hydrochloric acid and 150 cc. of water.

The reaction mixture, containing a solid addition compound, was allowed to warm up to room temperature and then was heated at 70° with stirring until the evolution of nitrogen ceased (½ to 1 hour). The crude *m*-chloropropiophenone was distilled with steam from the reaction mixture and extracted from the distillate with benzene. The benzene solution was washed with water, then with 5% sodium hydroxide, again with water and dried over calcium chloride. After distilling off the benzene, *m*-chloropropiophenone was obtained as colorless crystals by recrystallization of the crude product from dilute alcohol (charcoal).

o-Chloropropiophenone. This ketone was prepared by the method used for the *m*-isomer from *o*-aminopropiophenone hydrochloride. The crude product obtained was distilled *in vacuo* and yielded the *o*-chloro ketone as a light yellow oil.

m- and o-Bromopropiophenone. These ketones were also obtained by the Sandmeyer reaction from *m*- and *o*-aminopropiophenone hydrochloride.

The aminopropiophenone hydrochloride (92.7 g., 0.5 mole) was neutralized with 20% sodium hydroxide and the free amine which separated from the aqueous portion was removed, washed with water, and added to a mixture of 84 cc. of concentrated sulfuric acid and 350 cc. of water. This mixture was diazotized, and the diazonium compound was converted to the corresponding bromopropiophenone with a cuprous bromide-hydrobromic acid solution by the procedure used for the preparation of the *m*-chloropropiophenone.

The cuprous bromide used was obtained by replacing the sodium chloride in the procedure described for the preparation of cuprous chloride with 72 g., (0.7 mole) of sodium bromide. After washing with water by decantation, the cuprous bromide was dissolved in a mixture of 200 cc. of 48% hydrobromic acid and 100 cc. of water.

m-Bromopropiophenone was obtained as colorless crystals by recrystallization of the crude product from dilute alcohol (charcoal).

o-Bromopropiophenone was obtained as a light yellow oil by distillation of the crude product *in vacuo*.

Oxidation of the halogenated propiophenones. The position of the halogen in the ring in the nine halogenated propiophenones was verified by permanganate oxidation of the ketones to the corresponding halogenated benzoic acids.

Synthesis of Isonitroso Ketones

Nitrosation of ketones. The halogenated propiophenones were nitrosated by the general procedure described by Levin and Hartung (16), using *n*-butyl nitrite as the nitrosating

TABLE III
ISONITROSO KETONES

$XC_6H_4COCCH_3$ ‖ NOH, X =	RECRYSTALLIZATION SOLVENT	M.P., °C	YIELD, %	FORMULA	NITROGEN %	
					Calc'd	Found
p-F	Toluene	106.5–107.5	88.4	$C_9H_8FNO_2$	7.73	7.73
m-F	Dilute Alcohol	109–110	85.6	$C_9H_8FNO_2$	7.73	7.50
o-F	Heptane	82–82.5	73.6	$C_9H_8FNO_2$	7.73	7.62
p-Cl[a]	Toluene	119–120	89.4	$C_9H_8ClNO_2$	7.09	7.06
m-Cl	Toluene	94–95	82.7	$C_9H_8ClNO_2$	7.09	6.94
o-Cl	Heptane	102.5–103	76.0	$C_9H_8ClNO_2$	7.09	6.96
p-Br[b]	Toluene	132–133	86.8	$C_9H_8BrNO_2$	5.79	5.75
m-Br	Toluene	104.5–105	76.4	$C_9H_8BrNO_2$	5.79	5.74
o-Br	Heptane	101–101.5	71.1	$C_9H_8BrNO_2$	5.79	5.72

[a] Reported m.p. 114° (9), 122–123° (2).
[b] Reported m.p. 113.6° (9).

TABLE IV
HYDROGENATION OF ISONITROSO KETONES

$XC_6H_4COCCH_3$ ‖ NOH, X =	KETONE MOLES	HYDROGENATION SOLVENT CC.	CATALYST[a] G.	HYDROGEN UPTAKE, EQUIV.	
				1st + 2nd eq. hrs.	3rd eq. hrs.
p-F	0.05	200	2	1.7	16
m-F	0.05	200	2	1.6	6
o-F	0.03	150	2	1.7	4
p-Cl	0.085	500	3	3	17.5
m-Cl	0.05	500	2	2	8
o-Cl	0.05	400	2	2.5	17.5
m-Br	0.05	400	2	3	6

[a] Initial amount; additional catalyst added after the 1st 2 equivalents of hydrogen had been taken up.

agent. After completion of the reaction, the ether was removed by distillation from a steam-bath, the distillation then being continued under reduced pressure to remove the butyl alcohol formed in the reaction. The residue was allowed to stand overnight in a vacuum desiccator over sulfuric acid, and was recrystallized from a suitable solvent. The experimental data on the various isonitroso ketones are given in Table III.

Synthesis of Amino Alcohols

Catalytic hydrogenations. The isonitroso ketones were hydrogenated in 2 *N* absolute ethanolic hydrogen chloride at approximately atmospheric pressure using an active[3] palladium charcoal catalyst, in a manner described elsewhere (1, 2, 22). The first two equivalents of hydrogen were taken up rapidly and the absorption of hydrogen ceased with the appearance of a precipitate of the amino ketone hydrochloride. In the case of the three fluorine compounds, fresh catalyst and sufficient water to dissolve the precipitate was added, and hydrogenation was continued until the third equivalent of hydrogen had been taken up. In the case of the three chlorine compounds and the *m*-bromo compound, fresh catalyst but no water was added at the two-thirds stage, and the precipitate was dissolved by blowing steam over the agitated reduction flask. In all cases the third equivalent of hydrogen was taken up much more slowly than the first two, and it was necessary to heat the reduction flask with steam from time to time to complete the absorption of the third equivalent of hydrogen. The reduction data are given in Table IV.

After filtering off the catalyst, the solvent was removed by distillation under reduced pressure. The crude hydrochloride was dried over sulfuric acid in a vacuum desiccator and washed with ether to remove most of the color. Recrystallization from absolute alcohol gave colorless crystals. Second crops of crystals were obtained by the addition of ether to the mother liquors.

TABLE V

NUCLEAR HALOGENATED PROPADRINE HYDROCHLORIDES

$XC_6H_4CH(OH)CH(NH_2)CH_3 \cdot HCl$ X =	M.P., °C	YIELD, %	FORMULA	CHLORINE[b] %	
				Calc'd	Found
p-F	225–226	78	$C_9H_{13}ClFNO$	17.24	17.27
m-F	210–211	68	$C_9H_{13}ClFNO$	17.24	17.38
o-F	231–232	65	$C_9H_{13}ClFNO$	17.24	17.39
p-Cl	244–245[a]	69	$C_9H_{13}Cl_2NO$	15.96	16.17
m-Cl	183–184	63	$C_9H_{13}Cl_2NO$	15.96	16.17

[a] Reported m.p. 245° (2).

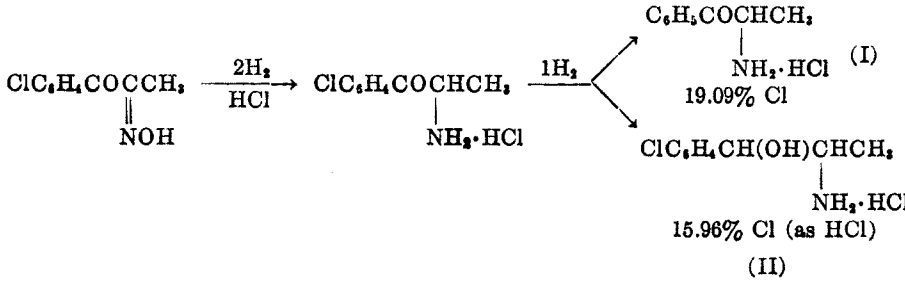
[b] Determined (as Cl^-) by the Volhard method.

When hydrogenation is incomplete, intermediate amino ketone hydrochlorides are produced; and they may be characterized by their reduction of Fehling's solution, by their melting with decomposition or effervescence, and by their undergoing spontaneous condensation in alkaline solution to dihydropyrazines which are readily oxidized to the more stable pyrazine derivatives (1, 2, 3, 23). Since these tests are not given by pure amino alcohols, they were used to determine whether the compounds isolated from the hydrogenations were the desired amino alcohols. In addition, permanganate oxidation to the corresponding halogenated benzoic acid was used to verify the presence and position of the halogen in the ring.

Hydrogenation of o-, m- and p-fluoroisonitrosopropiophenone; and m- and p-chloroisonitrosopropiophenone. By the hydrogenation of these compounds as described under *catalytic hydrogenations*, the corresponding halogenated propadrines were obtained as their hydrochlorides. Tests for the presence of amino ketone were negative, and permanganate oxidation produced the corresponding halogenated benzoic acids.

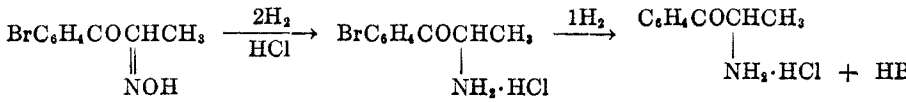
[3] The preparation of an active palladium catalyst with the aid of sodium acetate has been previously described (20, 21).

Hydrogenation of o-chloroisonitrosopropiophenone. The hydrogenated product, after several recrystallizations from absolute alcohol, melted at 182–183°, and further recrystallization produced no significant rise in melting point. It reduced Fehling's solution, gave ray pazine test, gave only a small yield of *o*-chlorobenzoic acid on permanganate oxidation, and contained 17.20% of chlorine (as HCl). Since the absorption of 3 equivalents of hydrogen could proceed in several directions,



the above evidence suggested that the product was a mixture of compounds I and II.

Hydrogenation of m-bromoisonitrosopropiophenone. The hydrogenated product, after several recrystallizations from sec.-butyl alcohol, gave colorless crystals, m.p. 164–165°. On permanganate oxidation it produced benzoic acid, indicating that the bromine had been removed. It gave tests for an amino ketone, reduced Fehling's solution, and formed a dihydropyrazine, m.p. 94–96°. Gabriel (23) reported the m.p. 99–100° for the dihydropyrazine obtained from $C_6H_5COCH(NH_2)CH_3$. Quantitative analysis for halogen (as HX) indicated the product to be a mixture of the hydrochloride and hydrobromide salts of α-aminopropiophenone; and qualitative analysis verified the presence of bromide ion. This evidence seemed to indicate that the hydrogenation apparently had taken the course:



SUMMARY

1. In order to study the physiological effect of nuclear halogen substitution in propadrine (phenylpropanolamine), the synthesis of a series of monohalogenated propadrines was undertaken.

2. For this purpose, nine halogenated propiophenones containing F, Cl, or Br in the *o*-, *m*-, and *p*-positions were prepared.

3. These ketones were then nitrosated to obtain their isonitroso derivatives.

4. Catalytic hydrogenation of the *o*-, *m*-, and *p*-fluoro, and the *m*- and *p*-chloro isonitroso ketones produced the desired corresponding halogenated propadrines. Hydrogenation of the *o*-chloro and *m*-bromo intermediates resulted in the removal of the halogen from the ring.

5. A study was made of the effect of temperature on the nitration of propiophenone.

6. A preliminary pharmacological examination of the five halogenated propadrines obtained indicated that only fluorine in the ortho position produces any appreciable increase in the pressor activity of the parent molecule.

BALTIMORE, MD.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

COMPOUNDS OF PHARMACEUTICAL INTEREST FROM 4-METHOXY-1-NAPHTHYLAMINE

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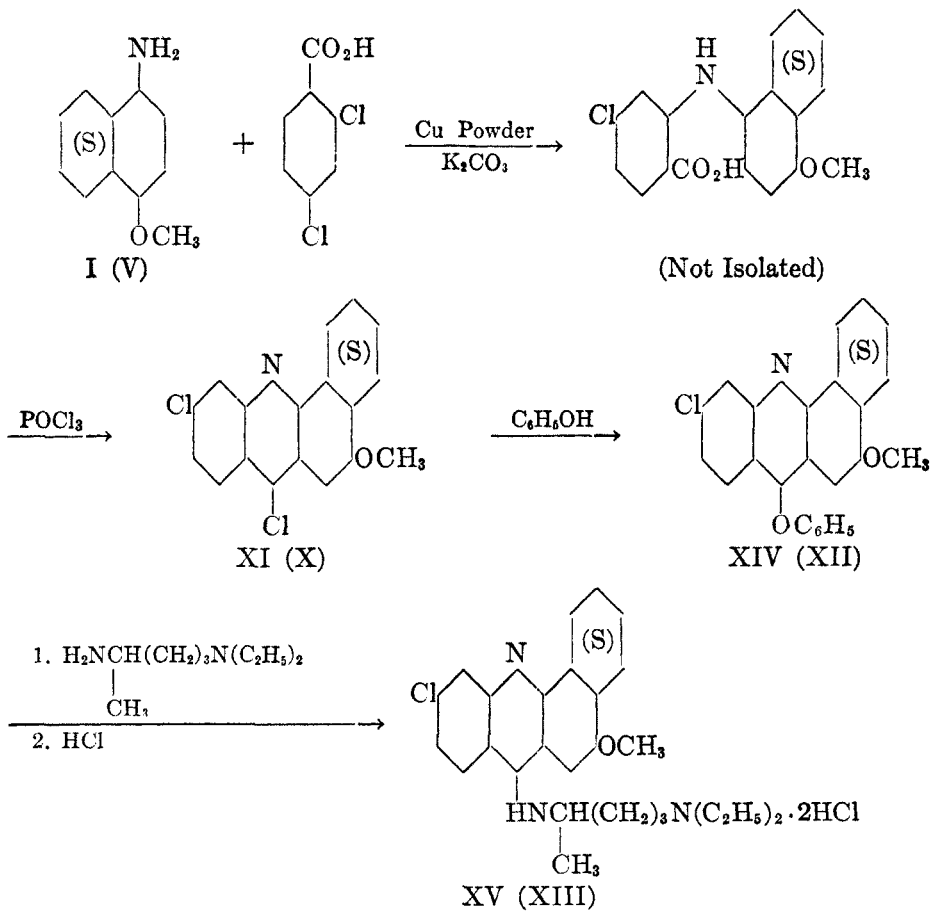
From 4-methoxy-1-naphthylamine and its tetrahydride, 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine, have been prepared substituted benz(c)acridines and benzo(h)quinolines similar to compounds of known antimalarial activity.

Benz(c)acridines. The above amines were condensed with 2,4-dichlorobenzoic acid, the resulting acids were cyclized to chlorobenz(c)acridines with phosphorus oxychloride, and the amine side chain introduced by heating the chloroacridines with 5-diethylamino-2-pentylamine in the presence of phenol.



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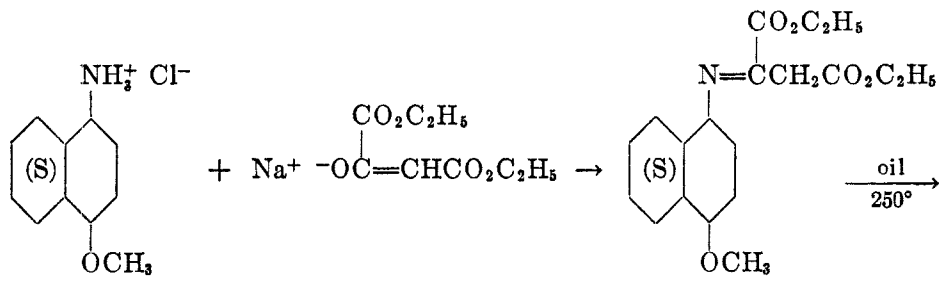
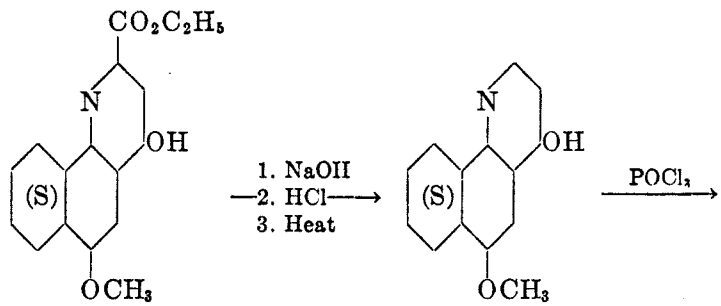
(S) indicates a saturated ring when the tetrahydronaphthylamine is used as the starting material. The numerals in parentheses refer to these hydrogenated compounds.

It has been demonstrated that the phenoxy compound is an intermediate in the last step of the Atabrine synthesis (1) and in this work small amounts of the phenoxy intermediates (XII, XIV) were isolated when the reaction conditions were too mild.

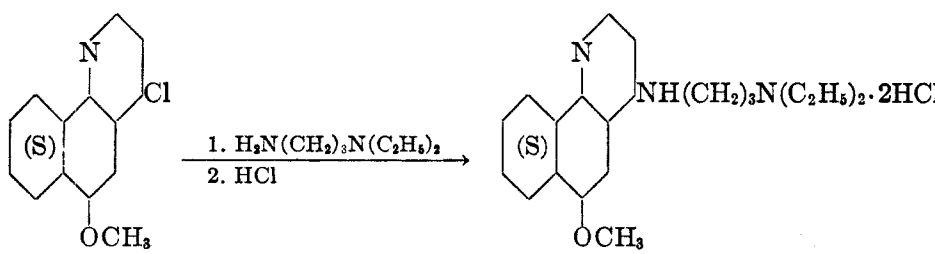
Benzo(h)quinolines. A successful method of preparing benzo(h)quinolines from the naphthylamines was developed employing Mueller and Hamilton's modification (2) of the Conrad-Limpach reaction. Condensation of the amines with sodium ethyl ethoxalylacetate gave compounds which were readily cyclized by heating in mineral oil. Saponification, decarboxylation, and chlorination then yielded chlorobenzo(h)quinolines which were treated with 3-diethylaminopropylamine to obtain the desired products. Such compounds without the 6-methoxyl group have been described in a patent (3) as possessing antimalarial activity.



XXIII (XVII)



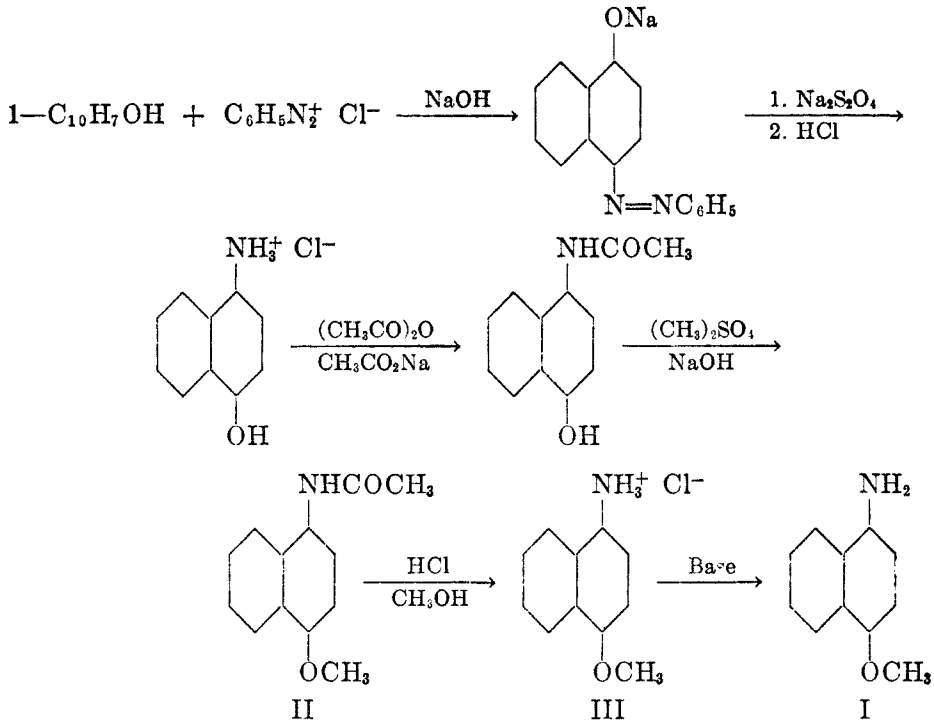
XXIV (XVIII) XXVI (XX)



XXVII (XXI) XXVIII (XXII)

The original plan for the preparation of the chlorobenzo(h)quinolines involved submitting the amines to a Skraup reaction, converting the benzo(h)quinolines so obtained to N-oxides, treating these with phosphorus oxychloride and separating the resulting mixture of 2- and 4-chlorobenzo(h)quinolines (4). The yields from the Skraup reaction were so poor that this approach was abandoned.

4-Methoxy-1-naphthylamine (I) used in the above syntheses was prepared by coupling *alpha*-naphthol with benzenediazonium chloride; the azo dye was reduced, acetylated, methylated, and deacetylated to produce the amine hydrochloride, which gave the free base on neutralization.



4-Methoxy-5,6,7,8-tetrahydro-1-naphthylamine (V) was prepared by a high-pressure catalytic (nickel) hydrogenation of 1-acetamido-4-methoxynaphthalene (II) in dioxane solution. The product was deacetylated to the amine hydrochloride which gave the free base on neutralization.

It was originally planned to prepare the tetrahydroamine (V) by reducing 1-methoxy-4-nitroso-5,6,7,8-tetrahydronaphthalene, but the latter compound could not be obtained. During nitrosation of 1-methoxy-5,6,7,8-tetrahydronaphthalene hydrolysis of the ether linkage occurred giving 4-nitroso-5,6,7,8-tetrahydro-1-naphthol. This demethylation is similar to the reaction observed by Meyer and co-workers (5) who found that nitrous acid acts on 1-naphthyl methyl ether with loss of the methyl group.

Pharmacological testing. Tested by oral administration three times per day

for five days on malaria-infected ducklings only compound XXVIII showed activity (Q 0.32).

Acknowledgments. We wish to express our thanks to Eli Lilly and Company and the Purdue Research Foundation for the financial support of this investigation, and to the former for pharmacological tests.

EXPERIMENTAL

4-Methoxy-1-naphthylamine (I). *Alpha*-naphthol was coupled with benzene diazonium chloride and the azo dye reduced to 4-hydroxy-1-naphthylamine hydrochloride according to the method described in Organic Syntheses (6). The product melted at 265–267° (decomp.). It was converted to 4-acetamido-1-naphthol (7) in 75% yield by using Fieser's general procedure (8). Methylation with dimethyl sulfate gave 4-acetamido-1-methoxynaphthalene (9) (II) in 90% yield. This was hydrolyzed to 4-methoxy-1-naphthylamine hydrochloride (III) [m.p. 278–279° (decomp.) from ethanol] in 90% yield by refluxing for six hours with a 1 *N* solution of hydrochloric acid in methanol. Neutralization of a decolorized solution of the hydrochloride with sodium carbonate gave 4-methoxy-1-naphthylamine (10).

4-Acetamido-1-methoxy-5,6,7,8-tetrahydronaphthalene (IV). Forty grams of II was dissolved in 600 ml. of dioxane and 5 g. of finely ground U.O.P. nickel catalyst added. The II was reduced at 130–140° and 1500–2000 pounds hydrogen pressure. After recrystallization from ethanol, the white product melted at 188–189°; yield 70–85%.

Anal. Calc'd for $C_{13}H_{17}NO_2$: C, 71.18; H, 7.81.
Found: C, 71.10, 71.38; H, 7.74, 7.66.

4-Methoxy-5,6,7,8-tetrahydro-1-naphthylamine (V). The hydrochloride of this amine was prepared from IV by refluxing an alcoholic hydrochloric acid solution for six hours; yield of crude product 95%, m.p. 250–253° (decomp.). The free base, m.p. 61°, was obtained on neutralization. It oxidized rapidly in air and turned purple. It was analyzed as the stable hydrochloride.

Anal. Calc'd for $C_{11}H_{15}NO \cdot HCl$: C, 61.82; H, 7.55.
Found: C, 62.15, 61.74; H, 7.67, 7.81.

It was originally planned to prepare the tetrahydroamine by reducing 1-methoxy-4-nitroso-5,6,7,8-tetrahydronaphthalene, but the latter compound could not be obtained. During nitrosation of 1-methoxy-5,6,7,8-tetrahydronaphthalene, hydrolysis of the ether linkage occurred giving 4-nitroso-5,6,7,8-tetrahydro-1-naphthol (VI) in 68.5% yield; m.p. 161–163°; literature value 163° (11).

4-Amino-5,6,7,8-tetrahydro-1-naphthol (VII). The moist crude nitrosonaphthol (VI), 40 g., was dissolved in 450 ml. of conc'd ammonium hydroxide and 800 ml. of water. The reddish brown solution was filtered to remove resinous material, and hydrogen sulfide gas was bubbled into the filtrate until the precipitation of the amino compound was complete. The free base was filtered, washed with cold water, dissolved in 50 ml. of conc'd hydrochloric acid and 750 ml. of water, and decolorized. Upon reprecipitation of the amine with ammonia a white product was obtained which rapidly oxidized in air; yield 67%. A sample was purified by vacuum sublimation, m.p. 144–146° (decomp.); literature value 146–147° (12).

4-Acetamido-5,6,7,8-tetrahydro-1-naphthol (VIII). Acetylation of VII was accomplished by the same procedure used to prepare II; yield 90%, m.p. 188–189°.

This compound was also prepared by the catalytic hydrogenation of 4-acetamido-1-naphthol. Twenty-eight grams was dissolved in 250 ml. of dry dioxane and 5 g. of finely ground U.O.P. nickel catalyst added. The reduction was accomplished at 1400 pounds hydrogen pressure and 130°. The dioxane solution was reduced in volume by vacuum distillation and a 75% yield of crude material isolated. The mixed melting point of samples of the compound prepared by both methods showed no depression.

Anal. Calc'd for $C_{13}H_{15}NO_2$: C, 70.19; H, 7.37.
Found: C, 70.32, 70.44; H, 7.47, 7.20.

This naphthol was methylated in an alkaline solution with methyl sulfate to produce IV identical with the product obtained by reduction of II.

4-Acetamido-1-ethoxy-5,6,7,8-tetrahydronaphthalene (IX). The ethylation of VIII was carried out similarly to the methylation of the same compound. The temperature of the reaction mixture had to be raised to 40° for complete reaction. A 70% yield of crude product was obtained. Three recrystallizations from ethanol and water gave a white product with m.p. 195–196°.

Anal. Calc'd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.15; N, 6.09.
Found: C, 71.7, 71.9; H, 8.35, 8.22; N, 6.23, 6.26.

7,10-Dichloro-5-methoxy-1,2,3,4-tetrahydrobenz(c)acridine (X). Sixteen and one-half grams (0.093 mole) of V, 16.2 g. (0.085 mole) of 2,4-dichlorobenzoic acid (Heyden Chemical Corporation), 12 g. of anhydrous potassium carbonate, and 0.75 g. of reduced copper powder were suspended in 100 ml. of butanol. The mixture was stirred and heated to reflux. Carbon dioxide was given off very rapidly at first but at the end of three hours the rate was slow. The addition of 1 g. more of potassium carbonate and 0.3 g. of copper-bronze powder did not cause the rate of evolution to increase. At the end of seven hours heating, 25 ml. of 20% sodium hydroxide was added and the butanol removed by steam distillation. The dark purple residue could not be decolorized; and, on cooling, a tarry mass separated, leaving the water layer practically colorless. A filterable solid was obtained by heating to redissolve the tar and then bubbling carbon dioxide into the hot solution. The dark powder had the melting range 200–225° and was practically insoluble in organic solvents. The yield of crude 4-chloro-N-(4-methoxy-5,6,7,8-tetrahydro-1-naphthyl)anthranilic acid was 40%.

Twenty-two and eight-tenths grams of crude acid and 82.5 ml. of distilled phosphorus oxychloride were refluxed and stirred for four hours. At the end of this time the volume of the solution was reduced one-half by vacuum distillation. The residue was poured slowly into a beaker containing 650 g. of ice, 500 ml. of conc'd ammonium hydroxide and 500 ml. of chloroform. After hydrolysis of the excess phosphorus oxychloride was complete, the product was isolated by extraction with three 60-ml. portions of chloroform. Decolorization, drying, and evaporation of the chloroform solution gave a crude product, which, after recrystallization from benzene-heptane, was yellow and melted at 190–191°; yield 8.8 g., 39%.

Anal. Calc'd for $C_{18}H_{15}Cl_2NO$: C, 65.05; H, 4.55; N, 4.22.
Found: C, 65.01, 65.13; H, 4.48, 4.52; N, 4.30, 4.36.

7,10-Dichloro-5-methoxybenz(c)acridine (XI). The preparation of 4-chloro-N-(4-methoxy-1-naphthyl)anthranilic acid from I and 2,4-dichlorobenzoic acid followed the same procedure used with the hydrogenated amine.

The preparation of this compound was also completed starting with III and using a sufficient excess of potassium carbonate to liberate the amine *in situ*. The dark colored crude acid melted in the range 275–280° and was obtained in yields of 35–40%.

A white, acidic by-product, melting range 225–242°, was also obtained. This was soluble in sodium bicarbonate solution and contained chlorine but no nitrogen. It was not identified.

The crude anthranilic acid was treated with phosphorus oxychloride as in the preparation of X. The yellow product was recrystallized from a benzene-heptane mixture, m.p. 199–200°, yield 46%.

Anal. Calc'd for $C_{18}H_{11}Cl_2NO$: C, 65.86; H, 3.36; N, 4.27; Cl, 21.64.
Found: C, 65.84, 65.79; H, 3.41, 3.36; N, 4.28, 4.36; Cl, 21.56, 21.63.

10-Chloro-5-methoxy-7-phenoxy-1,2,3,4-tetrahydrobenz(c)acridine (XII). A mixture of 3.32 g. (0.01 mole) of X and 10 g. of phenol was heated in an oil-bath at 120–125° until solution was complete. To this hot solution was added 1.74 g. (0.011 mole) of rectified 5-diethylamino-2-pentylamine (Winthrop Chemical Company). The mixture seemed to solid-

ify at first but the solid soon dissolved to form a red-orange solution. Heating was continued for three hours, and then the hot solution was poured slowly into a cold mixture of 50 ml. of ether and 50 ml. of 10% sodium hydroxide solution. A small amount of insoluble material separated and was removed by filtration. This insoluble material melted above 335° and was assumed to be the acridone resulting from hydrolysis of X, since treatment of the material with phosphorus oxychloride reconverted it to X. The remaining reaction products were separated from the alkaline solution by repeated extractions with ether. The ether extracts were dried and the ether evaporated leaving a yellow solid. Three recrystallizations from heptane gave a product melting at 193–195° which was shown by analysis to be the yellow phenoxy intermediate (XII).

Anal. Calc'd for $C_{24}H_{20}ClNO_2$: C, 73.93; H, 5.17; N, 3.59.
Found: C, 73.93, 74.00; H, 5.21, 5.18; N, 3.61, 3.52.

10 - Chloro - 7 - (5 - diethylamino - 2 - pentylamino) - 5 - methoxy - 1,2,3,4 - tetrahydrobenz(c)acridine dihydrochloride (XIII). The heptane mother liquors from the above described reaction were evaporated leaving a brilliant yellow residue, m.p. 90–93°, which was the desired free base in a hydrated form. This hydrate was stable at room temperature, but lost water on standing in a desiccator over calcium chloride and changed to a gummy mass. It was not possible to obtain a crystalline sample of the anhydrous base. The most satisfactory procedure found for purifying the product was to recrystallize it from ethanol and water in the completely hydrated form. This material was then dissolved in ethanol and treated with hydrogen chloride gas until the solution was acid to Congo Red. Crystallization was induced by heating the ethanol solution to boiling and adding isopropyl ether to the first faint trace of cloudiness. The hydrated hydrochloride, yield 30%, was not hygroscopic, and it lost its water of crystallization only after prolonged heating at 140° at 15 mm. pressure in the presence of phosphorus pentoxide. This yellow hydrate showed a transition point with dehydration at 175–178°. The residue melted at 247–250° with decomposition.

Anal. Calc'd for $C_{27}H_{36}ClN_3O \cdot 2HCl$: C, 61.50; H, 7.27.
Found: C, 61.34, 61.49; H, 7.38, 7.42.

10-Chloro-5-methoxy-7-phenoxybenz(c)acridine (XIV). 7,10-Dichloro-5-methoxybenz-(c)acridine (XI) was treated with 5-diethylamino-2-pentylamine in the presence of phenol in the same manner as the tetrahydro compound (X). The yellow phenoxy intermediate was isolated from this reaction as before and recrystallized from heptane, m.p. 182–183°.

Anal. Calc'd for $C_{24}H_{16}ClNO_2$: C, 74.68; H, 4.18; N, 3.63.
Found: C, 74.82, 74.73; H, 4 55, 4 60; N, 4.00, 4.09.

10-Chloro - 7 - (5-diethylamino - 2 - pentylamino) - 5 - methoxybenz(c)acridine dihydrochloride (XV). The condensation of XI with 5-diethylamino-2-pentylamine was accomplished in seven hours at 135°. The yellow hydrochloride was recrystallized from ethanol-isopropyl ether, m.p. 233–235° (decomp.) with a transition point at 215–216°; yield 41%.

Anal. Calc'd for $C_{27}H_{32}ClN_3O \cdot 2HCl \cdot \frac{1}{2} H_2O$: C, 60.94; H, 6.64; Cl, 20.01.
Found: C, 60.93, 60.02; H, 6.81, 6.77; Cl, 19.97, 20.01.

6-Hydroxy-7,8,9,10-tetrahydrobenzo(h)quinoline (XVI). Since both 4-acetamido-1-methoxy-5,6,7,8-tetrahydronaphthalene (IV) and 4-acetamido-1-ethoxy-5,6,7,8-tetrahydronaphthalene (IX) were dealkylated by the conditions of the Skraup reaction, 4-acetamido-5,6,7,8-tetrahydro-1-naphthol (VIII) was used as the starting material. Thirty-one grams (0.15 mole) of VIII, 70 ml. (0.96 mole) of glycerol and 9.15 ml. (0.09 mole) of nitrobenzene were heated while stirring until complete solution was obtained. Thirty-nine ml. (0.7 mole) of conc'd sulfuric acid was added dropwise through the reflux condenser over a period of one hour. The reflux temperature gradually dropped from 144° to 133° during three hours. The mixture was poured over ice and diluted to 500 ml. The acid-insoluble tar was filtered off, and the filtrate was neutralized with 15% sodium hydroxide solution. A grayish white precipitate that turned dark on standing formed at the neutral point. Attempts to purify this fraction by alcohol or alkali extraction were unsuccessful. However, a white solid material was obtained when the product was

distilled at 1 mm. pressure. After three recrystallizations from alcohol, white plates, m.p. 257–258°, were obtained in 25–30% yields. This material was soluble in alkali and formed a hydrochloride, m.p. 270–272° (decomp.).

Anal. Calc'd for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.04.
Found: C, 78.30, 78.29; H, 6.68, 6.68; N, 7.05, 6.98.

Diethyl 2-(4-methoxy-5,6,7,8-tetrahydro-1-naphthylimino)succinate (XVII). The procedure of Mueller and Hamilton (2) was used to condense 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine hydrochloride and sodium ethyl ethoxalylacetate. A 93% yield of a brown solid was obtained. This was purified by recrystallization from methanol-water, m.p. 54°.

Anal. Calc'd for $C_{19}H_{25}NO_5$: C, 65.67; H, 7.26.
Found: C, 65.31, 65.65; H, 7.36, 7.34.

2-Carbethoxy-4-hydroxy-6-methoxy-7,8,9,10-tetrahydrobenzo(h)quinoline (XVIII). Ring closure was obtained by dropping XVII into mineral oil at 250°. The white crystalline solid that separated on cooling was washed free of oil with petroleum ether and purified for analysis by recrystallization from benzene; m.p. 212–214°; yield 75%.

Anal. Calc'd for $C_{17}H_{19}NO_4$: C, 67.74; H, 6.36.
Found: C, 68.05, 67.84; H, 6.55, 6.35.

2-Carboxy-4-hydroxy-6-methoxy-7,8,9,10-tetrahydrobenzo(h)quinoline (XIX). Twenty grams of XVIII was suspended in 500 g. of 10% sodium hydroxide solution and the mixture was stirred and heated on the steam-bath for two hours. Acidification with hydrochloric acid gave a 90% yield of the white acid which was not very soluble in organic solvents. A sample was recrystallized from a large volume of ethanol, m.p. 263–264° (decomp.).

Anal. Calc'd for $C_{15}H_{15}NO_4$: C, 65.90; H, 5.53.
Found: C, 65.88, 65.54; H, 5.62, 5.55.

4-Hydroxy-6-methoxy-7,8,9,10-tetrahydrobenzo(h)quinoline (XX). Two grams of XIX was ground with 0.5 g. of copper-chromite catalyst (13). The solid was heated in an oil-bath preheated to 250°. Ten minutes was usually sufficient time to obtain complete decarboxylation as determined by the rate of evolution of carbon dioxide. The black residue was powdered and extracted with 10 ml. of 10% sodium hydroxide solution. After filtration and decolorization, the basic solution was saturated with carbon dioxide to precipitate XX. Reprecipitation from alkali or recrystallization from ethanol-water gave a white product, m.p. 257–258°, yield 60–70%.

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.32; H, 6.60.
Found: C, 73.46, 73.59; H, 6.72, 6.66.

4-Chloro-6-methoxy-7,8,9,10-tetrahydrobenzo(h)quinoline (XXI). Two grams of crude XX was heated to reflux, 105–110°, for two hours with 20 ml. of phosphorus oxychloride. Ten milliliters of the solution was removed by vacuum distillation and the residue was poured slowly over 50 g. of ice. After hydrolysis of the excess phosphorus oxychloride at 0°, 5 ml. of conc'd hydrochloric acid was added, the solution was filtered, decolorized, and then neutralized at 20–30° with ammonium hydroxide. The gummy precipitate solidified on standing. It was very soluble in most organic solvents. Recrystallization from methanol-water gave a white product, m.p. 107°, yield 75%.

Anal. Calc'd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70.
Found: C, 67.93, 67.98; H, 5.62, 5.75.

4-(3-Diethylaminopropylamino)-6-methoxy-7,8,9,10-tetrahydrobenzo(h)quinoline dihydrochloride (XXII). A mixture of 0.25 g. of XXI and 0.31 g. (100% excess) of purified 3-diethylaminopropylamine (Sharples Chemicals Inc.) was refluxed for eight hours. The product gradually solidified during the later stages of heating. The cooled solid was washed with water to remove the excess amine, dissolved in ether, and extracted with 5% sodium hydroxide solution. The ether extract was then washed with dil. hydrochloric acid and the washings treated with alkali to precipitate the free base as a brown oil. An oily hydrochloride was obtained under anhydrous conditions in an ether solution. It reprecipitated as an oil from ethanol-isopropyl ether solution and finally crystallized on long standing in

the cold. Every effort to obtain a crystalline hydrated hydrochloride failed. The yellow anhydrous hydrochloride (yield 70%) melted at 252–254° (decomp.) and was very hygroscopic.

Anal. Calc'd for $C_{21}H_{21}N_3O \cdot 2HCl$: C, 60.86; H, 8.03; N, 10.14.
Found: C, 60.52, 60.43; H, 7.91, 7.95; N, 10.07, 9.98.

Diethyl 2-(4-methoxy-1-naphthylimino)succinate (XXIII). 4-Methoxy-1-naphthylamine hydrochloride (III) was treated with sodium ethyl ethoxalylacetate according to Mueller and Hamilton's procedure (2). The yellow Schiff base (yield 85%) was purified by recrystallization from methanol, m.p. 77°.

Anal. Calc'd for $C_{19}H_{21}NO_5$: C, 66.45; H, 6.17.
Found: C, 66.45, 66.36; H, 6.09, 6.19.

2-Carbethoxy-4-hydroxy-6-methoxybenzo(h)quinoline (XXIV). XXIII was dropped into five times its weight of preheated mineral oil in the same manner as in the preparation of XVIII. The yellow cyclized product was recrystallized from benzene; m.p. 180–181°, yield 88%.

Anal. Calc'd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09.
Found: C, 68.76, 68.83; H, 5.12, 5.23.

2-Carboxy-4-hydroxy-6-methoxybenzo(h)quinoline (XXV). XXIV was hydrolyzed to the acid by treatment with 10% sodium hydroxide as in the preparation of XIX. The acid was not very soluble in organic solvents, but a sample of the yellow compound was recrystallized for analysis from a large volume of ethanol, m.p. 253–255° (decomp.). The yield of crude acid was 77%. An alkali-insoluble residue (20%) was also obtained.

Anal. Calc'd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12.
Found: C, 66.78, 67.20; H, 4.36, 4.28.

4-Hydroxy-6-methoxybenzo(h)quinoline (XXVI). The decarboxylation of XXV was accomplished in the same manner as in the preparation of XX. The loss of carbon dioxide was not as rapid at 250–260° as it was with XX, and increasing the temperature to 270° gave a large amount of alkali-insoluble tar. The yield of white reprecipitated material was 46.5%. A pure sample, m.p. 269–270°, was obtained by recrystallization from methanol-water.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92.
Found: C, 74.33, 74.47; H, 5.19, 5.05.

4-Chloro-6-methoxybenzo(h)quinoline (XXVII). Chlorination of XXVI was accomplished by using phosphorus oxychloride as in preparation of XXI. The yield of crude product was 31.5%. An analytical sample recrystallized from methanol-water was yellow and melted at 101–102°.

Anal. Calc'd for $C_{14}H_{10}ClNO$: C, 68.99; H, 4.14.
Found: C, 68.76, 68.77; H, 4.27, 4.27.

4-(3-Diethylaminopropylamino)-6-methoxybenzo(h)quinoline dihydrochloride (XXVIII). XXVII was heated with an excess of purified 3-diethylaminopropylamine for eight hours. The product was worked up in a manner similar to that used for XXII. It was impossible to obtain a solid free base but the yellow anhydrous hydrochloride melted at 246–248° (decomp.), yield 70%.

Anal. Calc'd for $C_{21}H_{27}N_3O \cdot 2HCl$: C, 61.46; H, 7.10; N, 10.24.
Found: C, 61.22, 61.10; H, 6.96, 7.07; N, 10.09, 10.02.

Ethyl 3-(4-methoxy-5,6,7,8-tetrahydro-1-naphthylamino)crotonate (XXIX). A solution of 3.37 g. (0.02 mole) of 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine (V) in 4.0 g. (0.03 mole) of ethyl acetoacetate was allowed to stand sixteen hours at room temperature. The mixture first became cold but gradually warmed and finally had to be cooled. An immiscible layer of water separated and was removed. The product was dissolved in ether and the solution was extracted three times with 5% sodium hydroxide solution, washed with water to remove excess base, and dried. A dark brown solid was obtained from the ether, which, after recrystallization from ethanol and water, became white and melted at 81–82°, yield 70%.

Anal. Calc'd for $C_{17}H_{23}NO_3$: C, 70.59; H, 7.96.
Found: C, 70.54, 70.43; H, 8.04, 8.14.

4-Hydroxy-6-methoxy-2-methyl-7,8,9,10-tetrahydrobenzo(h)quinoline (*XXX*). Eighteen and three-tenths grams of XXIX was added slowly with stirring to 150 g. of paraffin oil preheated to 260°. The mixture was heated for five minutes after all foaming had ceased, then cooled, and the crystalline solid filtered out and washed with petroleum ether until free of oil. A 78.5% yield of crude material which melted 5° low, was isolated. The analytical sample recrystallized from methanol-water was white and melted at 273°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.03; H, 7.05.
Found: C, 74.04, 74.32; H, 7.19, 7.11.

4-Chloro-6-methoxy-2-methyl-7,8,9,10-tetrahydrobenzo(h)quinoline (*XXXI*). A mixture of 5.53 g. (0.025 mole) of XXX and 32 ml. of phosphorus oxychloride was refluxed for four hours. The excess phosphorus oxychloride was removed under reduced pressure, and the residue was poured into a mixture of 200 g. of ice. 150 ml. of ammonium hydroxide, and 150 ml. of chloroform. The chloroform layer was separated after the phosphorus oxychloride had completely hydrolyzed. The aqueous layer was extracted with fresh chloroform, and the extracts were combined and dried by shaking with calcium chloride. The chloroform was removed by distillation and left a dark residue (yield 51.5%). A sample purified for analysis by recrystallization from methanol was white and melted at 104–105°.

Anal. Calc'd for $C_{15}H_{16}ClNO$: C, 68.81; H, 6.17.
Found: C, 68.99, 69.19; H, 6.17, 6.24.

SUMMARY

4-Methoxy-1-naphthylamine and 4-methoxy-5,6,7,8-tetrahydro-1-naphthylamine have been used as starting materials to prepare heterocyclic compounds of pharmaceutical interest.

Benz(c)acridine benzologs of Atabrine, and 4-diethylaminopropylaminobenzo-(h)quinolines have been prepared from the amines.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

4-CHLORO-2-(3-PYRIDYLAMINO)BENZOIC ACID AND ITS CONVERSION TO 6-CHLORO-9-HYDROXY-PYRIDO[3,2-b]QUINOLINE[1]

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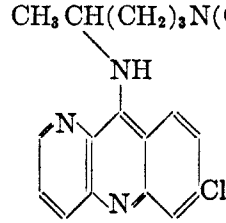
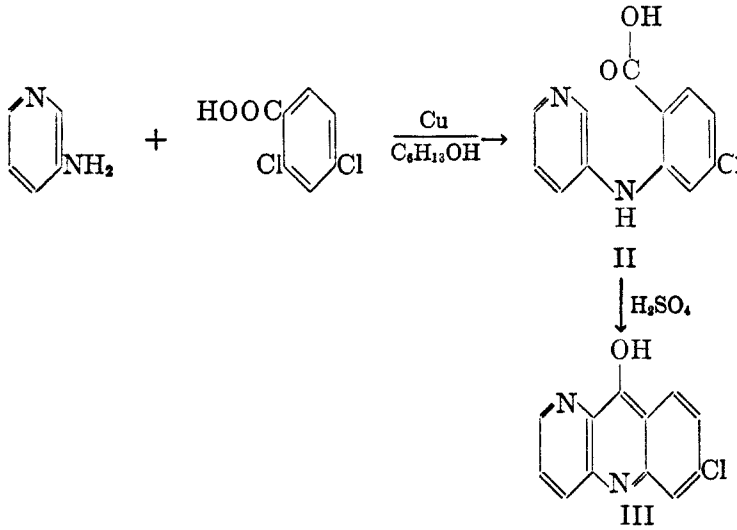
In view of the success of quinacrine (Atabrine) as a drug for the suppression of malaria, it was considered of interest to prepare an analog (I) in which one of the benzo rings was replaced by a pyrido ring. This substance would also have some structural features similar to another powerful antimalarial drug, pamaquine (Plasmochin).



I

The synthesis proposed for I followed the procedures successful for the preparation of quinacrine. 3-Aminopyridine[4] was condensed with 2,4-dichloro-



[1] The work described in this paper was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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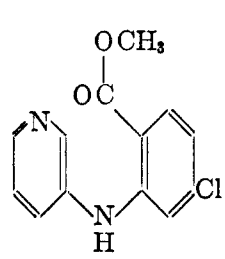
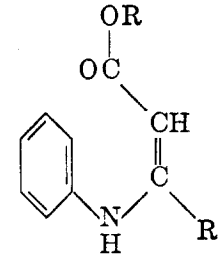
[4] We are grateful to Professor C. R. Hauser of Duke University for a sample of 3-aminopyridine.

benzoic acid to yield 4-chloro-2-(3-pyridylamino)benzoic acid (II). This acid was cyclized by treatment with concentrated sulfuric acid. In view of the established closure of β-aminopyridine in the α-position in the Skraup, Doebner-von Miller, and Doebner reactions (1), the cyclization of II has been presumed to occur at the same position to yield 6-chloro-9-hydroxypyrido [3,2-b] quinoline (III). Attempts to convert this material to the 6,9-dichloro compound by treatment with phosphorus oxychloride were unsuccessful, yielding only a black amorphous mass.

The ester (IV) of the acid II would have some formal resemblance to the β-anilinoacrylates (V) successfully cyclized by Conrad and Limpach (2) but attempts to cyclize IV to III by thermal treatment were unsucessful.

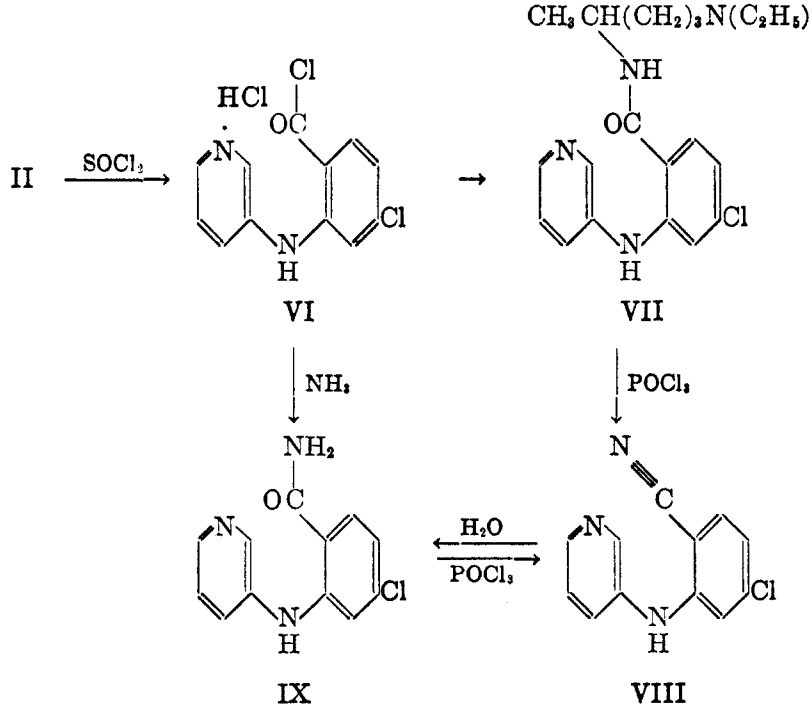


IV



V

Since the preparation of the desired drug (I) through the 9-chloro derivative was unsuccessful, an alternate quinacrine synthesis (3) involving cyclization of



the dialkylaminoalkylamide (VII) of the acid II was attempted. However, the course of the reaction was quite remarkable in that the product isolated from treatment of VII with phosphorus oxychloride proved to be the nitrile (VIII) of the original acid (II). This was demonstrated by analysis and by hydrolysis to the amide (IX), identical with a sample prepared by treatment of the acid chloride (VI) with ammonia.

EXPERIMENTAL[5]

4-Chloro-2-(3-pyridylamino)benzoic acid. The preparation of this compound by the condensation of 2,4-dichlorobenzoic acid with 3-aminopyridine was accomplished in good yield only after an extensive investigation of variations in experimental conditions. It appeared that the amount of solvent, amount of catalyst, and perhaps the efficient removal of the water produced in the condensation were the most critical factors.

A mixture of 32.0 g. (0.341 mole) of 3-aminopyridine, 48.8 g. (0.255 mole) of 2,4-dichlorobenzoic acid, 53.2 g. (0.38 mole) of anhydrous potassium carbonate, 0.17 g. of copper bronze, and 64 cc. of *n*-hexanol was stirred and heated to boiling. The reflux condenser was filled with hot water so that the *n*-hexanol was returned to the reaction mixture while the water produced by the reaction was allowed to escape. After heating and stirring for two hours, the *n*-hexanol was removed by steam distillation. For small scale preparations, it was convenient to remove the solvent by ether extraction. To the aqueous solution (*ca.* 250 cc.) remaining after distillation of the *n*-hexanol, 20 cc. of concentrated ammonium hydroxide and 10 g. of Norit were added and the mixture was boiled for half an hour. The charcoal was removed and 55 cc. of glacial acetic acid was added to the hot filtrate. After the mixture was allowed to cool to room temperature, the precipitated product was collected. The brown solid was redissolved in 100 cc. of concentrated ammonium hydroxide and 400 cc. of water, treated with another 12 g. of charcoal and reprecipitated with acetic acid. The tan powdery 4-chloro-2-(3-pyridylamino)benzoic acid weighed 41.0 g. (65%). The product was further purified by recrystallization from glacial acetic acid, yielding microscopic needles, m.p. 263–265°, dec. The behavior of this amino acid with 10% sodium hydroxide and 10% hydrochloric acid was interesting. When either solution was added to a small amount of the acid in a test tube, it dissolved immediately. On standing a few minutes, crystals of the sodium salt or hydrochloride began to separate. A sample of the hydrochloride was recrystallized from ethanol containing a few drops of hydrochloric acid; the pure salt decomposed at 262–263°.

Anal. Calc'd for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.54; H, 3.54.
Found: C, 50.62; H, 3.48.

Methyl 4-chloro-2-(3-pyridylamino)benzoate. A 2.0-g. sample of 4-chloro-2-(3-pyridylamino)benzoic acid hydrochloride was boiled for one hour in 150 cc. of methanol containing 31 g. of hydrogen chloride. After cooling overnight, it was diluted with an equal volume of ice-water and neutralized to litmus with concentrated ammonium hydroxide. The crystalline methyl ester, m.p. 90–91°, weighed 1.59 g. (86%). The product was prepared for analysis by recrystallization from Skellysolve B (b.p. 60–68°) as beautiful fine white needles, m.p. 91–92°.

Anal. Calc'd for $C_{13}H_{11}ClN_2O_2$: C, 59.43; H, 4.22.
Found: C, 59.52; H, 4.35.

Attempt to cyclize the ester thermally. Methyl 4-chloro-2-(3-pyridylamino)benzoate (0.200 g.) in diphenyl ether (16 cc.) was boiled for an hour. The cooled reaction mixture was diluted with 25 cc. of petroleum ether and extracted with three portions of 10% sodium hydroxide solution. The combined alkaline extracts were neutralized with acetic acid, yielding only a trace of precipitate. The diphenyl ether-petroleum ether solution was extracted with several portions of 10% hydrochloric acid, these extracts were neutralized with

[5] Analyses by Miss Theta Spoor and Mr. Howard Clark.

10% sodium hydroxide and 0.138 g. of crystalline starting material, m.p. 90–91.5°, was recovered.

Treatment of the ester with sodium ethoxide. Anhydrous ethanol was prepared by the method of Manske (4) and 0.5 g. of freshly cut sodium was dissolved in 5 cc. A 0.107-g. sample of the methyl ester was added, whereupon a bright yellow color was produced. The mixture was protected from moisture with a calcium chloride tube and boiled under reflux for one hour. On cooling in an ice-bath, the sodium ethoxide crystallized to give a semi-solid mass. About 5 or 6 cc. of water was added, producing a colorless solution. When the solution was neutralized with acetic acid, a white precipitate formed; this was collected and dried, yielding 0.070 g. of white solid; m.p. 265–268°, dec. This was evidently 4-chloro-2-(3-pyridylamino)benzoic acid. It was soluble in cold dilute ammonium hydroxide and in warm 10% sodium hydroxide and hydrochloric acid. Crystals separated from the latter two solutions upon cooling.

Treatment of 4-chloro-2-(3-pyridylamino)benzoic acid with sulfuric acid. A 3.00-g. sample of the amino acid with 30 cc. of concentrated sulfuric acid was heated in an oil-bath at 122–124° for seven and one-half hours. The dark green fluorescent solution was poured onto 60 g. of ice and water. The bright yellow crystals were collected and dried in a vacuum desiccator. This product (2.1 g.), which darkened but did not melt below 320°, was recrystallized from dilute sulfuric acid and washed with water. From the analysis, its composition corresponded to that of a partial sulfate of *6-chloro-9-hydroxypyrido[3,2-b]-quinoline.*

Anal. Calc'd for $C_{12}H_7ClN_2O \cdot 0.321H_2SO_4$: C, 55.00; H, 2.94.
Found: C, 55.00; H, 3.13.

A second sample of the *sulfate* was prepared and washed with dilute sulfuric acid. Its composition corresponded satisfactorily to the sulfate.

Anal. Calc'd for $C_{12}H_7ClN_2O \cdot H_2SO_4$: C, 43.85; H, 2.76.
Found: C, 43.66; H, 2.97.

A sample of the *hydrochloride* was similarly prepared, m.p. 320°.

Anal. Calc'd for $C_{12}H_7ClN_2O \cdot HCl \cdot \frac{1}{2}H_2O$: C, 52.40; H, 3.27.
Found: C, 52.72; H, 3.28.

Attempts to convert this material to the chloro compound with phosphorus oxychloride, with or without added phosphorus pentachloride, yielded an intractable, black carbon-like amorphous mass.

4-Chloro-2-(3-pyridylamino)benzoyl chloride hydrochloride. To 13 g. of dry 4-chloro-2-(3-pyridylamino)benzoic acid was added 65 cc. of pure thionyl chloride. The mixture was boiled to reflux for forty-five minutes and the excess thionyl chloride was then rapidly removed by distillation under reduced pressure. The residue was dried *in vacuo* overnight over phosphorus pentoxide. The light tan powdery solid weighed 15.1 g. (95%) and had an odor similar to that of benzoyl chloride. It did not have a definite melting point but turned dark at 195° and was liquid at 210°. It was insoluble in ether, benzene, chloroform, and dioxane but dissolved in ethanol when warmed. When boiled in water it was hydrolyzed to the acid. To confirm the structure further, 1 g. was boiled with 15 cc. of methanol for half an hour. The reaction mixture was cooled, diluted with water, and neutralized with ammonia, yielding white needles, which, after one recrystallization, melted at 91–92° and by a mixed melting point were shown to be identical with the methyl ester prepared above from the acid.

Attempted ring closure of the substituted amide: 4-Chloro-2-(3-pyridylamino)benzonitrile. To the acid chloride hydrochloride prepared from 5.0 g. (0.02 mole) of acid as described above was added 50 cc. of dry benzene and 10 g. (0.033 mole) of purified 4-amino-1-diethylaminopentane. The mixture warmed as the acid chloride hydrochloride dissolved. After boiling under reflux for one hour, crystals of diamine hydrochloride had separated from solution. The mixture was allowed to cool, 92 g. of phosphorus oxychloride was added, and it was reheated for nine hours. The benzene was decanted from the black semi-solid prod-

uct and 150 cc. of ethanol was added. The mixture was warmed to boiling and the residue, 0.88 g. of tan powdery solid (A), was collected. The alcohol was removed from the filtrate by distillation and replaced with 50 cc. of water and 20 cc. of concentrated ammonium hydroxide. The mixture was extracted with several portions of ether. The ether extracts were dried over magnesium sulfate and treated with dry hydrogen chloride, which precipitated a brown oil. The ether was decanted and 50 cc. of hot 95% ethanol was added to dissolve the oil. Cooling the alcoholic solution gave a tan powdery solid (B), 0.44 g. A and B were recrystallized separately from 95% ethanol giving light tan crystals which decomposed at 267–270° and 268–271°, respectively. A mixture of the two had the same decomposition point. The two products were then combined, dissolved in 75 cc. of hot water, treated with Norit, and neutralized with 5 cc. of concentrated ammonium hydroxide. An oil first separated but it quickly crystallized in the form of fine white needles. These were recrystallized from 50% ethanol; fine cottony needles, 1.3 g. (25%), of *4-chloro-2-(3-pyridylamino)benzonitrile* were obtained, m.p. 132–133°.

Anal. Calc'd for $C_{12}H_8ClN_3$: C, 62.75; H, 3.51; N, 18.30.
Found: C, 62.90; H, 3.73; N, 18.06.

The structure was proved by synthesis of the same compound from the corresponding amide (IX) and by hydrolysis, which yielded a mixture of the amide (IX) and the acid (II).

4-Chloro-2-(3-pyridylamino)benzamide. A 1.5-g. sample of 4-chloro-2-(3-pyridylamino)-benzoyl chloride hydrochloride was added to 25 cc. of concentrated ammonium hydroxide with stirring. The mixture was warmed to boiling and then allowed to stand at room temperature for several hours. A tan solid, weighing about 1 g. (82%), was obtained. Charcoal treatment and several recrystallizations from 50% ethanol yielded slender white rods, m.p. 235–236°, sintering from 220°.

Anal. Calc'd for $C_{12}H_{10}ClN_3O$: C, 58.19; H, 4.07.
Found: C, 57.53; H, 4.08.

A small sample of the amide (*ca.* 0.1 to 0.2 g.) was placed in a test tube and boiled with 3 cc. of phosphorus oxychloride for two minutes. The solution was allowed to cool a few minutes, then poured out into 10 cc. of ice and water. The light tan crystals, m.p. 266–268°, were dissolved in hot water and ammonium hydroxide was added, precipitating an oil which crystallized immediately. Recrystallized from 50% ethanol, the fine white needles obtained melted at 132–133° and did not depress the melting point of 4-chloro-2-(3-pyridylamino)benzonitrile obtained from the substituted amide.

Hydrolysis of 4-chloro-2-(3-pyridylamino)benzonitrile. A 0.500-g. sample of the nitrile was boiled under reflux with 20 cc. of 10% sodium hydroxide for one hour. The solid appeared to go into solution with the production of a yellow color, but reprecipitation of a white solid occurred simultaneously so that the solution was never clear. At the end of the heating the yellow color had disappeared. The cooled mixture was filtered and 0.35 g. of white solid was collected, m.p. 225–235°. This product was purified by dissolving in 10 cc. of hot 10% hydrochloric acid, filtering and reprecipitating with ammonium hydroxide. The white crystals weighed 0.333 g., m.p. 230–233°, and gave no depression in melting point when mixed with 4-chloro-2-(3-pyridylamino)benzamide.

The filtrate from the 0.35 g. of amide was diluted with water and neutralized with glacial acetic acid. The white precipitate was digested by heating to boiling. The mixture was cooled and filtered to yield 0.138 g. of white solid, m.p. 265–268°, dec. This was proved to be 4-chloro-2-(3-pyridylamino)benzoic acid by converting a 50-mg. sample to the methyl ester in 80% yield.

SUMMARY

Attempts to convert 4-chloro-2-(3-pyridylamino)benzoic acid to an analog of quinacrine were unsuccessful. It could be cyclized to 6-chloro-9-hydroxypyrido [3,2-b] quinoline but replacement of the hydroxyl group by chlorine could not

be effected. An attempt to cyclize the N-(1-diethylamino-4-pentyl)amide of the acid produced only the nitrile of the acid.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

LEVINSTEIN MUSTARD GAS. I. 2-HALOALKYLSULFENYL HALIDES[1]

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Since the development, during World War I, of the Levinstein process for making mustard gas many attempts have been made to follow the course of the reaction and to determine the nature of the contaminants. The research reported in this series of papers was directed to this same end. It was a cooperative effort, valuable assistance being received from many sources, notably the Chemical Warfare Service.

One of the most interesting theories in this connection, put forth by Conant, Hartshorn, and Richardson (1), postulated 2-chloroethylsulfenyl chloride (I) as an intermediate in the formation of mustard gas (II) by the condensation of ethylene with sulfur chlorides. With sulfur dichloride, for example, the reactions would be as follows:

$$CH_2{=}CH_2 + SCl_2 \rightarrow \underset{\text{I}}{ClCH_2CH_2SCl}$$

$$ClCH_2CH_2SCl + CH_2{=}CH_2 \rightarrow \underset{\text{II}}{(ClCH_2CH_2)_2S}$$

Similar equations can be written for the Levinstein process, which involves the condensation of ethylene with sulfur monochloride at 35°. However, these investigators, as well as Mann and Pope (2), failed to obtain the sulfenyl chloride in pure form. In the present work it has been found possible to produce 2-chloroethylsulfenyl chloride by the chlorinolysis of *bis*(2-chloroethyl) disulfide (III).

$$\underset{\text{III}}{(ClCH_2CH_2)_2S_2} + Cl_2 \rightarrow 2\ ClCH_2CH_2SCl$$

The sulfenyl chloride is an orange-colored liquid with an odor resembling that of the sulfur halides. It decomposes, slowly at room temperature and very rapidly at 110°, with the evolution of hydrogen chloride and the formation of a black tar. The sulfenyl chloride can be purified by distillation; it boils undecomposed at 47–47.5° (15 mm.).

2-Chloroethylsulfenyl chloride is the first sulfenyl halide with *alpha* hydrogen atoms to be prepared by the chlorinolysis of a disulfide. In fact, the only other sulfenyl halides with *alpha* hydrogen atoms are those formed by the action of

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

sufur dichloride on *N*,*N*′-di-*n*-propylmalonamide and the *N*,*N*′-dinaphthylmalonamides (3).

The reactions of 2-chloroethylsulfenyl chloride are similar to those of sulfenyl halides in general. It was reconverted to the original *bis*(2-chloroethyl) disulfide with aqueous potassium iodide. Treatment of the sulfenyl chloride with water also produced the disulfide, together with unidentified malodorous material which was probably the thiolsulfonic ester (4). Oxidation with dilute nitric acid yielded 2-chloroethanesulfonic acid, which was isolated as the ammonium salt.

2-Chloroethylsulfenyl chloride reacted readily with sulfur to yield a mixture of products including sulfur monochloride, *bis*(2-chloroethyl) disulfide and *bis*(2-chloroethyl) trisulfide.

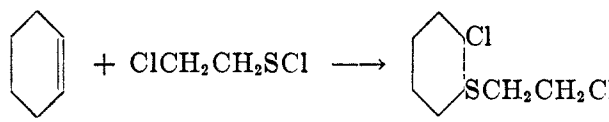
$$2\ ClCH_2CH_2SCl + xS \rightarrow (ClCH_2CH_2)_2S_x + S_2Cl_2$$

A similar result has been reported by Klason (5) for the reaction between sulfur and trichloromethylsulfenyl chloride. Such a reaction was postulated by Conant, Hartshorn, and Richardson (1) as a possible source of the polysulfides present in Levinstein mustard gas; the sulfur was assumed to arise from dismutation of the sulfur monochloride.

The most interesting reactions of 2-chloroethylsulfenyl chloride are those with olefins, particularly that with ethylene. When ethylene was bubbled through the pure sulfenyl chloride no reaction took place. If the sulfenyl chloride was dissolved in carbon tetrachloride, however, reaction with ethylene was extremely rapid with the evolution of heat and the formation of *bis*(2-chloroethyl) sulfide. This result substantiates the hypothesis of Conant, Hartshorn and Richardson that 2-chloroethylsulfenyl chloride is an intermediate in the preparation of mustard gas from ethylene and sulfur chlorides.

The failure to obtain a reaction in the absence of a solvent is probably due to the low solubility of ethylene in the sulfenyl chloride. A similar observation has been made in the reaction of ethylene with sulfur monochloride; the reaction is extremely slow unless a solvent or "seed charge" is employed (6).

The only examples of the addition of sulfenyl chlorides to olefins which are reported in the literature involve ethylene (7). In the present work it has been found that this type of reaction is general for olefins. Cyclohexene, for example, combines with 2-chloroethylsulfenyl chloride to form 2-chlorocyclohexyl 2-chloroethyl sulfide.



In a similar manner, it has been found possible to condense 2-chloroethylsulfenyl chloride with acetylene to produce 2-chloroethyl 2-chlorovinyl sulfide. A comparison of properties shows this sulfide to be identical with that obtained by Lawson and Dawson (8) by the action of chlorine on *bis*(2-chloroethyl) sulfide.

Thus the unequivocal synthesis reported here serves to confirm the conclusion of these authors that their product was 2-chloroethyl 2-chlorovinyl sulfide.

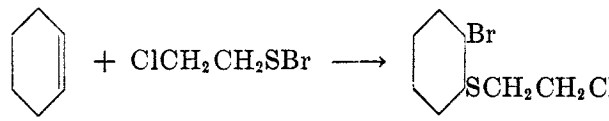
2-Chloroethylsulfenyl chloride reacts normally with active methylene compounds; for example, its condensation with acetone produced acetonyl 2-chloroethyl sulfide.

$$ClCH_2CH_2SCl + CH_3COCH_3 \rightarrow ClCH_2CH_2SCH_2COCH_3 + HCl$$

Likewise, it condensed readily with piperazine to form a disulfenamide, *N,N'-bis*(2-chloroethylthio)piperazine.

2-Chloroethylsulfenyl bromide was prepared by a method similar to that used for making 2-chloroethylsulfenyl chloride. Treatment of *bis*(2-chloroethyl) disulfide with bromine produced a red liquid, which fumed in moist air and possessed a characteristic sulfur halide odor. It was too unstable to be distilled. However, it was found possible to condense the crude reaction product with cyclohexene to produce 2-bromocyclohexyl 2-chloroethyl sulfide.

$$(ClCH_2CH_2)_2S_2 + Br_2 \rightarrow 2\ ClCH_2CH_2SBr$$



The mixed sulfide was characterized by the preparation of its *p*-toluenesulfilimine derivative.

EXPERIMENTAL

2-Chloroethylsulfenyl chloride. To a well-agitated solution of 453 g. (2.37 moles) of *bis*-(2-chloroethyl) disulfide, prepared according to the method of Bennett (9), in dry carbon tetrachloride was added 169 g. (2.38 moles) of chlorine at such a rate that the temperature did not rise above 10°. The solvent was evaporated at reduced pressure and the product was distilled; b.p. 47–47.5° (15 mm.); n_D^{20} 1.5290; yield 355 g., or 57%. In other runs yields up to 79% have been obtained. The sulfenyl chloride was an orange liquid with a very unpleasant odor. It was moderately stable when stored in a brown bottle and kept in the refrigerator. It was necessary to distil it immediately before using.

Anal. Calc'd for $C_2H_4Cl_2S$: C, 18.33; H, 3.07.
Found: C, 18.30; H, 3.03.

The residue from the original distillation of the 2-chloroethylsulfenyl chloride weighed 173 g. and contained *bis*(2-chloroethyl) disulfide and a new compound which had the composition of a monochloro derivative of the disulfide. The two compounds were obtained from the residue by fractional distillation. The new compound was a yellow liquid ($n_D^{21.8}$ 1.5768) which on standing darkened and developed a disagreeable odor.

Anal. Calc'd for $C_4H_7Cl_3S_2$: C, 21.29; H, 3.13; Cl, 47.15.
Found: C, 21.94; H, 3.17; Cl, 47.02.

Reactions of 2-chloroethylsulfenyl chloride. a. *With potassium iodide.* A sample of the sulfenyl chloride was dissolved in aqueous acetone and treated with potassium iodide. The iodine formed was removed with sodium sulfite, and the acetone was evaporated. The insoluble oil was taken up in chloroform and dried over sodium sulfate. Removal of the solvent left a colorless oil, n_D^{20} 1.5608, with an odor resembling that of *bis*(2-chloroethyl) disulfide (for the pure disulfide n_D^{20} 1.5656).

b. *With water.* Twenty grams of the sulfenyl chloride and 300 ml. of water were placed

in a glass-stoppered flask and agitated mechanically. The orange color of the chloride soon disappeared, leaving the hydrolysis product as a colorless oil. It was dried with sodium sulfate and fractionally distilled under diminished pressure. It was possible to isolate *bis*(2-chloroethyl) disulfide; b.p. 83–88° (2 mm.); n_D^{20} 1.5670; m.p. 1°. A small amount of higher-boiling liquid could not be characterized.

c. *With sulfur.* An equimolar mixture of 2-chloroethylsulfenyl chloride and sulfur was heated at 60–65° for three hours. The product, a clear orange liquid, was distilled under diminished pressure. A volatile fraction containing sulfur monochloride was obtained followed by a higher-boiling fraction of *bis*(2-chloroethyl) disulfide (9) and trisulfide (10). The latter were separated by fractionation *in vacuo* (0.2 mm.), and identified by comparison of their physical properties with authentic specimens.

d. *Oxidation with nitric acid.* To an aqueous solution of 4.8 g. of the sulfenyl chloride was added dropwise with stirring 30 ml. of nitric acid (*d.* 1.42). The mixture was heated on a steam-bath until clear, and evaporated to dryness. An excess of ammonium hydroxide was added; the resulting solution, upon evaporation, yielded crystals which melted at 191–193° after recrystallization from ethanol. Ammonium 2-chloroethanesulfonate is reported (11) to melt at 194°. The total yield was 4.2 g. (79%).

e. *With ethylene.* Ethylene gas was conducted into a solution of 10 g. of the sulfenyl chloride in 90 ml. of carbon tetrachloride. Heat was liberated and the reddish-orange color of the solution disappeared in a short time, leaving the reaction mixture water-white. The solvent was evaporated on a steam-bath and the product distilled under reduced pressure. It consisted of *bis*(2-chloroethyl) sulfide; b.p. 54–55° (1 mm.); n_D^{20} 1.5281 (12). The yield was 70%.

f. *With cyclohexene.* To 9.0 g. of the sulfenyl chloride was added slowly 7.0 g. of cyclohexene dissolved in 25 ml. of carbon tetrachloride. Distillation of the colorless reaction mixture yielded 10 g. (69%) of 2-chlorocyclohexyl 2-chloroethyl sulfide; b.p. 84–86° (0.2 mm.).

The *p-toluenesulfilimine* was made by mixing a solution of 1 g. of the sulfide in 5 ml. of acetone with 20 ml. of a 10% aqueous solution of Chloramine-T. The mixture was warmed slightly, shaken for a few minutes, and allowed to stand one hour. The crystalline product was removed and recrystallized from ethanol; m.p. 145.5–146° in a preheated bath.

Anal. Calc'd for $C_{15}H_{21}Cl_2NO_2S_2$: C, 47.12; H, 5.54; N, 3.66.
Found: C, 47.04; H, 5.47; N, 3.69.

g. *With acetylene.* 2-Chloroethyl 2-chlorovinyl sulfide was prepared by the condensation of the sulfenyl chloride with acetylene. Fifteen hundred milliliters of ethyl acetate was cooled in an ice-salt bath and acetylene (dried by passing through concentrated sulfuric acid) was bubbled in, with stirring, for one and one-half hours. Then, with continued addition of acetylene, 185 g. of the sulfenyl chloride was added dropwise over a period of two hours. One hour later the addition of acetylene was discontinued and the solvent was removed by distillation with a water-pump. The residual oil was distilled through a 6-in column packed with Berl Saddles. The yield of colorless 2-chloroethyl 2-chlorovinyl sulfide was 125 g., or 56%; b.p. 46° (0.75 mm.), 30° (0.15 mm.); n_D^{20} 1.5480; m.p. −24°.

Anal. Calc'd for $C_4H_6Cl_2S$: C, 30.60; H, 3.85; Cl, 45.16; S, 20.39.
Found: C, 30.81; H, 3.99; Cl, 44.0; S, 21.2.

The *p-toluenesulfilimine* of this product was prepared in the usual way. It was recrystallized successively from absolute ethanol and carbon tetrachloride; m.p. 105–105.5°.

Anal. Calc'd for $C_{11}H_{13}Cl_2NO_2S_2$: C, 40.51; H, 4.02; N, 4.29.
Found: C, 40.58; H, 4.18; N, 4.26.

The *sulfone*, prepared in the usual way (13), crystallized from low-boiling petroleum ether in white platelets; m.p. 37.5–38°.

Anal. Calc'd for $C_4H_6Cl_2O_2S$: C, 25.41; H, 3.20.
Found: C, 25.37; H, 3.18.

h. *With acetone.* Thirty-five grams of the freshly-distilled sulfenyl chloride was added to 50 g. of dry acetone. An exothermic reaction occurred, accompanied by rapid decoloriza-

tion of the mixture and the evolution of hydrogen chloride. When the reaction was complete, water was added and an oily layer separated. It was dried over anhydrous sodium sulfate and distilled through a column packed with Berl Saddles; b.p. 76–85° (0.75 mm.). The acetonyl 2-chloroethyl sulfide was characterized by preparation of the semicarbazone, which was recrystallized from methanol; m.p. 145–146°.

Anal. Calc'd for $C_6H_{12}ClN_3OS$: C, 34.36; H, 5.77.
Found: C, 34.31; H, 5.80.

i. *With piperazine.* This reaction was carried out according to the directions of Rheinboldt and Mott (14) for the corresponding derivative with *t*-butylsulfenyl chloride. The *N,N'-bis*(2-chloroethylthio)piperazine crystallized from absolute ethanol as white needles; m.p. 117–118°.

Anal. Calc'd for $C_8H_{16}Cl_2N_2S_2$: C, 34.90; H, 5.86.
Found: C, 35.17; H, 5.55.

2-Bromocyclohexyl 2-chloroethyl sulfide. Eighty grams of bromine was added over a period of one hour to a solution of 95 g. of *bis*(2-chloroethyl) disulfide in 150 ml. of carbon tetrachloride. After the mixture had been stirred overnight, the solvent and unchanged bromine were removed by distillation *in vacuo* at room temperature. The 2-chloroethylsulfenyl bromide remained as a red liquid which had the odor characteristic of sulfur halides. It fumed when exposed to moist air and decomposed into the starting materials when attempts were made to distil it at a pressure of 3 mm.

In another experiment cyclohexene was added to a carbon tetrachloride solution of the sulfenyl bromide. The red color of the solution gradually faded and the mixture assumed the light yellow color of the product, 2-bromocyclohexyl 2-chloroethyl sulfide. The crude sulfide, which was obtained in a 75% yield, decomposed slightly during distillation at 0.35 mm.

The *p-toluenesulfilimine*, made in the usual way, was recrystallized from ethanol; m.p. 145–146°.

Anal. Calc'd for $C_{15}H_{21}BrClNO_2S_2$: C, 42.21; H, 4.96.
Found: C, 42.61; H, 4.77.

SUMMARY

2-Chloroethylsulfenyl chloride has been made by the action of chlorine on *bis*(2-chloroethyl) disulfide.

It has been condensed with ethylene to produce *bis*(2-chloroethyl) sulfide; this result further substantiates the belief that it is an intermediate in the formation of mustard gas from ethylene and sulfur chlorides.

It has been condensed with cyclohexene to produce 2-chlorocyclohexyl 2-chloroethyl sulfide, with acetylene to yield 2-chloroethyl 2-chlorovinyl sulfide, with acetone to form acetonyl 2-chloroethyl sulfide, and with piperazine to give *N,N'-bis*(2-chloroethylthio)piperazine.

2-Chloroethylsulfenyl bromide has been obtained in crude form by the action of bromine on *bis*(2-chloroethyl) disulfide. The bromide was found to combine with cyclohexene to yield 2-bromocyclohexyl 2-chloroethyl sulfide.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

LEVINSTEIN MUSTARD GAS. II. THE ADDITION OF 2-CHLOROETHYLSULFENYL CHLORIDE TO PROPYLENE[1]

REYNOLD C. FUSON, CHARLES C. PRICE, AND DONALD M. BURNESS

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One of the most interesting reactions of 2-chloroethylsulfenyl chloride (I) is its condensation with propylene to give 2-chloroethyl 2-chloro-*n*-propyl sulfide (II).

$$\underset{\text{I}}{ClCH_2CH_2SCl} + CH_2{=}CHCH_3 \longrightarrow \underset{\text{II}}{ClCH_2CH_2SCH_2CHClCH_3}$$

$$\underset{\text{III}}{ClCH_2CH_2S\overset{CH_3}{\overset{|}{C}}HCH_2Cl}$$

In the early stages of the investigation it seemed likely that the product was 2-chloroethyl 2-chloroisopropyl sulfide (III) rather than the normal isomer, since it was found that the same compound was produced by the following sequence of reactions.

$$HOCH_2CH_2SH + CH_2{=}CHCH_2OH \xrightarrow{S} \underset{\text{IV}}{HOCH_2CH_2S\overset{CH_3}{\overset{|}{C}}HCH_2OH} \xrightarrow{HCl} \text{II or III}$$

This synthesis would be expected to yield the isopropyl derivative since it is known that in the absence of peroxides, mercaptans add to unsymmetrical olefins according to Markovnikov's rule (1). Also, the replacement of the hydroxyl groups with chlorine occurred with ease, a characteristic which was shown by Bennett and Hock (2) to distinguish β-hydroxy from γ-hydroxy sulfides.

This evidence, which pointed to the iso structure (III) for the product of the addition of 2-chloroethylsulfenyl chloride to propylene, tended to invalidate the mechanism proposed by Conant, Hartshorn, and Richardson (3) for the preparation of *bis*(2-chloroethyl) sulfide (V) from ethylene and sulfur chlorides.

$$CH_2{=}CH_2 \xrightarrow[\text{or } S_2Cl_2]{SCl_2} ClCH_2CH_2SCl \xrightarrow{CH_2{=}CH_2} \underset{\text{V}}{(ClCH_2CH_2)_2S}$$

For this mechanism, if correct, should serve equally well for the reaction between propylene and sulfur monochloride; however, the product of this reaction has been reported by Pope and Smith (4) to have the normal (VI) rather

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

than the iso (VII) structure. Although no structure proof was given, it has become generally accepted that this material actually is *bis*(2-chloro-*n*-propyl) sulfide (VI).

$$CH_3CHClCH_2SCH_2CHClCH_3 \qquad ClCH_2\underset{\displaystyle CH_2}{CH}S\underset{\displaystyle CH_3}{CH}CH_2Cl$$

VI VII

It is obvious that if both III and VI are correct structures, any mechanism for the Levinstein process which involves a sulfenyl chloride as an intermediate will be untenable.

In the present work a rigorous proof of structure has been carried out for the addition product of 2-chloroethylsulfenyl chloride and propylene. It has been shown that this product and that from the glycol (IV), are indeed, identical and that *they have the normal (II) rather than the iso (III) structure.*

The proof of structure consisted in the conversion of the dichloro sulfide to ethyl *n*-propyl sulfone (VIII) according to the following scheme.

$$ClCH_2CH_2SCH_2CHClCH_3 \xrightarrow{H_2O_2} ClCH_2CH_2SO_2CH_2CHClCH_3 \xrightarrow{(C_2H_5)_3N}$$

$$CH_2{=}CHSO_2CH{=}CHCH_3 \xrightarrow[(Ni)]{H_2} CH_3CH_2SO_2CH_2CH_2CH_3$$

VIII

The melting point (24–25°) of the sulfone (VIII) agreed with that given by Fenton and Ingold (5). Moreover, comparison of the sulfone with an authentic specimen of ethyl isopropyl sulfone (m.p. −9° to −6°) showed the two compounds to be unlike.

The foregoing results make it clear that a rearrangement of the product (IV) from allyl alcohol and monothioglycol must have occurred during the replacement of the hydroxyl group by chlorine.

$$HOCH_2CH_2S\underset{\displaystyle CH_3}{CH}CH_2OH \xrightarrow{HCl} ClCH_2CH_2SCH_2CHClCH_3$$

IV III

confirmation of this conclusion was obtained by experiments with ethyl 2-hydroxyisopropyl sulfide (IX) and ethyl 2-hydroxy-*n*-propyl sulfide (X). When treated with hydrochloric acid or thionyl chloride, these compounds yielded the same product, 2-chloro-*n*-propyl ethyl sulfide (XI).

$$C_2H_5S\underset{\displaystyle CH_3}{CH}CH_2OH \qquad C_2H_5SCH_2\underset{\displaystyle Cl}{CH}CH_3$$

IX XI

$$C_2H_5SCH_2\underset{\displaystyle OH}{CH}CH_3$$

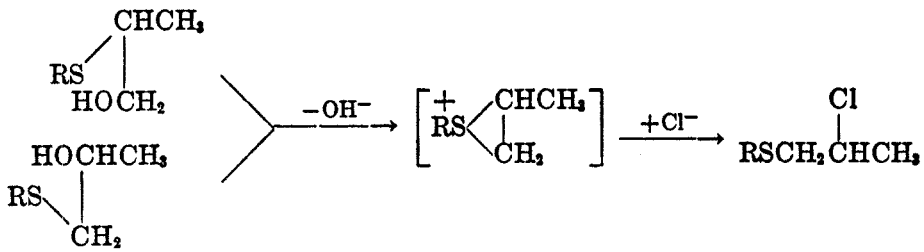
X

The structure of the two products was established by converting them to ethyl *n*-propyl sulfone.

It seemed safe to conclude that the condensation product of propylene with sulfur monochloride likewise has the normal structure (VI). This conclusion has been confirmed by conversion of the dichloro sulfide to the known (6) *n*-propyl sulfone (XII).

$$(CH_3CHClCH_2)_2S \rightarrow (CH_3CHClCH_2)_2SO_2 \rightarrow$$
$$\text{VI}$$
$$(CH_3CH{=}CH)_2SO_2 \rightarrow (CH_3CH_2CH_2)_2SO_2$$
$$\text{XII}$$

The rearrangement of the isopropyl to the *n*-propyl structure is readily explained by the suggestion that nucleophilic replacement reactions in β-thioalkyl radicals may occur through a cyclic sulfonium intermediate.[2]



Bennett (7) cites evidence for such a mechanism in the case of δ-hydroxy sulfides, where a stable five-membered ring is possible; extension of this idea to β-hydroxy sulfides is supported by the theory advanced by Winstein and his collaborators in a series of articles (8) to explain the observed retention of configuration in certain nucleophilic replacement reactions. This steric effect was attributed to the participation in the reaction of a neighboring group, with the production of a cyclic onium ion intermediate.

Since the ring might break on either side of the sulfur atom, it is theoretically possible for the resulting chloro compound to be a mixture of the two isomers. It is also possible that the two isomeric chloro compounds occur together as an equilibrium mixture; in such a case, isolation of either form in a pure state might not be possible. In either event it should be possible to detect the presence of any appreciable amount of a second isomer by conversion of the sulfide to the sulfone or sulfilimine, since in these derivatives the sulfur atom would no longer be able to promote isomerization by formation of the sulfonium ion intermediate. In the present work, however, a second sulfone or sulfilimine was not obtained.

EXPERIMENTAL

Condensation of 2-chloroethylsulfenyl chloride with propylene.[3] A rapid stream of propylene was passed into a solution of 58 g. of freshly-distilled 2-chloroethylsulfenyl chloride

[2] This same hypothesis was formulated independently by Dr. P. D. Bartlett (O.S.R.D. report) for the reverse reaction, hydrolysis of the chloro compounds.

[3] This experiment was carried out by Dr. R. A. Bauman.

(9) in 100 ml. of dry carbon tetrachloride at about 5°. At the end of eighty minutes the reaction mixture was colorless. The solvent was removed with an aspirator and the residual liquid distilled; b.p. 89–92° (6 mm.); n_D^{20} 1.5268. The *tribromophenate* was prepared by heating under reflux an ethanolic solution containing equimolar amounts of the product and the sodium salt of 2,4,6-tribromophenol. After recrystallization from ethanol the derivative melted at 132.5–134°.

Anal. Calc'd for $C_{17}H_{14}Br_6O_2S$: C, 26.80; H, 1.85.
Found: C, 27.00; H, 2.03.

The *p-toluenesulfilimine*, prepared in the usual way (9), melted at 135.5–136°.

Anal. Calc'd for $C_{12}H_{17}Cl_2NO_2S$: C, 42.10; H, 5.01.
Found: C, 42.28; H, 5.10.

The dichloro sulfide was made also from *2-hydroxyethyl 2-hydroxyisopropyl sulfide*,[4] which was prepared by the method of Jones and Reid (1). When an equimolecular mixture of monothioglycol and allyl alcohol was heated under reflux for twelve hours in the presence of sulfur, a 46% yield of the glycol was obtained; b.p. 110–116° (0.5 mm.); n_D^{20} 1.5103. This was converted to the dichloro compound by treatment with concentrated hydrochloric acid (10); b.p. 53–56° (0.4 mm.); n_D^{20} 1.5181. The tribromophenate of this compound melted at 133.5–135°. A mixture of the two samples of the tribromophenate melted at 132.5–134.5°. The *p*-toluenesulfilimine of this compound melted at 135.5–136°. The melting point of a mixture of the two samples of the sulfilimine was not depressed.

2-Chloroethyl 2-chloro-n-propyl sulfone. To a solution of the sulfide (0.17 mole), product of the addition of the sulfenyl chloride to propylene, in glacial acetic acid was added slowly an aqueous solution of hydrogen peroxide (0.17 mole). Then an additional 0.34 mole of hydrogen peroxide was added rapidly. The reaction mixture was stirred at 60° for twenty-four hours. The solvents were removed at the water-pump and the residual oil was distilled. The yield of colorless sulfone was 88%; b.p. 117–119° (0.1 mm.); m.p. 21–25°; n_D^{20} 1.4983.

Anal. Calc'd for $C_5H_{10}Cl_2O_2S$: C, 29.28; H, 4.91.
Found: C, 28.93; H, 4.83.

Ethyl n-propyl sulfone. The dichloro sulfone was dehydrochlorinated by the method of Alexander and McCombie (11). A solution of the sulfone (0.15 mole) in 250 ml. of dry benzene was treated with 0.30 mole of triethylamine. The amine hydrochloride separated almost immediately. The mixture was stirred overnight at room temperature and filtered; the triethylamine salt amounted to 91% of the theory. The benzene solution was washed twice with water and the solvent distilled. The crude, yellow *Δ¹-propenyl vinyl sulfone* was obtained in a yield of 97%; n_D^{20} 1.4867.

The unsaturated sulfone (0.14 mole) was dissolved in 150 ml. of absolute ethanol and hydrogenated in the presence of Raney nickel at a pressure of 2 to 3 atmospheres. The reduction was complete in eight hours. Removal of the solvent left a 72% yield of the crude saturated sulfone as a pale yellow oil. It crystallized readily from a mixture of ether and petroleum ether as white needles; m.p. 24–25°; n_D^{30} 1.4460. Fenton and Ingold (5) reported the melting point to be 25°. *Ethyl isopropyl sulfone* [b.p. 90–91° (2 mm.); m.p. −9 to −6°; n_D^{30} 1.4463] was prepared from the corresponding sulfide (12) by the method described for 2-chloroethyl 2-chloro-*n*-propyl sulfone.

Anal. Calc'd for $C_5H_{12}O_2S$: C, 44.09; H, 8.82.
Found: C, 43.82; H, 8.95.

A mixture melting point of the two sulfones was 8–14°.

Ethyl 2-hydroxyisopropyl sulfide. In a heavy-walled glass tube were placed 21.7 g. of ethyl mercaptan, 20.3 g. of freshly-distilled allyl alcohol, and 0.4 g. of sulfur. The tube

[4] The synthesis of this compound was first described in a British Chemical Warfare Report.

was sealed and supported on corks inside a small steel bomb partially filled with ethyl ether to equalize the pressure on the tube. The temperature was raised gradually, over a three-hour period, to 120° and maintained there for sixty-seven hours. The tube was cooled slowly and opened. The nearly colorless contents were distilled through a 4-in. packed column. The yield of the colorless sulfide was 59%; b.p. 80–90° (17 mm.); n_D^{20} 1.4777.

Anal. Calc'd for $C_5H_{12}OS$: C, 49.96; H, 10.06.
Found: C, 49.71; H, 9.84.

The *α-naphthylurethan* of ethyl 2-hydroxyisopropyl sulfide was purified by recrystallization from ligroin; m.p. 66.5–68°.

Anal. Calc'd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62.
Found: C, 66.79; H, 6.43.

Distillation of the residue (8 g.) yielded 2 g. of the pure isomer, ethyl 3-hydroxy-*n*-propyl sulfide; b.p. 103.5–105.5° (16 mm.); n_D^{20} 1.4823. The boiling point of this compound was recorded as 104° (15 mm.) by Rothstein (13).

The *α-naphthylurethan* of ethyl 3-hydroxy-*n*-propyl sulfide, after repeated recrystallization from ligroin, melted at 42–43°.

Anal. Calc'd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62.
Found: C, 66.41; H, 6.63.

Conversion of ethyl 2-hydroxyisopropyl sulfide to the corresponding chloro sulfide. (a) *With hydrochloric acid.* One hundred twenty-five milliliters of concentrated hydrochloric acid was added, with stirring, to 13.9 g. of the alcohol, the temperature being kept below 30°. The mixture was stirred overnight at room temperature. The chloride, which formed the oily, upper layer, was dissolved in ether and the solution washed well with water. It was dried over magnesium sulfate, and the ether removed at the water-pump. The yield of crude product was 81%; n_D^{20} 1.4780.

The *p-toluenesulfilimine*, after three recrystallizations from ethanol, melted at 120–121.5°.

Anal. Calc'd for $C_{12}H_{18}ClNO_2S_2$: C, 46.82; H, 5.89.
Found: C, 46.90; H, 5.87.

(b) *With thionyl chloride.* By this method the yield of chloride was 78%; n_D^{20} 1.4782. The sulfilimine, after a single recrystallization, melted at 120–122°. A mixture with the product from (a) melted at 120–122°.

The chloro sulfide was converted to the *sulfone* in the manner described for 2-chloroethyl 2-chloro-*n*-propyl sulfone. The main fraction, obtained by distillation, boiled at 88.5–92.5° (0.12–0.20 mm.); n_D^{20} 1.4752 and was used in the subsequent reactions leading to the preparation of ethyl *n*-propyl sulfone. A small amount of unidentified material distilled at 92.5–94° (0.20–0.25 mm.); n_D^{20} 1.4716.

After dehydrochlorination and hydrogenation, the main fraction was distilled *in vacuo*; b.p. 96.5–97.5° (1.9 mm.); m.p. 12–17°; n_D^{20} 1.4495. After repeated recrystallization from a mixture of ether and petroleum ether, the compound melted at 24–25°, the value for the melting point of ethyl *n*-propyl sulfone. A mixture melting point of the new sample with the one prepared from 2-chloroethyl 2-chloro-*n*-propyl sulfone showed them to be alike.

Ethyl 2-hydroxy-n-propyl sulfide. Acetonyl ethyl sulfide was prepared according to the method of Autenrieth (14). The pale yellow product distilled at 63.5–71° (20 mm.); n_D^{20} 1.4710; yield 58%. It readily formed a 2,4-dinitrophenylhydrazone, m.p. 86.5–87.5°, and a *p*-toluenesulfilimine, m.p. 123–124°.

A mixture of 55.2 g. of the acetonyl ethyl sulfide and 300 ml. of a one-molar solution of aluminum isopropoxide in absolute isopropyl alcohol was placed in a 500-ml. flask surmounted by a 15-in. column packed with Berl Saddles. The reaction mixture was heated on a steam-bath and the acetone was distilled as it formed. After nine hours the distillate gave a negative test for acetone with a 0.1% solution of 2,4-dinitrophenylhydrazine in

2 *N* hydrochloric acid. After the solution had been heated under reflux, however, the test again was positive. The reaction, accordingly, was allowed to continue overnight. The ethyl 2-hydroxy-*n*-propyl sulfide, isolated by conventional procedures, was a pale yellow oil, boiling at 83.5–85° (23 mm.); n_D^{20} 1.4737; yield 56%. Redistillation of the product yielded 22 g. of colorless oil; b.p. 76.5° (15 mm.); n_D^{20} 1.4734. Dawson (15) reported the boiling point 83° (25.5 mm.) for this compound.

Anal. Calc'd for $C_5H_{12}OS$: C, 49.96; H, 10.06.
Found: C, 50.01; H, 10.05.

The *α-naphthylurethan* crystallized from ligroin in fine, colorless needles; m.p. 85.5–86°.

Anal. Calc'd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62.
Found: C, 66.74; H, 6.58.

Conversion of ethyl 2-hydroxy-n-propyl sulfide to the corresponding chloride. The hydrochloric acid and thionyl chloride procedures led to yields of 72% and 76%, respectively, of the crude chloro sulfide. It was an orange-yellow oil; n_D^{20} 1.4780. The *p-toluenesulfilimines* of the products prepared by the two procedures melted at 120–121.5° and 121.5–122.5°, respectively. Mixture melting points with the sulfilimine derived from the chloro compound prepared from ethyl 2-hydroxyisopropyl sulfide were not depressed, showing all the compounds to be alike.

bis(2-Chloro-n-propyl) sulfone. *bis*(2-Chloro-*n*-propyl) sulfide was prepared[5] by treating a saturated solution of propylene in chloroform with sulfur monochloride at −10° and then bubbling propylene through the mixture, which gradually was allowed to warm up to room temperature. From 50 g. of sulfur monochloride was obtained 19.8 g. of the redistilled sulfide, b.p. 107–109.5° (13 mm.) (4); n_D^{20} 1.5015–1.5026. The dichloro sulfide was converted to the sulfone according to the procedure described for making 2-chloroethyl 2-chloro-*n*-propyl sulfone. The sulfone was a colorless oil; b.p. 107–108° (0.04 mm.); n_D^{20} 1.4903–1.4917; yield 90% of the theory. It solidified completely at 10° but no attempt was made to purify it by recrystallization.

Anal. Calc'd for $C_6H_{12}Cl_2O_2S$: C, 32.88; H, 5.52.
Found: C, 33.16; H, 5.63.

The sulfone was prepared also from a sample of the dichloro sulfide made from *bis*(2-hydroxy-*n*-propyl) sulfide (16). It melted at 56–56.5°. That this compound was identical, except for degree of purity, with that obtained by the other method was shown by a mixture melting point of the two corresponding halogen-free products obtained by dehydrochlorination and hydrogenation.

bis(Δ¹-Propenyl) sulfone. The dehydrochlorination, carried out in the usual way (11), yielded the sulfone as a colorless oil; b.p. 97.5–100° (0.7 mm.); n_D^{20} 1.4852; yield 72%.

Anal. Calc'd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89.
Found: C, 48.34; H, 6.58.

All fractions of the product turned yellow when allowed to stand.

n-Propyl sulfone. Hydrogenation, performed according to the procedure used to prepare ethyl *n*-propyl sulfone, gave an 84% yield of the saturated sulfone as a pale yellow oil which was crystallized from an ether-petroleum ether mixture; m.p. 29.5–30.5°; n_D^{20} 1.4456.

Anal. Calc'd for $C_6H_{14}O_2S$: C, 47.97; H, 9.39.
Found: C, 47.51; H, 9.48.

The melting point reported (6) for *n*-propyl sulfone is 29–30°.

An authentic sample of *n*-propyl sulfone, obtained from the Eastman Kodak Co., melted at 27.5–30.5° and had the refractive index n_D^{20} 1.4456. The mixture melting point of this sample and that obtained by hydrogenation was 27.5–30°. Diisopropyl sulfone melts at 36° (17).

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[5] This sulfide was prepared by Dr. W. J. Shenk, Jr.

SUMMARY

It has been established that 2-chloroethylsulfenyl chloride condenses with propylene in such a manner that the chloropropyl radical has the normal rather than the iso structure. Likewise, the compound obtained from propylene and sulfur monochloride has been shown to be *bis*(2-chloro-*n*-propyl) sulfide.

Treatment of 2-hydroxyethyl 2-hydroxyisopropyl sulfide with hydrochloric acid has been shown to convert it to 2-chloroethyl 2-chloro-*n*-propyl sulfide. Similarly, ethyl 2-hydroxyisopropyl sulfide has been found to yield ethyl 2-chloro-*n*-propyl sulfide when treated with hydrochloric acid or thionyl chloride.

A mechanism has been proposed to account for the isomerization of the chloropropyl sulfides.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

LEVINSTEIN MUSTARD GAS. III. THE STRUCTURE OF THE MONOCHLORINATION PRODUCT OF MUSTARD GAS[1]

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When mustard gas (I) is made by the condensation of ethylene with sulfur monochloride according to the Levinstein process, the distilled product contains small amounts of 2-chloroethyl 2-chlorovinyl sulfide (IV) as an impurity (1). For this reason it has been assumed that chlorination of the *bis*(2-chloroethyl) sulfide occurs in the process.

This assumption is based upon the observations of several investigators. When Lawson and Dawson (2) treated *bis*(2-chloroethyl) sulfide with one equivalent of chlorine at 0°, they succeeded in isolating *bis*(2-chloroethyl) sulfonium chloride (II). This compound proved to be unstable; it decomposed spontaneously into 2-chloroethyl 1,2-dichloroethyl sulfide (III), which slowly underwent further decomposition at room temperature with the evolution of hydrogen chloride and the formation of 2-chloroethyl 2-chlorovinyl sulfide (IV).

$$\underset{\text{I}}{(ClCH_2CH_2)_2S} \xrightarrow{Cl_2} \underset{\text{II}}{(ClCH_2CH_2)_2SCl_2} \rightarrow \underset{\text{III}}{ClCH_2CH_2SCHClCH_2Cl} \rightarrow \underset{\text{IV}}{ClCH_2CH_2SCH{=}CHCl}$$

Sartori (3) has cited Libermann as authority for saying that sulfur monochloride also reacts with the dichloro sulfide (I) to give II, while Mann and Pope (4) have reported the isolation of the trichloro compound (III) as a product of the action of sulfur monochloride on *bis*(2-chloroethyl) sulfide.

Another possibility, which hitherto has not been considered, is that the unsaturated sulfide (IV) may result from the action of an intermediate in the Levinstein process. The discovery of a method for the synthesis (5) of 2-chloroethylsulfenyl chloride (V), a probable intermediate in the preparation of *bis*(2-chloroethyl) sulfide, opened the way for the investigation of this possibility. Experiment has shown that the sulfenyl chloride and pure mustard gas react with each other, and that 2-chloroethyl 2-chlorovinyl sulfide (IV) actually is produced along with *bis*(2-chloroethyl) disulfide (VI). [The disulfide also has been identified as one of the impurities in the crude product of the condensation of ethylene with sulfur monochloride (6)]. Presumably, the intermediate products are 2-chloroethyl 1,2-dichloroethyl sulfide (III) and 2-chloroethyl mercaptan. The latter would be expected (7) to react with another molecule of 2-chloroethylsulfenyl chloride to produce the disulfide (VI).

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

$$\underset{V}{ClCH_2CH_2SCl} + \underset{I}{ClCH_2CH_2SCH_2CH_2Cl} \rightarrow$$

$$\underset{III}{ClCH_2CH_2SCHClCH_2Cl} + ClCH_2CH_2SH$$

$$ClCH_2CH_2SCHClCH_2Cl \xrightarrow{-HCl} \underset{IV}{ClCH_2CH_2SCH{=}CHCl}$$

$$ClCH_2CH_2SCl + ClCH_2CH_2SH \rightarrow \underset{VI}{(ClCH_2CH_2)_2S_2} + HCl$$

Although it has been accepted generally and without proof that the unstable precursor of 2-chloroethyl 2-chlorovinyl sulfide has the designated structure (III), it became a matter of special interest to establish its identity beyond any reasonable doubt.

The only other structure which was considered for the trichloro compound was 2-chloroethyl 2,2-dichloroethyl sulfide (VIII). By use of the method of Salzberg and Lazier (8) it has been found possible to produce the corresponding hydroxy compound (VII) from monothioglycol and vinylidene chloride. It was converted to the trichloro compound by the action of thionyl chloride.

$$HOCH_2CH_2SH + CH_2{=}CCl_2 \rightarrow \underset{VII}{HOCH_2CH_2SCH_2CHCl_2}$$

$$\xrightarrow{SOCl_2} \underset{VIII}{ClCH_2CH_2SCH_2CHCl_2}$$

The structure of the trichloro sulfide was established by hydrolysis, which converted the compound to the expected (2-hydroxyethylthio)acetaldehyde (IX).

$$ClCH_2CH_2SCH_2CHCl_2 \xrightarrow{H_2O} \underset{IX}{HOCH_2CH_2SCH_2CHO}$$

The 2,4-dinitrophenylhydrazone derived from this aldehyde was found to be the same as that prepared from (2-hydroxyethylthio)acetal (X), made by the condensation of chloroacetal with the sodium salt of monothioglycol.

$$ClCH_2CH(OC_2H_5)_2 + NaSCH_2CH_2OH \rightarrow \underset{X}{HOCH_2CH_2SCH_2CH(OC_2H_5)_2}$$

The new trichloro compound was characterized further by preparation of the sulfone, the *p*-toluenesulfilimine, and the morpholyldithiocarbamate derivatives.

The stability of this trichloro compound excluded the possibility that it was a precursor of 2-chloroethyl 2-chlorovinyl sulfide; it was possible to dehydrochlorinate it only to the extent of 3% by long heating with triethylamine. It is interesting that dehydrochlorination of the sulfone occurred with ease; treatment with one mole of triethylamine yielded 2-chloroethyl 2-chlorovinyl sulfone (XI).

$$\underset{\substack{\uparrow\\ \downarrow\\ O}}{ClCH_2CH_2S(O)CH_2CHCl_2} \xrightarrow{-HCl} \underset{\substack{\uparrow\\ \downarrow\\ O}}{ClCH_2CH_2S(O)CH{=}CHCl}$$

XI

The sulfone was characterized by comparison with a sample obtained from 2-chloroethyl 2-chlorovinyl sulfide made by the condensation of 2-chloroethylsulfenyl chloride with acetylene (5).

EXPERIMENTAL

Reaction of 2-chloroethylsulfenyl chloride with bis(2-chloroethyl) sulfide.[2] Sixty-six grams of the sulfenyl chloride was added, during the course of fifteen minutes and at room temperature, to 40 g. of the sulfide. The sulfenyl chloride was decolorized rapidly and hydrogen chloride was evolved. The product was distilled repeatedly at a pressure of 1 mm. until hydrogen chloride ceased to be evolved. Fractionation of this liquid yielded *bis*(2-chloroethyl) disulfide and a compound which is believed to be 2-chloroethyl 2-chlorovinyl sulfide (5). The latter compound was a colorless liquid (n_D^{20} 1.5458) which gave a reddish-brown color when treated with sulfuric acid.

Anal. Calc'd for $C_4H_6Cl_2S$: Cl, 45.16. Found: Cl, 45.15.

2-Chloroethyl 2,2-dichloroethyl sulfide. In a 500-ml. Vycor flask, fitted with a reflux condenser and a Glas-Col heater were placed 126 g. of redistilled monothioglycol, 318 g. of vinylidene chloride (dried over magnesium sulfate), and 1 g. of benzoyl peroxide. The mixture was irradiated with ultraviolet light for twenty-one hours at a temperature of 40–45°. Two additional 0.5-g. portions of the peroxide were added during the irradiation period. The excess vinylidene chloride was allowed to evaporate, and the unchanged monothioglycol (96 g.) was removed at a pressure of 0.3 mm. The residual oil (96 g.), which was not heated above 80°, was dissolved in 180 g. of chloroform and the solution washed with water. The solution was dried over anhydrous magnesium sulfate and filtered. The crude 2,2-dichloroethyl 2-hydroxyethyl sulfide was kept in chloroform solution, since in the absence of a solvent it gradually darkened.

The chloroform solution of the hydroxy compound was added, dropwise over a two-hour period, to a well-stirred solution of 73 g. of thionyl chloride in 75 ml. of dry chloroform. Removal of the solvent and fractional distillation of the residue yielded 35.3 g. of 2-chloroethyl 2,2-dichloroethyl sulfide boiling at 68–69° (0.05 mm.); n_D^{20} 1.5380. The yield was 11.3% if based on the amount of monothioglycol taken, 47.3% if based on the quantity of monothioglycol actually consumed in the reaction.

Anal. Calc'd for $C_4H_7Cl_3S$: C, 24.82; H, 3.63; Cl, 54.96; S, 16.57.
Found: C, 24.74; H, 3.44; Cl, 54.79; S, 17.22.

Sulfilimine. The trichloro sulfide was treated with Chloramine-T in an acetone-water solution. The product, after three recrystallizations from dilute ethanol, melted, with decomposition, at 157–158°.

Anal. Calc'd for $C_{11}H_{14}Cl_3NO_2S_2$: C, 36.44; H, 3.87.
Found: C, 36.58; H, 3.75.

Morpholyldithiocarbamate. A solution of 18.8 g. of potassium hydroxide, 29 g. of morpholine, and 60 ml. of absolute ethanol was dropped slowly into a well-stirred solution of 31.5 g. of carbon disulfide in 50 ml. of ether. The reaction vessel was kept in an ice-bath during the addition. The potassium morpholyldithiocarbamate was isolated by filtration and washed with absolute ethanol; yield 63.5 g., or 94%. Six grams of the trichloro sulfide was dissolved in 100 ml. of ethanol, and 8 g. of the potassium salt in 80 ml. of water was added. The mixture was heated under reflux for sixteen hours, cooled, and kept at 0° for twenty-four hours. The crystals which formed were separated by filtration and recrystallized four times from dilute ethanol; m.p. 77–80°.

Anal. Calc'd for $C_9H_{15}Cl_2NOS_3$: C, 33.75; H, 4.77.
Found: C, 34.56; H, 4.71.

The composition of the product corresponds approximately to that calculated for the derivative in which one chlorine atom has been replaced.

[2] This experiment was carried out by Dr. E. W. Maynert.

Sulfone. Two and two-tenths grams of 30% hydrogen peroxide was added slowly to a solution of 3.8 g. of the trichloro sulfide in 20 ml. of glacial acetic acid. After the introduction of an additional 5.2 g. of the peroxide solution, the mixture was heated under reflux for thirty minutes, cooled, and poured into ice-water. Two grams of white, crystalline sulfone separated. After three recrystallizations from dilute ethanol, the white needles melted at 73–74°.

Anal. Calc'd for $C_4H_7Cl_3O_2S$: C, 21.30; H, 3.13.
Found: C, 21.39; H, 3.36.

When a mixture of 4 g. (0.017 mole) of the sulfone, 1.8 g. (0.017 mole) of triethylamine, and 50 ml. of absolute ether was heated to boiling, a heavy, white precipitate of triethylamine hydrochloride formed immediately. The precipitate was removed by filtration, the ether evaporated, and the resulting liquid poured into ice-water. The white, plate-like crystals which separated were recrystallized from petroleum ether; m.p. 38–39°. A mixture of this compound with an authentic sample of *2-chloroethyl 2-chlorovinyl sulfone* (5) (m.p. 37.5–38.5°.) melted at 38–39°.

Attempted dehydrohalogenation of 2-chloroethyl 2,2-dichloroethyl sulfide. One-tenth of a mole each of the sulfide and triethylamine were heated in 50 ml. of absolute ether at 37° for nine days. Only 0.003 mole of triethylamine hydrochloride separated. Upon long standing at room temperature the solution turned black, but no more of the hydrochloride separated.

Hydrolysis of 2-chloroethyl 2,2-dichloroethyl sulfide. A mixture of 23.5 g. of the sulfide and 600 ml. of water was stirred at room temperature for seven days. The insoluble residue (1.9 g.) was shown to be unchanged trichloro sulfide by preparation of the sulfilimine. Titration of the water solution indicated that 75% of the maximum possible amount of hydrochloric acid had been formed. The *(2-hydroxyethylthio)acetaldehyde* was extracted with ether and the resulting solution dried over sodium sulfate. Distillation of the solvent left 7 g. (48%) of the aldehyde as a pale yellow oil; n_D^{20} 1.5050. It possessed a sweet, ester-like odor, gave a positive fuchsin test, and reduced Tollens' reagent. The *2,4-dinitrophenylhydrazone*, formed in the usual way, was recrystallized twice from dilute ethanol; m.p. 74–75°.

Anal. Calc'd for $C_{10}H_{12}N_4O_5S$: C, 40.00; H, 4.03; N, 18.66; S, 10.67.
Found: C, 40.12; H, 4.09; N, 18.36; S, 10.85.

Preparation of (2-hydroxyethylthio)acetal. Fifteen and six-tenths grams of redistilled monothioglycol was added to a solution of sodium ethoxide prepared from 4.6 g. of sodium and 125 ml. of absolute ethanol. To this solution was added slowly, with stirring, 30.4 g. of chloroacetal. The mixture became cloudy but no sodium chloride was precipitated. A small amount of potassium iodide was added, and the mixture was heated overnight at 55°, with stirring. After removal of the salt by filtration and evaporation of the ethanol, the residual oil was extracted with dry ether. Evaporation of the ether left the *(2-hydroxyethylthio)acetal* as a dark orange oil; yield 15 g. or 38.6% of the theory.

A mixture of 3 ml. of the acetal and 5 ml. of dilute hydrochloric acid was warmed, and a solution of 1.5 g. of 2,4-dinitrophenylhydrazine in 100 ml. of boiling ethanol was added. The solution was shaken for a few minutes, 2 ml. of concentrated hydrochloric acid was added, and the mixture was heated under reflux for seven minutes. When the solution was cooled and diluted with water, a large amount of yellow crystals separated; m.p. 62–67°. They were purified by repeated recrystallization from ethanol; m.p. 74–75°. A mixture of this compound with the 2,4-dinitrophenylhydrazone prepared from the hydrolysis product of the trichloro sulfide, showed no lowering of the melting point.

SUMMARY

Evidence has been presented in support of the belief that the monochlorination product of mustard gas is 2-chloroethyl 1,2-dichloroethyl sulfide. The

isomeric monochloro derivative, 2-chloroethyl 2,2-dichloroethyl sulfide, has been prepared, and the two products have been shown to be different.

The 2,2-dichloroethyl compound was made by the addition of monothioglycol to vinylidene chloride. Its structure was established by hydrolysis, which converted it to (2-hydroxyethylthio)acetaldehyde.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

LEVINSTEIN MUSTARD GAS. IV. THE *bis*(2-CHLOROETHYL) POLYSULFIDES[1]

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Mustard gas made by the Levinstein process is known to contain a considerable amount of material which has a high sulfur content and which has been thought to consist of the *bis*(2-chloroethyl) polysulfides (1). The present work deals with the identification and a study of some properties of these substances. The problem has been attacked not only by attempts to isolate pure compounds from the high-boiling fraction obtained by the Levinstein process but also by the preparation of the polysulfides by synthetic methods.

THE SYNTHESIS OF THE POLYSULFIDES

The synthesis of *bis*(2-chloroethyl) disulfide was carried out by converting monothioglycol to *bis*(2-hydroxyethyl) disulfide and treating the latter with concentrated hydrochloric acid.

$$2\ HOCH_2CH_2SH + H_2O_2 \rightarrow (HOCH_2CH_2)_2S_2 + 2\ H_2O$$
$$(HOCH_2CH_2)_2S_2 + 2\ HCl \rightarrow (ClCH_2CH_2)_2S_2 + 2\ H_2O$$

The procedure was essentially that of Bennett (2). The last step has been modified so as to be continuous, greatly facilitating the preparation of large amounts of material. This method is of especial value in the synthesis of vesicant compounds; for example, *bis*(2-chloroethyl) sulfide, 1,2-*bis*(2-chloroethylthio)ethane, and 2-chloroethyl 2-chloro-*n*-propyl sulfide have been prepared in yields of 85, 92, and 61%, respectively.

bis(2-Chloroethyl) trisulfide was isolated by Mann, Pope, and Vernon (3) from the product obtained by the reaction between sulfur monochloride and ethylene at 60°. It has now been prepared by a straightforward synthesis from ethylene chlorohydrin and sodium polysulfide followed by treatment of the resulting glycol with thionyl chloride.

$$2\ HOCH_2CH_2Cl + Na_2S_3 \rightarrow (HOCH_2CH_2)_2S_3 + 2\ NaCl$$
$$(HOCH_2CH_2)_2S_3 + 2\ SOCl_2 \rightarrow (ClCH_2CH_2)_2S_3 + 2\ SO_2 + 2\ HCl$$

The trisulfide is a white, crystalline compound melting at 30.5–31.5°. Distillation of the crude reaction product yielded a considerable quantity of the disulfide. Later it was found that the pure trisulfide actually decomposes under the influence of heat to give *bis*(2-chloroethyl) disulfide.

bis(2-Chloroethyl) pentasulfide was isolated first in studies of the hydrolysis

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

of mustard gas which had been made by the Levinstein process. It was noticed that hydrolysis with water appeared to be incomplete. The method of "exhaustive" hydrolysis was then developed for the isolation of the polysulfides corresponding to mustard gas. It consisted in subjecting a mixture of Levinstein mustard gas and water to vigorous agitation. The progress of the hydrolysis was followed by titration to determine hydrogen or chloride ion concentration. When the rate of hydrolysis had become negligibly small, the unhydrolyzed residue was found to amount to about 30% by weight of the original mustard gas. The composition of the residues from various samples varied from values corresponding to those for the hexasulfide to those for the nonasulfide.

The unhydrolyzed residues were observed to deposit sulfur slowly. Because sulfur dissolves only slightly in Cellosolve, whereas polysulfides are fairly soluble, the possibility suggested itself of using this solvent as a means of separating the excess sulfur rapidly from the polysulfides. When the Levinstein residue was treated with Cellosolve, sulfur separated in crystalline form and, in addition, a small amount of viscous oil remained undissolved. This oil had the composition, indicated by analysis, of a higher polysulfide such as $(ClCH_2CH_2)_2S_{11}$. It invariably deposited sulfur within a few days and took on the appearance of yellow, crystalline sulfur.

The Cellosolve solution was washed with water to remove the Cellosolve; the water-insoluble oil was dried in ether solution and then freed from the ether. A clear, amber oil was obtained, which consisted almost entirely of *bis*(2-chloroethyl) pentasulfide.

It is impossible to purify the pentasulfide by ordinary distillation because of its thermal instability; nevertheless the volatile materials such as the disulfide can be removed by steam-distillation, either before or after treatment with Cellosolve. However, due to autosulfurization of the pentasulfide, which is described later, stripping with Cellosolve after distillation is always necessary. The purest pentasulfide obtained was an amber liquid of high refractive index (n_D^{20} 1.6853) which could not be induced to crystallize, even at $-80°$.

Oils which had the composition of the higher sulfides were made also by treatment of *bis*(2-chloroethyl) trisulfide with sulfur under mild conditions and by heating the corresponding disulfide with sulfur under more drastic conditions. When these oils were stripped of excess sulfur by the Cellosolve treatment they resembled the Cellosolve-stripped Levinstein residues in appearance, odor, refractive index, density, and composition. Also, polarographic studies revealed the same reduction potential for the synthetic pentasulfides as for that isolated from Levinstein mustard gas.

PROPERTIES OF THE POLYSULFIDES

A few of the properties of the *bis*(2-chloroethyl) polysulfides have been mentioned in the preceding section; notably, the sulfurization of the di- and trisulfides with sulfur and the stripping of the higher polysulfides to *bis*(2-chloroethyl) pentasulfide with Cellosolve. A number of the reactions presently to be mentioned also have been of value in the synthesis of the polysulfides.

Sulfurization. Following the suggestion of Dr. E. Emmett Reid (4) that alkyl polysulfides might be better sulfurizing agents than sulfur itself, experiments were run in which *bis*(2-chloroethyl) disulfide, trisulfide, and pentasulfide were heated with methyl tetrasulfide. The assumption was made that at the temperature and pressure employed, the volatile methyl trisulfide would be removed as it was formed, allowing the reaction to proceed to completion. In this way *bis*(2-chloroethyl) pentasulfide and higher polysulfides identical with the polysulfides obtained by other methods were prepared from the trisulfide and pentasulfide.

$$(ClCH_2CH_2)_2S_3 + 2\ (CH_3)_2S_4 \rightarrow (ClCH_2CH_2)_2S_5 + 2\ (CH_3)_2S_3$$

bis(2-Chloroethyl) disulfide was not sulfurized by methyl tetrasulfide under the same conditions.

The autosulfurization of *bis*(2-chloroethyl) pentasulfide also is a reaction which falls into this category. When the pentasulfide was subjected to steam distillation, the distillate was found to contain the corresponding trisulfide. The residue had the composition of polysulfides higher than the pentasulfide. Evidently, under these conditions autosulfurization of the pentasulfide occurred, the removal of the trisulfide forcing the reaction to proceed.

$$(ClCH_2CH_2)_2S_5 \rightarrow (ClCH_2CH_2)_2S_{5+x} + (ClCH_2CH_2)_2S_3$$

It was mentioned that when the non-hydrolyzable Levinstein residues were stripped with Cellosolve, not only sulfur, but also a gum was obtained which had the analytical composition of a high polysulfide, $(ClCH_2CH_2)_2S_{11}$. It was found that when *bis*(2-chloroethyl) trisulfide or pentasulfide was heated with sulfur, and the reaction mixtures subsequently extracted with Cellosolve and ether, there remained viscous oils which had the composition indicated by analysis of high polysulfides of the order of the dodecasulfide or greater. These polysulfides were often stable for days at room temperature even in the presence of sulfur, although the presence of ammonia caused their rapid degradation to the pentasulfide and sulfur (see section on Stripping).

The fact that the higher sulfides readily give up sulfur suggested that they might not be definite compounds but merely solutions of sulfur in the pentasulfide. This hypothesis seems untenable in view of the observation that when mixtures of finely divided sulfur and the pentasulfide were shaken for extended periods at room temperature, less than one gram atom of sulfur dissolved.

Stripping. It has been seen that sulfurization is a most important reaction of the polysulfides; by the same token, the reverse procedure, stripping, plays a prominent rôle in the chemistry of these unusual compounds.

It had been discovered by other investigators (5) that treatment of the high-boiling fraction of Levinstein mustard gas with moist, gaseous ammonia caused rapid precipitation of sulfur. Examination of the analytical data showed that the residual oil corresponded closely in composition to *bis*(2-chloroethyl) pentasulfide. This report has been confirmed, although it appears that ammonia-

stripping is not as efficacious as the Cellosolve method already described. With ammonia alone some sulfur seems to remain dissolved in the pentasulfide.

Although *bis*(2-chloroethyl) pentasulfide is stable to moist ammonia and to Cellosolve alone, it is readily stripped to the trisulfide by ammonia in the presence of either Cellosolve or ether. The degradation of the pentasulfide to the trisulfide by steam-distillation has already been mentioned in another connection.

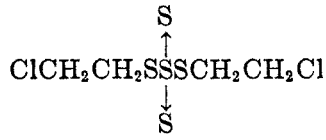
Up to this point no reference has been made to *bis*(2 chloroethyl) tetrasulfide. The evidence that such a compound actually exists is meager. The only indication of a true level of stability for a polysulfide of this composition was found in a study of the stripping of the pentasulfide with boiling acetone. In experiments using *bis*(2-chloroethyl) pentasulfide from several different sources, the limit of degradation appeared to be at the tetrasulfide level.

STRUCTURE OF THE POLYSULFIDES

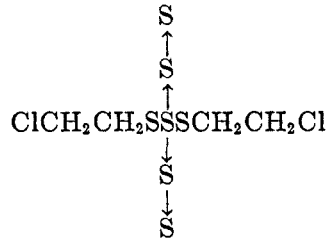
The linear structure for *bis*(2-chloroethyl) disulfide follows from its method of synthesis. The stability of the corresponding pentasulfide and trisulfide and the degradation of the former to the latter indicate that these compounds are related structurally. The disulfide, known to be linear, takes up an atom of sulfur only with difficulty. Then two additional atoms of sulfur may be added with comparative ease to produce the pentasulfide, degradation of which yields the trisulfide. These facts may be explained plausibly by assuming that a sulfur atom enters the disulfide molecule to produce a linear trisulfide.

$$ClCH_2CH_2SSCH_2CH_2Cl + S \rightarrow ClCH_2CH_2SSSCH_2CH_2Cl$$

The trisulfide then easily takes up two additional sulfur atoms to yield the pentasulfide, the newly added sulfur being joined to the central sulfur atom as in the following formula.



The structure of the higher polysulfides could be of the following type.



This type of structure is in accord with the facts that sulfur atoms are naturally chain-forming and that the polysulfides above the pentasulfide readily lose sulfur. The gradual conversion of plastic sulfur, $S\mu$, which is supposed to consist

of long sulfur chains, to the stable λ-sulfur is accelerated by ammonia (6). This may be related to the observed stripping of higher polysulfides to the pentasulfide by ammonia.

bis(2-CHLOROETHYL) DISULFIDE

Reports of the existence of *bis*(2-chloroethyl) disulfide in Levinstein mustard gas are in disagreement. This is not at all surprising in view of the tendency of the higher polysulfides to decompose under the influence of heat to give the trisulfide which in turn is degraded to the disulfide by distillation. It is apparent that any reliable method for determining the amount of the disulfide in the Levinstein product must involve only mild conditions.

There is one report (5) that Levinstein mustard gas contains about 6% of *bis*(2-chloroethyl) disulfide. If this were true, about 20% of the non-hydrolyzable portion of the product and an even greater proportion of the stripped residue would consist of the disulfide, since it has been found to resist hydrolysis under the conditions employed. Analysis of the stripped residue indicated that the proportion of *bis*(2-chloroethyl) disulfide was much lower than this figure.

It was observed that the refractive indices of mixtures of the disulfide and pentasulfide, and of the disulfide and trisulfide, followed a linear relationship with respect to the mole fraction of the constituents. Thus, measurement of the refractive indices of the stripped residue from the hydrolysis of Levinstein mustard gas, and of the steam-distillate of the residue, indicated the presence of 1 to 1.8% of the disulfide in the crude mustard gas. This value is in good agreement with that obtained by MacInnes and Belcher (7) by analysis of a fraction from the molecular distillation of Levinstein mustard gas.

Crystalline derivatives of *bis*(2-chloroethyl) disulfide were prepared using thiosalicylic acid, potassium morpholyldithiocarbamate, and piperidine. All but the last are useful for the identification of the disulfide. Attempts to prepare similar derivatives of *bis*(2-chloroethyl) trisulfide gave intractible solids or oils, from which no pure compound could be isolated.

EXPERIMENTAL

Preparation of bis(2-chloroethyl) disulfide. The preparation of this compound was carried out by a modification of a method used by Bennett (2). Five hundred three grams of 30% hydrogen peroxide was added slowly, with stirring, to 624 g. of monothioglycol over a period of two hours. The temperature was maintained at 50–60° by careful cooling. After the addition was complete the reaction mixture was allowed to stand for two hours; then it was heated on a steam-cone under reduced pressure to remove the water. The crude *bis*(2-hydroxyethyl) disulfide was mixed with 2800 ml. of concentrated hydrochloric acid and the mixture heated on a steam-cone for one and one-half hours. The aqueous layer was decanted and the dichloride distilled through a heated, packed 12-inch column. The yield of *bis*(2-chloroethyl) disulfide, boiling at 97–98° (0.4 mm.), was 580 g., or 94%; n_D^{20} 1.5656.

For large scale production the last step has been modified so as to be continuous. A diagram of the apparatus used is shown in Fig. 1. One hundred grams of the glycol was added from the dropping-funnel over a period of forty minutes to 130 ml. of concentrated hydrochloric acid, with constant bubbling of gaseous hydrogen chloride through the solution. The temperature, initially at 75°, soon rose to 90° where it remained for the duration

of the reaction. The chloride which separated was removed continuously by the suction provided by the vacuum line. The yield of the dichloro disulfide obtained by this procedure was 94%.

Preparation of bis(2-chloroethyl) trisulfide.[2] A solution of sodium trisulfide was prepared by dissolving 256 g. of sulfur in 960 g. of sodium sulfide nonahydrate and 1300 ml. of water.

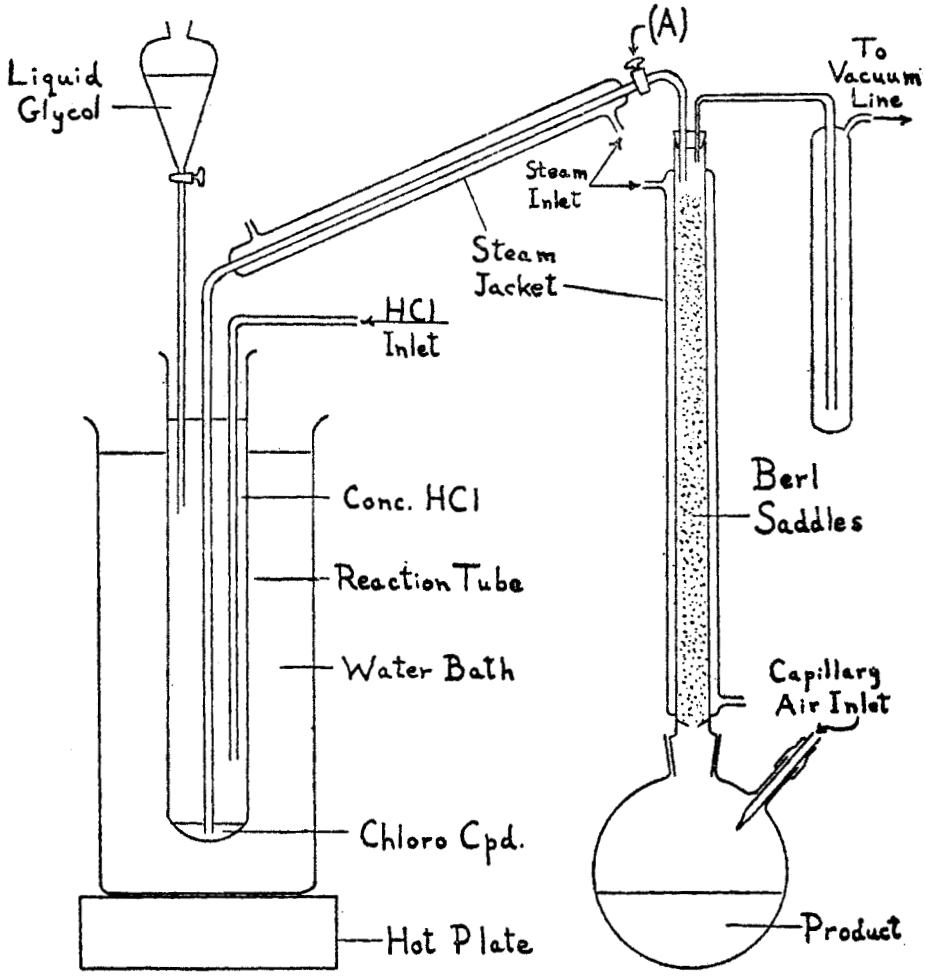


FIG. 1

To this red solution was added over a period of one-half hour, with stirring, 644 g. of ethylene chlorohydrin. Heat was evolved, and the flask was cooled with ice-water. The crude glycol, *bis*(2-hydroxyethyl) trisulfide, began to separate when about two-thirds of the chlorohydrin had been added. After an additional four hours of stirring the oily layer was removed, and water and excess chlorohydrin were distilled under reduced pressure.

The residual glycol, which corresponded to an 80% yield, was converted to the chloride

[2] From a British Chemical Warfare report it appears that a similar procedure was developed independently by Kinnear and Harley-Mason.

by the use of thionyl chloride in chloroform solution (8). When the reaction was complete, the chloroform and excess thionyl chloride were removed at water-pump pressures and the crude chloride fractionally distilled at a pressure of 0.01 mm. The fractions with refractive indices between 1.59 and 1.62 were combined and crystallized from absolute ethanol; the white, crystalline trisulfide melted at 30.5–31.5°; n_D^{20} 1.6110. Mann, Pope, and Vernon (3) report the melting point 27°. From 600 g. of crude chloride about 200 g. of the pure solid was obtained.

Anal. Calc'd for $C_4H_8Cl_2S_3$: C, 21.54; H, 3.62; Cl, 31.80; S, 43.13.
Found: C, 21.78; H, 3.57; Cl, 31.55, 31.76; S, 43.14.

Preparation of bis(2-chloroethyl) pentasulfide. a. *From Levinstein mustard gas.*[3] A sample of Levinstein mustard gas (1210 g.) was stirred vigorously with water for eleven days. The water was changed frequently during this period until finally the hydrogen ion concentration became negligible, indicating the hydrolysis of *bis*(2-chloroethyl) sulfide to be complete. The unhydrolyzed polysulfide residue, amounting to 29.1% of the total weight of mustard used, was dissolved in Cellosolve. The precipitated sulfur (77.5 g.) and a small amount of viscous oil were removed by filtration and the Cellosolve subsequently washed out with water. The composition of the polysulfide originally present was $(ClCH_2CH_2)_2S_{7.6}$, based on the weight-percent of residue obtained and $(ClCH_2CH_2)_2S_{7.5}$, based on the amount of sulfur obtained by stripping. The crude pentasulfide (n_D^{20} 1.6763) had the following composition.

Anal. Calc'd for $C_4H_8Cl_2S_5$: C, 16.72; H, 2.81.
Found: C, 17.93; H, 2.74.

It was purified by steam distillation (to remove any disulfide and trisulfide present) followed by stripping with Cellosolve. During the steam distillation, fractions of the distillate were collected and the refractive index of the oil was determined. When the index of the oil reached 1.61 (approximately the value for the trisulfide) the distillation was halted. The weight of oil was 10% of the total weight of the crude pentasulfide taken. The residue had the index 1.685. After being stripped with Cellosolve, the water-insoluble oil was dried in ether solution and the ether removed *in vacuo* at 30°. The light amber pentasulfide amounted to 70% of the original crude pentasulfide; n_D^{20} 1.6853; d_4^{10} 1.5013. It did not freeze at −80°.

Anal. Calc'd for $C_4H_8Cl_2S_5$: C, 16.72; H, 2.81; Cl, 24.74; S, 55.74.
Found: C, 16.98; H, 2.82; Cl, 23.76; S, 56.64.

b. *By sulfurization of bis(2-chloroethyl) trisulfide with sulfur.* The trisulfide was heated with sulfur in the molecular proportions to produce the penta-, hexa-, octa-, and decasulfides. The heating was varied from six to thirty-six hours and the temperature from 115° to 140°. In every case a homogeneous product was obtained, which when allowed to stand in a refrigerator for several days deposited sulfur. The amount of sulfur deposited closely approached that taken in excess of the amount required to produce the pentasulfide. Several samples, the composition of which had approached that of the pentasulfide, were observed to deposit no more sulfur over a period of three weeks. Treatment of the polysulfides with Cellosolve as described in the previous experiment removed further small amounts of sulfur. The resulting pale yellow oils had properties (refractive index, density, and composition) which corresponded closely to those of *bis*(2-chloroethyl) pentasulfide.

c. *By sulfurization of bis(2-chloroethyl) disulfide with sulfur.* It was found that when the disulfide was heated with sulfur under conditions which were adequate to sulfurize the trisulfide, most of the sulfur was reprecipitated on cooling. However, when the mixture was heated at higher temperatures (145–150°) for twenty to thirty hours a polysulfide was formed which had the same properties as that obtained from *bis*(2-chloroethyl) trisulfide. Here, as before it was observed that sulfur precipitated slowly until the composition of the residual oil approached that of *bis*(2-chloroethyl) pentasulfide.

[3] This procedure was developed from preliminary experiments conducted by Dr. Orville H. Bullitt, Jr.

Isolation of a high polysulfide from Levinstein mustard. When the residue from the hydrolysis of Levinstein mustard gas is stripped with Cellosolve, there is obtained, in addition to sulfur, a small amount of Cellosolve-insoluble oil. A portion of this dark, viscous oil was filtered, washed well with water, and dried in carbon disulfide solution over magnesium sulfate. After removal of the drying agent and solvent a sample was analyzed.

Anal. Calc'd for $C_4H_8Cl_2S_{11}$: C, 10.0; H, 1.7; S, 73.5; Cl, 14.8.
Found: C, 10.1; H, 1.8; S, 75.9; Cl, 14.7.

The material slowly deposited crystalline sulfur on standing.

Preparation of methyl tetrasulfide.[4] This compound was prepared by a modification of the method of Levi and Baroni (9) for ethyl tetrasulfide. Equimolar quantities of sulfur and sulfur monochloride were heated on a steam-cone for five hours. Carbon disulfide was added and methyl mercaptan introduced. The addition was continued for some time after the evolution of hydrogen chloride had ceased. The carbon disulfide was evaporated, and the residue was heated for sixteen hours and distilled *in vacuo*. The fraction boiling at 56–69° (1 mm.) was collected; n_D^{20} 1.6403. The yield was 25%. Redistillation gave the pure tetrasulfide; b.p. 68–70° (1.5 mm.); n_D^{20} 1.6621; d_4^{25} 1.3008.

Anal. Calc'd for $C_2H_6S_4$: C, 15.20; H, 3.81.
Found: C, 15.43; H, 3.68.

Attempted sulfurization of bis(2-chloroethyl) disulfide with methyl tetrasulfide. The disulfide (0.05 mole) was mixed with methyl tetrasulfide (0.15 mole) and treated in a manner similar to that described for the sulfurization of *bis*(2-chloroethyl) trisulfide. At a bath temperature of 90° and a pressure of 1 mm. the liquid distilled completely. The refractive indices of the various fractions indicated that they consisted of mixtures of *bis*(2-chloroethyl) disulfide and methyl polysulfides.

Sulfurization of bis(2-chloroethyl) trisulfide with methyl tetrasulfide. A mixture of methyl tetrasulfide (0.14 mole) and *bis*(2-chloroethyl) trisulfide (0.06 mole) was warmed at 35–40° (3–4 mm.) in a distillation apparatus. After a few hours the receiver, which was immersed in Dry Ice, contained material of refractive index, n_D^{20} 1.5999 (methyl trisulfide, n_D^{20} 1.5890). The slow distillation was continued at 60° (1 mm.) for five hours; distillate n_D^{20} 1.6180; residue n_D^{20} 1.6684. Finally the temperature was increased to 120° for two hours at the same pressure. The oil which remained, n_D^{20} 1.6840, had only a slight odor of methyl polysulfide. It was dried in ether solution and the solvent evaporated. The yield of pale yellow pentasulfide was 50%; n_D^{20} 1.6850.

Sulfurization of bis(2-chloroethyl) pentasulfide with methyl tetrasulfide. A mixture of *bis*(2-chloroethyl) pentasulfide and two molecular equivalents of methyl tetrasulfide was heated at 75° for four hours, and then distilled at water-pump pressure in a nitrogen atmosphere. Finally, the temperature of the bath was raised to 130° for several hours. The residue was a clear, brown, viscous liquid (n_D^{20} >1.74) whose weight corresponded to a 97% yield of *bis*(2-chloroethyl) heptasulfide. It deposited sulfur upon standing overnight. The resulting oil was shown by analysis to have an average composition of $(ClCH_2CH_2)_2S_{6.3}$.

Anal. Calc'd for $C_4H_8Cl_2S_7$: C, 13.66; H, 2.28.
Found: C, 14.57; H, 2.46.

This material was insoluble in acetone, alcohol, and ether, but soluble in chloroform and carbon disulfide. Stripping with moist ammonia (see below) reconverted it to the original *bis*(2-chloroethyl) pentasulfide (n_D^{20} 1.6740).

The above experiment was repeated using amounts of methyl tetrasulfide calculated to yield the octasulfide and nonasulfide. The results were analogous, except that the polysulfides formed were relatively less stable. For example, the nonasulfide deposited sulfur on standing only a few hours to give a compound whose composition corresponded closely to that of *bis*(2-chloroethyl) heptasulfide.

Anal. Found: C, 13.89; H, 2.15.

Autosulfurization of bis(2-chloroethyl) pentasulfide. The residue from the steam distilla-

[4] This compound was prepared by Dr. Curtis W. Smith.

tion of a 10-g. sample of the pentasulfide, which had been distilled until 400 ml. of aqueous distillate had been collected, was dried by filtration and allowed to stand for one week. No sulfur precipitated, so the clear, amber oil (n_D^{20} 1.702) was submitted for analysis. It had the average composition $(ClCH_2CH_2)_2S_{5.5}$.

Anal. Calc'd for $C_4H_8Cl_2S_{5.55}$: C, 15.80; H, 2.64.
Found: C, 15.80; H, 2.67.

Another sample of the pentasulfide which had been steam-distilled more extensively yielded a residue whose composition corresponded to $(ClCH_2CH_2)_2S_{5.8}$.

Anal. Calc'd for $(ClCH_2CH_2)_2S_{5.8}$: C, 15.36; H, 2.54.
Found: C, 15.38; H, 2.49.

Sulfurization of bis(2-chloroethyl) pentasulfide with sulfur. Ten grams of the pentasulfide was heated with 9.0 g. of sulfur at 110° for three days. When the mixture was cooled and allowed to stand for several hours, it deposited a large amount of sulfur which was removed by filtration. The filtrate was shaken with Cellosolve, and the residue extracted several times with ether; the insoluble oil was dried *in vacuo*. The composition of the resultant red, viscous oil approximated that of the dodecasulfide.

Anal. Calc'd for $C_4H_8Cl_2S_{12}$: C, 9.17; H, 1.57.
Found: C, 9.43; H, 1.52.

Solubility of sulfur in polysulfides. a. *bis(2-chloroethyl) trisulfide.* Finely divided sulfur, obtained by filtration of a suspension of "milk of sulfur" (10), was shaken with a sample of the trisulfide (n_D^{20} 1.6125) for several days. The amount which dissolved was estimated by difference to be 4.58%. The resulting solution (n_D^{20} 1.6216) was stripped with Cellosolve. The amount of sulfur recovered indicated a solubility of 4.18%. The average of these results indicates that *bis*(2-chloroethyl) trisulfide dissolved up to 4.4% of its weight of sulfur, which is equivalent to one-third of an atom.

b. *bis(2-Chloroethyl) pentasulfide.* In a similar manner a sample of crude pentasulfide (n_D^{20} 1.6758) dissolved up to 7.4% (average value) of its weight of sulfur. This corresponds approximately to two-thirds of an atom. The index of refraction of the saturated solution was n_D^{20} 1.6850.

Stripping of polysulfides. It has already been shown in the preparation of *bis*(2-chloroethyl) pentasulfide from Levinstein mustard gas that the higher polysulfides are stripped to the pentasulfide with Cellosolve. Stripping of polysulfides also has been accomplished by the following methods.

a. *With moist ammonia.* A sample of *bis*(2-chloroethyl) pentasulfide, synthesized from the trisulfide, was treated with moist ammonia gas for several hours. No sulfur precipitated.

In a similar manner a portion of the polysulfide residue remaining from the exhaustive hydrolysis of Levinstein mustard gas was treated with moist ammonia gas for several hours. The sulfur which precipitated was removed by filtration. The composition of the stripped residue, n_D^{20} 1.672, was that of the pentasulfide.

Anal. Calc'd for $C_4H_8Cl_2S_5$: Cl, 24.74. Found: Cl, 24.8.

In another experiment it was noticed that subsequent treatment of the stripped residue with Cellosolve yielded an additional amount of sulfur, 5.2% by weight. This indicates that some sulfur must have remained dissolved in the pentasulfide after treatment with ammonia.

b. *With ammonia in the presence of Cellosolve or ether.* A sample of *bis*(2-chloroethyl) pentasulfide was dissolved in moist ether and the solution was saturated with ammonia. The sulfur which precipitated was removed by filtration and the process repeated until there was no further separation of sulfur, even when the solution was cooled to 0°. The resulting ether solution was dried and the solvent evaporated. The composition of the red oil (n_D^{20} 1.6244) was estimated from the amount of sulfur obtained to be $(ClCH_2CH_2)_2S_{3.5}$. Analysis indicated a composition closer to that of *bis*(2-chloroethyl) trisulfide.

Anal. Calc'd for $C_4H_8Cl_2S_{3.2}$: C, 20.89; H, 3.51.
Found: C, 20.97; H, 3.50.

A similar result was obtained when Cellosolve was used instead of ether. It was found necessary to use at least 40 ml. of Cellosolve in order to strip completely a 15-g. sample of the pentasulfide.

c. *With acetone.* A 4.0-g. sample of *bis*(2-chloroethyl) pentasulfide (n_D^{20} 1.6855) isolated from Levinstein mustard gas was boiled under reflux for two days with 100 ml. of acetone. The precipitated sulfur was removed by filtration and the filtrate allowed to reflux for another two-day period. A small additional amount of sulfur separated. The total weight of sulfur recovered (0.460 g.) indicated the composition of the product to be approximately that of *bis*(2-chloroethyl) tetrasulfide. The refractive index of the oil after removal of the acetone was n_D^{20} 1.6545.

Anal. Calc'd for $C_4H_8Cl_2S_4$: C, 18.92; H, 3.16; Cl, 27.78; S, 50.24.
Found: C, 19.04; H, 3.27; Cl, 26.56; S, 51.11.

A sample of pentasulfide (n_D^{20} 1.6858) obtained from Levinstein mustard gas prepared at 20° was subjected to the same treatment. The amount of sulfur obtained was 0.457 g.; the residual yellow oil, n_D^{20} 1.6480, had the following composition.

Anal. Found: C, 19.45; H, 3.06; S, 50.41.

When the experiment was repeated with a sample of the pentasulfide (n_D^{20} 1.6852) prepared from *bis*(2-chloroethyl) disulfide, 0.460 g. of sulfur again was obtained. The composition of the resulting oil, n_D^{20} 1.6520, again corresponded closely to that of the tetrasulfide.

Anal. Found: C, 19.27; H, 3.34; S, 51.19.

d. *With steam.* Ten-gram samples of *bis*(2-chloroethyl) pentasulfide prepared from Levinstein mustard gas, from *bis*(2-chloroethyl) disulfide and sulfur, and from the trisulfide and sulfur were subjected to steam distillation. In each case a pale yellow oil collected slowly in the receiver. Except for the first few drops, the index of refraction of this oil remained nearly constant. After about 3 ml. of oil had distilled, it was separated, dried in ether solution, and the ether removed. The refractive indices (n_D^{20}) of the distillates from the three different sources were 1.622, 1.605, and 1.611, respectively. One of these oil-distillates (n_D^{20} 1.611) was examined more thoroughly. It melted at 13° and its chlorine content corresponded closely to that of *bis*(2-chloroethyl) trisulfide. (The pure trisulfide melts at 30.5–31.5°; n_D^{20} 1.6110.)

Anal. Calc'd for $C_4H_8Cl_2S_3$: Cl, 31.8 Found: Cl, 31.4.

Stability of bis(2-chloroethyl) trisulfide toward heat. A sample of pure *bis*(2-chloroethyl) trisulfide was placed in a distillation apparatus and heated at 145–160° at a pressure of 0.5 mm., under which conditions the trisulfide would not distil, but any lower-boiling material would be removed. The distillate proved to be *bis*(2-chloroethyl) disulfide, n_D^{20} 1.5690. The residue in the distilling flask was shown to be a mixture of sulfur and polysulfides from which no trisulfide could be isolated.

Attempted hydrolysis of bis(2-chloroethyl) disulfide and trisulfide. Five grams of the disulfide and five grams of the trisulfide each were shaken with 100-ml. portions of water for one week under conditions similar to those employed in the hydrolysis of Levinstein mustard gas. Very little hydroysis occurred, as evidenced by the low chloride-ion concentration in the aqueous layer.

Estimation of the amount of bis(2-chloroethyl) disulfide present in Levinstein mustard gas. A 1208-g. sample of Levinstein mustard gas was subjected to exhaustive hydrolysis and the residue stripped with Cellosolve as in the preparation of *bis*(2-chloroethyl) pentasulfide. It was assumed that the stripped residue contained no polysulfides other than the disulfide and the pentasulfide. This assumption is believed to be a reasonable one in view of the ease of sulfurization of the trisulfide, etc. by the higher polysulfides. This residue weighed 288 g.; n_D^{20} 1.6740. It was observed experimentally that an almost linear relationship exists between refractive index and weight-per cent for mixtures of the di- and penta-sulfide. On this basis, with n_D^{20} 1.6835 for the pentasulfide and n_D^{20} 1.5656 for the disulfide, the stripped residue must have contained 7.5% of *bis*(2-chloroethyl) disulfide. Therefore, the sample of Levinstein mustard gas used contained 1.8%.

The stripped residue was submitted to steam distillation until the refractive index of the oil distillate reached that of *bis*(2-chloroethyl) trisulfide, which undoubtedly was being formed from the stripping of the pentasulfide (see above). From the weight and refractive index of the oil distillate the amount of disulfide present was estimated and found to be equivalent to about 1% of the original Levinstein mustard gas. The lower result in this case can be attributed to losses due to volatilization and partial hydrolysis of the disulfide at 100°. The total loss in the steam distillation was 5%.

Reactions of bis(2-chloroethyl) disulfide. a. *With thiosalicylic acid.* Three and one-tenth grams of the disulfide was added slowly to a solution of 5.5 g. of commercial 90% thiosalicylic acid and 2.6 g. of sodium hydroxide in 150 ml. of 95% ethanol. The mixture was heated under reflux for one hour, allowed to cool, and poured into 400 ml. of water. Acidification with dilute hydrochloric acid precipitated the *bis*(2-thiosalicylethyl) disulfide. It was collected on a filter and dissolved in a solution of sodium bicarbonate. The salt solution was extracted with ether and the disalicyl derivative reprecipitated by the addition of dilute acid. Two recrystallizations from ethanol gave 5.1 g. of product melting at 175–182°. After repeated recrystallization from ethanol the compound melted at 185–186°.

Anal. Calc'd for $C_{18}H_{18}O_4S_4$: C, 50.67; H, 4.25.
Found: C, 50.89; H, 4.21.

b. *With potassium morpholyldithiocarbamate.* A solution of 7 g. of the disulfide in 50 ml. of methanol was added, with stirring, to a solution of 16.5 g. of potassium morpholyldithiocarbamate (11) in 125 ml. of methanol and 15 ml. of water. The mixture was warmed on a steam-cone for two hours and allowed to stand overnight. The precipitate was removed by filtration and the filtrate concentrated to yield a second crop of crystals. The product crystallized from 95% ethanol in fine needles; m.p. 109–110°; yield 15 g., or 92%.

Anal. Calc'd for $C_{14}H_{24}N_2O_2S_6$: C, 37.81; H, 5.42.
Found: C, 37.94; H, 5.27.

c. *With piperidine.* The disulfide was added to an excess of piperidine in boiling petroleum ether solution and the mixture allowed to reflux for thirty-six hours. The piperidine hydrochloride was removed and the filtrate washed with water to get rid of excess piperidine. The *bis*[2-(N-piperidyl)ethyl] disulfide was extracted with dilute hydrochloric acid and recovered by treating the acid solution with sodium hydroxide, followed by extraction with petroleum ether. After evaporation of the solvent the product remained as an oil; n_D^{29} 1.5478; yield 53%.

Two grams of the oil was dissolved in petroleum ether and treated with dry hydrogen chloride. The dihydrochloride, which separated as a white solid, was immediately collected and recrystallized from absolute ethanol; m.p. 236°.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2S_2$: C, 46.52; H, 8.37.
Found: C, 43.54; H, 8.00.

From the analysis it seemed probable that 2-chloroethyl 2-(N-piperidylethyl) disulfide was present as a contaminant.

SUMMARY

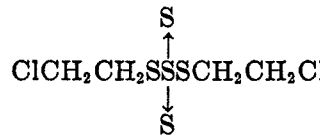
Methods have been given for the preparation of *bis*(2-chloroethyl) disulfide, trisulfide, and pentasulfide.

Exhaustive hydrolysis of Levinstein mustard gas has been found to yield a residue which is thought to be a mixture of higher *bis*(2-chloroethyl) polysulfides. The pentasulfide has been prepared by subjecting this mixture to steam distillation and to stripping with Cellosolve or ammonia. The same compound has been made by sulfurization of the corresponding di- and tri-sulfides with sulfur and of the trisulfide with methyl tetrasulfide.

bis(2-Chloroethyl) pentasulfide has been stripped to the trisulfide by ammonia

in the presence of Cellosolve or ether and to the tetrasulfide by boiling acetone. Steam distillation of the pentasulfide was found to cause its degradation to the trisulfide.

It has been concluded that both the disulfide and trisulfide possess the linear rather than the angular structure. The following structure is proposed for the pentasulfide.



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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

LEVINSTEIN MUSTARD GAS. V. THE ACTION OF CHLORINE AND SULFUR CHLORIDES ON THE *bis*(2-CHLOROETHYL) POLYSULFIDES[1]

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The discovery that *bis*(2-chloroethyl) disulfide is cleaved by chlorine (1) to yield 2-chloroethylsulfenyl chloride (I) raised the question as to the behavior of the higher polysulfides toward this reagent.

$$ClCH_2CH_2SSCH_2CH_2Cl + Cl_2 \rightarrow 2\ \underset{I}{ClCH_2CH_2SCl}$$

Experiment has shown that *bis*(2-chloroethyl) trisulfide behaves in a similar manner. When it was treated with two moles of chlorine, 2-chloroethylsulfenyl chloride and sulfur dichloride were obtained.

$$ClCH_2CH_2SSSCH_2CH_2Cl + 2\ Cl_2 \rightarrow 2\ ClCH_2CH_2SCl + SCl_2$$

As to the mode of formation of the sulfenyl chloride from *bis*(2-chloroethyl) trisulfide, two possibilities were considered: (a) the trisulfide is stripped to *bis*(2-chloroethyl) disulfide which then undergoes cleavage, or (b) the trisulfide, itself, is first cleaved by chlorine to produce a mixture of 2-chloroethylsulfenyl chloride (I) and 2-chloroethyl dithiochloride (II). A sample of the dichloro trisulfide was treated with one molecular equivalent of chlorine, and propylene was passed into the mixture. Two products were obtained and identified as 2-chloroethyl 2-chloro-*n*-propyl sulfide (III) and disulfide (IV), proving beyond doubt that the reaction involves direct cleavage of the trisulfide (course b).

$$ClCH_2CH_2SSSCH_2CH_2Cl + Cl_2 \rightarrow \underset{I}{ClCH_2CH_2SCl} + \underset{II}{ClCH_2CH_2SSCl}$$

$$ClCH_2CH_2SCl + CH_3CH{=}CH_2 \rightarrow \underset{III}{ClCH_2CH_2SCH_2CHClCH_3}$$

$$ClCH_2CH_2SSCl + CH_3CH{=}CH_2 \rightarrow \underset{IV}{ClCH_2CH_2SSCH_2CHClCH_3}$$

This result also tends to confirm the linear structure for *bis*(2-chloroethyl) trisulfide (2). If the angular structure, $ClCH_2CH_2S(\downarrow S)CH_2CH_2Cl$, were the correct one, the first point of attack by chlorine would be expected to occur at the angular sulfur atom causing the reaction to follow the first course (1), and no dithiochloride would be formed.

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

When the trisulfide was treated with chlorine until reaction had ceased, the product consisted of sulfur dichloride and a mixture of di- and tri-chloroethylsulfenyl chlorides. A similar mixture was obtained by Phillips, Davies, and Mumford (3) by the exhaustive chlorination of mustard gas.

In view of the ease with which chlorine cleaves *bis*(2-chloroethyl) disulfide and trisulfide it seemed likely that the sulfur chlorides might have a similar action, since they are known to be effective chlorinating agents.

Although only a very small amount of the disulfide is present in the final product of the Levinstein reaction (2, 4), it is quite possible that it plays an important role as an intermediate in the process. Higher polysulfides, such as *bis*(2-chloroethyl) trisulfide and pentasulfide, are known (2) to form a large fraction of the crude reaction product; therefore, these compounds, as well as the disulfide, undoubtedly are in contact with the sulfur chlorides during the course of the Levinstein reaction. In an attempt to determine the results of such contact, the polysulfides were subjected to the action of the sulfur chlorides.

It was found that sulfur monochloride, like chlorine, acts upon *bis*(2-chloroethyl) disulfide to produce 2-chloroethylsulfenyl chloride, probably according to the following equation:

$$(ClCH_2CH_2)_2S_2 + 3\ S_2Cl_2 \rightarrow 2\ ClCH_2CH_2SCl + 2\ S_3Cl_2$$

This conclusion is based on the following experiment. A mixture of *bis*(2-chloroethyl) disulfide with sulfur monochloride was allowed to stand two days, then treated with cyclohexene. Distillation of the reaction mixture yielded 2-chlorocyclohexyl 2-chloroethyl sulfide and a viscous liquid having the composition of *bis*(2-chlorocyclohexyl) trisulfide. Further experiments showed that cleavage of the disulfide by sulfur monochloride was rapid, but not instantaneous.

These observations suggest a satisfactory explanation for the virtual absence of *bis*(2-chloroethyl) disulfide in Levinstein mustard gas. It is reasonable to expect that ethylene would react directly with sulfur monochloride to form the disulfide, probably by way of the dithiochloride (II) intermediate.

$$CH_2{=}CH_2 + S_2Cl_2 \rightarrow \underset{\text{II}}{ClCH_2CH_2SSCl} \xrightarrow{CH_2=CH_2} (ClCH_2CH_2)_2S_2$$

The disulfide then must undergo cleavage by sulfur monochloride, almost as fast as it appears, with the formation of 2-chloroethylsulfenyl chloride and sulfur tritadichloride as indicated above. These cleavage products then react normally with ethylene to produce *bis*(2-chloroethyl) sulfide and trisulfide, respectively.

$$ClCH_2CH_2SCl + CH_2{=}CH_2 \rightarrow (ClCH_2CH_2)_2S$$
$$S_3Cl_2 + 2\ CH_2{=}CH_2 \rightarrow (ClCH_2CH_2)_2S_3$$

In contrast to its behavior with the disulfide, sulfur monochloride failed completely to cleave *bis*(2-chloroethyl) trisulfide. Its only effect was to sulfurize the trisulfide to higher polysulfides; for example, treatment of the trisulfide with two equivalents of sulfur monochloride produced *bis*(2-chloroethyl) pentasulfide.

$$(ClCH_2CH_2)_2S_3 + 2\ S_2Cl_2 \rightarrow (ClCH_2CH_2)_2S_5 + 2\ SCl_2$$

Clearly this result offers a plausible explanation for the existence of polysulfides higher than *bis*(2-chloroethyl) trisulfide in Levinstein mustard gas. The sulfur dichloride formed as by-product of the sulfurization undoubtedly reacts at once with ethylene to produce mustard gas itself. Elementary sulfur and methyl tetrasulfide also have been observed to sulfurize the trisulfide (2).

With sulfur dichloride, *bis*(2-chloroethyl) trisulfide was found to undergo extensive cleavage, with the formation of 2-chloroethylsulfenyl chloride. Reactions involving *bis*(2-chloroethyl) pentasulfide and chlorine, or sulfur dichloride, were more complex. Briefly, it may be stated that when the pentasulfide was treated with different amounts of chlorine, 2-chloroethylsulfenyl chloride and polychloroethylsulfenyl chlorides were obtained. Cleavage of the dichloro pentasulfide by sulfur dichloride also occurred with the formation of 2-chloroethylsulfenyl chloride, which was identified by means of its cyclohexene adduct, 2-chlorocyclohexyl 2-chloroethyl sulfide. There was evidence for the existence of the corresponding disulfide, which would indicate the formation of the dithiochloride (II) in the reaction.

EXPERIMENTAL

Action of chlorine on bis(2-chloroethyl) trisulfide. a. *Exhaustive chlorinolysis.* To a solution of 30 g. of *bis*(2-chloroethyl) trisulfide (2) in dry carbon tetrachloride was added 63 g. of chlorine at such a rate that the temperature did not exceed 10°. The solvent was evaporated and the product distilled under reduced pressure; b.p. 72.5–75° (13 mm.). After refractionation, the main portion of the product distilled at 77.5° (22 mm.); n_D^{20} 1.5468. An analysis indicated a mixture of dichloro- and trichloro-ethylsulfenyl chlorides which could not be separated.

Anal. Calc'd for $C_2H_2Cl_4S$: C, 12.00; H, 1.00; Cl, 70.9.
Calc'd for $C_2H_3Cl_3S$: C, 14.45; H, 1.81; Cl, 64.3.
Found: C, 13.10; H, 1.27; Cl, 65.9.

b. *Limited chlorinolysis.* The above experiment was repeated limiting the amount of chlorine to that necessary to produce 2-chloroethylsulfenyl chloride. This was accomplished by treatment of the solution of trisulfide with chlorine for twenty minutes. After standing at 0–5° for three hours, the mixture upon distillation yielded 2-chloroethylsulfenyl chloride; b.p. 44° (12 mm.); n_D^{20} 1.5370. It was characterized by means of its piperazine derivative, m.p. 117–118° (1).

c. *Mechanism of chlorinolysis.* A solution of 31.0 g. (0.14 mole) of *bis*(2-chloroethyl) trisulfide in 110 ml. of dry carbon tetrachloride was treated with 9.0 g. (0.13 mole) of chlorine at such a rate that the temperature did not exceed 3°. A 50% excess of propylene was passed in and the solution allowed to stand overnight. Removal of the solvent followed by fractionation *in vacuo* yielded 25–30 g. of 2-chloroethyl 2-chloro-*n*-propyl sulfide, b.p. 69.5° (2 mm.), n_D^{20} 1.5157 (5), and 10 g. of a compound distilling at 74–74.5° (1 mm.), n_D^{20} 1.5518. This proved to be the mixed disulfide in 35% of the theoretical yield.

Anal. Calc'd for $C_5H_{10}Cl_2S_2$: C, 29.3; H, 4.92; Cl, 34.7; S, 31.3.
Found: C, 29.2; H, 4.67; Cl, 34.62; S, 31.38.

Action of sulfur monochloride on bis(2-chloroethyl) disulfide. A mixture of 0.1 mole of *bis*(2-chloroethyl) disulfide (2) and 0.2 mole of sulfur monochloride was allowed to stand at room temperature for two days; then a solution of 0.4 mole of cyclohexene in carbon tetrachloride was added with stirring. Several hours later the mixture was distilled; 13 g. of unchanged disulfide and 7.5 g. of 2-chlorocyclohexyl 2-chloroethyl sulfide, b.p. 104–108° (1 mm.), n_D^{20} 1.5490, were obtained. The sulfide was characterized by means of its *p*-toluene-

sulfilimine, m.p. 147–148° (1). An alcohol extract of the residue yielded a brown, viscous liquid, which had the approximate composition of *bis*(2-chlorocyclohexyl) trisulfide; it slowly evolved hydrogen chloride.

Anal. Calc'd for $C_{12}H_{20}Cl_2S_3$: C, 43.49; H, 6.08; Cl, 21.40; S, 29.03.
Found: C, 44.08; H, 6.46; Cl, 18.97; S, 32.03.

In an attempt to determine the rapidity of the cleavage of *bis*(2-chloroethyl) disulfide, the above reaction was repeated. The slow, simultaneous addition of sulfur monochloride and cyclohexene to a well-stirred solution of the disulfide in carbon tetrachloride, followed promptly by distillation, yielded none of the expected 2-chlorocyclohexyl 2-chloroethyl sulfide.

In a third experiment a mixture of the disulfide (0.1 mole) and sulfur monochloride (0.3 mole) was stirred at 35° for twenty minutes. Then 0.6 mole of cyclohexene in carbon tetrachloride was added dropwise over a two-hour period. From this mixture was isolated by distillation 19.8 g. of 2-chlorocyclohexyl 2-chloroethyl sulfide, 47% of the theoretical amount.

Action of sulfur monochloride on bis(2-chloroethyl) trisulfide. A mixture of *bis*(2-chloroethyl) trisulfide with two molecular equivalents of sulfur monochloride was allowed to stand at room temperature for one week. The low-boiling sulfur chloride was removed by distillation *in vacuo*. The residual oil was dissolved in ether, washed with a dilute solution of potassium carbonate followed by water, and dried. Evaporation of the solvent yielded an oil whose physical properties and composition agreed with those of *bis*(2-chloroethyl) pentasulfide (2).

Another experiment was carried out in an attempt to detect the presence of any cleavage product (sulfenyl chloride) in the reaction mixture. A two-day old mixture of the trisulfide with four molecular equivalents of sulfur monochloride was treated with an excess of cyclohexene in carbon tetrachloride. Distillation of the product *in vacuo* yielded no 2-chlorocyclohexyl 2-chloroethyl sulfide.

Action of sulfur dichloride on bis(2-chloroethyl) trisulfide. A mixture of *bis*(2-chloroethyl) trisulfide (0.1 mole) with sulfur dichloride (0.3 mole) was allowed to stand for twenty-four hours. The red solution was diluted with carbon tetrachloride, and 0.6 mole of cyclohexene was added slowly. After removal of the volatile materials, distillation of the residue *in vacuo* yielded 29 g. of 2-chlorocyclohexyl 2-chloroethyl sulfide, b.p. 102–105° (0.2–0.4 mm.) (1). This corresponds to 67% of the theoretical amount.

Action of chlorine on bis(2-chloroethyl) pentasulfide. This reaction was carried out according to the procedure used in the chlorination of the trisulfide. In the first experiment the theoretical amount of chlorine required to convert the pentasulfide (2) to 2-chloroethylsulfenyl chloride and sulfur monochloride was used. Distillation of the product yielded the sulfenyl chloride in fair yield and a residue of unchanged *bis*(2-chloroethyl) pentasulfide (n_D^{20} 1.670), which amounted to 20% of the original starting material.

The next experiment involved sufficient chlorine to convert the three odd sulfur atoms to sulfur dichloride. Cleavage of the polysulfide was complete; the distillate consisted of two fractions. The first, b.p. 45–47.5° (14 mm.), proved to be 2-chloroethylsulfenyl chloride while the second fraction was a mixture of di- and tri-chloroethylsulfenyl chlorides, b.p. 55.5–57.5° (8 mm.), n_D^{20} 1.5490.

Anal. Calc'd for $C_2H_3Cl_3S$: C, 14.45; H, 1.81.
Found: C, 13.78; H, 1.61.

A similar mixture was obtained by the exhaustive chlorinolysis of *bis*(2-chloroethyl) trisulfide.

Action of sulfur dichloride on bis(2-chloroethyl) pentasulfide. The procedure described for the reaction between sulfur dichloride and the trisulfide was repeated using 0.1 mole of *bis*(2-chloroethyl) pentasulfide, 0.5 mole of sulfur dichloride, and 0.9 mole of cyclohexene. Distillation of the product yielded 12.6 g. of 2-chlorocyclohexyl 2-chloroethyl sulfide, b.p. 91–109° (0.3 mm.), n_D^{20} 1.5473 (1), and 10.7 g. of a higher-boiling fraction which distilled at 116–122° (0.4 mm.), n_D^{20} 1.5603.

Anal. Calc'd for $C_8H_{14}Cl_2S$: C, 45.07; H, 6.62; Cl, 33.27.
Calc'd for $C_8H_{14}Cl_2S_2$: C, 39.16; H, 5.76; Cl, 28.9.
Found: C, 41.30; H, 6.02; Cl, 29.11.

The analysis and refractive index of this second fraction indicate a mixture of the unsymmetrical sulfide and disulfide. Thus, it appears that approximately 53% of the *bis*(2-chloroethyl) pentasulfide underwent cleavage.

SUMMARY

It has been shown that *bis*(2-chloroethyl) trisulfide is cleaved by chlorine to yield 2-chloroethylsulfenyl chloride and 2-chloroethyl dithiochloride. The use of two molecular equivalents of chlorine converts the trisulfide to the sulfenyl chloride and sulfur dichloride. Sulfur dichloride likewise brings about a cleavage of the trisulfide to the sulfenyl chloride.

bis(2-Chloroethyl) disulfide has been found to undergo cleavage with sulfur monochloride, yielding 2-chloroethylsulfenyl chloride. In contrast to this observation, it has been found that the trisulfide is not cleaved by sulfur monochloride; it undergoes sulfurization to higher polysulfides.

These observations afford a satisfactory explanation of the fact that the disulfide is virtually absent from Levinstein mustard gas.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

LEVINSTEIN MUSTARD GAS. VI. THE MODE OF FORMATION[1]

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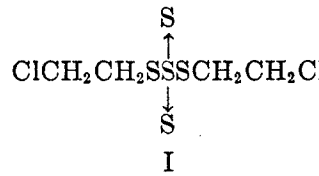
Mustard gas, prepared from ethylene and sulfur monochloride by the Levinstein process (in which the reaction is carried out at 35°), is composed chiefly of *bis*(2-chloroethyl) sulfide (approximately 70%) and polysulfides (approximately 30%). The polysulfides vary in composition and stability and have the general formula $(ClCH_2CH_2)_2S_x$. Three of the sulfur atoms in the polysulfides appear to be held in a stable linear trisulfide skeleton (1) and cannot be removed by stripping. The pentasulfide represents another stable level and has been assigned the following formula I.



I

The amount of sulfur removed by stripping, the amount of pentasulfide which can be obtained, and the freezing point of fresh material indicate that the polysulfides in freshly prepared Levinstein mustard gas may have an average composition varying from that of the hexasulfide to that of the nonasulfide. Usually the composition of the polysulfide corresponds to that of the heptasulfide.

MECHANISM

In 1920 a mechanism for the formation of mustard gas from ethylene and the sulfur chlorides was postulated by Conant, Hartshorn, and Richardson (2). From the evidence then available they assumed that 2-chloroethylsulfenyl chloride (II) was an intermediate in the process.

$$CH_2{=}CH_2 \xrightarrow[S_2Cl_2]{SCl_2 \text{ or}} ClCH_2CH_2SCl \xrightarrow{CH_2=CH_2} (ClCH_2CH_2)_2S$$

II

This theory recently has been substantiated by the isolation of 2-chloroethylsulfenyl chloride in pure form and by its reaction with ethylene to produce *bis*(2-chloroethyl) sulfide (3).

Further evidence that 2-chloroethylsulfenyl chloride is an intermediate has been obtained by using an equimolecular mixture of ethylene and cyclohexene in the Levinstein process instead of ethylene alone. *bis*(2-Chloroethyl) sulfide, *bis*(2-chlorocyclohexyl) sulfide, and 2-chlorocyclohexyl 2-chloroethyl sulfide were obtained.

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

In a similar manner an equimolar mixture of ethylene and cyclohexene was passed into a solution of sulfur dichloride in mustard gas. The same three products were obtained, demonstrating that the reaction of ethylene with sulfur dichloride proceeds in two steps and involves the intermediate formation of 2-chloroethylsulfenyl chloride.

Any mechanism which is to account for the formation of Levinstein mustard gas must also afford a satisfactory explanation for the formation of polysulfides derived from the linear trisulfide as well as the virtual absence of the disulfide and of free sulfur (1). The following mechanism appears to fulfill these conditions.

Although sulfur monochloride may react only as such with ethylene (4), there is chemical and physical evidence to support the assumption that it may undergo disproportionation to form sulfur dichloride and sulfur tritadichloride (5).

(a) $$2\ S_2Cl_2 \rightleftarrows SCl_2 + S_3Cl_2$$

In the Levinstein process, accordingly, the ethylene may react with the dichloride (b), the monochloride (c), or the tritadichloride (d).

(b) $$2\ C_2H_4 + SCl_2 \rightarrow ClCH_2CH_2SCH_2CH_2Cl$$
(c) $$2\ C_2H_4 + S_2Cl_2 \rightarrow ClCH_2CH_2SSCH_2CH_2Cl$$
(d) $$2\ C_2H_4 + S_3Cl_2 \rightarrow ClCH_2CH_2SSSCH_2CH_2Cl$$

If higher polythio sulfur chlorides such as S_4Cl_2 were present they might condense in a manner analogous to that represented by equation (d).

The reaction of sulfur dichloride with ethylene is known to be very rapid. Accordingly, the excess of ethylene which is always present should serve to keep the concentration of sulfur dichloride at a very low value, thus promoting the displacement of the equilibrium (a) to the right and increasing the rate of formation of the tritadichloride.

This would bring about a corresponding decrease in the amount of sulfur monochloride which could react with ethylene to produce *bis*(2-chloroethyl) disulfide. However, it is to be expected that the reaction of ethylene with sulfur monochloride should proceed at least as rapidly as with sulfur tritadichloride (equations c and d). Therefore, the only way to account for the virtual absence of *bis*(2-chloroethyl) disulfide in Levinstein mustard gas is to assume that the disulfide is attacked rapidly by sulfur monochloride in the manner previously observed (4).

(e) $$ClCH_2CH_2SSCH_2CH_2Cl + 3\ S_2Cl_2 \rightarrow 2\ ClCH_2CH_2SCl + 2\ S_3Cl_2$$

The formation of sulfur tritadichloride as a product of this reaction obviates the necessity of assuming the disproportionation of sulfur monochloride (equation a) to account for the formation of *bis*(2-chloroethyl) trisulfide. However, that is still considered a definite possibility.

The trisulfide, formed according to equation d, has been shown (4) to be sulfurized readily at 30–35° by sulfur monochloride to higher polysulfides (equations

f, g, and h); and sulfur dichloride is the other product of the reaction. It reacts immediately with ethylene to produce mustard gas.

(f) $ClCH_2CH_2SSSCH_2CH_2Cl + S_2Cl_2 \rightarrow (ClCH_2CH_2)_2S_4 + SCl_2$

(g) $(ClCH_2CH_2)_2S_4 + S_2Cl_2 \rightarrow (ClCH_2CH_2)_2S_5 + SCl_2$

(h) $(ClCH_2CH_2)_2S_5 + S_2Cl_2 \rightarrow (ClCH_2CH_2)_2S_6 + SCl_2$

etc.

Because sulfur dichloride is generated in the reaction mixture only as a product of other reactions, and because an excess of ethylene is always present, the concentration of sulfur dichloride can never be very great. For this reason, overchlorination is not as serious a problem as in the processes involving the use of sulfur dichloride directly (2).

The net result of this series of reactions is the production of a mixture of *bis*(2-chloroethyl) sulfide and the corresponding polysulfides. All these equations may be combined to give the over-all equation for the Levinstein process.

(i) $2x\ C_2H_4 + x\ S_2Cl_2 \rightarrow (x - 1)ClCH_2CH_2SCH_2CH_2Cl + (ClCH_2CH_2)_2S_{x+1}$

The composition of the polysulfide as well as its concentration in fresh Levinstein mustard gas depends on the conditions under which the reaction was run, especially on the temperature, degree of agitation, amount of seed charge, rate of addition of ethylene, and very likely many other factors, such as previous history of the sulfur monochloride, have an important effect.

So long, however, as there is no sulfur precipitated during the reaction, there must be according to the general equation above, a definite relationship between the composition of the polysulfide and its concentration. Empirically, one sulfur atom is produced each time a molecule of *bis*(2-chloroethyl) sulfide is formed and this sulfur must all be present as polysulfides. The higher the sulfur content of the polysulfide, the lower need be its concentration. The table which follows illustrates this relationship. The monosulfide-polysulfide ratios tabulated are those which would be required to satisfy the general equation. The table lists other properties, based on theory, which the original mixtures should have. Also included are the calculated pentasulfide-monosulfide ratios in the products obtained by stripping or aging the original mixtures.

The theoretical values which appear in the table are in excellent agreement with the great quantity of experimental data on Levinstein mustard gas compiled at Edgewood Arsenal and other Chemical Warfare Service laboratories (6).

THE EFFECT OF TEMPERATURE ON THE LEVINSTEIN PROCESS

The mechanism for the Levinstein process which has just been outlined is further supported by results obtained in a study of the effect of temperature on the reaction. The amount of impurity (polysulfides) in the resulting Levinstein mustard gas depends on the rate of formation of the trisulfide and on the rate of its sulfurization by sulfur monochloride. The increase in the rate of the reactions with increase in temperature is partially offset for those reactions involving ethylene because of the decreased solubility, and therefore concentration, of

ethylene in the warmer solvent. Thus, the sulfurization reactions (f, g, and h) would be expected to proceed relatively more rapidly than the other reactions which depend upon the concentration of ethylene. Each time an atom of sulfur is added to a polysulfide molecule, a molecule of *bis*(2-chloroethyl) sulfide must be formed concurrently in order to preserve the stoichiometric relationship. Thus, at elevated temperatures the reaction between ethylene and sulfur monochloride might be expected to proceed more rapidly and to produce a greater yield of *bis*(2-chloroethyl) sulfide at the expense of the polysulfide fraction. However, the polysulfides which were formed would have a higher sulfur content

TABLE I

RELATIONSHIP BETWEEN COMPOSITION AND PROPERTIES OF POLYSULFIDES

bis(2-CHLOROETHYL) POLYSULFIDE-MONOSULFIDE MIXTURES WHICH SATISFY THE GENERAL EQUATION						*bis*(2-CHLOROETHYL) PENTASULFIDE-MONOSULFIDE MIXTURES PRODUCED BY STRIPPING
Mixture	Mole Ratio	Mole %	Weight %	Calc'd F.P.	Weight % Strippable Sulfur	Weight %
1. Monosulfide	3	75	62.5	5.6	0	62.5
Pentasulfide	1	25	37.5			37.5
2. Monosulfide	4	80	66.8	7.2	3.4	69.0
Hexasulfide	1	20	33.2			31.0
3. Monosulfide	5	83.3	69.5	8.5	5.5	73.6
Heptasulfide	1	16.7	30.5			26.4
4. Monosulfide	6	85.7	71.5	9.1	7.2	76.9
Octasulfide	1	14.3	28.5			23.1
5. Monosulfide	7	87.5	72.9	9.7	8.4	79.6
Nonasulfide	1	12.5	27.1			20.4
6. Monosulfide	8	88.9	74.1	10.4	9.3	81.7
Decasulfide	1	11.1	25.9			18.3

than those produced at low reaction temperatures. These considerations have been borne out by the following experimental observations.

When the sulfur monochloride-ethylene reaction was carried out at 60° (2), the reaction proceeded rapidly to give high yields (80%) of *bis*(2-chloroethyl) sulfide and large amounts of free sulfur. If the rate of sulfurization was high, then as fast as *bis*(2-chloroethyl) trisulfide was produced it was sulfurized by sulfur monochloride to higher polysulfides. Since a molecule of *bis*(2-chloroethyl) sulfide was produced each time a sulfur atom was added to a polysulfide molecule, the amount of *bis*(2-chloroethyl) sulfide was large also in this case. The higher polysulfides produced are unstable at elevated temperatures and deposit sulfur readily.

When run at 35°, as in the Levinstein process, the reaction proceeded somewhat more slowly, the yield of *bis*(2-chloroethyl) sulfide was less (70%), and sulfur was observed to precipitate only after the product had been allowed to stand for several weeks. Here, the rate of sulfurization was moderate, and the polysulfides formed were of lower molecular weight and consequently more stable. MacInnes and Belcher (7) carried out the reaction at 27°, and obtained a still lower yield of mustard gas and a polysulfide fraction of still lower molecular weight.

When the sulfur monochloride-ethylene reaction was carried out at 20°, the yield of *bis*(2-chloroethyl) sulfide was only 61%, and the polysulfide portion made up 39% of the total product. The polysulfide proved to be nearly pure *bis*(2-chloroethyl) pentasulfide and contained only traces of higher polysulfides. Apparently the rate of sulfurization was low, and the yield of *bis*(2-chloroethyl) sulfide correspondingly low. Indeed, if no sulfurization at all took place the yield of the sulfide would be only 50 mole-per cent (41.6% by weight), and *bis*(2-chloroethyl) trisulfide would be the other product.

It is likely that the latter is sulfurized to *bis*(2-chloroethyl) pentasulfide so readily that it would not be possible to carry out the reaction to produce polysulfides lower than the pentasulfide. This contention seems to be borne out by the results obtained when the reaction was run at a still lower temperature (12°). The polysulfide obtained had an average composition higher than *bis*(2-chloroethyl) pentasulfide.

As with the preceding papers in this series, valuable assistance has been afforded by cooperating groups. The authors wish to make special acknowledgment of the help of Dr. R. Macy of the Edgewood Arsenal.

EXPERIMENTAL

Reaction between sulfur monochloride and a mixture of ethylene and cyclohexene. In this reaction pure *bis*(2-chloroethyl) sulfide (157 g.) was used as the "seed charge" (8) because it could be removed easily in subsequent operations. Ethylene (1.35 moles) was bubbled through 1.35 moles (111 g.) of warm cyclohexene and the mixture of gases introduced into the well-stirred reaction mixture at 32° over a period of three hours. Sulfur monochloride was added simultaneously and kept in moderate excess until 1.35 moles (182.5 g.) had been added. Finally, ethylene was passed into the mixture for three hours longer to remove excess sulfur monochloride.

The product (440 g.) was distilled *in vacuo*, yielding 285 g. of yellow oil, b.p. 60–135° (1–2 mm.) and 140 g. of a liquid residue. Redistillation through an efficient column yielded 183 g. of *bis*(2-chloroethyl) sulfide, b.p. 54–57° (0.25 mm.), and 59 g. (0.277 mole) of 2-chlorocyclohexyl 2-chloroethyl sulfide (3), b.p. 115–118° (1.35 mm.). If the original 157 g. of *bis*(2-chloroethyl) sulfide used as the seed charge is subtracted, then the yield of pure mustard gas from the reaction is 26 g. (0.165 mole).

Furthermore, if it is assumed that the usual 30% yield of polysulfide is obtained then 85 g. of the non-distillable residue is polysulfides and the remainder (55 g., 0.207 mole) is the *bis*(2-chlorocyclohexyl) sulfide.

Reaction between sulfur dichloride and a mixture of ethylene and cyclohexene.[2] The procedure used in the preceding experiment was followed, except that one-molar proportions

[2] This experiment was performed by Mr. Lester J. Reed.

of sulfur dichloride and cyclohexene were used, and the temperature was maintained below 15°. The final distillation yielded 32 g. of 2-chlorocyclohexyl 2-chloroethyl sulfide.

The effect of temperature on the Levinstein process. a. *The reaction at 20°.* The Levinstein reaction as ordinarily carried out was modified by the use of pure *bis*(2-chloroethyl) sulfide as a "seed charge" and a temperature of 20°, rather than 35°. Alcohol-free, dry ethylene was passed into the vigorously-stirred reaction mixture at such a rate that ethylene escaped freely. During the first four hours sulfur monochloride was added slowly, maintaining a moderate excess; then, ethylene was passed in for five hours longer. The yield of pale yellow liquid was 96% based on the sulfur monochloride used. It did not darken or deposit sulfur during three months observation.

A 542-g. sample of this product was hydrolyzed exhaustively by stirring vigorously with water for several days. The clear, pale yellow, residual oil weighed 125 g.; n_D^{20} 1.6906. The material hydrolyzed had contained 38.2% of pure mustard gas (the seed charge); therefore, only 61.8% or 322 g. of the sample had furnished the 125 g. of residue. Thus the residue amounts to 38.8% by weight of the hydrolyzed Levinstein mustard gas. This weight of residue and its refractive index indicate its composition to be approximately that of *bis*(2-chloroethyl) pentasulfide.

Sixty-nine grams of the non-hydrolyzable residue was subjected to treatment with Cellosolve, etc., as described in the preparation of *bis*(2-chloroethyl) pentasulfide from Levinstein mustard (1). About 1 g. of oil was insoluble in the Cellosolve, and a very small amount of sulfur precipitated. The final product weighed 48 g.; the refractive index, n_D^{20} 1.6884, was in good agreement with the value obtained previously for the purified pentasulfide (1).

b. *The reaction at 12°.* The experiment just described was repeated except that the temperature of the reaction was 12°. The results of the hydrolysis indicated that the Levinstein mustard gas formed had contained 34.3% by weight of polysulfide with an average composition slightly less than that of *bis*(2-chloroethyl) hexasulfide.

The non-hydrolyzable residue (106 g.), after stripping with Cellosolve, yielded an oil of refractive index, n_D^{20} 1.6911. A considerable amount (22 g.) of Cellosolve-insoluble residue, consisting of sulfur and an amber oil, was obtained. The oil was removed by filtration, washed with ether, and submitted for analysis. The results were in excellent agreement with values calculated for a polysulfide containing thirteen atoms of sulfur.

Anal. Calc'd for $C_4H_8Cl_2S_{13}$: C, 8.83; H, 1.48; Cl, 13.0; S, 76.6.
Found: C, 8.71; H, 1.41; Cl, 14.0; S, 76.3.

SUMMARY

A mechanism has been suggested which accounts satisfactorily for the composition of mustard gas obtained by the Levinstein process.

URBANA, ILL.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

2-CHLOROETHYL 2-HYDROXYETHYL SULFIDE[1]

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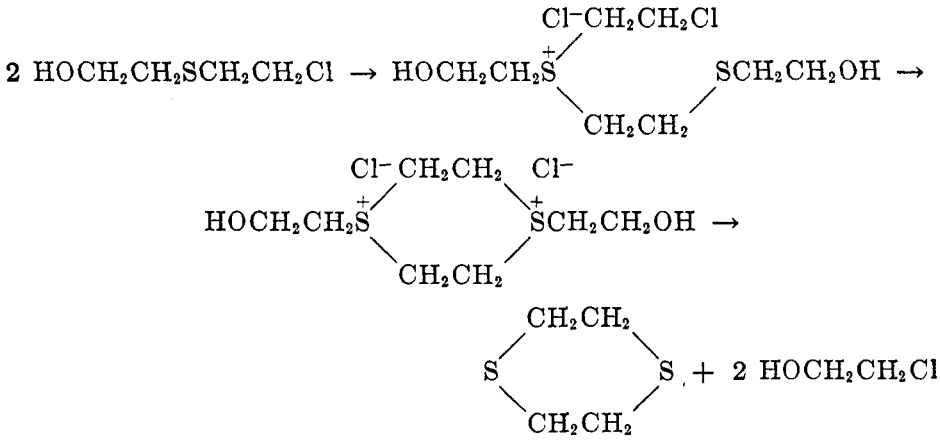
2-Chloroethyl 2-hydroxyethyl sulfide (I) is of interest because it is the half hydrolysis product of mustard gas (1). Of the various methods which might be suitable for its synthesis (2) that of Salzberg and Lazier (3) seemed most promising. This method, which has been described also by Morrison, Rueggeberg, and Dawson (4), involves photochemical addition of mercaptans to olefins. In the present work it has been found possible to condense monothioglycol with vinyl chloride in satisfactory yields.

$$HOCH_2CH_2SH + CH_2{=}CHCl \rightarrow \underset{\text{I}}{HOCH_2CH_2SCH_2CH_2Cl}$$

The same reaction was carried out, apparently while this work was in progress, by Rueggeberg and Cook (5) under somewhat different conditions.

The 2-chloroethyl 2-hydroxyethyl sulfide can be converted to mustard gas in high yield by treatment with concentrated hydrochloric acid. It was characterized further by the preparation of the *p*-toluenesulfilimine, the morpholyldithiocarbamate, and the α-naphthylurethan.

2-Chloroethyl 2-hydroxyethyl sulfide was found to boil almost undecomposed at 100° (0.6 mm.). At room temperatures it decomposed almost completely in four days. The criterion of degree of decomposition was the change in the refractive index. The refractive index, when taken immediately after distillation, was n_D^{20} 1.5188. When the liquid was allowed to stand the index rose gradually to 1.5600. At temperatures near 0° the compound was comparatively



[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

stable; a sample which had been kept at this temperature for one week was distilled with 75% recovery of pure material. When the compound was stored in solid carbon dioxide it appeared to remain unchanged.

The decomposition products of this compound have never been investigated thoroughly. It was noted, however, that large amounts of *p*-dithiane collected in the condenser during the distillation of the 2-chloroethyl 2-hydroxyethyl sulfide. The following mechanism for the formation of *p*-dithiane seems probable on the basis of the work of Bell, Bennett, and Hock (6).

Treatment of 2-chloroethyl 2-hydroxyethyl sulfide with ethanolic sodium hydroxide yielded, instead of the desired 2-hydroxyethyl vinyl sulfide, a mixture of 1,4-thioxane and 2-ethoxyethyl 2-hydroxyethyl sulfide.

EXPERIMENTAL

Synthesis of 2-chloroethyl 2-hydroxyethyl sulfide. The procedure of Salzberg and Lazier (3) was followed. A mixture of 39 g. of redistilled monothioglycol, and 0.8 g. of benzoyl peroxide was placed in a 500-ml. quartz flask and cooled to about −30° in a dry-ice bath. From 75 to 95 g. of liquid vinyl chloride was added to the reaction mixture, which was connected immediately to a thimble-type reflux condenser filled with powdered dry ice. A calcium chloride tube was connected to the outlet tube of the condenser. The reaction mixture was irradiated for four hours with an ultraviolet lamp, an additional 0.4 g. of the peroxide added, and irradiation continued for another four hours. The mixture was allowed to stand overnight at room temperature; during this time the vinyl chloride gradually volatilized. Residual low-boiling material was removed under diminished pressure and the crude 2-chloroethyl 2-hydroxyethyl sulfide was distilled *in vacuo*; b.p. 100° (0.6 mm.); yield 40 g. (57)%; n_D^{20} 1.5260. Redistillation produced 31 g. of the pure compound; n_D^{20} 1.5188.

Anal. Calc'd for C_4H_9ClOS: C, 34.16; H, 6.45; Cl, 25.22; S, 22.81.
Found: C, 34.14; H, 6.46; Cl, 25.39; S, 21.92.

Fourteen grams of the chloro hydroxy sulfide was heated under reflux for one hour with 70 ml. of concentrated hydrochloric acid. The yield of mustard gas was 11.6 g.; b.p. 75–80° (0.9–1.0 mm.); m.p. 14.5°; n_D^{20} 1.5262 (7). With Chloramine-T the compound yielded the known *bis*(2-chloroethyl)-*p*-toluenesulfilimine; m.p. 143.5° (8).

p-Toluenesulfilimine. The *p*-toluenesulfilimine of 2-chloroethyl 2-hydroxyethyl sulfide, made by the general method of Mann and Pope (8), was found to exist in dimorphs. The low-melting form crystallized from ethanol in colorless leaflets melting at 122.5–123°.

Anal. Calc'd for $C_{11}H_{16}ClNO_3S_2$: C, 42.64; H, 5.21; N, 4.52.
Found: C, 43.00; H, 5.03; N, 4.42.

The product obtained in another experiment melted at 137–138°.

Anal. Found: C, 43.03; H, 5.21; N, 4.72.

Mixtures of the high-melting form with the *p*-toluenesulfilimine of mustard gas (m.p. 144°) and with *p*-toluenesulfonamide(m.p. 135°) melted, respectively, at 122–123° and 103.5–105.5°. A mixture of the dimorphic sulfilimines melted at 137–137.5°. Seeding the low-melting with the high-melting form caused the melting point to change from 122.5–123° to 137–138°.

Morpholyldithiocarbamate. To a solution of 7.5 g. of potassium morpholyldithiocarbamate (9) in 100 ml. of 45% ethanol was added a solution of 5.0 g. of 2-chloroethyl 2-hydroxyethyl sulfide in 10 ml. of 95% ethanol. The mixture was heated under reflux for one hour and poured into 500 ml. of water. The oil which separated was found to solidify; m.p. 64–65°. The solid was dissolved in the minimum amount of hot 75% ethanol and allowed to cool to room temperature. The fine, long needles which separated were recrystallized from ethanol; m.p. 128.5–129°. A mixture of this material with an authentic specimen of the morpholyldithiocarbamate of mustard gas (2) showed no lowering of the melting point.

Concentration of the mother liquor yielded a second crop of crystals weighing 4.9 g. It separated from aqueous ethanol in white, pearly leaflets; m.p. 66–67°.

Anal. Calc'd for $C_9H_{17}NO_2S_2$: C, 40.42; H, 6.41.
Found: C, 40.59; H, 6.20.

α-Naphthylurethan. This derivative was made in the usual way and recrystallized from high-boiling petroleum ether. The pure white needles melted at 96.5–97.5°.

Anal. Calc'd for $C_{16}H_{16}ClNO_2S$: C, 58.15; H, 5.20; N, 4.52.
Found: C, 58.15; H, 5.36; N, 4.38.

Dehydrohalogenation. To a solution of 0.21 mole of sodium hydroxide in 100 ml. of absolute ethanol at 10° was added 0.20 mole of 2-chloroethyl 2-hydroxyethyl sulfide. The mixture was heated under reflux for one hour and allowed to stand at room temperature for two days. The sodium chloride was removed by filtration and the filtrate acidified with dry ice. The solvent was removed under diminished pressure and the residue distilled *in vacuo*. Two fractions were obtained.

The first fraction (1–2 g.) distilled at 45–55° (22 mm.); n_D^{18} 1.4865. This distillate, upon treatment with aqueous Chloramine-T, yielded a sulfilimine; m.p. 147.5–148.5°. A mixture melting point with an authentic sample of 1,4-thioxane-*p*-toluenesulfilimine (m.p. 147.5–148.5°) was not depressed. The sulfilimine used for comparison was prepared from 1,4-thioxane which had been made by distilling a mixture of thiodiglycol and concentrated sulfuric acid, a modification of the method of Fromm and Unger (10).

Anal. Calc'd for $C_{11}H_{15}NO_3S_2$: C, 48.33; H, 5.53; N, 5.13.
Found: C, 48.04; H, 5.28; N, 5.05.

The second fraction [6.3 g., b.p. 115–125° (22 mm.)] was redistilled through a modified Claisen head; b.p. 100° (1.5 mm.); n_D^{18} 1.4800. This distillate absorbed very little bromine from a carbon tetrachloride solution, but reacted with sodium with the evolution of hydrogen. The boiling point and analysis correspond closely to the values for 2-ethoxyethyl 2-hydroxyethyl sulfide (11).

Anal. Calc'd for $C_6H_{14}O_2S$: C, 47.97; H. 9.39; S, 21.34.
Found: C, 48.67; H, 9.54; S, 21.30.

SUMMARY

The synthesis of 2-chloroethyl 2-hydroxyethyl sulfide has been accomplished by the addition of monothioglycol to vinyl chloride. The structure of the product has been confirmed by conversion to mustard gas and by the preparation of the *p*-toluenesulfilimine, the morpholyldithiocarbamate, and the α-naphthylurethan.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THERMAL CONVERSION OF MUSTARD GAS TO 1,2-*bis*(2-CHLOROETHYLTHIO)ETHANE AND *bis*[2-(2-CHLOROETHYLTHIO)-ETHYL]SULFIDE[1]

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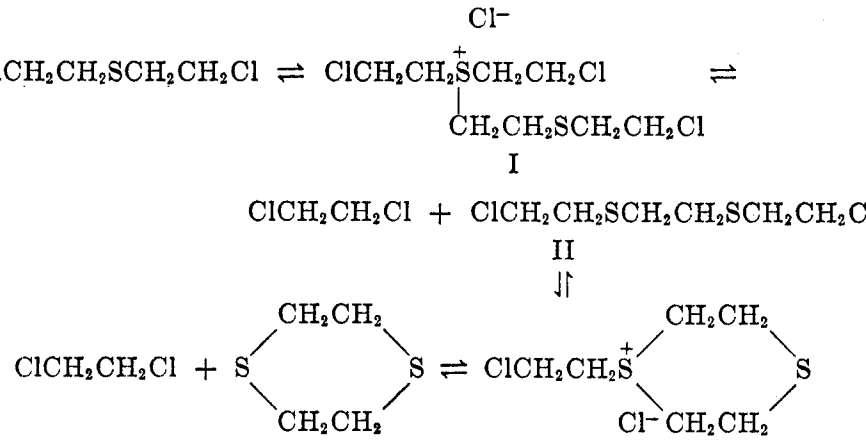
It has been observed that when mustard gas is heated, compounds of higher molecular weight are formed. Investigation has shown that two of these are 1,2-*bis*(2-chloroethylthio)ethane (II) and *bis*[2-(2-chloroethylthio) ethyl]sulfide (III).

In a similar study Bell, Bennett, and Hock (1) noted that when mustard gas was heated in a sealed tube, ethylene chloride and *p*-dithiane were produced. They postulated that 1,2-*bis*(2-chloroethylthio)ethane (II) was an intermediate in this reaction, and proposed the following mechanism to account for these changes. It involves the formation of the sulfonium salt (I) which breaks down to yield the disulfide (II). Intramolecular condensation of the latter compound followed by thermal decomposition of the resulting cyclic sulfonium salt would account for the formation of the ethylene chloride and *p*-dithiane.



Obviously, this mechanism is directly applicable to the present observation that heated mustard gas contains 1,2-*bis*(2-chloroethylthio)ethane. Evidence for a similar reaction in which compound II is formed from 2-chloroethyl methyl sulfide was obtained by Snyder, Howe, Cannon, and Nyman (2).

The formation of *bis*[2-(2-chloroethylthio)ethyl] sulfide (III) can be explained by assuming that compound II reacts with mustard gas in a similar manner.

[1] This paper is based on work done for the Office of Scientific Research and Development under Contracts Nos. OEMsr-300 and OEMsr-48 with the Board of Trustees of the University of Illinois.

$$\underset{\text{II}}{ClCH_2CH_2SCH_2CH_2SCH_2CH_2Cl} + ClCH_2CH_2SCH_2CH_2Cl \rightleftharpoons$$

$$ClCH_2CH_2SCH_2CH_2\overset{+}{S}(CH_2CH_2Cl)CH_2CH_2SCH_2CH_2Cl\ Cl^- \rightleftharpoons$$

$$\underset{\text{III}}{(ClCH_2CH_2SCH_2CH_2)_2S} + ClCH_2CH_2Cl$$

Condensation of compound III with itself, with mustard gas, or with compound II would result in the formation of higher analogs, which would account for some of the highly insoluble material present in samples of heated mustard gas.

The presence of compound II in the heated material was established by isolation of its disulfone, which was compared with an authentic sample of the disulfone of 1,2-*bis*(2-chloroethylthio)ethane. The amount of compound II present was determined by treating the residue from the distillation of heated mustard gas with an ethanolic solution of sodium methyl mercaptide, and separating the resulting mixture of methylthio ethers by distillation.[2] The isolation of *bis*[2-(2-methylthioethylthio)ethyl] sulfide from this mixture was interpreted as indicating the presence of compound III in heated mustard gas.

The observation that ethylene chloride and *p*-dithiane are formed when mustard gas is heated has been confirmed. Ethylene chloride was identified by its physical constants and by formation of a derivative, 2-(β-naphthoxy)ethyl chloride. *p*-Dithiane was identified by comparison with an authentic sample of this material.

It had been shown (1) that the thermal conversion of mustard gas to *p*-dithiane and ethylene chloride is a reversible reaction, for when the latter two substances were heated together in a sealed tube the product contained mustard gas. However, when the ethylene chloride is allowed to escape, as in the present experiments, the reactions outlined above would no longer be reversible and the amounts of compounds II and III (and the higher analogs) present in the mixture might reach limiting values and then gradually diminish. This theory has been confirmed by experiment. When a sample of mustard gas was heated at 140° at atmospheric pressure for three days, the product contained only 2.7% of compound II. In another experiment a sample of mustard gas containing 20% of compound II was heated at 140° for three days. Analysis of the resulting mixture indicated that only 5.1% of compound II remained. Likewise, the expectation that only a small amount of compound III would be formed by heat treatment of mustard gas has been realized by experiment.

$$BrCH_2CH_2Br + Na_2S \rightarrow (-CH_2CH_2S-)_x \rightarrow \begin{array}{c} CH_2CH_2 \\ S \quad\quad S \\ CH_2CH_2 \end{array}$$

[2] This method of analysis was developed by Rosser, Meade, and Glover. Their results are published in British Chemical Warfare Reports.

During the course of this investigation an improved method for synthesis of *p*-dithiane was developed. It involves the formation of polyethylene sulfide from ethylene bromide and sodium sulfide, followed by thermal decomposition of the polymer in the presence of ethylene bromide and phenol.

EXPERIMENTAL

Preliminary examination of heated mustard gas. a. *Isolation and identification of ethylene chloride.* Pure mustard gas (250 g., m.p. 14.5°) prepared by the action of concentrated hydrochloric acid on thiodiglycol (3), was heated at 150–160° (oil-bath temperature) in an atmosphere of nitrogen for forty-eight hours. During the heating, 6.8 g. of ethylene chloride (weighed after fractionation to remove mustard gas) distilled and was collected in an ice-trap. The ethylene chloride was identified by its boiling point (82°), its index of refraction (n_D^{25} 1.4440), and its conversion to 2-(β-naphthoxy)ethyl chloride (4), m.p. 83°, by heating overnight in acetone solution with potassium iodide and sodium β-naphthoxide. A mixture melting point with a sample prepared from ethylene chloride was not depressed.

b. *Isolation and identification of 1,2-bis(2-chloroethylthio)ethane (II).* The heated mustard gas was cooled and distilled *in vacuo*. The distillate, which contained a little *p*-dithiane, was nearly pure mustard gas, b.p. 68° (2 mm.), m.p. 14°. The dark residue (22 g.) was dissolved in ether and the solution cooled. The solid which precipitated was removed by filtration. Concentration of the filtrate produced more solid material which appeared to be a mixture of 1,2-*bis*(2-chloroethylthio)ethane (II) and *bis*[2-(2-chloroethylthio)ethyl] sulfide (III) contaminated with other substances. This mixture was not investigated further.

The ether was distilled from the final filtrate and the residual oil was heated on a steam-bath for three hours with a mixture of acetic acid and 30% hydrogen peroxide. When cooled the solution deposited a solid (2.34 g.) which was purified by recrystallization from a mixture of absolute ethanol and acetic acid. It melted at 205–206° and was identified as 1,2-bis(2-chloroethylthio)ethane disulfone by comparison with an authentic sample of this material[3] made from 1,2-*bis*(2-chloroethylthio)ethane (5).

Detailed investigation. a. *Analysis of heated mustard gas.* A 1-liter three-necked flask, equipped with a stirrer, thermometer, and gas-inlet tube, was completely immersed in an oil-bath and connected to traps cooled in a water-ice mixture for the collection of any distillate. Pure mustard gas (401 g., m.p. 14.5°) was placed in the flask and heated at 137–145° in an atmosphere of nitrogen for three days. The liquid (15.5 g.) which collected in the traps was fractionated to yield 9.4 g. of ethylene chloride, b.p. 80–83°, and 4.3 g. of mustard gas. The black liquid remaining in the reaction flask weighed 362 g., indicating a loss of 26 g. This loss represents mainly gaseous products produced by pyrolysis of the mustard gas. Distillation of the reaction mixture yielded 330 g. of unchanged mustard gas. *p*-Dithiane sublimed during the preliminary stages of the distillation.

To prove the presence of *p*-dithiane in the distillate a sample was stirred vigorously with boiling water until all of the mustard gas had been hydrolyzed (two hours). A small amount of solid material remained, which melted at 109–110° and did not lower the melting point of an authentic sample of *p*-dithiane. The preparation of *p*-dithiane is described below.

Analysis of the residue (27 g.) from the distillation was accomplished by treatment with 189 ml. of a 2 *N* ethanolic solution of sodium methyl mercaptide (6) and heating the resulting mixture under reflux for one-half hour. A solution of 15 ml. of acetic acid in 100 ml. of chloroform was added, and the mixture was cooled and shaken with 250 ml. of water. The chloroform layer was separated and filtered. An insoluble material weighing 2.5 g. (probably polyethylene sulfide) remained on the filter. The chloroform was evaporated from

[3] Unpublished results of Dr. Royston M. Roberts of this Laboratory.

the filtrate and the residue distilled *in vacuo*. The first fraction (3.6 g.), b.p. 100–150° (0.5 mm.), m.p. 15°,[4] consisted mainly of the methylthio ether of mustard gas. The second fraction (12.6 g.), b.p. 150–180° (0.5 mm.), m.p. 52–55°, was recrystallized consecutively from methanol and petroleum ether (90–110°). The pure material, m.p. 63–64°, did not lower the melting point of an authentic sample of 1,2-*bis*(2-methylthioethylthio)ethane, prepared from 1,2-*bis*(2-chloroethylthio)ethane (5).

The residue from the last distillation was extracted with hot methanol. When the resulting solution was cooled it deposited solid material, which after recrystallization from methanol melted at 80.5–83°.[4] A mixture melting point with an authentic sample of *bis* [2-(2-methylthioethylthio)ethyl] sulfide, described below, was not depressed.

The weights of methylthio ethers were converted back to weights of the corresponding chloro compounds. The results of the analysis of the heated mustard gas are as follows.

11.0 g. (2.7%) of 1,2-*bis*(2-chloroethylthio)ethane.
6.1 g. (1.5%) of *bis*[2-(2-chloroethylthio)ethyl] sulfide and higher analogs.
337. g. (84.5%) of mustard gas (containing some *p*-dithiane).
2.5 g. (0.6%) of polyethylene sulfide.
26 g. (6.5%) of gaseous products.
9.4 g. (2.3%) of ethylene chloride.

Total....392 g. (98.0%) of the mustard gas accounted for.

b. *Analysis of a heated mixture of mustard gas and 1,2-bis(2-chloroethylthio)ethane (II).* A mixture of 80 g. of pure mustard gas (m.p. 14.5°) and 20 g. of the dithio compound (m.p. 53–54°) was heated at 139–142° in an atmosphere of nitrogen for three days. During the heating 1.2 g. of *p*-dithiane and less than 1 ml. of liquid collected in the traps. There was a loss in weight of 18 g. (gaseous products).

The black liquid (80 g.) remaining was distilled under reduced pressure; the distillate (66 g.) consisted of mustard gas and *p*-dithiane. The mustard gas was destroyed by hydrolysis, and the aqueous solution extracted with ether. Evaporation of the ether solution yielded only a small amount of *p*-dithiane. The aqueous solution was made alkaline and again extracted with ether. This time 3.1 g. of *p*-dithiane was recovered.

The black residue (12 g.) from the distillation was analyzed as described in the preceding experiment. The results of the analysis are given below.

5.1 g. (5.1%) of 1,2-*bis*(2-chloroethylthio)ethane.
1.7 g. (1.7%) of polyethylene sulfide.
1.5 g. (1.5%) of *bis*[2-(2-chloroethylthio)ethyl] sulfide and higher analogs.
18. g. (18%) of gaseous products.
4.3 g. (4.3%) of *p*-dithiane.
66. g. (66%) of mustard gas.

Total.....96.6 g. (96.6%) of the mixture accounted for.

p-Dithiane.[5] Four hundred fifty-three grams of sodium sulfide nonahydrate was dissolved in a solution of 200 ml. of ethanol and 800 ml. of water. The solution was heated at 60–65°, and 355 g. of ethylene bromide added with stirring at such a rate that the solvent refluxed gently. The reaction mixture was heated under reflux for two hours after the addition was complete. The polyethylene sulfide was collected on a filter and washed consecutively with alcohol and ether. The yield of dry polymer was 104.5 g. (92% of the theoretical amount).

[4] Rosser, Meade, and Glover, *loc. cit.*, report the following melting points for pure compounds: *bis*(2-methylthioethyl) sulfide, 24.32°; 1,2-*bis*(2-methylthioethylthio)ethane, 66.5°; *bis*[2-(2-methylthioethylthio)ethyl] sulfide, 88.0° (84°); *bis*[2-(2-chloroethylthio)ethyl] sulfide, 73–75°.

[5] This synthesis was developed by Dr. E. W. Maynert.

The polymer did not melt at 180°. Heating at 155–160° for one day did not result in the sublimation of an appreciable amount of *p*-dithiane. The polymer therefore was treated as a Class I polymer of polyethylene sulfide (1). Thirty grams of polymer was heated at 130° for one hour with 18 g. of ethylene bromide, 40 g. of phenol was added, and the mixture was boiled overnight. A solution of sodium hydroxide was added slowly to the cool reaction mixture. The solid material was collected on a filter, washed thoroughly with water and dried. It was completely soluble in ether. The yield of *p*-dithiane (m.p. 108–110°) was 24.4 g. One recrystallization from ethanol gave pure *p*-dithiane (m.p. 111–111.5°).

bis[*2-(2-Methylthioethylthio)ethyl*] *sulfide.* *bis*[2-(2-Hydroxyethylthio)ethyl] sulfide (5) was heated with an ether solution of thionyl chloride for two hours. When the solvent was evaporated a wax-like solid remained. After two recrystallizations from alcohol-chloroform (1:2) and four from absolute methanol the *bis*[2-(2-chloroethylthio)ethyl] sulfide melted at 72–75°.[4,6]

The dichloro compound was converted to *bis*[2-(2-methylthioethylthio)ethyl] sulfide by treatment with an ethanolic solution of sodium methyl mercaptide. This derivative, after recrystallization from a methanol-chloroform solution, melted at 80.5–83°.[4]

SUMMARY

It has been shown that 1,2-*bis*(2-chloroethylthio)ethane and *bis*[2-(2-chloroethylthio)ethyl] sulfide are formed when mustard gas is heated.

The amount of these substances formed is limited, and in the case of the former compound does not exceed a value of 5 to 6 % of the quantity of mustard gas subjected to heating.

The mode of formation and decomposition of these substances is discussed.

An improved method for the synthesis of *p*-dithiane is described.

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[6] This synthesis was carried out by Mr. W. E. Parham.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] I. THE TRANSFORMATIONS OF METHYL-BIS(β-CHLOROETHYL)AMINE IN WATER

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The work to be presented in this series of papers was undertaken in order to elucidate certain aspects of the chemistry of a new group of vesicant chemical warfare agents, the nitrogen mustards. These substances are bis(β-chloroethyl) substituted tertiary amines of the general formula $RN(CH_2CH_2Cl)_2$. One compound of this series, tris(β-chloroethyl)amine, was first described by Ward (1).

The transformations undergone by the nitrogen mustards in water were chosen as the first point of attack since a detailed knowledge of these reactions seemed essential to an understanding of the general chemistry of the nitrogen mustards. Furthermore, the transformations of the nitrogen mustards in water are of interest from the biochemical point of view, since water is a major constituent of all biological systems. Finally, the possibility that the nitrogen mustards might be employed in chemical warfare as water contaminants made it imperative to study exhaustively the chemical reactions undergone by these agents in water.

The experimental results presented in this communication concern the sequence of chemical reactions undergone by methyl-bis(β-chloroethyl)amine (MBA) when this agent reacts with water in the presence or the absence of bicarbonate. On the basis of these results, a reaction mechanism (*cf.* Figure 1) has been proposed to explain the complex transformations of MBA in aqueous solutions. Two types of experimental evidence will be presented. The first involves an analytical study of the reactions undergone by MBA in aqueous bicarbonate solution buffered at *p*H 8 and in unbuffered aqueous solution [*cf.* also (2)]. The second type of evidence involves the isolation, in crystalline form, of the successive transformation products of MBA and a study of their properties.

The transformations of methyl-bis(β-chloroethyl)amine in bicarbonate solution. When MBA (0.02 *M*) reacts with water at *p*H 8 (bicarbonate buffer), it goes into solution rapidly with the liberation of nearly one equivalent of Cl^- and the appearance of negligibly small amounts of H^+ (Table I). It will be noted from Figure 1 that this is the result to be expected on formation of the 1-methyl-1-

[1] This work was done in whole under Contract No. OEMsr-313 between The Rockefeller Institute for Medical Research and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein. The experiments were performed during the period June 1942–January 1944.

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[4] Died, November 7, 1944.

(β-chloroethyl)ethylenimonium ion (I). Analytical evidence for the reaction was first presented by Hartley, Powell, and Rydon (3), and careful kinetic studies have been made by Bartlett (4) and Cohen (5). The cyclization of MBA

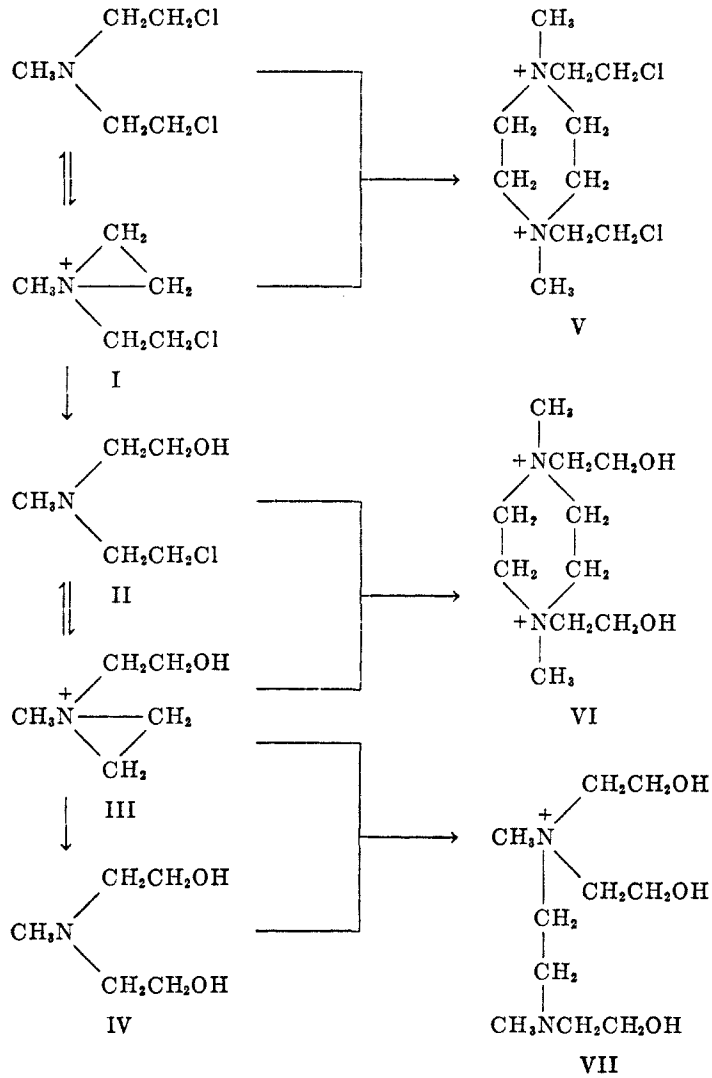


FIG. 1

is a special case of the conversion of chloroalkylamines into heterocyclic compounds, investigated by Freundlich (6).

Additional evidence for the rapid and nearly quantitative conversion of MBA to the ethylenimonium form is provided by the data given in Table I on the thiosulfate consumption of the solution. The rapid reaction of the ethylenimonium forms of MBA with thiosulfate and the use of the thiosulfate titer as an

index of ethylenimonium formation is discussed in detail in a subsequent section. Conclusive evidence for the formation of I is furnished by its isolation as a crystalline salt of picrylsulfonic acid from solutions of MBA aged for 30 minutes at *p*H 8.

As the hydrolysis in bicarbonate proceeds, there is observed a slow liberation of additional Cl^- and H^+ in approximately equivalent amounts and a progressive fall in the thiosulfate titer. These observations are in accord with the reaction sequences presented in Figure 1. As will be noted from the Figure, the hydrolysis of ethylenimonium rings to form hydroxyethyl groups is accompanied by the liberation of H^+ but not of Cl^-. On the other hand, when compounds containing quaternary nitrogen are formed, Cl^- is liberated without the appearance of H^+.

TABLE I

THE HYDROLYSIS OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) IN BICARBONATE SOLUTION

Concentration of reactants per cc.: 0.02 *mM* of MBA·HCl; 0.02 *mM* of NaOH; 0.08 *mM* of $NaHCO_3$.

Temperature 25°; *p*H 8.

TIME, MIN.	Cl^- LIBERATED PER *mM* OF MBA M.EQUIV.	H^+ LIBERATED PER *mM* OF MBA M.EQUIV.	(Cl^-)-(H^+) M.EQUIV.	$Na_2S_2O_3$ CONSUMED IN 10 MIN. PER *mM* OF MBA M.EQUIV.
20	0.945	0.085	0.86	1.13
60	1.20	.14	1.06	1.08
120	1.31	.25	1.06	1.06
240	1.50	.48	1.02	0.94
420	1.65	.65	1.00	.82
1200	1.83	.99	0.84	.28
4320	1.90			.06[a]

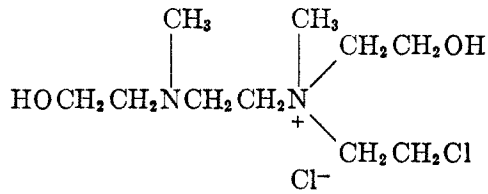
[a] This value represents the thiosulfate consumed in 1 hour.

The steady liberation of greater amounts of Cl^- than of H^+ during the hydrolysis in bicarbonate is evidence for the formation, during the reaction, of compounds containing quaternary nitrogen atoms. The difference between the values for the Cl^- and H^+ liberated represents the amount of quaternary nitrogen present. It will be noted that the thiosulfate titer has decreased markedly after 20 hours without an equivalent diminution in the amount of quaternary nitrogen. This finding indicates that a portion of the intermediates having ethylenimonium rings and chloroethyl groups have been converted into quaternary nitrogen compounds which do not react with thiosulfate under these conditions.

At the end of three days nearly the theoretical amount of Cl^- has been liberated. The low one-hour thiosulfate titer at this time indicates the absence of any significant quantities of compounds containing chloroethyl groups or ethylenimonium rings. As will be shown later in this paper, the products isolated as picrylsulfonates from a solution aged in this manner were methyldiethanolamine

(IV) and the dihydroxy cyclic dimer [N,N′-dimethyl-N,N′-bis(β-hydroxyethyl)piperazinium salt (VI)]. The latter compound also has been obtained (7) from the chlorohydrin [methyl-β-chloroethyl-β-hydroxyethylamine (II)] in alkaline solution. The dichloro cyclic dimer [N,N′-dimethyl-N,N′-bis(β-chloroethyl)piperazinium salt (V)] is not formed in appreciable amount in the presence of bicarbonate, but as will be shown later, is a major product of the reaction of MBA in unbuffered solution.

It will be noted from Figure 1 that the formation of the dihydroxy cyclic dimer is thought to occur by combination of the chlorohydrin (II) and the 1-methyl-1-(β-hydroxyethyl)ethylenimonium ion (III). It has been suggested (5) that these compounds condense to give a chlorinated intermediate (VIII) which subsequently cyclizes to the dihydroxy cyclic dimer VI.



(VIII)

An alternative mechanism would involve the direct interaction of two molecules of III to give the cyclic compound. The latter mechanism appears unlikely, however; since, as will be shown later, the dihydroxy cyclic dimer (VI) results from the transformation of the chlorohydrin (II) at *p*H 7–8 while, under similar conditions, III yields only the linear compound VII and methyldiethanolamine. These results suggest that compounds containing chloroethyl groups must participate in the reactions which lead to the formation of the dihydroxy cyclic dimer.

It will be noted from Figure 1 that the dihydroxy cyclic dimer (VI), the linear compound VII, and methyldiethanolamine should result from the transformations in bicarbonate solution of both I and MBA itself. After aging I (0.02 *M*) in aqueous bicarbonate, compounds VI and VII were isolated. MBA (0.02 *M*), however, yields the dihydroxy cyclic dimer (VI) and methyldiethanolamine; the expected linear compound VII could not be isolated. No satisfactory explanation can be offered at present for this result.

The results presented above, and in what follows, strongly support the reaction sequence given in Figure 1. It should be pointed out, however, that after hydrolysis of MBA, the relative amounts of the various end products given in Figure 1 will vary depending upon the concentration of MBA employed. Cohen (5) has shown that in very dilute solution the predominant reaction is hydrolysis to methyldiethanolamine. As the concentration of MBA is raised, however, the formation of dimers is favored and hydrolysis is reduced.

The reaction with thiosulfate as an index of the formation of ethylenimonium compounds. It will be noted from Table I that the difference between the Cl^- and H^+ content of the solution does not change greatly during the course

of the transformation of MBA. The Cl^- not balanced by H^+ must be balanced by an equivalent amount of quaternary nitrogen. This quaternary nitrogen, according to Figure 1, may be either in the form of the ethylenimonium compounds I or III, the dimers V or VI, or the linear compound VII. Consequently, on the basis of determinations of H^+ and Cl^- alone, it is impossible to establish whether the quaternary nitrogen present in solution is in the form of reactive ethylenimonium compounds or in the form of relatively unreactive products containing quaternary nitrogen.

An approximate differentiation may be made, however, by the use of thiosulfate as a reagent for the ethylenimonium compounds. The use of thiosulfate in this manner was suggested by earlier observations of Ogston (8) on the reactivity of solutions of MBA with thiosulfate. The compounds V, VI, or VII do not react with thiosulfate to any measurable extent in 24 hours at 25°. On the other hand, a study of the isolated transformation products of MBA has shown

TABLE II

THE REACTIONS OF THE PICRYLSULFONATES OF I AND III WITH $Na_2S_2O_3$

Concentration of reactants per cc.: 0.01 *mM* of imonium salt; 0.025 *mM* of $Na_2S_2O_3$; 0.04 *mM* of $NaHCO_3$.

Temperature 25°.

TIME, MIN.	$Na_2S_2O_3$ CONSUMED PER *mM* OF	
	I M.EQUIV.	III M.EQUIV.
10	1.01	0.91
20	1.40	.94
60	1.80	.94
120	1.89	.94

that the ethylenimonium ring of I or III reacts with thiosulfate very rapidly and consumes one equivalent of thiosulfate in 10 minutes (Table II). In the case of I the reaction proceeds further, the remaining chloroethyl group cyclizes, and a second equivalent of thiosulfate is consumed within the succeeding 110 minutes. As will be shown later, the chlorohydrin (II) also reacts with thiosulfate, presumably with prior cyclization to III. In 10 minutes, about 0.66 *mM* of thiosulfate are consumed per *mM* of chlorohydrin, under the conditions employed in these experiments. Consequently, the 10-minute thiosulfate titer of an aged solution of MBA containing chlorohydrin would measure a part of the chlorohydrin in addition to the ethylenimonium groups present in the solution. In aged bicarbonate solutions of MBA, the amount of chlorohydrin present at a given time must be small, however, and the 10-minute thiosulfate titer will give a sufficiently accurate measure of the amount of the quaternary nitrogen in such solutions which is in the form of ethylenimonium compounds. The remainder of the quaternary nitrogen may be assigned to compounds such as V, VI, or VII.

It will be noted from the data in Table I that during the transformation of

MBA (0.02 *M*) in bicarbonate, the 10-minute thiosulfate titer and the quaternary nitrogen content are approximately equal during the first 120–240 minutes of the reaction. This indicates that during this period nearly all of the quaternary nitrogen is probably in the form of imonium compounds. However, as the hydrolysis proceeds for longer periods of time (1200 min.), the 10-minute thiosulfate titer becomes much less than the quaternary nitrogen content. It may be concluded, therefore, that during this latter period unreactive quaternary nitrogen compounds are formed.

The mechanism of the reactions that occur between MBA and thiosulfate has been studied by Cohen (5). The isolation of the final product in the reaction of MBA with thiosulfate, the "Bunte salt" of MBA, is described in the experimental section of the present communication.

The transformations of methyl-bis(β-chloroethyl)amine in unbuffered solution. When MBA (0.02 *M*) is shaken with water it goes into solution rapidly, and one equivalent of Cl^- and a comparatively much smaller amount of H^+ are

TABLE III

THE HYDROLYSIS OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) IN UNBUFFERED SOLUTION

Concentration of reactants per cc.: 0.02 *mM* of MBA·HCl; 0.02 *mM* of NaOH.
Temperature 25°; *p*H *ca.* 7 (at start); *p*H *ca.* 5 (at end).

TIME, MIN.	Cl^- LIBERATED PER *mM* MBA, *mM*	H^+ LIBERATED PER *mM* MBA, *mM*	$Na_2S_2O_3$ CONSUMED IN 10 MIN. PER *mM* MBA, *mM*
20	0.86	0.15	1.23
60	0.99	.22	1.30
180	1.01	.345	1.10
1200	1.03	.84	0.65

liberated in a short time (Table III). According to Figure 1, this is the result to be expected upon the formation of I. As the hydrolysis proceeds, the Cl^- and H^+ are liberated at about equal rates, indicating that both hydrolysis and the formation of quaternary nitrogen compounds are occurring. A small amount (6%) of the dichloro cyclic dimer (V) was isolated, as a dipicrylsulfonate, from a 20-hour aged solution of MBA (0.02 *M*). As shown by Hartley, Powell, and Rydon (3), dimerization to the dichloro cyclic dimer (V) occurs to an appreciable extent in such solutions. It appears likely that, as shown in Figure 1, the formation of V results from the combination of MBA with I. This mechanism is analogous to that postulated for the formation of the dihydroxy cyclic dimer (VI) in bicarbonate solution.

It will be noted from Table III that the reaction mixture becomes acid during the hydrolysis and that nearly one equivalent of HCl is liberated per mole of MBA. These data suggest that the change in *p*H leads to the stabilization of the chlorohydrin (II) because of salt formation. This is supported by the finding that II is the major product of the hydrolysis since it could be isolated as a picrylsulfonate in 52% yield without any attempt at quantitative separation.

The fact that the evolution of Cl^- does not exceed one equivalent indicates

that the imonium compound (III) and methyldiethanolamine (IV) are formed only in small amounts in unbuffered solution. This is in contrast to the reactions observed for MBA in bicarbonate buffered solutions.

It will be noted in Figure 1 that the formation of I and III is written as a reversible reaction. It is believed (4) that the Cl^- produced during the hydrolysis of MBA interacts in part with these imonium compounds to regenerate MBA and the chlorohydrin (II) respectively. Direct evidence that this can occur will be presented in later sections of this paper.

In the last column of Table III, data are presented on the thiosulfate consumption of aging solutions of MBA. The 10-minute thiosulfate titer has been shown to be a convenient means for estimating the concentration of ethylenimonium groups in the solutions of MBA aged in the presence of bicarbonate. However, when applied to the study of the reactions of MBA in unbuffered solutions, it does not give the approximate concentrations of ethylenimonium forms. Whereas in bicarbonate solution the chloroethyl group of the chlorohydrin (II) rapidly cyclizes to III, at *p*H 5 this process does not occur to an appreciable extent. Since the aged unbuffered solution of MBA contains large amounts of chlorohydrin, the 10-minute thiosulfate titer of an aliquot of such a solution is a measure not only of the ethylenimonium forms present in the solution, but also of part of the chloroethyl groups present.

The high thiosulfate titer of the MBA hydrolysate after 20 hours points to the possibility of ethylenimonium compounds being present in the aged solution. This was confirmed by the isolation of 10% of I as a picrylsulfonate from the 20-hour solution.

In the isolation studies to be reported below, the 2-hour thiosulfate titer was found to be much more useful than the 10-minute thiosulfate test and was employed almost exclusively in place of the latter. MBA and those of its transformation products which consume thiosulfate react quantitatively with this reagent within 2 hours. Thus, when the 2-hour thiosulfate test was applied to the isolated compounds, it was frequently possible to estimate their purity.

The isolation of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate. Data in a previous section of this communication have shown that I is unstable in aqueous solution. Consequently, freshly prepared solutions of I must be used in any attempt to isolate this compound. For this purpose, such solutions were prepared by shaking the hydrochloride of MBA for 30 minutes at room temperature with water containing one mole equivalent of NaOH. The addition of sodium picrylsulfonate[5] gave a sparingly soluble salt which reacted readily with sodium thiosulfate and had the correct elementary composition for the picrylsulfonate of I. The same picrylsulfonate was also formed when MBA picrylsulfonate was stirred with aqueous bicarbonate. The isolated imonium salt contained picrylsulfonic acid and chlorine in equivalent amounts. The picrylsulfonate of MBA contains picrylsulfonic acid and chlorine in a ratio of 1:2. The picrylsulfonate of the dichloro cyclic dimer (V) has the same ratio

[5] A description of the preparation of picrylsulfonic acid and its sodium salt is given in the experimental section. Stein, *et al.* (9) have investigated the possible application of picrylsulfonic acid as a reagent for amino acids.

of picrylsulfonic acid to chlorine as the I picrylsulfonate; the dimer salt, however, does not react appreciably with thiosulfate. It must, therefore, be concluded that the compound isolated is the picrylsulfonate of the ethylenimonium form of MBA.

The hydrolysis of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate. The hydrolysis of the picrylsulfonate in the presence of $NaHCO_3$ was followed

TABLE IV

THE HYDROLYSIS OF THE TRANSFORMATION PRODUCTS OF METHYL-BIS(β-CHLOROETHYL)AMINE IN BICARBONATE SOLUTION

Concentration of reactants per cc.: 0.02 *mM* of picrylsulfonate of I, II, or III; 0.08 *mM* of $NaHCO_3$.

Temperature 25°; *p*H 8 (unless otherwise noted).

TIME, MIN.	Cl^- LIBERATED PER *mM* OF		H^+ LIBERATED PER *mM* OF			$Na_2S_2O_3$ CONSUMED IN 10 MIN. PER *mM* OF		
	I M.EQUIV.	II M.EQUIV.	I M.EQUIV.	II[a] M.EQUIV.	III M.EQUIV.	I M.EQUIV.	II M.EQUIV.	III[b] M.EQUIV.
20	0.09	0.62	0.30	0.01		1.07	0.89	
60	0.27	0.89	0.44	0.03	0.12	0.92	0.90	0.84
120	0.59		0.78			0.84		
180		0.99		0.14	0.26		0.85	0.69
240	0.89		1.19			0.54		
420	0.94		1.37			0.29		
1200	0.97	1.02	1.68	0.46	0.67	0.00	0.36	0.00
2400		1.03		0.69			0.00	

[a] Corrected for H^+ arising from picrylsulfonic acid. This was found to be 1 m.equiv. per *mM* of II picrylsulfonate.

[b] The rate of disappearance of III in this experiment appears to be more rapid than in the aging of the chlorohydrin (II). In the latter experiment the initial *p*H was 7.3 and rose to 8.2 after 20 hours, whereas in the experiment with III the initial *p*H was 8.4 and rose to 8.7 after 20 hours. The lower initial *p*H in the chlorohydrin experiment may, therefore, explain the greater persistence of III in the aged chlorohydrin solution.

in the same manner as the hydrolysis of the parent nitrogen mustard, MBA. The results are given in Table IV together with similar data for the other transformation products of MBA.

As noted in a previous section, the I picrylsulfonate also is formed when the picrylsulfonate of MBA is stirred with aqueous bicarbonate. The MBA picrylsulfonate dissolves on stirring in bicarbonate solution, but within one hour at 25° the solution deposits crystals which have the characteristic appearance of the I picrylsulfonate. Upon further constant stirring, these crystals gradually disappear. The concentration of the ethylenimonium ion under these conditions is thus considerably less during the early stages of the hydrolysis than it would have been if the hydrolysis had been carried out in the absence of the picrylsulfonate ion. It is not surprising, therefore, to find that the titration data for the picrylsulfonates of MBA and I obtained after 20 hours, have much in common. In both instances, the extent of hydrolysis is greater, and the extent of

formation of compounds containing quaternary nitrogen is less, than was found to be the case with MBA under the same conditions.

It will be noted from the data in Table IV on the hydrolysis of the I picrylsulfonate, that after 20 hours, 1.68 m.equiv. of H^+ and nearly one m.equiv. of Cl^- are produced per *mM* of ethylenimonium salt. The complete hydrolysis of the ethylenimonium salt to form methyldiethanolamine would liberate two equivalents of H^+ and one equivalent of Cl^-. The failure of the H^+ to reach the theoretical value is due to the formation of VI and VII.

Two compounds were isolated from the 20-hour hydrolysate of I picrylsulfonate. The one, present in larger amount, was characterized as a picrylsulfonate and a Reineckate. This substance is the open-chain compound VII of Figure 1. The other compound was characterized as a picrylsulfonate and was found to be the dihydroxy cyclic dimer (VI).

The identification of the linear compound VII is based on the following evidence:

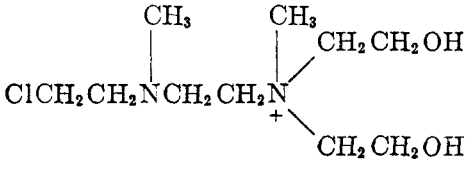
1. The analytical data show that the elementary composition of the picrylsulfonate is $(C_{11}H_{16}N_4O_{11}S)_x$. This elementary composition agrees equally well with that of the monopicrylsulfonate of methyldiethanolamine and the dipicrylsulfonate of a linear compound such as VII containing one molecule of water of crystallization.

2. At 115°, the isolated picrylsulfonate loses the amount of water of crystallization to be expected for the picrylsulfonate of the linear compound.

3. The isolated picrylsulfonate and the Reineckate differ in melting point from the corresponding salts of pure methyldiethanolamine. This, and the loss of water of crystallization, show that the isolated salts are not those of methyldiethanolamine.

4. When dissolved in bicarbonate solution, the isolated picrylsulfonate neutralizes only one-half as much bicarbonate as does a like amount of methyldiethanolamine picrylsulfonate. Methyldiethanolamine is a tertiary base and, therefore, its picrylsulfonate consumes an amount of bicarbonate equivalent to all of the picrylsulfonic acid present in the salt. The picrylsulfonate of the linear compound contains two equivalents of picrylsulfonic acid; one equivalent is neutralized by the strongly basic quaternary ammonium ion, whereas the second equivalent of picrylsulfonic acid can react with bicarbonate. Thus, the picrylsulfonate of the linear compound should consume an amount of bicarbonate equivalent to one-half of the picrylsulfonic acid present in this salt.

5. Finally, the isolated picrylsulfonate agrees in melting point and mixed melting point with the hydrolysis product obtained from the dipicrylsulfonate of the compound IX (*cf.* Paper VII of this series).



(IX)

A likely mechanism for the formation of the linear compound VII is given in Figure 1. Another possibility is that methyldiethanolamine reacts with unchanged I to give the chlorinated linear compound IX which, on removal of the chlorine by hydrolysis, yields VII.

The reaction of the 1-methyl-1-(β-chloroethyl)ethylenimonium ion with chloride. In the hydrolysis of MBA in unbuffered solution, the ethylenimonium ion initially formed is believed to react with the Cl^- produced in the later stages of hydrolysis to regenerate some MBA (3). Direct evidence for this view has been obtained from a study of the reaction of I picrylsulfonate with HCl. The difficultly soluble ethylenimonium salt gradually dissolves in dilute HCl and after 20 hours at 25°, the picrylsulfonate of MBA can be isolated from the reaction mixture. The MBA picrylsulfonate can be distinguished readily from the corresponding ethylenimonium salt by virtue of the difference in chlorine content.

It should be noted that, in order to effect reversal of the cyclization of MBA, it is necessary to perform the reaction in acid solution. In neutral or alkaline solution, the reaction is not reversible because the imonium ion hydrolyzes rapidly to the chlorohydrin.

The isolation and hydrolysis of the chlorohydrin (II). The chlorohydrin has been isolated from aged unbuffered solutions of MBA as a salt of picrylsulfonic acid. The chlorohydrin picrylsulfonate is readily soluble in bicarbonate. In the presence of bicarbonate, the chlorohydrin is almost completely cyclized to III in one hour at 25°. This is shown by the liberation (per *mM* of chlorohydrin salt) of 0.9 m.equiv. of Cl^- with practically no concomitant production of H^+, as well as by the thiosulfate consumption of 0.9 m. equiv. (Table IV). After 3 hours, the Cl^- reaches the theoretical value, the thiosulfate titer decreases, and the H^+ begins to increase. The value attained by the H^+ is far below the Cl^- concentration, however. This indicates the occurrence both of hydrolysis and the formation of stable compounds containing quaternary nitrogen.

The data in Table IV show that, on hydrolysis of 0.02 *M* I picrylsulfonate in bicarbonate, no ethylenimonium groups were present after 20 hours at 25°. It is of interest, therefore, that considerable amounts of III are present in the chlorohydrin hydrolysate even after 20 hours. The persistence of III for long periods of time makes its isolation feasible. Similarly, when 0.02 *M* MBA itself was subjected to hydrolysis in bicarbonate (Table I) an appreciable amount of ethylenimonium compounds (I and/or III) remained.

The isolation and hydrolysis of the 1-methyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate. The analytical data presented in Table IV show that the chlorohydrin (II) cyclizes to form compound III. This cyclic compound has been isolated as a picrylsulfonate from an aqueous solution of the chlorohydrin aged at *p*H 7–8 for 30 minutes. The yield was 38%. Other products isolated from the reaction were the dihydroxy cyclic dimer (23%) and unchanged chlorohydrin (10%). The recovery of the latter compound indicates incomplete cyclization of the chlorohydrin and/or reversion of III brought about by the HCl added

during the isolation procedure. The possibility of reversion is supported by the finding that the III picrylsulfonate can react with Cl^- in acid solution to form the corresponding salt of the chlorohydrin.

The picrylsulfonate of III dissolves readily in aqueous bicarbonate and is rapidly hydrolyzed in this medium (*cf.* Table IV). After 20 hours at 25°, the 10-minute thiosulfate titer is zero, indicating the complete disappearance of the imonium ion. The failure of the H^+ to reach the theoretical value of one equivalent shows that hydrolysis to methyldiethanolamine is not the only reaction which has occurred. From the 20-hour hydrolysate, methyldiethanolamine and the linear compound VII are obtained; the dihydroxy cyclic dimer (VI) is absent. From the data of Table IV, it may be calculated that 66% of the initial imonium salt (III) was converted to the compound VII in 20 hours. The amount of VII actually isolated represented 63% of the theoretical maximum.

The toxicity of the transformation products of methyl-bis(β-chloroethyl)amine. It was reported in earlier sections of this communication that all the transformation products of MBA in bicarbonate solution were isolated as salts of picrylsulfonic acid. In order to study the toxicity of these compounds, it was necessary to devise a method for converting the picrylsulfonates into soluble chlorides or hydrochlorides. It was found that dilute aqueous solutions of the ethylenimonium and chlorohydrin picrylsulfonates underwent a double decomposition when treated with the non-toxic dichloro cyclic dimer (V) of MBA whereby the dipicrylsulfonate of V immediately precipitated from solution in almost quantitative yield and the ethylenimonium chloride or chlorohydrin hydrochloride was the only product remaining in solution. The dipicrylsulfonate of the linear compound VII was split in the same manner. Such solutions were tested for toxicity upon intraperitoneal injection into mice. The results are given in Table V.

Smith *et al.* (10) have reported an LD_{50} of 2.4 mg./kg. for the chloride of I on subcutaneous injection into mice. These investigators have also found that the LD_{50} of the chlorohydrin hydrochloride for mice was 16.0 mg./kg. on subcutaneous injection, 22.5 mg./kg. on intravenous injection, and 34 mg./kg. on intraperitoneal injection. The LD_{50} of the chloride of III for mice was 4.7 mg./kg. on subcutaneous injection, 4.2 mg./kg. on intravenous injection, and about 7 mg./kg. on intraperitoneal injection. The approximate toxicities of II and III, as given in Table V, are in good agreement with Smith's LD_{50} values. The linear compound VII was found to be relatively non-toxic.

If a solution of the chlorohydrin hydrochloride is adjusted to *p*H 7 and maintained at 25° for one hour, at the end of that time period, all the chlorine is in the ionic form and the thiosulfate titer is about 90% of one equivalent. The toxicity of such an aged solution is given in Table V. The results confirm the observations of Boyland (11) on the increased toxicity of aged chlorohydrin solutions. The analytical data given above indicate that the increase in toxicity of the aged chlorohydrin is due to the formation of the imonium ion III. This

conclusion is further substantiated by the finding that the toxicity of III agrees with that of the aged chlorohydrin solution (*cf.* Table V).

TABLE V

TOXICITY TO MICE OF TRANSFORMATION PRODUCTS OF METHYL-BIS(β-CHLOROETHYL)AMINE

SUBSTANCE (EMPLOYED AS HYDROCHLORIDE OR CHLORIDE)	DOSAGE	NUMBER OF MICE INJECTED	EFFECT ON MICE
	mg./kg.		
II	300	6	All dead within 17–27 min.
	150	6	All dead within 21–46 min.
	75	6	5 dead within 26–60 min. 1 alive after 4 days.
	30	6	All alive after 4 days.
Solution of chlorohydrin (II) aged at *p*H 7 for 1 hour[a]	150	3	All dead within 13–15 min.
	75	3	All dead within 21–22 min.
	30	6	All dead within 18–30 min.
	15	6	All dead within 19–30 min.
	7.5	3	1 dead within 55 min. 2 alive after 4 days.
	3.75	3	All alive after 4 days.
III	55	3	All dead within 20–33 min.
	37.5	3	All dead within 15–30 min.
	15	3	All dead within 15–21 min.
	7.5	3	All alive after 6 days.
	3.5	3	All alive after 6 days.
VII	2000	3	2 dead within 4–6 min. 1 alive after 6 days.
	1000	3	1 dead within 12 min. 2 alive after 6 days.
	500	3	All alive after 6 days.

[a] The dosage is based on the chlorohydrin originally present.

EXPERIMENTAL

Analytical methods. The liberation of Cl^- was determined by titration with 0.1 *N* $AgNO_3$ using dichlorofluorescein as an adsorption indicator (12). The liberation of H^+ was followed by acidification of an aliquot of the reaction mixture and removal of the liberated CO_2 by evacuation, followed by back titration in 80–90% alcohol with 0.1 *N* NaOH. The H^+ liberation was determined as the difference between the NaOH required by the MBA solution and that required by a control solution containing no MBA. Control experiments showed that, in the presence of alcohol, HCl can be titrated quantitatively in the presence of tertiary amines such as methyldiethanolamine, ethyldiethanolamine, or triethanolamine. The thiosulfate titer of the reaction mixture was determined by adding excess thiosulfate to an aliquot and, after 10 minutes, titrating the unreacted thiosulfate with iodine.

Isolation of products from the hydrolysis of MBA in bicarbonate solution. A reaction mixture (600 cc.) containing per cc., 0.02 *mM* of MBA·HCl and 0.10 *mM* of $NaHCO_3$, was allowed to stand at 25° for 3 days. At the end of this time aliquots were removed and the thio-

sulfate titer (0.06 *mM* of thiosulfate per *mM* of MBA originally present) and the chloride ion liberation (1.90 *mM* of Cl^- per *mM* of MBA) were determined. The reaction mixture was cooled, acidified with HCl and treated with an aqueous solution of 4.2 g. (11.5 *mM*) of picrylsulfonic acid. The compound which separated immediately (1.1 g., yield 24%) was the dipicrylsulfonate of the dihydroxy cyclic dimer (VI). It did not melt up to 250°. Analyzed preparations are reported below.

The filtrate was concentrated under reduced pressure to 75 cc. and cooled. The precipitate which formed was filtered off and dried in air; yield 2.0 g. (55%) of methyldiethanolamine picrylsulfonate; m.p. 173–176°. After recrystallization from water, its m.p. was 178–180°. The same m.p. was obtained on admixture with an authentic sample of methyldiethanolamine picrylsulfonate. The pure compound melted at 182–183°.

Isolation of products from the hydrolysis of MBA in unbuffered solution. MBA·HCl (1.93 g., 10 *mM*) was added to 500 cc. of water containing exactly 10 *mM* of NaOH. After 20 hours at room temperature, the solution was cooled to 0°, and acidified with HCl to Congo Red. Sodium picrylsulfonate (10.5 *mM* in 35 cc. of 0.5 *N* HCl) was added and the mixture was allowed to remain at 4° for 1 hour. The precipitate which formed was filtered off and dried *in vacuo* over P_2O_5; yield 0.26 g., 6%. The substance did not react with thiosulfate in the course of 2 hours. Its analysis agreed with that calculated for the dipicrylsulfonate of the dichloro cyclic dimer (V). This quaternary compound occurs in two stereoisomeric forms (7). It has not been determined which of the isomers are present in the isolated product.

Anal. Calc'd for $C_{10}H_{22}Cl_2N_2 \cdot 2C_6H_2N_3O_9S$: C, 32.0; H, 3.2; N, 13.6.
Found: C, 31.9; H, 3.0; N, 13.7.

The mother liquor was concentrated *in vacuo* to about 150 cc. and kept at 4° overnight. The salt which had crystallized, was filtered off, washed with cold acetone, and dried *in vacuo* over P_2O_5. It was the picrylsulfonate of I; yield 0.40 g., 10%. The 2-hour thiosulfate consumption of this substance was 1.82 *mM* per *mM* of the ethylenimonium salt.[6] The salt was recrystallized from an acetone-petroleum ether mixture and dried *in vacuo* over P_2O_5. Its 2-hour thiosulfate titer was now 1.85 *mM* per *mM* of the salt.

Anal. Calc'd for $C_5H_{11}ClN \cdot C_6H_2N_3O_9S$: C, 32.0; H, 3.2; N, 13.6; Cl. 8.6.
Found: C, 31.9; H, 3.3; N, 13.5; Cl, 8.5.

The mother liquor remaining after the removal of I picrylsulfonate, was concentrated *in vacuo* to 60 cc. and kept at 4°. The salt which had separated was filtered off and dried *in vacuo* over P_2O_5. It was the picrylsulfonate of the chlorohydrin (II); yield 2.25 g., 52%. The 2-hour thiosulfate consumption was 1.05 *mM* per *mM* of chlorohydrin salt. The salt was recrystallized twice from an acetone-petroleum ether mixture and dried as before. Its thiosulfate titer was now 0.94 and its analysis agreed well with that expected for the picrylsulfonate of methyl-β-chloroethyl-β-hydroxyethylamine (II); m.p. 142–144°.

Anal. Calc'd for $C_5H_{12}ClNO \cdot C_6H_2N_3O_9S$: C, 30.7; H, 3.5; N, 13.0; Cl, 8.2.
Found: C, 30.7; H, 3.6; N, 13.0; Cl, 8.2.

The isolation of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate. MBA hydrochloride (7.7 g., 40 *mM*) was added to 250 cc. of water containing exactly 40 *mM* of NaOH. After shaking the reaction mixture for one-half hour at room temperature, the solution was cooled to 0°, acidified with HCl to Congo Red, and 170 cc. of 0.3 *N* sodium picrylsulfonate (in 0.5 *N* HCl) was added. After 15 minutes the precipitate was filtered off, washed with cold acetone, and dried over P_2O_5 *in vacuo*. The finely powdered salt was stirred for 30 minutes at room temperature with 2 liters of acetone and filtered.

The imonium salt readily crystallized from the acetone filtrate upon addition of 600 cc. of petroleum ether and cooling at 0°; yield 5.3 g.

Anal. Calc'd for $C_5H_{11}ClN \cdot C_6H_2N_3O_9S$: C, 32.0; H, 3.2; N, 13.6; Cl, 8.6.
Found: C, 32.2; H, 3.3; N, 13.6; Cl, 8.4.

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[6] Unless otherwise stated, all subsequent thiosulfate titers are for 2 hours.

A sample of the salt, when allowed to react with thiosulfate for 2 hours, consumed 1.89 *mM* of thiosulfate per *mM* of the salt, the thiosulfate titer of MBA (under comparable conditions) was 1.90 equivalents.

The thiosulfate titer of the imonium picrylsulfonate was determined in the following manner: 45 mg. of the salt was added to 10 cc. of a solution, 0.025 *N* in thiosulfate and 0.044 *N* in bicarbonate. After stirring at 25° for 2 hours, the excess thiosulfate was titrated with 0.03 *N* iodine.

A sample of I picrylsulfonate was stored for a week *in vacuo* over P_2O_5 at room temperature and showed no decrease in the 2-hour thiosulfate titer. After a month at 4°, with intermittent exposure to room temperature, there was a 4% decrease in the thiosulfate titer.

In the preparation of I picrylsulfonate from MBA, an acetone-insoluble fraction is obtained which does not consume thiosulfate. The analysis of this substance indicates that it is the dipicrylsulfonate of the dichloro cyclic dimer (V).

Anal. Calc'd for $C_{10}H_{22}Cl_2N_2 \cdot 2C_6H_2N_3O_9S$: C, 32.0; H, 3.2; N, 13.6; Cl, 8.6.
Found: C, 31.9; H, 3.4; N, 13.6, Cl, 8.6.

The picrylsulfonate of I also was prepared by shaking MBA·HCl in an aqueous suspension of $BaCO_3$ at room temperature and subsequently removing the barium ion at 0°. MBA·HCl (1.54 g., 8 *mM*) was added to 50 cc. of water in which 3.16 g. (16 *mM*) of $BaCO_3$ was suspended. After shaking for one hour at room temperature, the mixture was cooled to 0° and was maintained at 0–4° during the remainder of the treatment. The excess barium carbonate was filtered off and the filtrate was freed from barium ion with sulfuric acid. Sodium picrylsulfonate (8 *mM* in 25 cc. of 0.05 *N* HCl) was added. After 10 minutes the precipitated picrylsulfonate was filtered off and dried *in vacuo* over P_2O_5 at 4°; yield 2.2 g.

The crude product was recrystallized twice by stirring it in a large volume of acetone, filtering, and evaporating off most of the acetone. The thiosulfate titer of the twice recrystallized product was 1.80 *mM* of thiosulfate per *mM* of imonium salt. Under comparable conditions, a freshly prepared solution of I consumes 1.90 *mM* of thiosulfate per *mM* of MBA employed. On this basis the I picrylsulfonate may be considered to be 95% pure.

Anal. Calc'd for $C_5H_{11}ClN \cdot C_6H_2N_3O_9S$: C, 32.0; H, 3.2; N, 13.6; Cl, 8.6.
Found: C, 32.3; H, 3.1; N, 13.3; Cl, 8.4.

The hydrolysis of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate. The picrylsulfonate of I (1.322 g., 3.2 *mM*) was continuously stirred in 160 cc. of 0.08 *N* sodium bicarbonate at 25°. Aliquots were removed at regular intervals and analyzed for H^+, Cl^- and the extent of thiosulfate consumption. In view of the heterogeneous character of the reaction mixture it is of interest that the same final results were obtained when individual samples of the salt were employed instead of aliquots of the reaction mixture. (Preliminary experiments showed that Cl^- can be determined quantitatively in the presence of sodium picrylsulfonate.)

For isolation of the products of hydrolysis, 2.06 g. (5 *mM*) of I picrylsulfonate were stirred continuously in 250 cc. of 0.08 *N* $NaHCO_3$ for 20 hours at room temperature. The mixture was filtered from a small amount of suspended solid (60 mg.), acidified with HCl to Congo Red, and cooled at 4° for 12 hours. The salt which crystallized was filtered off and dried; yield 300 mg. For analysis it was recrystallized from an acetone-water mixture and dried in air. The elementary analysis agreed with that for the dipicrylsulfonate of the dihydroxy cyclic dimer (VI). This compound, like the corresponding dichloro derivative, occurs in two stereoisomeric forms (7).

Anal. Calc'd for $C_{10}H_{22}N_2O_2 \cdot 2C_6H_2N_3O_9S \cdot \frac{1}{2}H_2O$: C, 33.1, H, 3.7; N, 14.0; H_2O, 1.1.
Found: C, 32.8; H, 3.6; N, 13.9; H_2O, 0.9.

The mother liquor remaining after removal of the dihydroxy cyclic dimer was concentrated to 50 cc. and again cooled at 4° for 12 hours. The material which crystallized had the melting point 201–203° with decomposition; yield, 0.9 g. After two recrystallizations from water and drying in air, the compound melted at 203–205° and its mixed melting point with an authentic sample of the dipicrylsulfonate of the linear compound VII was 203–203°.

The compound lost one mole of water when dried at 115°; the anhydrous salt melted at 204–206°.

Anal. Calc'd for $C_{10}H_{26}N_2O_2 \cdot 2C_6H_2N_3O_9S \cdot H_2O$: C, 32.0; H, 3.9; N, 13.6; H_2O, 2.2. Found: C, 32.0; H, 4.05; N, 13.65; H_2O, 2.3.

The picrylsulfonate of pure methyldiethanolamine melts at 182–183° and its mixture with the isolated picrylsulfonate melted at 175–177°.

The isolated picrylsulfonate (81.4 mg., 0.039 *mM*) neutralized 0.0365 *mM* of $NaHCO_3$, whereas the same weight of methyldiethanolamine picrylsulfonate neutralized twice as much $NaHCO_3$. These determinations were performed by dissolving the salts in bicarbonate solution, adding excess HCl, and after removal of carbon dioxide *in vacuo*, titrating the excess HCl in 80% alcohol with NaOH.

The isolated picrylsulfonate was converted into a Reineckate by treating its hot aqueous solution with dichloro cyclic dimer to remove picrylsulfonic acid, followed by the addition of the calculated quantity of Reinecke salt dissolved in methanol. The Reineckate was dried *in vacuo* over P_2O_5 at room temperature. It decomposed at 147–148°. The Reineckate lost 1½ moles of water when dried at 100° *in vacuo* over P_2O_5. The anhydrous salt decomposed at 148–149°. The Reineckate of pure methyldiethanolamine decomposes at 168°. The elementary analysis accords with the theory for the Reineckate of compound VII.

Anal. Calc'd for $C_{10}H_{26}N_2O_2 \cdot 2\ C_4H_6CrN_6S_4 \cdot 1\frac{1}{2}H_2O$: C, 24.4; H, 4.7; N, 22.1; H_2O, 3.05. Found: C, 24.1; H, 4.6; N, 22.2; H_2O, 3.2.

The isolated picrylsulfonate was also converted into a rhodanilate by the same procedure used for the preparation of the Reineckate. The rhodanilate decomposed at 181°. An attempt to prepare a pure rhodanilate of methyldiethanolamine was unsuccessful.

The reaction of the 1-methyl-1-(β-chloroethyl)ethylenimonium ion with chloride. The picrylsulfonate of I (413 mg., 1 *mM*) was added to 50 cc. of water containing 5 *mM* of HCl. After stirring at 25° for 20 hours, the reaction mixture was filtered from a small amount of suspended solid (10 mg.) and concentrated *in vacuo* to a small volume (5–10 cc.). During this time a solid separated which increased in amount upon cooling the mixture at 0°. The substance was filtered off and dried *in vacuo* over P_2O_5; yield, 260 mg.; m.p. 136–140°. The authentic picrylsulfonate of MBA melts at 145–148° and the mixture of the two substances melted at 135–142°. The reaction product was recrystallized from water and dried as before; m.p. 138–141°, and mixed m.p. 140–145°.

Anal. Calc'd for $C_5H_{12}Cl_2N \cdot C_6H_2N_3O_9S$: C, 29.4; H, 3.1; N, 12.5; Cl, 15.8. Found: C, 29.7; H, 3.15; N, 12.5; Cl, 15.7.

The thiosulfate titer was 1.82 *mM* per *mM* of MBA picrylsulfonate.

The amount of MBA picrylsulfonate isolated corresponds to 0.58 *mM*. When correction is made for the solubility of this salt, namely, 1.3% at 0°,[7] the total yield amounts to 73 to 87%.

In order to prepare an authentic sample of MBA picrylsulfonate for comparison with the above product, 1.54 g. (8 *mM*) of MBA·HCl was dissolved in 10 cc. of water, and the solution was added to 50 cc. of 0.5 *N* HCl containing 2.8 g. (8 *mM*) of sodium picrylsulfonate. Upon cooling at 0°, the picrylsulfonate of MBA crystallized. It was filtered off and dried over P_2O_5; yield 2.43 g. For analysis, it was recrystallized from water and dried as before; m.p. 145–148°.

Anal. Calc'd for $C_5H_{12}Cl_2N \cdot C_6H_2N_3O_9S$: C, 29.4; H, 3.1; N, 12.5; Cl, 15.8. Found: C, 29.2; H, 3.1; N, 12.5; Cl, 15.6.

The thiosulfate titer (2 hours) was 1.86 *mM* per *mM* picrylsulfonate.

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[7] MBA forms sparingly soluble salts with several aromatic sulfonic acids other than picrylsulfonic acid. The approximate solubility, in 0.5 *N* HCl at 0°, of the flavianate is 2.5%; that of the 2,6-diiodophenol-4-sulfonate is 1.8%; and that of the 5-nitronaphthalene-1-sulfonate is 2.9%.

The conversion of the picrylsulfonate of the chlorohydrin (II) to the corresponding hydrochloride. The chlorohydrin picrylsulfonate (124 mg., 0.29 *mM*) was dissolved in 6 cc. of water. To this solution, 0.48 cc. of a 0.3 *M* solution of dichloro cyclic dimer was added. The picrylsulfonate of the dimer precipitated immediately. The mixture was left for 15 minutes at room temperature and for 15 minutes at 4°. The precipitate was filtered off and dried over P_2O_5 *in vacuo*; yield 116 mg. (97.5%). This substance did not dissolve in, and did not react with, aqueous thiosulfate. The filtrate after removal of the dimer salt was stored at 4° for one-half hour before being used for the toxicity experiments.

An approximate measurement of the solubility of the dichloro cyclic dimer dipicrylsulfonate was made by determining the total nitrogen in an aliquot of a saturated aqueous solution of the dimer salt. In this manner, the solubilities at 0° and 25° were found to be 0.05% and 0.07% respectively.

The cyclization of the chlorohydrin (II). The chlorohydrin hydrochloride solution was brought to *p*H 7 with $NaHCO_3$, diluted to the desired volume and maintained at 25° for one hour. Aliquots were removed for Cl^- determination and thiosulfate titer and the remainder was immediately injected into mice. The Cl^- liberated was 0.97 *mM* per *mM* of chlorohydrin and the thiosulfate consumption (10 min.) was 0.86 *mM* per *mM* of the chlorohydrin originally present.

The isolation of 1-methyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate. The hydrochloride of the chlorohydrin[8] (1.801 g., 10.3 *mM*) was added to 100 cc. of water containing 10.3 *mM* of NaOH. After 30 minutes at 25°, the reaction mixture was cooled to 0°, and acidified with HCl to Congo Red. A solution of 3.51 g. (10.5 *mM*) of sodium picrylsulfonate in 35 cc. of 0.3 *N* HCl was then added and, after standing 15 minutes at 0°, the precipitate which formed was filtered off. This substance was dried *in vacuo* over P_2O_5 at room temperature; yield 0.96 g. (23%). It was insoluble in, and did not react with, thiosulfate. Its elementary analysis shows it to be the dipicrylsulfonate of the dihydroxy cyclic dimer (VI).

Anal. Calc'd for $C_{10}H_{24}N_2O_2 \cdot 2C_6H_2N_3O_9S \cdot H_2O$: C, 32.8; H, 3.75.
Found: C, 32.7; H, 3.7,

A sample of this compound, isolated as a hydrolysis product of I picrylsulfonate, lost one-half mole of water (0.9%) when dried at temperatures up to 130°. The present sample behaves in the same manner; the analysis of the substance dried at 130° is given below.

Anal. Calc'd for $C_{10}H_{24}N_2O_2 \cdot 2C_6H_2N_3O_9S \cdot \frac{1}{2}H_2O$: C, 33.1; H, 3.7; N, 14.1.
Found: C, 33.1; H, 3.7; N, 14.1.

After removal of the dihydroxy cyclic dimer, the filtrate was concentrated *in vacuo* to 50 cc. and cooled at 4° for 3 hours. The salt which crystallized was the picrylsulfonate of III. It was dried *in vacuo* over P_2O_5 at room temperature; yield 1.55 g. (38%). The substance consumed 0.94 mole equivalents of thiosulfate.

Anal. Calc'd for $C_5H_{12}NO \cdot C_6H_2N_3O_9S$: C, 33.5; H, 3.6; N, 14.2.
Found: C, 33.4; H, 3.7; N, 14.3.

The compound was recrystallized from acetone-petroleum ether. Its thiosulfate titer and elementary analysis were unchanged. The compound decomposed at 220° and gave a negative test for chlorine (sodium fusion).

The mother liquor remaining after removal of the III picrylsulfonate was concentrated *in vacuo* to about 25 cc. and cooled for one hour at 4°. The picrylsulfonate of the chlorohydrin (II) crystallized from the mixture. It was filtered off and dried *in vacuo* over P_2O_5; yield 0.46 g. (10%); m.p. 140–143°. After recrystallization from acetone-petroleum ether, its melting point and mixed melting point with the authentic compound was 142–144°. Its 2-hour thiosulfate titer was 0.92 mole equivalents.

The hydrolysis of 1-methyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate. The III picrylsulfonate (1.62 g., 4.1 *mM*) was added to 205 cc. of $NaHCO_3$ solution (0.08 *M*). The resulting solution was maintained at 25° for 20 hours and then was cooled, acidified with HCl and concentrated *in vacuo* to about 50 cc. The crystalline material which separated

[8] We are indebted to Dr. R. L. Shriner for a sample of the chlorohydrin hydrochloride.

was collected on a filter, washed with water, and dried over P_2O_5 *in vacuo*; yield 0.9 g. (53%) of the dipicrylsulfonate of the linear compound VII; m.p. 203–205°; mixed m.p. 204–206°. The authentic compound melted at 205–207°. From the mother liquor another crop of the dipicrylsulfonate of the linear compound was obtained; yield 0.37 g. (10%); m.p. 204–206°; mixed m.p. 205–207°.

Further fractionation of the mother liquor yielded 0.12 g. of sodium picrylsulfonate and 0.10 g. (6%) of methyldiethanolamine picrylsulfonate; m.p. 177–180°; mixed m.p. 178–181°. The isolated compound was recrystallized from water; m.p. 179–181°; mixed m.p. 179–182°.

The reaction of the 1-methyl-1-(β-hydroxyethyl)ethylenimonium ion with chloride). The III picrylsulfonate (187 mg., 0.5 *mM*) was dissolved in 10 cc. of 0.2 *N* HCl. After standing 24 hours at room temperature, the solution was concentrated *in vacuo*. Alcohol was added to the residue and the concentration was repeated. After removal of the alcohol, the residue was identified as the chlorohydrin picrylsulfonate, m.p. 136–139°, mixed m.p. 138–141°. The compound was recrystallized from water; m.p. and mixed m.p. 139–141°; thiosulfate titer, 0.95 *mM* per *mM* of chlorohydrin salt.

Conversion of the III picrylsulfonate to the corresponding chloride. The III picrylsulfonate (43 mg., 0.109 *mM*) was dissolved in 7 cc. of water and the solution was treated with 0.185 cc. of a 0.3 *M* dichloro cyclic dimer solution. The mixture was cooled at 0° for 15 minutes and filtered. The dried precipitate (dipicrylsulfonate of the dichloro cyclic dimer) weighed 41 mg. (91%). The filtrate was made up to 10 cc. and immediately used for injection into mice.

Preparation of the "Bunte Salt" of MBA. A solution of MBA·HCl (10 g., 8 *mM*) was added to 40 cc. of a solution containing 8 g. of $Na_2S_2O_3 \cdot 5\ H_2O$ (32 *mM*), 1.34 g. of $NaHCO_3$ (16 *mM*), and 8 cc. of *N* NaOH. The mixture was shaken for 30 minutes and then left at room temperature for 6 hours. The clear reaction mixture was evaporated to dryness under reduced pressure and the residue was extracted with hot absolute alcohol. On concentration of the alcohol extract under reduced pressure, the crystalline product was obtained; yield 2.0 g. The material was dried in air for analysis.

Anal. Calc'd for $C_5H_{11}NNa_2O_6S_4 \cdot \frac{1}{2}H_2O$: C, 16.5; H, 3.3; N, 3.8; S, 35.1; Na 12.6.
Found: C, 16.2; H, 3.7; N, 3.7; S, 34.8; Na, 12.8.

Preparation of sodium picrylsulfonate. Sodium bisulfite, A.R. (100 g. finely ground) was added to 100 g. of picryl chloride suspended in 1200 cc. of absolute ethanol. The mixture was heated on the steam-bath for 6 hours (no condenser). The alcohol which boiled off was replaced. The reaction mixture was cooled to 0°, and then filtered. The solid was stirred into 200 cc. of water and the aqueous suspension was heated to boiling. The mixture was kept boiling gently until most of the solid had dissolved (about 10 minutes). During this time the deep red color of the solution became pale orange. The hot solution was filtered and the filtrate cooled at 0°. The sodium picrylsulfonate which crystallized was filtered off and recrystallized once from water and once from 50% alcohol; yield 75 g. of nearly colorless crystals.

Anal. Calc'd for $C_6H_2N_3NaO_9S \cdot 2\ H_2O$: C, 20.5; H, 1.7; N, 12.0; H_2O, 10.3.
Found: C, 20.6; H,1.8; N, 12.1; H_2O, 10.4.

Preparation of picrylsulfonic acid. Sodium picrylsulfonate (100 g.) was dissolved in 1 liter of acetone, charcoal was added, and the solution filtered. Fifty cc. of concentrated HCl was added to the filtrate. The NaCl which precipitated was filtered off, and the filtrate concentrated *in vacuo* to about 300 cc. Any additional NaCl was filtered off, and the filtrate concentrated to dryness. The residue was crystallized from a hot mixture of 50 cc. of alcohol, 30 cc. of water, and 70 cc. of concentrated HCl; yield 63 g. of pale yellow needles.

Anal. Calc'd for $C_6H_3N_3O_9S \cdot 4\ H_2O$: C, 19.7; H, 3.0; N, 11.5; H_2O, 19.7.
Found: C, 19.9; H, 3.1; N, 11.6; H_2O, 19.6.

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[a] Unpublished data obtained in the United States.
[b] Unpublished data obtained in Great Britain.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] III. THE TRANSFORMATIONS OF ETHYL-BIS(β-CHLOROETHYL)AMINE IN WATER

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In the course of a systematic study of the chemical reactions of the nitrogen mustard gases (1, 2), experiments were performed to determine the sequence of reactions undergone by ethyl-bis(β-chloroethyl)amine (EBA) in water. The methods employed in this series of experiments were analogous to those used in the case of the lower homolog, methyl-bis(β-chloroethyl)amine (MBA). As may be expected from its close structural similarity to the latter compound, the behavior of EBA, in many respects, is similar to that of its homolog, MBA.

The transformations of ethyl-bis(β-chloroethyl)amine in bicarbonate solution. When EBA (0.02 *M*) is shaken with aqueous bicarbonate (*p*H 8), somewhat more than one equivalent of Cl^- is released during the first 15 minutes (Table I). During this period very little H^+ is liberated. The 2-hour thiosulfate titer of an aliquot is very high. From these three sets of data, it must be concluded that EBA has been transformed into ethylenimonium form (I) (*cf.* Figure 1). The use of the 2-hour thiosulfate titer represents a departure from the procedure employed in the case of MBA. As pointed out previously (1), it required 10 minutes for the theoretical uptake of one equivalent of thiosulfate per mole of MBA. On the other hand, EBA reacts with thiosulfate at a faster rate than does MBA; thus, even when the time employed for its reaction with thiosulfate is reduced to 5 minutes, the thiosulfate test gives a value much higher than that theoretically possible for one equivalent of ethylenimonium group per mole of EBA. For this reason, in the present communication, the total thiosulfate consumption after 2 hours is used; when taken in conjunction with the data on Cl^- and H^+ liberation, it provides a measure of the extent of ethylenimonium ion formation. When the reaction is allowed to go to completion, EBA like MBA consumes 2 equivalents of thiosulfate to form the "Bunte salt" (*cf.* experimental section).

As will be noted from Table I, during the later stages of the reaction of EBA in bicarbonate, there is released a second equivalent of Cl^-. This process is completed within 24 hours, and is accompanied by an appreciable liberation of H^+. There also occurs a progressive decrease in the concentration of quaternary compounds as represented by the difference between the Cl^- and H^+ values.

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The H^+ liberation continues after all the theoretically possible Cl^- has appeared, and after 96 hours reaches the value of 1.68 milliequivalent of H^+ per *mM* of EBA. At this time, the thiosulfate titer has dropped to a low value which is not appreciably different from that for the concentration of quaternary

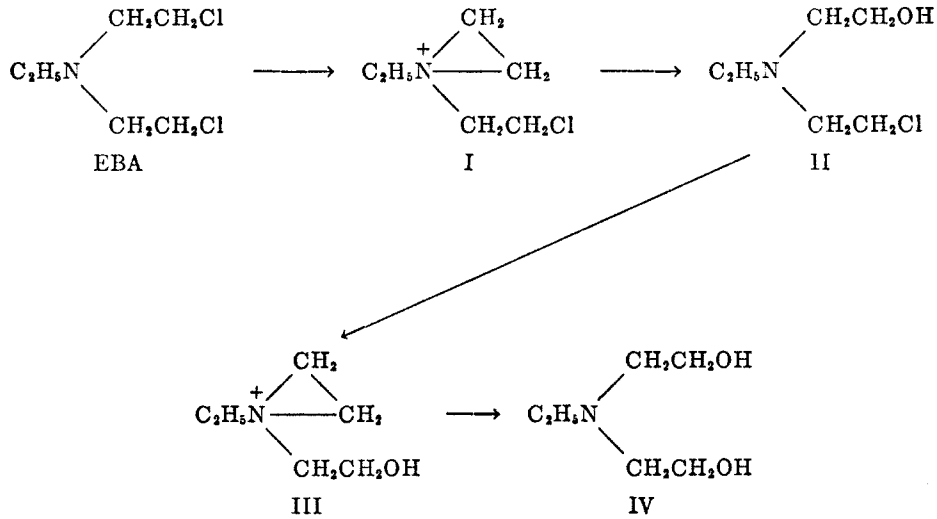

FIG. 1

TABLE I

THE HYDROLYSIS OF ETHYL-BIS(β-CHLOROETHYL)AMINE (EBA) IN BICARBONATE SOLUTION

Concentration of reactants per cc.: 0.02 *mM* of EBA·HCl; 0.02 *mM* of NaOH; 0.08 *mM* of $NaHCO_3$.

Temperature 25°; *p*H 8.

TIME, MIN.	Cl^- LIBERATED PER *mM* OF EBA M.EQUIV.	H^+ LIBERATED PER *mM* OF EBA M.EQUIV.	(Cl^-)-(H^+) M.EQUIV.	$Na_2S_2O_3$ CONSUMED IN 2 HOURS PER *mM* OF EBA M.EQUIV.
15	1.11	0.08	1.03	1.87
60	1.19	0.18	1.01	1.80
120	1.27	0.22	1.05	1.68
300	1.47	0.43	1.05	1.46
600	1.70	0.65	1.05	1.27
1440	2.00	1.10	0.90	0.76
2880	2.02	1.43	0.59	0.44
5760	(2.00)	1.68	(0.32)	0.27

nitrogen present. These data are best interpreted as indicating nearly complete hydrolysis of EBA to ethyldiethanolamine. This conclusion receives confirmation from the data presented in Table III which show that the EBA transformation products II and III are hydrolyzed rather completely to form ethyldiethanolamine.

When the initial concentration of EBA is increased from 0.02 *M* to 0.13 *M*, compounds containing stable quaternary nitrogen are formed. The extent of

the formation of these compounds is much less in the case of EBA, however, than had been observed previously for MBA under the same experimental conditions.

The transformations of ethyl-bis(β-chloroethyl)amine in unbuffered solution. When EBA (0.02 *M*) is shaken with water in the absence of bicarbonate (Table II), somewhat more than one equivalent of Cl^- is liberated rapidly (within 15 minutes) but no further Cl^- liberation is observed during the next 48 hours. Since, within 15 minutes, little H^+ has been liberated and the 2-hour thiosulfate titer is very high, most of the EBA must have been transformed into the ethylenimonium form (I). As the reaction proceeds, H^+ is liberated, but much more slowly than during the hydrolysis in aqueous bicarbonate. The acid liberation in the unbuffered solution gradually approaches one equivalent of H^+ per mole of EBA. The thiosulfate titer drops much more slowly than in the experiment with bicarbonate.

TABLE II

THE HYDROLYSIS OF ETHYL-BIS(β-CHLOROETHYL)AMINE (EBA) IN UNBUFFERED SOLUTION

Concentration of reactants per cc.: 0.02 *mM* of EBA·HCl; 0.02 *mM* of NaOH.
Temperature 25°; *p*H *ca.* 7 (at start); *p*H *ca.* 5 (at end).

TIME, MIN.	Cl^- LIBERATED PER *mM* OF EBA M.EQUIV.	H^+ LIBERATED PER *mM* OF EBA M.EQUIV.	$Na_2S_2O_3$ CONSUMED IN 2 HRS. PER *mM* OF EBA M.EQUIV.
15	1.12	0.10	1.88
90	1.15	.25	1.85
300	1.15	.35	1.68
1440	1.17	.75	1.25
2880	1.16	.87	1.10

It is of interest that at any time the sum of the milliequivalents of thiosulfate consumed in 2 hours and the milliequivalents of H^+ liberated is equal to two, within the limits of experimental error. This finding indicates that, under these experimental conditions, hydrolysis is the only reaction occurring in unbuffered solution. The presence in the solution of compounds containing stable quaternary nitrogen is, therefore, precluded. This conclusion is supported further by evidence to be presented below. It will be recalled that, under similar conditions, MBA gives rise to compounds containing stable quaternary nitrogen. It would appear, therefore, that, as was noted in bicarbonate solution, EBA has less of a tendency to form dimeric products in unbuffered solution than does MBA.

The isolation of 1-ethyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate. As shown above, EBA is rapidly converted into the ethylenimonium form (I). This imonium compound has been isolated as its picrylsulfonate from a 30-minute old unbuffered solution of EBA (0.133 *M*). The procedure was essentially the same as that employed in the isolation of the corresponding ethylenimonium form of MBA (1).

The precipitate formed on addition of sodium picrylsulfonate to a 30-minute

old solution of EBA is pure I picrylsulfonate. In the case of MBA, the initial precipitate contained large amounts of the dipicrylsulfonate of the dichloro cyclic dimer of MBA [N,N′-dimethyl-N,N′-bis(β-chloroethyl)piperazinium dichloride]. It is of interest that under comparable conditions no appreciable quantity of dimeric products can be detected in the case of EBA.

The isolation and hydrolysis of the chlorohydrin (II). After the hydrolysis of EBA in unbuffered solution has proceeded for 48 hours, one equivalent of Cl^- and nearly one equivalent of H^+ have been liberated, suggesting that the principal product present at this time is the chlorohydrin (II). This chlorohydrin

TABLE III

THE HYDROLYSIS OF THE TRANSFORMATION PRODUCTS OF ETHYL-BIS(β-CHLOROETHYL)AMINE IN BICARBONATE SOLUTION

Concentration of reactants per cc.: 0.02 *mM* of picrylsulfonate of II or III; 0.08 *mM* of $NaHCO_3$.

Temperature 25°. In the hydrolysis of II the *p*H was 7.4 at the start, 8.2 after 20 hours, and 8.8 after 44 hours. In the hydrolysis of III the *p*H was 8.3 at the start and 8.6 after 24 hours.

TIME, MIN.	Cl^- LIBERATED PER *mM* II M.EQUIV.	H^+ LIBERATED PER *mM*		$Na_2S_2O_3$ CONSUMED IN 5 MIN. PER *mM*	
		II M.EQUIV.	III[a] M.EQUIV.	II M.EQUIV.	III M.EQUIV.
30	0.95	0.02		1.05	
60	0.97	.05	0.10	1.00	0.90
180	1.00	.18		0.85	
300			.25		.75
480			.35		.60
1200	1.00	.47		.60	
1440			.95		.10
2640	1.01	.75		.30	

[a] It will be noted that the disappearance of III occurs more rapidly than when it is formed during the hydrolysis of II. The higher initial *p*H during the hydrolysis of III may be the reason for this effect.

has been isolated as a salt of picrylsulfonic acid from such a 48-hour aged solution of EBA. The yield corresponded to 90% of the original EBA.

As may be seen from Table III, the picrylsulfonate of the chlorohydrin (II) dissolves readily in aqueous bicarbonate and, within 30 minutes at 25°, is completely converted into the ethylenimonium form (III). The hydrolysis of this ethylenimonium compound to ethyldiethanolamine (IV) proceeds slowly. After 20 hours at 25°, only about 40% is hydrolyzed, while after 44 hours, the extent of hydrolysis attains about 70%. The hydrolysis evidently is not complete even after 44 hours because, as will be noted from Table III, there is an appreciable thiosulfate titer indicating that the solution still contains some III. As shown below, III hydrolyzes to ethyldiethanolamine in bicarbonate solution.

The isolation and hydrolysis of 1-ethyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate. Compound III has been isolated in the form of a picrylsulfonate from

a solution of the chlorohydrin picrylsulfonate which had been aged at *p*H 7–8 for 30 minutes at 25°. The yield was 84%. It will be noted from Table III that during the hydrolysis of III in bicarbonate solution, H^+ gradually appears and after 24 hours, the H^+ liberation reaches a value of nearly one equivalent. The liberation of H^+ is accompanied by a corresponding drop in the thiosulfate titer. These results indicate that in bicarbonate solution, III hydrolyzes to ethyldiethanolamine (IV). Under comparable conditions, the corresponding ethylenimonium compound derived from MBA is only partially hydrolyzed to methyldiethanolamine, the principal product being a linear compound formed by the reaction of the imonium compound with methyldiethanolamine.

TABLE IV

THE TOXICITY TO MICE OF THE TRANSFORMATION PRODUCTS OF ETHYL-BIS(β-CHLOROETHYL)AMINE

SUBSTANCE (EMPLOYED AS CHLORIDE OR HYDROCHLORIDE)	DOSAGE	NO. OF MICE INJECTED	EFFECT ON MICE
	mg./kg.		
II	55	3	All dead within 15–63 min.
	40	3	2 dead within 23–25 min. 1 dead within 2 days.
	20	3	1 dead within 28 min. 2 dead within 2–4 days.
	10	6	3 dead within 4 days. 3 alive after 5 days.
	7.5	3	All alive after 5 days.
	4.5	3	All alive after 5 days.
III	19.5	3	All dead within 18–26 min.
	13.5	3	All dead within 17–19 min.
	8.5	3	All dead within 29–45 min.
	5.5	3	All alive after 7 days.
	2.75	3	All alive after 7 days.

The toxicity of the transformation products of ethyl-bis(β-chloroethyl)amine. In order to study the toxicity of the transformation products of EBA, their picrylsulfonates were converted to the corresponding chlorides or hydrochlorides by double decomposition with the dichloro cyclic dimer of MBA as described previously (1). The approximate toxicities of these compounds upon intraperitoneal injection into mice are given in Table IV. The results are in good agreement with the LD_{50} values of Smith *et al.* (3). These investigations reported that for mice the chlorohydrin (II) has an LD_{50} of less than 8 mg./kg. intraperitoneally or subcutaneously. The LD_{50} value for III was about 7.5 mg./kg. intraperitoneally, 5.5 mg. subcutaneously, and 5.0 mg./kg. intravenously. For I, the LD_{50} was less than 2 mg./kg. upon subcutaneous injection into mice.

In contrast to the behavior of the corresponding ethylenimonium compound derived from MBA, compound III is no more toxic than its parent compound,

the chlorohydrin (II). This might be explained by the fact that the cyclization of the chlorohydrin to III occurs much more rapidly than does the corresponding reaction in the MBA series.

EXPERIMENTAL

Analytical methods. The mehods for determining the Cl^- and H^+ liberation, and the thiosulfate consumption have been described previously (1, 2).

The isolation of 1-ethyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate. An aqueous solution (25 cc.) containing 20 *mM* of EBA·HCl was added to 200 cc. of 0.1 *N* NaOH. The mixture was shaken for 30 minutes, then chilled to 0° and acidified with HCl to Congo Red. A solution of 8 g. of sodium picrylsulfonate was then added. After 20 minutes, the crystalline precipitate was filtered and dried over P_2O_5; yield 5.2 g.

Anal. Calc'd for $C_6H_{13}ClN \cdot C_6H_2N_3O_9S$: C, 33.8; H, 3.5; N, 13.1; Cl, 8.3.
Found: C, 33.8; H, 3.6; N, 13.0; Cl, 8.4.

The 2-hour thiosulfate titer, performed in the manner already described (2), was 2.02 equivalents.

The isolation of the chlorohydrin (II) as a picrylsulfonate. To 400 cc. of water containing exactly 20 *mM* of NaOH were added 4.13 g. of EBA·HCl (20 *mM*). The mixture was shaken for 15 minutes and the resulting clear solution was left at 25° for 48 hours. After chilling to 0°, the solution was acidified with HCl to Congo Red. Sodium picrylsulfonate (7.5 g. in 80 cc. of 0.5 *N* HCl) then was added. The solution was concentrated under reduced pressure (bath temperature 35–40°) to a volume of 100 cc. and kept at 0° overnight. The crystals which formed were filtered off and dried *in vacuo* over P_2O_5; yield 8.0 g. (90%). The 2-hour thiosulfate consumption of this substance was 1.06 equivalents. The salt was recrystallized from acetone-petroleum ether. Its thiosulfate titer was now 1.02 equivalents; m.p. 110–111°.

Anal. Calc'd for $C_6H_{14}ClNO \cdot C_6H_2O_9N_3S$: C, 32.4; H, 3.6; N, 12.6; Cl, 8.0.
Found: C, 32.6; H, 3.7; N, 12.4; Cl, 7.9.

The isolation of 1-ethyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate. The chlorohydrin picrylsulfonate (2.23 g., 5 *mM*) was stirred for 30 minutes at 25° with 50 cc. of 0.1 *N* $NaHCO_3$. A slight amount of undissolved material was filtered off and the filtrate was chilled to 0° and acidified to Congo Red. Crystallization began quickly. After standing at 0° overnight, the crystals were filtered off and dried *in vacuo* over P_2O_5. The filtrate was concentrated to 25 cc. under reduced pressure and a second crop of crystals was collected. The total yield was 1.7 g. (84%). The 2-hour thiosulfate titer of each fraction was 1.01 equivalents. On sodium fusion, the material gave a negative test for chloride. For analysis, the substance was recrystallized from acetone-petroleum ether.

Anal. Calc'd for $C_6H_{14}NO \cdot C_6H_2N_3O_9S$: C, 35.3; H, 4.0; N, 13.7.
Found: C, 35.4; H, 4.0; N, 13.5.

Preparation of "Bunte Salt" of EBA. Five cc. of a solution containing 4 *mM* of EBA·HCl were added to 20 cc. of a solution containing 16 *mM* of $Na_2S_2O_3$, 16 *mM* of $NaHCO_3$, and 4 *mM* of NaOH. The mixture was shaken for 30 minutes and left at room temperature for 6 hours. The solution was evaporated to dryness under reduced pressure and the residue was extracted with three 100-cc. portions of hot absolute alcohol. On concentration of the alcohol extract under reduced pressure, the "Bunte Salt" was obtained in crystalline form; yield 2.2 g. The substance was recrystallized from alcohol-ether. For analysis, the material was dried to constant weight in air.

Anal. Calc'd for $C_6H_{13}NNa_2O_6S_4 \cdot 2\ H_2O$: C, 17.8; H, 4.2; N, 3.5; S, 31.6; Na, 11.3; H_2O, 8.9.
Found: C, 17.6; H, 4.2; N, 3.4; S, 31.4; Na, 11.3; H_2O, 8.9.

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[a] Unpublished data obtained in the United States.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] II. THE COMPOSITION OF AGED UNBUFFERED SOLUTIONS OF METHYL-BIS(β-CHLOROETHYL)AMINE

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It has been found (1, 2, 3) that, upon standing at room temperature for 24 hours or longer, 1% aqueous solutions of methyl-bis(β-chloroethyl)amine (MBA) exhibit a neurotoxic action upon administration to experimental animals. The present investigation was undertaken to determine the nature of the transformation products of MBA responsible for this pharmacological action.

Hartley, Powell, and Rydon (1) studied the composition of 1% solutions of MBA aged for 48 hours and found, by fractionation of picrates, that the solutions contained 25% of the dichloro cyclic dimer [N,N′-dimethyl-N,N′-bis-(β-chloroethyl)piperazinium dichloride (V)[4]], 15% unchanged MBA, and 35% of the chlorohydrin [methyl-β-chloroethyl-β-hydroxyethylamine (II)]. In a later report (3), Hanby and Rydon stated that the composition of a 1% aged solution was 25% dimer, 20% unchanged MBA, 35% chlorohydrin, and 20% methyldiethanolamine. The values for the last two components were based on analytical rather than isolation data, however.

The fractionation of aged solutions by the picrate method has been repeated in this laboratory. The amounts of dimer and unchanged MBA present in our aged solutions, to judge from the weights and thiosulfate titers of the crude picrate fractions, were about 30% and 10%, respectively. The yield of chlorohydrin was 37% of the MBA employed. Measurements of the thiosulfate titer of the mother liquors, however, indicated that the presence of an additional 7% of chlorohydrin, and about half of this amount was, in fact, isolated as a picrylsulfonate. No methyldiethanolamine could be isolated as a picrate from the mother liquors. The picrate procedure, therefore, permitted the isolation of only about 75% of the original MBA.

It has been found that picrylsulfonic acid (*cf.* Paper I of this series) is a better reagent than picric acid for the isolation of the components of aged solutions of MBA; cleaner separations and much higher total yields (over 90%) are obtained. The picrylsulfonate isolation procedure was applied to the following 48-hour aged solutions of MBA: (a) a 1% solution of the free base, (b) a 1% solution of

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[4] The structural formulas of this, and the other transformation products of MBA referred to in this paper, are given in Figure 1 in the previous paper of this series. In the present communication, the numbering is unchanged.

the base, containing one equivalent of NaCl (from neutralization of the MBA hydrochloride), and (c) a 1.56% (0.10 *M*) solution of the base containing one equivalent of NaCl. The results of these experiments are given in Table I. It will be noted that the presence of NaCl and/or an increase in initial concentration of MBA leads to an increase in the amount of dichloro cyclic dimer and a decrease in the extent of hydrolysis. Under these different conditions, the amount of unchanged MBA remains fairly constant.

In each of these isolation experiments, the results obtained by the picrylsulfonate method were checked against the analytical data obtained on the aged solution before any manipulation had been performed upon it. Such a comparison should reveal changes in the composition of the aged solution produced by the experimental procedures incident to the isolation. The analytical data obtained on the aged solutions just prior to the isolations are given in Table II. The analyses include measurements of the Cl^- and H^+ liberated, and the 2-hour thiosulfate titer; the difference between the values for the Cl^- and H^+ represents the Cl^- neutralized by quaternary nitrogen.

Comparison of the analytical data of the 1% solutions aged in the presence and absence of NaCl shows that the latter has a higher thiosulfate titer but is not significantly different in other respects from the former. It appears that, in the presence of NaCl, the amount of dimer is decreased while the amount of imonium compounds and/or chlorohydrin is increased. The isolation data of Table I show that the solution aged in the absence of NaCl actually has less dimer and more chlorohydrin than is present in the solution aged in the presence of NaCl. Under the conditions of the isolation, any 1-methyl-1-(β-hydroxyethyl)ethylenimonium chloride (III) would be expected to revert to the chlorohydrin (II). As was mentioned in the previous paper of this series, a reversion occurs when III picrylsulfonate is allowed to stand in dilute HCl solution.

The 1.56% aged solution of MBA contains more quaternary nitrogen but less H^+ and has a lower thiosulfate titer than does the corresponding 1% solution. This indicates a greater degree of dimerization and less hydrolysis at 1.56% than at 1% concentration.

If no alteration in the composition of the aged solutions had occurred during the isolation procedures, there should be a fairly good quantitative agreement between the analytical values and the corresponding values calculated from the isolation data, since more than 90% of the original MBA has been accounted for in each isolation. Such a comparison is given in Table II. It will be noted that all the carbon-bound chlorine has been accounted for, but that the calculated values for H^+, Cl^-, and thiosulfate titer are appreciably lower than the corresponding titration values. This may mean that the material not accounted for is largely methyldiethanolamine and the hydroxyethyl imonium compound III. It is likely that only III and not the chloroethyl imonium compound I would be present because the picrylsulfonate of the latter would have been one of the first to precipitate during the isolation procedure.

The titration data of Table II show that for the aged solutions the thiosulfate titers are higher than are the values for the H^+ liberated. This difference may

be taken as a further indication for the presence of ethylenimonium compounds in the aged solutions. As reported in Paper I of this series, the imonium compound I was isolated from the aged 0.02 *M* MBA solution. This shows that ethylenimonium compounds may remain in unbuffered solutions of MBA for long periods of time.

From the results given above, it would appear that the composition of 48-hour aged solutions of MBA is known within narrow limits. Since the cyclic

TABLE I

COMPOSITION OF 48-HOUR AGED SOLUTIONS OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA)

CONCENTRATION OF MBA, %	NaCl	COMPONENTS ISOLATED				
		Dichloro cyclic dimer (V), %	Chlorohydrin (II), %	Methyldiethanolamine (IV), %	Unchanged MBA, %	Total, %
1	absent	22	58	2	11	93
1	present	31	49	3	9	92
1.56	present	44	39	0.3	8	91.3

TABLE II

THE ANALYSIS OF 48-HOUR AGED SOLUTIONS OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA)

The values in parentheses are calculated from the isolation data given in Table I.

CONCENTRATION OF MBA %	NaCl	Cl^- LIBERATED PER *mM* MBA M.EQUIV.	CARBON-BOUND Cl PER *mM* MBA M.EQUIV.	H^+ LIBERATED PER *mM* MBA M.EQUIV.	QUATERNARY N(Cl^--H^+) M.EQUIV.	$Na_2S_2O_3$ CONSUMED IN 2 HRS. PER *mM* MBA M.EQUIV.
1	absent	1.00	1.00	0.66	0.34	0.87
		(0.84)	(0.91)	(0.62)	(0.22)	(0.80)
1	present	0.99	1.01	0.64	0.35	0.73
		(0.86)	(0.98)	(0.55)	(0.31)	(0.67)
1.56	present	1.00	1.00	0.54	0.46	0.63
		(0.84)	(0.99)	(0.40)	(0.44)	(0.55)

dimer (V) is relatively non-toxic, it is concluded that the toxicity of the aged solutions of MBA is to be attributed to the presence of the chlorohydrin (II), unchanged MBA and possibly also to small amounts of the imonium compound (III).

EXPERIMENTAL

Isolation of products from an aged 1% (0.064 M) unbuffered solution of MBA (NaCl absent). One liter of a solution containing 10 g. (64 *mM*) of MBA (freshly distilled) was maintained at 25° for 48 hours. A 35-cc. aliquot was removed for the analyses reported in Table II. The remainder of the solution was cooled to 0°, acidfied with HCl to Congo Red and then treated with a cold aqueous solution of 22.6 g. (62.0 *mM*) of picrylsulfonic acid. After standing several hours at 4°, the dipicrylsulfonate of the dichloro cyclic dimer (V) separated; it was filtered off and dried over P_2O_5; yield 5.55 g. (22%). The compound did not react with thiosulfate and did not melt up to 250°.

The filtrate was concentrated under reduced pressure to 600 cc. and upon cooling at 4°, the solution deposited the pure chlorohydrin picrylsulfonate; yield 10.0 g. (38%); m.p. and mixed m.p. 141–143°. The compound consumed 0.99 equivalents of thiosulfate in 2 hours.

The filtrate was concentrated *in vacuo* to 400 cc. and cooled at 4°. The crude MBA picrylsulfonate (1.4 g.) crystallized (fraction 1); m.p. 123–128°; thiosulfate titer, 1.75 *mM* per *mM* of MBA picrylsulfonate. The compound was recrystallized twice from 10-cc. portions of hot water containing HCl; yield 0.9 g. (3%) of MBA picrylsulfonate; m.p. and mixed m.p. 144–146°; an authentic sample melted at 145–147°. Thiosulfate titer, 1.96 *mM* per *mM* of MBA picrylsulfonate.

After removal of fraction 1, the filtrate was concentrated to 200 cc. and cooled at 0°. A mixture of the MBA and chlorohydrin picrylsulfonates crystallized; yield 1.9 g., (fraction 2); m.p. 125–128°; thiosulfatetiter, 1.3. When recrystallized from acetone, this fraction yielded 0.85 g. (3%) of the chlorohydrin picrylsulfonate; m.p. 141–142°; mixed m.p. 140–142°. The 2-hour thiosulfate titer was 0.97 *mM* of chlorohydrin salt.

After removal of fraction 2, the filtrate was concentrated to 50 cc. and cooled at 0°; yield 5.9 g. (fraction 3) of a mixture containing mostly the chlorohydrin picrylsulfonate; m.p. 122–130°; thiosulfate titer, 1.1. This fraction was recrystallized from 100 cc. of boiling acetone; yield 3.13 g. of the chlorohydrin picrylsulfonate; m.p. 139–141°; mixed m.p. 139–142°; thiosulfate titer, 0.88. The acetone filtrate was concentrated to 25 cc. and upon cooling deposited a second crop of the chlorohydrin picrylsulfonate; yield 0.9 g. (3%); m.p. and mixed m.p. 139–141°; thiosulfate titer, 0.91. The low thiosulfate titer of the first crop pointed to the presence of about 10% of methyldiethanolamine picrylsulfonate in this fraction. By digesting this material in 100 cc. of boiling acetone and then allowing the mixture to stand at room temperature for 2 hours, crude methyldiethanolamine picrylsulfonate was obtained as an insoluble portion; yield 0.22 g. (0.9 %); m.p. 150–160°. After recrystallization from acetone, it melted at 174–177° and a mixture with the authentic compound melted at 177–180°. The authentic compound melted at 182–183°. From the acetone solution remaining after removal of the crude methyldiethanolamine salt, 2.63 g. of the chlorohydrin picrylsulfonate was recovered by the addition of petroleum ether to the acetone filtrate; m.p. 139–140°; mixed m.p. 139–142°; thiosulfate titer, 0.97 *mM* per *mM* of chlorohydrin salt.

After removal of fraction 3, the filtrate was concentrated to 10 cc. and cooled; yield 0.7 g. of a mixture containing methyldiethanolamine, the chlorohydrin (II), and/or MBA picrylsulfonates. It was digested in a small volume of boiling acetone and then allowed to stand several hours at room temperature. The insoluble material (fraction 4) was methyldiethanolamine picrylsulfonate; yield 0.25 g. (1.0%); m.p. 177–180°; mixed m.p. 177–181°.

The mother liquors remaining from working up fractions 1–4 were combined, evaporated nearly to dryness, and the residue was dissolved in 50 cc. of hot water containing HCl. After cooling overnight at 4°, 2.12 g. (8%) of MBA picrylsulfonate crystallized out; m.p. 140–143°; mixed m.p. 142–145°; thiosulfate titer, 1.92 *mM* per *mM* of MBA picrylsulfonate. The mother liquor was concentrated to 20 cc. and again cooled overnight; yield 1.0 g. (4%) of the chlorohydrin picrylsulfonate; m.p. 136–139°; mixed m.p. 138–141°; thiosulfate titer, 1.02. After recrystallization from acetone the m.p. and mixed m.p. were 141–143° and the thiosulfate titer was 0.98.

The remaining mother liquor was evaporated nearly to dryness. Alcohol was added and the evaporation was repeated. The residue was taken up in 10 cc. of alcohol, cooled at 0°, and filtered; yield 0.45 g. (2%) of crude chlorohydrin picrylsulfonate; m.p. 136–139°; mixed m.p. 138–140°. A small amount (50 mg.) of methyldiethanolamine picrylsulfonate was removed from this portion by digesting it in a little acetone; m.p. 176–179°; mixed m.p. 177–181°. The chlorohydrin salt was recovered from the acetone filtrate by evaporating it and recrystallizing the residue from water; m.p. and mixed m.p. 138–140°; thiosulfate titer, 0.92.

Isolation of compounds from an aged 1% (0.064 M) unbuffered solution of MBA (NaCl present). To 1500 cc. of an aqueous solution containing 18.5 g. (96 *mM*) of MBA·HCl there was added at 0°, 96 *mM* of NaOH. The mixture was allowed to stand at room temperature (26°) for 48 hours, then cooled to 0°, acidified with HCl and treated with a cold aqueous

solution of 33.7 g. (96 *mM*) of sodium picrylsulfonate. After cooling overnight at 4°, the precipitate which had formed was filtered off and washed with cold water and acetone and dried *in vacuo* over P_2O_5; yield 12.15 g. (31%) of the dipicrylsulfonate of the dichloro cyclic dimer (V). The compound did not melt up to 250° and was insoluble in and did not react with thiosulfate.

The filtrate was concentrated *in vacuo* to 1400 cc. and cooled overnight at 4°; yield 7.3 g. (18%) of the chlorohydrin picrylsulfonate; m.p. and mixed m.p. 140–142°. The isolated compound consumed 0.99 equivalents of thiosulfate in 2 hours.

After removal of the first fraction of chlorohydrin salt, the filtrate was concentrated to 700 cc. and cooled as before. A mixture of the picrylsulfonates of the chlorohydrin and MBA crystallized out; yield 11.0 g. (fraction 1); m.p. 128–131°; thiosulfate titer, 1.16 *mM* per *mM* of chlorohydrin salt.

The filtrate was concentrated *in vacuo* to 300 cc. and upon cooling deposited a mixture of the picrylsulfonates of the chlorohydrin and MBA; yield 3.9 g. (fraction 2); m.p. 127–131°; thiosulfate titer, 1.29. The mother liquor (filtrate A) was reserved for further study.

Fractions 1 and 2 were combined and dissolved in 250 cc. of hot acetone. Upon cooling overnight at 4°, 7.4 g. (18%) of pure chlorohydrin picrylsulfonate crystallized out; m.p. and mixed m.p. 141–143°; thiosulfate titer, 0.94. The mother liquor was concentrated to a volume of 25 cc. Another crop of the chlorohydrin picrylsulfonate crystallized out upon cooling the solution overnight at 4°; yield 1.9 g. (4.6%); m.p. and mixed m.p. 140–142°; thiosulfate titer, 0.98. The acetone mother liquor was evaporated and the residue again dissolved in 25 cc. of warm acetone. Upon standing overnight at room temperature, MBA picrylsulfonate crystallized out; yield 1.8 g. (4.2%); m.p. and mixed m.p. 143–147°; thiosulfate titer, 1.82 *mM* per *mM* of MBA picrylsulfonate. The acetone residue (2.8 g.) contained the typical crystals of both the chlorohydrin and MBA picrylsulfonates. It was dissolved in 25 cc. of warm acidulated water and cooled for 1 hour at 0°; yield 1.5 g. (3.5%) of MBA picrylsulfonate; m.p. 142–145°; mixed m.p. 143–146°; thiosulfate titer, 1.87 *mM* per *mM* of MBA picrylsulfonate. Upon concentration of the filtrate to *ca.* 10 cc., 0.65 g. of impure chlorohydrin picrylsulfonate was obtained (thiosulfate titer, 1.08). It was dissolved in 25 cc. of warm acetone and the solution, upon cooling overnight at 4°, deposited 0.2 g. of the chlorohydrin salt; m.p. and mixed m.p. 140–142°; thiosulfate titer, 0.95.

Filtrate A was evaporated to dryness *in vacuo* and the residue was extracted with 1 liter of boiling acetone. The extract was evaporated and its residue was taken up in 250 cc. of water containing a little HCl. This solution was evaporated to 25 cc., cooled at 4° overnight, and filtered; yield 5.5 g. (fraction 3) of a mixture containing methyldiethanolamine, chlorohydrin and MBA picrylsulfonates. The filtrate was discarded since its thiosulfate titer was negligible (equivalent to 1.3 *mM* of chlorohydrin picrylsulfonate).

Fraction 3 was dissolved in 200 cc. of boiling acetone. Upon standing for 3 hours at room temperature, the solution deposited 0.7 g. (1.8%) of methyldiethanolamine picrylsulfonate. This compound did not react with thiosulfate; m.p. 178–180°; mixed m.p. 179–182°.

The mother liquor was concentrated to 50 cc. in two stages to yield 2.2 g. of chlorohydrin picrylsulfonate mixed with a little methyldiethanolamine picrylsulfonate; m.p. 139–142°; mixed m.p. 139–143°. The thiosulfate titer of the impure salt was 0.81, indicating that it contained about 15% of methyldiethanolamine.

The acetone residue, 1.1 g., was not fractionated further. From its thiosulfate titer of 1.4 and its chlorine content of 12.15% it is estimated to be a mixture of picrylsulfonates containing about 45% MBA picrylsulfonate and about 55% chlorohydrin picrylsulfonate. (A 10–15% error in this estimation will make no apparent difference in the over-all yields.)

Isolation of products from a 1.56% (0.1 M) aged unbuffered solution of MBA (NaCl present). To 500 cc. of an aqueous solution containing 9.93 g. (51.5 *mM*) of MBA·HCl was added 51.5 *mM* of NaOH. The mixture was maintained at 25° for 48 hours. After removal of a 25 cc. aliquot for titration, the remainder of the solution was cooled to 0°, acidified to Congo Red with HCl and treated with a cold solution of 17.4 g. (49.5 *mM*) of sodium picrylsulfonate

dissolved in 210 cc. of 0.35 *N* HCl. After cooling overnight at 4°, the precipitate of the dipicrylsulfonate of the dichloro cyclic dimer (V) was filtered off and dried; yield 9.05 g. (44%). The compound showed the same properties as in the previous experiment.

The filtrate was concentrated *in vacuo* to 125 cc. and then cooled for 2 days at 4°. Crude chlorohydrin picrylsulfonate (9.05 g., fraction 1) was thus obtained; m.p. 131–135°; thiosulfate titer, 1.13 *mM* per *mM* of chlorohydrin salt.

The filtrate was evaporated to dryness *in vacuo* and the residue was extracted with 1 liter of boiling acetone. After evaporation of the acetone, the residue was taken up in 25 cc. of warm water containing a little HCl and then cooled; yield 1.8 g. (fraction 2) of crude chlorohydrin picrylsulfonate; m.p. 128–133°; thiosulfate titer, 0.95 *mM* per *mM* of chlorohydrin picrylsulfonate. The mother liquor (filtrate A) was reserved for further treatment.

Fractions 1 and 2 were combined and recrystallized from 200 cc. of warm acetone; yield 6.2 g. (29%) of pure chlorohydrin picrylsulfonate; m.p. and mixed m.p. 141–144°. The compound consumed 0.94 equivalents of thiosulfate in 1 hour.

The mother liquor was evaporated and the residue was dissolved in 25 cc. of warm acetone. After cooling overnight at 4°, another crop of the chlorohydrin salt was obtained; yield 1.4 g. (7%); m.p. 139–141°; mixed m.p. 140–143°; thiosulfate titer, 0.94. Evaporation of the mother liquor left 2.35 g. of a mixture composed mainly of chlorohydrin and MBA picrylsulfonates (thiosulfate titer, 1.7). This residue was dissolved in 20 cc. of warm acidulated water and then cooled for 1 hour at 0°; yield 1.8 g. (8%) of MBA picrylsulfonate. The compound consumed 1.89 equivalents of thiosulfate in 2 hours; m.p. 139–143°; mixed m.p. 140–144°. Crystals of the chlorohydrin picrylsulfonate appeared in the filtrate upon standing at 4°; yield 0.2 g. (1%); m.p. 131–134°; mixed m.p. 134–139°. Thiosulfate titer, 0.97 *mM* per *mM* of chlorohydrin salt. After recrystallization from acetone-petroleum ether, its m.p. was 140–142°; mixed m.p. 141–143°.

Filtrate A was concentrated to about 5 cc. and upon cooling deposited 0.6 g. of chlorohydrin picrylsulfonate mixed with a little methyldiethanolamine picrylsulfonate; m.p. 125–130°; mixed m.p. 130–133°; thiosulfate titer 0.85. When dissolved in acetone and allowed to stand at room temperature, the picrylsulfonate of methyldiethanolamine crystallized out; yield 70 mg. (0.3%); m.p. 179–181°; mixed m.p. 179–182°. The compound did not react with thiosulfate. The chlorohydrin picrylsulfonate crystallized from the mother liquor upon addition of petroleum ether; yield 0.35 g. (2%); m.p. 139–142°; mixed m.p. 139–143°.

Isolation of products from a 1% (0.064 M) aged unbuffered solution of MBA by the picrate method (NaCl present). A 1% solution (1500 cc.) of MBA was prepared and aged as before. After 2 days, it was treated with 195 cc. of 0.5 *N* calcium picrate solution. After 1 hour at room temperature, the precipitate which had formed was filtered and dried; yield 10.0 g. of crude dipicrate of the dichloro cyclic dimer (V); m.p. 164–176°. The compound was only slightly soluble in, and did not react with, aqueous thiosulfate. After recrystallization from water, the compound melted at 183–187° and a mixture with an authentic sample melted at 189–193°. The pure compound melted at 201–203°.

The filtrate was concentrated *in vacuo* to 1 liter (bath temperature 40°) and cooled overnight at 4°. The fraction which separated was evidently a mixture of the picrates of the dichloro cyclic dimer and MBA since it was not completely soluble in thiosulfate and contained no detectable amounts of the large orange prisms of the chlorohydrin salt; yield 5.6 g.; m.p. 114–120°; thiosulfate titer, 1.30. From its thiosulfate consumption, it is estimated to contain about 70% MBA picrate (10%). After recrystallization from water, its m.p. was 120–124°; mixed m.p. 120–128°. The pure compound melted at 129–131° and consumed 1.94 equivalents of thiosulfate in 2 hours.

The filtrate was concentrated *in vacuo* to 600 cc. and, upon cooling overnight at 4°, deposited the large orange prisms of the chlorohydrin picrate; yield 11.0 g. (31%); m.p. 66–68°; thiosulfate titer, 1.00 *mM* per *mM* of chlorohydrin picrate. A second crop of the chlorohydrin was obtained by concentrating the mother liquor to 300 cc. and cooling as before; yield 2.1 g. (6%); m.p. 66–69°; thiosulfate titer, 0.99. The two crops were combined and

recrystallized from ethyl acetate-benzene to yield 11.2 g. of the pure chlorohydrin picrate; m.p. 70–73°.

Anal. Calc'd for $C_5H_{12}ClNO \cdot C_6H_3N_3O_7$: C, 36.0; H, 4.1.
Found: C, 35.7; H, 4.25.

Attempts to isolate any further compounds from the aqueous filtrate yielded only calcium picrate. However, the thiosulfate titer of an aliquot of the filtrate indicated the presence of 6.4 *mM* (6.7%) of chlorohydrin in the mother liquor. Part of this was isolated by adding an aqueous solution of sodium picrylsulfonate to the aqueous mother liquor, discarding the initial precipitate and allowing the filtrate to stand at room temperature. Crystals of the chlorohydrin picrylsulfonate soon appeared; yield 1.3 g.; m.p. 139–142°; mixed m.p. 139–143°; thiosulfate titer, 0.94 *mM* per *mM* of chlorohydrin salt.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] IV. THE TRANSFORMATIONS OF TRIS(β-CHLOROETHYL)-AMINE IN WATER

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In two previous papers (1, 2) of this series, data were presented concerning the sequence of reactions undergone by methyl-bis(β-chloroethyl)amine (MBA) and ethyl-bis(β-chloroethyl)amine (EBA) in water. In addition to these nitrogen mustards, which contain two chloroethyl groups, much attention has been given to tris(β-chloroethyl)amine (TBA) (3) which contains three chloroethyl groups. As will be demonstrated in this communication, this alteration in structure results in appreciable differences in chemical and toxicological properties. The present investigation is concerned with the course of the transformations of TBA in water. The experimental methods employed are similar to those used for MBA and EBA.

The transformations of tris(β-chloroethyl)amine in bicarbonate solution. The transformations of TBA (0.01 *M*) in bicarbonate solution at *p*H 8 were studied in a manner similar to that used in the study of the transformations of MBA and EBA (1, 2). The reactions were studied by following, over a period of 24 hours, the formation of Cl^- and H^+ and by determining the thiosulfate titer.

It will be noted from Table I that initially there is a rapid release of the first equivalent of Cl^-. This occurs before the TBA is completely dissolved, *i.e.*, in less than 15 minutes. The second equivalent of Cl^- is formed at a somewhat slower rate (within about 60 minutes). The third equivalent is formed very slowly and Cl^- is still being liberated after 240 minutes.

The release of Cl^- during the first 15 minutes of the reaction is accompanied by the formation of a much smaller quantity of H^+, indicating that quaternary nitrogen compounds are formed. During the succeeding 105 minutes, H^+ is formed at about the same rate as is Cl^-. This shows that the amount of quaternary nitrogen remains fairly constant during this period and equals approximately 1 m.equiv. per *m*M of TBA. As the reaction proceeds, the difference between Cl^- and H^+ decreases and after 24 hours the liberated H^+ and Cl^- are nearly equal. This indicates that appreciable quantities of quaternary nitrogen compounds are no longer present in the reaction mixture.

The data on the thiosulfate consumption given in Table I provide additional information concerning the course of the transformation of TBA in water.

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Initially there is a thiosulfate consumption within 12 minutes of about 2 equivalents per mole of TBA. The thiosulfate consumption decreases at about the same rate as the H^+ concentration increases, and after 24 hours, no thiosulfate is consumed.

These data suggest that the quaternary nitrogen formed during the transformations of TBA in water is present largely in the form of ethylenimonium compounds. This conclusion is supported by the fact that the concentration of quaternary nitrogen compounds never exceeds one equivalent, which represents the theoretical maximum for the formation of ethylenimonium groups. The advantages and limitations of the thiosulfate titer as an index of the concentration of ethylenimonium compounds have been discussed in detail previously (1, 2). It was found in preliminary studies that TBA reacts with thiosulfate very rapidly, one equivalent of thiosulfate being consumed within one minute.

TABLE I

THE HYDROLYSIS OF TRIS(β-CHLOROETHYL)AMINE (TBA) IN BICARBONATE SOLUTION

Concentration of reactants per cc.: 0.01 *mM* of TBA·HCl; 0.01 *mM* of NaOH; 0.05 *mM* of $NaHCO_3$.

Temperature 25°C.

TIME OF HYDROLYSIS, MIN.	Cl^- LIBERATED PER *mM* TBA M.EQUIV.	H^+ LIBERATED PER *mM* TBA M.EQUIV.	(Cl^-)-(H^+) M.EQUIV.	$Na_2S_2O_3$ CONSUMED IN 12 MIN. PER *mM* TBA M.EQUIV.
15	1.37	0.47	0.90	2.03
30	1.71	0.71	1.00	1.87
60	2.02	1.01	1.01	1.56
120	2.37	1.32	1.05	1.21
240	2.63	1.93	0.70	0.85
1440	2.71	2.77		0.01

The reaction with the second equivalent of thiosulfate proceeds somewhat more slowly and usually is complete within about 12 minutes. For convenience, this time period was employed in the thiosulfate tests recorded in Table I. The third equivalent of thiosulfate is taken up very slowly. When thiosulfate is present in a freshly prepared solution of TBA, the thiosulfate consumption after 40 minutes corresponds to 86% of three equivalents. If the reaction is allowed to continue for a longer period, no appreciable increase in the thiosulfate consumption is observed. The fact that 100% is not attained is possibly due to the simultaneous hydrolysis of some of the chloroethyl groups of TBA. When larger amounts of TBA are employed (0.133 *mM* per cc. of reaction mixture), the final thiosulfate consumption reaches 93% of three equivalents. The product of this reaction, the "Bunte salt" of TBA, has been isolated (*cf.* experimental section).

The data in Table I may be best interpreted on the basis of the reactions postulated in Figure 1. Proof for the formation of the intermediates given in the Figure is provided by their isolation as described subsequently in this paper.

The transformations of tris(β-chloroethyl)amine in unbuffered solution. The transformations of TBA (0.01 *M*) in unbuffered solution was studied by following the liberation of H^+ and Cl^- in the aging solution. The results, given in Table II, show that the chloride ions, particularly during the early stages of the

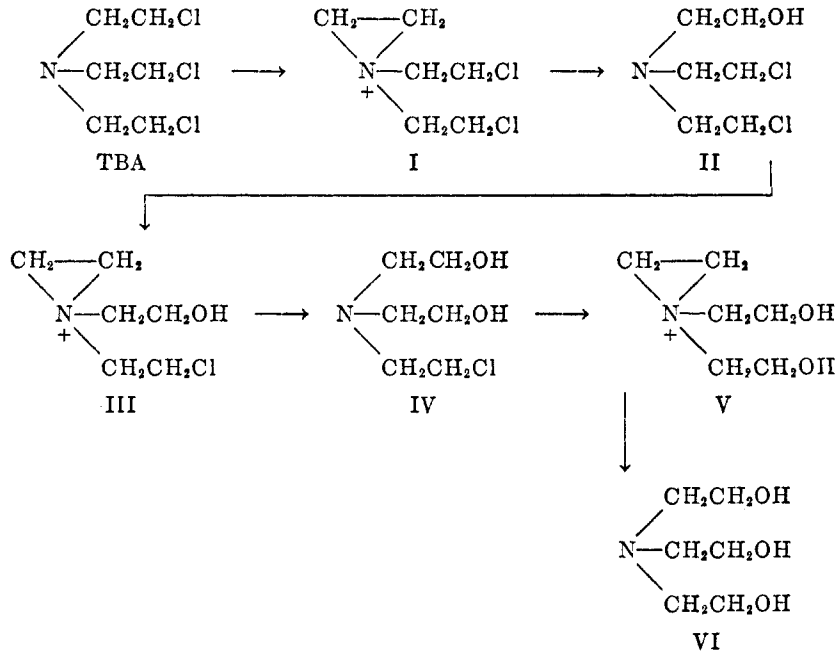


FIG. 1

TABLE II

THE HYDROLYSIS OF TRIS(β-CHLOROETHYL)AMINE (TBA) IN UNBUFFERED SOLUTION

Concentration of reactants per cc.: 0.01 *mM* of TBA·HCl; 0.01 *mM* of NaOH. Temperature 25°, *p*H 5 (15 min.), *p*H 3 (20 hours).

TIME, MIN.	Cl^- LIBERATED PER *mM* TBA M.EQUIV.	H^+ LIBERATED PER *mM* TBA M.EQUIV.	(Cl^-)-(H^+) M.EQUIV.
30	1.02	0.51	0.51
60	1.04	0.69	.35
180	1.16	0.89	.27
1200	1.36	1.17	.19
2640	1.46	1.33	.13

hydrolysis, appear at a faster rate than do the hydrogen ions. It will be noted that the extent of formation of quaternary nitrogen compounds, as measured by the difference between Cl^- and H^+, is not as great as in the hydrolysis of TBA in dilute bicarbonate solution. Furthermore, the hydrolysis in unbuffered solution slows up after the liberation of one equivalent of HCl, whereas the hydroly-

sis in bicarbonate solution proceeds to completion in less than one day. In a more concentrated unbuffered solution (0.10 *M*), exactly one equivalent of HCl is present in the solution after 20 hours. Such an aged solution reacts with 1.80 equivalents of thiosulfate in 2 hours, indicating that the principal hydrolytic product is bis(β-chloroethyl)-β-hydroxyethylamine (II). This compound was isolated from a 20-hour aged solution as a salt of picrylsulfonic acid.

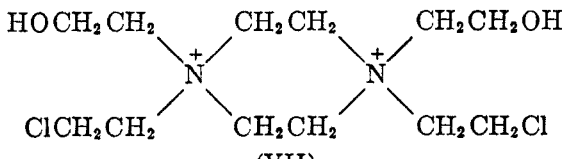
Crane and Rydon (4) have shown that the hydrolysis of a 1% solution (0.0489 *M*) of TBA proceeds very slowly after the formation of one equivalent of H^+ and Cl^-. From a 3-day old solution, these workers isolated bis(β-hydroxyethyl)-β-chloroethylamine (IV) as a picrate.

The isolation of the transformation products of TBA and their hydrolysis in bicarbonate solution. Evidence has been presented to show that the hydrolysis of TBA in dilute bicarbonate solution proceeds through the intermediate imonium compounds, 1,1-bis(β-chloroethyl)ethylenimonium ion (I), 1-(β-chloroethyl)-1-(β-hydroxyethyl)ethylenimonium ion (III), and 1,1-bis(β-hydroxyethyl)-ethylenimonium ion (V). After 15 minutes, most of the TBA has been transformed into I, while after one hour, the compound III predominates. When the solutions are acidified with HCl, and the products present are isolated as picrylsulfonates, it is found that in the 15-minute solution, I has reverted to TBA, while in the one-hour solution, III has reverted to the compound II. TBA and II have been isolated from such acidified solutions as salts of picrylsulfonic acid.

In Table III are given the results of a study of the hydrolysis of the picrylsulfonate of II in bicarbonate solution. During the first 3 hours of the hydrolysis, Cl^- is liberated at a faster rate than is H^+, indicating that there is an appreciable accumulation of the ethylenimonium ion during this period. Later, the production of H^+ increases to such an extent that in 20 hours the concentration of H^+ approaches that of Cl^-. This shows that the over-all reaction is mainly one of hydrolysis.

This study of the hydrolysis of II showed that it is successively transformed into III, IV, V, and finally triethanolamine (VI). All of these compounds have been isolated as crystalline picrylsulfonates. A description of their isolation and hydrolysis is presented in what follows.

Compound III was obtained by aging the picrylsulfonate of II (0.10 *M*) in unbuffered solution for 15 minutes. Hydrolysis of II for 20 hours in unbuffered solution led to the formation of IV and a small amount of the dipicrylsulfonate of the cyclic dimer [N,N′-bis(β-chloroethyl)-N,N′-bis(β-hydroxyethyl)piperazinium ion (VII)]. It should be noted that the cyclic compound VII was obtained from a 0.10 molar solution of II, whereas the data in Table III, which



(VII)

showed that little or no stable quaternary nitrogen was formed, were obtained with a 0.02 molar solution of II.

After aging a 0.10 molar unbuffered solution of the picrylsulfonate of IV for 15 minutes, V was isolated as its picrylsulfonate.

The picrylsulfonates of compounds III, IV, and V were hydrolyzed in aqueous bicarbonate. The results given in Table III show that III hydrolyzes rapidly to IV which then cyclizes quickly to V. The latter reaction is made more evident by the data on the hydrolysis of II which show that cyclization of this

TABLE III

THE HYDROLYSIS OF TRANSFORMATION PRODUCTS OF TRIS(β-CHLOROETHYL)AMINE

Concentration of reactants per cc.: 0.02 *mM* of substance; 0.08 *mM* of $NaHCO_3$. Temperature 25°; *p*H 7–8.

SUBSTANCE (EMPLOYED AS THE PICRYLSULFONATE)	TIME, MIN.	Cl^- LIBERATED PER *mM* OF SUBSTANCE M.EQUIV.	H^+ LIBERATED PER *mM* OF SUBSTANCE M.EQUIV.	(Cl^-)-(H^+) M.EQUIV.	$Na_2S_2O_3$ CONSUMED IN 10 MIN. PER *mM* OF SUBSTANCE M.EQUIV.
II	20	1.12	0.21	0.91	1.21
	60	1.35	0.45	.90	1.27
	180	1.69	0.89	.80	0.91
	1200	1.88	1.70	.18	0.08
III	60	0.76	0.89		1.10
	180	0.94	1.22		0.72
	1200	1.02	1.85		.05
IV	20	0.94	0.04	.90	.87
	60	.96	.15	.81	.78
	180	.98	.31	.67	.59
	1200	.98	.84	.14	.11
V	60		.38		.63
	180		.60		.37
	1200		.95		.00

compound takes place in less than 20 minutes. The results in Table III also show that V hydrolyzes rapidly to triethanolamine.

These hydrolytic studies indicate that in 20 hours the hydrolysis of each compound has proceeded practically (90–95%) to completion, triethanolamine being the principal product formed. Triethanolamine picrylsulfonate was isolated from a 72-hour hydrolysate of the picrylsulfonate of IV.

The toxicity of the transformation products of TBA. To study the toxicities of the intermediate hydrolysis products, their picrylsulfonates were converted to the corresponding chlorides or hydrochlorides by double decomposition with the dichloro cyclic dimer of methyl-bis(β-chloroethyl)amine as described previously (1).

The data given in Table IV show that both II and III have an LD_{50} of approximately 1.5 mg./kg. upon intraperitoneal injection into mice. The LD_{50}

of the hydrochloride of IV is approximately 16 mg./kg. on intraperitoneal injection into mice. The *p*H of the injected solution was 6. Argentometric titration of Cl^- indicated that no appreciable cyclization to the imonium ion V had occurred in this solution prior to its administration. Crane and Rydon

TABLE IV

THE TOXICITY TO MICE OF TRANSFORMATION PRODUCTS OF TRIS(β-CHLOROETHYL)AMINE

SUBSTANCE (EMPLOYED AS HYDROCHLORIDE OR CHLORIDE)	DOSAGE	NUMBER OF MICE INJECTED	EFFECT ON MICE
	mg./kg.		
II	25	3	All dead within 1–2 days
	20	3	All dead within 1–2 days
	15	3	All dead within 1–2 days
	10	3	All dead within 2 days
	5	3	All dead within 2 days
	2.5	3	All dead within 3–5 days
	1.75	3	All dead within 4–6 days
	1.0	3	All alive after 8 days
III	7.2	3	All dead within 4–5 days
	5.4	3	All dead within 3–4 days
	3.6	3	All dead within 4–5 days
	2.5	4	3 dead within 4–5 days 1 alive after 8 days
	1.8	3	1 dead within 3 days 2 alive after 8 days
	1.0	4	2 dead within 4–5 days 2 alive after 8 days
	0.72	3	All alive after 8 days
IV	18	3	All dead within 15–30 min.
	14.4	3	All alive after 8 days
	10.8	3	All alive after 8 days
	7.2	3	All alive after 8 days
V	25	3	All dead within 10–12 min.
	20	3	All dead within 13–18 in.
	15	3	All dead within 12 min.
	10	6	5 dead within 10–150 min. 1 alive after 6 days
	5	6	3 dead within 19–25 min. 3 alive after 6–7 days
	2.5	6	1 dead within 30 min. 5 alive after 6–7 days

(4) report an LD_{50} for this substance of 5 mg./kg. upon subcutaneous injection into mice. The higher toxicity found by the British workers probably may be attributed to the difference in the route of administration. Smith *et al.* have shown (5) that the chlorohydrin derived from MBA (1) has an LD_{50} of 34 mg./kg. when injected intraperitoneally into mice, while the same compound adminis-

tered subcutaneously has an LD_{50} of 15 mg./kg. The LD_{50} of the imonium ion V is approximately 5 mg./kg. on intraperitoneal injection into mice.

EXPERIMENTAL

Analytical methods. The methods for determining the Cl^- and H^+ liberation, and the thiosulfate consumption, were described previously (1, 2).

Isolation of bis(β-chloroethyl)-β-hydroxyethylamine (II) as a picrylsulfonate from an aged unbuffered solution of TBA. A reaction mixture (80 cc.) containing 8 *mM* of TBA·HCl and 8 *mM* of NaOH was shaken at room temperature for 20 hours. The resulting clear solution was then cooled to 0° and an aqueous solution of 8.0 *mM* of picrylsulfonic acid was added. After cooling overnight, the crystalline picrylsulfonate of II was filtered off and dried *in vacuo* over P_2O_5; m.p. 127–129°. The compound consumed 2.04 mole equivalents of thiosulfate in 2 hours. A second crop of the salt was obtained by concentrating the mother liquor under reduced pressure and cooling at 4°; m.p. 126–128°. This fraction consumed 1.93 equivalents of thiosulfate in 2 hours; total yield, 2.65 g. (70%). The two fractions were combined, rapidly recrystallized from warm water, and dried *in vacuo* over P_2O_5; m.p. 127–129°.

Anal. Calc'd for $C_6H_{14}Cl_2NO \cdot C_6H_2N_3O_9S$: C, 30.1; H, 3.4; N, 11.7; Cl, 14.8
Found: C, 30.1; H, 3.45; N, 11.5; Cl, 14.75.

The isolation was repeated on a larger scale. Starting with 32 *mM* of TBA·HCl, there was obtained 14.2 g. of picrylsulfonate of II (93%); m.p. 127–129°.

The isolation of the picrylsulfonate[5] *of TBA from an aged solution of TBA.* An aqueous solution of 1 *mM* of TBA·HCl was added to 100 cc. of water containing 1 *mM* of NaOH. The mixture was shaken for 15 minutes at room temperature. The clear solution which resulted was cooled to 0°, acidified with HCl to Congo Red and treated with an aqueous solution of 365 mg. (1 *mM*) of picrylsulfonic acid. The solution was concentrated under reduced pressure to 50 cc. and cooled at 4°. The picrylsulfonate of TBA crystallized and was dried *in vacuo* over P_2O_5; yield 160 mg.; m.p. 175–178°. The authentic compound melts at 180–182° and a mixture of the authentic and isolated salts melted at 176–179°. The isolated salt consumed 2.52 equivalents of thiosulfate in 2 hours. Under comparable conditions, TBA consumes 2.54 equivalents of thiosulfate.

Isolation of bis(β-chloroethyl)-β-hydroxyethylamine (II) as a picrylsulfonate from an aged buffered solution of TBA. A reaction mixture (250 cc.) containing 2.5 *mM* of TBA·HCl and 15 *mM* of $NaHCO_3$ was shaken for 15 minutes at room temperature and then maintained at 25° for an additional 45 minutes. The solution was cooled to 0°, acidified with HCl to Congo Red and treated with an aqueous solution of 2.5 *mM* of sodium picrylsulfonate. The solution was concentrated to 25 cc. and cooled for one hour at 4°. The crystals which separated were filtered off and dried *in vacuo* over P_2O_5; yield 0.36 g. A sample of the compound consumed 1.87 equivalents of thiosulfate in 2 hours. For analysis, it was recrystallized once from acetone-petroleum ether and once from water; m.p. 126–128°.

Anal. Calc'd for $C_6H_{14}Cl_2NO \cdot C_6H_2N_3O_9S$: C, 30.1; H, 3.4; N, 11.7; Cl, 14.8.
Found: C, 30.3; H, 3.4; N, 11.7; Cl, 14.6.

Isolation of 1-(β-chloroethyl)-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate. The picrylsulfonate of II (2.4 g., 5 *mM*) was added to 50 cc. of 0.10 *N* $NaHCO_3$. After stirring for 15 minutes at room temperature, the reaction mixture was cooled to 0°, acidified to Congo Red and stored at 4° overnight. The picrylsulfonate of III was filtered off and dried over P_2O_5 *in vacuo*; yield 1.65 g. (75%); m.p. 135–136°. The compound reacted with 1.94 equivalents of thiosulfate in 2 hours.

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[5] TBA forms sparingly soluble salts with several aromatic sulfonic acids. The approximate solubility, in 0.5 *N* HCl at 0°, of the picrylsufonate is 0.15%; of the flavianate is 0.3%; of the 2,6 diiodophenol-4-sulfonate is 0.5%; and of the 5-nitronaphthalene-1-sulfonate is 1.4%.

Anal. Calc'd for $C_6H_{13}ClNO \cdot C_6H_2N_3O_9S$: C, 32.55; H, 3.4; N, 12.65; Cl, 8.0.
Found: C, 32.4; H, 3.6; N, 12.7; Cl, 8.1.

Isolation of bis(β-hydroxyethyl)-β-chloroethylamine picrylsulfonate. A solution of the hydrochloride of II, prepared by the hydrolysis of TBA (0.10 *M*) in unbuffered solution was treated with an equivalent amount of NaOH and allowed to stand at room temperature for 20 hours. Analysis of the hydrolysate showed there had been a liberation of 0.93 m.equiv. of Cl^- and 0.88 m.equiv. of H^+ per *mM* of II. The hydrolysate reacted with 0.78 *mM* of thiosulfate per *mM* of II in 2 hours, indicating that the major product present was IV. After removal of the aliquots for analysis, the remainder of the hydrolysate was cooled to 0°, acidified to Congo Red and treated with an aqueous solution of 9 *mM* of picrylsulfonic acid. After 4 hours, the precipitate was filtered off and dried over P_2O_5 *in vacuo*; yield, 0.27 g., corresponding to the transformation of 6.7% of II to the dimer VII. This compound reacted only slightly with thiosulfate and not at all after washing it with acetone. The elementary analysis of the compound agrees with that expected for the dipicrylsulfonate of the dimer VII.

Anal. Calc'd for $C_{12}H_{26}Cl_2N_2O_2 \cdot 2C_6H_2N_3O_9S$: C, 32.55; H, 3.4; N, 12.65; Cl, 8.0.
Found: C, 32.25; H, 3.7; N, 12.65; Cl, 8.0.

There are possible two stereoisomeric forms (cis and trans) of VII. It has not been established whether the isolated compound is the cis or the trans form or a mixture of the two.

After removal of the dimer salt, the filtrate was concentrated to 25 cc. and cooled at 4°. The picrylsulfonate of IV crystallized in nearly pure form; yield 3.07 g. (76%); m.p. 169–171°. The compound reacted with 0.9 equivalents of thiosulfate. For analysis it was recrystallized rapidly from warm water; m.p. 170–171°.

Anal. Calc'd for $C_6H_{15}ClNO_2 \cdot C_6H_2N_3O_9S$: C, 31.3; H, 3.7; N, 12.2; Cl, 7.7.
Found: C, 31.2; H, 3.7; N, 12.1; Cl, 7.6.

For further identification the picrylsulfonate of IV was converted to the picrate in the following manner. An aqueous solution of the picrylsulfonate was treated with the dichloro cyclic dimer of MBA to remove picrylsulfonic acid and the resulting solution of the hydrochloride was treated with aqueous sodium picrate. After evaporation of the reaction mixture to dryness, the residue was washed with benzene and the resulting picrate was recrystallized twice from ethyl acetate; orange prisms, m.p., 115°. Crane and Rydon (4) report the melting point 119° for this compound.

Isolation of 1-bis(β-hydroxyethyl)ethylenimonium picrylsulfonate. The picrylsulfonate of IV (1.61 g., 3.5 *mM*) was stirred in 35 cc. of 0.1 *N* $NaHCO_3$ for 15 minutes at room temperature. The subsequent procedure was similar to that described for the isolation of the picrylsulfonate of III; yield 0.45 g. The picrylsulfonate of V reacted with 0.95 equivalents of thiosulfate in 2 hours and gave a negative test for chloride after sodium fusion.

Anal. Calc'd for $C_6H_{14}NO_2 \cdot C_6H_2N_3O_9S$: C, 34.0; H, 3.8; N, 13.2.
Found: C, 33.9; H, 3.85; N, 13.0.

A second but less pure crop was obtained by concentrating the mother liquor; yield 0.4 g.; thiosulfate titer (2 hrs.), 0.8 equivalents.

In a second preparation, employing a more concentrated solution of the reactants (0.25 *N*), the yield of analytically pure V picrylsulfonate was 80% of the theory.

Isolation of triethanolamine from an aged bicarbonate solution of bis(β-hydroxyethyl)-β-chloroethylamine picrylsulfonate. A solution containing 0.02 *mM* of the picrylsulfonate of IV and 0.08 *mM* of $NaHCO_3$ per cc. was allowed to stand at 25° for 72 hours. The aged solution was chilled, acidified to Congo Red and concentrated *in vacuo*. Upon cooling, triethanolamine picrylsulfonate crystallized; m.p. 185–187°; mixed m.p. with an authentic sample 186–188°. The isolated compound did not react with thiosulfate.

An authentic sample of triethanolamine picrylsulfonate was prepared in 90% yield by adding a concentrated aqueous solution of picrylsulfonic acid to a solution of triethanolamine in HCl; m.p. 187–189°.

Anal. Calc'd for $C_6H_{16}NO_3 \cdot C_6H_2N_3O_9S$: C, 32.6; H, 4.1; N, 12.7.
Found: C, 32.4; H, 4.1; N, 12.5.

Preparation of "Bunte salt" of TBA. TBA·HCl (1.54 g., 8 *mM*) was added to 50 cc. of water containing 51 *mM* of $Na_2S_2O_3$, 31.6 *mM* of $NaHCO_3$, and 8 *mM* of NaOH. The mixture was shaken for 20 hours at room temperature. The resulting clear solution was evaporated to dryness *in vacuo* and extracted with 100 cc. of hot 80% ethanol. The product crystallized on cooling to 0°; yield 3.45 g. The product was recrystallized from 80% ethanol. For analysis, it was recrystallized from water and dried in air.

Anal. Calc'd for $C_6H_{12}NNa_3O_9S_3 \cdot 4\frac{1}{2}\ H_2O$: C, 12.3; H, 3.6; N, 2.4; Na, 11.8; H_2O, 13.9.
Found: C, 12.5; H, 3.8; N, 2.3; Na, 11.8; H_2O, 14.1.

The salt was also prepared by the addition of TBA·HCl to water containing the theoretical quantity of thiosulfate and sufficient NaOH to liberate the amine.

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[a] Unpublished data obtained in Great Britain.
[b] Unpublished data obtained in the United States.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] V. THE REACTIONS OF THE NITROGEN MUSTARD GASES WITH PROTEIN CONSTITUENTS

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It is generally believed that many of the physiological effects of vesicant agents are a consequence of reactions of the vesicant with tissue proteins, particularly enzyme proteins (1–18). The nitrogen mustard gases have been shown to inhibit, and hence probably to react with, numerous enzymes (10–18). It follows, therefore, that an understanding of the physiological action of the nitrogen mustards requires a detailed study of the reactions of these agents with proteins, amino acids, and peptides. Aside from their significance as protein constituents, amino acids and peptides also occur as such in blood and other body fluids and tissues. In addition to the reactive α-amino and α-carboxyl groups common to most amino acids, certain of the amino acids possess characteristic side chains, many of which exist in an uncombined state in proteins. The reactions of these groups with the nitrogen mustards are, therefore,worthy of study.

The reaction of methyl-bis(β-chloroethyl)amine, ethyl-bis(β-chlorocthyl)amine, and tris(β-chloroethyl)amine with the amino groups of amino acids and peptides. The data given in Table I show the extent of the decrease in amino nitrogen when amino acids or peptides are treated with the nitrogen mustards at weakly alkaline *p*H values. The reactions were carried out at room temperature, and the disappearance of amino nitrogen was followed by means of the Van Slyke nitrous acid method. In the case of methyl-bis(chloroethyl)amine (MBA) and ethyl-bis(β-chloroethyl)amine (EBA) the reaction mixtures were shaken for 4 hours to obtain homogeneous solutions and were then allowed to stand for 16 hours. Since under the experimental conditions employed, tris(β-chloroethyl)amine (TBA) does not pass into solution as rapidly as do MBA and EBA, the reaction mixtures containing TBA were shaken during the entire 20-hour period. It will be noted that in the experiments with MBA and EBA, 4 milliequivalents of amino groups were employed per millimole of nitrogen mustard; whereas, in the experiments with TBA 6 milliequivalents of amino groups were employed. In all experiments, therefore, 2 equivalents of amino groups were employed for each chloroethyl group.

From the data in Table I it is evident that extensive reaction occurs when the α-amino groups of amino acids are treated with any one of the nitrogen

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mustards at *p*H 8. The results presented in Table I indicate that the α-amino groups of all the amino acids tested, with the exception of histidine, react at *p*H 8 to about the same extent with MBA. This also seems to be the case for EBA and TBA.

The fact that the α-amino group of histidine reacts with any given nitrogen mustard to a much lesser extent than do the α-amino groups of the other amino acids is of particular interest. As is shown later in this communication and in Paper VI of this series (19), this abnormal behavior is due to a rapid reaction of the nitrogen mustards with the imidazole group of histidine. Thus, the greater part of the available nitrogen mustard is removed from the reaction before the slower action of the vesicant on the α-amino group of histidine can occur.

The data in Table I indicate that the β-amino group of β-alanine reacts with MBA and EBA to a slightly smaller extent than do the amino groups of the α-amino acids. This difference does not appear to hold in the case of TBA.

It will be noted from Table I that the amino group of *l*-alanine does not react at *p*H 8 to a greater extent with any given nitrogen mustard than do the amino groups of the more complex amino acids serine, threonine, glutamic acid, arginine, and tyrosine (as amide).[4] It must be concluded, therefore, that under these conditions the aliphatic hydroxyl group of serine and threonine, the γ-carboxyl group of glutamic acid, the guanido group of arginine, and the phenolic hydroxyl group of tyrosine do not interfere appreciably with the reaction of the nitrogen mustards with α-amino groups.

It will be noted that in the case of the peptides investigated, the extent of the reaction with a given nitrogen mustard is considerably greater than in the case of amino acids such as alanine. On the other hand, the ε-amino group of benzoyl-*l*-lysineamide does not react with MBA to the same degree as do the α-amino groups. It is of interest that analogous findings were obtained in the study of the reaction of mustard gas with the amino groups of amino acids and peptides (20).

The amino acids phenylalanine, tryptophane, and methionine are sparingly soluble at *p*H 8. They, therefore, were employed as sodium salts at *p*H 9.5. It will be noted that at *p*H 9.5 the α-amino group of alanine reacts with a given nitrogen mustard to a greater extent than at *p*H 8. The amino groups of phenylalanine and tryptophane react at *p*H 9.5 to about the same extent as does that of alanine. This indicates that the indole nucleus of tryptophane does not react appreciably with the nitrogen mustards.

The amino group of methionine was found to react with TBA at *p*H 9.5 to less than half the extent observed for the amino groups of alanine, phenylalanine and tryptophane. With MBA and EBA, a decreased reactivity of the amino group of methionine was also observed but to a very much lesser degree. It will be shown in another paper (21) that mustard gas itself reacts readily with the $-SCH_3$ group of methionine to form a sulfonium salt. The simplest interpretation of the findings with the nitrogen mustards is that these agents

[4] The amino acid tyrosine was not studied as such because of its low solubility at *p*H 8. In its place, the acetate of *l*-tyrosineamide was employed.

also have a tendency to combine with the —SCH_3 group of methionine, presumably with the formation of a sulfonium salt. In the case of TBA this tendency is quite marked, although not so great as observed with mustard gas itself. For MBA and EBA, the tendency is so small as to be questionable.

The discussion thus far has been concerned with the relative reactivity of a given nitrogen mustard towards various protein constituents. It is also possible,

TABLE I

REACTION OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA), ETHYL-BIS(β-CHLOROETHYL)-AMINE (EBA), AND TRIS(β-CHLOROETHYL)AMINE (TBA) WITH THE AMINO GROUPS OF AMINO ACIDS AND PEPTIDES

Concentration of reactants per cc.: 0.134 *mM* of MBA or EBA; 0.127 *mM* of TBA. (The nitrogen mustards were employed as hydrochlorides, and one equivalent of NaOH was added to liberate the free base.) 0.534 m.equiv. of NH_2-N (in the case of MBA or EBA); 0.762 m. equiv. of NH_2-N (in the case of TBA). 0.534 *mM* of $NaHCO_3$ for MBA or EBA; 0.526 *mM* of $NaHCO_3$ for TBA.

Temperature 25°; reaction period, 20 hours (4 hours shaking, 16 hours standing for MBA and EBA; 20 hours shaking for TBA).

SUBSTANCE	*pH*	DECREASE IN NH_2-N PER CC.			DECREASE IN NH_2-N PER *mM* OF AGENT		
		MBA, M.EQUIV.	EBA, M.EQUIV.	TBA, M.EQUIV.	MBA, M.EQUIV.	EBA, M.EQUIV.	TBA, M.EQUIV.
Glycine	8	0.096	0.114	0.15	0.72	0.86	1.2
l-Alanine	8	.100	.117	.145	.75	0.88	1.15
l-Serine	8	.100	.150	.19	.75	1.13	1.5
dl-Threonine	8	.117	.142	.18	.87	1.06	1.4
l-Glutamic acid	8	.100	.136	.16	.75	1.02	1.3
l-Arginine	8	.083	.123	.18	.62	0.92	1.4
l-Lysine	8	.112	.135	.16	.84	1.01	1.3
l-Histidine	8	.015	.037	.07	.11	0.28	0.6
l-Alanine	9.5	.147	.156	.19	1.1	1.17	1.5
l-Phenylalanine[a]	9.5	.167	.153	.22	1.25	1.15	1.7
dl-Methionine[a]	9.5	.117	.125	.09	0.87	0.94	0.7
l-Tryptophane[a]	9.5	.161	.156	.25	1.2	1.17	1.9
β-Alanine	8	.067	.080	.18	0.50	0.60	1.4
l-Tyrosineamide acetate	8	.133			1.0		
Benzoyl-*l*-lysineamide	8	.021			0.10		
Glycylglycine	8	.147	.188	.23	1.1	1.41	1.8
l-Leucylglycine	8	.161	.190		1.2	1.43	
l-Leucylglycylglycine	8	.148	.172		1.1	1.30	

[a] These sparingly soluble amino acids were dissolved as the sodium salts, and the same amount of bicarbonate was added as in the other experiments.

on the basis of the data given in Table I, to obtain a rough comparison of the reactivity of the three nitrogen mustards towards the compounds listed. Since TBA contains three chloroethyl groups and MBA and EBA each contain but two chloroethyl groups, the comparison should be made on the basis of the milliequivalents of amino nitrogen which have reacted per chloroethyl group. The data for such a comparison are given in Table II.

Before commenting upon the data presented in Table II, it should be em-

phasized that any conclusions which can be drawn from the data may be valid only for the experimental conditions employed, and probably have no general kinetic applicability. This reservation is necessary, because at the beginning of the experiments homogeneous solutions were not obtained, and the three nitrogen mustards passed into solution at different rates, TBA being by far the slowest. Hence, the concentration of reactive ethylenimonium groups in solution was not known and was not the same for each agent.

With the above reservations it appears from Table II that the chloroethyl groups of all the nitrogen mustards have about the same reactivity towards the amino groups of most of the compounds listed. The order of reactivity appears to be EBA > TBA > MBA, although the differences among the three

TABLE II

COMPARISON OF THE REACTIVITIES OF TRIS(β-CHLOROETHYL)AMINE (TBA), METHYL-BIS-(β-CHLOROETHYL)AMINE (MBA), AND ETHYL-BIS(β-CHLOROETHYL)AMINE (EBA) WITH THE AMINO GROUPS OF AMINO ACIDS AND PEPTIDES

The data in this table are calculated from those given in Table I.

SUBSTANCE	*p*H	DECREASE IN NH_2-N PER M.EQUIV. OF CHLOROETHYL GROUPS		
		TBA, M.EQUIV.	MBA, M.EQUIV.	EBA, M.EQUIV.
Glycine	8	0.40	0.36	0.43
l-Alanine	8	.38	.38	.44
l-Serine	8	.50	.38	.56
dl-Threonine	8	.47	.42	.53
l-Glutamic acid	8	.43	.38	.51
l-Lysine	8	.43	.42	.50
l-Arginine	8	.47	.31	.46
l-Histidine	8	.20	.06	.14
β-Alanine	8	.47	.25	.30
l-Alanine	9.5	.50	.55	.58
l-Phenylalanine	9.5	.57	.62	.57
l-Tryptophane	9.5	.63	.60	.58
dl-Methionine	9.5	.23	.44	.47
Glycylglycine	8	.60	.55	.70

agents are not very marked.[5] TBA seems to have a greater reactivity toward the β-amino group of β-alanine and toward the sulfide group of methionine than do MBA or EBA. MBA, on the other hand, seems to have the highest reactivity toward the imidazole group of histidine, followed by EBA and TBA [see also Paper VI of this series (19)].

[5] It should be pointed out that, while the concentrations of TBA, MBA, and EBA are identical in these experiments, the concentrations of chloroethyl groups are not. The TBA reaction mixture contains half again as many chloroethyl groups per cc. as do the EBA or MBA reaction mixtures. In order to circumvent this difficulty, the experiment with alanine and TBA at *p*H 8 was repeated, with the concentration of the reactants reduced to two-thirds of its former value. In this case, the decrease in m.equiv. of amino-nitrogen per m.equiv. of chloroethyl group fell from 0.38 to 0.33. Once again it appears that the reactivities of TBA, MBA and EBA towards the amino group are quite similar with MBA appearing, on this basis, to be slightly more reactive than TBA.

The reaction of MBA with the amino groups of proteins. When aqueous solutions of crystalline egg albumin or of gelatin are treated at slightly alkaline *p*H values with MBA, a significant decrease in the amino nitrogen content of the protein solution is observed (Table III). In this behavior MBA differs from mustard gas, since it has been found that the latter does not appear to combine to an appreciable extent with the amino groups of egg albumin or gelatin (22). The data in Table III indicate that about one-fourth of the free amino groups of egg albumin and about one-third of the free amino groups of gelatin have disappeared during the reaction.

The mechanism of the reaction of MBA with amino groups. In view of the complex reactions that occur when the nitrogen mustards react with water

TABLE III

REACTION OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) WITH AMINO GROUPS OF PROTEINS

Time of reaction, 24 hours at 25°; *p*H 7.5 (bicarbonate).

MBA was employed as the hydrochloride and one equivalent of NaOH added to liberate the base.

PROTEIN	PROTEIN PER CC.	MBA PER CC.		NH_2-N[a] PER CC.	DECREASE IN NH_2-N PER CC.		DECREASE IN NH_2-N PER *mM* MBA
	mg.	*mM*	*mg.*	*mg.*	*mg.*	*mM*	*mM*
Egg albumin	114	0	0	0.92			
	114	0.08	12.5	0.68	0.24	0.017	0.21
Gelatin	100	0	0	0.71			
	100	0.08	12.5	0.50	0.21	0.015	0.19

[a] 30 minutes shaking in the Van Slyke amino nitrogen apparatus.

(9), it seemed desirable to determine whether the reaction with amino groups involved direct reaction with the nitrogen mustard itself or with one or more of the transformation products of the nitrogen mustard.

To this end, a study was made of the reaction of MBA with alanine in bicarbonate solution. The following analytical procedures were applied: (a) disappearance of amino nitrogen; (b) formation of chloride ions; (c) formation of hydrogen ions as measured by the consumption of bicarbonate; and (d) disappearance of the ethylenimonium ion as measured approximately by the reaction with thiosulfate in 10 minutes (23).

The data in Table IV show the following:

(a) During the first 20 minutes, when all of the MBA is transformed into the 1-methyl-1-(β-chloroethyl)ethylenimonium ion, only about 0.02 m.equiv. of NH_2-N disappear per *mM* of MBA. Thus, the direct reaction of MBA itself with amino groups is negligibly small. After 24 hours, when the decrease in amino groups has stopped, only 0.75 m.equiv. of NH_2-N per *mM* of MBA have disappeared. The maximum possible value is 2 m.equiv. of NH_2-N per *mM* of MBA.

Separate experiments with *l*-glutamic acid and glycylglycine have shown that in these cases also MBA is converted into the ethylenimonium ion before appreciable disappearance of amino nitrogen is observed.

(b) The initial rate of chloride liberation is much the same in the presence of alanine as in bicarbonate alone, but during the period when most of the amino nitrogen disappears, the chloride liberation is more rapid. In the presence of alanine the extent of the chloride liberation is also more complete (93%).

(c) The liberation of H^+ is more rapid during the period when most of the amino nitrogen disappears. However, the H^+ liberated after 24 hours corresponds to only 47% of the amount to be expected if the two chlorine atoms had reacted directly with amino groups or with water. As in the absence of alanine, the H^+ liberated corresponds to one-half of the Cl^- formed.

TABLE IV

REACTIONS OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) IN THE PRESENCE AND ABSENCE OF ALANINE

Concentration of reactants per cc.: 0.127 *mM* of MBA·HCl (one equivalent of NaOH added to liberate the base); 0.536 *mM* of *l*-alanine; 0.526 *mM* of $NaHCO_3$.

REACTION MIXTURE	TIME	NH_2-N DISAPPEARED PER *mM* MBA	Cl^- LIBERATED PER *mM* MBA	H^+ LIBERATED PER *mM* MBA	(Cl^-)-(H^+)	THIOSULFATE USED IN 10 MIN. PER *mM* MBA
	min.	*m.equiv.*	*m.equiv.*	*m.equiv.*	*m.equiv.*	*m.equiv.*
Bicarbonate alone	20		1.10	0.17	0.93	1.06
	40		1.21	.36	.85	1.04
	60		1.31	.43	.88	0.97
	360		1.53	.70	.83	.58
	1440		1.69	.87	.82	.24
Bicarbonate plus *l*-alanine	20	0.02	1.07	.21	.86	.91
	40	.14	1.25	.37	.88	.79
	60	.24	1.34	.58	.76	.64
	360	.72	1.73	.90	.83	.17
	1440	.75	1.85	.93	.92	.03

(d) As in the experiment without alanine, the increase in Cl^- after the first 20 minutes is accompanied by an approximately equivalent increase in H^+.

(e) The rate of disappearance of the ethylenimonium form is definitely more rapid in the presence of alanine than in bicarbonate alone. After 24 hours, the quantity of imonium ion is negligibly small.

The above observations may perhaps best be summarized on the basis of the following reactions (*cf.* Figure 1):

In bicarbonate solution, Reaction A, which occurs within the first 20 minutes, is the formation of the first ethylenimonium ring. This is shown by the liberation of more than half of the expected Cl^-, very little H^+, and the rapid consumption of 1 equivalent of added thiosulfate. The imonium compound then undergoes several different reactions. The occurrence of Reactions B, C, and D in bicarbonate solution has been demonstrated in Paper I of this series (23).

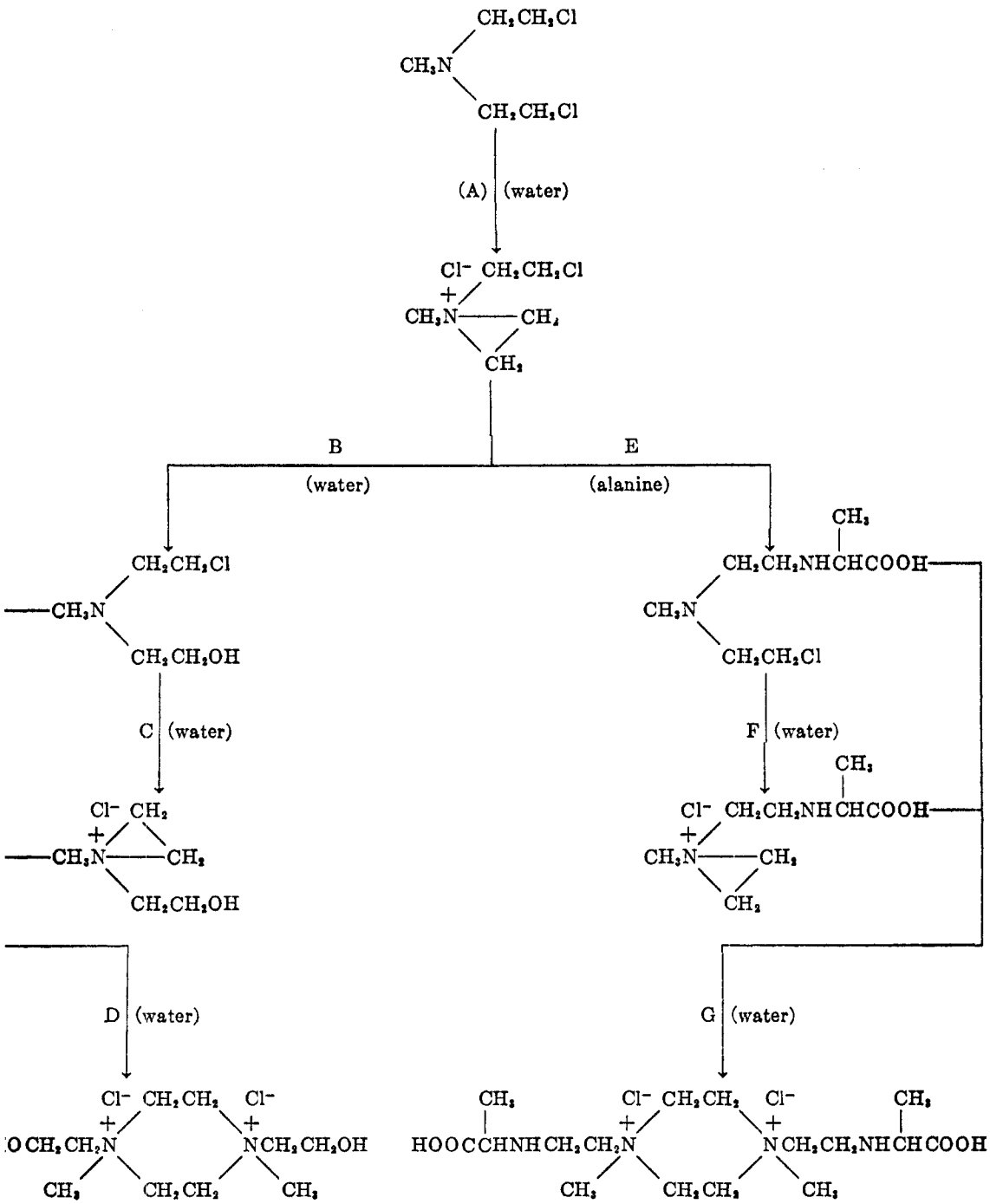
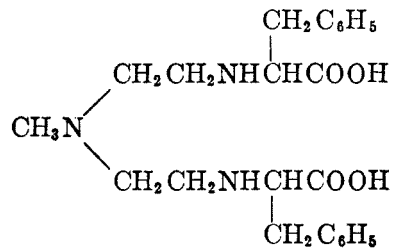


FIG. 1

In the presence of alanine, Reaction A takes place also. About 75% of the imonium compound then reacts with the amino group of alanine as shown by the gradual disappearance of amino groups (Reaction E). This reaction probably involves the ethylenimonium group. At the end of the reaction, 93% of the theoretical Cl^- and 47% of the maximum possible H^+ have been liberated; consequently, the final product of the reaction of MBA with alanine must contain quaternary nitrogen. Since the final 10-minute thiosulfate titer is low, this quaternary nitrogen cannot be ethylenimonium nitrogen. It may be assumed, therefore, that whatever monomeric reaction product is formed dimerizes rapidly according to Reactions F and G. In the presence of alanine, only about 25% of the first ethylenimonium compound follows the sequence of reactions postulated for the MBA-bicarbonate system.

The isolation of a reaction product of MBA with phenylalanine. It was shown in Table I that the amino group of phenylalanine reacts at *p*H 9.5 with MBA. Under the experimental conditions employed, 1.25 m.equiv. of NH_2-N disappeared per *mM* of MBA. This would indicate that at least a portion of the MBA had reacted in such a manner that 1 molecule of MBA (or its ethylenimonium form) had combined with 2 molecules of phenylalanine to give a product of the following structure:



This substance has been isolated from the reaction mixture.

As previously stated, it was necessary to perform the reaction of MBA with phenylalanine at *p*H 9.5 because of the slight solubility of the amino acid at *p*H 7.5–8. The relatively high yield and the structure of the product is of interest, since in the reaction of MBA with alanine at *p*H 8, the analytical data suggested that the principal product was formed from 2 molecules of MBA and 2 molecules of alanine and was, probably, a derivative of the dichloro cyclic dimer of MBA.

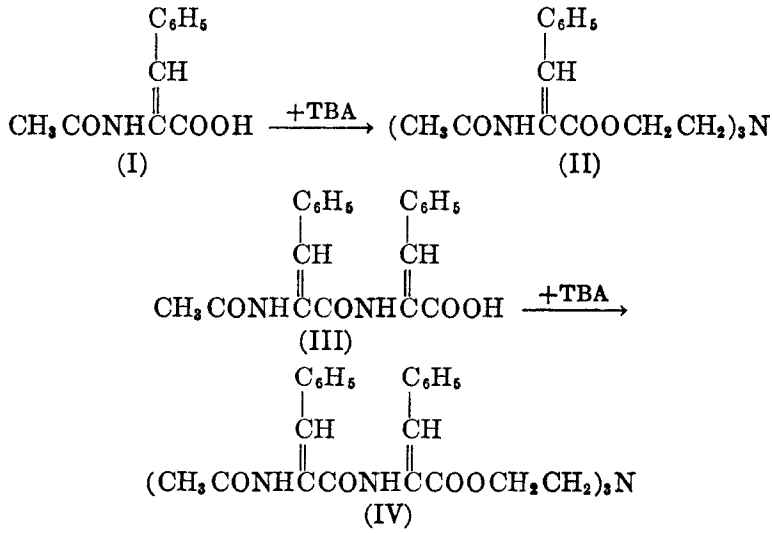
The reaction of MBA with the imidazole group of histidine. As shown earlier, the imidazole group of histidine interferes markedly with the reaction of MBA with α-amino groups at *p*H 8. Thus, in the case of histidine, the extent of the disappearance of amino nitrogen was 0.11 m.equiv. of NH_2-N per *mM* of MBA, while with other amino acids about 0.75 m.equiv. of NH_2-N reacted per *mM* of MBA. In order to eliminate the complicating effect of the α-amino group of histidine, acetylhistidine was prepared and the influence of this compound on the reaction between MBA and alanine was studied.

MBA (0.32 *mM*) was treated with 1.28 *mM* of *l*-alanine in the presence of 1.28 *mM* of acetyl-*dl*-histidine and 1.0 *mM* of $NaHCO_3$. After 24 hours, 0.048 m.equiv. of amino nitrogen had disappeared (0.15 m.equiv. of NH_2-N per

mM of MBA). In a control experiment, in which acetylhistidine had been omitted, the decrease in amino nitrogen was 0.230 *mM* (0.72 m.equiv. of NH_2-N per *mM* of MBA). This result shows that the imidazole group of acetylhistidine reacts with MBA more readily than does the α-amino group of alanine.

The reaction of MBA, EBA, and TBA with carboxyl groups. The reaction of a nitrogen mustard with carboxyl groups might be expected to lead to the formation of esters, which upon treatment with alkali, would be saponified with the disappearance of titratable alkali. Accordingly, MBA and EBA were treated with sodium acetate or sodium hippurate for 18 to 24 hours in bicarbonate solution, and the amount of saponifiable esters was determined. Bicarbonate controls were necessary, since even in the absence of a carboxylic acid, products were formed from MBA and EBA which decomposed in alkaline solution with the liberation of acid. In these experiments, no evidence of ester formation was obtained. These results are not surprising, in view of the later findings of Cohen and Van Artsdalen (24). Kinetic studies by these investigators showed that the first ethylenimonium compound derived from MBA reacts with propionate in aqueous solution at *p*H 7.4. The resulting ester of methyldiethanolamine was found to be unstable, however, saponifying at *p*H 7.4 with such rapidity that little or no ester could be detected in the reaction mixture after 24 hours.

With TBA, unequivocal evidence for the formation of esters was obtained. In the presence of sodium acetate, sodium hippurate, sodium acetyldehydrophenylalanine (I), or sodium acetyldehydrophenylalanyldehydrophenylalanine (III), approximately 25% of the chloroethyl groups of TBA were found to have reacted to form esters. In the experiments with acetate and hippurate the products of the reaction were not isolated. The products of the reaction with acetyldehydrophenylalanine and acetyldehydrophenylalanyldehydrophenylalanine have been isolated, however, and found to be triacyl derivatives of triethanolamine (Compounds II and IV).



DISCUSSION

The experiments outlined in this paper show that the nitrogen mustards are capable of reacting *in vitro* with the functional groups of a number of protein constituents. Since many of these functional groups are normally present in intact protein molecules, it seems likely that the nitrogen mustards can react with proteins *in vivo*. Among the functional groups which are found free in many proteins and which might serve as possible points of attack for the nitrogen mustards, may be mentioned the ϵ-amino groups of lysine residues or any free terminal amino groups of the peptide chains, the imidazole group of histidine residues, the sulfide group of methionine residues, the β- or γ-carboxyl groups of aspartic or glutamic acid residues, and any free terminal carboxyl groups of the peptide chains. To this list must be added sulfhydryl groups, as shown by Hellerman *et al.* (25).

The studies on the mechanism of the reaction between MBA and the amino group of alanine, furnish strong evidence for the view now generally held that the nitrogen mustards must first cyclize to the water-soluble ethylenimonium form prior to undergoing alkylation reactions.

EXPERIMENTAL

The reaction of the nitrogen mustards with amino groups of amino acids and peptides. The procedure employed (except for benzoyl-*l*-lysine amide) involved adding 2 cc. of an aqueous solution containing 1.6 *mM* of the nitrogen mustard hydrochloride to 10 cc. of a solution containing 6.4 m.equiv. of amino nitrogen (9.6 *mM* in the experiments in which TBA was employed), 6.4 *mM* of $NaHCO_3$, and 1.6 cc. of *N* NaOH. The reaction mixture was shaken for 4 hours and the solution was left at room temperature for 16 hours longer. In the experiments employing TBA, shaking was continued for 20 hours. One cc. was removed, diluted to 10 cc. and 1-cc. aliquots were used for NH_2-N determinations by the Van Slyke nitrous acid method. In the case of the reaction with lysine and benzoyllysine amide the shaking time was 30 minutes; with the other compounds it was 5 minutes. In the case of benzoyllysine amide, the reaction was carried out on a micro scale. A reaction mixture (1.2 cc.) containing 0.21 *mM* of MBA·HCl, 0.32 *mM* of benzoyllysine amide HCl, 0.8 *mM* of $NaHCO_3$, and 0.2 *mM* of NaOH was shaken for 4 hours. After standing for 16 hours longer, 0.2-cc. samples were used for NH_2-N determinations.

The mechanism of the reaction of MBA with amino groups. The reaction mixtures were made up to the concentrations indicated in Table IV in the manner described above. The Cl^- and H^+ liberation and thiosulfate consumption were estimated in the manner previously described (23).

The isolation of a reaction product of MBA with phenylalanine. To 4.23 g. of *l*-phenylalanine (25.6 *m*M) dissolved in 26 cc. of *N* NaOH were added 1.6 g. of $NaHCO_3$ and 6.4 cc. of *N* NaOH followed by the addition of 8 cc. of an aqueous solution of MBA·HCl (6.4 *mM*). The mixture was shaken for 24 hours at 25°. The gelatinous precipitate which separated out was filtered and washed with cold water. The product after drying *in vacuo* over P_2O_5 weighed 850 mg. (31%). The substance was sparingly soluble in water, alcohol, or organic solvents. It was soluble in dilute acid and could be precipitated by neutralization with alkali. The material retained traces of ash tenaciously, and even after several reprecipitations 0.2% of ash was still present.

Anal. Calc'd for $C_{23}H_{31}N_3O_4 \cdot \frac{1}{2}H_2O$: C, 65.4; H, 7.7; N, 9.9.
Found: C, 65.4; H, 7.8; N, 9.9.

$[\alpha]_D^{30}$ +29.8° (2% in *N* HCl)

The reaction of the nitrogen mustards with carboxyl groups. The procedure employed in

the experiments with MBA and EBA was essentially the same, and, therefore, will be given in detail only for the latter.

The carboxylic acid (12 *mM*, employed as the sodium salt) was treated with 4 *mM* of EBA·HCl in the presence of 4 *mM* of NaOH and 12 *mM* of $NaHCO_3$. After 24 hours at 25°, the solution was acidified and evacuated to remove CO_2. Absolute ethanol[6] (250 cc.) was added and after neutralization to phenolphthalein, 3.0 cc. of 1.06 *N* NaOH were introduced into the solution. After 30 minutes, the excess alkali was back-titrated to phenolphthalein with 0.1 *N* HCl. A control experiment (without the carboxylic acid) was also performed and the alkali consumption found in the presence of the carboxylic acid was corrected accordingly.

It was found that, in the presence of hippuric acid, the alkali consumption exceeded the control value by 2.1 cc. of 0.1 *N* NaOH. This indicates that only about 2.6% of the chloroethyl groups of EBA had reacted to form saponifiable esters of hippuric acid. Similarly, in the presence of acetic acid, it was found that only about 1.9% of the chloroethyl groups of MBA had reacted to form saponifiable esters. The results with MBA were essentially similar.

The experiments with TBA were performed in the following manner: To 2.67 *mM* of TBA·HCl was added a solution containing 12 *mM* of the Na salt of the acid, 12 *mM* of $NaHCO_3$, and 2.7 cc. of *N* NaOH. The mixture (total volume 25 cc.) was shaken for 48 hours at 25°. In each case a precipitate appeared during the reaction. HCl was added and the CO_2 was removed *in vacuo*. Absolute alcohol (100 cc.) was added to give a clear solution and *N* NaOH was added to neutrality (phenolphthalein). Five cc. of *N* NaOH was then added and the solution was left at room temperature for 30 minutes. Back-titration with 0.1 *N* HCl gave the amount of ester saponified. The titration in the experiment with compound III was made difficult by the yellow color of the solution.

Isolation of triacyl derivatives of triethanolamine. Compound II. This substance separated as a solid when 2.67 *mM* of TBA·HCl was shaken with a solution containing 12 *mM* of the Na salt of (I), 12 *mM* of $NaHCO_3$, and 2.7 cc. of *N* NaOH. It was recrystallized by careful addition of water to an alcoholic solution of the substance; m.p. 179–180°.

Anal. Calc'd for $C_{39}H_{42}N_4O_9$: C, 65.9; H, 6.0; N, 7.9.
Found: C, 66.0; H, 6.1; N, 7.9.

Compound IV. When 2.67 *mM* of TBA·HCl was shaken with a solution containing 12 *mM* of the Na salt of III and 12 *mM* of $NaHCO_3$, there appeared a white precipitate mixed with a yellow oil. A creamy white solid was obtained by repeated recrystallization from aqueous alcohol. The air-dried material melted at 120–130°.

Anal. Calc'd for $C_{56}H_{63}N_7O_{12}\cdot 2H_2O$: C, 67.0; H, 5.7; N, 8.3.
Found: C, 66.6; H, 5.7; N, 8.5.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] VI. THE REACTIONS OF THE NITROGEN MUSTARD GASES WITH CHEMICAL COMPOUNDS OF BIOLOGICAL INTEREST

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In a previous paper of this series (1) it was shown that the nitrogen mustards react readily *in vitro* with a number of functional groups of protein constituents. It was concluded, therefore, that the nitrogen mustards would be likely to react with cellular proteins *in vivo*. The experiments to be reported in this communication were undertaken to ascertain whether chemical substances of biological interest other than proteins could also be expected to react with the nitrogen mustards. It has been found that the nitrogen mustards can combine with a large number of chemical compounds essential to the economy of the living cell. Among the more significant of such compounds, in addition to proteins, may be mentioned several vitamins (nicotinic acid or its amide, pyridoxine, and thiamin), and organic phosphate compounds.

The reaction of various substances with the nitrogen mustards as measured by their competition with alanine. Since it was desired to investigate a number of substances of widely different chemical structure, it was necessary to devise a simple general method to determine the reactivity of the nitrogen mustards towards a given substance. Certain of the observations reported in paper V of this series (1) form the basis for such a method. It will be recalled that the amino group of *l*-alanine reacts at *p*H 7.5–8 with the water-soluble transformation products formed when the nitrogen mustards are dissolved in an aqueous bicarbonate solution. When to the system containing alanine and a nitrogen mustard there is added a substance that also reacts with the nitrogen mustard, the amount of nitrogen mustard available for reaction with alanine is decreased, and consequently, the extent of the disappearance of amino nitrogen is reduced. Thus, the reaction between a nitrogen mustard and alanine may be used to determine whether the nitrogen mustard or its transformation products react with a given substance, and further to obtain an estimate of the rate of this reaction relative to the rate of the reaction of the nitrogen mustard with alanine. Obviously, alanine can be replaced as the reference compound by other substances that react with the nitrogen mustard at a suitable rate. This method, in principle, is similar

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to the competition method used by Ogston in his study of the chemical reactions of mustard gas (2).

The competition method was previously used to demonstrate that the imidazole group of acetyl-*dl*-histidine reacts with methyl-bis(β-chloroethyl)-amine (MBA). The reaction of several other substances with the three nitrogen mustards, MBA, ethyl-bis(β-chloroethyl)amine (EBA), and tris(β-chloroethyl)-amine (TBA), has also been studied by this method and the results are presented in Table I.

The data in Table I show that in the presence of *l*-proline, the extent of the reaction of any of the above nitrogen mustards with alanine is slightly more than half that of the value obtained in the absence of proline. This indicates that the three nitrogen mustards react with proline, EBA being the most, and TBA the least, reactive. Although the possibility of esterification at the carboxyl cannot be excluded, it seems most likely that the reaction involves the imino group of proline.

In view of the important role played by pyridine derivatives in biological systems, the strong competitive effect of pyridine, nicotinic acid, nicotinic acid amide, and pyridoxine is striking. The data in Table I indicate that all of the nitrogen mustards combine very readily with the pyridine nitrogen atom, MBA and EBA reacting with greater ease than TBA. The product of the reaction must be a quaternary pyridinium derivative. A strong competitive effect was also observed with 2-thiopyridine, while piperidine competes with alanine only to a slight extent.

It is of interest that MBA reacts with adenosine and that thiamin also competes effectively with alanine for reactions with both MBA and EBA. In the case of thiamin, the possibility should be borne in mind that the reaction may involve secondary products formed from the vitamin at *p*H 8.

Imidazole also competes effectively with the amino group of alanine in the reaction with each of the nitrogen mustards. MBA has the greatest tendency to combine with imidazole, EBA is slightly less reactive, and TBA is definitely the least reactive. The results given in Table I confirm the conclusion already reached (1) that the nitrogen mustards are capable of reacting with the imidazole nucleus of histidine. Moreover, the order of reactivity of the various nitrogen mustards towards imidazole itself, is the same as that postulated earlier for the reactivity of these agents towards the imidazole group of histidine (1).

In paper V of this series, experiments were presented on the reactivity of the nitrogen mustards towards carboxyl groups. The results of further experiments bearing on this point are presented in Table I. It will be noted that acetic acid exerts a negligible competitive effect upon the reaction of MBA or EBA with alanine, but does compete effectively in the case of TBA. Hence, TBA is definitely the most reactive of the nitrogen mustards towards the carboxyl group of acetic acid. A comparison of the data on MBA reveals, however, that the reactivity of a carboxyl group depends upon the structure of the carboxylic acid. Thus, hippuric acid is a slightly better competitor for MBA than is acetic acid, and carbobenzoxy-*l*-glutamic and carbobenzoxy-*l*-aspartic acids are both rather

effective competitors for MBA. In the latter cases it seems probable that it is the γ-carboxyl of glutamic acid and the β-carboxyl of aspartic acid which are involved. In contrast to the results with MBA, carbobenzoxy-*l*-glutamic acid does not compete at all with alanine for reaction with EBA. The results presented here, coupled with those given earlier (1), make it appear probable that

TABLE I

COMPETITIVE EFFECT OF VARIOUS SUBSTANCES ON THE REACTION OF THE NITROGEN MUSTARDS WITH THE AMINO GROUP OF ALANINE

Concentration of reactants per cc.: For MBA; 0.127 *mM* of MBA, 0.536 *mM* of *l*-alanine, 0.536 *mM* of competing substance, 0.526 *mM* of $NaHCO_3$; for EBA; 0.133 *mM* of EBA, 0.534 *mM* of *l*-alanine, 0.534 *mM* of competing substance, 0.534 *mM* of $NaHCO_3$; for TBA; 0.127 *mM* of TBA, 0.762 *mM* of *l*-alanine, 0.762 *mM* of competing substance, 0.526 *mM* of $NaHCO_3$.

Temperature, 25.4°; *p*H 7.5–8.0; reaction period, for MBA and EBA, 15 minutes shaking and 20 hours standing; for TBA, 20 hours shaking.

SUBSTANCE ADDED	NH_2-N DISAPPEARED PER *mM* OF			DECREASE IN ALANINE REACTING WITH					
				MBA		EBA		TBA	
	MBA, M.EQUIV.	EBA, M.EQUIV.	TBA, M.EQUIV.	M.EQUIV.	%	M.EQUIV.	%	M.EQUIV.	%
None	0.75	0.86	1.15						
l-Proline	.41	.44	0.68	0.34	45	0.42	49	0.47	40
Pyridine	.04	.15	.37	.71	95	.71	83	.78	70
Nicotinic acid[a]	.09	.17	.24	.66	88	.69	80	.91	80
Nicotinic acid amide	.04	.20	.36	.71	95	.66	77	.79	70
Pyridoxine	.30	.02		.45	60	.84	98		
2-Thiopyridine	.05	.05	.38	.70	93	.81	94	.75	65
Piperidine	.61			.14	19				
Adenosine[b,d]	.46			.29	39				
Thiamine[b]	.11	.29		.64	85	.57	66		
Imidazole	.12	.18	.63	.63	84	.68	79	.52	45
Hippuric acid[a]	.65			.10	13				
Acetic acid[a]	.72	.79	.85	.03	4	.07	8	.30	25
Carbobenzoxy - *l* - glutamic acid[a]	.44	.84		.31	41	.02	2		
Carbobenzoxy - *l* - aspartic acid[a]	.44			.31	41				
Carbobenzoxy - *dl* - methionine	.66			.09	12				
Thiodiglycol	.50	.54	.67	.25	33	.32	37	.48	40
Triethanolamine[c]	.50	.53	.80	.25	33	.33	38	.35	30
Methyldiethanolamine[c]	.32		.85	.43	57			.30	25
Ethyldiethanolamine[c]		.46				.40	47		

[a] Employed as sodium salts.

[b] The amino group of this substance does not react appreciably with nitrous acid in the 5-minute period required for complete deamination of alanine.

[c] The solutions of these substances were brought to *p*H 8 by the addition of HCl prior to the addition of $NaHCO_3$.

[d] Separate experiments have shown that when adenosine reacts with MBA, the amount of adenine amino nitrogen is decreased.

the order of reactivity of the nitrogen mustards towards carboxyl groups is TBA > MBA > EBA.

The competitive effect of a derivative of methionine was also studied. It will be noted that, in the reaction with MBA, carbobenzoxy-*dl*-methionine has the same competitive effect as hippuric acid. It cannot be decided on the basis of this experiment alone, therefore, whether the slight reaction of carbobenzoxy-*dl*-methionine with MBA involves the thioether sulfur or the free carboxyl group. The experiments with thiodiglycol [bis(β-hydroxyethyl)sulfide], however, prove definitely that all of the nitrogen mustards are capable of reacting with thioether sulfur, with the formation of a sulfonium salt [*cf.* also (3)].

TABLE II

THE REACTION OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) AND ETHYL-BIS(β-CHLOROETHYL)AMINE (EBA) WITH PHOSPHATE

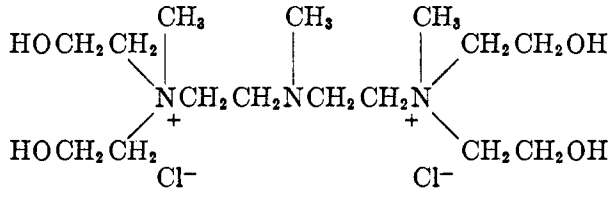
Concentration of reactants per cc.: 0.10 *mM* of MBA·HCl or EBA·HCl; 0.40 *mM* of Na_2HPO_4; 0.32 *mM* of $NaHCO_3$.

Temperature 25°; *p*H 7.5.

TIME, HOURS	INORGANIC PHOSPHATE[a] REACTED PER *mM* OF	
	MBA, *mM*	EBA, *mM*
3	0.7	1.0
6	1.0	1.3
24	1.3	1.4
48	1.3	1.5

[a] Determined by the Fiske-SubbaRow method.

The fact that the nitrogen mustards are capable of reacting with tertiary amines is indicated by the results obtained with triethanolamine, methyldiethanolamine, and ethyldiethanolamine. The reactivity of the various nitrogen mustards towards these bases seems to be about the same, with the exception of MBA which reacts readily with methyldiethanolamine. The product of this reaction has been isolated, and has the formula (I) given below.



(I)

Since at one time it was suspected that this product might be formed during the reaction of MBA with water, the toxicity of compound I was investigated. On intraperitoneal injection into mice, compound I was found to possess an LD_{50} of about 1 g./kg.

In addition to the compounds listed in Table I, it should be mentioned that, at *p*H 7.5, MBA and EBA react with inorganic phosphate (TBA was not investigated). In Table II data are presented on the rate of the disappearance of

inorganic phosphate when MBA or EBA are treated with aqueous Na_2HPO_4. Gilman, Goodman, and Philips (4) have reported that MBA and EBA react readily with phosphate and, under their experimental conditions, consume about one equivalent of phosphate per mole of nitrogen mustard.

Additional evidence for the reaction of MBA with phosphate-containing compounds has been obtained by use of the alanine competition method. Secondary sodium phosphate, sodium pyrophosphate, sodium glycerophosphate, several hexose phosphates, and two nucleotides (barium salts of cytidine diphosphate and adenosine triphosphate) were allowed to compete with the α-amino group of

TABLE III

THE COMPETITIVE EFFECT OF PHOSPHATES AND OF SUBSTANCES RELATED TO NUCLEIC ACID ON THE REACTION OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) WITH THE AMINO GROUP OF ALANINE

Concentration of reactants per cc.: 0.133 *mM* of MBA·HCl; 0.534 *mM* of *l*-alanine; 0.534 *mM* of competing substance; 0.526 *mM* of $NaHCO_3$.
*p*H 7.5–8.0. Reaction period, 20 hours at 25°.

SUBSTANCE	NH_2-N DISAPPEARED PER *mM* MBA, M.EQUIV.	DECREASE IN ALANINE REACTING WITH MBA	
		M.EQUIV.	%
None	0.77		
Na_2HPO_4	.41	0.36	47
$Na_4P_2O_7$	.46	.31	40
Na glycerophosphate	.53	.24	30
Fructose 1-phosphate Ba	.20	.57	74
Fructose 6-phosphate Ba	.04	.73	95
Glucose 3-phosphate	.58	.19	25
Glucose 6-phosphate	.20	.57	74
Cytidine diphosphate Ba	.31	.46	60
Adenosine triphosphate Ba	.31	.46	60
Theophylline glucoside	.79	−.02	0
Desoxyribose	.74	.03	4

alanine for reaction with MBA. The results are presented in Table III. It will be noted that, in addition to sodium phosphate and pyrophosphate, the organic phosphate compounds also show evidence of reaction with MBA. Ogston (2) has shown that mustard gas reacts with pyrophosphate and glycerophosphate.

It is of interest that the nucleoside, theophylline glucoside, which does not contain a phosphate group does not appear to react with MBA; neither does desoxyribose, which is a constituent of certain nucleic acids. It may be concluded, therefore, that nucleic acids are capable of reaction with the nitrogen mustards through their phosphate groups as well as through the 6-amino group of the adenine residue (*cf.* Table I, footnote *d*).

The extensive reaction of MBA with hexose phosphates suggests the possibility that the nitrogen mustards may influence the course of carbohydrate metabolism by reacting not only with some of the enzymes involved [*cf.* references 10–18 in the preceding paper of this series (1)], but with some of the substrates as well.

Organic phosphates such as triose and hexose phosphates, adenylic acid, adenosine triphosphate, thiamin pyrophosphate, creatine phosphate, etc., are of importance in the maintenance of normal metabolic processes. Moreover, nucleic acids, phospholipids, and certain proteins are esters of phosphoric acid. The fact that MBA reacts with such organic phosphates is, therefore, of interest for the problem of the physiological action of the nitrogen mustards.

The use of thiosulfate in the study of the reaction of the MBA system with various substances. In addition to the alanine competition method described above, a second method for determining whether a given substance reacts with a nitrogen mustard has been employed. The method has only been worked out and applied in the case of MBA, although it undoubtedly is applicable to other nitrogen mustards as well.

TABLE IV

THE DISAPPEARANCE OF THE ETHYLENIMONIUM FORMS OF METHYL-BIS(β-CHLOROETHYL)-AMINE (MBA) IN THE PRESENCE OF VARIOUS SUBSTANCES

Concentration of reactants per cc.: 0.127 *mM* of MBA·HCl; 0.536 *mM* of added substance; 0.526 *mM* of $NaHCO_3$; 0.127 *mM* of NaOH.

*p*H, 7.5–8.0. Temperature, 25.4°.

ADDED SUBSTANCE	10-MINUTE THIOSULFATE TITER PER CC. REACTION MIXTURE AFTER		
	40 min., M.EQUIV.	120 min., M.EQUIV.	240 min., M.EQUIV.
None	0.126	0.098	0.074
l-Alanine	.100	.048	.030
l-Proline	.080	.032	.010
Hexamethylene tetramine	.000	.000	
Pyridine	.004	.000	
Nicotinic acid	.002	.000	
Imidazole	.014	.000	
Histidine	.036	.006	
Sodium acetate	.118	.078	.056
Ammonium chloride	.114	.076	.054

As has been shown earlier (5), when MBA reacts with an aqueous bicarbonate solution, there occurs a progressive decrease in the concentration of ethylenimonium ions in the solution. The approximate ethylenimonium content is determined after various time intervals by measuring the thiosulfate consumption of aliquots of the reaction mixture. When alanine is also present in the reaction mixture, the rate of the disappearance of the ethylenimonium ion is accelerated. Thus, by measuring the rate at which the ethylenimonium ion disappears in the presence of a given substance, such as alanine, it is possible to determine whether the substance reacts with the MBA system. Several substances have been tested in this manner. The results are presented in Table IV.

Like alanine, proline produces an accelerated disappearance of the ethylenimonium ion. The effect of proline is even somewhat greater than that observed with alanine. This result, when combined with the finding in Table I, may be taken to indicate that proline reacts with the ethylenimonium form of

MBA. The presence of pyridine, nicotinic acid, imidazole, and histidine results in a nearly complete disappearance of the ethylenimonium ion in 40 minutes. These findings are in accord with those reported in Table I, and indicate the high reactivity of these compounds towards MBA. Sodium acetate and ammonium chloride, on the other hand, cause but a slight acceleration in the rate of disappearance of the ethylenimonium ion.

As will be noted from Table IV, hexamethylene tetramine causes a complete disappearance of the ethylenimonium form in 40 minutes. It became of interest to determine, therefore, whether hexamethylene tetramine was more reactive than thiosulfate towards the nitrogen mustards. By means of a competition experiment using thiosulfate as the reference substance, it was found that hexamethylene tetramine is an effective competitor in the reaction of thiosulfate with MBA and EBA. The extent of the competition indicated, however, that thiosulfate was the more reactive of the substances. It should be mentioned that the reaction of hexamethylene tetramine with MBA has been investigated in detail by Gurin and co-workers (6).

The thiosulfate method has also been applied to the study of the reactions of 1-methyl-1-(β-hydroxyethyl)ethylenimonium picrylsulfonate (II). This compound reacts completely with thiosulfate in 10 minutes, one equivalent of thiosulfate being consumed (5). Since none of the reaction products of II consume thiosulfate, the 10-minute thiosulfate titer is a direct measure of the concentration of II in the solution. Hence, if a given substance has reacted with II, the thiosulfate titer of the reaction mixture must differ from that of a solution of II to which the substance has not been added.

By the use of this method, II was found to react rapidly in bicarbonate solution with *l*-proline, nicotinic acid, imidazole, hexamethylene tetramine, methyldiethanolamine, and thiodiglycol (Table V). No appreciable reaction with sodium acetate was observed.

Periodides of MBA and TBA. In the course of the investigations described in this and preceding papers, it was observed that the nitrogen mustards form insoluble periodides. It has long been known that both organic and inorganic halides combine with one or more molecules of free halogen to give perhalides, of which KI_3, $[(CH_3)_4N]I_3$, $[(CH_3)_4N]ClI_4$, and $[R_3NH]I_3$ are examples. With some tertiary amines, iodine forms products of the formula $[R_3NI]I$ (7, 8). Quaternary ammonium halides form perhalides of the type $R_4N \cdot X_n$ in which X represents halogen and n may be 3, 5, 7, 9 or more (9). Likewise, the formation from mustard gas of perhalides of the type $[(ClCH_2CH_2)_2S]X_n$ in which n may be 2, 4, or 6 has been noted (10).

The formation of a periodide of MBA and TBA was demonstrated by adding a solution of the amine hydrochloride to an excess of 0.1 *N* iodine-potassium iodide solution. A purple crystalline solid separated which was removed by filtration. Titration of the filtrate with sodium thiosulfate showed that about 2 atoms of iodine had been removed per mole of nitrogen mustard hydrochloride. "Aged" solutions of MBA produced similar crystalline precipitates with iodine-potassium iodide solution, but consumed somewhat less iodine.

TABLE V

THE REACTION OF 1-METHYL-1-(β-HYDROXYETHYL)ETHYLENIMONIUM PICRYLSULFONATE (II) WITH VARIOUS COMPOUNDS

Concentration of reactants per cc.: 0.02 *mM* of II; 0.08 *mM* of added substance; 0.08 *mM* of $NaHCO_3$.

Temperature 25°; *p*H 8.

ADDED SUBSTANCE	II REACTED AFTER			II REACTED WITH ADDED SUBSTANCE		
	20 min., %	60 min., %	180 min., %	20 min., %	60 min., %	180 min., %
None	3	17	32			
l-Proline	61	66	87	58	49	55
Nicotinic acid[a]	55	75	100	52	58	68
Imidazole	35	52	84	32	35	52
Hexamethylene tetramine	100	100		97		
Methyldiethanolamine[b]	35	60	93	32	43	61
Thiodiglycol	32	38	64	29	21	32
Sodium acetate	9	16	35	6	−1	3

[a] Employed as the sodium salt.

[b] Brought to *p*H 7 with HCl before reaction.

TABLE VI

THE LIMIT OF PRECIPITATION OF NITROGEN MUSTARDS AND RELATED SUBSTANCES BY I_2-KI

COMPOUND	CONCENTRATION OF INITIAL SOLUTION, P.P.M.[a]	LIMIT OF PRECIPITATION AFTER AGING PERIOD			
		30 min., P.P.M.[a]	1 hr., P.P.M.[a]	20 hrs., P.P.M.[a]	40 hrs., P.P.M.[a]
MBA·HCl	100			12	12
MBA	100			25	25
	10,000	12			12
MBA·HCl + 6 equiv. $NaHCO_3$	100	6	6	25	50
1 - Methyl - 1 - (β-chloroethyl)ethylenimonium picrylsulfonate	100	12		12	
Methyl - β - chloroethyl - β - hydroxyethylamine·HCl	400[b]	100		100	
Methyl - β - chloroethyl - β - hydroxyethylamine picrylsulfonate	400[b]	100		200	
Methyl - β - chloroethyl - β - hydroxyethylamine·HCl + 6 equiv. $NaHCO_3$	400[b]	100		100	
N,N′ - Dimethyl - N,N′ - bis(β-chloroethyl)piperazinium dichloride	100[b]	6		6	
N,N′ - Dimethyl - N,N′ - bis(β-chloroethyl)piperazinium dipicrylsulfonate	100[b]	6		6	
Methyldiethanolamine	10,000	5,000		5,000	
TBA·HCl	1,000			120	120
TBA·HCl + 6 equiv. $NaHCO_3$	1,000	16	120	500	1,000
Triethanolamine	20,000	20,000		20,000	
Tetraethanolammonium hydroxide	5,000	2,500			

[a] Parts per million.

[b] Expressed as equivalent concentration of MBA.

It seemed of interest to determine whether the formation of insoluble periodides could be used for the detection of the nitrogen mustards and their transformation products. To determine the lowest concentration at which iodine-potassium iodide solution could be used to detect the nitrogen mustards, their transformation products or closely related compounds, an iodine solution was added to portions of the progressively diluted solution to be tested. The greatest dilution at which a precipitate was formed was determined. The results listed in Table VI were determined as follows: To 5 cc. of the solution to be tested, 0.1 g. of sodium bicarbonate and 1.0 cc. of 1 *N* iodine-potassium iodide solution were added. The highest dilution at which a turbidity was produced was determined by comparison with a control test tube. This comparison was best made within about 10 minutes after adding the reagents by observing the tubes while they were strongly illuminated from the side.

EXPERIMENTAL

The reaction of various substances with the nitrogen mustards as measured by their competition with alanine. The requisite amount of nitrogen mustard·HCl was added to the solution containing $NaHCO_3$, alanine, and the competing substance as well as the calculated quantity of NaOH to liberate the nitrogen mustard free base. The reaction mixture was shaken at 25.4° for 15 minutes and then left for 20 hours at 25.4°. In the case of TBA the shaking was continued for 20 hours. One-cc. aliquots were withdrawn, diluted to 10 cc., and amino nitrogen determinations were carried out on 1-cc. samples of the diluted solution (5 minutes' shaking in the Van Slyke apparatus). The *p*H of the undiluted reaction mixture was measured by means of the glass electrode.

The reaction of MBA with methyldiethanolamine. A solution (10 cc.) of MBA·HCl containing 8 *mM* of MBA was shaken with 4 cc. of methyldiethanolamine (34 *mM*) for one hour. The clear solution was left at room temperature for 20 hours and then concentrated under reduced pressure. The syrup which resulted was dissolved in 20 cc. of absolute alcohol and 100 cc. of acetone was added. The oil which separated crystallized on scratching and chilling. The substance was recrystallized twice from absolute ethanol; yield 2.7 g. (84%); m.p. 93–95°.

Anal. Calc'd for $C_{15}H_{37}Cl_2N_3O_4$: C, 45.6; H, 9.5; N, 10.6; Cl, 18.0.
Found: C, 45.7; H, 9.6; N, 10.4; Cl, 17.9.

The use of thiosulfate in the study of the reaction of the MBA system with various substances. The requisite amount of MBA·HCl was added to the solution of $NaHCO_3$ to which had been added the test substance and the calculated quantity of NaOH to liberate the MBA base. The reaction mixture was shaken for 10–15 minutes at 25.4° until a clear solution resulted and kept at this temperature during the experiment. Five-cc. aliquots were withdrawn after 40 minutes, 2 hours, and 4 hours, and added to 10 cc. of 0.1 *N* thiosulfate. After exactly 10 minutes, the unreacted thiosulfate was titrated with 0.1 *N* iodine.

The experiments with compound II were performed in the same manner except that no NaOH was added.

Competition between thiosulfate and hexamethylene tetramine (HMT) for reaction with the nitrogen mustards. MBA·HCl (3.2 *mM*) plus 3.2 *mM* of NaOH was treated with 12.8 *mM* of sodium thiosulfate in the presence of bicarbonate (*p*H 8). After 2 hours at 25.4°, the disappearance of thiosulfate had ceased; 6.29 *mM* of thiosulfate had reacted (98% of theory for the formation of the "Bunte salt"). When 3.2 *mM* of MBA was treated with a solution containing 12.8 *mM* of thiosulfate and 12.8 *mM* of HMT at *p*H 8, at the end of the reaction (2 hours) only 4.27 *mM* of thiosulfate had reacted (67%).

This result indicates that although HMT shows great reactivity with MBA, it is not as reactive as thiosulfate.

When 1.6 *mM* of EBA·HCl (plus 1.6 *mM* of NaOH) was allowed to react with 5 *mM* of $Na_2S_2O_3$ in the presence of bicarbonate, the amount of thiosulfate that had reacted after 2 hours at 25° was determined by iodometric titration and was found to be 3.2 *mM* (100% of the theory for the formation of the "Bunte salt"). However, when 1.6 *mM* of EBA was treated with 5 *mM* of HMT, only 2.24 *mM* of thiosulfate had reacted after 2 hours (70%).

This result shows that, as in the case of MBA, EBA reacts readily with HMT, but more readily with thiosulfate. It is of interest that, although the reaction of EBA with thiosulfate is more rapid than is that of MBA, the competitive effect of HMT is nearly the same for EBA and for MBA (30 and 33% respectively).

Periodides of MBA and TBA. The reaction mixtures were made up to contain per cc.: 0.02 *mM* of nitrogen mustard or nitrogen mustard hydrochloride and 0.06 m.equiv. iodine in potassium iodide. In each case, the mixture was shaken for 6 hours, filtered, and the purple solid washed with water. The unused iodine in the filtrate was titrated with thiosulfate.

The MBA hydrochloride (481 mg., 2.5 *mM*) consumed 5.07 m.equiv. (0.643 g.) of iodine and yielded 0.994 g. of a dark purple solid. The crude product melted at 94–98°.

The TBA hydrochloride (482 mg., 2.0 *mM*) consumed 5.1 m.equiv. (0.652 g.) of iodine and yielded 0.968 g. of a dark purple solid. The crude product melted at 74–78°.

A 2% solution of 2.5 *mM* MBA was aged for 3 hours. The I_2-KI solution was then added. After a further 6 hours, 4.48 m.equiv. of iodine was consumed and 0.834 g. of purple solid was obtained. This crude product formed a dark melt at 150–160°. Another sample of the 2% MBA solution was aged for 6 hours. After the addition of I_2-KI and shaking for 6 hours, it consumed 3.89 m.equiv. of iodine and 0.659 g. of purple solid was obtained. This crude product formed a dark melt at 120–130°.

These melting points of the crude periodides are mentioned only to indicate that the periodides obtained from the fresh solutions and from the aged solutions were different.

The authors wish to express their indebtedness to the late Dr. Max Bergmann for the constant advice and encouragement which he gave in the course of this research. Thanks are due also to Miss Rosalind E. Joseph for assistance in the conduct of these experiments and to Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

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[a] Unpublished data obtained in Great Britain.
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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] VII. MONOSUBSTITUTION PRODUCTS OF ETHYL-BIS(β-CHLOROETHYL)AMINE AND METHYL-BIS (β-CHLOROETHYL)AMINE

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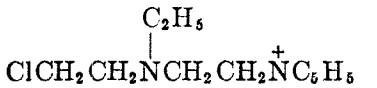
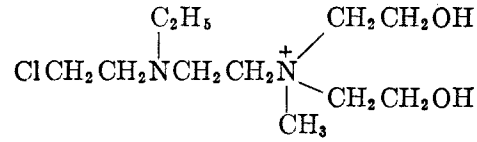
When one of the chloroethyl groups of either ethyl-bis(β-chloroethyl)amine (EBA) or methyl-bis(β-chloroethyl)amine (MBA) reacts with a tertiary base or sulfide, it is to be expected that the chemical nature of the group which is introduced into the nitrogen mustard will influence the reactivity of the second chloroethyl group. In order to secure information on this question, the preparation of monosubstitution products of the nitrogen mustards was undertaken.

The isolation of monosubstitution products of EBA and MBA containing one chloroethyl group. When equimolar amounts of 1-ethyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate (1) and pyridine are allowed to react in acetone solution (to minimize hydrolysis), the monopyridinium derivative of EBA [ethyl-β-chloroethyl-β-pyridiniumethylamine (I)] is formed in good yield. The imonium picrylsulfonate also reacts with methyldiethanolamine under the same conditions to give N-ethyl-N-β-chloroethyl-N-β-[N′-methyl-N′-bis(β-hydroxyethyl)ammonium] ethylamine (II).



(I)



(II)

In the MBA series, 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate (2) has been found to undergo a similar type of condensation with pyridine to form methyl-β-chloroethyl-β-pyridiniumethylamine (III). With nicotinic acid the analogous 3-carboxypyridinium derivative (IV) is formed. With thiodiglycol N-methyl-N-β-chloroethyl-N-β-[N′-bis(β - hydroxyethyl)sulfonium] ethylamine (V) is obtained. The imonium compound also reacts with methyldiethanolamine to form N-methyl-N-β-chloroethyl-N-β-[N′-methyl-N′-bis(β-hydroxyethyl)ammonium]ethylamine (VI), and with hexamethylene tetramine to yield the hexamethylene tetraminium derivative (VII). Gurin and co-workers

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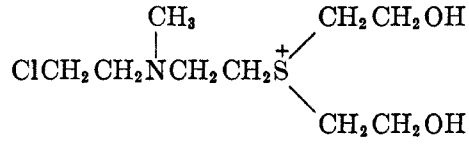
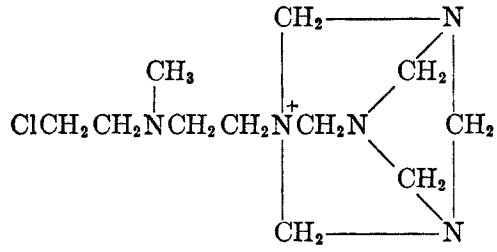
(3) have reported the isolation of compound VII as a chloride. In the present work, all the monosubstitution products of EBA and MBA were isolated, in excellent yields, as dipicrylsulfonates.



(V)

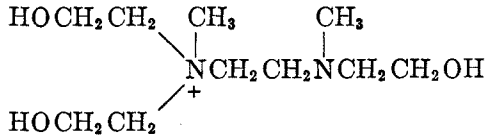


(VII)

The properties of monosubstitution products of EBA and MBA. The reaction of the compounds I–VII with thiosulfate was studied by following the rate of disappearance of thiosulfate from the reaction mixtures. The results are given in Table I together with comparable data (1, 2) on the reaction with thiosulfate of the chlorohydrins (ethyl-β-chloroethyl-β-hydroxyethylamine and methyl-β-chloroethyl-β-hydroxyethylamine) derived from EBA and MBA respectively. It will be noted that the monosubstitution products react with thiosulfate at a much slower rate than do the corresponding chlorohydrins. On the other hand, the speed of the reaction of each EBA derivative is considerably greater than that found for the corresponding compound of the MBA series. The parent mustards, EBA and MBA, are also known to show this difference in the rate of their reaction with thiosulfate (1, 2).

When a monosubstitution product of MBA is subjected to hydrolysis at *p*H 8, it is found that the liberation of Cl^- from the chloroethyl group is slower than in the case of the chlorohydrin of MBA. Thus, in the hydrolysis of the nicotinic acid derivative about one hour is required for the release of the chlorine as Cl^-, whereas less than 20 minutes are necessary for a similar liberation of Cl^- from the chlorohydrin of MBA (2).

When the dipicrylsulfonate of VI is hydrolyzed in the presence of bicarbonate, nearly one equivalent of HCl is liberated in 20 hours. From the hydrolysate, compound (VIII) was isolated as a dipicrylsulfonate.



(VIII)

Compound (VIII) was previously isolated as a product of the hydrolysis of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate in bicarbonate solution (2).

TABLE I

THE REACTION OF MONOSUBSTITUTION PRODUCTS OF ETHYL-BIS(β-CHLOROETHYL)AMINE (EBA) AND METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) WITH THIOSULFATE

Concentration of reactants per cc.: 0.01 *mM* of EBA or MBA derivatives (employed as the dipicrylsulfonate); 0.025 *mM* of $Na_2S_2O_3$; 0.04 *mM* of $NaHCO_3$.
Temperature 25°.

PARENT NITROGEN MUSTARD	SUBSTITUENT	$Na_2S_2O_3$ CONSUMED PER *mM* OF DERIVATIVE AFTER, *mM*			
		10 min.	20 min.	60 min.	120 min.
EBA	Hydroxyl (chlorohydrin)	0.93	0.96	0.98	0.98
	Methyldiethanolamine	.47	.72	.92	.98
	Pyridine	.41	.62	.89	.97
MBA	Hydroxyl (chlorohydrin)		.81	.97	.97
	Pyridine		.20	.50	.72
	Nicotinic acid		.22	.40	.62
	Methyldiethanolamine		.24	.46	.71
	Hexamethylenetetramine[a]		.08	.18	.34
	Thiodiglycol		.17	.32	.51

[a] The titrations in this instance were carried out at 0° to retard fading of the endpoint.

TABLE II

THE TOXICITY TO MICE OF MONOSUBSTITUTION PRODUCTS OF ETHYL-BIS(β-CHLOROETHYL)-AMINE (EBA) AND METHYL-BIS(β-CHLOROETHYL)AMINE (MBA)

The chlorohydrins were injected as their hydrochlorides, and the monosubstitution products were injected as their chloride hydrochlorides.

COMPOUND	LD_{50} (APPROX.)[a]
	mg./kg.
EBA chlorohydrin	10
MBA chlorohydrin	30
II	200
VI	350
I	75
III	100

[a] Determined by intraperitoneal injection of a graded series of doses into sets of three mice.

The toxicity of monosubstitution products of EBA and MBA. For the toxicity studies, the dipicrylsulfonates of the EBA and MBA derivatives were converted into the corresponding chloride hydrochlorides by treatment with the dichloro cyclic dimer of MBA. This method of splitting picrylsulfonates has been described earlier (2). The approximate LD_{50} obtained for each derivative upon intraperitoneal injection into mice is given in Table II. It will be noted that the methyldiethanolammonium derivatives II and VI and the pyridinium derivatives I and III were less toxic than the corresponding chlorohydrins. Furthermore,

each compound of the EBA series is more toxic than its MBA analog. These data, coupled with the results given in Table I, suggest that there is a correlation between the chemical reactivity of the nitrogen mustard derivatives and their toxicity, the more reactive compounds being the more toxic.

EXPERIMENTAL

Ethyl-β-chloroethyl-β-pyridiniumethylamine (I). To 1.70 g. (4.0 *mM*) of 1-ethyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate in 100 cc. of acetone was added 316 mg. (4.0 *mM*) of pyridine in acetone solution. The mixture was kept for one-half hour at room temperature, and then the acetone was evaporated off. The residue was taken up in 50 cc. of acetone and filtered from a slight amount of undissolved material. After addition of an acetone solution of 1.46 g. (4.0 *mM*) of picrylsulfonic acid, the dipicrylsulfonate of I crystallized at once; yield 2.85 g. (91%); m.p. 202–205° with decomposition.

Anal. Calc'd for $C_{11}H_{19}ClN_2 \cdot 2C_6H_2N_3O_9S$: C, 34.6; H, 2.9; N, 14.0; Cl, 4.4.
Found: C, 34.6; H, 3.05; N, 14.0; Cl, 4.4.

N-Ethyl-N-β-chloroethyl-N-β-[N'-methyl-N'-bis(β-hydroxyethyl)ammonium] ethylamine (II). To 1.7 g. (4.0 *mM*) of 1-ethyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate in 100 cc. of acetone was added 475 mg. (4.0 *mM*) of methyldiethanolamine dissolved in 25 cc. of acetone. The remainder of the procedure was the same as that for compound I; yield 2.9 g. (87%); m.p. 191–192°.

Anal. Calc'd for $C_{11}H_{27}ClN_2O_2 \cdot 2C_6H_2N_3O_9S$: C, 32.9; H, 3.7; N, 13.35; Cl, 4.2.
Found: C, 33.2; H, 3.9; N, 13.2; Cl, 4.05.

Methyl-β-chloroethyl-β-pyridiniumethylamine (III). A solution of 413 mg. (1 *mM*) of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate in 100 cc. of acetone was treated with 80 mg. (1 *mM*) of pyridine dissolved in 5 cc. of acetone. After standing one hour at room temperature, the acetone was removed under reduced pressure. The residue was dissolved in 25 cc. of acetone and treated with 293 mg. (1 *mM*) of anhydrous picrylsulfonic acid dissolved in 10 cc. of acetone. Tiny prismatic crystals appeared in a few minutes. After cooling at 0°, the crystals were filtered off and dried *in vacuo* over P_2O_5; yield 580 mg. (74%). The substance was difficultly soluble in acetone but could be recrystallized from a large volume of this solvent by addition of petroleum ether.

Anal. Calc'd for $C_{10}H_{17}ClN_2 \cdot 2C_6H_2N_3O_9S$: C, 33.7; H, 2.7; N, 14.3; Cl, 4.5.
Found: C, 33.5; H, 3.0; N, 14.2; Cl, 4.4.

Methyl-β-chloroethyl-β-(3-carboxy)pyridiniumethylamine (IV). To a solution of 2.672 g. (6.47 *mM*) of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate in 500 cc. of acetone was added 796 mg. (6.47 *mM*) of nicotinic acid dissolved in 400 cc. of acetone. The reaction mixture was concentrated under reduced pressure to about 150 cc., and after standing for an hour at room temperature, the remainder of the acetone was removed *in vacuo*. The residue was dissolved in 100 cc. of acetone and then 6.47 *mM* of picrylsulfonic acid dissolved in a little acetone was added. To this solution was added 150 cc. of petroleum ether. The dipicrylsulfonate of compound IV precipitated as an oil which crystallized upon scratching and cooling. The product was dried *in vacuo* over P_2O_5; yield 4.8 g. (90%). For analysis, the compound was recrystallized from acetone-ether solution; m.p. 163–165°.

Anal. Calc'd for $C_{11}H_{17}ClN_2O_2 \cdot 2C_6H_2N_3O_9S$: C, 33.3; H, 2.6; N, 13.5; Cl, 4.3.
Found: C, 33.4; H, 2.7; N, 13.7; Cl, 4.5.

N-Methyl-N-β-chloroethyl-N-β-[N'-bis(β-hydroxyethyl)sulfonium]ethylamine (V). A mixture of 1.652 g. (4.0 *mM*) of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate and 488 mg. (4.0 *mM*) of thiodiglycol was dissolved in 350 cc. of acetone and the solution was allowed to stand at room temperature for one hour. The acetone was removed under reduced pressure. The residual oil was taken up in 50 cc. of acetone and filtered from a small amount of crystalline material (0.5 g.). To the filtrate was added 4.0 *mM* of picrylsulfonic acid dissolved in a little acetone. The dipicrylsulfonate of V crystallized out of the reaction mixture upon cooling at 4° overnight. It was filtered off and dried *in vacuo* over P_2O_5; yield 86%; m.p. 158–160°.

Anal. Calc'd for $C_9H_{22}ClNO_2S \cdot 2C_6H_2N_3O_9S$: C, 30.5; H, 3.2; N, 11.8; Cl, 4.3.
Found: C, 30.7; H, 3.4; N, 11.7; Cl, 4.1.

N-Methyl-N-β-chloroethyl-N-β-[N'-methyl-N'-bis(β-hydroxyethyl) ammonium] ethylamine (VI). Methyldiethanolamine (0.565 g., 4.75 *mM*) was added to 2.065 g. (5.0 *mM*) of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate dissolved in 400 cc. of acetone. The solvent was removed under reduced pressure. The residual oil was dissolved in 60 cc. of acetone and an acetone solution of 5.0 *mM* of picrylsulfonic acid was added. The dipicrylsulfonate of VI rapidly crystallized out of the reaction mixture in pure form. After cooling for an hour at 4°, the compound was filtered off and dried *in vacuo* over P_2O_5; yield 3.0 g. (77%); m.p. 213–215°.

Anal. Calc'd for $C_{10}H_{25}ClN_2O_2 \cdot 2C_6H_2N_3O_9S$: C, 32.0; H, 3.5; N, 13.6; Cl, 4.3.
Found: C, 32.1; H, 3.7; N, 13.6; Cl, 4.4.

Methyl-β-chloroethyl-β-(hexamethylenetetraminium) ethylamine (VII). A solution of 2.065 g. (5.0 *mM*) of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsulfonate in 400 cc. of acetone was treated with 701 mg. (5.0 *mM*) of hexamethylenetetramine dissolved in 250 cc. of acetone. The solvent was removed *in vacuo*. The residue was dissolved in 100 cc. of acetone and treated with 5.0 *mM* of picrylsulfonic acid dissolved in a little acetone. After standing overnight at 4°, the crystalline dipicrylsulfonate of VII was filtered off and dried over P_2O_5 *in vacuo*; yield 3.65 g. (87%); m.p. 130–133° (decomp.).

Anal. Calc'd for $C_{11}H_{24}ClN_5 \cdot 2C_6H_2N_3O_9S$: C, 32.65; H, 3.3; N, 18.2; Cl, 4.2.
Found: C, 32.4; H, 3.4; N, 17.9; Cl, 3.9.

The hydrolysis of N-methyl-N-β-chloroethyl-N-β-[N'-methyl-N'-bis(β-hydroxyethyl)ammonium]ethylamine dipicrylsulfonate. The dipicrylsulfonate of VI (865 mg., 1.05 *mM*) was added to 70 cc. of 0.08 *N* $NaHCO_3$. The mixture was stirred at room temperature for 20 hours. Ten-cc. aliquots of the reaction mixture were withdrawn for Cl^- and H^+ determinations. Found, Cl^-, 0.015 *mM* per cc. and H^+, 0.014 *mM* per cc. Theory, Cl^-, 0.015 *mM* per cc.; H^+, 0.015 *mM* per cc.

The remainder of the reaction mixture was cooled, acidified to Congo Red and filtered. The initial precipitate (0.35 g.) was separated from a small amount of high-melting substance (m.p. 250°, possibly a cyclic dimer) by extraction with hot water. The dipicrylsulfonate of compound VIII was obtained on cooling the filtrate; m.p. 196–200° with decomposition. It was again recrystallized from water and dried *in vacuo* over P_2O_5 at room temperature. When dried at 115°, the compound lost about one-half mole of water.

Anal. Calc'd for $C_{10}H_{26}N_2O_3 \cdot 2C_6H_2N_3O_9S \cdot \frac{1}{2}H_2O$: C, 32.4; H, 3.8; H_2O, 1.2.
Found: C, 32.7; H, 3.9; H_2O, 1.5.

A further quantity of VIII was obtained when the mother liquor was concentrated to about 25 cc., cooled and filtered. The salt was dried *in vacuo* over P_2O_5; yield 0.30 g.; m.p. 202–205° with decomposition. For analysis it was recrystallized from water; m.p. 204–206°.

Anal. Calc'd for $C_{10}H_{26}N_2O_3 \cdot 2C_6H_2N_3O_9S \cdot \frac{1}{2}H_2O$: C, 32.4; H, 3.8; N, 13.7; H_2O, 1.2.
Found: C, 32.2; H, 4.0; N, 13.7; H_2O, 1.5.

The two samples of the salt described above, on admixture, melted at 201–205°.

The authors wish to acknowledge with thanks the helpful cooperation of Miss Rosalind E. Joseph, who assisted in the conduct of these experiments, and of Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF THE NITROGEN MUSTARD GASES.[1] VIII. THE OXIDATION OF THE NITROGEN MUSTARD GASES BY PERACIDS

MARK A. STAHMANN[2] AND MAX BERGMANN[3]

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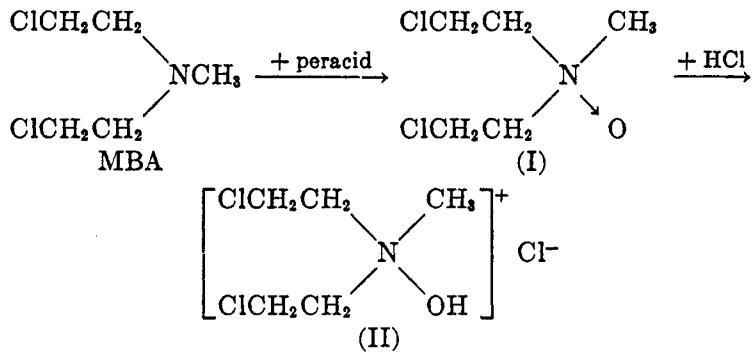
The rate and extent of oxidation by peracids. It has been observed that the nitrogen mustards are oxidized to the corresponding N-oxides by peracids in aqueous solution. This oxidation is rapid in weakly alkaline solution but is slow in acid solution. At *p*H 7.7, each of the three nitrogen mustards [methyl-bis(β-chloroethyl)amine (MBA), ethyl-bis(β-chloroethyl)amine (EBA), tris(β-chloroethyl)amine (TBA)], as well as methyldiethanolamine, consumes about one equivalent of peracetic acid within 15 minutes. At *p*H 3.2, the peracetic acid consumption was 10% or less of the amount found at *p*H 7.7. The slower oxidation of the nitrogen mustards in acid solution might be due to ammonium salt formation.

Peracids other than peracetic acid also oxidize the nitrogen mustards. When a bicarbonate buffered solution of MBA was shaken with a chloroform solution of perbenzoic acid or was treated with an aqueous solution of monoperphthalic acid, within 15 minutes 1.42 and 0.85 equivalents of peracid respectively were consumed.

The preparation of the N-oxides of the nitrogen mustards. The principal product of the peracid oxidation of each of the nitrogen mustards, the N-oxide, has been isolated as its hydrochloride from a bicarbonate buffered reaction mixture containing excess peracetic acid. The oxidation of MBA to methyl-bis(β-chloroethyl)amine oxide (I) and the formation of its hydrochloride (II) may be represented by the following equation:



[1] This work was done in whole under Contract No. OEMsr-313 between The Rockefeller Institute for Medical Research and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein. The experiments were performed during the period June 1942–January 1944.

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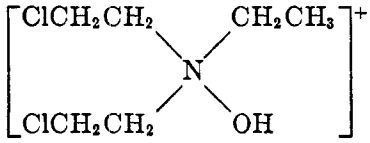
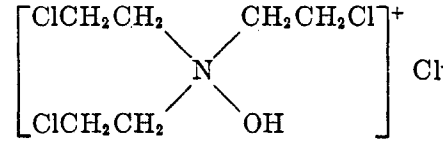
[3] Died, November 7, 1944.

Ethyl-bis(β-chloroethyl)amine oxide hydrochloride (III) and tris(β-chloroethyl)amine oxide hydrochloride (IV) have also been prepared from EBA and TBA respectively by a procedure similar to that used for the preparation of II.



(III)



(IV)

In all three cases, the amine oxide was isolated in a yield of 78–85% of theory. This high yield indicates that oxidation of the nitrogen atom proceeds much more rapidly than does hydrolysis of the β-chloroethyl groups.

TABLE I

THE REACTION OF METHYL-BIS(β-CHLOROETHYL)AMINE (MBA) OXIDE WITH WATER AND WITH THIOSULFATE

Concentration of reactants per cc.: 0.02 *mM* of MBA oxide HCl; 0.02 *mM* of NaOH; 0.06 *mM* of $NaHCO_3$.

In the experiment given in Column 4, 0.05 *mM* of $Na_2S_2O_3$ per cc. was also present. *p*H 8; temperature 25°.

TIME, HOURS (1)	Cl^- LIBERATED PER *mM* OF MBA OXIDE M. EQUIV. (2)	H^+ LIBERATED PER *mM* OF MBA OXIDE M. EQUIV. (3)	TOTAL $Na_2S_2O_3$ UPTAKE PER *mM* OF MBA OXIDE M. EQUIV. (4)	3-HOUR $Na_2S_2O_3$ UPTAKE[a] PER *mM* OF MBA OXIDE M. EQUIV. (5)
1	0.18	0.02	0.25	0.84
4	0.30	0.11	1.12	0.82
7	0.67	0.17	1.21	
24	1.03	0.45	1.79	0.20
72	1.11	0.69	1.79	0.00

[a] This value was determined by adding, after the indicated time interval, excess $Na_2S_2O_3$ to an aliquot of the hydrolysis mixture; after exactly 3 hours the unreacted thiosulfate was titrated.

The chemical reactions of MBA and TBA N-oxides. The stability of the chloroethyl groups of these N-oxides and their reaction with thiosulfate[4] were studied by measuring the liberation of Cl^- and H^+ and the consumption of thiosulfate in a bicarbonate solution. Table I shows that, under these condition, within 72 hours, II liberates 1.11 equivalents of Cl^- and only 0.69 equivalents of H^+. The smaller H^+ liberation suggests that the over-all process is of a complex nature and warrants further investigation. Column 5 of Table I shows that the thiosulfate titer decreases as the hydrolysis proceeds and that the final hydrolysis products show no thiosulfate consumption.

The Cl^- and H^+ liberation, and thiosulfate consumption of IV in bicarbonate solution were measured in a manner similar to that employed for the study of II.

[4] The use of the reaction with thiosulfate as an index of the presence of reactive ethylenimonium or β-chloroethyl groups has been discussed in previous papers of this series.

The data in Table II show that within one hour in bicarbonate solution at 25°, 0.97 equivalents of Cl^- and 0.52 equivalents of H^+ are liberated and 1.32 equivalents of $Na_2S_2O_3$ are consumed. In marked contrast, II liberates within the same time only 0.18 equivalents of Cl^-, 0.02 equivalents of H^+ and reacts with only 0.25 equivalents of $Na_2S_2O_3$. It will be noted that in the hydrolysis of IV, the rate of Cl^- liberation is greater than is the rate of H^+ liberation. The same observation was made with II. Column 4 of Table II shows that IV is capable of reacting with approximately 2 equivalents of thiosulfate within 4 hours. Column 5 indicates that the 35-minute thiosulfate titer decreases as hydrolysis proceeds.

Two reaction products have been isolated from a 48-hour old bicarbonate buffered solution of IV. The isolation of β-hydroxyethyl-bis(β-chloroethyl)amine

TABLE II

THE REACTION OF TRIS(β-CHLOROETHYL)AMINE (TBA) OXIDE WITH WATER AND WITH THIOSULFATE

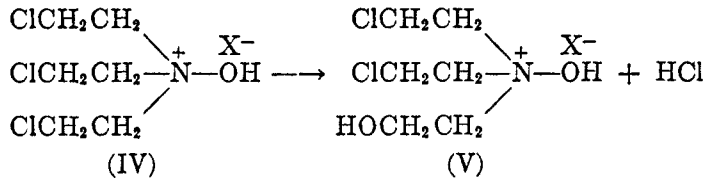
Concentration of reactants per cc.: 0.02 *mM* of TBA oxide HCl; 0.02 *mM* of NaOH; 0.08 *mM* of $NaHCO_3$.

In the experiment given in Column 4, 0.07 *mM* of $Na_2S_2O_3$ per cc. was also present. Temperature 25°; *p*H 8.

TIME, MIN. (1)	Cl^- LIBERATED PER *mM* OF TBA OXIDE M.EQUIV. (2)	H^+ LIBERATED PER *mM* OF TBA OXIDE M.EQUIV. (3)	TOTAL $Na_2S_2O_3$ UPTAKE PER *mM* OF TBA OXIDE M.EQUIV. (4)	35-MINUTE $Na_2S_2O_3$ UPTAKE PER *mM* OF TBA OXIDE[a] M.EQUIV. (5)
15	0.57	0.09	0.81	1.08
30	0.76	0.29	0.96	1.08
60	0.97	0.52	1.32	1.07
120	1.18	0.79	1.73	0.90
240	1.33	0.91	2.04	0.53

[a] These values were determined by removing, at the time indicated, an aliquot of the hydrolysis mixture, adding excess $Na_2S_2O_3$, and after exactly 35 minutes titrating the unreacted thiosulfate.

N-oxide (V) in a yield of 54% indicates that the major portion of IV is hydrolyzed under these conditions as follows:



Triethanolamine also was isolated from the reaction mixture in a yield of 20%. It is possible that triethanolamine is not a normal product of the decomposition of the N-oxide but was produced during the isolation procedure. Triethanolamine could arise as the result of decomposition of a portion of the N-oxide to yield TBA. Subsequent hydrolysis of the TBA would yield triethanolamine. A similar reaction was observed by Bamberger and Leyden (1) who found that the

N-oxide of dimethylaniline decomposes on heating to form the original amine, dimethylaniline.

The toxicity of the N-oxides of the nitrogen mustards. The toxicity of II, III, and IV was determined by intraperitoneal injection of graded doses into sets of three mice. The results indicate that the LD_{50} for II is 75–125 mg./kg.; for III, 50–100 mg./kg.; and for IV, 2.5–5.0 mg./kg. By this method of administration, the LD_{50} for MBA hydrochloride is 2.4 mg./kg. (2) and for EBA hydrochloride is 1.05 mg./kg. (3). It is of interest that oxidation of the nitrogen mustards to the corresponding N-oxides results in the formation of compounds which still possess appreciable toxicity. From the above data and those of Table II, it will be noted that the greater toxicity of IV is associated with an increase in the rate of Cl^- liberation and thiosulfate consumption.

EXPERIMENTAL

Preparation of peracids. Peracetic acid was prepared by stirring at 0° for 2 hours a mixture of 153 g. (1 mole) of sodium perborate and 71 cc. (0.75 mole) of acetic anhydride in 400 cc. of water. The mixture was filtered, the filtrate acidified to Congo Red with 5 *N* sulfuric acid and the peracetic acid was separated from the inorganic salts by extraction with ether or by distillation under reduced pressure.

Monoperphthalic acid was prepared from sodium perborate and phthalic anhydride by a similar procedure. After filtration, the reaction mixture was extracted with ether and an aqueous solution of monoperphthalic acid was obtained by shaking the ether extract with water.

Perbenzoic acid was prepared by the method of Bergmann and Witte (4).

Oxidation of the nitrogen mustards. The rate of oxidation of the nitrogen mustards by peracetic acid was measured by estimation of the peracid consumption in a reaction mixture containing per cc.: 0.05 *mM* of nitrogen mustard hydrochloride, 0.10 *mM* of peracetic acid, and 0.45 *mM* of sodium bicarbonate. The *p*H was 7.7 and the temperature was maintained at 25°. A control solution was made up without the nitrogen mustard. After 15 minutes, the unreacted peracetic acid was determined by the addition of an excess of sulfuric acid and potassium iodide followed by titration of the liberated iodine. The oxidations at *p*H 3.2 were carried out in a similar manner with a reaction mixture containing per cc. 0.09 *mM* of the nitrogen mustard hydrochloride and 0.18 *mM* of peracetic acid.

The estimation of the extent of oxidation of MBA by monoperphthalic acid in $NaHCO_3$ solution was carried out as described above.

The oxidation by perbenzoic acid was carried out at 25° by shaking a mixture of 5 cc. of a 0.2 *N* chloroform solution of perbenzoic acid and 10 cc. of a solution containing 0.05 *mM* of MBA and 0.45 *mM* of $NaHCO_3$ per cc. After 15 minutes, the perbenzoic acid remaining in the mixture was determined.

The isolation of methyl-bis(β-chloroethyl)amine oxide hydrochloride (II). A solution of 25 g. of MBA·HCl (0.12 *M*) in 100 cc. of water was added over a period of 15 minutes with stirring to 1500 cc. of 0.26 *N* peracetic acid (0.39 *M*) containing 98 g. of $NaHCO_3$ (1.16 *M*). The $NaHCO_3$ was added to the peracid solution immediately before beginning the addition of the MBA·HCl. The mixture was stirred at 25° for 15 minutes, and then acidified with HCl to Congo Red. The acid solution was concentrated to dryness (bath temperature, 40°) under reduced pressure. Anhydrous acetone (50 cc.) was added and the mixture was again concentrated to dryness. The operation was repeated three times. The residue was then extracted with three 150-cc. portions of anhydrous acetone. The combined acetone extracts were filtered and concentrated under reduced pressure to a thin syrup. This was dissolved in 200 cc. of absolute ethyl alcohol, and 2 liters of anhydrous ether was then added with stirring. The amine oxide hydrochloride first separated as an oil which crystal-

lized when allowed to stand at 4°. The product was collected by filtration, washed with dry ether, and dried over P_2O_5. The yield was 21.3 g. (85%). After recrystallization from an anhydrous ethyl alcohol-ether mixture, the melting point was 109–110°.

Anal. Calc'd for $C_5H_{11}Cl_2NO \cdot HCl$: C, 28.8; H, 5.8; N, 6.7; Cl, 51.1; Cl^-, 17.1.
Found: C, 28.6; H, 5.6; N, 6.7; Cl, 50.6; Cl^-, 17.3.

The isolation of ethyl-bis(β-chloroethyl)amine oxide hydrochloride (III). The preparation of III was carried out in a manner similar to that employed for II. From 1.65 g. of EBA·HCl, 1.52 g. (85%) of the corresponding amine oxide hydrochloride was obtained. After recrystallization from an anhydrous alcohol-ether mixture the melting point was 85–86°.

Anal. Calc'd for $C_6H_{14}Cl_3NO$: C, 32.4; H, 6.3; N, 6.3; Cl, 47.8; Cl^-, 15.9.
Found: C, 32.1; H, 6.3; N, 6.3; Cl, 47.4; Cl^-, 16.0.

The isolation of tris(β-chloroethyl)amine oxide hydrochloride (IV). The preparation of IV was performed in a manner similar to that employed for II. From 1.94 g. of TBA·HCl, 1.79 g. (78%) of the corresponding amine oxide hydrochloride was obtained. After recrystallization from an anhydrous alcohol-ether mixture, the melting point was 91–92°.

Anal. Calc'd for $C_6H_{13}Cl_4NO$: C, 28.0; H, 5.0; N, 5.5; Cl, 55.2; Cl^-, 13.8.
Found: C, 28.1; H, 5.1; N, 5.7; Cl, 55.2; Cl^-, 13.8.

The hydrolysis of tris(β-chloroethyl)amine oxide hydrochloride (IV). A reaction mixture containing 10.27 g. (40 *mM*) of IV, 13.44 g. (160 *mM*) of $NaHCO_3$, and 40 cc. (40 *mM*) of *N* NaOH in 2 liters of water was allowed to stand for 48 hours at 25° and was then extracted with four 300-cc. portions of ether. The ether extracts were combined and then divided into two equal portions. To one portion of the combined ether extracts, 40 cc. of *N* HCl was added and the ether was removed under reduced pressure until only an oily aqueous suspension remained. A solution of 7.06 g. of Reinecke salt in 60 cc. of absolute methyl alcohol was added with stirring to this suspension. The Reinecke salt of β-hydroxyethyl-bis(β-chloroethyl)amine oxide (V) separated. The mixture was allowed to stand at 4° for 24 hours, filtered, and the product washed with about 50 cc. of dilute HCl. The yield was 6.16 g. (54%). The Reineckate was recrystallized by dissolving in 50 cc. of absolute methyl alcohol followed by the addition of 100 cc. of dilute HCl; m.p. 146°.

Anal. Calc'd for $C_6H_{14}Cl_2N_2O \cdot C_4H_6CrN_6S_4$: C, 23.0; H, 3.8; N, 18.8; Cl, 13.6; S, 24.6.
Found: C, 23.0; H, 3.6; N, 18.4; Cl, 13.7; S, 24.2.

The aqueous phase remaining after the ether extraction was acidified with HCl to Congo Red and then concentrated under reduced pressure to dryness (bath temperature, 40°). Absolute alcohol (100 cc.) was added to the residue and the mixture again was concentrated to dryness. The addition of alcohol and concentration was repeated three times. The residue was then extracted with 150 cc. of boiling absolute alcohol. The hot alcoholic extract was filtered, cooled, 150 cc. of dry ether was added, and the mixture was allowed to stand at 4° for 24 hours. The product was then collected by filtration and washed with dry ether. The yield of triethanolamine hydrochloride was 1.50 g. (20%). After two recrystallizations from absolute methyl alcohol, the melting point was 176–177°. Knorr (5) reports the melting point of triethanolamine hydrochloride as 177°. No depression of the melting point was observed on admixture of the isolated material with an authentic sample of triethanolamine hydrochloride.

Anal. Calc'd for $C_6H_{15}NO_3 \cdot HCl$: C, 38.8; H, 8.6; N, 7.5; Cl, 18.6.
Found: C, 38.8; H, 8.7; N, 7.6; Cl, 19.1.

The authors wish to acknowledge with thanks the helpful cooperation of Miss Rosalind E. Joseph, who assisted in the conduct of these experiments, and of Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

STUDIES ON THE SYNTHESIS OF POLYMETHYLATED PHENANTHRENES BY THE DIENE REACTION OF VINYLNAPHTHALENES

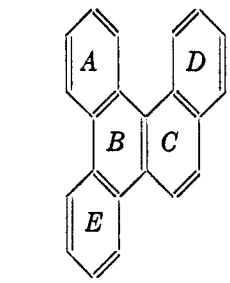
FELIX BERGMANN AND ANNA WEIZMANN

Received April 1, 1946

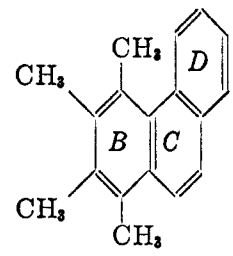
The systematic study of carcinogenic hydrocarbons has revealed a striking parallelism between a monomethyl or dimethyl derivative of a basal aromatic skeleton and the corresponding "benz" derivative (1). This parallelism led to the discovery that 1, 2, 3, 4-tetramethylphenanthrene (II), the simplest "methyl homolog" of 1,2,3,4-dibenzphenanthrene (I), possesses a definite carcinogenic activity (2). In addition to the previously stated moderate activity of 1- and 2-methyl-3,4-benzphenanthrene (3), this new observation showed that it is possible to replace *two* aromatic rings by aliphatic side chains without destroying the cancer-producing properties of the parent structure, I. It was, therefore, of interest to examine generally which parts of the five-condensed-ring structure of I could be replaced by methyl groups. We wish to describe here our experiments on the synthesis of 3,4,9,10-tetramethylphenanthrene (III), which lacks rings D and E of compound I, and which represents at the same time an "open-chain homolog" of 1,2-dimethyltriphenylene (IV) (4) and of 1,2-dimethyl-3,4-benzphenanthrene (V), a still unknown hydrocarbon of presumably strong carcinogenic activity.

Preliminary studies were made on the applicability of the Diels-Alder reaction to methylated vinylnaphthalenes. Cohen and Warren (5) obtained the adducts of 1- and 2-vinylnaphthalene in xylene solution in 32% and 6% yields, respectively. Fieser and Daudt (6), on the other hand, who applied the method to 1-propenylnaphthalene without the use of a solvent, isolated the condensation product in 77% yield. We have observed that 2-isopropenylnaphthalene (VI) and 2-(1,2-dimethylvinyl)naphthalene (X) gave very low yields when heated with maleic anhydride in the absence of solvent or in acetic anhydride. The yellow adducts, which because of their color may well be formulated as VII and XI, could not be dehydrogenated by sulfur, and by the use of selenium only very small amounts of the aromatic anhydrides (VIII) and (XII) were obtained. Condensation of the components in nitrobenzene (7) proved of distinct advantage in all cases and was, therefore, adopted as standard method. Decarboxylation by dry distillation of the potassium salts yielded the expected hydrocarbons, 1-methyl-(IX) and 1,2-dimethyl-phenanthrene (XIII) (8, 9).

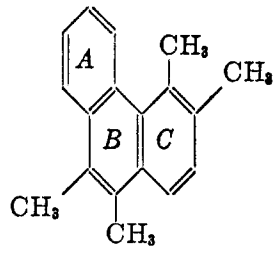
However, the corresponding 1-naphthyl derivatives (XIV) and (XVII) gave not so clear results. Thus the aromatic anhydride XV, when decarboxylated *via* its barium salt, in the presence of copper, produced an oil whose picrate (m.p. 141°) showed it to be the expected 4-methylphenanthrene (XVI) (8a, 10). The potassium salt of XV, however, required a reaction temperature (~450°), which was about 100 degrees higher than in the former experiment, and gave a very



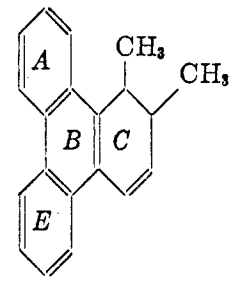
I



II



III



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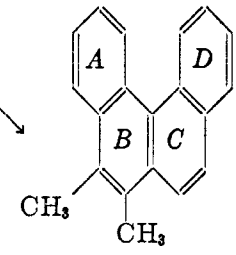


V

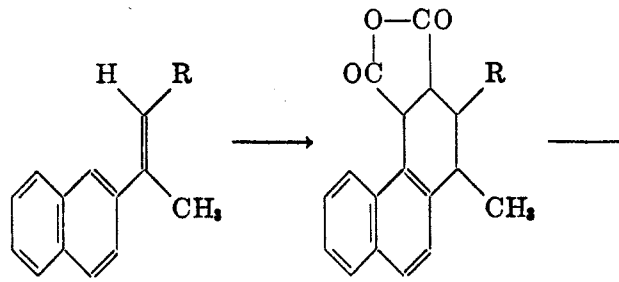
small amount of a mixture of hydrocarbons, from which a high-melting picrate (m.p. 164–166°) was isolated. Although no comparison with an authentic specimen could be made, it appears possible that at the high reaction temperature dehydrogenation and cyclization to 4,5-methylenephenanthrene (XX) had occured, the picrate of which is reported (11) as having the m.p. 166°.

Again, the aromatized adduct (XVIII), on decarboxylation of its barium salt, yielded the expected 3,4-dimethylphenanthrene (XIX). The potassium salt reacted only at about 450° and yielded, among others, a solid of m.p. 120–122° (picrate m.p. 150°) which was identified as 1,2-dimethylphenanthrene (XIII). This shows that a profound rearrangement of the original structure has taken place and that caution is indicated in the explanation of results with methylated 1-vinylnaphthalenes.

For the synthesis of III, we started with 1-acetyl-3,4-dimethylnaphthalene

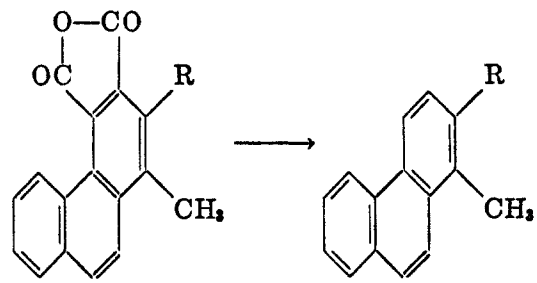
(XXI), which was prepared from 1,2-dimethylnaphthalene by the Friedel-Crafts reaction with acetic anhydride in carbon disulfide. In the mean time, XXI has been described by Plattner and Ronco (12) who synthesized it by a slightly different method and proved its orientation by oxidation to the known 3,4-dimethyl-1-naphthoic acid. The appropriate Grignard reaction of the ketone XXI yielded the vinyl derivatives XXII and XXIV. The former gave the aromatic adduct XXIII in such a small yield that we did not investigate it further.

The hydrocarbon XXIV was converted into the aromatic anhydride XXV in about 5% yield. However, two isomers of m.p. 236° and 212° respectively, were isolated. As the separation of the anhydrides involved heavy losses of material, we decarboxylated the crude XXV *via* its barium salt and obtained a mixture of hydrocarbons, from which two isomeric picrates were isolated.



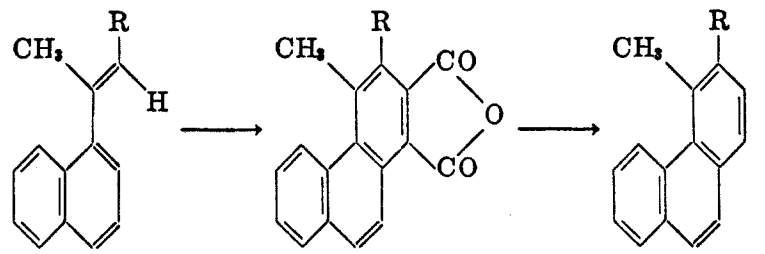
VI, R = H
X, R = CH_3

VII, R = H
XI, R = CH_3



VIII, R = H
XII, R = CH_3

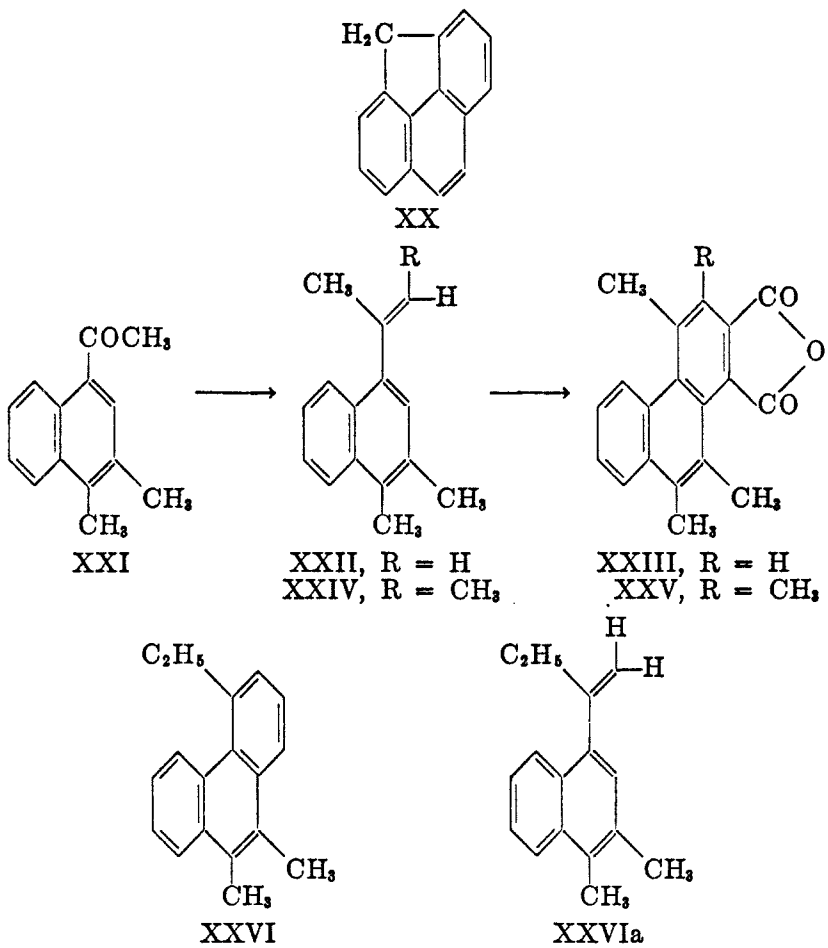
IX, R = H
XIII, R = CH_3



XIV, R = H
XVII, R = CH_3

XV, R = H
XVIII, R = CH_3

XVI, R = H
XIX, R = CH_3



(a) The main fraction showed the m.p. 227°; the hydrocarbon regenerated from this picrate had the m.p. 115°. We assume, pending a spectrographic examination, that this hydrocarbon represents the required 3,4,9,10-tetramethylphenanthrene (III), although its structure has not been elucidated.[1]

(b) From the mother liquors, a low-melting picrate (124°) was isolated. The corresponding hydrocarbon of m.p. 69°, proved to be isomeric with III. We consider it as possible that this isomer represents 4-ethyl-9,10-dimethylphenanthrene (XXVI), and therefore, that the dehydration of methylethyl-(3,4-dimethylnaphthyl-1)carbinol produced a mixture of XXIV and the methylene derivative XXIVa.

On the whole, we may conclude: Methylation of the side chain of vinylnaphthalenes reduces their reactivity to such a degree that the Diels-Alder reaction with maleic anhydride does not constitute a practical method for the synthesis of

[1] The compounds have been submitted to Dr. R. Norman Jones for spectrographical analysis.

alkylated phenanthrenes. Our results, however, appear theoretically interesting enough to warrant publication.

EXPERIMENTAL

1-Methylphenanthrene-3,4-dicarboxylic acid anhydride (VIII). 2-Isopropenylnaphthalene (VI) (13) (8.4 g.) and maleic anhydride (25 g., 5 equiv.) in nitrobenzene (75 cc.) were refluxed for four hours. Then the solvent was removed by steam and the tarry residue purified by distillation. A yellow oil of b.p. 180–200° (1 mm.) was obtained, which, upon trituration with methanol, yielded 0.5 g. (4%) of crystalline material. Recrystallization from butyl acetate gave yellow needles of m.p. 241–242° (VIII).

Anal. Calc'd for $C_{17}H_{10}O_3$: C, 77.9; H, 3.8.
Found: C, 77.8; H, 3.6.

The potassium salt, prepared from VIII (0.5 g.) with methanolic potassium hydroxide, was distilled at ordinary pressure (*ca.* 300°) in the presence of calcium oxide, and yielded 0.1 g. of distillate. The substance (IX) was recrystallized from glacial acetic acid and showed thereafter the m.p. 117–118°. Its picrate, prepared in ethanolic solution, had the m.p. 137°, not depressed by admixture of an authentic specimen of 1-methylphenanthrene.

1,2-Dimethylphenanthrene-3,4-dicarboxylic acid anhydride (XII). 2-(1,2-Dimethylvinyl)naphthalene (X) (13, 14) (8 g.) and maleic anhydride (25 g.) in acetic anhydride (75 cc.) were refluxed for five hours. The solvent was distilled and the residue fractionated in a high vacuum. A small fraction, b.p. 240–245° (0.1 mm.) was isolated which crystallized from butyl acetate in fine, bright yellow needles of m.p. 231° (XI).

Anal. Calc'd for $C_{18}H_{16}O_3$: C, 77.1; H, 5.7.
Found: C, 77.3; H, 5.5.

Dehydrogenation with sulfur at 300–320° was unsuccessful and gave back the original tetrahydro product.

When the diene X (15 g.) and maleic anhydride (50 g.) in nitrobenzene (150 cc.) were refluxed for five hours and the mixture steam-distilled, a black residue was obtained, which was best purified in the following way: extraction with boiling acetic acid, which left an insoluble greenish powder (1.2 g.), which upon recrystallization from butyl acetate and then from acetic anhydride formed dark yellow needles of m.p. 242–243° (XII).

Anal. Calc'd for $C_{18}H_{12}O_3$: C, 78.3; H, 4.3.
Found: C, 78.0, 78.3; H, 4.2, 4.5.

The portion which had dissolved in acetic acid (2.7 g.) was distilled, b.p. 185–195° (0.1 mm.), and yielded an oil which crystallized upon treatment with methanol. Recrystallization from butyl acetate gave a product of m.p. 230°, identical with the tetrahydro derivative (XI). This product did not react with sulfur. When it was heated with selenium at 320–350°, it yielded, after sublimation in a high vacuum, a small amount of the aromatic anhydride (XII).

XII (0.6 g.) was converted into its potassium salt as above, and distilled at ordinary pressure at about 250° in the presence of calcium oxide. The greenish-yellow distillate crystallized spontaneously (0.15 g., 33% yield). It was obtained from acetic acid in colorless plates of m.p. 143° (XIII). Its picrate showed m.p. 154°, not depressed by admixture of an authentic specimen of 1,2-dimethylphenanthrene.

Anal. Calc'd for $C_{16}H_{14}$: C, 93.2; H, 6.8.
Found: C, 92.9; H, 6.8.

4-Methylphenanthrene-1,2-dicarboxylic acid anhydride (XV). 1-Isopropenylnaphthalene (15) has been prepared by us in two ways, either by reaction of 1-acetylnaphthalene with methylmagnesium iodide, or by Grignardization of acetone with 1-naphthylmagnesium bromide and dehydration of the intermediary carbinol (of m.p. 102°).

1-Isopropenylnaphthalene (XIV) (10 g.) and maleic anhydride (26 g.) in acetic anhydride (100 cc.) were refluxed for six hours and the crude product was distilled, b.p. 260–300° (0.3 mm.). The red oil (5 g.) so obtained crystallized on treatment with ethanol. Two

crystallizations from butyl acetate gave light yellow needles of m.p. 210°; yield 1.2 g., 8%. This compound represents the tetrahydro anhydride, isomeric with VII.

Anal. Calc'd for $C_{17}H_{14}O_3$: C, 76.7; H, 5.3.
Found: C, 76.8; H, 5.1.

The yield was slightly better (*ca.* 10%) when the crystalline carbinol was condensed directly with maleic anhydride in the same solvent.

This adduct (2.1 g.) and sulfur (0.55 g.) were melted together at 200°. Evolution of hydrogen sulfide started at 250°, and the temperature was slowly raised to 300°. Sublimation of the black product yielded 1.4 g. of a yellow substance which was extracted with acetic acid. A small, insoluble part was recrystallized from acetic anhydride, then from nitrobenzene; orange-yellow, thin rods of m.p. 282–284° (XV).

Anal. Calc'd for $C_{17}H_{10}O_3$: C, 77.9; H, 3.8.
Found: C, 77.9; H, 4.1.

The acetic acid solution deposited on cooling yellow lancets of m.p. 208°, identified as the starting material.

1-Isopropenylnaphthalene (11 g.) and maleic anhydride (36 g.) in nitrobenzene (100 cc.) were refluxed for five hours. The crude product was distilled, b.p. 280–300° (1 mm.). The distillate crystallized on trituration with ethanol-acetone. Recrystallization from nitrobenzene gave 0.9 g. of orange-yellow rods, m.p. 282–284°, identical with the aromatic anhydride (XV). The substance shows in solution an intense green-yellow fluorescence.

Decarboxylation. (*a*) *With barium hydroxide and copper.* Three-tenths of a gram each of the anhydride XV, barium hydroxide, and copper were thoroughly mixed and distilled at ordinary pressure. The oily distillate (0.1 g.) was converted directly into the picrate in ethanolic solution. Dark needles of m.p. 139° were obtained which showed no depression on admixture of an authentic specimen of the picrate of 4-methylphenanthrene (XVI).

(*b*) *With potassium hydroxide.* The anhydride XV (0.5 g.) was converted into the dipotassium salt as described above, and distilled in the presence of calcium oxide at 400–450°. One drop of a red oil passed over, which became semisolid at room temperature. This mixture was dissolved in acetic acid, and picric acid added. Upon cooling, beautiful, deep red flat rods crystallized out, m.p. 164–166°. They were recrystallized from acetic acid (XX ?).

Anal. Calc'd for $C_{21}H_{13}N_3O_7$: N, 10.0. Found: N, 10.0.

From the mother liquor a mixture of other picrates crystallized, which could not be separated because of the small amount available.

3,4-Dimethylphenanthrene-1,2-dicarboxylic acid anhydride (XVIII). 1-(1,2-Dimethylvinyl)naphthalene (XVII) was prepared according to Salkind and Soniss (16), and also from methyl ethyl ketone and 1-naphthylmagnesium bromide.

XVII (13 g.) and maleic anhydride (30 g.) were refluxed in nitrobenzene (90 cc.) for five hours and the solvent steam-distilled. The black residue was sublimed at 250–300° (0.2 mm.) and the sublimate treated with ethanol-acetone; yield 0.8 g., 4%. The substance (XVIII) was recrystallized twice from acetic anhydride and formed intensely yellow, slender needles, m.p. 242°. Its solutions show intense green fluorescence. Its mixture with the isomer (XII) showed a melting point depression of about 12°.

Anal. Calc'd for $C_{18}H_{12}O_3$: C, 78.3; H, 4.3.
Found: C, 78.3; H, 4.6.

Decarboxylation. (*a*) *With barium hydroxide and copper.* The anhydride XVIII (0.5 g.) was heated with equal amounts of barium hydroxide and copper to 300° (25 mm.). The yellow oil which passed over crystallized spontaneously. The product was dissolved in methanol and cooled to −18°. The substance (XIX) showed the m.p. 53–54°. The picrate was obtained from ethanol as short, orange needles, m.p. 128°. Haworth (9b) reports 129–130°. Although no comparison with an authentic specimen could be made, it is probable that the compound represents the expected 3,4-dimethylphenanthrene.

(*b*) *With potassium hydroxide.* The anhydride XVIII (0.5 g.) was converted into the dipotassium salt and distilled at 400–450° in the presence of calcium oxide (0.5 g.). The

green-yellow distillate (25 mg.) crystallized partly. The crystals were pressed onto a porous plate and showed the m.p. about 130°. They were converted directly into the picrate in acetic acid solution, m.p. 150°. Mixed m.p. with the picrate of 1,2-dimethylphenanthrene, 152°.

4,9,10-Trimethylphenanthrene-1,2-dicarboxylic acid anhydride (XXIII). 1-Acetyl-3,4-dimethylnaphthalene (XXI): To a solution of 1,2-dimethylnaphthalene (22 g.) and acetic anhydride (45 g.) in carbon disulfide (250 cc.) cooled in an ice-salt bath, aluminum chloride (72 g.) was added in portions and the mixture stirred at room temperature for twelve hours. After steam distillation, hydrochloric acid was added and the mass extracted with benzene, which left a residue boiling at 150° (0.6 mm.); yield 20 g., 70%. The picrate, when recrystallized from butanol, showed the m.p. 133–134° (12).

1-Isopropenyl-3,4-dimethylnaphthalene (XXII): When the ketone (18 g.) was added to a solution of methylmagnesium iodide, a thick white precipitate was formed. After two hours' boiling, the mixture was worked up as usual, and the resulting syrup dehydrated by means of potassium bisulfate at 160°. The diene (XXII) distilled at 103° (0.1 mm.) as a colorless oil; yield 14 g., 79% $n_D^{20.5}$ 1.6040.

Anal. Calc'd for $C_{15}H_{16}$: C, 91.8; H, 8.2.
Found: C, 91.3; H, 8.3.

The picrate crystallized from ethanol in beautiful orange rods of m.p. 115°.

Anal. Calc'd for $C_{21}H_{19}N_3O_7$: C, 59.3; H, 4.5; N, 9.9.
Found: C, 59.7; H, 4.6; N, 10.2.

The diene XXII (5 g.) and maleic anhydride (12 g.) in nitrobenzene (50 cc.) were refluxed for four hours. The black residue which remained after steam distillation was distilled twice, b.p. 240–250° (0.1 mm.). The yellow syrup (1.2 g.) crystallized upon treatment with a mixture of ethyl acetate and ethanol, yielding 150 mg. (2%) of a yellow solid; intensely yellow, long, thin prismatic rods from acetic acid, m.p. 256° (XXIII).

Anal. Calc'd for $C_{19}H_{14}O_3$: C, 78.6; H, 4.8.
Found: C, 78.8, 78.8; H, 5.1, 4.8.

3,4,9,10-Tetramethylphenanthrene-1,2-dicarboxylic acid anhydride (XXV). 1-(1,2-Dimethylvinyl)-3,4-dimethylnaphthalene (XXIV): The Grignard reaction of the ketone XXI with ethylmagnesium bromide, carried out as described above, yielded the diene XXIV as a colorless oil of b.p. 100–110° (0.1 mm.); n_D^{20} 1.5968; yield 80%.

Anal. Calc'd for $C_{16}H_{18}$: C, 91.4; H, 8.6.
Found: C, 91.2; H, 8.2.

The picrate formed orange rods from methanol, m.p. 101–102°.

Anal. Calc'd for $C_{22}H_{21}N_3O_7$: N, 9.6. Found: N, 9.5.

The diene XXIV (17 g.) and maleic anhydride (80 g.) in nitrobenzene (200 cc.) were refluxed for six hours. The black, viscous syrup which remained after steam distillation was sublimed at 240° (5 mm.), yielding a mixture of oil and crystals. Upon treatment with acetone and alcohol, 0.8 g. of a yellow powder was isolated, which crystallized from butyl acetate in fine yellow needles of m.p. 235–236° (XXV).

Anal. Calc'd for $C_{20}H_{16}O_3$: C, 78.9; H, 5.3.
Found: C, 78.9; H, 5.3.

When the mother liquor, containing the oily portion, was worked up again by distillation, it gave a brown oil, b.p. 240–250° (0.8 mm.), which upon treatment with acetone deposited 0.4 g. of a yellow powder. Recrystallization from acetic acid gave small crystals of m.p. 212°. Analysis showed the substance to be isomeric with XXV.

Anal. Found: C, 78.6; H, 5.2.

Because of the low yields in aromatic anhydrides, we applied a different method to the isolation of the adduct. The residue from the steam distillation was extracted with acetic acid and this solution then fractionated. The fractions boiling at 220–250° (4 mm.) were extracted with sodium hydroxide, and the solution of sodium salts was precipitated with hydrochloric acid. The crude acid (corresponding to XXV) so obtained was directly used for decarboxylation.

Five grams of crude acid dissolved in dioxane (20 cc.) was added slowly to a solution of

barium hydroxide (15 g.), and the precipitate dried at 110°. It was then mixed thoroughly with copper-bronze (2.5 g.) and decarboxylated at 320° (25 mm.). One and two-tenths grams of oil passed over, which was converted to the picrate in acetic acid. The first crop which crystallized from this solvent had m.p. 164–165°. By alternating recrystallization from ethanol and acetic acid, the m.p. was raised to 227° (picrate of III ?); yield 0.8 g. of dark red rods.

Anal. Calc'd for $C_{24}H_{21}N_3O_7$: C, 62.2; H, 4.5; N, 9.1.
Found: C, 61.9; H, 4.3; N, 9.3.

Decomposition of this picrate yielded an oil which upon sublimation *in vacuo* at 220° (0.6 mm.) gave a crystalline sublimate. From alcohol it was obtained as flat rods of m.p. 115° (III ?).

Anal. Calc'd for $C_{18}H_{18}$: C, 92.3; H, 7.7.
Found: C, 92.3; H, 7.3.

The mother liquor from the first picrate gave a second crop which after repeated crystallizations from ethanol yielded clusters of fine orange needles of m.p. 123°.

Anal. Found: C, 62.2; H, 4.6.

This picrate (0.15 g.) gave, after decomposition and sublimation in a high vacuum, a semisolid product. After standing for several days, the crystals (flat rods) were separated from the adhering oil on a porous plate, showing thereafter the m.p. 65–67°.

Anal. Found: C, 91.9; H, 8.0.

SUMMARY

The condensation of isopropenyl- and *sec.*-butenyl-naphthalenes with maleic anhydride in nitrobenzene gives aromatic adducts, but in low yields. Decarboxylation of the adducts derived from β-vinylnaphthalenes yields the expected methylated phenanthrenes. The derivatives of α-vinylnaphthalene, however, may give anomalous products when their potassium salts are decarboxylated.

Application of these experiences to the synthesis of 3,4,9,10-tetramethylphenanthrene is described.

REHOVOTH, PALESTINE

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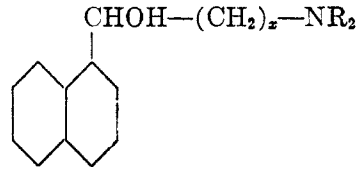
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

THE SYNTHESIS OF CERTAIN 4-DIALKYLAMINO-1-(1-NAPHTHYL)-1-BUTANOLS[1]

BYRON RIEGEL, R. I. JACKSON, J. G. SANDZA, AND L. T. SHERWOOD, JR.

Received April 15, 1946

In the course of investigating various types of compounds as possible antimalarials, it was suggested by Dr. Lyndon F. Small that a series of ω-dialkylamino-1-(1-naphthyl)-1-alkanols (I) be prepared in which R is a straight-chain primary alkyl group containing one to eight carbons and X is 3, 4, or 5. Seven compounds in which X is 3 have been prepared in this Laboratory and submitted for testing.



I

The general method of preparation is that of Marxer (1) and Small (2) and consists of preparing the Grignard reagent from the proper 1-chloro-3-dialkylaminopropane and treating it with 1-naphthaldehyde. Distilling twice at about 10^{-3} mm. gives a pure product. The results of these preparations are summarized in Table I.

Attempts to prepare derivatives of the hydroxyl group in these carbinols were not successful because of their tendency to lose the elements of water. To establish whether this took place during the distillation, especially for the higher members, micro Zerewitinoff determinations were made for active hydrogen. These are given in Table II. Since none of these compounds proved to be effective antimalarials the series where X was 4 or 5 was not prepared.

EXPERIMENTAL

1-Chloro-3-dialkylaminopropanes. These compounds were prepared by essentially standard procedures from 1-bromo-3-chloropropane and the appropriate amine (2).[2]

4-Dialkylamino-1-(1-naphthyl)-1-butanols (General Procedure). Excess magnesium was placed in a one-liter 3-necked flask and rinsed with anhydrous ether. Fifty to 100 ml. of dry ether was distilled into the flask from an ether solution of ethylmagnesium bromide and, with stirring, a few crystals of iodine and 1 ml. of butyl bromide were added. When the reaction subsided, an additional 1 ml. of butyl bromide was added and, as soon as the reaction became vigorous, the 1-chloro-3-dialkylaminopropane (about ⅓ mole) was added over a period of one to two minutes. During the next half hour, 100 to 250 ml. of dry ether was distilled into the flask and the mixture was stirred and heated to gentle refluxing for 14 to

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Reearch and Development and Northwestern University.

[2] We are indebted to Dr. R. C. Elderfield for furnishing us with the dialkylamines.

18 hours. The Grignard reagent from the higher molecular weight amines seemed to be formed more rapidly and in better yields, probably because of their greater solubility in ether.

Sufficient ether was then distilled into the mixture to give a total volume of 400 to 700 ml. and the 1-naphthaldehyde was added, one-half to one ml. at a time, until further additions caused no refluxing. About half the ether was distilled back into the ethylmagnesium bromide solution and was replaced with ordinary ether. The mixture was decomposed with a saturated ammonium chloride solution.

TABLE I

DIALKYLAMINONAPHTHYLBUTANOLS

R	% YIELD (PURE)	DISTILLATION TEMP. AT 10^{-3} MM.	M.P. °C	N	
				CALC'D	FOUND[a]
CH_3—	51	160	62–63	5.76	5.57
C_2H_5—[b]	23			5.16	5.03
C_3H_7—	58	180–220	46–50[c]	4.68	4.61
C_5H_{11}—	21	187–195	oil	3.94	4.12
C_6H_{13}—	38	200	oil	3.65	3.81
C_7H_{15}—	46	215–225	oil	3.40	3.50
C_8H_{17}—	53		oil	3.19	3.64

[a] The microanalyses were performed by F. Marx and Lois E. May of Columbia University and by Margaret Ledyard of Northwestern University.

[b] This compound was previously prepared by Marxer (*loc. cit.*). It was distilled at 158–164° at 0.07 mm. and melted at 59–62°.

[c] This material could not be recrystallized. The melting point was taken on the solidified distillate.

TABLE II[a]

DETERMINATION OF ACTIVE HYDROGEN

R	G. USED	MOLES OF METHANE	
		Calc'd	Found
CH_3—	0.0392	1.64×10^{-4}	1.78×10^{-4}
C_6H_{13}—	0.0631	1.65×10^{-4}	1.525×10^{-4}
C_7H_{15}—	0.1292	3.14×10^{-4}	3.24×10^{-4}
C_8H_{17}—	0.0132	3.0×10^{-5}	2.8×10^{-5}

[a] We are indebted to Mr. A. H. Schlesinger for assistance in these determinations

To work up the dimethyl, diethyl, and dipropyl compounds, the ether solution was decanted from the magnesium and the magnesium salts and extracted with ice and 4 *N* hydrochloric acid until the extract was acid to Congo Red. Excess potassium hydroxide solution was added to the acid extract and the mixture was extracted three times with ether. The extracts were dried with anhydrous potassium carbonate and the ether removed. The residue was heated to 130–140° at 2–3 mm. and distilled twice at 10^{-3} mm.

The remaining compounds were worked up by the following procedure. The ether solution was washed with ice and 4 *N* hydrochloric acid until the washings were acid to Congo Red. To the remaining one or two layers (depending on the product and the amount of ether present) was added 150 to 200 ml. of petroleum ether (b.p. 60–70°) and the solutions

were mixed thoroughly. The upper (petroleum ether) layer was discarded and the lower was treated with excess potassium hydroxide solution. The product layer was separated and the aqueous layer was extracted twice with ether. The ether extract was added to the product, dried over potassium carbonate, and the ether was removed. The residue was distilled in the same manner as the lower molecular weight compounds.

All attempts to prepare crystalline salts of these compounds with hydrochloric acid, sulfuric acid, picric acid, and 4,4′-methylene-bis-(3-hydroxy-2-naphthoic acid) failed.

SUMMARY

A series of 4-dialkylamino-1-(1-naphthyl)-1-butanols were prepared by the reaction of 1-naphthaldehyde with 3-dialkylaminopropylmagnesium chloride. They proved ineffective as antimalarials.

EVANSTON, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

THE SOLUBILITIES OF THE NORMAL SATURATED FATTY ACIDS. III

C. W. HOERR, R. S. SEDGWICK, AND A. W. RALSTON

Received April 22, 1946

Previous reports from this laboratory (1, 2) have presented the solubilities of the normal saturated fatty acids from caprylic to stearic, inclusive, in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl acetate, butyl acetate, glacial acetic acid, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, nitroethane, acetonitrile, and water. In view of the usefulness of such data, the scope of this investigation has been expanded to include a number of the more common aromatic solvents, as well as several simple, substituted hydrocarbons. This paper reports the solubilities of caprylic, capric, lauric, myristic, palmitic, and stearic acids in toluene, *o*-xylene, chlorobenzene, nitrobenzene, 1,4-dioxane, furfural, 1,2-dichloroethane, and nitromethane.

EXPERIMENTAL

The lauric and myristic acids used in this investigation were those employed in the previous studies (2). The caprylic and capric acids were obtained by vacuum fractionation of Armour Neo-Fat 7 and Neo-Fat 15, respectively, in a Stedman packed column. The stearic acid was prepared by repeated recrystallization of Armour Neo-Fat 1-65 from acetonitrile. The freezing points of these highly purified fatty acids are listed in Table I. These values are in good agreement with, and in most cases exceed, the best freezing points reported for these compounds.

The solvents which were used were twice distilled from the best grade of commercial products, those with higher boiling points being distilled under reduced pressure. The boiling points and refractive indices of these solvents were in good agreement with the data in the International Critical Tables.

The solubilities of the fatty acids were determined by the methods described previously (3–5).

RESULTS AND DISCUSSION

The solubilities of the fatty acids in the benzene derivatives, toluene, *o*-xylene, chlorobenzene, and nitrobenzene, are listed in Table II–V, respectively, and the solubilities in toluene and in nitrobenzene are shown graphically in Figs. 1 and 2, respectively. The solubilities in toluene, *o*-xylene, and chlorobenzene are remarkably similar in spite of the fact that the first two solvents possess only a very slight polarity while the third is a moderately polar solvent. Upon an equimolar basis these solubilities are practically identical, indicating that moderate differences between the respective polarities of the solvent and solute exert much less influence upon the solubilities of the fatty acids than do other factors, such as the relative internal pressures of the molecules, intermolecular attractive forces, etc. The relatively high polarity of nitrobenzene, on the other hand, results in somewhat lower solubilities of the fatty acids. The high polarity of the solvent, however, is accompanied by other changes in its physical properties, such as in-

TABLE I

FREEZING POINTS OF PURIFIED FATTY ACIDS

ACID	NO. OF C ATOMS	F.P., °C
Caprylic	8	16.51
Capric	10	31.35
Lauric	12	43.92
Myristic	14	54.15
Palmitic	16	62.82
Stearic	18	69.60

TABLE II

SOLUBILITIES OF FATTY ACIDS IN TOLUENE

NO. OF C ATOMS	G. ACID PER 100 G. TOLUENE						
	−10.0°	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°
8	69.5	168	605	∞	∞	∞	∞
10	25.2	57.0	127	323	4100	∞	∞
12	5.2	15.3	40.6	97	251	1410	∞
14	0.6	3.2	10.2	30.4	82.1	230	1350
16		0.2	2.2	8.7	30.0	80.6	244
18[a]			<0.1	2.0	10.6	36.6	103

[a] 15.75 g. per 100 g. toluene at 25° (6, 7).

TABLE III

SOLUBILITIES OF FATTY ACIDS IN *o*-XYLENE

NO. OF C. ATOMS	G. ACID PER 100 G. *o*-XYLENE						
	−10.0°	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°
8	57.0	154	562	∞	∞	∞	∞
10	20.3	47.9	117	316	4050	∞	∞
12	3.6	11.2	34.8	92	238	1360	∞
14	0.3	2.4	8.4	26.1	75.4	221	1320
16		0.1	1.9	7.9	25.2	77.0	235
18			<0.1	1.7	9.1	34.6	102

TABLE IV

SOLUBILITIES OF FATTY ACIDS IN CHLOROBENZENE

NO. OF C ATOMS	G. ACID PER 100 G. CHLOROBENZENE						
	−10.0°	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°
8	73.6	178	725	∞	∞	∞	∞
10	16.7	43.0	108	305	4500	∞	∞
12	2.0	10.6	31.9	87.0	239	1360	∞
14	0.4	2.0	7.2	23.6	72.4	220	1280
16		<0.1	1.6	7.8	25.8	76.4	230
18			<0.1	2.2	10.8	38.3	102

TABLE V

SOLUBILITIES OF FATTY ACIDS IN NITROBENZENE

NO. OF C ATOMS	G. ACID PER 100 G. NITROBENZENE					
	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	365	∞	∞	∞	∞	∞
10	18.0	131	3550	∞	∞	∞
12	2.7	8.8	66.3	790	∞	∞
14	1.3	3.0	7.1	34.2	560	∞
16[a]		0.1	1.2	6.4	55.5	1215
18[b]			<0.1	1.4	9.8	112

[a] The solubilities reported (7) for palmitic and stearic acids in this solvent at 0° are obviously erroneous, since nitrobenzene freezes at 5.7°.

[b] 1.25 g. per 100 g. nitrobenzene at 25° (6).

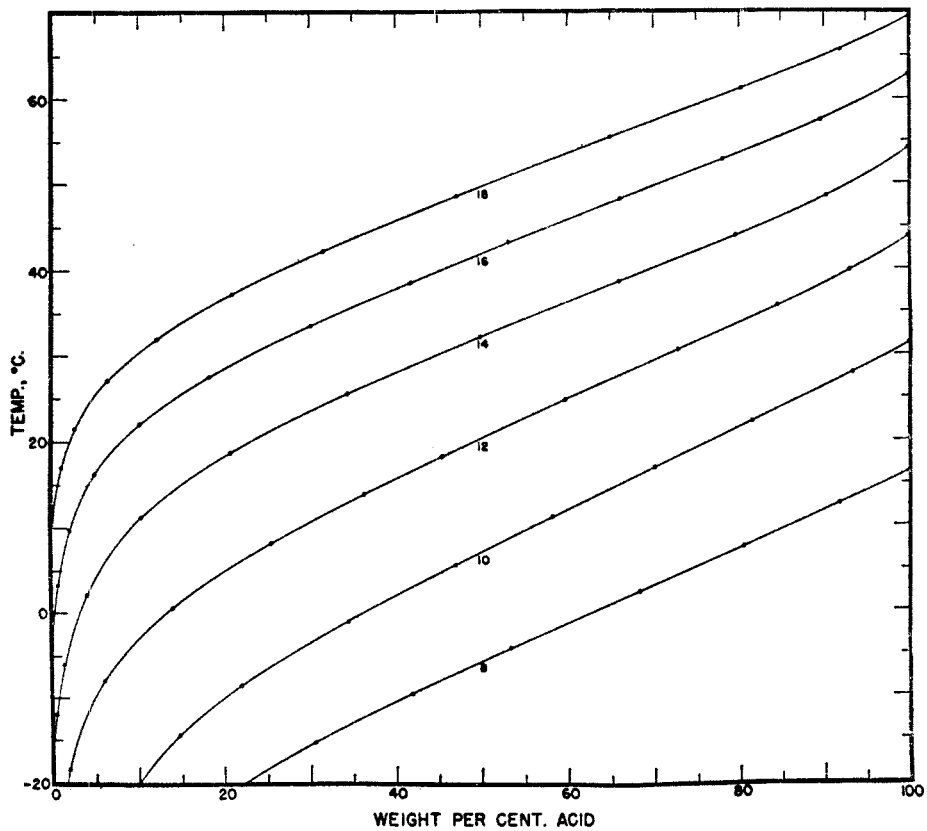

FIG. 1. Solubilities of Fatty Acids in Toluene. The numbers on the curves refer to the number of carbon atoms in the fatty acid molecule.

creased internal pressure, and consequetly, nitro benzene is a poorer solvent for the fatty acids than are the other benzene derivatives investigated. The solu-

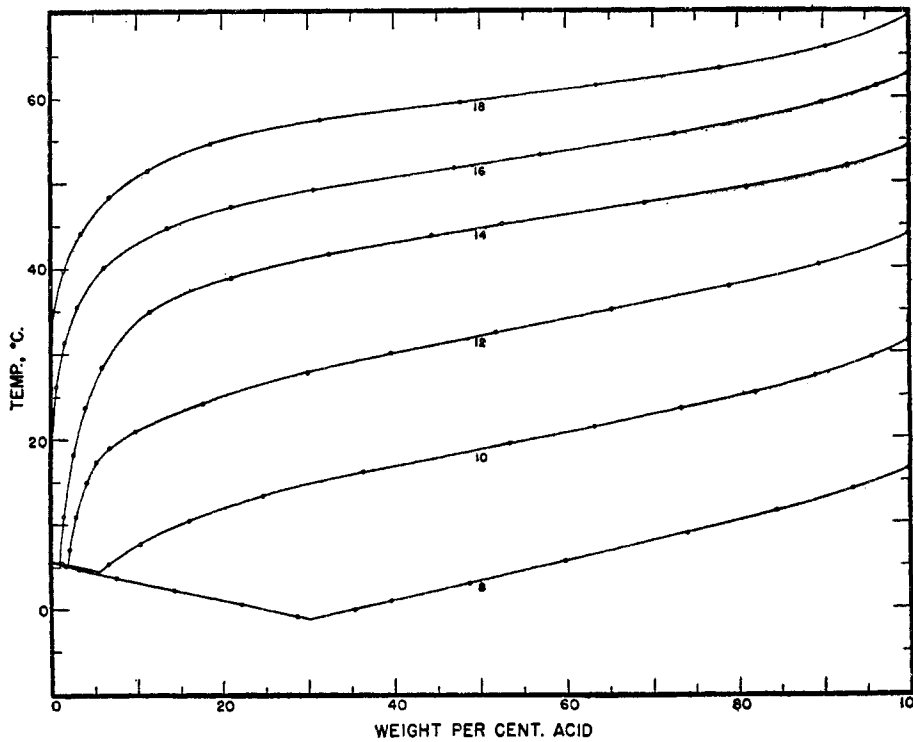

FIG. 2. Solubilities of Fatty Acids in Nitrobenzene

TABLE VI

SOLUBILITIES OF FATTY ACIDS IN 1,4-DIOXANE

NO. OF C ATOMS	G. ACID PER 100 G. 1,4-DIOXANE				
	20.0°	30.0°	40.0°	50.0°	60.0°
10	356	4450	∞	∞	∞
12	101	246	1270	∞	∞
14	32.6	88	228	1100	∞
16	10.9	32.8	91	248	1730
18	4.3	15.3	48.8	132	415

TABLE VII

SOLUBILITIES OF FATTY ACIDS IN FURFURAL

NO. C ATOMS	G. ACID PER 100 G. FURFURAL						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	22.5	216	∞	∞	∞	∞	∞
10	3.8	8.9	42.5	3470	∞	∞	∞
12		0.3	3.7	20.9	1210	∞	∞
14				1.5	13.6	792	∞
16					1.6	15.9	1800
18						2.6	28.5

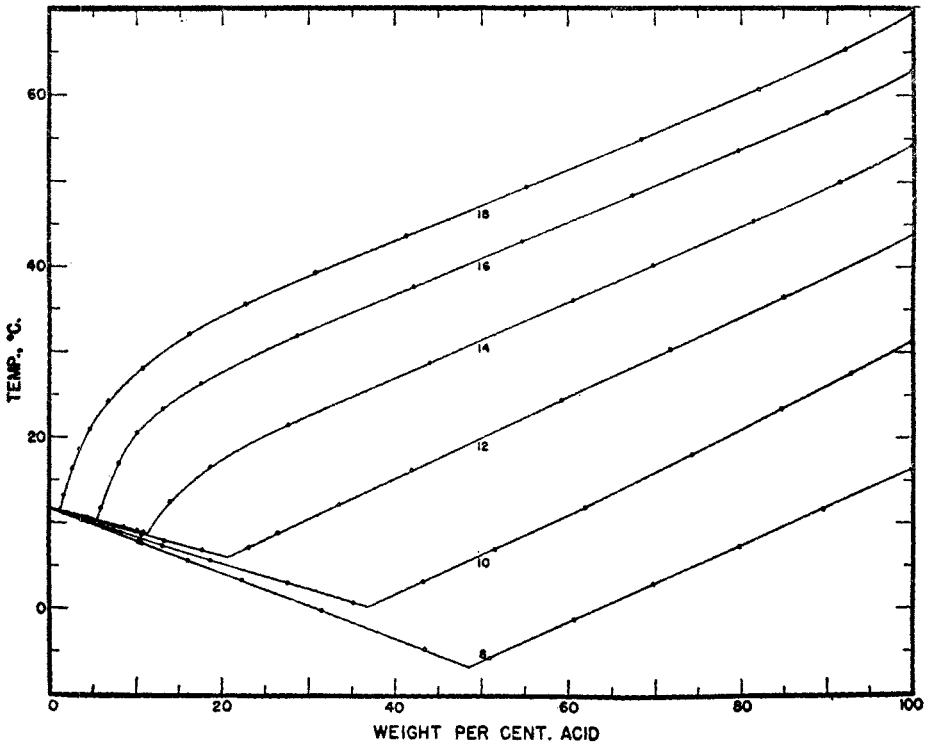

FIG. 3. Solubilities of Fatty Acids in 1,4-Dioxane

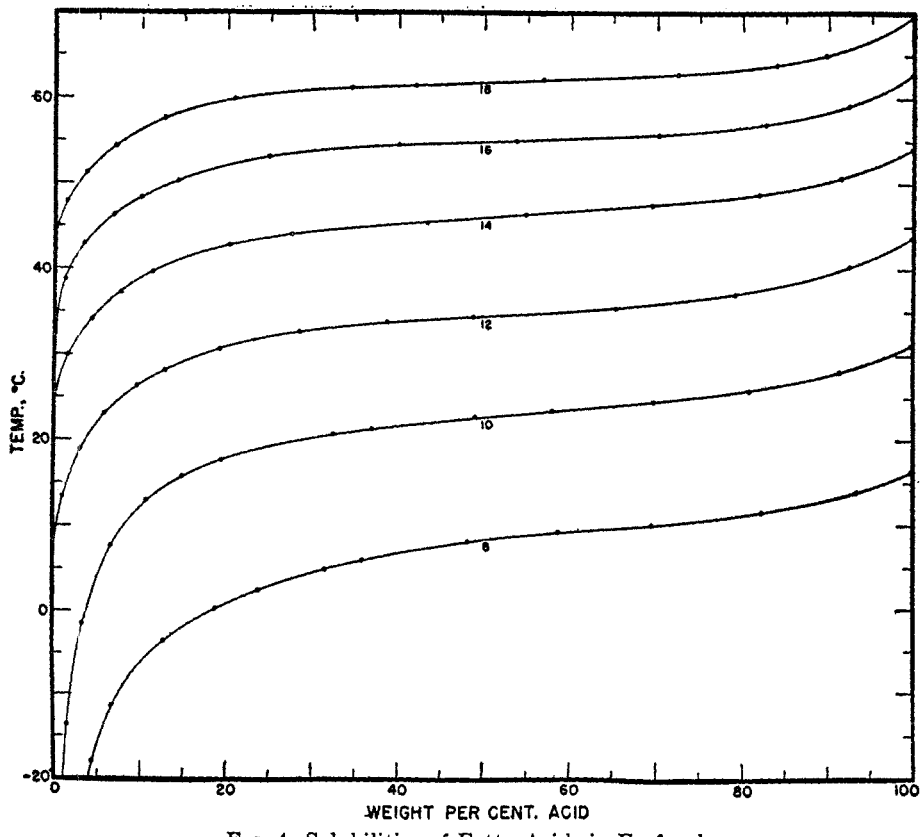

FIG. 4. Solubilities of Fatty Acids in Furfural

bilities of the acids in these solvents are considerably less than their corresponding solubilities in benzene (1). This behavior suggests that the resonating character of the benzene molecules exerts a specific solubilizing influence upon the fatty acids.

The solubilities of the acids in 1,4-dioxane and in furfural are listed in Tables VI and VII, respectively, and are shown graphically in Figs. 3 and 4, respectively. These curves illustrate the contrasting behavior of the acids in a cyclical oxygen-containing solvent of relatively low polarity and in one of quite high polarity. The acids above capric acid in the series are readily soluble in 1,4-dioxane, their solubilities in this solvent approximating those in trichloromethane (2). Such

TABLE VIII

SOLUBILITIES OF FATTY ACIDS IN 1,2-DICHLOROETHANE

NO. OF C ATOMS	G. ACID PER 100 G. 1,2-DICHLOROETHANE						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	144	630	∞	∞	∞	∞	∞
10	21.7	78	260	4060	∞	∞	∞
12	1.2	6.7	36.5	170	1230	∞	∞
14		0.8	5.0	35.5	164	1150	∞
16			0.6	6.0	39.7	187	1650
18				1.0	10.0	70	280

TABLE IX

SOLUBILITIES OF FATTY ACIDS IN NITROMETHANE

NO. OF C ATOMS	G. ACID PER 100 G. NITROMETHANE							
	20.0°	30.0°	40.0°	50.0°	60.0°	70.0°	80.0°	90.0°
10[a]	4.6	9.4	14.3	25.6	∞	∞	∞	∞
12[b]	1.1	2.8	6.6	9.7	15.7	34.1	∞	∞
14[c]	0.7	1.3	2.3	4.7	7.1	11.1	19.2	∞
16	0.5	0.9	1.4	2.2	4.1	5.8	8.9	15.3
18	0.4	0.7	1.0	1.3	1.9	3.6	5.5	0.1

[a] ∞ above 54.8°.
[b] ∞ above 72.0°.
[c] ∞ above 87.8°.

behavior is evidence of either a dipole-dipole attraction of the dioxane molecules for those of the acid, or of the occurrence of hydrogen bonding between these molecules, as there appears to be between acid and trichloromethane molecules. The relatively lower solubilities of the acids in furfural result from the extensively "associated" nature of this highly polar solvent.

The solubilities of the fatty acids in the substituted paraffin solvents 1,2-dichloroethane and nitromethane are listed in Tables VIII and IX, respectively, and the solubility curves in the latter solvent are shown in Fig. 5. The solubilities of the acids in 1,2-dichloroethane are intermediate between those in trichloromethane and in tetrachloromethane (2), indicating that there is evidently some hydrogen bonding of the acids with the solvent molecules. The

solubilities of the acids in nitromethane are so limited that the systems exist as two immiscible liquids over large ranges of concentration. In this respect, the acids are considerably more soluble in nitroethane (2) than in nitromethane, demonstrating that the latter solvent is more highly associated than the former.

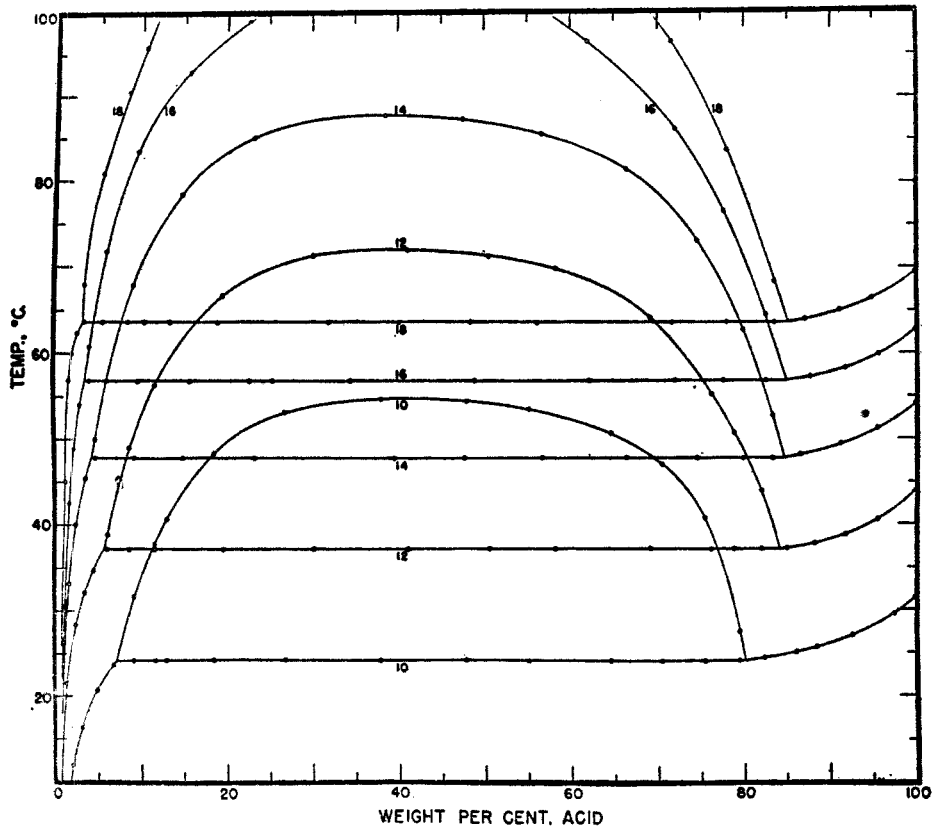

FIG. 5. Solubilities of Fatty Acids in Nitromethane

SUMMARY

The solubilities of caprylic, capric, lauric, myristic, palmitic, and stearic acids have been determined in toluene, *o*-xylene, chlorobenzene, nitrobenzene, 1,4-dioxane, furfural, 1,2-dichloroethane, and nitromethane.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

MELEZITOSE MONOHYDRATE AND ITS OXIDATION BY PERIODATE[1]

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The composition of the large, clear crystals of melezitose (1) which crystallize from its aqueous solutions at room temperature was established definitely by Georges Tanret (2) as $C_{18}H_{32}O_{16} \cdot 2H_2O$. These crystals lose their transparency as a result of efflorescence, and on complete drying by heat the loss of both molecules of water of crystallization can be demonstrated. The specific rotation has been reported by most investigators to be $[\alpha]_D$ +88° to +89° for dried, "anhydrous" melezitose, but similar values have also been quoted for melezitose dihydrate.

As a preliminary step in the present investigation, melezitose dihydrate was prepared by crystallization from water. The large, clear crystals, upon standing in the air at room temperature, became completely white within a few days, and their weight became constant after one molecule of water of crystallization had been lost. The second molecule of water of crystallization was removed readily by heating the powdered monohydrate at 110° *in vacuo*. However, the anhydrous melezitose absorbed moisture very rapidly until it had regained one molecule of water of crystallization. Melezitose monohydrate, $C_{18}H_{32}O_{16} \cdot H_2O$, thus appears to be the stable form of the sugar under normal atmospheric conditions; the use of this monohydrated form is recommended for the preparation of melezitose solutions of accurate composition.

The specific rotation of melezitose monohydrate was determined as $[\alpha]_D^{20}$ +88.5° in water (*c*, 2), which corresponds to $[\alpha]_D^{20}$ +85.6° for melezitose dihydrate, and to $[\alpha]_D^{20}$ +91.7° for anhydrous melezitose. From this experience we may conclude that most samples of "dried" melezitose whose rotations were measured by previous investigators consisted essentially of melezitose monohydrate.

The generally accepted formulation of melezitose (I) as [3-(α-D-glucopyranosyl)-β-D-fructofuranosyl]-α-D-glucopyranoside has been developed in the course of many researches since the isolation of the sugar over a century ago by Bonastre (1). All points in this formula have been established with reasonable certainty except that the β-D-fructofuranosyl linkage is written only by analogy with the corresponding linkages in the other naturally occurring sugars—sucrose, gentianose, raffinose, and probably stachyose (3) and verbascose (4). Unlike those sugars, melezitose cannot be hydrolyzed by invertase (β-D-fructofuranosidase) (5), presumably because of the nearness of the fructofuranoside linkage to the glucosyl radical which is attached through oxygen to carbon 3 of the fructose moiety; hence definite proof that this linkage is of the β- rather than of the α-type is lacking.

[1] Presented in part before the Washington Section of the American Chemical Society, May 10, 1945.

The pyranoid-ring structures of the two glucosyl groups were established by Zemplén and Braun (6), and by Leitch (7), through the methylation of melezitose and the subsequent hydrolysis of the hendecamethylmelezitose. Although their conclusions concerning the sirupy trimethylfructose portions were found later to be incorrect, the fact that Miss Leitch was able to convert her trimethylfructose to a sirupy tetramethyl derivative which agreed in its index of refraction and in its rotation in several solvents with the standard values for 1,3,4,6-tetramethyl-D-fructose is regarded as strong evidence for a fructofuranoid ring in melezitose.

The presence of the fructofuranoid ring has now been proved conclusively, and the presence of two glucopyranoid rings has been confirmed, by the oxidation of melezitose (I) with sodium metaperiodate and with periodic acid by the procedures developed in this Laboratory by Jackson and Hudson (8). When one mole of the sugar was allowed to react with an excess of sodium periodate, four moles of oxidant were consumed, and two moles of formic acid were liberated; no formaldehyde could be detected in the reaction mixtures.[2] The absence of formaldehyde shows that the ring structures must be limited to 2,5 or 2,6 in the fructose unit and to 1,5 and 1,6 in the glucose units. A 2,6-ring in fructose would require one mole of periodate; 1,5- and 1,6-rings in glucose would require two and three moles of periodate, respectively, for each glucose unit; since the total consumption of periodate was only four moles, a 2,6-ringed fructose cannot be present in melezitose because the two glucose units alone must consume at least four moles of periodate. Therefore the fructose unit must have a 2,5 (furanoid)-ring and each glucose unit must have a 1,5 (pyranoid)-ring in order to account for the periodate consumed and for the two moles of formic acid liberated. Very similar results were obtained by the oxidation of melezitose with periodic acid.

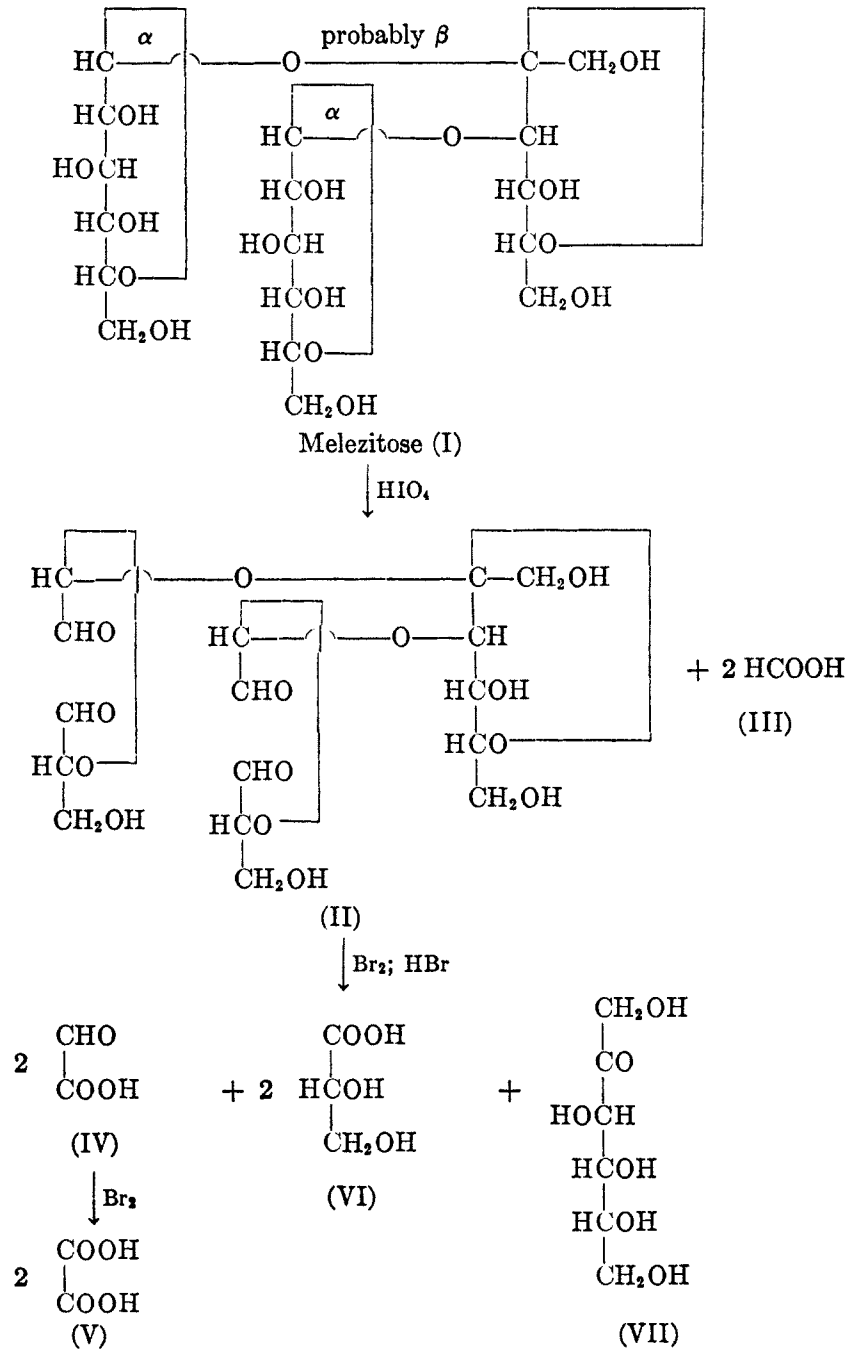
The evidence from the analytical data was supplemented through the isolation and identification of formic acid (III) as the crystalline barium salt. The structure of the tetraaldehyde (II) was confirmed by its further oxidation with bromine water to the corresponding tetrabasic acid, and subsequent hydrolysis of the latter to three products: glyoxylic acid (IV), which was converted to crystalline oxalic acid (V) for identification; D-glyceric acid (VI), which yielded crystalline calcium D-glycerate; and D-fructose (VII), which was levorotatory in solution, formed D-glucose phenylosazone when heated with phenylhydrazine, and could be identified conclusively by its conversion to the characteristic D-fructose *p*-nitrophenylhydrazone.

All these results are in complete accord with those predicted by theory for the oxidation of melezitose of the structure shown by formula I.

EXPERIMENTAL PART

Melezitose monohydrate. Sixty grams of purified melezitose, prepared from honey-dew honey (9), was dissolved in an equal weight of warm water. The solution was filtered into a

[2] In a study of the determination of free primary hydroxyl groups in methylated sugars, Jeanloz [*Helv. Chim. Acta*, **27**, 1517 (1944)] showed that no formaldehyde was liberated in the reaction between melezitose and potassium periodate; he did not determine the amount of reagent consumed.



crystallizing dish and allowed to stand, loosely covered, for several weeks undisturbed in a room kept at 20°. The crystals separated as clusters of large, clear prisms; these were removed, wiped carefully with filter paper to free them from adhering mother liquor, and left

overnight in the air. There was no change in their appearance. An 18-g. portion of the clear crystals was powdered and weighed quickly. Efflorescence began at once with the loss in weight becoming constant at 3.35% within three days in the air at room temperature; the calculated value for the loss of one molecule of water from melezitose dihydrate, $C_{18}H_{32}O_{16}\cdot 2H_2O$, is 3.33%.

The remainder of the large, clear crystals, also 18 g., after standing an additional twenty-four hours in the air, began to show pinpoints of white spots which grew in size until the crystals became entirely white. The crystals retained their original form without becoming crumbly, and their faces had a shiny luster. The loss in weight after about two weeks was constant at 3.5%, corresponding again to the loss of one molecule of water of crystallization by efflorescence and the formation of melezitose monohydrate.

A smaller sample of powdered melezitose monohydrate was dried for six hours at 110° *in vacuo*. The water of crystallization was removed completely, but was regained with such rapidity under atmospheric conditions that considerable difficulty was experienced at first in securing an accurate weight of the anhydrous material. The return from the anhydrous to the monohydrated stage became complete in about two days in the air at room temperature; the weight remained constant thereafter except for slight increases during periods of humid weather.

Anal. Calc'd for $C_{18}H_{32}O_{16}\cdot H_2O$: C, 41.38; H, 6.56; H_2O, 3.45.
Found: C, 41.30; H, 6.58; H_2O, 3.45.

Dr. W. T. Haskins of this Laboratory has recrystallized melezitose by dissolving it in an equal weight of water at 60° and then adding four volumes of warm 95% alcohol. The granular product thus obtained was filtered, washed, and dried in the air overnight. It also had the composition of a melezitose monohydrate.

Anal. Calc'd for $C_{18}H_{32}O_{16}\cdot H_2O$: H_2O, 3.45.
Found (4 hours at 110° *in vacuo*): H_2O, 3.44.

Specific rotation of melezitose monohydrate. The purified melezitose which had been recrystallized from water as described above was identical in rotation with a sample which had been twice recrystallized from water and alcohol by Dr. Haskins. This rotation, $[\alpha]_D^{20}$ +88.5° in water (*c*, 2 to 4), characterizes melezitose monohydrate; from it may be calculated the values $[\alpha]_D^{20}$ +85.6° for melezitose dihydrate and $[\alpha]_D^{20}$ +91.7° for anhydrous melezitose. The rotations +88° to +89° reported for "dried melezitose" by many earlier investigators undoubtedly referred to samples which at the time of weighing consisted principally of melezitose monohydrate.

Oxidation of melezitose with sodium metaperiodate. To 2.6122 g. of melezitose monohydrate in 175 ml. of water was added 60 ml. of 0.4365 *M* aqueous sodium periodate (5.22 molecular equivalents), and the volume was adjusted exactly to 250 ml. The rotation, observed in a 4-dm. tube, dropped from +3.70° (circular degrees, calc'd) to +1.19° during the first hour, to +1.04° in two hours, and to +0.90° in four hours, then rose slowly to +1.04° by the end of twenty-four hours and remained constant for several days. This final rotation corresponds to $[\alpha]_D^{20}$ +29.5° for the expected tetraaldehyde (II). The titration of aliquots showed the consumption of 3.57, 3.68, 3.96, 4.00, and 4.04 equivalents of periodate after two, five, twenty-four, forty-eight, and seventy-two hours, respectively. The production of formic acid seemed to approach the theoretical value of two equivalents more slowly, the titrations indicating 1.67, 1.77, and 1.85 equivalents after twenty-four, forty-eight, and seventy-two hours, respectively. These values increased very slowly thereafter, presumably due to secondary oxidation reactions. No formaldehyde could be detected with dimethyldihydroresorcinol.

Oxidation of melezitose with periodic acid. A solution of 26.12 g. of melezitose monohydrate in 1600 ml. of water was cooled to 4°, and to it was added 413 ml. of cold 0.5445 *M* periodic acid (4.5 molecular equivalents). The mixture was kept in the refrigerator at 4° because the reaction proceeded too rapidly at room temperature. The volume was adjusted to 2000 ml. After twenty-four and forty-five hours the titration of aliquots showed that 3.87 and 4.03 equivalents of periodic acid had been consumed, and that 1.78 and 1.98 equiva-

lents of periodic acid had been consumed, and that 1.78 and 1.98 equivalents of formic acid had been liberated, respectively. No formaldehyde could be detected. The oxidation was stopped after forty-six hours, to avoid secondary reactions, by adding aqueous barium hydroxide to the ice-cold reaction mixture until it was faintly alkaline to phenolphthalein. The insoluble barium iodate and barium periodate were removed by filtration. The rotation of the filtrate corresponded to $[\alpha]_D^{20}$ +29.6° for the expected tetraaldehyde (II), in excellent agreement with the value +29.5° which had been obtained by the oxidation of melezitose with sodium periodate.

At this point in one experiment the filtrate was concentrated *in vacuo* to a dry sirup and 200 ml. of methyl alcohol was added to extract the expected tetraaldehyde. The undissolved residue consisted of 9.2 g. of elongated prisms which were recrystallized from water and identified as barium formate; the theoretical yield was 10.2 g.

Anal. Calc'd for $C_2H_2BaO_4$: C, 10.56; H, 0.89; Ba, 60.40.
Found: C, 10.60; H, 1.04; Ba, 60.39.

In the principal experiment the filtrate was acidified and oxidation of the tetraaldehyde effected by the addition of 25 ml. of bromine. The rotation changed from positive to weakly negative, becoming constant within four days; after four more days the excess bromine was removed by aeration. To hydrolyze the expected tetrabasic acid, the solution was heated at 85° for twenty-three hours, the rotation reaching a constant and somewhat higher rotation than before. Next, the expected glyoxylic acid (IV) was oxidized to oxalic acid (V) by adding 5 ml. of bromine and allowing the mixture to stand in the dark for two days; excess bromine was removed by aeration. Aqueous barium hydroxide was then added until the solution was barely alkaline to phenolphthalein. The precipitated barium oxalate weighed 4.1 g., representing only a 37% yield, although in a nearly parallel experiment a 71% yield was obtained. This product was dissolved in hot dilute hydrochloric acid, and the barium ions were precipitated with sulfuric acid; upon concentration of the filtrate, oxalic acid dihydrate was obtained and identified, after two recrystallizations from water, by its melting point and mixed melting point, and by titrations with alkali and with potassium permanganate.

The filtrate from the barium oxalate precipitate was freed from barium ions with sulfuric acid, and from bromide ions with silver carbonate; the excess silver ions were precipitated with hydrogen sulfide, and the solution was aerated to expel the dissolved hydrogen sulfide. The solution, which presumably contained D-fructose and D-glyceric acid, was concentrated, neutralized barely to phenolphthalein with limewater, and the calcium salts were precipitated, in several fractions, with methyl and ethyl alcohols. The final filtrate was concentrated to a sirup which was extracted with absolute ethyl alcohol.

The crude calcium salts were dissolved in water and the solution was treated with decolorizing carbon and concentrated. The crystalline product which separated as a hard cake of prisms weighed 7.8 g. It was recrystallized from water to a constant rotation of $[\alpha]_D^{20}$ +15.5° in water (c, 0.7), and melting point about 142° with decomposition; these values are in agreement with those reported by Jackson and Hudson (10), and, with the analyses below, identify the product as calcium D-glycerate dihydrate.

Anal. Calc'd for $C_6H_{10}CaO_8 \cdot 2H_2O$: Ca, 14.00; H_2O, 12.59.
Found: Ca, 13.90; H_2O (at 110° *in vacuo*), 12.42.

The absolute alcohol extract had a levorotation equivalent to 3.3 g. of fructose; the theoretical yield was 8.9 g., but undoubtedly a portion of the sugar was lost through the destructive action of the warm acid solution which was used to hydrolyze the tetrabasic acid. One-third of this solution was concentrated to remove the alcohol, and the residue was dissolved in water. Phenylhydrazine and a small amount of acetic acid were added, and the mixture, after being warmed on the steam-bath for two hours, yielded 1.5 g. of D-glucose phenylosazone, m.p. 210° with decomposition. The product was identified further by converting 1 g. of it to 0.44 g. of D-glucose phenylosotriazole according to Hann and Hudson (11); the rotation, $[\alpha]_D^{20}$ −81.7° in pyridine (c, 0.8), and melting point, 195–196°,

are in agreement with the values reported by those authors. A mixed melting point with an authentic sample of the osotriazole showed no depression.

Another third of the absolute alcohol extract was concentrated to 75 ml. and boiled gently for two minutes with 1.3 g. of *p*-nitrophenylhydrazine. The solution, upon concentration *in vacuo* to a small volume, yielded 1.5 g. of reddish, pellet-like crystals which melted at 174–175° with decomposition. The product was recrystallized once from 95% alcohol, once from water, and then twice from 95% alcohol; the melting point of 182° with decomposition, the analysis, and the habit of crystallizing first in yellow, prismatic needles which changed to yellow prisms (see the following paragraph), identified the substance as D-fructose *p*-nitrophenylhydrazone.

Crystalline modifications of D-*fructose p-nitrophenylhydrazone.* The reaction between D-fructose and *p*-nitrophenylhydrazine according to the directions of van der Haar (12) yielded yellow, prismatic needles melting at 182° with decomposition. However, the first attempts to isolate this compound from the absolute alcohol extract which was presumed to contain fructose from the melezitose oxidation and degradation products resulted in the separation of small, yellow plates. Further recrystallizations of the "known" fructose *p*-nitrophenylhydrazone from 95% alcohol then revealed that in our Laboratory this compound now usually crystallizes from concentrated solutions, upon cooling, as fine, yellow, prismatic needles which begin to change spontaneously within two or three hours at room temperature to clusters of darker yellow, plate-like prisms; the change is complete within one or two days; from more dilute solutions only the latter prismatic form may appear. In the experiments just performed, all samples of D-fructose *p*-nitrophenylhydrazone, whether prepared from pure fructose or from the fructose solution derived from melezitose, crystallized subsequently from 95% alcohol in this manner. There appears to be no difference in melting point or composition between the two modifications.

Anal. Calc'd for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.44; N, 13.33.

Found (needles, from pure fructose): C, 45.71; H, 5.27; N(Kjeldahl[3]), 13.08. (prisms, from pure fructose): C, 45.93; H, 5.32; N, 13.13. (prisms, from "melezitose" fructose): C, 45.70; H, 5.46; N, 13.23.

The authors wish to thank Dr. Arthur T. Ness and Mr. Charles A. Kinser of this Institute for carrying out the microchemical analyses.

SUMMARY

The stable form of crystalline melezitose under normal conditions is the monohydrate, $C_{18}H_{32}O_{16} \cdot H_2O$, with $[\alpha]_D^{20}$ +88.5° in water.

A study of the oxidation of melezitose with sodium metaperiodate and with periodic acid has proved conclusively the presence of the fructofuranoid ring in this sugar.

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DERIVATIVES OF SULFATHIAZOLE

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A number of derivatives of sulfathiazole having alkyl or aryl substituents in the thiazole nucleus have been synthesized and shown to possess antibacterial activity (1). Other properties, however, render this type of derivative unsuitable for chemotherapeutic use. In view of this adverse effect of the alkyl and aryl groups, a study has been made of the properties of sulfathiazole derivatives containing functional substituents in the thiazole ring. The results reported in previous papers (2, 3) have shown that the introduction of a carboxylic acid group reduced the antibacterial activity and also restricted absorption from the intestinal tract following oral administration. Compounds of this type may be useful therapeutic agents, particularly where limited absorption is desirable (3, 4). The present paper describes the preparation and properties of sulfathiazole derivatives having a *tert.*-amino, mercapto, or hydroxyl group on the alkyl substituent of the thiazole nucleus.

Recently we have described methods for the preparation of 2-aminothiazoles with aminoalkyl, alkylmercaptoalkyl, or hydroxymethyl substituents (5, 6). In general, these compounds formed sulfonamides by reaction with a sulfonyl chloride in the presence of pyridine. The solubility characteristics of the sulfonamido-*tert.*-aminoalkylthiazoles necessitated some modification of the usual isolation procedure and the products were handled more satisfactorily as salts.

The synthesis of *tert.*-aminoalkylsulfathiazoles through the reaction of N-acetylsulfanilylthiourea with α-bromo-*tert.*-amino ketone salts was unsatisfactory. Although 1-bromo-4-dimethylamino-2-butanone hydrobromide afforded a very low yield of 2,N^4-acetylsulfanilamido-4-(2-dimethylaminoethyl)thiazole hydrobromide by this method, no sulfonamide was isolated when several other bromoamino ketone salts were used. This type of synthesis of sulfathiazole derivatives has been employed successfully by Földi and co-workers (7) with a variety of α-halogen carbonyl compounds.

The condensation of N-acetylsulfanilyl chloride with 2-amino-4-[2-(1,2,3,4-tetrahydroisoquinolino)ethyl]thiazole, 2-amino-4-dimethylaminomethylthiazole, 2-amino-4-hydroxymethylthiazole and bis-(2-amino-4-thiazolylmethyl)disulfide gave only tars or poorly defined amorphous solids.

Since the sulfonyl chloride condensation with 2-amino-4-hydroxymethylthiazole failed, 2-sulfanilamido-4-hydroxymethylthiazole was prepared in low yield by the method of Földi (7) through the reaction of N-acetylsulfanilylthiourea with α,γ-dichloroacetone followed by hydrolysis of the chloromethyl compound.

Sulfapyridine and sulfadiazine derivatives having a free amino group in the heterocyclic nucleus (8, 9, 10) as well as disulfanilamidopyridine (9) and disulfanilamidopyrimidine (10) have been described. The preparation of anal-

ogous compounds in the thiazole series by the usual procedures would require a diaminothiazole as a starting material. The hydrochloride of one such diamine was obtained by the reaction of chloroacetonitrile and thiourea in hot alcohol solution. The product may be represented as 2,4-diaminothiazole (II). The reaction probably proceeds through S-cyanomethylisothiourea (I) which has been prepared previously (11) by carrying out the reaction in acetone at room temperature. The isothiourea readily yielded II on warming in alcohol solution. Although the product of these reactions can be formulated as the diamine II, its chemical properties more nearly agree with those expected of the amine-imine III.[1] Hydrolysis under mild conditions yielded 2-amino-4-thiazolone (IV). The reaction of the hydrochloride of II with either one or two equivalents of N-acetylsulfanilyl chloride in pyridine gave a black amorphous product that

TABLE I

2-SULFANILAMIDO-R-THIAZOLES

SN[a]	R	MAX. BLOOD CONC.[b] MG./100 ML.	*In Vitro*[c] ANTIBACTERIAL ACTIVITIES
5400	4-Piperidinomethyl	1.1	0.10
5398	4-(2-Dimethylaminoethyl)	2.9	0.06
5392	4-Dimethylaminomethyl-4,5,6,7-tetrahydrobenzo	2.3	0.20
8462	4-Methylmercaptomethyl	20.5	0.70
	4-Ethylmercaptomethyl	11.9	0.50
	4-Hydroxymethyl	8.0	0.04
1649	4,5,6,7-Tetrahydrobenzo[d]	2.2	0.20
106	4-Methyl[d]	12.6	0.90
103	H (Sulfathiazole)[d]	18.3	1.00

[a] See footnote 3.

[b] Maximum blood concentration of drug attained in mice following the oral administration of 1.0 g./kg. The concentration reached the maximum two hours after the dose.

[c] Activity against *E. coli* expressed as a fraction of the activity of sulfathiazole.

[d] Known compounds used as standards for comparison.

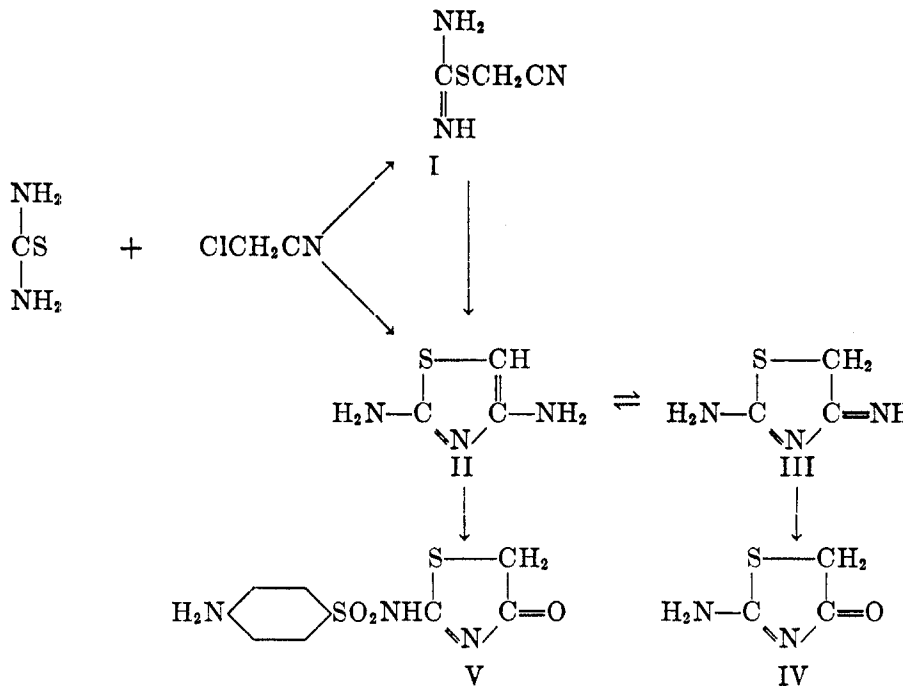
resisted purification. Hydrolysis of this material gave 2-sulfanilamido-4-thiazolone (V) which had been prepared (12) previously from 2-amino-4-thiazolone (IV).

The antibacterial activities against *E. coli in vitro* and the blood concentrations following oral administration to mice are summarized in Table I.[2]

The introduction of the hydroxymethyl group or dialkylaminoalkyl groups into sulfathiazole caused a marked reduction in activity when compared with sulfathiazole or sulfamethylthiazole. On the other hand, the introduction of a dimethylaminomethyl group in the 4-position of 2-sulfanilamido-4,5,6,7-tetrahydrobenzothiazole did not alter the activity. The alkylmercaptomethyl

[1] Since this work was completed, a German Patent has described the preparation of 2,4-diaminothiazole from thiourea and a haloacetonitrile; Ger. Pat. 729,583; *cf. Chem. Abstr.*, **38**, 382 (1944).

[2] We are indebted to the Departments of Bacteriology and Pharmacology of this laboratory for the biological data. (Table I.)



compounds showed activities higher than those of the *tert.*-aminoalkyl derivatives and comparable with the activity of sulfathiazole.

The concentration of drug in the blood following oral administration to mice of a single dose reached only very low levels with the amino derivatives, a somewhat higher level with the hydroxymethyl compound, and high levels with the two alkylmercapto derivatives. Again, the presence of the dimethylaminomethyl group in the tetrahydrobenzothiazole compound had little influence; the parent compound and the substituted derivative gave comparable blood levels.

Urinary excretion studies in dogs showed that the low blood concentration of the amino derivatives was due not alone to poor absorption from the gastrointestinal tract but also to rapid renal elimination. Two compounds, 2-sulfanilamido-4-piperidinomethylthiazole and 2-sulfanilamido-4-dimethylaminomethyl-4,5,6,7-tetrahydrobenzothiazole, were excreted in the urine to the extent of 30–60 % of the administered dose in 72 hours. These values lie between those obtained with succinylsulfathiazole (12–26%), or phthalylsulfathiazole (12–16%), and sulfaguanidine (60%). With the exception of the mercapto derivatives, none of the compounds exhibited any significant therapeutic activity against experimental streptococcal or pneumococcal infection in mice. Some of these compounds and the itermediate 2-aminothiazoles were tested also in avian malaria.[3]

[3] These tests were carried out by the Survey of Antimalarial Drugs of the National Research Council. The survey number (SN in Table I) identifies the compound in a forthcoming monograph, A Survey of Antimalarial Drugs 1941–1945. The activity and pharmacology will be given in this monograph.

EXPERIMENTAL[4]

The aminoalkyl-2-aminothiazoles (5, 6) were dissolved in dry pyridine and cooled in an ice-bath while a 10% excess of N-acetylsulfanilyl chloride was added in small portions. The solutions were kept overnight at room temperature and then distilled *in vacuo* at 50–60° to remove most of the pyridine. Since the free bases tended to form oils, the products were converted to crystalline salts by the addition of an excess of aqueous hydrochloric or hydrobromic acid.

The acetylsulfanilamido derivatives of the alkylmercaptomethylthiazoles (5) were prepared and isolated in the usual manner (13).

Deacetylation to the sulfonamido derivatives was effected by heating the acetyl derivatives for two to four hours on a steam-bath with aqueous sodium hydroxide or hydrochloric acid or by refluxing with alcoholic hydrogen chloride solution.

2-Sulfanilamido-4-piperidinomethylthiazole. The hydrochloride of the acetyl derivative usually crystallized out of the pyridine solution. Occasionally, however, it was necessary to concentrate the solution. The hydrochloride was dissolved in cold dilute sodium hydroxide solution and reprecipitated by the addition of an excess of concentrated hydrochloric acid. After recrystallization from dilute alcohol, it melted at 253–255° dec., yield 40%.

Anal. Calc'd for $C_{17}H_{22}N_4O_3S_2 \cdot HCl$: Cl, 8.23. Found: Cl, 8.17.

The acetyl derivative was hydrolyzed with 3 *N* hydrochloric acid and the free base was precipitated by neutralizing the solution with sodium hydroxide; yield 85%. An analytical sample, m.p. 209.5–210.5° dec., was prepared by recrystallization from dilute methanol.

Anal. Calc'd for $C_{15}H_{20}N_4O_2S_2$: C, 51.16; H, 5.73; N, 15.90.
Found: C, 50.96; H, 5.33; N, 15.78.

2-Sulfanilamido-4-(2-dimethylaminoethyl)thiazole. The pyridine reaction mixture was filtered to remove a solid that was found to be the hydrochloride of the aminothiazole. The solid was washed with a little ethanol and the combined filtrate and washings were concentrated *in vacuo*. The residue was diluted with water and made strongly acid with 48% hydrobromic acid. The hydrobromide separated slowly as a yellow powder. Recrystallization from water gave light yellow needles, m.p. 230–231° dec., yield 40%.

Anal. Calc'd for $C_{15}H_{20}N_4O_3S_2 \cdot HBr$: N, 12.47; Br, 17.79.
Found: N, 12.39; Br, 17.72.

The acetyl derivative was hydrolyzed with 10% sodium hydroxide solution. The hemihydrate of the sulfonamide, m.p. 164–165° dec., was obtained in 72% yield after recrystallization from water. A rapidly cooled water solution of this compound gave crystals, m.p. 179–180°, that reverted to the lower-melting form on subsequent crystallization from a slowly cooling solution. Dehydration *in vacuo* was accompanied by the evolution of dimethylamine and resinification of the residue.

Anal. Calc'd for $(C_{13}H_{18}N_4O_2S_2)_2 \cdot H_2O$: N, 16.71. Found: N, 16.79.

2,p-Nitrobenzenesulfonamido-4-dimethylaminomethyl-4,5,6,7-tetrahydrobenzothiazole was prepared by adding one molecular equivalent of *p*-nitrobenzenesulfonyl chloride to a pyridine solution of the aminothiazole. After standing overnight at room temperature the reaction mixture was dissolved in dilute sodium hydroxide solution and the *hydrochloride* of the sulfonamide was precipitated by the addition of an excess of concentrated hydrochloric acid. Recrystallization from very dilute hydrochloric acid gave a 68% yield of bright yellow crystals, m.p. 237–238° dec.

Anal. Calc'd for $C_{16}H_{21}N_4O_4S_4 \cdot HCl$: N, 12.94; Cl, 8.19.
Found: N, 12.85; Cl, 8.17.

2-Sulfanilamido-4-dimethylaminomethyl-4,5,6,7-tetrahydrobenzothiazole. A. The residue obtained after the removal of pyridine was diluted with water and neutralized with sodium hydroxide. The dark oily precipitate slowly changed to a cotton-like mass of crystals. The moist product dissolved readily in 6 *N* hydrochloric acid and a copious pre-

[4] All melting points are uncorrected.

cipitate of the crystalline *hydrochloride monohydrate* of the acetyl derivative separated almost immediately; yield 45%. White crystals, m.p. 226–228° dec., were obtained by crystallization from 95% alcohol.

Anal. Calc'd for $C_{18}H_{24}N_4O_8S_2 \cdot HCl \cdot H_2O$: N, 12.12; Cl, 7.66.
Found: N, 12.08; Cl, 7.70.

The deacetylation was carried out in 6 *N* hydrochloric acid. The sulfanilamido compound was obtained as a *monohydrate*, m.p. 156–158° dec., by recrystallization from water.

Anal. Calc'd. for $C_{16}H_{22}N_4O_5S_2 \cdot H_2O$: N, 14.57. Found: N, 14.37.

B. 2,*p*-Nitrobenzenesulfonamido-4-dimethylaminomethyl-4,5,6,7-tetrahydrobenzothiazole was reduced with iron and 8% acetic acid and the amino compound was recrystallized from water. The melting point and mixed melting point showed that it was identical with the sulfanilamido compound prepared from acetylsulfanilyl chloride.

The free base formed complexes with many of the common solvents and the removal of solvent was always accompanied by evolution of dimethylamine.

The *dihydrochloride*, m.p. 214–216° dec., separated as white crystals when a solution of the free base in methanolic hydrogen chloride solution was diluted with ethyl acetate. The yield, based on the acetyl derivative, was 89%.

Anal. Calc'd for $C_{16}H_{22}N_4O_2S_2 \cdot 2HCl$: N, 12.75; Cl, 16.14.
Found: N, 12.62; Cl, 16.19.

2-Sulfanilamido-4-piperidinomethyl-4,5,6,7-tetrahydrobenzothiazole. The *hydrochloride dihydrate* of the acetyl derivative was obtained as a crystalline solid by diluting the residue from the pyridine distillation with water and adding an excess of concentrated hydrochloric acid. Recrystallization from water gave a 57% yield of pale yellow crystals that melted with decomposition at about 160° in a rapidly heated bath.

Anal. Calc'd for $C_{21}H_{29}N_4O_3S_2 \cdot HCl \cdot 2H_2O$: Cl, 6.81. Found: Cl, 6.88.

Hydrolysis with 6 *N* hydrochloric acid gave the sulfanilamido derivative which was precipitated by neutralizing the hydrolysis mixture and purified by recrystallization from a large volume of methanol; yield 55%. The pure compound melted at 189–190° dec.

Anal. Calc'd for $C_{19}H_{26}N_4O_2S_2$: C, 56.16; H, 6.45; N, 13.80.
Found: C, 55.47; H, 6.59; N, 13.56.

2-Sulfanilamido-4-methylmercaptomethylthiazole. The crude acetyl derivative was difficult to crystallize. After most of the pyridine was removed by distillation *in vacuo*, the residue was diluted with water and adjusted to *p*H 5 with sodium hydroxide. Concentration of the resulting solution *in vacuo* left a gummy residue that solidified slowly. After two reprecipitations from sodium hydroxide solution by acidification with hydrochloric acid the sulfonamide separated in crystalline form. Crystallization from dilute ethanol gave a 70% yield of white product, m.p. 216–218°.

Anal. Calc'd for $C_{13}H_{15}N_3O_3S_3$: N, 11.76. Found: N, 11.67.

The acetyl derivative was hydrolyzed with boiling 4 *M* hydrochloric acid. The sulfanilamido compound separated as an oil when the mixture was neutralized. It was obtained in crystalline form by dissolving it in boiling alcohol and slowly adding water to the solution; yield 70%. After two recrystallizations from a benzene-alcohol mixture, the melting point was 138–139°.

Anal. Calc'd for $C_{11}H_{13}N_3O_2S_3$: N, 13.33. Found: N, 13.21.

2-Sulfanilamido-4-ethylmercaptomethylthiazole. The acetyl derivative was precipitated by acidification of the diluted reaction mixture. Reprecipitation followed by crystallization from ethanol gave a 65% yield of white crystals, m.p. 208–210°.

The acetyl derivative was deacetylated in boiling 10% alcoholic hydrogen chloride. The hydrochloride of the sulfanilamido compound, which separated on cooling, was decomposed with sodium hydroxide solution and the free base was crystallized from dilute ethanol. A 48% yield of white plates, m.p. 149–150° was obtained.

Anal. Calc'd for $C_{12}H_{15}N_3O_2S_3$: N, 12.77. Found: N, 12.74.

2-Sulfanilamido-4-carboxymethylmercaptomethylthiazole. 2-Amino-4-carbethoxymethylmercaptomethylthiazole was treated with acetylsulfanilyl chloride in the usual manner.

After removal of the pyridine, the residue was stirred with water until it solidified. Reprecipitation from sodium hydroxide solution followed by two crystallizations from 30% alcohol gave a 56% yield of white crystals, m.p. 208–210° dec. The solubility of the product in sodium bicarbonate showed that the ester group had been hydrolyzed during the isolation.

Anal. Calc'd for $C_{14}H_{15}N_3O_5S_2$: N, 10.47. Found: N, 10.43.

The acetyl derivative was hydrolyzed with 10% sodium hydroxide. The sulfanilamido compound was precipitated by acidification to *p*H 2 and the product was recrystallized from water three times. A 65% yield of material melting at 158–160° was obtained.

Anal. Calc'd for $C_{12}H_{13}N_3O_4S_3$: N, 11.70. Found: N, 11.47.

The *ethyl ester*, m.p. 114–115°, was prepared by esterification with alcoholic hydrogen chloride followed by recrystallization from dilute alcohol.

Anal. Calc'd for $C_{14}H_{17}N_3O_4S_3$; N, 10.85. Found: N, 10.77.

2-Sulfanilamido-4-hydroxymethylthiazole. This sulfonamide, m.p. 200–201° dec., was prepared in 17% yield from N^4-acetylsulfanilylthiourea by the method by Földi. (7).

2-Amino-4-imino-2-thiazoline hydrochloride (III).[5] *A.* Chloroacetonitrile (8.5 g., 0.11 mole), thiourea (7.6 g., 0.1 mole), and 60 cc. of alcohol were mixed and warmed under reflux on a steam-bath. The thiourea dissolved rapidly and the exothermic reaction caused the alcohol to boil vigorously. The product separated as a fine white crystalline solid and the filtrate gave a negative test for thiourea with ammoniacal silver nitrate. The yield of hydrochloride was 13.0 g. (86%). It was recrystallized rapidly from water or dilute alcohol solution. Both the crude and recrystallized material gave the same analyses and were unmelted at 350°.

Anal. Calc'd for $C_3H_6ClN_3S$: N, 27.70; Cl, 23.39.
Found: N, 27.62; Cl, 23.30.

B. A solution of S-cyanomethylisothiourea hydrochloride (11) in alcohol was refluxed on a steam-bath. After a few minutes, a fine crystalline precipitate of the hydrochloride began to form. The solid was identical with that obtained under *A*.

Anal. Found: N, 27.54.

The addition of saturated aqueous picric acid to a solution of the hydrochloride in water gave a crystalline picrate. This did not melt up to 350°.

Anal. Calc'd for $C_3H_5N_3S \cdot C_6H_3N_3O_7$: N, 24.40. Found: N, 24.35.

Recrystallization of the hydrochloride from hot water containing hydrochloric acid gave 2-amino-4-thiazolone hydrochloride (IV) which did not melt at 350° and was identical with a sample prepared from thiourea and chloroacetic acid (14).

Anal. Calc'd for $C_3H_5ClN_2OS$: N, 18.35; Cl, 23.24.
Found: N, 18.37; Cl, 23.43.

SUMMARY

Derivatives of sulfathiazole having *tert.*-aminoalkyl, hydroxymethyl, or alkylmercaptomethyl groups in the thiazole nucleus have been prepared. The effect of these groups upon the antibacterial activity and the absorption following oral administration is discussed.

An attempt to prepare 2,4-disulfanilamidothiazole was not successful.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

THE PREPARATION AND PROPERTIES OF SEVERAL ISOMERIC UNSYMMETRICAL ANHYDRIDES OF THE SATURATED ALIPHATIC MONOCARBOXYLIC ACIDS

A. W. RALSTON AND R. A. RECK

Received May 22, 1946

Several years ago Wallace and Copenhaver (1) determined the melting points of the symmetrical anhydrides of the saturated aliphatic acids from enanthic to stearic acid inclusive and compared these melting points with those of the parent acids. The melting points of the acids, within this range of chain length, show a decided alternation, that of an odd-carbon-membered acid being lower than those of the two adjacent even acids. The melting points of the anhydrides, on the other hand, show a much weaker alternation which differs from that of the acids in that the anhydride of an odd acid melts slightly higher than the mean of the two adjacent even members. It is significant that, for the compounds investigated, only a small difference exists between the melting point of an anhydride and that of its parent acid. This indicates that the melting points of the anhydrides are more greatly influenced by the length of the longest chain than by the total number of carbon atoms in the molecule. Consequently, we have synthesized several mixed anhydrides, all of which contain eighteen carbon atoms, in which the length of the longest chain varies from ten to sixteen carbon atoms and have compared their physical properties with those of the symmetrical anhydrides and of the parent acids.

These mixed anhydrides were prepared by the reaction of the higher acid chlorides with the anhydrous sodium soaps, which method was first employed by Gerhardt (2) and later by Villier (3) and by Krafft and Rosiny (4) for the synthesis of a number of symmetrical aliphatic anhydrides. The melting points of the mixed anhydrides, the higher parent acids and their corresponding symmetrical anhydrides are shown in Table I.

The values recorded in Table I show that the melting points of the four isomeric mixed anhydrides differ over a wide range, the values decreasing progressively with decrease in the chain length of the longest chain. It is noteworthy that there is only a small difference between the melting point of a mixed anhydride containing a C_{12}, C_{14}, or C_{16} chain and that of the corresponding long chain acid or the symmetrical anhydride of this acid. This correlation, however, disappears with the mixed C_8—C_{10} anhydride and the C_{10}—C_{10} anhydride both of which melt considerably lower than capric acid.

The unsymmetrical anhydrides are soluble in both polar and non-polar organic solvents. In the polar organic solvents such as acetone or acetonitrile, solution is attended by a disproportionation reaction. This tendency is especially marked where the difference in chain length is appreciable, such as with acetic-palmitic anhydride. Such anhydrides cannot, therefore, be satisfactorily crystallized from polar organic solvents. The mixed anhydrides may be crystal-

lized from non-polar solvents, such as petroleum ether, although prolonged heating of acetic-palmitic anhydride in this solvent results in the formation of some acetic anhydride and palmitic anhydride. The mixed anhydrides are apparently rapidly hydrolyzed by water, the rate of hydrolysis increasing with greater differences in the chain lengths. Since the actual rates of hydrolysis have not been determined the above conclusions are speculative.

EXPERIMENTAL

Preparation of the acid chlorides. Capryl, lauroyl, myristoyl, and palmitoyl chlorides were prepared by a method similar to that previously described by Ralston and Selby (6) which includes refluxing the acids with a three molar ratio of thionyl chloride for 3 hours, removing the excess of thionyl chloride, and fractionally distilling the products. The acid chlorides had the following boiling points: capryl, 120–122°$_{26\ mm.}$; lauroyl, 140–141°$_{12\ mm.}$; myristoyl, 171–172°$_{13\ mm.}$; palmitoyl, 187–188°$_{14\ mm.}$

Preparation of acetic-palmitic anhydride. Palmitoyl chloride (27.4 g., 0.1 mole) was weighed into a three-necked, 200-cc. flask, equipped with a mechanical stirrer and thermometer. Anhydrous sodium acetate (8.5 g., 0.103 mole) was added over a period of 5 minutes. The mixture was heated in an oil-bath with stirring for thirty minutes. It was then allowed to cool and the solid mass which formed was extracted with petroleum ether. The

TABLE I

THERMAL CONSTANTS OF MIXED ANHYDRIDES, ACIDS AND SYMMETRICAL ANHYDRIDES

MIXED ANHYDRIDES	M.P., °C.	F.P.,		SYMMETRICAL ANHYDRIDE	M.P., °C. (1)
		ACID	°C. (5)		
C_{16}—C_2	62.5	C_{16}	62.41	C_{16}—C_{16}	63.9
C_{14}—C_4	52.7	C_{14}	53.78	C_{14}—C_{14}	53.5
C_{12}—C_6	42.4	C_{12}	43.86	C_{12}—C_{12}	42.1
C_{10}—C_8	16.0	C_{10}	30.92	C_{10}—C_{10}	24.7

product was then recrystallized three times from petroleum ether (b.p. 65–67°) after which it melted at 62.5° (yield 70%). The neutralization equivalents employing aqueous sodium hydroxide and also alcoholic sodium methoxide were determined by the method of Smith and Bryant (7) (found: with NaOH, 152; with $NaOCH_3$, 298; calc'd: 149, 298).

Preparation of butyric-myristic anhydride, caproic-lauric anhydride, and caprylic-capric anhydride. Anhydrous potassium butyrate, potassium caproate, and potassium caprylate were prepared by dissolving the respective acids in 95% ethanol and neutralizing to phenolphthalein with alcoholic potassium hydroxide. The soaps were obtained by evaporating the solutions to dryness under a vacuum. They were then treated with the respective acid chlorides according to the procedure described above with the exception that longer reaction times and higher temperatures were employed (2 hrs. at 90°). The products were recrystallized from petroleum ether and possessed the following physical and chemical constants: butyric-myristic anhydride, m.p. 52.7°, neutral. equivs. 148.1, 297.8, yield 81%; caproic-lauric anhydride, m.p. 42.4°, neutral. equivs. 149.7, 298.9, yield 85%; caprylic-capric anhydride, m.p. 16.0°, neutral. equivs. 146.8, 296.7, yield 85%.

CHICAGO, ILL.

SUMMARY

The isomeric anhydrides: acetic-palmitic anhydride, butyric-myristic anhydride, caproic-lauric anhydride, and caprylic-capric anhydride have been

prepared and their melting points compared with those of the acids and the symmetrical anhydrides.

For the unsymmetrical anhydrides prepared the melting points are more dependent upon the length of the longest hydrocarbon chain than upon the total number of carbon atoms in the compound.

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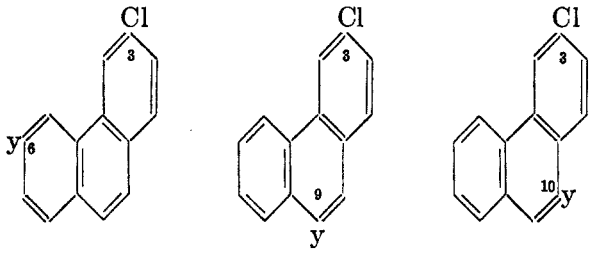
[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XVIII.[1,2] AMINO ALCOHOLS OF THE TYPE—$CHOHCH_2NR_2$ DERIVED FROM 3-BROMO-10-ACETYLPHENANTHRENE

EVERETTE L. MAY AND ERICH MOSETTIG

Received July 23, 1945

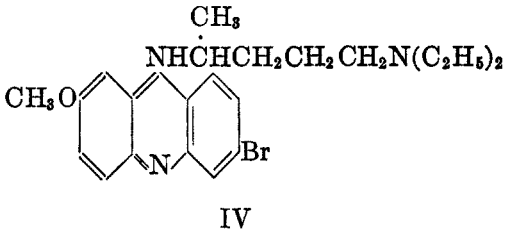
In previous papers (1, 2, 3) of this series we described the synthesis of nuclear-chlorinated phenanthryl alkamines of the formulas I, II, and III, and compared their plasmodicidal effectiveness with that of the corresponding "des-chloro" compounds.



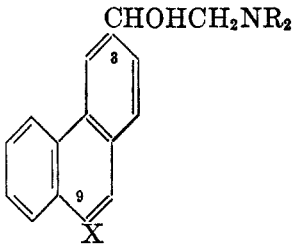
I II III

y = $-CHOHCH_2NR_2$

Mauss (4) reports that the bromine-analog (IV) of Atabrine is only half as active (*Plasmodium cathemerium*, canary) as Atabrine itself. On the other hand, Schultz, Goldberg, Ordas, and Carsch (5, 6) demonstrated that there is no significant difference in therapeutic action (*P. gallinaceum*) between analogous members of the 9-bromophenanthryl-3-alkamine series (Va) and the 9-chloro-phenanthryl-3-alkamine series (Vb).



IV



Va, X = Br
Vb, X = Cl

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXXIV.

Thus it appeared to be of interest to replace the chlorine in I, II, or III by bromine, in order to study the effect of this chemical change upon therapeutic effectiveness.

Of types I, II, and III the bromine analog of III appeared most readily available, and a convenient starting material for its preparation, namely 3-bromo-10-phenanthrenecarboxylic acid has been described (7). This acid was converted by the Arndt-Eistert reaction *via* the diazo ketone to 3-bromo-10-ω-bromoacetylphenanthrene. We prepared four amino alcohols (dibutylamino to diheptylamino derivative) by exchanging the ω-bromine atom with the appropriate amine, and reducing the resulting amino ketones with aluminum isopropoxide.

In comparing the biological data (8, 9) of the nuclear-brominated alkamines[3] and their "chloro analogs" (3), one finds no significant difference between the two series. The tolerated doses lie in the same range. The therapeutic effectiveness of the members of the bromo series is approximately of the same order (or slightly higher) than that of the corresponding "chloro analogs". None of

TABLE I
AMINO ALCOHOLS

SN	$C_{14}H_8$ {3-Br, 10-$CHOHCH_2$—}	SOLVENT	M.P., °C	APPEARANCE	FORMULA	CALC'D		FOUND	
						C%	H%	C%	H%
12739	$N(C_4H_9)_2 \cdot HCl$	Absolute EtOH	225–226.5	Clusters of rods	$C_{24}H_{31}BrClNO$	62.00	6.72	62.12	6.48
13038	$N(C_5H_{11})_2 \cdot HCl$	Absolute EtOH-Me_2CO	214–215	Slim rods	$C_{26}H_{35}BrClNO$	63.35	7.16	63.06	7.05
13464	$N(C_6H_{13})_2 \cdot HCl$	Absolute EtOH-Me_2CO	199–200	Prisms	$C_{28}H_{39}BrClNO$	64.55	7.54	64.25	7.23
13465	$N(C_7H_{15})_2 \cdot HCl$	Absolute EtOH-Me_2CO	191–192	Needle clusters	$C_{30}H_{43}BrClNO$	65.63	7.90	65.91	7.66

the four amino alcohols described herein, shows any activity against sporozoite-induced *gallinaceum* malaria (9).

Acknowledgments. We wish to thank Mr. Edward A. Garlock, Jr. for carrying out the microanalyses. We are indebted to Mr. H. George Latham, Jr. for valuable assistance.

EXPERIMENTAL[4]

3-Bromo-10-phenanthrenecarboxylic acid was prepared as described by Pschorr and Schütz (7). These authors reported the m.p. 187° for the intermediate α-(*p*-bromophenyl)-*o*-nitrocinnamic acid. We observed the m.p. 169–170°. Occasionally, when the temperature rise was gradual, it would sinter at 175° and melt at 191–192.5 °, suggesting dimorphism.

3-Bromo-10-phenanthroyl chloride. A mixture of 5 g. of the acid and 20 cc. of freshly-distilled thionyl chloride was refluxed for one to two hours. Excess reagent was evaporated *in vacuo* and the residue recrystallized from benzene-ligroin (30–60°); yield 4.6 g. (87%),

[3] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph. The SN of the drugs which were submitted to biological test, are given in the Experimental (Table I).

[4] All melting points given, are uncorrected.

m.p. 158–159.5°. Recrystallized again from benzene, followed by sublimation in high vacuum, the material melted at 160–161°; large needles.

Anal. Calc'd for $C_{15}H_8BrClO$: C, 56.37; H, 2.52.
Found: C, 56.23; H, 2.77.

When a mixture of benzene and thionyl chloride was used in this preparation, there was only partial conversion (about 40%) to the acid chloride. The remainder of the material was recovered as a difficulty soluble solid (probably anhydride) of m.p. 279–283°. It was insoluble in alkali but could be hydrolyzed to 3-bromo-10-phenanthrenecarboxylic acid with refluxing sodium hydroxide-dioxane solution.

3-Bromo-10-ω-bromoacetylphenanthrene. To a stirred mixture of 300 cc. of an ether solution of diazomethane (from 30 g. of nitrosomethylurea) and 130 cc. of dry benzene was added 16 g. of 3-bromo-10-phenanthroyl chloride during one hour (temperature 0° to 5°). The resulting suspension was stirred an additional 1.5 hours at 0° to 5° and for ten hours at room temperature. After thorough cooling in ice, the diazo ketone (12, g. of m.p. 150° with gas evolution) was collected, stirred in suspension with 120 cc. of dioxane, and a solution of 8 cc. of 40% HBr in 8 cc. of dioxane added during twenty minutes (temperature 20–25°). Five grams of sodium carbonate in 10 cc. of water was added and the dioxane evaporated *in vacuo* at a bath temperature below 50°. The residue was partitioned between warm benzene and water, the benzene layer dried over sodium sulfate and concentrated to 25–30 cc. On dilution with ligroin (30–60°), the bromo ketone separated in a yield of 12.5 g. (66% based on acid chloride), m.p. 121–124.5°. It crystallized from ethyl acetate in large, pale yellow needles of m.p. 129–130°.

Anal. Calc'd for $C_{16}H_{10}Br_2O$: C, 50.83; H, 2.67; Br, 42.28.
Found: C, 51.87; H, 2.90.

Another recrystallization did not change the m.p.
Found: C, 51.63; H, 2.82; Br, 43.05.

In later runs another crystalline modification (m.p. about 110°) of the bromo ketone was isolated.

3-Bromo-10-acetylphenanthrene. A mixture of 0.5 g. of the crude bromo ketone above (either modification), 0.3 g. of palladium-charcoal (5% Pd), and 25 cc. of absolute ethanol absorbed one mole of hydrogen in forty-five minutes. After warming on the steam-bath, catalyst was removed and the filtrate concentrated to about 10 cc. On cooling, 3-bromo-10-acetylphenanthrene separated in a yield of 0.3 g., m.p. 142.5–144°. One recrystallization from absolute ethanol followed by sublimation in a high vacuum gave needles of m.p. 144.5–145.5°.

Anal. Calc'd for $C_{16}H_{11}BrO$: C, 64.22; H, 3.71.
Found: C, 64.40; H, 3.61.

Amino alcohols. A mixture of 5 g. of 3-bromo-10-ω-bromoacetylphenanthrene, two equivalents of secondary amine, 22 cc. of dry ether, and 3 cc. of acetone was shaken for two to six hours, cooled in the ice-box and secondary amine hydrobromide filtered off. The filtrate was evaporated to dryness *in vacuo* and the residue reduced with 20–30 cc. of 3 *N* aluminum isopropoxide (10) (1.5–2 hours). The residue from evaporation of the isopropanol *in vacuo*, was partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water, dried over sodium sulfate and acidified with 5–6 cc. of 20% alcoholic HCl to give the crystalline amino alcohol hydrochlorides in 63–68% yields (based on bromo ketone).

SUMMARY

Four amino alcohols derived from 3-bromophenanthrene, and carrying the alkamine side chain in position 10 have been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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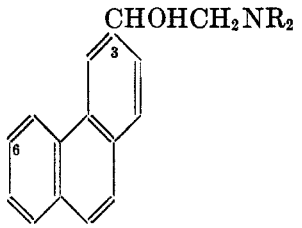
[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY,
NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XIX.[1,2] AMINO ALCOHOLS OF THE TYPE —CHOHCH$_2$NR$_2$ DERIVED FROM DICHLOROPHENANTHRENES

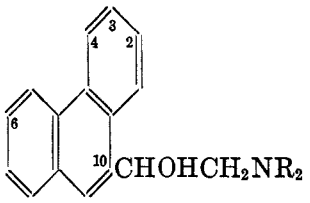
EVERETTE L. MAY AND ERICH MOSETTIG

Received July 23, 1945

In foregoing communications (1, 2, 3) of this series we have shown that by introducing a chlorine into position 6 of compounds of formula I, and into position 6 or 3 of compounds of formula II, plasmodicidal activity (*P. gallinaceum*) is considerably enhanced.



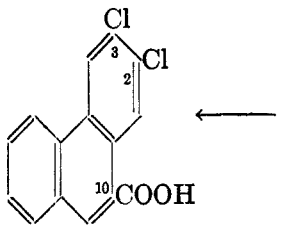
I



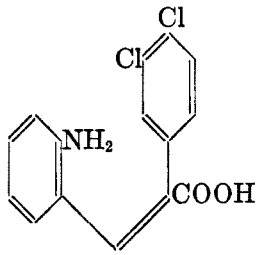
II

In this communication we are describing amino alcohols of formula II, carrying two chlorine atoms in the phenanthrene nucleus, namely, in positions 2,3 and 3,4.

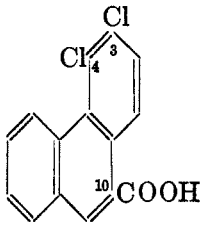
By diazotization-ring closure of the cinnamic acid derivative III, two dichlorophenanthroic acids, IV and V, were obtained in a total yield of approximately 75%, and were separated by fractional crystallization.



IV



III



V

No efforts were made to prove for either acid the location of the chlorine atoms. The ratio of the acids "A" and "B" was approximately 1:2.5. The less soluble acid "A", its chloride, the bromomethyl ketone and methyl ketone derived from it, have consistently higher melting points (from 25° to 55°) than the corresponding derivatives of the "B series". This relationship apparently holds true also

[1]The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2]Studies in the phenanthrene series XXXV.

for the amino alcohols. These were obtained from the acids "A" and "B" by methods employed previously (3, 4) (—COOH → —$COCHN_2$ → —$COCH_2Br$ → —$COCH_2NR_2$ → $CHOHCH_2NR_2$). We prepared of series "A", the diamylamino alcohol (SN 13664)[3] and the diheptylamino alcohol (SN 13037), and of series "B", the dihexylamino alcohol (SN 13036).

In respect to toxicity (5) and therapeutic value (6) no significant difference can be observed between the members of the "dichloro series" and the corresponding members of the 3-chloro-10-alkamine series (3). None of the three amino alcohols described in this paper showed any activity against sporozoite-induced *gallinaceum* malaria (6).

Acknowledgments. We wish to thank Mr. Edward A. Garlock, Jr., for carrying out the microanalyses, and Heyden Chemical Corporation for a generous sample of 3,4-dichlorobenzyl chloride.

EXPERIMENTAL[4]

3,4-Dichlorophenylacetic acid. To a steam-heated mixture of 40 g. of sodium cyanide and 40 cc. of water was added during thirty minutes, a solution of 100 g. of 3,4-dichlorobenzyl chloride in 160 cc. of 95% ethanol. After refluxing the mixture for an additional ninety minutes, it was cooled, filtered, and the ethanol distilled *in vacuo*. The residue was refluxed for three to four hours with a solution of 60 g. of potassium hydroxide and 180 cc. of water. After dilution to about 1000 cc., Norit was added, the mixture heated to boiling, cooled to 50°, filtered, and the filtrate acidified with conc'd HCl to yield 95 g. of acid of m.p. 70–77°. Two recrystallizations from ligroin (30–60°)-benzene gave large needles of m.p. 82–82.5°.

Anal. Calc'd for $C_8H_6Cl_2O_2$: C, 46.87; H, 2.95.
Found: C, 46.81; H, 3.02.

α-(3,4-Dichlorophenyl)-o-nitrocinnamic acid. A mixture of 95 g. of the above acid (m.p. 70–77°), 200 cc. of absolute ethanol, and 29.5 g. of potassium hydroxide was heated to homogeneity, the solution filtered and diluted with 200 cc. of dry ether to yield, after cooling, 70 g. of crystalline potassium 3,4-dichlorophenylacetate. A second fraction of 30 g. was obtained from the filtrate. Ten grams of this salt (dried in a desiccator),[5] 6.5 g. of *o*-nitrobenzaldehyde, and 50 cc. of acetic anhydride were heated together on the steam-bath for about sixteen hours. Excess acetic anhydride was decomposed with 100 cc. of water. On cooling, the nitro acid separated and was recrystallized from acetic acid; yield 6.5 g., m.p. 183–185.5°. Another recrystallization gave yellow plates of m.p. 185–186.5°.

Anal. Calc'd for $C_{15}H_9Cl_2NO_4$: C, 53.32; H, 2.68.
Found: C, 53.23; H, 2.62.

α-(3,4-Dichlorophenyl)-o-aminocinnamic acid (III). A hot solution of the above nitro acid (25 g.) in 145 cc. of water and 61 cc. of conc'd NH_4OH was added gradually to a mixture of 163 g. of ferrous sulfate, 410 cc. of water, and 305 cc. of conc'd NH_4OH (temperature 80–85°). After boiling for 10–15 minutes the mixture was filtered (Filter-Cel) and the filtrate acidified with acetic acid. The yield of amino acid (m.p. 208–209.5°) was 21.0 g. It crystallized from ethanol in oblong plates of m.p. 208–209°.

Anal. Calc'd for $C_{15}H_{11}Cl_2NO_2$: C, 58.45; H, 3.60.
Found: C, 58.68; H, 3.53.

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[3]The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph.

[4]All melting points given are uncorrected.

[5]If the salt is dried at 110°, the optimal reaction time is 2–2.5 hours, while for air-dried material it is 20–25 hours.

3,x-Dichloro-10-phenanthrenecarboxylic acid (A) and 3,y-dichloro-10-phenanthrenecarboxylic acid (B).[6] A stirred suspension of 24 g. of III in 250 cc. of 15% alcoholic HCl (temperature −5° to 0°) was treated with 35 cc. of isoamyl nitrite during 10–20 minutes. After stirring for two hours at −5° to 0°, the mixture was poured slowly into a stirred mixture of 80 g. of sodium hypophosphite, 3.5 g. of copper-bronze, four drops of conc'd H_2SO_4 and 125 cc. of water (temperature not above 45°) and the mass stirred for forty-five minutes. The solids were collected, boiled with an excess of dilute sodium hydroxide (Norit), and the whole filtered. Acidification of the filtrate yielded 17 g. of a mixture of phenanthroic acids which was combined with 29 g. from another run and the whole digested with 300 cc. of boiling dioxane. The hot solution was filtered and chilled in the ice-box, giving 15 g. of solid which, on recrystallization from dioxane, yielded 9 g. of acid A, m.p. 297–306°. After sublimation in a high vacuum followed by recrystallization it appeared as long, slender needles of m.p. 307–310°.

Anal. Calc'd for $C_{15}H_8Cl_2O_2$: C, 61.90; H, 2.77.
Found: C, 62.08; H, 2.95.

The first dioxane filtrate above, on concentrating to about 50 cc., diluting with an equal volume of water and cooling, yielded 18.5 g. of B of m.p. 247–251°. Similarly, the second dioxane filtrate gave 5 g. of B, m.p. 250–256°. After sublimation followed by recrystallization from absolute ethanol and acetic acid in succession it appeared as fine, curved needles of m.p. 253–255°.

Anal. Calc'd for $C_{15}H_8Cl_2O_2$: C, 61.90; H, 2.77.
Found: C, 61.76; H, 2.72.

3,x-Dichloro-10-phenanthroyl chloride. A mixture of 6.5 g. of A (m.p. 295–305°), 25 cc. of dry benzene, and 25 cc. of thionyl chloride was refluxed for five hours. Solvent and excess reagent were evaporated *in vacuo* and the resulting solid recrystallized from benzene; yield 5.4 g., m.p. 177–179°. After another recrystallization followed by high vacuum sublimation the chloride melted at 180–181°; large needles.

Anal. Calc'd for $C_{15}H_7Cl_3O$: C, 58.19; H, 2.28.
Found: C, 58.55; H, 2.27.

3,x-Dichloro-10-ω-bromoacetylphenanthrene. To a stirred mixture of 175 cc. of an ether solution of diazomethane (from 18 g. of nitrosomethylurea) and 120 cc. of dry benzene was added at 0° to 5°, 7.7 g. of the foregoing acid chloride during forty-five minutes. The mixture was stirred for five hours at room temperature, allowed to stand overnight and cooled in ice; yield of diazo ketone 6.4 g., m.p. 154–155° with gas evolution. It was stirred in suspension with 200 cc. of dioxane, and a mixture of 6.5 cc. of 40% HBr and 6.5 cc. of dioxane was added during ten minutes. After ten more minutes, 6.5 g. of sodium carbonate and 200 cc. of water were added, the precipitate was collected, and washed with 95% ethanol. It crystallized from benzene in a yield of 6.7 g., m.p. 184–185°; fine needles.

Anal. Calc'd for $C_{16}H_9BrCl_2O$: C, 52.22; H, 2.46.
Found: C, 52.64; H, 2.52.

3,x-Dichloro-10-acetylphenanthrene. A mixture of 0.5 g. of the above bromo ketone, 0.2 g. of palladium-charcoal (5% Pd), and 25 cc. of absolute ethanol absorbed 0.9 mole of hydrogen in one hour. After warming, removal of catalyst, and concentration of the filtrate to about 20 cc., 0.2 g. of ketone, m.p. 173–175°, separated. It crystallized from absolute ethanol in silky needles of m.p. 174.5–176.5°.

Anal. Calc'd for $C_{16}H_{10}Cl_2O$: C, 66.46; H, 3.49.
Found: C, 66.65; H, 3.58.

3,y-Dichloro-10-phenanthroyl chloride. A mixture of 11.7 g. of B (m.p. 248–253°), 25 cc. of benzene, and 25 cc. of thionyl chloride was refluxed for two hours. Solvent and excess reagent were removed *in vacuo*, the crystalline residue dissolved in 50 cc. of boiling benzene and the solution left at room temperature for 1.5 hours. The acid chloride (10.2 g.) was

[6]The Pschorr synthesis was modified as suggested by Ruggli and Staub (7). See also Lewis and Elderfield (8) and ref. 9.

again recrystallized; yield 7.4 g., m.p. 146–151°. Another recrystallization followed by a high vacuum sublimation gave the constant m.p. 155.5–157°; needles.

Anal. Calc'd for $C_{16}H_7Cl_3O$: C, 58.19; H, 2.28.
Found: C, 58.00; H, 2.10.

3,y-Dichloro-10-ω-bromoacetylphenanthrene. The preceding acid chloride (7.4 g., m.p. 146–151°) was converted to the diazo ketone (3.7 g., after cooling in ice-salt) essentially as described above, with 150 cc. of an ether solution of diazomethane (from 15 g. of nitrosomethylurea) and 75 cc. of dry benzene. The 3.7 g. of diazo ketone and 40 cc. of dioxane were stirred together, and a solution of 3 cc. of 40% HBr and 3 cc. of dioxane was added during fifteen minutes (20–25°). Potassium carbonate (3.5 g.) in 10 cc. of water was added to the solution and the dioxane evaporated *in vacuo*. The residue was partitioned between benzene and water, the benzene layer dried (Na_2SO_4), concentrated to 10–15 cc. and diluted to a faint turbidity with ligroin (30–60°). The yield of bromo ketone of m.p. 133–137°, was 3.4 g. It crystallized from ethyl acetate (Norit) in long needles or prisms, m.p. 132.5–133°. The melt solidified and remelted at 137–138°. If the temperature rise was slow only the higher m.p. was observed.

Anal. Calc'd for $C_{16}H_9BrCl_2O$: C, 52.22; H, 2.46.
Found: C, 52.97; H, 2.41.

3,y-Dichloro-10-acetylphenanthrene. The preceding bromo ketone (0.5 g.) was debrominated as described above for the 3,x-isomer. The yield of ketone (m.p. 147–150°) was 0.2 g. After a sublimation in high vacuum followed by recrystallization from absolute ethanol, the m.p. was 150–151°. The solidified melt remelted at 117–117.5°. This form was converted by recrystallization to the one melting at 150–151°.

Anal. Calc'd for $C_{16}H_{10}Cl_2O$: C, 66.46; H, 3.49.
Found: C, 66.15; H, 3.47.

3,x-Dichloro-10-(2-diamylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 13,664). 3,x-Dichloro-10-ω-bromoacetylphenanthrene (3.6 g.), 3.1 g. of diamylamine, 15 cc. of dry ether, and 3 cc. of acetone were shaken together for five hours, the mixture was cooled and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue reduced with 20 cc. of 3 *N* aluminum isopropoxide (75–90 minutes) (10). After evaporation of the isopropanol *in vacuo*, the residue was partitioned between ether and an excess of 10% sodium hydroxide. The ether layer was washed twice with water, dried, and acidified to Congo Red with dry gaseous HCl; yield of amino alcohol hydrochloride 2.7 g., m.p. 224–226°. It crystallized from absolute ethanol-acetone in slender needles of m.p. 225–227°.

Anal. Calc'd for $C_{26}H_{34}Cl_3NO$: C, 64.67; H, 7.10.
Found: C, 64.53; H, 7.13.

3,x-Dichloro-10-(2-diheptylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 13,037). This compound was prepared like the foregoing one. The yield from 5 g. of bromo ketone was 4.5 g., m.p. 200–208°. Two recrystallizations from absolute ethanol-acetone gave the constant m.p. 208–209.5°; felted needles.

Anal. Calc'd for $C_{30}H_{42}Cl_3NO$: C, 66.85; H, 7.86.
Found: C, 66.62; H, 7.63.

3,y-Dichloro-10-(2-dihexylamino-1-hydroxyethyl)phenanthrene hydrochloride (SN 13,036). From 5 g. of 3,y-dichloro-10-ω-bromoacetylphenanthrene, 2.5 g. of this hydrochloride, m.p. 179–182° was obtained, using the same procedure as in the two preceding cases; large prisms from absolute ethanol-acetone, m.p. 180–182°.

Anal. Calc'd for $C_{28}H_{38}Cl_3NO$: C, 65.81; H, 7.50.
Found: C, 65.44; H, 7.15.

SUMMARY

Three amino alcohols of the type —$CHOHCH_2NR_2$, and derived from dichlorophenanthrenes have been prepared.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XX.[1,2] AMINO ALCOHOLS OF THE TYPE—$CH_2CHOHCH_2NR_2$ DERIVED FROM PHENANTHRENE AND TETRAHYDROPHENANTHRENE

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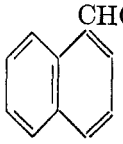
We have shown in previous communications (1,2) that amino alcohols of the type—$CHOHCH_2NR_2$, carrying this side chain in position 9 of tetrahydrophenanthrene and phenanthrene, exhibit considerable antimalarial activity, in some instances equal to that of quinine. Furthermore, Fry and Mosettig (3)[3] have found that some naphthyl alkamines (I) with the side chain in position 1, also have a definite, though rather weak plasmodicidal effect (*P. gallinaceum*)(5).

In 1930 Fourneau and associates (6) reported that the amino alcohol II shows a slight activity in avian malaria.



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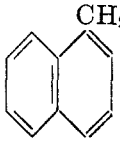
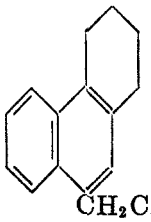
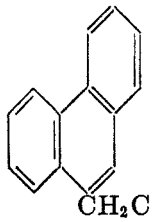


II

We had suspected from the beginning of our investigations, that in the vast group of amino alcohols studied, antimalarial activity is linked with the structural arrangement Ar—CHOH—. In other words the secondary carbinol group of the alkamine chain should be directly attached to an aromatic ring (or hetero ring with aromatic character). In order to test this hypothesis we synthesized, of each of III and IV, two characteristic representatives.



III



IV

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] Studies in the Phenanthrene Series XXXVI.

[3] See also Jacobs and associates (4).

Starting from phenanthryl-9-acetic acid and its tetrahydro analog we prepared compounds of types III and IV as follows:

$$—CH_2COOH \rightarrow —CH_2COCl \rightarrow —CH_2COCHN_2 \rightarrow$$
$$—CH_2COCH_2Br \rightarrow —CH_2COCH_2NR_2 \rightarrow —CH_2CHOHCH_2NR_2 .$$

In neither series were any particular difficulties encountered. Although not needed in the present synthesis we prepared in both series the acetone derivatives $—CH_2COCH_3$ by catalytic dehalogenation of the corresponding ω-bromo ketones. When we were able to isolate crystalline amino ketone hydrochlorides, we reduced them catalytically, otherwise the oily amino ketone bases were reduced with aluminum isopropoxide.

The amino alcohols (SN 12984, SN 12986, SN 13666, SN 13669)[4] submitted to biological tests (5, 7) are, as a whole, slightly more toxic than the corresponding lower homologs of the tetrahydrophenanthrene series (1) and phenanthrene series (2). They are, as we expected, ineffective against *P. gallinaceum*. On the other hand the new amino alcohols are much more effective inhibitors of plasma cholinesterase than their lower homologs (8, 1, 2). They did not show any activity against sporozoite-induced *gallinaceum* malaria (5).

Acknowledgment. We wish to thank Mr. Edward A. Garlock, Jr. for carrying out the microanalyses.

EXPERIMENTAL[5]

1,2,3,4-Tetrahydrophenanthrene-9-acetyl chloride. A mixture of 24 g. of 1,2,3,4-tetrahydrophenanthrene-9-acetic acid (9), 25 cc.of thionyl chloride, and 25 cc. of dry benzene was refluxed for one hour. Solvent and excess reagent were evaporated *in vacuo*, and the residue was recrystallized from dry ligroin (90–100°); yield 19 g., m.p. 65.5–67°. Another recrystallization followed by high vacuum sublimation gave the constant m.p. 66.5–67.5°; prisms.

Anal. Calc'd for $C_{16}H_{15}ClO$: C, 74.28; H, 5.84.
Found: C, 74.48; H, 6.04.

9-(3-Bromo-2-oxopropyl)-1,2,3,4-tetrahydrophenanthrene (*V*). A solution of 19 g. of the preceding chloride in 100 cc. of dry ether was added during forty-five minutes to 400 cc. of a stirred ether solution of diazomethane (from 40 g. of nitrosomethylurea) at 5° to 17°. The mixture was stirred for 5–6 hours at room temperature and left in the ice-box overnight. The precipitated diazo ketone (VI) (16 g., m.p. 126–128° to a frothy melt) was stirred in suspension with 50 cc. of benzene and 100 cc. of dry ether, while 18 cc. of 40% HBr in 18 cc. of U.S.P. ether was added (25–35 minutes). The resulting solution was washed with water, filtered, washed with sodium bicarbonate solution and dried (Na_2SO_4). It was concentrated *in vacuo* to about 60 cc., diluted with an equal volume of ligroin (30–60°), and cooled in the ice-box; yield of bromo ketone 16.5 g., m.p. 105–106.5°. Two recrystallizations from ethyl acetate-ether gave large needles of m.p. 107–108°.

Anal. Calc'd for $C_{17}H_{17}BrO$: C, 64.37; H, 5.40.
Found: C, 65.10; H, 5.44.

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[4] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. Activities of drugs so listed will be published in a forthcoming monograph.

[5] All melting points given are uncorrected.

9-(2-Oxopropyl)-1,2,3,4-tetrahydrophenanthrene. (a) By the method of Wolfrom and Brown (10), 0.5 g. of VI was converted to 0.2 g. of this ketone, m.p. 58–60°. After two recrystallizations from methanol and a high vacuum sublimation, the m.p. was 63–64°; prisms.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.70; H, 7.61.
Found: C, 85.60; H, 7.70.

(b) A mixture of 0.5 g. of V, 0.2 g. of palladium-charcoal (5% Pd) and 14 cc. of absolute ethanol absorbed one mole of hydrogen in forty minutes. After removal of catalyst, the filtrate was concentrated to about 3 cc. to give 0.3 g. of the ketone identical with that obtained by method (a).

Occasionally this ketone crystallized in broad, flat needles of m.p. 58–60°. After solidification it remelted at 62–63.5°.

9-(3-Diethylamino-2-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 12,984). Two grams of V, 1.5 cc. of diethylamine, and 10 cc. of dry ether were shaken together for one hour. The cooled, filtered mixture was washed four times with water and dried (Na_2SO_4). After evaporation, almost to dryness, acetone, 2 cc. of 15% alcoholic HCl, and ether were added in succession. The amino ketone hydrochloride which crystallized was recrystallized from absolute ethanol-ether to give 1.7 g. of needles, m.p. 75–87°. With 0.05 g. of platinum oxide and 17 cc. of methanol, it absorbed one mole of hydrogen in one hour. The catalyst was removed and the filtrate evaporated to dryness, leaving a syrup which crystallized from acetone-ether in a yield of 1.2 g., m.p. 126–129°; large needles from acetone-ether; m.p. 129–131°. The somewhat hygroscopic compound was dried in a desiccator.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69.
Found: C, 72.28; H, 8.72.

The picrate crystallized from 95% ethanol in yellow needles of m.p. 125–126.5°.

Anal. Calc'd for $C_{27}H_{32}N_4O_8$: C, 59.99; H, 5.97.
Found: C, 60.33; H, 5.75.

9-(3-Diheptylamino-2-hydroxypropyl)-1,2,3,4-tetrahydrophenanthrene hydrochloride (SN 12,986). A mixture of 5.0 g. of V. 6.0 g. of diheptylamine and 25 cc. of dry ether was shaken for 5–10 hours, cooled, and filtered from 4.0 g. of diheptylamine hydrobromide. The filtrate was evaporated to dryness *in vacuo* and the residue reduced with 25 cc. of 3 *N* aluminum isopropoxide (1). After two hours the isopropanol was distilled *in vacuo*. The residue was partitioned between ether and an excess of 10% sodium hydroxide, the ether layer washed twice with water, dried and acidified to Congo Red with 15% alcoholic HCl. On seeding[6] the salt separated in a yield of 3.6 g., m.p. 133–136°. It crystallized from acetone in fine needles of m.p. 136.5–137.5°.

Anal. Calc'd for $C_{31}H_{50}ClNO$: C, 76.26; H, 10.32.
Found: C, 75.85; H, 10.15.

Phenanthrene-9-acetyl chloride. A mixture of 17. g of phenanthrene-9-acetic acid (11) and 35 cc. of thionyl chloride was refluxed for 1–2 hours and excess reagent removed *in vacuo*. The residue crystallized from dry ligroin (90–100°) in a yield of 16.5 g., m.p. 90–93°. After another recrystallization followed by sublimation in a high vacuum, the chloride melted at 92–93°; broad needles.

Anal. Calc'd for $C_{16}H_{11}ClO$: C, 75.42; H, 4.35
Found: C, 75.09; H, 4.39.

9-(3-Bromo-2-oxopropyl)phenanthrene (VII). The foregoing acid chloride (16 g.) was added during forty minuutes to a stirred ether solution of diazomethane (from 32 g. of nitrosomethylurea), cooled to 4–7°. The mixture was stirred at 0–5° for one hour and for five hours without cooling, chilled in ice and filtered. The 14.5 g. of diazo ketone resulting (m.p. 157–158°, gas evolution) was stirred in suspension with 70 cc. of benzene and 50 cc. of dioxane, while 15 cc. of 40% HBr in 15 cc. of dioxane was added (fifteen minutes, 20–25°).

[6] The hydrochloride could be obtained crystalline (for the first time) only from an amino alcohol base that had been distilled in high vacuum.

After an additional thirty minutes, 150–200 cc. of benzene was added and the solution shaken successively with water, dilute sodium bicarbonate, and water, dried (Na_2SO_4) and concentrated to 70–80 cc. On slight dilution with ligroin (30–60°), the bromo ketone separated in a yield of 15.8 g., m.p. 127–129°. It crystallized from benzene in long needles of m.p. 128.5–129.5°.

Anal. Calc'd for $C_{17}H_{13}BrO$: C, 65.20; H, 4.18.
Found: C, 65.13; H, 4.38.

9-(2-Oxopropyl)phenanthrene. A mixture of 0.5 g. of VII, 0.2 g. of palladium-charcoal (5% Pd), and 25 cc. of absolute ethanol absorbed one mole of hydrogen in twenty-five minutes. The ketone crystallized from methanol in long needles of m.p. 98.5–99°; yield 0.25 g.

Anal. Calc'd for $C_{17}H_{14}O$: C, 87.15; H, 6.02.
Found: C, 86.42; H, 5.98.

9-(3-Dibutylamino-2-hydroxypropyl)phenanthrene hydrochloride (SN 13,666). Dibutylamine (5.7 g.), 7 g. of VII, 30 cc. of dry ether, and 5 cc. of acetone were shaken together for 1–2 hours. After cooling in ice, filtering, and evaporating the filtrate to dryness *in vacuo*, the residue was reduced with 35 cc. of 3 *N* aluminum isopropoxide (1) as described for SN 12,986. On diluting the alcoholic HCl-acidified ether solution with ligroin (30–60°) and seeding,[6] the hydrochloride separated in a yield of 2.5 g., m.p. 169–171.5°. A second fraction (0.9 g.) was obtained from the filtrate; prisms from absolute ethanol-ether, m.p. 173–174°.

Anal. Calc'd for $C_{25}H_{34}ClNO$: C, 75.06; H, 8.57.
Found: C, 75.18; H, 8.64.

9-(3-Diamylamino-2-oxopropyl)phenanthrene hydrochloride. A mixture of 5 g. of VII, 5 g. of diamylamine, 20 cc. of dry ether, and 5 cc. of acetone was shaken for three hours, cooled in ice, and diamylamine hydrobromide filtered. The filtrate was acidified to Congo Red with 15% alcoholic HCl. Upon cooling in the ice-box, 5.0 g. of amino ketone salt, m.p. 168–170.5°, crystallized; thin prisms from absolute ethanol-ether, m.p. 172–173°.

Anal. Calc'd for $C_{27}H_{38}ClNO$: C, 76.13; H, 8.52.
Found: C, 76.08; H, 8.63.

9-(3-Diamylamino-2-hydroxypropyl)phenanthrene hydrochloride. A mixture of 6.0 g. of the preceding compound, 0.1 g. of platinum oxide, and 50 cc. of methanol absorbed one mole of hydrogen in 1.5–2 hours. After removal of the catalyst, the filtrate was evaporated to dryness *in vacuo*. The syrupy residue crystallized from acetone in a yield of 5.8 g., m.p. 112–115°. Another recrystallization gave the m.p. 113–115°; thin prisms.

Anal. Calc'd for $C_{27}H_{38}ClNO$: C, 75.77; H, 8.93.
Found: C, 76.01; H, 9.19.

If, instead of acetone, ethanol was used as the solvent, a compound melting at about 85–90° and giving erratic analytical results, was obtained.

The picrate crystallized from 95% ethanol in yellow prisms, m.p. 115–117°.

Anal. Calc'd for $C_{33}H_{40}N_4O_8$: C, 63.85; H, 6.50.
Found: C, 64.23; H, 6.53.

SUMMARY

Four amino alcohols, two derived from phenanthrene and two from tetrahydrophenanthrene, and carrying the side chain $—CH_2CHOHCH_2NR_2$ in position 9 have been described.

The evaluation of these compounds as antimalarials is discussed.

BETHESDA, MD.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE ACADEMY OF COMMERCE OF VIENNA]

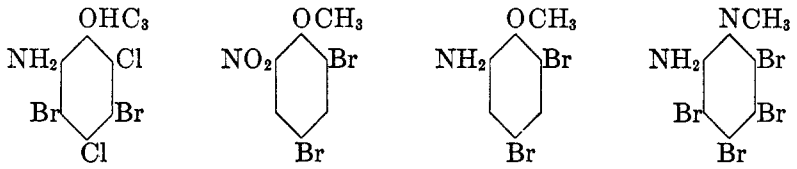
THE PREPARATION OF TETRAHALOGENATED *o*-ANISIDINES

MORITZ KOHN[1] AND OSKAR KRASSO

Received February 6, 1946

Trihalogenated *o*-anisidines were employed in previous studies for the preparation of trihalogenated phenols (1). In this connection a series of tetrasubstituted *o*-anisidines, as well as the first example of a tetrahalogenated *o*-anisidine, a dichlorodibromo-*o*-anisidine, 1-methoxy-2,4-dichloro-3,5-dibromo-6-aminobenzene (I), were prepared. This paper deals with the preparation of other tetrahalogenated *o*-anisidines.

Tetrabromo-*o*-anisidine was prepared from phenol as follows: phenol was converted to the 2,4-dibromo derivative, and this by nitration to 2,4-dibromo-6-nitrophenol. The silver salt of the latter, with methyl iodide, gave 2,4-dibromo-6-nitroanisole (II) (2). By reduction this yielded the corresponding anisidine, 1-methoxy-2,4-dibromo-6-aminobenzene (III) (2), which on bromination gave 2,3,4,5-tetrabromo-*o*-anisidine (IV).



I II III IV

2,4-Dibromo-*o*-anisidine was converted to the acetyl derivative, which with fuming nitric acid and sulfuric acid gave the dinitrodibromoacetanisidide (V); this was deacetylated with concentrated sulfuric acid at water-bath temperature to 2,4-dibromo-3,5-dinitro-*o*-anisidine (1-methoxy-2,4-dibromo-3,5-dinitro-6-aminobenzene, (VI).

Like 2,4-dichloroanisole (3), 2-bromo-4-chloroanisole can be nitrated with fuming nitric acid to 2-bromo-4-chloro-6-nitroanisole. The 2-bromo-4-chloroanisole was obtained by bromination of 4-chlorophenol with one mole of bromine; the redistilled 2-bromo-4-chlorophenol was methylated with alkali and dimethyl sulfate. On treatment of the anisole (VII) with fuming nitric acid, 2-bromo-4-chloro-6-nitroanisole (VIII) was obtained, which on reduction gave 2-bromo-4-chloro-*o*-anisidine (1-methoxy-2-bromo-4-chloro-6-aminobenzene, IX). This product takes up two bromine atoms in glacial acetic acid, whereby 2,3,5-tribromo-4-chloro-*o*-anisidine (1-methoxy-2,3,5-tribromo-4-chloro-6-aminobenzene, X) is formed. 2-Bromo-4-chlorophenol (XII) can also be prepared by bromination of 4-chlorophenol with two moles of bromine to 4-chloro-2,6-dibromophenol (XI), and partial debromination of this by 45-minute boiling with

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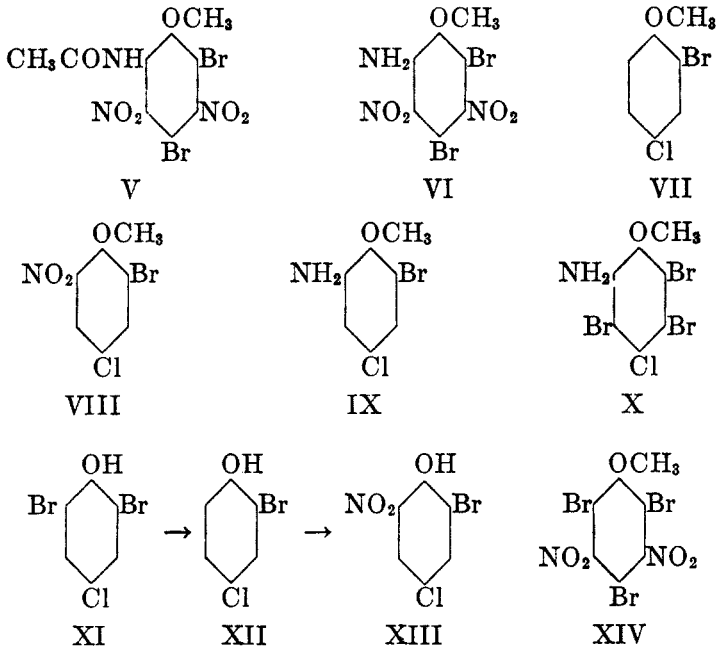
zinc dust in glacial acetic acid. Nitration of XII results in 2-bromo-4-chloro-6-nitrophenol (XIII), which was prepared by Ling (4) by another method.

The melting points of the tetrahalogenated *o*-anisidines lie fairly close together and are relatively low: I, m.p. 83°; X, m.p. 103°; IV, m.p. 112°. The above described preparation of 2,4-dibromo-6-nitroanisole (II) through the silver salt of the nitrophenol had to be followed because the nitration of 2,4-dibromoanisole with fuming nitric acid caused difficulties. When, however, 2,4-dibromoanisole was treated with fuming nitric acid and sulfuric acid, a nitro compound was obtained having the composition $C_7H_3Br_3N_2O_5$, that is, a tribromodinitroanisole.

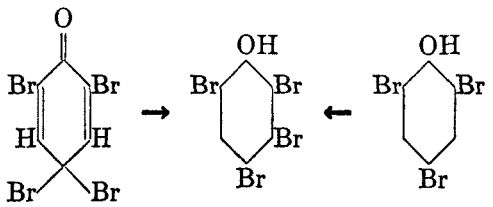


Demethylation of this gave the corresponding tribromodinitrophenol. The anisole is identical in melting point and other properties with the 2,4,6-tribromo-3,5-dinitroanisole (XIV) prepared in the Vienna laboratory by Kohn and Strassmann (5) by nitration of 2,4,6-tribromoanisole, and the above tribromodinitrophenol has the melting point of their 2,4,6-tribromo-3,5-dinitrophenol.

The investigation of the nitration of 2,4-dibromoanisole has thus led to the remarkable result, that during nitration a bromine atom was introduced. This can only be explained by the assumption that a portion of the 2,4-dibromoanisole was completely destroyed, and the liberated bromine served to brominate the remaining 2,4-dibromoanisole; the intermediate tribromoanisole was then converted to the dinitro derivative. Because of this complication, the yield of dinitro product is poor.

For the preparation of 2,3,4,6-tetrabromophenol and a series of other tetrahalogenated phenols we have always used the procedure of Benedikt (6). The

phenol is transformed by the action of excess bromine into the corresponding keto bromide, with phenol itself XV, which on heating with sulfuric acid rearranges to tetrabromophenol, XVI.



XV XVI XVII

It therefore seemed desirable to ascertain whether the keto bromide might be avoided, by treating the trihalogeno phenol (XVII) directly in sulfuric acid solution with bromine. Experiment showed that tetrabromophenol could be obtained in this way, but that the bromination proceeded very slowly.

EXPERIMENTAL

Tetrabromo-o-anisidine from phenol. Phenol was converted in the usual way to 2,4-dibromophenol, which was distilled. A solution of 25 g. of 2,4-dibromophenol in 100 cc. of glacial acetic acid was treated with 10 cc. of colorless conc'd nitric acid. It was warmed gently, and as the color darkened, cooled, whereupon crystallization took place. It was diluted strongly with water, and the nitro compound purified from a small volume of alcohol; m.p. 115°.

The phenol was converted to the potassium salt, and from an aqueous solution of this the silver salt was precipitated with excess silver nitrate. It was heated on the water-bath until the precipitate coagulated; this was filtered, washed with methanol, and refluxed with methanol and methyl iodide until completely converted to silver iodide. Methanol and methyl iodide were distilled off, the residue extracted with boiling alcohol, and filtered from silver iodide. Dilution of the filtrate with water precipitated the crude anisole, which was filtered after several hours, and extracted with 3% NaOH; it was recrystallized from alcohol, m.p. 80°.

2,4-Dibromo-o-anisidine (III). 2,4-Dibromo-6-nitroanisole (10 g.) was added in small portions to a warm solution of 30 g. of stannous chloride in 30 cc. of 37% HCl. It was refluxed until the anisole dissolved completely (a little more stannous chloride sometimes necessary). It was cooled and poured cautiously into 33% NaOH, solid NaOH added until considerable excess was present, and the anisidine distilled with steam.

Tetrabromo-o-anisidine (IV). To a solution of 5 g. of 2,4-dibromo-*o*-anisidine in 50 cc. of glacial acetic acid was added with good stirring 2 molar equivalents of bromine diluted with an equal volume of acetic acid. The crude bromination product which separated immediately was allowed to stand 20 minutes with frequent stirring, filtered, and washed with acetic acid. It crystallized from alcohol in thin woolly needles of m.p. 112°.

Anal. Calc'd for $C_7H_5Br_4NO$: C, 19.11; H, 1.14; N, 3.19; Br, 72.9; OCH_3, 7.06.
Found: C, 19.30; H. 1.19; N, 3.36; Br, 73.13; OCH_3, 7.42.

2,4-Dibromo-3,5-dinitro-o-anisidine (VI). Dibromo-*o*-anisidine (10 g.) was refluxed for 1.5 hours with 40 g. of acetic anhydride, poured into water, and vacuum dried. Dried and finely powdered 2,4-dibromoacetanisidide (5 g.) was added in small portions to a mixture of 60 cc. of fuming nitric acid and 40 cc. of conc'd sulfuric acid. After complete solution, it was poured onto ice, filtered, washed well with water, and crystallized from alcohol; yellow, woolly needles, charring above 212°.

Anal. Calc'd for $C_9H_7Br_2N_3O_6$: N, 10.14. Found: N, 9.98.

Ten grams of the pure dry acetyl compound (V) was treated with 50 g. of conc'd H_2SO_4 and digested on the water-bath for 15 minutes. The substance yielded a dark solution which was cooled and poured into ice-water; the product was washed well with water and crystallized from alcohol; long yellow prisms, m.p. 173°.

Anal. Calc'd for $C_7H_5Br_2N_3O_6$: C, 22.64; H, 1.35.
Found: C, 22.81; H, 1.42.

Preparation of 2,3,5-tribromo-4-chloro-o-anisidine (X) from 4-chlorophenol. The 4-chlorophenol was brominated in CCl_4 in the usual way, and distilled at atmospheric pressure; b.p. 230–235°. Methylation with alkali and dimethyl sulfate gave 2-bromo-4-chloroanisole (VII), a colorless oil of b.p. 244–250°. Eleven grams of VII was treated cautiously with 10 cc. of fuming nitric acid, poured onto ice, and the product triturated with water. It was extracted with 3% NaOH to remove phenolic material, and crystallized from alcohol; m.p. 58°.

Anal. Calc'd for $C_7H_5BrClNO_3$: OCH_3, 11.65. Found: OCH_3, 12.21.

For reduction to the anisidine (IX), 18 g. of the nitroanisole (VIII) was refluxed with a solution of 55 g. of stannous chloride in 55 cc. of fuming hydrochloric acid. After treatment with excess conc'd alkali, the anisidine was steam distilled, extracted into ether, and vacuum distilled; a yellow oil of b.p. 151–154°/14 mm.

Ten grams of IX was refluxed with 30–40 g. of acetic anhydride for 1.5 hours, poured into water, and after an hour filtered and washed with water; from alcohol, leaflets of m.p. 108°.

Anal. Calc'd for $C_9H_9BrClNO_2$: C, 38.85; H, 3.24; OCH_3, 11.15.
Found: C, 38.91; H, 3.28; OCH_3, 11.11.

2,3,5-Tribromo-4-chloro-o-anisidine (X). The bromination of IX was carried out like that of III. The crude product was washed with a little acetic acid, sulfurous acid, and water. After drying, it was crystallized from ligroin (charcoal), giving thin needles of m.p. 103°.

Anal. Calc'd for $C_7H_5Br_3ClNO$: C, 21.32; H, 1.27; N, 3.55; Halogen, 69.80; OCH_3, 7.87.
Found: C, 21.61; H, 1.50; N, 3.72; Halogen, 69.57; OCH_3, 8.3.

Preparation of 2-bromo-4-chlorophenol (XII) by partial debromination of 2,6-dibromo-4-chlorophenol (XI). An aqueous suspension of 4-chlorophenol was treated with 2 molecular equivalents of bromine (as aqueous Br_2-KBr solution) with frequent shaking. The crude product was washed with water, melted, cooled, and excess water removed. The 2,6-dibromo-4-chlorophenol, with the same quantity of zinc dust and 5 parts of glacial acetic acid, was refluxed for 45 minutes, poured into water, and extracted with ether. The product distilled at atmospheric pressure at 228–235°. The nitration was carried out like that of 2,4-dibromophenol. The 2-bromo-4-chloro-6-nitrophenol melted at 125°, in agreement with Ling (4).

2,4,6-Tribromo-3,5-dinitroanisole (XIV) from nitration of 2,4-dibromoanisole. The methylation of 2,4-dibromophenol was done in the usual way, and the product purified by distillation, b.p. 263–269°. Finely powdered dibromoanisole (9 g.) was added in small portions to 50 cc. of fuming nitric acid.[2] Concentrated H_2SO_4 (150 cc.) was added in portions, with cooling if necessary. When about half of the acid was added, separation of crystals began. After 20–30 minutes standing cold, it was poured cautiously on ice, filtered, and washed with water as long as oil droplets separated from the washings. The solid product was crystallized from alcohol, m.p. 149°, yield about 10% of the amount of dibromoanisole.

Anal. Calc'd for $C_7H_3Br_3N_2O_5$: C, 19.3; H, 0.69; N, 6.43; Br, 55.17.
Found: C, 19.63, 19.56; H, 0.87, 0.97; N, 6.27, 6.75, 6.63; Br, 55.01.

The tribromodinitroanisole was demethylated with hydrogen bromide in acetic acid to give 2,4,6-tribromo-3,5-dinitrophenol, m.p. 195°.

Anal. Calc'd for $C_6HBr_3N_2O_5$: C, 17.1; H, 0.24; N, 6.65; Br, 57.0.
Found: C, 17.31; H, 0.79; N, 6.71, 6.67, 6.99; Br, 57.09.

[2] The preliminary experiments were carried out with the assistance of Alma Segel.

Bromination of 2,4,6-tribromophenol in sulfuric acid to 2,3,4,6-tetrabromophenol. To a suspension of 20 g. of 2,4,6-tribromophenol in 100 cc. of conc'd H_2SO_4 was added 3.5 cc. of bromine, and the mixture was heated in the oil-bath to 120°. After 18 hours, evolution of HBr had ceased. The sulfuric acid was poured off and the solidified cake washed with water and crystallized from glacial acetic acid; m.p. 111°. The methyl ether of this had the b.p. 340° (7); crystallized from alcohol, the m.p. 104° (8).

SUMMARY

1. Starting from phenol, the preparations of tetrabromo-*o*-anisidine and of 2,4-dibromo-3,5-dinitro-*o*-anisidine are described; from 4-chlorophenol, that of 4-chloro-2,3,5-tribromo-*o*-anisidine.

2. Intensive nitration of 2,4-dibromoanisole results in introduction of another bromine atom, with formation of 2,4,6-tribromo-3,5-dinitroanisole.

3. Bromination of 2,4,6-tribromophenol in sulfuric acid gives 2,3,4,6-tetrabromophenol.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

THE RELATIONSHIP BETWEEN OPTICAL ROTATORY POWER AND CONSTITUTION OF THE STEROLS. III

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In the previous two papers of this series (1) the application of the modern theories of optical rotatory power to steroids was discussed, and a method of calculation of the rotatory power of these compounds was developed. It was shown, for example, that α-steroids of the cholestanol type will always have a molecular rotation greater by 2540° ($CHCl_3$), in the positive direction, than the corresponding β-form. In the coprostanol series the α-form will always be higher by 2680°. It is our purpose in this paper to present evidence which shows that configurations can be assigned to diastereoisomers at the C_3 position of many other steroids from a knowledge of their optical rotatory powers. By these additional correlations, the validity of the assumptions made in our calculations (1) becomes more firmly established.

In this connection we have amplified the work of Callow and Young (2) who made a study of the relationship between optical rotatory power and the constitution of steroids. Among other things, these investigators pointed out that in fifteen out of eighteen cases an increase in the dextrorotatory power results from inversion of the C_3—OH group from the β- to the α-position. We have listed in Table V eighty-two pairs of compounds epimeric at the C_3 position with their melting points and, where known (fifty-seven pairs), optical rotatory powers. An analysis of these optical data has been made in Tables II, III, and IV and allows the following conclusion to be made:

The C_3 α-form of any steroid will have a higher positive rotatory power (sodium D light) than the corresponding β-form *regardless of the solvent used.*

We would like to point out that the only exceptions to this rule may be in its application to $\Delta^{5:6}$-stenols in solvents other than chloroform.

In fifty-one out of fifty-four cases ($\Delta^{5:6}$-stenols in alcohol are excluded) the α-form has the higher positive rotatory power. This fact corroborates, then, the basic assumptions made by us in calculating the rotatory powers of steroids. We are of the opinion that the three exceptions are in error which may be ascribed to the purity of the compounds involved or that an error was made in the determination of their rotations. Moreover, the chemist now has an additional method for assigning configurations to C_3-diastereomers purely on the basis of optical rotatory power.

We have also made a thorough study of the melting point relationship of α and β-diastereoisomers. Previous work on this subject may be found in the literature. Ruzicka, Wirz, and Meyer (3) have assumed on the basis of α-cholestanol

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having a higher melting point than β-cholestanol that the same melting point relationship would hold for the corresponding chlorides. Also Reindel and Niederländer (4) have made a comparison between the melting points of a large number of saturated stereoisomers. In both the cholestane and coprostane series, the member of an epimeric pair that gives an insoluble digitonide (*i.e.*, β-form) nearly always has the lower melting point.

TABLE I

(MELTING POINT)

CLASS OF COMPOUND	NO. OF C_3-EPIMERS IN WHICH THE α-FORM HAS A HIGHER M.P.	NO. OF C_3-EPIMERS IN WHICH THE β-FORM HAS A HIGHER M.P.
Saturated sterols	7	0
Saturated sterol derivatives	2	6
Unsaturated sterols	5	7
Unsaturated sterol derivatives	1	16
Bile acids	3	3
Bile acid methyl esters	2	3
Derivatives of bile acids or methyl ester	4	4
"Pregnane" compounds	2	1
"Pregnane" derivatives	0	2
Unsaturated "pregnane" compounds	1	1
Unsaturated "pregnane" derivatives	0	1
"Androstane" compounds	3	1
"Androstane" derivatives	1	0
Unsaturated "androstane" compounds	2	0
Unsaturated "androstane" derivatives	1	0
"Cardiac aglucon" derivative	1	0

TABLE II

(ROTATIONS: $CHCl_3$)

CLASS OF COMPOUND	NO. OF C_3-EPIMERS IN WHICH α-FORM HAS A HIGHER POSITIVE $[\alpha]_D$	NO. OF C_3-EPIMERS IN WHICH β-FORM HAS HIGHER POSITIVE $[\alpha]_D$
Saturated sterols	3	1
Saturated sterol derivatives	2	0
Unsaturated sterols	7	0
Unsaturated sterol derivatives	10	1
Bile acids	2	0
Bile acid derivatives	1	0
"Cardiac aglucon" derivative	1	0

However, Marker *et al.* (5) have pointed out in $\Delta^{5:6}$-stenols that the β-form has the higher melting point. Landenburg, Chakravorty, and Wallis (6) have also noted that application of the assumption that the α-forms have higher melting

TABLE III

(ROTATIONS: ALCOHOL OR ABSOLUTE ALCOHOL)

CLASS OF COMPOUND	NO. OF C_3-EPIMERS IN WHICH α-FORM HAS HIGHER POSITIVE $[\alpha]_D$	NO. OF C_3-EPIMERS IN WHICH β-FORM HAS HIGHER POSITIVE $[\alpha]_D$
Saturated sterols	1	0
Unsaturated sterols ($\Delta^{5:6}$)	0	1
Bile acids	3	0
"Pregnane" compounds	2	1
"Pregnane" derivatives	2	0
Unsaturated "pregnane" compounds ($\Delta^{5:6}$)	1	0
Unsaturated "pregnane" compounds ($\Delta^{17:20}$)	1	0
Unsaturated "pregnane" derivatives ($\Delta^{5:6}$)	1	0
"Androstane" compounds	1	0
Unsaturated "androstane" derivatives ($\Delta^{5:6}$)	0	2

TABLE IV

(ROTATIONS: MISCELLANEOUS SOLVENTS)

CLASS OF COMPOUND	NO. OF C_3-EPIMERS IN WHICH α-FORM HAS HIGHER POSITIVE $[\alpha]_D$	NO. OF C_3-EPIMERS IN WHICH β-FORM HAS HIGHER POSITIVE $[\alpha]_D$
Unsaturated sterols	1 (B)	0
Bile acid methyl ester	1 (D)	0
	2 (Ac)	0
Bile acid methyl ester derivatives	7 (Ac)	0
"Androstane" compounds	2 (M)	0
	1 (H)	0
"Androstane" derivatives	1 (M)	0

Ac = acetone; B = benzene; D = dioxane; H = 1 *N* acetic acid; M = methyl alcohol.

points than the corresponding β-forms leads to confusion in assigning configurations to the 3-cholorocholestanone-6's.

An analysis of the melting point data in Table V has been made in Table I, and the following conclusions can be made:

1. The C_3 α-form of an unsubstituted saturated sterol will have a higher melting point than the corresponding β-form.

TABLE V

COMPOUND	C_3 CONFIGURATION	M.P. °C	$[\alpha]_D$	SOLVENT[a]	REF.
A. Saturated Sterols					
1. Cholestanol	β	140–141	+23	C	7
			+29	A	8
	α	182–184	+32.2	C	7
			+34	A	8
2. Stigmastanol	β	136–137	+23.8	C	9
	α	203	+26.0	C	10
3. Ergostanol	β	141	+15.3	C	11
	α	205	+14.6	C	12
4. Coprostanol	β	101–102	+23.6	C	13
	α	116–118	+31.6	C	13
5. Norcoprostanol	β	117–118			4
	α	153–154	(+29.2	B)	14
6. Bisnorcoprostanol	β	126–127			4
	α	134–135			4
7. 24-Ethylcoprostanol	β	127			15
	α	137			15
B. Saturated Sterol Derivatives					
1. Cholestanyl acetate	β	109–110	(+11.5	C)	16
	α	95.5–96			17
2. Stigmastanyl acetate	β	129–129.5	+15.4	C	9
	α	88	+28.0	C	10
3. Ergostanyl acetate	β	143–144	+6.3	C	11
	α	144	+20.5	C	12
4. Coprostanyl acetate	β	88–89			18
	α	87–88	(+43.8	B)	14
5. Norcoprostanyl acetate	β	122–123			4
	α	93–94	(+48.2	B)	14
6. Bisnorcoprostanyl acetate	β	103–104			4
	α	93–94			4
7. 24-Ethylcoprostanyl acetate	β	89			15
	α	94			15

TABLE V—*Continued*

COMPOUND	C_3 CONFIGURATION	M.P. °C	$[\alpha]_D$	SOLVENT[a]	REF.
8. Coprostanyl benzoate	β	114–115			19
	α	85–86			20
C. Unsaturated sterols					
1. Allocholesterol	β	132	+43.7	B	21
	α	84	+120.8	B	21
2. Allo-β-sitosterol	β	158			22
	α	138			22
3. Cholesterol	β		−38.8	C	23
		147–149	−31.0	A	24
	α	140.5	−34	C	7
			−37.5	A	24
4. β-Sitosterol	β	136–137	(−36.6	C)	25
	α	135			5
5. Stigmasterol	β	168–170	(−51.0	C)	26
	α	151			5
6. 7-Dehydrocholesterol	β	142–143.5	−113.6	C	27
	α	124–126	−70.5	C	28
7. Allodehydrocholesterol	β	115–116	+10	C	29
	α	93–94	+80	C	29
8. Zymosterol	β	108–110	+49	C	30
	α	160–162	+55	C	31
9. Dihydrozymosterol	β	128–129	+50	C	30
	α	183	+56	C	31
10. Ergosterol-D	β	165–166	+22.0	C	32
	α	203–204	+36.2	C	33
11. Neoergosterol	β	152	−12	C (?)	34
	α	177	+28.7 av.	C	35
12. 22-Dihydroneo-ergosterol	β	150			36
	α	167	(+28.8	C)	35
D Unsaturated sterol derivatives					
1. Allocholesteryl acetate	β	85			21
	α	82.5			21

TABEL V—*Continued*

COMPOUND	C_3 CONFIGURATION	M.P.°C	$[\alpha]_D$	SOLVENT[a]	REF.
2. Allo-β-sitosteryl acetate	β	88			22
	α	92			22
3. Cholesteryl acetate	β	114.7–115.6	(−42.0	C)	23
	α	85			24
4. β-Sitosteryl acetate	β	125–126	(−41.0	C)	25
	α	66			5
5. Stigmasteryl acetate	β	143–144	(−55.6	C)	26
	α	98			5
6. 7-Dehydrocholesteryl-acetate	β	130	−77.6 (calc'd)	C	m.p. 37 rot. 38
	α	114–115	−35	C	28
7. Allodehydrocholes-terylacetate	β	109	−56.0	C	29
	α	96	+126.3	C	29
8. Zymosteryl acetate	β	106–108	(+34	C)	30
	α	83–85			31
9. Dihydrozymosteryl acetate	β	128–129	+31.5	C	30
	α	85–87	+40	C	31
10. Ergosteryl-D acetate	β	173–174	+20.7	C	33
	α	150	+40.6	C	33
11. Neoergosteryl acetate	β	122–123	−8	C	m.p. 34 rot. 39
	α	98	+27.2	C	
12. 22-Dihydroneoergos-teryl acetate	β	118	−3.1	C	36
	α	83	+24.6	C	35
13. Cholesteryl benzoate	β	148–50 and 177	−17.0	C	40
	α	99.5	−29	C	7
14. 7-Dehydrocholesteryl benzoate	β	139–40 and 183	−53.2	C	27
	α	118–119	+48.5	C	28
15. Allodehydrocholesteryl *m*-dinitrobenzoate	β	154(180–185)	−78.5	C	29
	α	150(180–185)	+159	C	29
16. Neoergosteryl *m*-dini-trobenzoate	β	218–220	−13	C	41
	α	204	+21.2	C	35

TABLE V—*Continued*

COMPOUND	C_3 CONFIGURATION	M.P.°C	$[\alpha]_D$	SOLVENT[a]	REF.
17. Neoergosteryl methyl ether	β	94	−5	C	35
	α	74	+18.4	C	35
E. Bile Acids					
1. 3-Hydroxycholanic acid	β	179	+25.1	A	8
	α	188	+33.6	A	8
2. 3-Hydroxyallocholanic acid	β	218	+17.2	C	m.p. 42 rot. 43
	α	208–210	+23.3	C	m.p. 44 rot. 43
3. 3-Hydroxynorallocholanic acid	β	226			42
	α	205–207	(+21.0	C)	10
4. 3-Hydroxybisnorallocholanic acid	β		−10.1 (calc'd)	C	38
	α	220	+17	C	10
5. 3-Hydroxy-12-ketocholanic acid	β	218–220	+90.5	A.A.	45
	α	164–165	+110.2	A.A.	45
6. Hyodesoxycholic acid	β	189–190	+5.1	A	46
	α	196–197	+8.4	A (?)	m.p. 47 rot. 46
7. 3-Hydroxy-11-cholenic acid	β	*ca.* 128	+27.8	D	48
	α	165–166	+33.2	D (?)	48
F. Bile acid methyl esters					
1. Methyl 3-hydroxyallocholanate	β	151	(+18.4	A)	44
	α	164	(+17.7	C)	44
2. Methyl 3-hydroxynorallocholanate	β	156			42
	α	169–170	(+21.0	C)	10
3. Methyl 3-hydroxy-11β, 12β-oxidocholanate	β	114–115	+27.1	Ac	48
	α	96–98	+35.7	Ac	48
4. Methyl 3-hydroxy-11-ketoetiocholanate	β	172–175	+72.1	Ac	49
	α	155–158			49
5. Methyl 3-hydroxy-11-etiocholenate	β	131–133	+70.7	Ac	50
	α	122–124	+77.7	Ac	50
G. Derivatives of bile acids or methyl esters					
1. 3-Acetoxybisnorallocholanic acid	β		−19.5 (calc'd)	C	38
	α	225–227	+2	C	10

TABLE V—*Continued*

COMPOUND	C_3 CONFIGURATION	M.P. °C	$[\alpha]_D$	SOLVENT[a]	REF.
2. Methyl 3-acetoxynorallocholanate	β	163			42
	α	189–190	(+26.0	C)	10
3. Methyl 3-acetoxy, 11β, 12β-oxido-cholanate	β	150–152	+31.2	Ac	48
	α	140–142	+52.8	Ac	48
4. Methyl 3-acetoxy-11-ketocholanate	β	173–174	+56.4	Ac	51
	α	132–133	+67.1	Ac	52
5. Methyl 3-acetoxy-11-etiocholenate	β	70–72	+62.5	Ac	50
	α	99–100	+87.7	Ac	50
6. Methyl 3-acetoxy-12-keto-9-cholenate	β	192–193	+73.9	Ac	51
	α	149–150	+102.5	Ac	52
7. Methyl 3-acetoxy-11α-hydroxycholanate	β	139–140	+50.0	Ac	51
	α	146–148	+70.7	Ac	52
8. Methyl 3-acetoxy-12-ketocholanate	β	184–186	+77.9	Ac	51
	α	153.5–154.5	+104.8	Ac	53
9. Methyl-3-acetoxy-11-ketoetiocholanate	β	129–131	+71.8	Ac	49
	α	147–149	+98.1	Ac	49
H. "Pregnane" compounds					
1. Allopregnan-ol-3-one-20	β	194	+90.5	A.A.	54
	α	176–178	+87.7	A.A.	54
2. Pregnan-ol-3-one-20	β	142–143	+101.6	A.A.	55
	α	148–149	+113.8	A.A.	55
3. 20-Methylpregnanediol-3,20	β	168–171	+16.5	A.A	55
	α	190–201	+23.0	A.A.(?)	55
I. "Pregnane" derivatives					
1. Allopregnanol-3-one-20 acetate	β	144	+79.8	A.A.	54
	α	141–142	+94.5	A.A.	54
2. Pregnanol-3-one-20 acetate	β	116.5	+86.5	A.A.	55
	α	99	+123.7	A.A.	55
J. Unsaturated "pregnane" compounds					
1. Δ^5-Pregnenol-3-one-20	β	189–190	+30	A	56
	α	148–152	+54.5	A	57
2. 20-Methyl-$\Delta^{17:20}$-pregnenol-3	β	141–142	+14.7	A.A.	55
	α	164–165.5	+45.4	A.A.(?)	55

TABLE V—*Concluded*

COMPOUND	C_3 CONFIGURATION	M.P. °C	$[\alpha]_D$	SOLVENT[a]	REF.
K. Unsaturated "pregnane" derivatives					
1. Δ^5-Pregnenolone acetate	β	149–150	+22	A	58
	α	147	+57.2	A (?)	57
L. "Androstane" compounds					
1. Androstanediol-3,17 (α)	β	164	+4.2	A (?)	59
	α	221	+12.6	A (?)	66
2. Androstan-ol-3-one-17	β	172	+88.6	M	61
	α	182–183	+103.5	M	62
3. 3-Hydroxy-D-homoandrostanone-(17a)	β	193–195	−66.5	M	63
	α	203–205	−35.5	M	63
4. 3,17-Dihydroxy-17-aminoethylandrostane	β	222–225	−16.5	H	63
	α	204–206	+4.5	H	63
M. "Androstane" derivatives					
1. 3-Acetoxy-D-homoandrostanone (17a)	β	124–125	−45	M	63
	α	150–151	−21.7	M	63
N. Unsaturated "androstane" compounds					
1. Dehydroandrosterone	β	148	+10.9	A	64
	α	221	0	A	65
2. Δ^5-Androstenediol-3,17 (α)	β	182–183	−49.4	A	m.p. 65 rot. 66
	α	208–209	−54	A	
O. Unsaturated "androstane" derivatives					
1. Dehydroandrosterone acetate	β	168–169 171–172	(+3.9	A)	64 67
	α	173–174.5			24
P. "Cardiac aglucon" derivative					
$\Delta^{20:22}$-3-Acetoxy-21-hydroxynorallocholenic acid lactone	β	193–194	+1	C	68
	α	230	+19	C	68

[a] C = chloroform.
A = alcohol.
A.A. = absolute alcohol.
B = benzene.
Ac = acetone.
D = dioxane.
M = methyl alcohol.
H = 1 *N* acetic acid.

2. Application of this rule to other steroids is unwarranted.

3. The rule is most likely reversed for $\Delta^{5:6}$-stenols and for certain derivatives of unsaturated sterols.

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FRAGMENTATION OF ALCOHOLS IN THE PRESENCE OF ALUMINUM CHLORIDE. II. 2,3,3-TRIMETHYL-2-BUTANOL

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The prediction of the course of aluminum chloride induced reactions is difficult because of the varied reactivity of this substance with most organic compounds. The first report of this series (1) has shown that the low yields of tertiary alkyl benzenes obtained from the condensation of highly branched aliphatic alcohols with benzene are due to fragmentation of the alcohol. The particular configuration of the alcohol determines the type of fragmentation, the fragments in some cases forming lower alkyl benzenes.

The carbinol, 2,3,3-trimethyl-2-butanol, is reported to give a seven per cent yield of the corresponding alkyl benzene (2), the lowest yield of any of the isomeric heptylbenzenes formed by the condensation of tertiary heptyl alcohols with benzene. A discussion of the results of the condensation of this alcohol, referred to as the carbinol, its chloride, 2,3,3-trimethyl-2-chlorobutane, referred to as the chloride, its unsaturated derivative, 2,3,3-trimethyl-1-butene, referred to as the alkene, follows.

Under the particular conditions of low temperature (10–15°), a 0.5/1.0 mole ratio of aluminum chloride to carbinol, and slow addition of the carbinol to a suspension of the aluminum chloride in benzene, there are two stages in the reaction. During the addition of the first half of the carbinol, hydrochloric acid is given off and the aluminum chloride in the flask is converted to a heavy red-orange complex. During the addition of the second half of the carbinol, no hydrochloric acid is given off and the red-orange complex is replaced by a dark red tarry complex. When either the chloride or the alkene of the carbinol is condensed with benzene, the dark red tarry complex is formed immediately. Hydrogen chloride is given off throughout the addition of the chloride; very little hydrochloric acid is given off during the addition of the alkene.

Analysis of the organic layer after hydrolysis shows that each condensation forms the same products, the expected *tert.*-heptylbenzene, lower *tert.*-alkylbenzenes, alkyl halides and the alkene. When the *tert.*-heptylbenzene produced by the above condensations is mixed with benzene and aluminum chloride at room temperature the same characteristic fragmentation products, *i.e.*, lower alkylbenzenes, are produced.

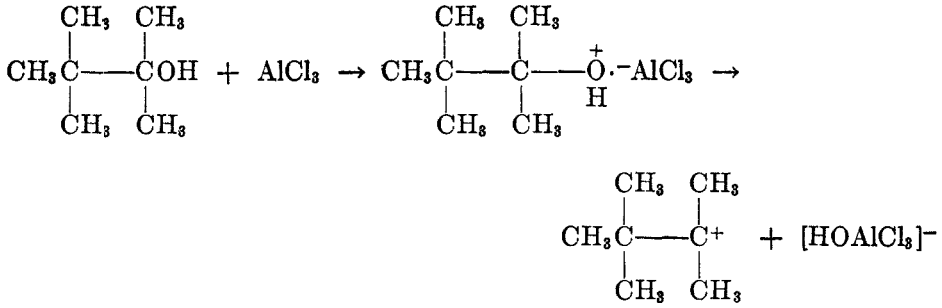
The presence, as reaction products, of chloromethane, 2-methylpropane, 2-chloropropane, 2,3,3-trimethyl-1-butene, 2,3,3-trimethyl-2-chlorobutane, 2-methyl-2-phenylpropane, 2-methyl-2-phenylbutane, 2,3-dimethyl-2-phenylbutane, and 2,3,3-trimethyl-2-phenylbutane is explained by the assumption that the initial step of the reaction is the combination of carbinol and aluminum

TABLE I

YIELDS OF PRODUCTS

CONDENSATION	1	2	3	4	5	6	7
Compound condensed (A)	Carbinol	Carbinol	Carbinol	Carbinol	Chloride	Alkene	*t*.-Heptylbenzene
Temperature, °C.	10	10	10	40	10	10	20
Charged: Moles per mole of A							
A	1.00	1.00	1.00	1.00	1.00	1.00	1.00
$AlCl_3$	0.43	0.50	0.66	0.65	0.50	0.50	0.50
Benzene	5.00	5.00	5.00	5.00	5.00	5.00	4.00
Recovered: Moles per mole of A							
HCl given off	0.35	0.42	0.62	0.46	—	—	—
Aqueous layer analysis							
Al	0.41	—	0.66	0.65	—	—	—
Cl	0.48	—	0.91	1.18	—	—	—
OH	0.81	—	1.07	0.78	—	—	—
Organic layer analysis							
Chloromethane	0.12	0.11	0.13	0.12	—	—	—
2-Methylpropane	0.02	0.03	0.04	0.05	—	—	—
2-Chloropropane	0.08	0.10	0.11	0.09	0.04	0.03	—
2,3,3-Trimethyl-1-butene	0.12	0.12	0.21	0.46	0.01	0.01	0.0
2,3,3-Trimethyl-2-chlorobutane	0.25	0.30	0.22	0.12	0.02	0.01	0.0
Benzene	4.60	4.50	4.49	4.60	4.0	4.0	3.8
2,3,3-Trimethyl-2-butanol	0.18	0.05	0.02	0.0	0.0	0.0	0.0
2-Methyl-2-phenylpropane	0.10	0.12	0.11	0.094	0.3	0.3	0.1
2-Methyl-2-phenylbutane	0.037	0.018	0.027	0.017	0.1	0.1	0.05
2,3-Dimethyl-2-phenylbutane	0.034	0.081	0.061	0.079	0.1	0.1	0.1
2,3,3-Trimethyl-2-phenylbutane	0.15	0.15	0.14	0.12	0.3	0.2	0.8
Higher boiling	0.06	0.10	0.17	0.07	0.2	0.3	0.1

chloride by means of a dative bond and the formation of an alkyl cation (3). 2,3,3-Trimethyl-2-chlorobutane may form the same cation through a dative bond while 2,3,3-trimethyl-1-butene may add a proton to give the cation or condense with benzene directly (4).

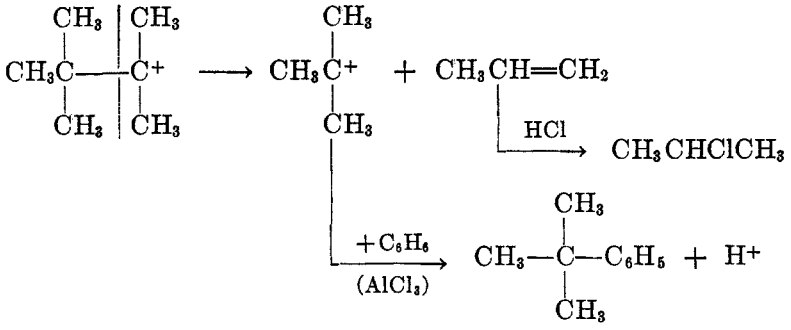


The alkyl cation may condense (1) with benzene to form 2,3,3-trimethyl-2-phenylbutane, lose a proton to form 2,3,3-trimethyl-1-butene or add a chlorine ion to form 2,3,3-trimethyl-2-chlorobutane.

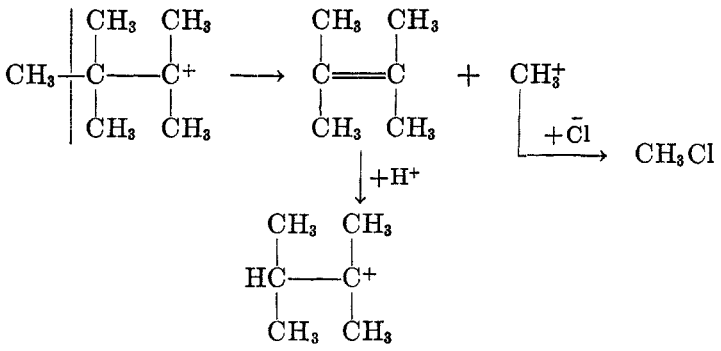
When 2,3,3-trimethyl-2-phenylbutane is treated with aluminum chloride, the same cation is formed by reversal of the process of condensation (3).

Since, with this particular carbinol, the total moles of alkyl benzenes are approximately equal to the moles of aluminum chloride charged, it would appear that aluminum chloride is necessary to carry the reaction to completion. [With lower tertiary alcohols and less branched tertiary heptyl alcohols, the moles of alkyl benzenes are higher than the moles of aluminum chloride charged (6).] After equal molar quantities of carbinol and aluminum chloride are present, the addition of more carbinol may form a dative bond with the $AlCl_2OH$ but the catalyst is not active enough to convert alkyl groups to alkyl benzenes. Upon hydrolysis at this stage the excess carbinol is recovered as its chloride. The addition of still more carbinol may or may not form a dative bond with $AlCl(OH)_2$ but in either case hydrolysis yields unchanged carbinol.

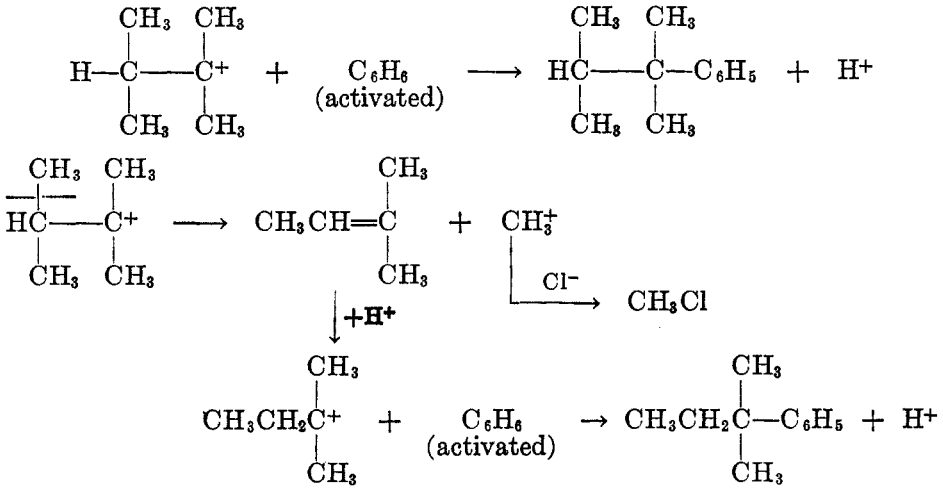
Fragmentation of the heptyl cation may yield *tert.*-butyl cation and isopropyl chloride.



Because of branching and proximity of the positive carbon, the wave functions are concentrated around the number two carbon and a positive methyl is eliminated (5).



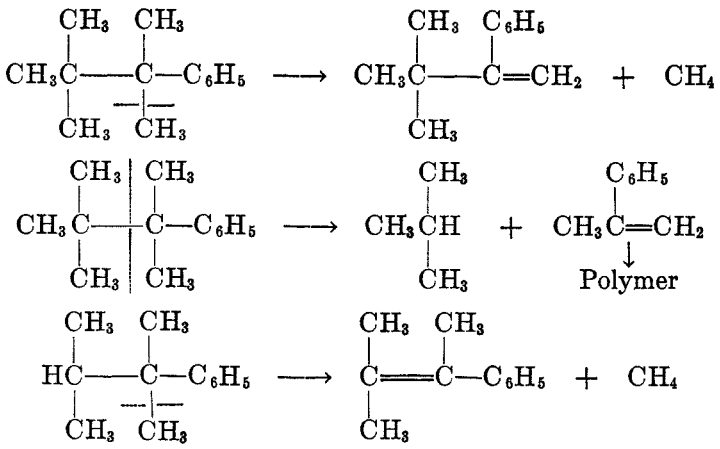
The hexyl cation again may either attack benzene or fragmentate again at the β-carbon.



It should be noted that all of the tertiary alkylbenzenes were found which are made possible by the fragmentation of the cation from 2,3,3-trimethyl-2-butanol. We could find no evidence of the formation of secondary alkylbenzene (2-phenylpropane).

The formation of the small amount of 2-methylpropane may be accounted for by the reduction of isobutene or/and by the direct cracking of 2,3,3-trimethyl-2-phenylbutane. 2-Methylpropane is a by-product in a large number of hydrocarbon-aluminum chloride reactions. In case of reduction, the unsaturated fragment of the hydrogen donor would tend to polymerize.

The distillates which came over between 185° and 215° contained, besides alkylbenzenes, some unsaturated compounds (see experimental part). It has been shown (7) that alkyl groups tend to split from the α-carbon of alkylbenzenes and and that this carbon has a tendency toward free radical formation (8). With this in mind, the following are proposed as possible fragmentations to form 2-methyl-3-phenyl-2-butene, 3,3-dimethyl-2-phenyl-1-butene, and 2-methylpropane.



Gaseous products which did not condense in the dry-ice trap burned with a faintly luminous flame.

EXPERIMENTAL

Synthesis of 2,3,3-trimethyl-2-butanol. The carbinol was prepared in 70–80% yield, by the reaction of pinacolone with methylmagnesium bromide (9). It was obtained as the crystalline hydrate (m.p. 80°), which was dried in ether solution by metallic sodium and then distilled from sodium (b.p. 128–130°). The hydrate is formed from the carbinol in moist air; it can be sublimed without decomposition. Pinacolone was prepared by the method given in Organic Syntheses (10).

2,3,3-Trimethyl-2-chlorobutane was prepared from the carbinol by use of thionyl chloride. It is a solid (m.p. 127°) which decomposes when distilled at atmospheric pressure to give HCl and the alkene (2,3,3-trimethyl-1-butene).

2,3,3-Trimethyl-1-butene was prepared from the carbinol by slow distillation from iodine at atmospheric pressure (11) (b.p. 78°).

Condensation of the carbinol and its derivates. The condensations were carried out in a three-necked flask fitted with a reflux condenser, mechanical stirrer, and dropping-funnel. A tube from the top of the condenser led to a dry-ice trap, then to a water scrubber (to absorb the HCl) and then to a liquid nitrogen trap which was connected to a manometer.

The carbinol (or the alkene) was added slowly to a suspension of aluminum chloride in benzene. The chloride was dissolved in half the benzene to facilitate addition. The reaction mixture was stirred for three hours and then hydrolyzed on ice. The organic layer was separated and washed with water until the washings were neutral. The combined aqueous layers were analyzed in the usual manner for aluminum and chloride.

The material in the dry ice and nitrogen traps was changed to a low-temperature Podbielniak column and fractionated. Orsat analysis was made on the individual fractions to establish their purity. No olefins were found to be present.

The organic layer was fractionated in a 25-plate column until all of the benzene had been taken off. The material in the kettle was then changed to a 100-plate column and fractionated at reduced pressure (20 mm.). The boiling temperatures reported in Table II were corrected to 760 mm. pressure.

Mixed melting points of the known and unknown derivatives in each case gave less than one degree melting point depression from that of the unknown.

Estimation of yields of 2,2,3-trimethyl-1-butene and 2,2,3-trimethyl-2-chlorobutane. The chloride was decomposed during fractionation at atmospheric pressure and came over as the alkene and hydrochloric acid along with benzene. The hydrochloric acid was taken up in standard sodium hydroxide. The benzene fractions were washed with water and the

combined aqueous layers titrated. The per cent of alkene in the benzene fraction was approximated by density measurements. The moles of chloride present in the unfractionated mixture was assumed to be equal to the moles of hydrochloric acid given off during fractionation. The alkene was determined by subtracting the moles of chloride from the moles of alkene. Since the mixture contains small amounts of lower tertiary alkyl chlorides, formed as by-products of fragmentation, the calculated yields should be considered as good approximations.

Identification of unsaturated compounds in the 2,3-dimethyl-2-phenylbutane and 2,3,3-trimethyl-2-phenylbutane fractions. The boiling points of these fractions were less constant than the others. They gave positive tests for unsaturation.

TABLE II

FRACTIONATION PRODUCTS

COMPOUND IDENTIFIED	BOILING RANGE, °C	DENSITY 20/4		SOLID DERIVATIVE	MELTING POINT, °C	
		Known	Unknown		Known	Unknown
Chloromethane	−26 to −23	—	Inert to cold conc'd H_2SO_4			
2-Methylpropane	−13 to −11	—	Inert to cold conc'd H_2SO_4			
2-Chloropropane	24 to 30	0.8603	0.8587	Anilide	103	102
2,3,3-Trimethyl-1-butene	76 to 78	0.7050	—	None		
2,3,3-Trimetyl-2-chlorobutane	76 to 78	—	—	None		
2,3,3-Trimethyl-2-butanol	128 to 130	—	—	Hydrate	80	80
2-Methyl-2-phenylpropane	167 to 169	0.8623	0.8629	*p*-Acetamino derivative	169	169
2-Methyl-2-phenylbutane	187 to 191	0.8720	0.8743	*p*-Acetamino derivative	139	138
2,3-Dimethyl-2-phenylbutane	207 to 211	0.8819	0.8835	*p*-Acetamino derivative	119	117–118
2,3,3-Trimethyl-2-phenylbutane	224 to 227	0.8867	0.8873	*p*-Nitro derivative	108	108

The 189–191° cut was found to contain trimethyl styrene (2-methyl-3-phenyl-1-butene). Cuts from several condensations were combined, hydrogenated with sodium and ethyl alcohol, and the extracted hydrocarbons fractionated. The 186–188° cut from this fractionation was nitrated, reduced, and acetylated to give a *p*-acetamino derivative (m.p. 147°) which showed no melting point depression when mixed with the known derivative of 2-methyl-3-phenylbutane. The unknown derivative did show melting point depression when mixed with the corresponding derivative of 2-methyl-2-phenylbutane.

Oxidation of this 189–191° cut with CrO_3 in glacial acetic acid at room temperature for 24 hours, yielded some acetophenone, which was identified by its semicarbazone (m.p. 193°). Mixed melting point showed no depression. This indicates that the double bond is on the α-carbon.

Oxidation of the 207–211° cut with CrO_3 in glacial acetic acid at room temperature for 24 hours yielded some phenyl *tert.*-butyl ketone, b.p. 85–89° (10 mm.). This was identified by its semicarbazone, which melted at 168°. 3,3-Dimethyl-2-phenyl-1-butene was made from pinacolone and phenylmagnesium bromide. It was oxidized in the same manner, and the ketone converted to the semicarbazone. Mixed melting point showed no depression.

Preparation of solid derivatives. The anilide of isopropyl chloride was prepared by the method given in Shriner and Fuson, "Identification of Organic Compounds."

The hydrate of the carbinol, as noted above, forms in moist air.

The *p*-acetamino derivatives were prepared by the method given by Ipatieff and Schmerling (12).

The nitro derivative was prepared by nitration of the *tert.*-heptylbenzene. This is the only one of the *tert.*-heptylbenzenes which forms a solid mononitro derivative.

SUMMARY

The condensation of 2,3,3-trimethyl-2-butanol with benzene in the presence of aluminum chloride, has given, in addition to the expected *tert.*-heptylbenzene (2,3,3-trimethyl-2-phenylbutane), a number of fragmentation products. These products were identified as chloromethane, 2-methylpropane, 2-chloropropane, 2,3,3-trimethyl-1-butene, 2,3,3-trimethyl-2-chlorobutane, 2-methyl-2-phenylpropane, 2-methyl-2-phenylbutane, and 2,3-dimethyl-2-phenylbutane.

Small amounts of 2-methyl-3-phenyl-2-butene and 3,3-dimethyl-2-phenyl-1-butene were found in the 2,3-dimethyl-2-phenylbutane and the 2,3,3-trimethyl-2-phenylbutane fractions respectively.

The condensation of 2,3,3-trimethyl-2-chlorobutane and of 2,3,3-trimethyl-1-butene produced these same fragmentation products. The tertiary heptylbenzene, when mixed with benzene and aluminum chloride, has also produced some of the same products. The theory of the intermediate formation of an alkyl cation from the carbinol or its derivatives and its fragmentation gives a satisfactory explanation.

EAST LANSING, MICH.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] I. THE TRANSFORMATIONS OF MUSTARD GAS IN WATER. FORMATION AND PROPERTIES OF SULFONIUM SALTS DERIVED FROM MUSTARD GAS

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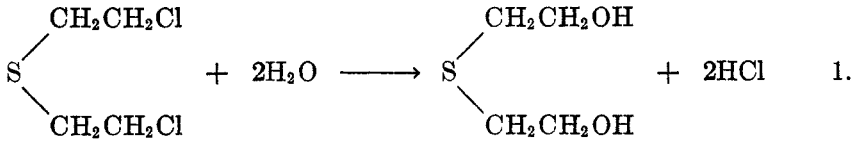
The physiological effects of mustard gas [bis(β-chloroethyl)sulfide, to be designated hereafter by its U. S. Chemical Warfare symbol, H] are the consequence of chemical processes which the agent initiates by its reaction with body constituents. The experiments to be described in this and subsequent papers of this series were performed in order to gain insight into the mode of action of H upon proteins, amino acids, and other constituents of biological systems. Since water is a major component of biological systems, the transformations undergone by H in water are the subject of this first paper.

The kinetics of the hydrolysis of H in nearly saturated aqueous solution (less than 0.1%) were studied in World War I (1), and these investigations have been greatly extended more recently (2, 3, 4, 5). The kinetic data show that in dilute aqueous solution H hydrolyzes according to Equation 1.



1.

Davies and Oxford (6), on the other hand, demonstrated that when the ratio of water to H is small (as in suspensions of H in water in the ratio 1:3), only a small quantity of thiodiglycol [bis(β-hydroxyethyl)sulfide, to be referred to hereafter by the symbol TG] and HCl are formed, most of the H being converted to a mixture of sulfonium chlorides. The experiments of Davies and Oxford, however, were performed under conditions quite dissimilar to those obtaining when H reacts with water under physiological conditions.

It was of interest to find, therefore, that when H was shaken with 50 volumes of water at room temperature until a clear solution resulted, *e.g.* for 24 hours[3] at 20°, the resulting solution contained only about 78% of the theoretical amount of HCl to be expected on complete hydrolysis of H according to Equation 1.

[1]This work was done in whole under Contract No. OEMsr-313 between The Rockefeller Institute for Medical Research and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein. The experiments were performed during the period January 1942–August 1944.

[2]Died, November 7, 1944.

[3]At the end of this period free H is absent, as proved by the fact that nothing can be extracted from the solution by ether.

On heating the neutralized solution at 100° for 2 hours, however, the remainder of the theoretically possible HCl was liberated.

The properties of the H hydrolysate just described, coupled with the observations of Davies and Oxford (6), suggested the presence in the hydrolysate of sulfonium salts. Northrop (7) arrived at similar conclusions. As will be shown later, the sulfonium salts derived from H under these conditions decompose on heating to 100° in aqueous solution with the formation of one equivalent of acid for each sulfonium group present. Hence the amount of acid produced on heating an hydrolysate to 100° is an index of the extent of sulfonium salt formation. On this basis, about 22% of the chlorine of the original H is found as sulfonium chloride after hydrolysis of H with 50 volumes of water at room temperature. If the ratio of water to H is increased to 200 volumes, the extent of sulfonium salt formation drops to about 16%, while if 1000 volumes of water is used, the extent of sulfonium salt formation falls to about 5%.

From the hydrolysate resulting when 26 g. of H was shaken with 50 volumes of water at room temperature, two different sulfonium salts have been isolated. One of these sulfonium salts, bis-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide dichloride (compound IV in Figure 1), is formed by the reaction of one molecule of H with 2 molecules of TG. From the hydrolysate, 3.3 g. of this sulfonium dichloride was isolated, indicating that at least 16% of the original H molecules had been transformed into this compound. This sulfonium salt was first described by Davies and Oxford (6), who prepared it by heating H with 3 volumes of water at 100°.

The second sulfonium salt isolated from the H hydrolysate was β-hydroxyethyl-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide chloride (III). This compound might be formed by the reaction of one molecule of H chlorohydrin [β-chloroethyl-β-hydroxyethylsulfide (I)] with one molecule of TG. From the hydrolysate, 10.3 g. of III was obtained as the picrylsulfonate, indicating that at least 26% of the original H molecules had been transformed into this compound. The total amount of sulfonium compounds isolated represents about 50% of the amount of sulfonium ion estimated above to be present in the hydrolysate.

In Figure 1 a mechanism is presented to explain the formation of sulfonium salts when H is hydrolyzed in the presence of moderate quantities of water. It should be mentioned that Ogston independently has proposed the same scheme (8). The sequence of reactions proceeding from H, through H chlorohydrin (I), to TG, is the same as the simple hydrolysis given earlier in Equation 1. The existence of H chlorohydrin as an intermediate in this reaction sequence has been proved by the work of Ogston (9) and Kinsey and Grant (10), who isolated the compound from H hydrolysates. In very dilute aqueous solutions simple hydrolysis occurs exclusively, since the concentration of TG is extremely low relative to that of water. As the ratio of water to H is decreased, however, some of the TG formed by hydrolysis of H undergoes further reaction to give the sulfonium salts isolated.

The formation of IV is envisaged in Figure 1 to occur by the stepwise reaction

of one molecule of H with two molecules of TG. The intermediate, β-chloroethyl-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide chloride (II), has not been isolated from H hydrolysates, but its existence as a precursor of IV is assumed on the basis of several lines of evidence. In the first place, it is improbable that two molecules of TG could react simultaneously with one molecule of

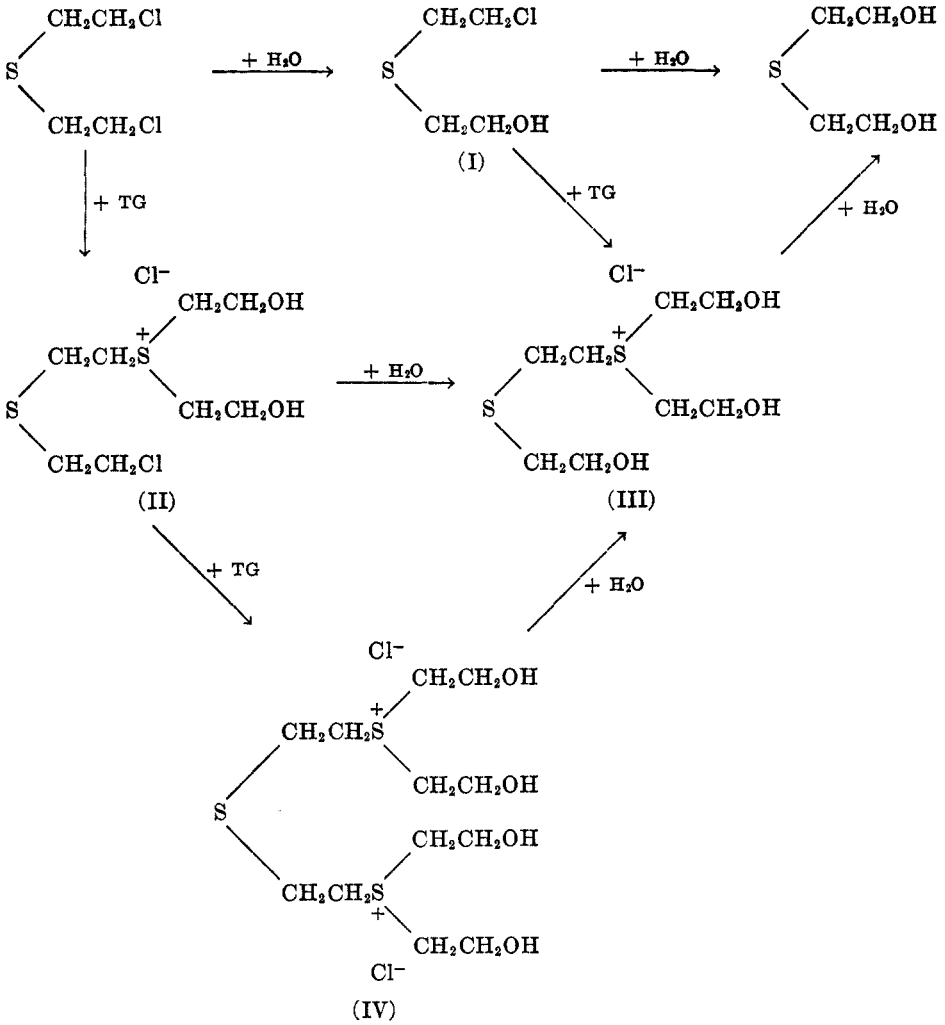


FIGURE 1.

H, since this would involve a trimolecular reaction. In addition, Rydon (11) has synthesized the sulfonium salt (II) by allowing equivalent molar quantities of H and TG to react in ethanol. The sulfonium chloride was found by Rydon to be an unstable oil. In a later part of this paper, the preparation of this sulfonium salt as a stable crystalline picrylsulfonate is described, and compound II is shown to be capable of reacting with TG in aqueous solution to form IV.

According to Figure 1, there are two reaction sequences which may give rise to the sulfonium salt III. One mechanism involves a direct reaction between I and TG; the other involves the hydrolysis of the chloroethyl group of II. The former mechanism is supported by the fact, to be demonstrated in a later paper of this series (12), that I readily reacts with TG in aqueous solution to form a sulfonium salt. Hydrolysis of the chloroethyl group of II, with the resultant formation of III, will be demonstrated later in this paper. Although the ultimate products of the decomposition have not been isolated, it seems likely that, given sufficient time, the various sulfonium salts pictured in Figure 1 will break down to TG.

The formation of sulfonium salts during the hydrolysis of H is of physiological as well as chemical interest, since, as will be shown below, these salts possess a relatively great toxicity. Accordingly, the chemical properties of the sulfonium salts were investigated in greater detail.

The chemical properties of the sulfonium salt IV. The sulfonium dichloride IV was prepared by shaking H with an excess of TG in water. For example, when 5 cc. of H is shaken for 18 hours with 250 cc. of water containing 20 cc. of TG, only 10–13% of the H is hydrolyzed, the remainder combining with TG to form the sulfonium dichloride, which may readily be isolated in good yield [*cf.* also (7)]. If the same amount of H is shaken with 33 cc. of TG and 250 cc. of water, 94% of the H combines with the TG. The reaction proceeds more readily in water than in non-aqueous solutions. No reaction was observed in chloroform or nitrobenzene, and lower yields were obtained in aqueous ethanol than in water alone.

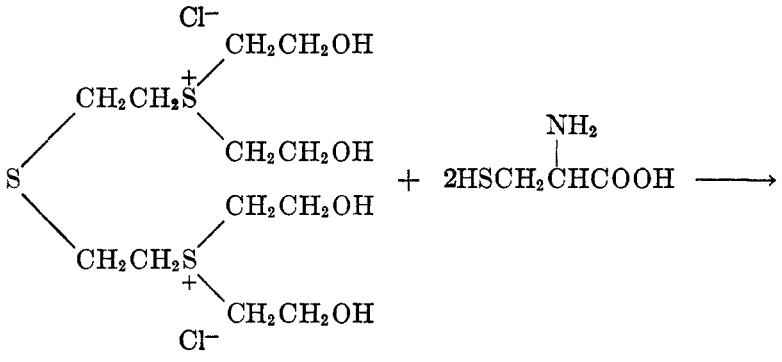
The sulfonium dichloride IV has an LD_{50} for mice of 50–100 mg./kg. If a solution of the sulfonium salt is heated at 100° for 1–2 hours, the toxicity is destroyed. At dosages of 250–1000 mg./kg. in mice, death occurs rapidly with flaccid paralysis and respiratory failure. When IV is administered at levels near the LD_{50}, death is delayed for a period of a week or more (13). It was also found that the sulfonium dichloride possesses a strong necrotizing action when injected intradermally into rabbits. The necrotizing action appeared to be roughly 1/10 as great as that of H itself (14).

The chemical properties of IV present several points of interest. With respect to the stability of the salt, Davies and Oxford (6) observed that in dilute aqueous solution, it is 30% decomposed with the liberation of acid upon standing at 15–20° for three weeks. As was mentioned previously, the sulfonium salt is completely decomposed when heated at 100° in dilute aqueous solution for one hour, two equivalents of acid being formed. In 0.03 *N* NaOH at 4°, the compound is fairly stable, only 25% of the theoretically possible acid being liberated in 24 hours. At *p*H 8.9 and 9.9 at 3°, the sulfonium salt does not form any acid within this time period.

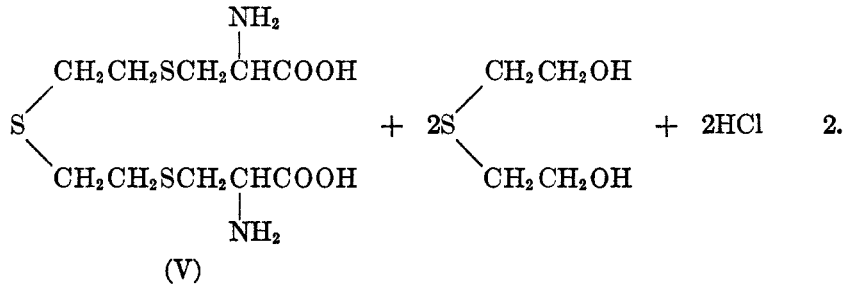
As will be noted from Column 3 of Table I, when IV is incubated at 37° in $NaHCO_3$ solution at *p*H 7.6, a slow liberation of acid occurs. If $Na_2S_2O_3$ is also present in the reaction mixture, a reaction occurs which consumes thiosulfate (Column 2). This finding indicates that in the course of its decomposi-

tion, IV liberates reactive alkylating groups capable of combining with thiosulfate. A comparison of the data in Columns 2 and 3 of Table I reveals that the speed of the reaction of the sulfonium salt with thiosulfate is only slightly greater than is the speed of its decomposition in aqueous $NaHCO_3$ in the absence of thiosulfate.

Further evidence for the formation of reactive products during the decomposition of IV is provided by an experiment performed in the presence of cysteine. When cysteine and IV are allowed to remain in aqueous bicarbonate at 37°, crystals slowly separate from the solution. The material thus formed has the structure V indicated below, and must have resulted from the reaction shown in Equation 2.



(IV)



(V)

The presence of TG in the reaction mixture has not been verified experimentally. Compound V has been isolated previously as a result of the reaction of H itself with two equivalents of cysteine (15). The formation of V coupled with the observations with thiosulfate reported above, make it appear that the sulfonium groups of IV possess, to a lesser degree, some of the reactive alkylating properties associated with the β-chloroethyl groups of H. This observation makes it appear probable that the toxicity of some sulfonium salts may be a reflection of their ability to decompose under physiological conditions with the formation of reactive, toxic products. Further data on this point will be presented in a subsequent paper of this series (16).

The chemical properties of the sulfonium salt II. Rydon first prepared the sulfonium salt II by allowing equivalent molar quantities of H and TG to react

in alcohol at room temperature for a week (11). The sulfonium compound was isolated by Rydon as the chloride, which he found to be a hygroscopic oil, unstable at room temperature. On standing for several days it decomposed with the formation of H and IV. If, however, picrylsulfonic acid is added to the week-old alcoholic reaction mixture described by Rydon, the pure picrylsulfonate of II separates at 0° in crystalline form.[4] The picrylsulfonate of II is not hygroscopic and has shown no tendency to decompose after storage at 0° for a period of months.[5] Neither has decomposition been observed after repeated short periods of exposure to room temperature aggregating many hours.

TABLE I

THE REACTION OF BIS-β-[BIS(β-HYDROXYETHYL)SULFONIUM]ETHYLSULFIDE DICHLORIDE (IV) WITH SODIUM THIOSULFATE AND SODIUM BICARBONATE

Column 2: conc. of reactants per cc.: 0.05 *mM* of IV
0.12 *mM* of $NaHCO_3$
0.10 *mM* of $Na_2S_2O_3$

Temperature, 37°; *p*H 7.3.

Column 3: conc. of reactants per cc.: 0.05 *mM* of IV
0.12 *mM* of $NaHCO_3$

Temperature, 37°; *p*H, 7.6.

TIME, HOURS	THIOSULFATE UPTAKE PER *mM* OF IV, M.EQUIV.	H^+ LIBERATED PER *mM* OF IV, M.EQUIV.
1.	2.	3.
2	0.08	0.08
17.5	0.37	0.34
41.5	0.80	0.68
65.5	1.10	0.90
89.5	1.40	1.06

The picrylsulfonate of II is soluble in about 10 volumes of acetone or methylcellosolve. It has a solubility of about 1% in water, and is very sparingly soluble in ethanol and methanol.

The picrylsulfonate of II decomposes in aqueous methylcellosolve (1 part methylcellosolve plus 4 parts water) at *p*H 7.5–8.0 and 25° with the liberation of one equivalent of chloride ion and nearly two equivalents of acid. As may be seen from Columns 2 and 3 of Table II, the reaction proceeds in two stages. The first stage, in which one equivalent of acid and all of the chloride ion are liberated, has a half-time of about 2.5–3 hours and is complete in less than 24 hours; whereas the second stage, in which the second equivalent of acid is liberated, is much slower and has a half-time of about 2 days. Rydon (11) found that, in 0.01 molar aqueous solution at 30° and *p*H 7.4, the chloride of II liberated acid, the half-time for the liberation of one equivalent of acid being about 3 hours.

[4]Compound IV also forms an insoluble picrylsulfonate, the preparation of which is described in the experimental section.

[5]Like many polynitro compounds, the picrylsulfonates darken on prolonged exposure to light. The picrylsulfonate of II should, therefore, be stored in a dark place.

In order to elucidate the mechanism of the decomposition of II, isolation of intermediate hydrolysis products was undertaken. For this purpose, the picrylsulfonate of II was allowed to hydrolyze in unbuffered aqueous methylcellosolve solution for 16 hours at 25°. After this time 0.95 equivalents of Cl^- and 1.2 equivalents of H^+ had been formed. (The liberation of Cl^- and the first equivalent of H^+ is somewhat slower in unbuffered solution than it is at *p*H 8.) The hydrolysate was found to contain a mixture of compounds. From it both the dipicrylsulfonate of IV, and the picrylsulfonate of the intermediate (III), have been isolated. The picrylsulfonate of IV was obtained in a yield of about 5% of the theory, whereas the picrylsulfonate of III was obtained in a yield of about 20% of the theory.

TABLE II

REACTION OF β-CHLOROETHYL-β-[BIS(β-HYDROXYETHYL)SULFONIUM]ETHYLSULFIDE PICRYLSULFONATE WITH WATER AND WITH THIOSULFATE

Composition of reaction mixture per cc.: 0.0305 *mM* of sulfonium salt
0.09 *mM* of $NaHCO_3$
In the experiment given in Column 4, 0.075 *mM* of $Na_2S_2O_3$ per cc. also was present.
*p*H, 7.5–8.0; temperature, 25°; solvent, aqueous methylcellosolve (4:1).

TIME, HOURS	Cl^- LIBERATED PER *mM* OF SULFONIUM SALT, M.EQUIV.	H^+ LIBERATED PER *mM* OF SULFONIUM SALT, M.EQUIV.	THIOSULFATE CONSUMPTION PER *mM* OF SULFONIUM SALT, M.EQUIV.
1.	2.	3.	4.
1.75	0.38	0.33	0.46
3.75			0.77
4.0	0.63	0.62	
6.25			0.93
7.0	0.70	0.85	
23	1.00	1.31	1.31
47	1.01	1.51	1.51
71		1.64	1.59
95		1.72	
167		1.84	

The formation of III proves that hydrolysis of the chloroethyl group of II is a primary step in its decomposition (*cf.* Figure 1). The formation of IV probably arises as a result of the reaction of II with some TG which is formed during hydrolysis. It has been found that if II is allowed to hydrolyze in the presence of TG (2 equiv.), the H^+ liberation is only half that observed in the absence of TG, whereas the Cl^- liberation is the same in both cases. This observation indicates that II reacts with TG. The reaction product, IV, has been isolated as a picrylsulfonate.

The evidence presented above offers support for the mechanism of the hydrolysis of H in moderate quantities of water presented in Figure 1. It should be mentioned that Rydon (11) on the basis of his work with II has come to substantially the same conclusions relative to the hydrolysis of this compound. He also has obtained some evidence that the sulfonium chloride is capable of regenerating a small quantity of H during its decomposition in water.

As may be seen from Column 4 of Table II, the picrylsulfonate of II reacts with thiosulfate. This reaction also proceeds in two stages. The first stage, in which one equivalent of thiosulfate is consumed has a half-time of about 2 hours, and is 90% complete in about 6 hours. The rate of the consumption of the first equivalent of thiosulfate is somewhat faster than the rate of the liberation of chloride ion in the absence of thiosulfate. It would appear probable that it is the chloroethyl group which reacts with the first equivalent of thiosulfate. The second stage of the reaction is much slower; after 71 hours, 0.59 equivalents of additional thiosulfate are consumed. This second reaction proceeds at a rate comparable to that of the liberation of the second equivalent of acid in the absence of thiosulfate. The second reaction probably involves the slow decomposition of the sulfonium group of the compound, and is analogous to the similar reactions discussed earlier for IV.

The sulfonium salt II has a noteworthy toxicity. The LD_{50} for this compound in mice is about 1.2 mg./kg., thus making it even more toxic to this species than is H itself. The pharmacological and toxicological properties of this substance are presented elsewhere (17). Although there is no direct evidence indicating that sulfonium salts are formed from H *in vivo*, the toxicity and mode of formation of the sulfonium salts described in this paper raise the possibility that these compounds may play a role in the physiological action of H.

EXPERIMENTAL

The extent of sulfonium salt formation on hydrolysis of H. The mustard gas used in this work was a pure sample made by the thiodiglycol process. The H was shaken with the requisite amount of water (50, 200, or 1000 volumes) at room temperature until a clear solution resulted (18–24 hours). The solution was titrated to phenolphthalein with standard alkali, thus permitting a calculation of the acidity produced on hydrolysis. The neutralized solution was heated to 100° for 1 hour, and the amount of acid produced thereby again titrated. This figure furnished an index of the extent of sulfonium salt formation.

Isolation of sulfonium salts from H hydrolysates. H (20 cc.) was shaken at room temperature with 1 liter of water for 16 hours. The resulting clear solution was concentrated *in vacuo* to a sirup (bath temperature, 40–45°). Alcohol was added and the mixture again concentrated to a sirup. This procedure was repeated twice more with alcohol and twice with acetone. The sirup was further dried by trituration with acetone, and 100 cc. of absolute alcohol was added. The resulting clear solution, on standing at 0°, deposited 5.3 g. of crystalline IV. After one crystallization from absolute alcohol this material melted at 97–102°; yield 3.3 g. A further recrystallization from alcohol yielded 2.5 g. of pure product, m.p. 101–103°. A pure sample of IV melts at 103° (see below).

To the alcoholic solution from which IV had been removed, 3 g. of picrylsulfonic acid was added. On cooling to 0° an oil separated which gradually solidified on standing. It was obviously a mixture, and was not investigated further. The bulk of the solution was decanted from this material, and 7 g. of picrylsulfonic acid added to the solution. On cooling to 0°, 10.4 g. of the crystalline picrylsulfonate of III was obtained; m.p. 76–78°; mixed m.p. with a sample of the same compound prepared by hydrolysis of the picrylsulfonate of II (see below), 76–77°.

Anal. Calc'd for $C_8H_{19}O_3S_2 \cdot C_6H_2N_3O_9S$: C, 32.4; H, 4.1; N, 8.1; S, 18.5.
Found: C, 32.6; H, 3.9; N, 8.0; S, 18.7.

Preparation of bis-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide dichloride (IV). H (5 cc.) was shaken for 24 hours with 250 cc. of an aqueous solution containing 20 cc. of TG. The resulting clear solution was concentrated *in vacuo* to a sirup (bath temperature 40–45°).

The sirup was triturated repeatedly with acetone, and the acetone discarded. The sticky residue was taken up in about 150 cc. of boiling absolute ethanol, the solution filtered, and stored at 0°. The crystalline sulfonium salt was filtered, washed with cold ethanol, filtered, and dried; yield 10.5 g.; m.p. 101.5°. This material is analytically pure, but the melting point may be raised to 103° by one further crystallization from alcohol. Davies and Oxford (6) report the melting point 101.5–103°.

Anal. Calc'd for $C_{12}H_{28}Cl_2O_4S_3$: C, 35.7; H, 7.0; Cl, 17.6; S, 23.8.
Found: C, 35.8; H, 7.1; Cl, 17.4; S, 23.6.

The sulfonium dichloride forms a chloroplatinate of the composition $C_{12}H_{28}O_4S_3 \cdot PtCl_6$, which crystallizes as microscopic needles melting at 138°.

Preparation of bis-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide dipicrylsulfonate. A solution of 2 g. of IV in 25 cc. of water was added to a solution of 3.65 g. of picrylsulfonic acid in 25 cc. of water. An oil separated which crystallized on scratching. After standing at 0° overnight, the dipicrylsulfonate was filtered off and washed with water and ethanol. For recrystallization the salt was dissolved in 45 cc. of acetone plus 15 cc. of water, filtered, and 150 cc. of ethanol added to the filtrate. An immediate crystallization occurred. After standing overnight at 0°, 3.6 g. of material was obtained; m.p. 138–139°.

Anal. Calc'd for $C_{12}H_{28}O_4S_3 \cdot 2C_6H_2N_3O_7S$: C, 31.45; H, 3.5; N, 9.2.
Found: C, 31.4; H, 3.7; N, 9.3.

The reaction of IV with sodium thiosulfate and sodium bicarbonate. The reaction mixtures were made up to the concentrations indicated in Table I. CO_2 was bubbled through the $Na_2S_2O_3$ solutions (which contained a small amount of borax as a stabilizer) to bring them to the desired *p*H. The thiosulfate consumption was determined by iodimetric titration in the usual manner. The extent of the liberation of hydrogen ions was determined in the following manner: To a 10-cc. aliquot of the $NaHCO_3$ solution containing IV, 15 cc. of 0.1 *N* HCl was added, the CO_2 removed *in vacuo*, and the solution titrated to phenolphthalein with 0.1 *N* NaOH. A control $NaHCO_3$ solution (containing no sulfonium salt) was treated in the same manner. The difference between the amounts of NaOH required by the two solutions is equal to the amount of hydrogen ions liberated during the decomposition of IV.

Controls were run to prove the stability of the $Na_2S_2O_3$ and $NaHCO_3$ solutions under the conditions of these experiments.

The reaction of IV with cysteine. Cysteine HCl [788 mg. (5 *mM*)], 1.0 g. (2.5 *mM*) of IV, and 925 mg. (11 *mM*) of $NaHCO_3$ were dissolved in 50 cc. of O_2-free water and kept at 37° under N_2. Crystals appeared in the reaction mixture after 18 hours. After 2 days the crystalline material was filtered off, washed, dried, and analyzed; yield 0.26 g. The nitroprusside test in the presence of cyanide was negative. The material was soluble in acids and alkalies, but insoluble in water.

Anal. Calc'd for $C_{10}H_{20}N_2O_4S_3$: C, 36.6; H, 6.1; N, 8.5.
Found: C, 36.3; H, 6.2; N, 8.3.

Preparation of β-chloroethyl-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide picrylsulfonate. H (40 g.) and TG (30.5 g.) were dissolved in 95% ethanol, made up to a volume of 1 liter with ethanol, and the mixture was allowed to stand at room temperature for a week. The solution was cooled to 0°, 30 g. of picrylsulfonic acid in 100 cc. of 95% ethanol was added, and the mixture was kept at 0° overnight. The picrylsulfonate crystallizes in large, heavy crystals, which are occasionally contaminated with small quantities of lighter crystals which can be removed by decantation. The salt was filtered, washed with alcohol, and dried over P_2O_5 *in vacuo* at 0°; yield 16.4 g.; m.p. 89–91°. The mother liquor was allowed to stand at room temperature for 4 days, 20 g. of picrylsulfonic acid added, and the mixture kept at 0° for 2–3 days. Twelve and two-tenths grams of sulfonium picrylsulfonate (m.p. 89–91°) was obtained. A repetition of this procedure yielded another 8.6 g. of salt.

For recrystallization, 10 g. of the picrylsulfonate was dissolved in 100 cc. of acetone, filtered, and 300 cc. of absolute ethanol was added. The clear solution was concentrated *in vacuo* (bath temperature, 40°) until a faint turbidity appeared, and placed at 0° overnight.

The crystalline product was filtered off, washed with ethanol, and dried as before; yield 8.5 g.

The picrylsulfonate was stable on storage for at least 4 weeks at room temperature, as evidenced by the fact that no change in melting point resulted after this treatment.

The picrylsulfonate is practically pure as it separates from the reaction mixture. The analyzed preparation had the melting point 91–92°.

Anal. Calc'd for $C_8H_{18}ClO_2S_2 \cdot C_6H_2N_3O_9S$: C, 31.3; H, 3.8; N, 7.8; S, 17.8; Cl, 6.6.
Found: C, 31.4; H, 3.8; N, 7.9; S, 18.2; Cl, 6.6.

Reactions of β-chloroethyl-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide picrylsulfonate with water and with thiosulfate. In the experiments recorded in Table II, the powdered salt was dissolved in methylcellosolve, and an aqueous solution of the other reactants was added. In the experiment employing $Na_2S_2O_3$, the reaction mixture was brought to *p*H 7.5 with CO_2. For the various analytical determinations, 10-cc. aliquots of the reaction mixture were withdrawn. For the determination of the chloride ion liberation, 0.02 *N* $AgNO_3$ solution was employed (dichlorofluorescein as indicator). Hydrogen ion liberation was determined in the manner already described for similar experiments with compound IV, except that 0.05 *N* acid and alkali were employed. Thiosulfate uptake was determined by titration with 0.05 *N* I_2 solution, the titration mixture being cooled in ice-water to prevent reaction of the I_2 with the methylcellosolve.

It should be mentioned that sodium picrylsulfonate reacts slowly with $Na_2S_2O_3$. A control experiment indicated that the extent of this reaction was negligible for the first 7 hours. Hence, the thiosulfate consumption in the first stage of the reaction of the sulfonium picrylsulfonate with thiosulfate can all be attributed to reaction with the sulfonium salt. During the second or slower stage, however, a control containing sodium picrylsulfonate and no sulfonium salt must be run simultaneously, and its thiosulfate consumption deducted from that of the reaction mixture containing the sulfonium salt. The initial thiosulfate concentration in this control, however, was 0.045 *mM* per cc., since the thiosulfate concentration in the reaction mixture containing the sulfonium salt at the start of the second stage reaction had been reduced to this value as a result of the more rapid first stage reaction.

Isolation of the products of the reaction of β-chloroethyl-β-[bis(β-hydroxyethyl)sulfonium]-ethylsulfide picrylsulfonate with water. The sulfonium picrylsulfonate (4.04 g.) was dissolved in 50 cc. of methylcellosolve and made up to a volume of 250 cc. with water. The mixture was kept at 25° for 16 hours, after which time a 10-cc. aliquot was withdrawn for the determination of H^+ and Cl^- content. The results indicated that 1.2 equivalents of H^+ and 0.95 equivalents of Cl^- had been formed. The bulk of the reaction mixture was concentrated *in vacuo* (bath temperature 40–45°) to a sirup. Acetone was added and the mixture was concentrated again. This was repeated three times. The sirup was dissolved in acetone, and 200 mg. of crystalline material was filtered off; m.p. 133–135°; yield 5%. The crystalline precipitate was dissolved in aqueous acetone (1 part water and 3 parts acetone) and precipitated by addition of ethanol; m.p. 133–135°. The dipicrylsulfonate of IV melts at 138–139°. A mixed melting point of the isolated compound and an authentic sample of the dipicrylsulfonate of IV was 133–135°.

The acetone solution obtained above was concentrated *in vacuo* to a sirup, and $CHCl_3$ added. The mixture was cooled to 0°, after which the $CHCl_3$ could be decanted from the sticky oil. The oil was dissolved in acetone, filtered, and ether was added to the filtrate. After cooling to 0° and scratching, the oil which had formed soon crystallized; yield 2.6 g. The substance melted over a range beginning at 65°. The crystalline material was treated with 100 cc. of hot absolute ethanol, and the solution decanted from a small oily residue. On cooling the solution to room temperature, a sticky solid deposited which was removed by filtration. Three volumes of ether was added to the filtrate. After cooling to 0°, 750 mg. of the crystalline picrylsulfonate of III was obtained; m.p. 73–76° with preliminary softening. The yield corresponds to about 20% of theory. For analysis the compound was recrystallized from acetone with the addition of ether, the first fraction which precipitated being discarded; m.p. 76–78°.

Anal. Calc'd for $C_8H_{19}O_9S_2 \cdot C_6H_2N_3O_9S$: C, 32.4; H, 4.1; N, 8.1; S, 18.5.
Found: C, 32.2; H, 4.2; N, 8.1; S, 18.6.

Reaction of β-chloroethyl-β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide picrylsulfonate with thiodiglycol. The picrylsulfonate [970 mg. (1.8 *mM*)] was dissolved in 12 cc. of methylcellosolve and 48 cc. of water containing 440 mg. (3.6 *mM*) of TG was added. After standing for 24 hours at 25°, the mixture was cooled to 0°. Seven hundred milligrams of the dipicrylsulfonate of IV, m.p. 138–139°, was obtained. This melting point is the same as that of an authentic sample of the salt. A mixed m.p. showed no depression.

Anal. Calc'd for $C_{12}H_{28}O_4S_3 \cdot 2C_6H_2N_3O_9S$: C, 31.5; H, 3.5; N, 9.2.
Found: C, 31.3; H, 3.6; N, 9.2.

The authors wish to acknowledge with thanks the helpful cooperation of Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] II. THE REACTION OF MUSTARD GAS WITH CARBOXYL GROUPS AND WITH THE AMINO GROUPS OF AMINO ACIDS AND PEPTIDES

STANFORD MOORE, WILLIAM H. STEIN, AND JOSEPH S. FRUTON[2]

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Biochemical studies on the reactions of mustard gas (H) have been based upon the reasonable assumption that the physiological effects of this agent are the consequence of chemical processes which H initiates by its reaction with body constituents. In the previous paper of this series (1), data were presented on the chemical reactions of H with water. The experiments described in the present communication concern the reactions of H with carboxyl groups and with the amino groups of amino acids and peptides.

The reaction of H with carboxyl groups. The reaction of H with carboxyl groups is of particular interest, since there is evidence that carboxyl groups are involved when H reacts with proteins both *in vitro* and *in vivo*. Other investigators have studied in detail the kinetics of the reactions of H with organic acids (2, 3). The experiments reported below, which were performed primarily from the preparative standpoint, show that in aqueous solution at *p*H 8, H reacts readily with sodium salts of carboxylic acids to form esters of thiodiglycol.

Measurement has been made of the amounts of organic esters of thiodiglycol present at the end of 24 hours when H is shaken with aqueous solutions of the sodium salts of a number of organic acids. The results reported in Table I indicate that, under the experimental conditions employed, about half of the initial H appears in the form of organic esters. The products of the reaction of H with the sodium salts of acetic, hippuric, salicylic, and diethylbarbituric acids have been prepared and found to be disubstituted derivates of thiodiglycol. The presence of monosubstituted derivatives is not excluded.

The reaction of H with substances such as acetate, hippurate, citrate, and succinate lends support to the belief that H is capable of reacting with some of the β-carboxyl groups of aspartic acid or the γ-carboxyl groups of glutamic acid which might exist in an uncombined state in proteins. Moreover, the reaction with simple organic acids, such as succinic, suggests that *in vivo* H may react with important cellular metabolites of this type. The reaction of H with stearate is of interest in view of the fact that Reichstein and Goldschmidt (4) isolated bis(β-hydroxyethyl)sulfoxide from adrenals. These authors expressed the view that this compound occurred naturally in the form of esters of higher fatty acids.

[1] This work was done in whole under Contract No. OEMsr-313 between The Rockefeller Institute for Medical Research and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein. The experiments were performed during the period January 1942–August 1944.

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Finally, the reactions with acetate, citrate, and veronal are of some practical consequence and point to the inadvisability of using substances of this type as buffers in experiments in which H is employed.

To determine whether the extent of the reaction of H with carboxyl groups of substituted amino acids is markedly influenced by structural differences between the various compounds bearing the carboxyl group, three acids of different

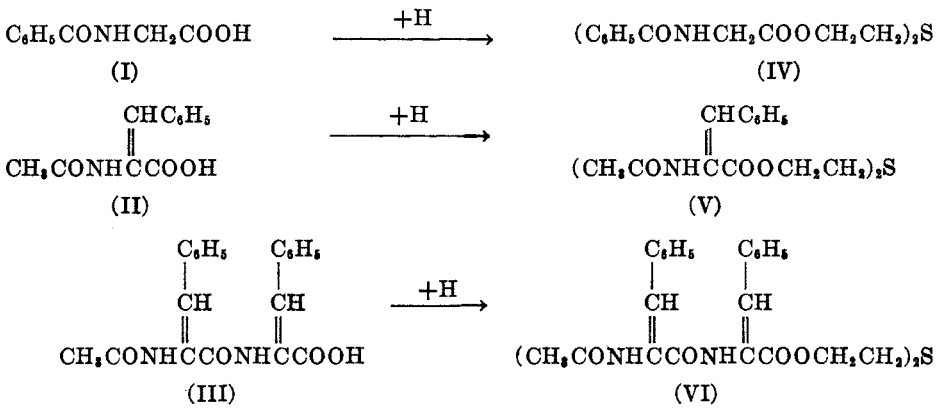
TABLE I

REACTION OF H WITH ORGANIC ACIDS

H (4 *mM*) was shaken at 20–25° for about 24 hours with an aqueous solution (25 cc.) of the reactant. Individual variations in this procedure, which were sometimes necessary, are given in the experimental section. The extent of esterification was determined in the manner described in the experimental section.

REACTANT	AMOUNT OF REACTANT, *mM*	H RECOVERED AS ESTER, %
Sodium acetate	16	40
Sodium acetate	60	80
Sodium stearate	16	50
Trisodium citrate	8	60
Disodium succinate	8	60
Sodium diethylbarbiturate (Veronal-Na)	16	60
Sodium hippurate	16	40
Sodium salicylate	16	45

structure were compared. These acids were hippuric acid (I), acetyldehydrophenylalanine (II), and acetyldehydrophenylalanyldehydrophenylalanine (III).



It was found that all three carboxylic acids combine with H to almost the same extent at *p*H 8 to form saponifiable esters of thiodiglycol. Under the conditions described in the experimental section, 37% of the available chloroethyl groups of H reacted with hippuric acid (I), while 35% combined with acid (II), and about 28% with acid (III). However, variations in the reactivities of widely differing organic acids have been observed (3).

The reaction of H with amino groups. In solutions buffered with $NaHCO_3$, H may react to a measurable extent with the amino groups of glycine, alanine, lysine, glycylglycine, and benzoyllysineamide (Table II). In these experiments, samples of H were shaken with aqueous solutions of the amino acids or peptides at room temperature and the decrease in NH_2-N determined by the Van Slyke nitrous acid method. In acidic solutions (absence of $NaHCO_3$) no reaction with the amino groups of glycine or glycylglycine was observed.

TABLE II

REACTION OF H WITH AMINO GROUPS OF AMINO ACIDS AND PEPTIDES

COMPOSITION OF AQUEOUS SOLUTION (VOLUME 25 CC.)			H ADDED, *mM*.	DECREASE IN NH_2-N, M.EQUIV.	DECREASE IN NH_2-N PER *mM* OF H, M.EQUIV.
Glycine	16	*mM*	4.0	1.3	0.32
$NaHCO_3$	8	*mM*			
Alanine	8	*mM*	4.0	1.0	0.25
$NaHCO_3$	12	*mM*			
Lysine 2 HCl	8	*mM*	4.0	1.8	0.45
(Neutr. with NaOH)				($\alpha + \epsilon$)	
$NaHCO_3$	12	*mM*			
Glycylglycine	16	*mM*	4.0	2.5	0.62
$NaHCO_3$	8	*mM*			
Glycine	16	*mM*	4.0	0.0	0.0
(Without $NaHCO_3$)					
Glycylglycine	18	*mM*	4.0	0.0	0.0
(Without $NaHCO_3$)					
Benzoyllysineamide	0.32	*mM*[a]	0.19	0.03	0.15
$NaHCO_3$	0.8	*mM*			

[a] Volume of solution was 1 cc.

In the reaction of H with amino groups, either secondary amines or thiazanes might result (5, 6). It has not been established which of these two structures is formed in the reactions reported in Table II.

The experiment with benzoyllysineamide (Table II) is more nearly analogous to the possible reaction of H with the amino groups in proteins than are the other examples. The lysine residue in benzoyllysineamide is bound in a manner similar to that in which lysine occurs in proteins; the ϵ-amino group in this structure is free whereas the α-amino group and the carboxyl group are blocked. It will be noted that, under similar conditions, the extent of the reaction of H with the ϵ-amino group of benzoyllysineamide is lower than that with α-amino groups.

The above experiments, carried out under mild conditions of *p*H and temperature, may be regarded as evidence that the amino groups of proteins, peptides,

and amino acids are to be considered among the groups which H may attack in biological systems.

The reaction of H with pyridine, nicotinamide, and nicotinic acid. H reacts readily with the pyridine nitrogen of these three compounds to form pyridinium compounds. The products of the reaction of H with pyridine and nicotinamide have been isolated in good yield (*cf.*, experimental section). Analytical data have been obtained to show that, under the experimental conditions employed, the reaction between H and nicotinic acid is nearly quantitative, 95% of the chloroethyl groups of H having reacted to form pyridinium compounds.

EXPERIMENTAL

Reaction of H with sodium acetate. The reaction mixture was made up in the manner indicated in Table I. After 24 hours shaking, no unreacted H remained. The resulting aqueous suspension of diacetylthiodiglycol was made alkaline with $NaHCO_3$ and extracted with ether. From the ether extract, diacetylthiodiglycol was obtained as a Cl-free oil in a yield of 40% (determined by saponification equivalent). This compound has been prepared previously (7, 8). The diacetate (500 mg.) was transformed into the crystalline sulfilimine by treatment in aqueous solution with 700 mg. of chloramine-T; yield 70%. The sulfilimine was recrystallized from benzene; m.p. 116–117.5°.

Anal. Calc'd for $C_{15}H_{21}NO_6S_2$: C, 48.0; H, 5.6; N, 3.8.
Found: C, 48.2; H, 5.8; N, 3.6.

In a control experiment no diacetate was formed when thiodiglycol (4 *mM*), acetic acid (8 *mM*), sodium acetate (8 *mM*), and NaCl (8 *mM*) in 25 cc. of water were kept at room temperature for three days.

Reaction of H with sodium stearate. The reaction was carried out with an aqueous suspension of sodium stearate. The extent of esterification (Table I) was determined by saponification of an ether extract of the alkaline reaction mixture.

Reaction of H with trisodium citrate and disodium succinate. The reactions were carried out in the manner described for the reaction with sodium acetate, except that the saponification equivalents were determined directly on the aqueous solution with an approximate correction for the presence of sulfonium chlorides. The esters obtained in these experiments are acidic esters, and are not extractable from neutral or alkaline solution with ether.

Reaction of H with sodium diethylbarbiturate (veronal-Na). The yield of ester (60%) given in Table I is based on the weight of products extractable by ether from alkaline solution. The ether extract was concentrated *in vacuo* and, upon addition of petroleum ether, the diveronal derivative of thiodiglycol crystallized. It was recrystallized from alcohol; m.p. 148–149°.

Anal. Calc'd for $C_{20}H_{30}N_4O_6S$: C, 52.9; H, 6.6; N, 12.3.
Found: C, 53.0; H, 6.6; N, 12.3.

Reaction of H with sodium hippurate. The reaction was carried out in 50 cc. of 60% acetone to ensure complete reaction of H. On removal of the acetone *in vacuo*, the dihippurylthiodiglycol crystallized; yield 650 mg., 37%. It was recrystallized from alcohol; m.p. 119°.

Anal. Calc'd for $C_{22}H_{24}N_2O_6S$: C, 59.4; H, 5.4; N, 6.4.
Found, C, 59.4; H, 5.4; N, 6.3.

In the absence of acetone, the ester separates during the reaction as an oily solid contaminated with unreacted H.

Reaction of H with sodium salicylate. The reaction mixture (Table I) was made alkaline with $NaHCO_3$ and extracted with ether. The yield of ester given in Table I is based upon the weight of the material found in the ether extract. The crude disalicylthiodiglycol obtained on removal of the ether was crystallized from alcohol; m.p. 74–75°.

Anal. Calc'd for $C_{18}H_{18}O_6S$: C, 59.7; H, 5.0.
Found: C, 59.7; H, 5.3.

Extent of reaction of H with hippuric acid (I), acetyldehydrophenylalanine (II), and acetyldehydrophenylalanyldehydrophenylalanine (III). H (4 *mM*) was shaken for 48 hours at about 25° with 12 *mM* of the sodium salts of I, II, and III in the presence of 12 *mM* of $NaHCO_3$. The total volume was 25 cc. In each case, a solid separated during the reaction. Hydrochloric acid was added and the CO_2 removed *in vacuo*. Absolute alcohol (50 cc.) was added to give a clear solution. The solution was neutralized to phenolphthalein, and 5.0 cc. of *N* NaOH were added. After the solution had stood at room temperature for 30 minutes, back titration with 0.1 *N* HCl gave the amount of ester saponified. In the case of the reaction with III, the titration was not completely satisfactory due to the yellow color of the solution.

Reaction of H with pyridine. H (2.55 cc., 20.0 *mM*) was added to 100 cc. of water containing 6.32 g. (80.0 *mM*) of pyridine. The mixture was shaken at room temperature for 24 hours and then evaporated to dryness *in vacuo*. The residue was washed with acetone and dissolved in absolute ethanol. Upon the addition of dry ether, crystallization of bis(β-pyridiniumethyl)sulfide dichloride occurred; yield 5.25 g. (83% of theory). The compound was recrystallized twice from an absolute ethanol-ether mixture and dried over P_2O_5 *in vacuo* at room temperature to constant weight. The substance is very hygroscopic.

Anal. Calc'd for $C_{14}H_{18}Cl_2N_2S$: C, 53.0; H, 5.7; N, 8.8; Cl^-, 22.35.
Found: C, 52.6; H, 5.9; N, 8.7; Cl^-, 22.2.

To convert the dichloride to the dipicrylsulfonate, 6.34 g. was dissolved in 200 cc. of water and a solution of 1.46 g. of picrylsulfonic acid in 10 cc. of water was added with stirring. The precipitate which separated was filtered off and discarded. A solution of 13.15 g. of picrylsulfonic acid in 90 cc. of water was then added with stirring. After standing at 4° for 4 hours, the product was collected and washed with water. The yield was 14.49 g. After recrystallization from a solution of 90% methylcellosolve it melted at 216–218°.

Anal. Calc'd for $C_{14}H_{18}N_2S \cdot 2\,C_6H_2N_3O_9S$: C, 37.6; H, 2.7; N, 13.5; S, 11.6.
Found: C, 37.5; H, 2.6; N, 13.5; S, 11.7.

Reaction of H with nicotinamide. A reaction mixture containing 7.3 g. (60 *mM*) of nicotinamide, 5.05 g. (60 *mM*) of $NaHCO_3$, and 1.9 cc. (15 *mM*) of H in 150 cc. water was shaken for 20 hours at room temperature. The solution was concentrated to dryness under reduced pressure and the residue was extracted with 200 cc. of hot absolute ethanol. The undissolved portion was taken up in 10 cc. of water, acidified with HCl and the resulting solution was evaporated under reduced pressure. The residue was evaporated once with absolute ethanol and once with absolute methanol to remove the last traces of water. The residue was then extracted with 150 cc. of boiling absolute methanol and filtered. Upon cooling the filtrate overnight at 4°, pink crystals of the dichloride of the nicotinamide derivative were obtained. The compound was recrystallized from absolute methanol and dried to constant weight in air; yield 0.8 g.; m.p. 151–153°.

Anal. Calc'd for $C_{16}H_{20}Cl_2N_4O_2S \cdot H_2O$: C, 45.6; H, 5.25; N, 13.3; Cl^-, 16.8; H_2O, 4.3.
Found: C, 45.6; H, 5.3; N, 13.3; Cl^-, 16.9; H_2O, 4.6.

A second but less pure crop was obtained by working up the methanolic mother liquors; yield 0.7 g.; m.p. 144–148°.

The reaction of H with nicotinic acid. H (0.5 cc., 4 *mM*) was shaken with 20 cc. of a solution of 16 *mM* of nicotinic acid (sodium salt) neutralized to phenolphthalein. After 20 hours, the liberated acid was titrated and found to be 0.4 *mM* (theory for complete hydrolysis of H, 8 *mM*). Thus, 95% of the chloroethyl groups had reacted to form "onium" compounds. In order to decide whether these "onium" compounds were of the sulfonium or the ammonium type, the solution was heated for 1 hour at 100°. The slight increase in acidity after heating indicated that not more than 1% of the "onium" compounds could be sulfonium salts.

The authors wish to express their indebtedness to the late Dr. Max Bergmann for the constant advice and encouragement which he gave in the course of this research. Thanks are due also to Miss Rosalind E. Joseph for assistance in the

conduct of these experiments and to Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] III. THE REACTION OF MUSTARD GAS WITH METHIONINE

WILLIAM H. STEIN AND STANFORD MOORE

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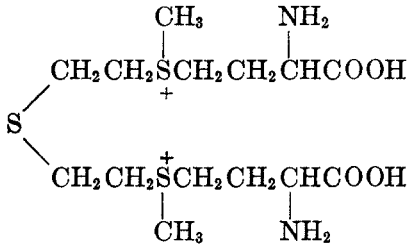
In the first paper of this series (1), the reaction of mustard gas (H) with the thioether sulfur of thiodiglycol was described. Since methionine is a protein constituent, and in addition plays an important rôle in biological transmethylation reactions, it seemed of interest to determine whether H was capable of reacting with the thioether sulfur of this amino acid.

When H is shaken at room temperature with an aqueous solution of methionine at *p*H 3, only 10% of the theoretically possible acid is liberated, indicating that 90% of the H has reacted with methionine to form a sulfonium salt. When the same reaction is carried out at *p*H 8.5, 60% of the H combines with methionine to yield a sulfonium salt. Under similar conditions 40% of the H reacts with the carboxyl group of sodium hippurate, and 8 to 15% combines with the ϵ-amino group of benzoyllysineamide [see (2)]. These data indicate that H reacts with methionine-sulfur more readily than it does with either the amino or carboxyl groups of the aforementioned substances.

From the reaction mixture resulting when H is shaken with methionine in acid solution the sulfonium base I has been isolated as a crystalline azobenzene sulfonate.[2] It will be noted that I is derived from one molecule of H and 2 molecules of methionine, and is analogous in structure to the sulfonium salt formed when H is allowed to react with thiodiglycol (1). Because of the unfavorable properties of I, the pure azobenzene sulfonate was only isolated in low yield.



(I)

[1] This work was done in whole under Contract No. OEMsr-313 between The Rockefeller Institute for Medical Research and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein. The experiments were performed in the period January 1942–August 1944.

[2] The analytical data presented in the experimental section indicate that the salt is composed of one mole of the sulfonium base and four moles of azobenzene sulfonic acid, two of which neutralize the two sulfonium groups, and two of which neutralize the two α-amino groups.

The fact, however, that during the reaction of H with methionine very little acid is liberated, is strong indication that I is the major product of the reaction. This supposition is further supported by the earlier studies on the analogous reaction of H with thiodiglycol, in which it was shown that the sulfonium salt derived from one molecule of H and 2 molecules of thiodiglycol was formed in excellent yield (1). In the discussion to follow, therefore, it is assumed that I is the principal product formed as a result of the reaction of H with methionine.

When the aqueous solution resulting from the reaction of 13 g. of H with 20 g. of methionine is heated at 100° for 2 hours, a heavy, water-insoluble oil (3.2 g.)

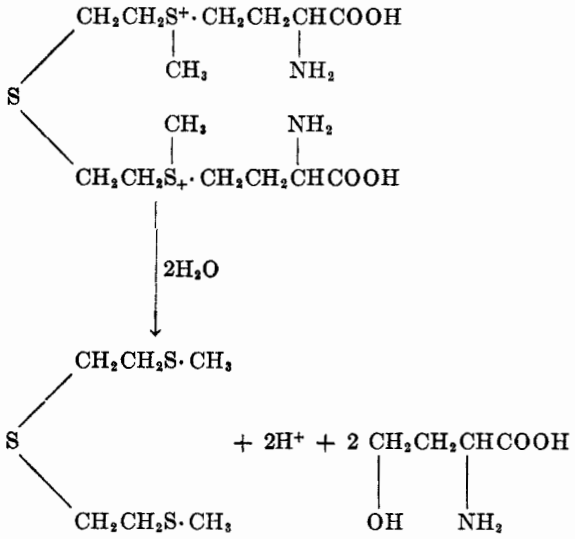


FIG. 1

separates, which has an unpleasant, persistent odor. It has been identified as a trisulfide, bis(methylthioethyl)sulfide, of the following structure:

$$CH_3SCH_2CH_2SCH_2CH_2SCH_3 \qquad (II)$$

Upon oxidation with nitric acid, the trisulfide was transformed into the trisulfoxide.

$$\underset{\underset{O}{\|}}{CH_3S}CH_2CH_2\underset{\underset{O}{\|}}{S}CH_2CH_2\underset{\underset{O}{|}}{S}CH_3 \qquad (III)$$

The trisulfide (II) probably arises from the decomposition of the sulfonium salt (I) in the manner given in Figure 1.

According to Figure 1, γ-hydroxy-α-aminobutyric acid (IV) also should be formed during the decomposition of the sulfonium salt. Additional evidence for the validity of the above reaction scheme was provided by the isolation of IV as a salt of *p*-hydroxyazobenzene-*p'*-sulfonic acid, from which the free amino acid IV could be obtained.

There is evidence, however, that the decomposition of I does not proceed solely according to Figure 1. The yield of trisulfide is far below the theoretical quantity to be expected from this scheme. Moreover, the recovery of considerable quantities of methionine after heat treatment of I indicates that only about one-quarter of it decomposes according to the above scheme, while the remaining three-quarters decomposes to regenerate methionine.

In a protein molecule both the amino and the carboxyl groups of methionine are bound in peptide linkage. In order to learn whether the methionine-sulfur in a structure of this type can react with H, the reaction of carbobenzoxymethionineamide with H was investigated.

It is noteworthy that H reacts with carbobenzoxymethionineamides to yield a sulfonium salt. When 0.25 cc. of H is allowed to act upon 2.3 g. of carbobenzoxymethionineamide in 100 cc. of 50% alcohol (alcohol is necessary in order to keep the carbobenzoxymethionineamide in solution), about half of the H hydrolyzes, and the other half reacts to form a sulfonium salt. Upon heating at 100° in water, this sulfonium salt decomposes to yield HCl, and considerable amounts of carbobenzoxymethionineamide. The characteristic odor of the trisulfide which is formed on decomposition of I can also be detected here, although no water-insoluble oil separates.

The yield of sulfonium salt is lower in the case of carbobenzoxymethionineamide than it is in the case of free methionine. This may be due, in part, to the fact that 50% alcohol was employed as solvent in the reaction. In this connection, it was shown earlier (1) that the reaction of H with thiodiglycol to yield a sulfonium salt was inhibited by the presence of alcohol.

In the case of a protein, the reaction of H with methionine-sulfur may be more complicated than in the model experiments discussed above. It seems unlikely that two methionine-sulfurs would be oriented in space in a manner permitting both chlorines of one H molecule to react with two methionines. It is much more probable that one chlorine of an H molecule would react with a methionine-sulfur, and that the other would react either with some other favorably situated reactive group in the protein molecule, or with water.

It should be pointed out that the over-all sequence of reactions starting with H and methionine, and ending with the trisulfide II, involves the transfer of the thiomethyl groups from 2 methionine molecules to a second substance, in this case a diethylsulfide residue. In other words, a "transthiomethylation" has occurred, the thiomethyl group of methionine having been labilized by sulfonium salt formation. It will be recalled that the methylsulfonium salt of methionine has been prepared by Toennies (3). As will be shown in a subsequent paper of this series (4), the methylsulfonium salt of methionine, in contrast to the sulfonium salt I, is quite stable. The lability of the methyl or thiomethyl group in a methionine sulfonium salt thus depends upon the structure of the other group attached to the sulfonium sulfur. Whether or not these findings have a bearing on the mechanism of biological transmethylation reactions remains for further investigations to determine.

EXPERIMENTAL

Extent of reaction of H with methionine. H (0.5cc.) was shaken at room temperature for 18 hours with a solution of 2.4 g. of methionine in 26 cc. of 0.31 *N* HCl (*p*H about 3). An aliquot of the resulting clear solution was titrated in 90% alcohol with thymolphthalein as the indicator. The main body of the reaction mixture was neutralized, heated at 100° for 2 hours, and an aliquot again titrated as before. The increase in acid produced on heating was taken as a measure of the sulfonium salt decomposed. The results indicated that 90% of the H had reacted to yield the sulfonium salt. On heating, the aqueous solution became cloudy and acquired a strong, unpleasant odor due to the formation of the trisulfide (II) (see below).

At alkaline *p*H values (about 8.5) the reaction of H with methionine is not as complete as at *p*H 3. H (0.5 cc.) was shaken with 2.4 g. of methionine and 700 mg. of $NaHCO_3$ in 25 cc. of 0.5 *N* NaOH. The extent of the reaction was determined as described above, except that the reaction mixture was acidified and CO_2 removed *in vacuo* prior to the titrations. The results indicated that about 60% of the H reacted to give the sulfonium salt.

Isolation of the Azobenzenesulfonate of I. H (0.5 cc.) was shaken for 24 hours at room temperature with 2.5 g. of methionine in 25 cc. of 0.65 *N* HCl. To the resulting clear solution 5 cc. of *N* HCl was added, the solution concentrated to a sirup *in vacuo*, and absolute ethanol added, which caused the precipitation of an oil. The ethanol was decanted, the oil dissolved in 2 to 3 cc. of water, and again precipitated with ethanol. The alcohol precipitation was repeated once more in order to ensure the removal of the hydrochloride of any unreacted methionine.

The oil was dissolved in water and a solution of 5 g. of azobenzene-*p*-sulfonic acid in water added. The mixture set to a crystal mass almost immediately. After standing at 0° the crystals were filtered off and washed with water. For recrystallization the salt was suspended in 50 cc. of acetone and 40 cc. of water was added. Any undissolved material was removed and the filtrate was set in an open beaker to allow the salt to crystallize slowly as the acetone evaporated; yield 700 mg. The salt was recrystallized in the same manner for analysis, and dried in a vacuum desiccator over Drierite; yield 300 mg. of the tetraazobenzenesulfonate of I.

Anal. Calc'd for $C_{62}H_{68}N_{10}O_{16}S_7 \cdot 3\ H_2O$: C, 50.0; H, 5.0; N, 9.4; NH_2-N, 1.9; S, 15.1; H_2O, 3.6.

Found: C, 49.6; H, 5.2; N, 9.3; NH_2-N, 2.2; S, 15.4; H_2O, 3.8.

The decomposition of I. H (10 cc.) was shaken for 24 hours with an aqueous solution of 20 g. of methionine. The resulting clear solution was heated at 100° for 2 hours, cooled, and extracted three times with ether. The ethereal extract was dried over Na_2SO_4, and after the ether had been removed *in vacuo*, 3.2 g. of an oil remained. After two distillations *in vacuo*, 1.2 g. of an oil, distilling at 93–94° under 0.2 mm. pressure, was obtained.

Anal. Calc'd for $C_6H_{14}S_3$: C, 39.5; H, 7.7; S, 52.8.

Found: C, 39.3; H, 7.8; S, 53.0.

The sulfur content of such sulfides, sulfoxides (see below), and of H derivatives is frequently found to be considerably too low when determined by the Pregl method. Hence, the Carius method was used in this case.

For the preparation of the sulfoxide, 350 mg. of the sulfide was added to a few cc. of concentrated HNO_3 and the mixture allowed to stand for 5 minutes. Two volumes of water was added, the solution concentrated to dryness under reduced pressure, alcohol added, and the solution concentrated again. The residue was taken up in alcohol, 10 volumes of ether added, and the solution stored at 0°. The crystalline product was removed and recrystallized from ethanol; yield 200 mg.; m.p. 155–160° with decomposition. After two additional crystallizations from alcohol the decomposition range was raised to 165–169°.

Anal. Calc'd for $C_6H_{14}O_3S_3$: C, 31.3; H, 6.1; S, 41.7.

Found: C, 31.1; H, 6.1; S, 41.7.

The sulfur was determined by the Parr bomb method.

The aqueous phase remaining after removal of the sulfide was freed of chloride ion with Ag_2CO_3 and of Ag^+ with H_2S. The resulting solution was concentrated *in vacuo* to 300 cc. and stored at 0°. Methionine (9.3 g.) was filtered off. The filtrate was concentrated to 50 cc. and another 1.1 g. of methionine recovered. The filtrate was concentrated to 25 cc. and 75 cc. of alcohol added. After standing at 0°, a further 4.1 g. of methionine was recovered, making the total yield of methionine 14.5 g.

The filtrate from which the bulk of the methionine had been removed was concentrated to dryness *in vacuo* to remove alcohol, and the residue dissolved in 30 cc. of water. An aqueous solution of 2 g. of *p*-hydroxyazobenzene-*p'*-sulfonic acid was added, and the solution placed at 0°. The crystals which deposited were recrystallized from hot water; yield 1.1 g.

Anal. Calc'd for $C_4H_9NO_3 \cdot C_{12}H_{10}N_2O_4S \cdot H_2O$: C, 46.4; H, 5.1; N, 10.1; S, 7.7; H_2O, 4.3.
Found: C, 46.1; H, 5.1; N, 10.2; S, 7.8; H_2O, 5.7.

For the isolation of γ-hydroxy-α-aminobutyric acid, 416 mg. of the hydroxyazobenzene sulfonic acid salt was dissolved in 5 cc. of hot water and 273 mg. of barium acetate monohydrate in 2 cc. of water added. The barium sulfonate precipitated immediately, and after cooling the mixture, was removed. The filtrate was freed exactly of barium and sulfate ions, decolorized with charcoal, and concentrated *in vacuo* to a sirup. The free amino acid crystallized upon addition of alcohol, and was recrystallized from water by the addition of alcohol; yield 55 mg.; m.p. 186–187° (dec.). Fischer and Blumenthal (5) reported m.p. 187° (dec.) for this compound.

Anal. Calc'd for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.8.
Found: C, 40.2; H, 7.5; N, 11.8.

The nitrogen was determined by the micro-Dumas method.

The reaction of H with carbobenzoxymethionineamide. H (0.25 cc.) was shaken for 24 hours with a solution of 2.3 g. of carbobenzoxymethionineamide in 100 cc. of 50% alcohol. The reaction mixture was concentrated *in vacuo* to a small volume to remove the alcohol, and 1.3 g. of unreacted carbobenzoxymethionineamide filtered off. The filtrate was titrated to phenolphthalein with 0.1 *N* NaOH. The titer indicated that 55% of the H employed had hydrolyzed. The neutral solution was heated at 100° for 2 hours, and the acid liberated again titrated. The results indicated that 45% of the H had reacted to form a sulfonium salt which was decomposed by heat with the liberation of acid. The characteristic odor of the trisulfide formed on the decomposition of the sulfonium salt (I) could also be detected. No water-insoluble oil separated, however. On cooling, 0.5 g. of carbobenzoxymethionineamide crystallized and was filtered off. At least this much carbobenzoxymethionineamide must, therefore, have been regenerated by the decomposition of the sulfonium salt.

The authors wish to acknowledge their indebtedness to the late Dr. Max Bergmann for the constant advice and encouragement which he gave in the course of this research. Thanks are due also to Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] IV. CHEMICAL REACTIONS OF β-CHLOROETHYL-β'-HYDROXYETHYLSULFIDE

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It has been shown (1, 2) that β-chloroethyl-β'-hydroxyethylsulfide (H-chlorohydrin, to be referred to hereafter as CH) is formed as an intermediate in the hydrolysis of mustard gas (H) *in vitro*. Since it is to be expected that this compound will play a rôle in the physiological action of H, a brief investigation of the reactions of CH with some chemical constituents of biological systems was undertaken.

The study of the chemical reactions of CH described in this communication indicates that, qualitatively, the reactions of CH are similar to those of H itself. The replacement of one chloroethyl group of H by a hydroxyethyl group does not appear to alter profoundly the chemical reactivity of the remaining chloroethyl group.

The reactions of CH in water. Kinsey and Grant (2) have shown that CH is hydrolyzed in water at a rate 40 to 50% faster than is H itself. They also demonstrated that appreciable quantities of sulfonium salts are formed from CH under their conditions (0.00035 to 0.0006 molar). It will be recalled that when H (16 *mM*) was shaken with 100 cc. of water, large quantities of sulfonium salts were formed (3). The hydrolysis of CH in water has also been investigated by Ogston (4).

In Table I are presented data on the hydrolysis of CH in more concentrated solutions (0.11 molar). It will be noted (Column 2) that two-thirds of the chlorine of CH has become ionized after 5 minutes, and that the reaction is virtually complete after 3 hours. It can be seen from Column 3 that the liberation of H^+ is slower than is the liberation of Cl^-, indicating the presence in the hydrolysis mixture of considerable quantities of sulfonium chlorides. The amount of sulfonium chlorides present is represented by the difference in the values of Cl^- and H^+, and is given in Column 4. In 0.02 molar CH solution, both the time required for liberation of all the Cl^- and the extent of sulfonium salt formation is less than in 0.11 molar solution.

The question arises as to the nature of the sulfonium compounds present after 1160 minutes' hydrolysis of CH (Table I) and, in particular, as to whether these sulfonium compounds contain an ethylensulfonium ring analogous to the ethylenimonium ring formed by the nitrogen mustards (5). Such an ethylensulfon-

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ium ring, as in Formula I, should react rapidly and completely with thiosulfate in 10 minutes, whereas other sulfonium compounds such as β-hydroxyethyl-

TABLE I

HYDROLYSIS OF CH IN WATER

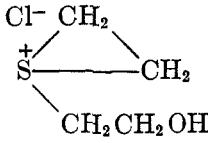
Concentration of reactants per cc.: 0.11 *mM* CH[a].
0.20 *mM* $NaHCO_3$.
*p*H, 7.0–7.5; temperature, 25°.

TIME, MIN. 1.	Cl^- LIBERATED PER *mM* CH, M.EQUIV. 2.	H^+ LIBERATED PER *mM* CH, M.EQUIV. 3.	($Cl^- - H^+$), M.EQUIV. 4.	$Na_2S_2O_3$ CONSUMED IN 10 MINUTES PER *mM* CH[b], M.EQUIV. 5.
5	0.67			
10	.76	0.48	0.28	0.14
30	.86	.56	.30	.044
180	.95	.64	.31	
1160	1.00	.78	.22	

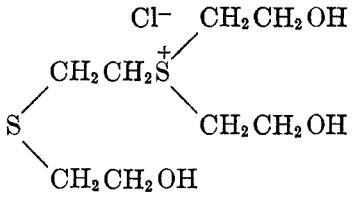
[a] The concentration of CH was determined by heating an aliquot of the reaction mixture at 100° for 1 hour. It was found that 0.11 *mM* of Cl^- and 0.11 *mM* of H^+ were present in the solution. The quantity of Cl^-, present after 1160 minutes hydrolysis at 25°, was not increased on heating the neutral solution at 100° for 1 hour. The quantity of H^+, present after 1160 minutes hydrolysis at 25°, was increased by heating for 1 hour at 100° to a value equal to the amount of Cl^-. This indicates that the sulfonium salts present in the hydrolysate are quantitatively decomposed by heating in neutral solution at 100° for 1 hour [*cf.* also (4)].

[b] 2 cc. of *N* $Na_2S_2O_3$ was added to the reaction mixture, and the thiosulfate consumption was measured by titration with 0.1 *N* I_2 solution.

β-[bis(β-hydroxyethyl)sulfonium]ethylsulfide chloride (II), should not react measurably with thiosulfate in this time interval (3).



(I)



(II)

If appreciable amounts of I were present in the hydrolysate, the 10-minute thiosulfate titer should be greater than the quantity of carbon-bound chlorine. As can be seen from Column 5 of Table I, it is actually slightly less, indicating that the thiosulfate consumption is all attributable to unchanged CH.

It may be concluded, therefore, that the sulfonium compounds present in the hydrolysate of CH are of the type II, and if compounds containing an ethylensulfonium ring are intermediates in the hydrolysis of CH, such ring compounds do not accumulate in the solution to any appreciable extent.

The reaction of CH with thiosulfate. The data presented in Table II show the

rate of reaction of CH with thiosulfate in the presence and absence of bicarbonate. Comparison of these data with the rate of chloride liberation in bicarbonate (*cf.* Table I) shows that the thiosulfate consumption proceeds more rapidly than does the chloride liberation. Thus after 5 minutes in bicarbonate solution, 0.67 m.equiv. of Cl^- have appeared per *mM* of CH while in the presence of thiosulfate, 0.84 m.equiv. of $Na_2S_2O_3$ disappear in this time interval.

It will be noted that CH, when kept for 10 minutes with thiosulfate in the presence of bicarbonate, takes up 1 m.equiv. of thiosulfate per *mM* of CH. This property permits the use of the 10-minute thiosulfate titer for the study of the hydrolysis of CH in bicarbonate solution (*cf.* Table I).

The reaction of CH with amino groups of amino acids and peptides. The extent of the reaction of CH with amino groups was determined by measurement of the decrease in the amino nitrogen content of the reaction mixture at the end of the reaction. The results presented in Table III show that at *p*H 7.5, the amino

TABLE II

REACTION OF CH WITH THIOSULFATE

Temperature, 25°.

CONCENTRATION OF REACTANTS PER CC.	*p*H	TIME, MIN.	THIOSULFATE CONSUMED PER *mM* CH, *mM*
0.11 *mM* CH 0.20 *mM* $Na_2S_2O_3$	6.5–7.0	5	0.80
		10	0.96
		20	1.00
		30	1.00
0.11 *mM* CH 0.20 *mM* $NaHCO_3$ 0.20 *mM* $Na_2S_2O_3$	7.5–8.0	5	0.84
		10	1.00
		20	1.01

groups of glycine, alanine, arginine, lysine, tyrosinamide, and leucinamide react with CH with the disappearance of 0.1–0.3 m.equiv. of NH_2-N per *mM* of CH. On the other hand, the amino group of histidine shows no reactivity with CH under these conditions. This indicates that the imidazole group of histidine is competing with the α-amino group for the available CH. The fact that the α-amino group of tyrosinamide reacts extensively with CH suggests that the phenolic hydroxyl is not competing appreciably with the amino group for the available CH.

The amino acid methionine is sparingly soluble at *p*H 7.5. It was therefore employed as its sodium salt at *p*H 9.5. The α-amino group of methionine reacts at *p*H 9.5 to a much smaller extent than does alanine at this *p*H. This indicates that the $-SCH_3$ group of methionine competes with the α-amino group for reaction with CH.

It will be noted in Table III that with arginine, the decrease in m.equiv. of NH_2-N per *mM* of CH is less than that found for glycine or alanine. This difference is outside the limits of experimental error; however, additional experimental

data are needed to permit any conclusion as to the possible reaction of the guanido group of arginine with CH.

At *p*H 7.5, CH reacts with the α-amino group of the peptide glycylglycine to a greater extent than it does with the α-amino groups of the amino acids.

The extent of the reaction of CH with the amino groups of glycine, alanine, lysine, and glyclyglycine is of the same order of magnitude as that observed per *mM* of chloroethyl group in the case of H (6). It has also been shown that H reacts with the imidazole group of histidine (7) and with the —SCH_3 group of methionine (6). In comparing the extent of reaction of amino groups with CH

TABLE III

THE REACTION OF CH WITH THE AMINO GROUPS OF AMINO ACIDS AND PEPTIDES

Concentration of reactants per cc.: 0.11 *mM* of CH.
0.20 m.equiv. of NH_2-N.
0.20 m.equiv. of $NaHCO_3$.

Temperature 25°; reaction period, 24 hours.

SUBSTANCE	*p*H	DECREASE IN NH_2-N PER CC., M.EQUIV.	DECREASE IN NH_2-N PER *mM* CH, M.EQUIV.
Glycine	7.5	0.021	0.19
l-Alanine	7.5	.014	.13
l-Histidine	7.5	−.001	.00
l-Arginine	7.5	.008	.07
l-Lysine	7.5	.018	.16
l-Tyrosinamide	7.5	.032	.29
l-Leucinamide	7.5	.016	.15
Glycylglycine	7.5	.060	.55
l-Alanine	9.5	.049	.45
dl-Methionine[a]	9.5	.016	.15

[a] This sparingly soluble amino acid was dissolved as the sodium salt and the same amount of $NaHCO_3$ was added as in the other experiments.

and H it must be borne in mind that the reactions of CH occur in homogeneous solution while those of H occur in a heterogeneous medium.

The reaction of CH with carboxyl groups. CH (0.11 molar) reacts with the carboxyl groups of sodium acetate and sodium hippurate (0.2 molar) at *p*H 7.5–8 and 25° to form saponifiable half-esters of thiodiglycol. It was found that, in aqueous $NaHCO_3$ solution and 25°, 22% of the CH reacted with sodium hippurate, and 23% with sodium acetate. The reaction reached completion within 2 hours.

When H (0.16 molar) was shaken with sodium acetate or sodium hippurate (0.64 molar) for 24 hours, the extent of esterification in each case was about 40% of the theory (6). The thiodiglycol esters formed from H were insoluble and separated from the reaction mixture, whereas in the case of CH, the half-esters were water-soluble, and a homogeneous reaction mixture resulted.

The reaction of CH with pyridine and nicotinic acid amide. CH (0.11 molar) reacts with pyridine and with nicotinic acid amide (0.20 molar) at *p*H 7.5–8 to form pyridinium compounds. In the case of pyridine the yield is 77% of the theory, whereas with nicotinic acid amide, the yield is 65% of the theory.

It was shown previously that H reacts readily with pyridine and nicotinic acid amide in unbuffered aqueous solution (6) to form pyridinium compounds.

The reaction of CH with thiodiglycol. CH (0.11 molar) reacts with thiodiglycol (TG, 0.20 molar) at *p*H 7.5 and 25°, the product of the reaction presumably being the sulfonium chloride II. In the formation of this sulfonium compound, no acid is liberated. Hence the extent of the reaction of CH with TG may be estimated by the decrease in acid formed in the presence of TG over that to be expected on complete hydrolysis of CH. It was found that after 1.5 hours, in the presence of TG, only 0.31 *mM* of acid was liberated from 1.1 *mM* of CH. Hence the total amount of II formed in the presence of TG is about 0.8 *mM* or 73% of the theory. In the formation of this quantity of sulfonium salt, however, some of the TG involved may have been derived from the CH by hydrolysis.

EXPERIMENTAL

H chlorohydrin (CH) was prepared by the excellent method of Kinsey and Grant (2). The preparation obtained in this manner gave the correct elementary analysis, and was completely soluble in ether, indicating the absence of sulfonium salts. Further evidence for the absence of sulfonium salts in the CH preparation is provided by the fact that the preparation rapidly consumed one equivalent of thiosulfate (*cf.* Table II). The material was stored in dry ice as a molar solution in ether, and was found to be stable under these conditions for the duration of the experiments described in this section.

Prior to use, the ethereal solution of CH was allowed to warm up from the temperature of dry ice to 4°, after which samples were withdrawn for the various experiments. For each experiment, the sample of CH was rapidly freed of ether *in vacuo*, and an aqueous solution of the various reactants added immediately.

Determination of the extent of liberation of Cl^- and H^+ was performed as described previously (3).

After removal of the ether from a sample of the CH solution, the resulting oil gave the following analysis:

Anal. Calc'd for C_4H_9ClOS: C, 34.2; H, 6.4; S, 22.8; Cl, 25.3.
Found: C, 34.1; H, 6.4; S, 22.6; Cl, 25.4.

The reaction of CH with carboxyl groups. CH (2.75 *mM*) was allowed to react at 25° with 5 *mM* of sodium acetate or sodium hippurate in the presence of 5 *mM* of $NaHCO_3$. The volume was 25 cc. After 2 hours a 10-cc. aliquot was removed, 5 cc. of *N* HCl added, and the CO_2 removed *in vacuo*. The solution was neutralized (phenolphthalein) with *N* NaOH, and an additional 2 cc. of *N* NaOH added. After standing for 30 minutes at room temperature, back titration with 0.1 *N* HCl gave the amount of ester saponified. The amount of saponifiable ester was unchanged after a reaction time of 20 hours.

A control solution of CH (containing no sodium acetate or hippurate) did not consume any alkali when subjected to the same procedure.

The reaction of CH with pyridine and nicotinic acid amide. CH (2.75 *mM*) was treated with 5 *mM* (0.4 cc.) of pyridine in the presence of 5 *mM* of $NaHCO_3$. The volume was 25 cc. After 2 hours at room temperature, a 10-cc. aliquot was removed, and the acid liberated in the course of the reaction was determined. It was found that 0.22 *mM* of acid had been liberated (theory for complete hydrolysis of CH, 1.1 *mM*), and thus 80% of the CH had reacted to yield "onium" compounds. No further increase in acid occurred after 20 hours reaction time at 25° or after heating at 100° for 1 hour. This shows that no appreciable

amount of the sulfonium chloride II was present and that almost all of the "onium" compounds formed were pyridinium compounds.

In a comparable experiment with nicotinic acid amide, it was found that 76% of the CH has reacted to form "onium" compounds, and that about 90% of these "onium" compounds were of the quaternary ammonium type.

The authors wish to acknowledge their indebtedness to the late Dr. Max Bergmann for the constant advice and encouragement which he gave in the course of this research. Thanks are due to Miss Rosalind E. Joseph for assistance in the conduct of these experiments, and to Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

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[a] Unpublished data obtained in Great Britain.
[b] Unpublished data obtained in the United States.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] V. THE CHEMICAL REACTIONS OF 1,2-BIS(β-CHLOROETHYLTHIO)ETHANE

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The experiments outlined in this communication were undertaken as part of a general investigation of the chemical reactions of the vesicant war gases. An attempt has been made to study the reactions of 1,2-bis(β-chloroethylthio)-ethane (I) with water and with various substances of biological interest.

$$\begin{array}{l} CH_2SCH_2CH_2Cl \\ | \\ CH_2SCH_2CH_2Cl \end{array} \qquad (I)$$

Interest in the chemical reactions of I arises from its structural relationship to mustard gas [bis(β-chloroethyl)sulfide] and from the fact that, like the mustard gas, I is a potent vesicant when applied to the skin. These vesicants differ markedly, however, in their physical properties. I is a solid melting at 54° while mustard gas is a liquid at room temperature. In addition, I is much less soluble in water than is mustard gas.

The hydrolysis of 1,2-bis(β-chloroethylthio)ethane (I). When a suspension of I is shaken with 50 volumes of water at room temperature, all of the carbon-bound chlorine is hydrolyzed to Cl^- in 48 to 72 hours.[4] On the other hand, the H^+ liberated after 72 hours' shaking equals only 80–85% of the amount to be expected on complete hydrolysis of I to yield two equivalents of HCl. The extent of H^+ liberation does not surpass 85% of theory after an additional 24 hours' standing at room temperature. This indicates that about 15% of the Cl^- is not neutralized by H^+, but by sulfonium ions. The extent of H^+ liberation may be raised to 95% of the theory if the 72-hour hydrolysate of I is neutralized and then heated at 100° for 2 hours.

The rate of the liberation of Cl^- and H^+ when I is shaken with 50 volumes of water is shown in Table I. It will be noted that in the course of the hydrolysis Cl^- is formed faster than is H^+, and that H^+ continues to be formed after all the Cl^- has been liberated. This observation makes it probable that some of the sulfonium salts formed during the hydrolysis of I are unstable. Thus, after 28 to 54 hours' shaking, about 30% of all the Cl^- present in solution is

[1] This work was done in whole under Contract No. OEMsr-313 between The Rockefeller Institute for Medical Research and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein. The experiments were performed during the period January 1942–August 1944.

[2] Present address, Yale University, New Haven, Connecticut.

[3] Died, November 7, 1944.

[4] Since I is extremely insoluble in water, the rate and extent of hydrolysis must depend upon the method of agitation and the particle size of the I employed. In these experiments no attempt was made to control these factors.

neutralized by sulfonium ion, while after 72 hours only about 15% is neutralized by sulfonium ion.

The hydrolysis of I on shaking with an aqueous $NaHCO_3$ solution (*p*H 8) appears to be somewhat slower than the hydrolysis of I shaken with water (*cf.* Table I). The amount of sulfonium ion at *p*H 8 is, at any given time, less than that found in the absence of bicarbonate.

After I has been shaken for 72 hours with either water or aqueous $NaHCO_3$, a precipitate is present in the reaction mixture. From 10 g. of I shaken with 50 volumes of water, 2.5 g. of insoluble material was obtained. This material, after two crystallizations from absolute ethanol, melted at 99–101° and contained no chlorine. The elementary analysis of the substance corresponded well with

TABLE I

HYDROLYSIS OF I IN WATER AND AQUEOUS $NaHCO_3$

TIME, HOURS	WATER (50 VOLUMES)			$NaHCO_3$ (0.3 N; 50 VOLUMES)		
	Cl^- liberated per *mM* I, m.equiv.	H^+ liberated per *mM* I, m.equiv.	$(Cl^-) - (H^+)$, m.equiv.	Cl^- liberated per *mM* I, m.equiv.	H^+ liberated per *mM* I, m.equiv.	(Cl^-)-(H^+), m.equiv.
2.5	0.17	0.13	0.04	0.14	0.13	0.01
6.5	0.52	0.32	0.20	0.33	0.25	0.08
28	1.57	1.06	0.51			
30.5				1.16	0.93	0.23
54	1.98	1.41	0.57			
72	2.00	1.74	0.26	1.99	1.91	0.08

the empirical formula $C_{10}H_{22}O_2S_4$. It was suspected that this product was 1,2-bis[2-(2-hydroxyethylthio)ethylthio]ethane (II), which may also be designated pentaethylene tetrasulfide-ω,ω'-diol.

$$\begin{matrix} CH_2SCH_2CH_2SCH_2CH_2OH \\ | \\ CH_2SCH_2CH_2SCH_2CH_2OH \end{matrix} \qquad \text{(II)}$$

For purposes of comparison with the isolated material, the tetrasulfide diol was synthesized by reaction of I with two equivalents of β-mercaptoethanol (III) in the following manner:

$$\begin{matrix} CH_2SCH_2CH_2Cl \\ | \\ CH_2SCH_2CH_2Cl \end{matrix} + 2HSCH_2CH_2OH \longrightarrow \begin{matrix} CH_2SCH_2CH_2SCH_2CH_2OH \\ | \\ CH_2SCH_2CH_2SCH_2CH_2OH \end{matrix} + 2HCl$$

(I) (III) (II)

The product obtained from the above reaction of I with β-mercaptoethanol was found to have the elementary composition required for compound II, and to have the melting point 108–111°. As was mentioned above, the product isolated from the hydrolysate of I had the same elementary composition, but the lower melting point 99–101°. Further recrystallization of this isolated

material [from water: ethanol (2:1) instead of from absolute ethanol] raised the melting point slightly to 102–104°. The mixed melting point of the two substances was 101–109°. In view of the discrepancy in melting points, proof of the identity of the isolated and synthesized products required the preparation of derivatives. For this purpose the diacetate and dibenzoate of both substances were prepared. The melting point of the derivative of the compound isolated from the hydrolysate of I was, in each case, the same as that of the corresponding derivative of the substance synthesized from I and β-mercaptoethanol. The elementary analyses were in good agreement with the theory, and the mixed melting points of the derivatives of the isolated and synthesized products showed no depression. The derivatives of the product isolated from the hydrolysate

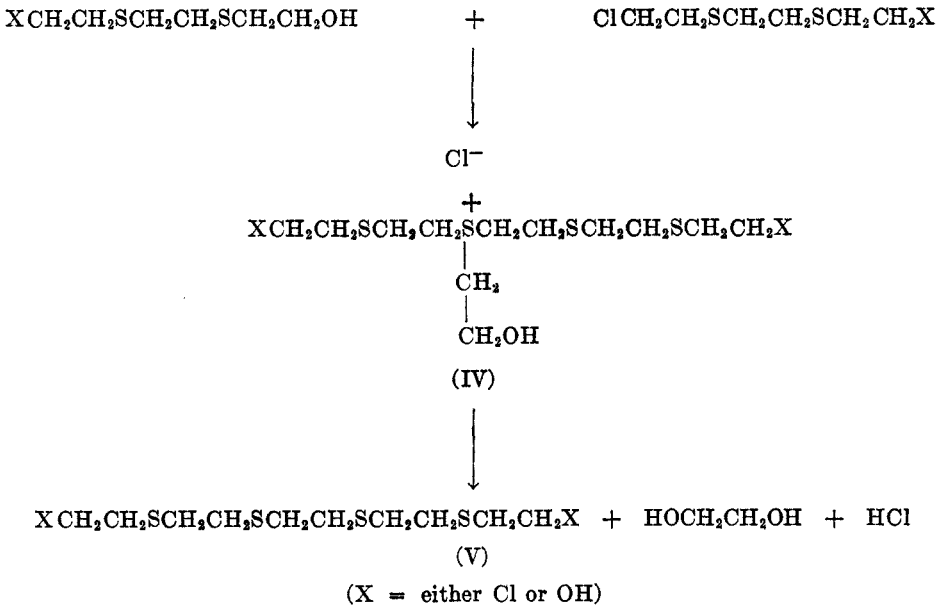


FIGURE 1

of I were more difficult to purify and were obtained in lower yield than were the corresponding derivatives of the synthetic product. It appears, therefore, that the substance isolated from the hydrolysate of I consisted largely of pentaethylene tetrasulfide-ω,ω′-diol, but contained as impurities some substances of similar properties which were difficult to remove.

The mechanism by which the tetrasulfide diol is formed on hydrolysis of I, and the probable nature of the impurities mentioned above, are discussed in what follows.

The tetrasulfide diol is probably formed as a result of the reaction of I chlorohydrin (or I) with I glycol (or I chlorohydrin) and subsequent decomposition in the manner indicated in Figure 1.

It cannot be stated at this time whether sulfonium salt formation and sub-

sequent elimination of ethylene glycol occurs prior to hydrolysis of the two chlorine atoms indicated in Formulas IV and V by an X. It seems highly probable, however, that the sulfur atom which reacts to become a sulfonium sulfur bears a hydroxyethyl and not a chloroethyl group. It is known that the tendency to form sulfonium salts is much greater with the group $HOCH_2CH_2S$— than it is with the group $ClCH_2CH_2S$—. It also seems probable that ethylene glycol, not ethylene chlorohydrin, is eliminated from compound IV. The chlorine of ethylene chlorohydrin is relatively resistant to hydrolysis in water, whereas, as was shown earlier, all the chlorine of I is liberated as chloride ion.

If the tetrasulfide diol actually is formed by a mechanism such as that portrayed in Figure 1, it is easy to see how similar reactions might lead to the formation of other sulfides of analogous structure, and thus account for the presence in the tetrasulfide diol of the impurities referred to above. The intermediate sulfonium salt (IV) was assumed, in Figure 1, to decompose by fission of a carbon-sulfur bond, thus yielding the tetrasulfide diol (II). It also seems possible, however, that the sulfonium salt IV might decompose in a different manner with the resulting formation of a tetraethylene trisulfide diol.

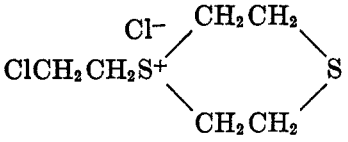
Furthermore, by analogy with mustard gas, I might give rise to a sulfonium salt formed from one molecule of I and two molecules of I-glycol. This sulfonium salt could decompose in several ways to yield a variety of products. Depending upon the particular carbon-sulfur bond broken, there would result the tetrasulfide diol (II), a hexaethylene pentasulfide diol, or a heptaethylene hexasulfide diol.

It should be pointed out that elementary analysis would scarcely distinguish between these various compounds. The carbon and hydrogen content is practically the same for all of the substances. The sulfur content is 39.7% for the trisulfide diol, 42.4% for the tetrasulfide diol, 44.2% for the pentasulfide diol, and 45.5% for the hexasulfide diol. The various compounds would also undoubtedly have similar properties and would be difficult to separate from one another. The presence of such a mixture of substances in hydrolysates of I would readily explain the difficulties encountered in purifying the tetrasulfide diol. It should be emphasized that much of the foregoing is speculative and would prove difficult to establish in detail. No attempt was made to isolate all the various homologs of the tetrasulfide diol which might be present in a hydrolysate of I. It should be mentioned that, in addition to the tetrasulfide diol, I-glycol (VI) has also been isolated from a hydrolysate of I in a yield of 20–25% of the theory. This substance would result, of course, from the hydrolysis of the two carbon-bound chlorine atoms of I.

$$\begin{matrix} CH_2SCH_2CH_2OH \\ | \\ CH_2SCH_2CH_2OH \end{matrix} \qquad \text{(VI)}$$

As will be noted from Formula VII, β-chloroethyl-1,4-dithiane sulfonium chloride is isomeric with I. It seemed possible, therefore, that VII might arise

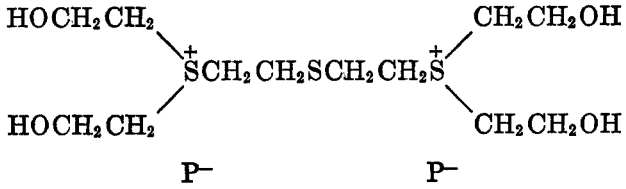
during the hydrolysis of I. Attempts to demonstrate the formation of VII during the hydrolysis of I, however, have been unsuccessful.



(VII)

After shaking I with water for 48 hours and removal of the precipitate, the filtrate was neutralized and boiled under reflux for 4 hours. Under these conditions, 1,4-dithiane sulfonium compounds decompose readily to yield 1,4-dithiane which sublimes into the reflux condenser (2). However, in the case of the hydrolysate of I no dithiane formation was observed on boiling. Similarly, when I was boiled under reflux with 50 volumes of water for 24 hours, no evidence for the formation of 1,4-dithiane was obtained.

The reaction of I with thiodiglycol and pyridine. It has been shown that mustard gas reacts with thiodiglycol (TG) in aqueous solution at room temperature to form a sulfonium salt derived from one molecule of mustard gas and two molecules of TG (1). This compound was isolated as a chloride and as a picrylsulfonate (VIII). It seemed of interest to determine, therefore, whether I behaves similarly. Accordingly, I was shaken with an aqueous solution of TG for 4 days. At the end of this period, the amount of Cl^- and H^+ present in the solution was determined.

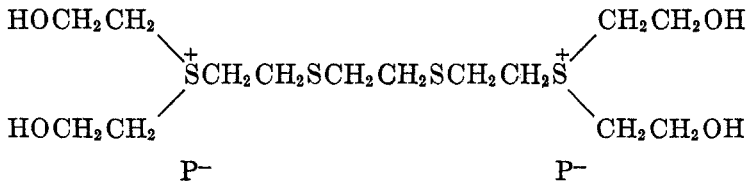


(VIII)

P^- = picrylsulfonate ion

It was found that only about 15% of the Cl^- present in the reaction mixture could be accounted for as HCl. The remainder of the Cl^-, therefore, must have been neutralized by sulfonium ion. It was shown in the preceding section of this paper that when I was shaken with water alone, 80–85 per cent of the theoretical H^+ was formed. It follows, therefore, that in the presence of excess TG, I forms a sulfonium salt. When the reaction mixture containing the sulfonium salt is heated at 100° for 2 hours, acid is formed. The extent of H^+ liberation is about 90% of that to be expected from complete hydrolysis of the I employed. Thus the sulfonium salt formed from I and TG is unstable at 100° in aqueous solution. This behavior is similar to that exhibited by the sulfonium salts formed from mustard gas and TG.

The product of the reaction between I and TG has been isolated as its crystalline dipicrylsulfonate (IX).



(IX)

P⁻ = picrylsulfonate ion

As shown in Paper I of this series, the corresponding sulfonium salt derived from mustard gas was shown to decompose with the liberation of acid on standing in aqueous $NaHCO_3$ at 37°, and to react slowly with both $Na_2S_2O_3$ and the

TABLE II

THE CHEMICAL REACTIVITY OF THE SULFONIUM SALTS VIII AND IX

Concentration of reactants per cc.: 0.005 *mM* of sulfonium salt in all experiments.
0.025 *mM* of $NaHCO_3$ in Columns 2, 3, 4, and 5.
0.025 *mM* of $Na_2S_2O_3$ in Columns 4 and 5.
Solvent, acetone-water (1:1); temperature, 25°.

TIME, HOURS	H^+ LIBERATED IN $NaHCO_3$ SOLUTION PER *mM* OF		$Na_2S_2O_3$ CONSUMED PER *mM* OF		H^+ LIBERATED IN UNBUFFERED SOLUTION PER *mM* OF
1.	IX, m.equiv. 2.	VIII, m.equiv. 3.	IX, m.equiv. 4.	VIII, m.equiv. 5.	IX, m.equiv. 6.
3					0.16
17			0.60	0.20	
18.5	0.75	0.16			
21					0.75
47	1.24	0.32	1.36	0.68	1.12
71	1.52	0.40	1.68	0.92	
74					1.52
92	1.72	0.52	1.76	1.00	
98					1.68
138	1.73	0.70	1.90	1.30	

SH group of cysteine at *p*H 8 and 37°. The appreciable chemical reactivity of this sulfonium salt (VIII) is of interest in view of the marked toxicity of the compound. It seemed worth while, therefore, to study the properties of the sulfonium salt IX for purposes of comparison.

As can be seen from Columns 2 and 6 of Table II, compound IX decomposes slowly in acetone-water solution with the liberation of acid, both in the presence and absence of $NaHCO_3$. The rate of the decomposition of IX at *p*H 8 (Column 2) is much greater than is that of VIII (Column 3) studied under the same conditions. As will be noted from the Table, IX reacts with thiosulfate (Column 4), the rate of this reaction also being far greater than that observed for VIII (Column 5). It would appear, therefore, that the sulfonium salt IX is markedly more reactive than is VIII.

When I is shaken with an aqueous solution of pyridine, only about 7–8%

of the Cl^- present is bound as HCl. It would appear, therefore, that I reacts with pyridine to form a strong base (a pyridinium compound) which neutralizes the remaining Cl^-.

The reaction of I with the amino groups of amino acids and peptides. The extent of the decrease in amino nitrogen when amino acids are treated with I at weakly alkaline *p*H values is given in Table III. The reactions were carried out by shaking I at room temperature for 5 days with an aqueous methyl cellosolve solution of the amino acids. At the start of the reaction the vesicant was not completely in solution. The disappearance of amino nitrogen was followed by the Van Slyke nitrous acid method.

TABLE III

REACTION OF I WITH THE AMINO GROUPS OF AMINO ACIDS AND PEPTIDES

Concentration of reactants per cc.: 0.205 *mM* of NH_2-N.
0.205 *mM* of $NaHCO_3$.
0.0523 *mM* of I.
Solvent, 23% methyl cellosolve in water.
Temperature, 20–25°; reaction time, 5 days.

SUBSTANCE	*p*H	DECREASE IN NH_2-N PER CC., M.EQUIV.	DECREASE IN NH_2-N PER *mM* OF I, M.EQUIV.
Glycine	8	0.0354	0.68
Alanine	8	.0238	.46
Histidine	8	.0354	.68
Arginine	8	.0238	.46
Lysine	8	.0277	.53
Glutamic acid[a]	8	.0308	.58
Serine	8	.0438	.84
Glycylglycine	8	.0631	1.21
Glycine[a]	9.5	.0785	1.50
Alanine[a]	9.5	.0462	0.88
Phenylalanine[a]	9.5	.0769	1.47
Methionine[a]	9.5	.0208	0.40

[a] One equivalent of NaOH also added.

It will be noted from Table III that, although I reacts at *p*H 8 with the amino groups of all the amino acids tested, the various amino groups differ in their reactivity towards I. Thus the amino groups of glycine, histidine, lysine, glutamic acid, and serine are more reactive than are those of alanine or arginine. I, therefore, appears to be more selective in its action on amino groups than are the nitrogen mustards, for it was found that the latter vesicants react to the same extent with the amino groups of all of these amino acids, with the exception of histidine and methionine (3). Sufficiently extensive data on mustard gas are not available for comparison.

From the data in Table III it would appear that the imidazole group of histidine is not competing very effectively with the amino group in the same molecule for reaction with I. It will be recalled that the imidazole ring reacts readily

with mustard gas (4) and with all the nitrogen mustards (5). On the basis of the evidence given here and further data to be presented in the next section of this paper, it cannot be stated with certainty whether or not the imidazole group of histidine reacts with I.

As can be seen from Table III, the amino group of glycylglycine, the only peptide investigated, reacts to a greater extent with I than do the amino groups of any of the amino acids. A similar observation was made with mustard gas and with the nitrogen mustards.

It will be noted that I, like mustard gas and the nitrogen mustards, reacts to a far greater extent with amino groups at *p*H 9.5 than it does at *p*H 8. At the higher *p*H the difference between the reactivities of glycine and alanine is accentuated. The behavior of phenylalanine resembles that of glycine rather than that of alanine. The amino group of methionine, on the other hand, reacts to only a slight extent at *p*H 9.5. It appears probable, therefore, that the —SCH_3 group of methionine reacts with I to form a sulfonium salt, and that this reaction removes part of the I which would otherwise be available for reaction with the amino group. Mustard gas also reacts with the —SCH_3 group of methionine to form a sulfonium salt (6).

The competitive effect of various substances on the reaction of I with the amino group of glycine. As shown in the previous section, I reacts with the amino group of glycine and other amino acids. In order to study the reaction of various substances with I, their competitive effect on the extent of the reaction between I and glycine was determined. The competitive effect of such substances on the extent of the disappearance of the glycine NH_2-N can be taken as an indication of the reactivity of these compounds with I.

The data in Table IV show that imidazole has an appreciable competitive effect on the reaction of I with glycine. The data presented in the previous section suggested that the imidazole ring of histidine did not compete appreciably with the amino group of this amino acid for reaction with I. The explanation for the difference between the effect of free imidazole and that of combined imidazole is not clear at present.

Both nicotinic acid and the corresponding amide react very readily with I, presumably with the formation of pyridinium derivatives. In this respect I resembles mustard gas (7) and the nitrogen mustards (5) which have been shown to react with pyridine nitrogen. In contrast to the appreciable reactivity observed with the aromatic tertiary nitrogen compounds such as pyridine, I reacts to a much lesser extent with aliphatic tertiary amines such as triethylamine or triethanolamine.

I reacts appreciably with organic phosphate compounds such as glycerophosphate and with inorganic phosphate. This behavior is also shown by mustard gas (8) and the nitrogen mustards (5). Like mustard gas, I reacts with the carboxyl groups of acetic acid or carbobenzoxyglutamic acid. Thiodiglycol also shows an appreciable competitive effect on the reaction of I with glycine. The product of the reaction between I and thiodiglycol has been isolated and was described earlier in this paper. I reacts with proline; however, the com-

petition data do not permit of a decision as to whether the imino group or the carboxyl group of the amino acid is involved.

The reaction of I with thiosulfate and with cysteine. On shaking I for 72 hours with thiosulfate, a clear solution resulted. Iodometric titration indicated that 1.92 equivalents of thiosulfate had been consumed. The product of the reaction of I with $Na_2S_2O_3$, the "Bunte salt" (X), has been isolated and found to have the expected composition.

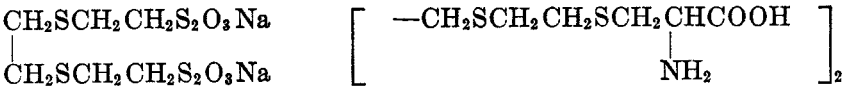
TABLE IV

COMPETITIVE EFFECT OF VARIOUS SUBSTANCES ON THE REACTION OF I WITH THE AMINO GROUP OF GLYCINE

Concentration of reactants per cc.: 0.205 *mM* of glycine.
0.205 *mM* of competing substance.
0.205 *mM* of $NaHCO_3$.
0.056 *mM* of I.
Solvent, 23% methyl cellosolve in water.
Temperature, 20–25°; *p*H 7.6–8.0; reaction time, 3 days.

COMPETING SUBSTANCE	DECREASE IN NH_2-N PER *mM* OF I, M.EQUIV.	DECREASE IN NH_2-N REACTING WITH I	
		m.equiv.	%
None	0.70		
Imidazole	.42	0.28	40
Nicotinic acid	.20	.50	71
Nicotinamide	.09	.61	87
Na_2HPO_4	.33	.37	53
Sodium glycerophosphate	.31	.39	56
Sodium acetate	.44	.26	37
Carbobenzoxyglutamic acid	.33	.37	53
l-Proline	.52	.18	26
Triethylamine	.56	.14	20
Triethanolamine	.66	.04	6
Thiodiglycol	.37	.33	47

I also reacts readily with the sulfhydryl group of cysteine to yield the compound (XI).



(X) (XI)

This compound was prepared by a method similar to that employed by Hellerman *et al.* (9) for the synthesis of the corresponding derivative of mustard gas.

EXPERIMENTAL

Hydrolysis of 1,2-bis(β-chloroethylthio)ethane (I). I was hydrolyzed by shaking with 50 volumes of water or 50 volumes of 0.3 *N* $NaHCO_3$ at room temperature. After filtering the mixture, the filtrate was made up to 100 cc., and Cl^- and H^+ determinations were performed in the manner described for mustard gas (1) and the nitrogen mustard gases (10).

Isolation of pentaethylene tetrasulfide-ω,ω'-diol from hydrolysate of I. I (10 g.) was shaken at room temperature for 5 days with 500 cc. of water. The precipitate which had formed was filtered off and dried; yield 2.1 g. This material should be handled cautiously since it frequently is contaminated by traces of unchanged I. After removal of the crude tetrasulfide diol, the filtrate was kept at 0° overnight. The precipitate was filtered off and recrystallized from ethanol, yielding an additional 0.4 g. of tetrasulfide diol. The crude tetrasulfide diol was recrystallized twice from absolute ethanol and dried over P_2O_5 *in vacuo* at room temperature; yield 1.4 g. of microscopic needles; m.p. 99–101° with preliminary softening at 96°. The compound contains no chlorine.

Anal. Calc'd for $C_{10}H_{22}O_2S_4$: C, 39.7; H, 7.3; S, 42.4.
Found: C, 39.7; H, 7.25; S, 42.3.

Further recrystallization of this product from water-ethanol (2:1) raised the melting point slightly to 102–104°.

Synthesis of pentaethylene tetrasulfide-ω,ω'-diol from I and β-mercaptoethanol. To 2.2 g. (0.01 *M*) of I in 40 cc. of ethanol were added, 3.1 g. (0.04 *M*) of β-mercaptoethanol in 5 cc. of water, and 2.6 g. (0.04 *M*) of KOH (86%) in 20 cc. of ethanol. Nitrogen was bubbled through the mixture for 2 hours, and the mixture was allowed to stand under N_2 for 48 hours. The precipitate which had formed was removed by filtration and dried; yield 2.6 g. After one crystallization from absolute ethanol, 2.0 g. of material melting at 102–108° was obtained. After three more crystallizations from absolute ethanol the melting point was 108–111°. The mixed melting point with the tetrasulfide diol isolated from a I hydrolysate was 101–109°. The substance contained no chlorine.

Anal. Calc'd for $C_{10}H_{22}O_2S_4$: C, 39.7; H, 7.3; S, 42.4.
Found: C, 39.4; H, 7.15; S, 42.1.

Pentaethylene tetrasulfide-ω,ω'-diol diacetate. The pentaethylene tetrasulfide-ω,ω'-diol (600 mg.) obtained from the reaction of I with β-mercaptoethanol was dissolved in 25 cc. of anhydrous pyridine and 0.8 cc. of acetic anhydride was added. The mixture was allowed to remain at room temperature for 24 hours, and the pyridine removed *in vacuo*. The residue was crystallized twice from absolute ethanol and once from acetone and petroleum ether; yield 400 mg.; m.p. 85–87° with softening at 83°.

Anal. Calc'd for $C_{14}H_{26}O_4S_4$: C, 43.5; H, 6.8; S, 33.2.
Found: C, 43.3; H, 6.7; S, 33.0.

When the diol isolated from a hydrolysate of I was subjected to the same procedure, 300 mg. of diacetate was obtained after two crystallizations from alcohol and two from acetone and petroleum ether; m.p. 81–83°; mixed m.p. 81–85°.

Anal. Found: C, 42.9; H, 6.5.

Further recrystallization of this product did not raise the melting point or change the elementary composition. The mother liquors from which this product was obtained yielded 75 mg. of the pure diacetate; m.p. 86–88°, mixed m.p. 85–88°.

Anal. Found: C, 43.6; H, 6.8; S, 33.2.

Pentaethylene tetrasulfide-ω,ω'-diol dibenzoate. The pentaethylene tetrasulfide diol (600 mg.) obtained from the reaction of I with β-mercaptoethanol was dissolved in 25 cc. of anhydrous pyridine and 1 cc. of benzoyl chloride was added. The mixture was allowed to stand for 24 hours at room temperature, and the pyridine was removed *in vacuo*. The residue was crystallized twice from absolute ethanol, once from acetone and petroleum ether, and once from ether and petroleum ether; yield 300 mg.; m.p. 60–63° with softening at 58°.

Anal. Calc'd for $C_{24}H_{30}O_4S_4$: C, 56.4; H, 5.9; S, 25.1.
Found: C, 56.4; H, 5.8; S, 25.2.

The diol isolated from a hydrolysate of I was subjected to the same procedure. Several recrystallizations from the above solvents were required before 175 mg. of the pure dibenzoate was obtained; m.p. 59–63°; mixed m.p. 59–63°.

Anal. Found: C, 56.4; H, 5.9; S, 25.1.

An additional 100 mg. of material, m.p. 58–62°, was obtained from the mother liquors.

Isolation of I-glycol from a hydrolysate of I. I (10 g.) was shaken at room temperature for 5 days with 500 cc. of water. After removal of the crude tetrasulfide diol from the hydrolysate of I by filtration, the filtrate was kept at 0° overnight. The precipitate which separated was filtered off. The clear aqueous filtrate was concentrated to a sirup *in vacuo*, alcohol was added and the mixture again was concentrated. This was repeated twice more. The sirup which remained was triturated with acetone, which dissolved about half of the sirup. The acetone solution was concentrated to a sirup *in vacuo*, and the residue shaken with about 100 cc. of ether. A small amount of material did not dissolve and was discarded. Petroleum ether was added to the ether solution, and the mixture cooled to 0°. Crude I glycol (2 g.) (m.p. 35–46°) was thus obtained. After three recrystallizations from ether-petroleum ether the glycol melted at 59–62° with preliminary softening at 57°.

Anal. Calc'd for $C_6H_{14}O_2S_2$: C, 39.5; H, 7.7; S, 35.2.
Found: C, 39.3; H, 7.4; S, 35.1.

Rosen and Reid (11) give the m.p. 114–117° for I-glycol. Their product, however, contained 37.4% sulfur, and could not have been pure. Bennet and Whincop (12) give m.p. 64° for this substance. Their product gave the correct elementary analysis for carbon and hydrogen. A sulfur analysis was not reported.

Preparation of the sulfonium salt IX. Thiodiglycol (5 g.) was shaken with 2 g. of I in 100 cc. of methyl cellosolve-water (1:3) for 4 days. The reaction mixture was filtered, and concentrated *in vacuo* (bath temperature, 45°) to a sirup. Alcohol was added and removed *in vacuo*. This procedure was repeated twice more, the residue triturated with acetone, and the acetone decanted. Since the residual sirup could not be induced to crystallize, it was dissolved in water and an aqeuous solution of 8 g. of picrylsulfonic acid added slowly with stirring. After the first 500 mg. of picrylsulfonic acid had been added, the solution was filtered, and the precipitate discarded. After all the picrylsulfonic acid had been added, the mixture was left at 0° overnight, the precipitate filtered off, and dried over P_2O_5 *in vacuo*, at room temperature; yield 4.8 g.; m.p. 125–127°.

Anal. Calc'd for $C_{14}H_{32}O_4S_4 \cdot 2C_6H_2N_3O_9S$: C, 32.0; H, 3.7; N, 8.6; S, 19.7.
Found: C, 32.2; H, 3.8; N, 8.6; S, 19.6.

The chemical reactivity of the sulfonium salts VIII and IX. For the study of the hydrolysis in unbuffered solution, IX was suspended in acetone, and water added slowly until the concentration reached about 10–15%. At this concentration the salt dissolved slowly, and after it was in solution, sufficient water was added to make the ratio of acetone to water 1:1. At the times indicated in Table II, aliquots were withdrawn and titrated to bromthymol blue with 0.1 *N* NaOH.

For the study of the rate of hydrolysis in $NaHCO_3$ solution, the solutions of both sulfonium salts were prepared as above, the requisite amount of $NaHCO_3$ being added to the clear solution. On standing, the reaction mixtures became red. At the indicated times, aliquots were withdrawn, acidified with a known quantity of 0.1 *N* HCl, and the solution concentrated *in vacuo* (bath temperature, 35°) for about 10 minutes to remove acetone and CO_2. The mixture was titrated to bromthymol blue with 0.1 *N* NaOH. Because of the red color of the solution, the end point is not sharp, the change being from clear red to a muddy purple. The acid generated is represented by the additional quantity of 0.1 *N* NaOH required to neutralize the sulfonium salt solution over that required to neutralize a control solution treated in the same manner but containing no sulfonium salt.

For the reaction with thiosulfate, the solutions were made up as above, the requisite amount of $Na_2S_2O_3$ being added. At the times indicated in Table II, aliquots were withdrawn, concentrated *in vacuo* to remove acetone, and titrated with 0.1 *N* I_2 solution. The solutions become highly colored on standing at 25°, thus making it somewhat difficult to observe the end point in the iodometric titration. The development of this color also indicates that the picrylsulfonate ion is undergoing some chemical reaction in the medium. It would seem unwise, therefore, to place too much reliance on the absolute values presented in Table II. The fact that IX is much more reactive than VIII is, however, not subject to this uncertainty.

"Bunte salt" of I. I (1.1 g.) was shaken for 72 hours at room temperature with 2.5 g. of $Na_2S_2O_3 \cdot 5H_2O$ in 50 cc. of water. The solution was filtered and concentrated to dryness under reduced pressure (bath temperature, 40°). The residue was extracted with boiling ethanol, and the extract filtered. The filtrate was concentrated under reduced pressure to a small volume, and the crystals which separated were filtered off, washed with ether, and dried in air; yield of crude product, 1.5 g. The product was recrystallized 3 times from hot ethanol.

Anal. Calc'd for $C_6H_{12}Na_2O_6S_6$: C, 17.2; H, 2.9; S, 45.9; Na, 11.0.
Found: C, 17.4; H, 3.1; S, 45.6; Na, 11.0.

Cysteine derivative of I (XI). To 1.8 g. of I suspended in 10 cc. of ethanol, was added a solution of 2.6 g. of cysteine-HCl in 5 cc. of water and 25 cc. of ethanol. Nitrogen was bubbled through the reaction mixture and a solution of 2.17 g. of KOH (85%) in 15 cc. of ethanol was added. After 48 hours under nitrogen, 50 cc. of water was added. The mixture was filtered and the *p*H of the filtrate was adjusted to 6.5 with acetic acid. The mixture was chilled for 12 hours and the precipitate was filtered. The product was recrystallized twice by dissolving it in concentrated NH_4OH and allowing the ammonia to evaporate at room temperature; yield 1.2 g. (38% of theory).

Anal. Calc'd for $C_{12}H_{24}N_2O_4S_4$: C, 37.0; H, 6.2; N, 7.2; S, 33.0.
Found: C, 36.7; H, 6.2; N, 7.0; S, 32.8.

The authors wish to acknowledge with thanks the helpful cooperation of Miss Rosalind E. Joseph and Miss Jean Grantham, who assisted in the conduct of these experiments, and of Mr. Stephen M. Nagy, who performed the microanalyses reported in this paper.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] VI. THE CHEMISTRY OF SULFONIUM SALTS RELATED TO MUSTARD GAS

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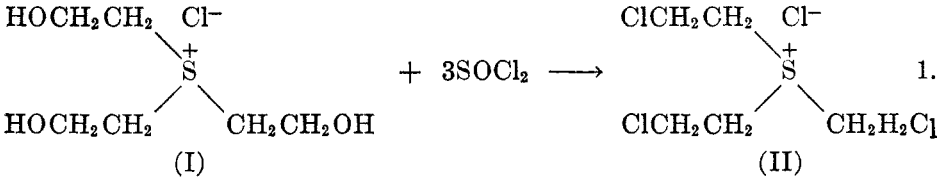
Received March 22, 1946

In a previous paper of this series (1) it was shown that, on hydrolysis with moderate quantities of water, mustard gas (H) gives rise to several different sulfonium salts. The interesting chemical and toxicological properties of these sulfonium derivatives prompted an investigation of the chemical and physiological properties of other sulfonium compounds of this type.

Preparation and properties of tris(β-chloroethyl)sulfonium chloride. Tris-(β-chloroethyl)sulfonium chloride (II) was prepared by treatment of the corresponding hydroxy compound (I) with thionyl chloride according to the method of Ettel and Kohlik (2).



(I) (II) 1.

So far as we are aware, compound II and its derivative (III) are unique in that they are the only compounds known in which the sulfur of bis(β-chloroethyl)sulfide is alkylated. In fact, there are several reports in the literature (2, 3, 4) which attest to the resistance to alkylation of the sulfur of β-chloroethylsulfides.

When II is dissolved in water, the *p*H falls rapidly to about 2.8. When the *p*H is raised by the addition of alkali, H^+ and Cl^- are formed in equivalent amounts, and at a rate which is markedly dependent upon *p*H (Table I). Thus, at *p*H 3.0, the half-time for the liberation of the first equivalent of HCl is about 3 minutes, and that for the second equivalent of HCl is about 25 minutes. The third equivalent of HCl is not liberated at this *p*H. As the *p*H is raised, both the speed and extent of HCl formation are increased, so that at *p*H 9, three equivalents of HCl are liberated in 10 minutes.

The data in Table II show that, at *p*H 7.5, the rate of liberation of HCl from II is reduced greatly by borate or bicarbonate and slightly by acetate or sulfate.

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TABLE I

INFLUENCE OF *p*H UPON THE REACTION OF TRIS(β-CHLOROETHYL)SULFONIUM CHLORIDE (II) WITH WATER

The H^+ liberation was followed electrometrically by adding NaOH (1.0 *N*) to maintain the *p*H at the desired value.

The Cl^- liberation was determined argentometrically on aliquots of the reaction mixture.

Temperature, 25°. Concentration of II, 0.05 *M*.

TIME, MIN.	*p*H 3.0		*p*H 7.5		*p*H 9.0	
	H^+ liber. per *mM* of II, M.EQUIV.	Cl^- liber. per *mM* of II, M.EQUIV.	H^+ liber. per *mM* of II, M.EQUIV.	Cl^- liber. per *mM* of II, M.EQUIV.	H^+ liber. per *mM* of II, M.EQUIV.	Cl^- liber. per *mM* of II, M.EQUIV.
1			2.00		2.00	
3			2.39		2.89	
5	0.73	0.79	2.45	2.30	2.97	2.92
10			2.57	2.54	2.99	3.00
15	1.25	1.30				
20			2.64	2.64		
30	1.62	1.59	2.73	2.70		
45			2.80	2.76		
60	1.87	1.84	2.84	2.78		
90	1.94	1.91	2.88	2.85		
150	2.00	1.98	2.94	2.91	3.00	3.00
270	2.00	2.02				

TABLE II

INFLUENCE OF VARIOUS ACIDS UPON ELIMINATION OF HCl FROM TRIS(β-CHLOROETHYL)-SULFONIUM CHLORIDE (II)

Concentration of reactants per cc. at start of reaction: 0.05 *mM* of II; 0.05 *mM* of acid. Temperature, 25°.

Unless otherwise noted, the acid solution was first neutralized to *p*H 7.5 with NaOH and II was then added. The H^+ liberation was followed electrometrically by adding NaOH (1.0 *N*) as required to maintain the *p*H about 7.5. The Cl^- liberation was also followed by titration of an aliquot at intervals with $AgNO_3$. H^+ and Cl^- were liberated at the same rate.

ACID	MILLIEQUIVALENTS OF HCl LIBERATED PER *mM* OF II WITHIN THE FOLLOWING TIME (IN MINUTES)							
	5	10	20	30	45	60	90	150
None	2.38	2.56	2.64	2.72	2.78	2.81	2.87	2.93
H_3BO_3	0.46	0.75	1.16	1.44	1.70	1.84	1.93	2.22
H_2CO_3[a]	0.82	1.11	1.47	1.67	1.84	1.96	2.14	2.42
H_2CO_3[a,b]	2.02	2.21	2.34	2.43	2.50	2.54	2.64	2.73
HCl	1.90	2.06	2.23	2.33	2.38	2.46	2.58	2.65
CH_3COOH	2.18	2.32	2.46	2.57	2.64	2.70	2.76	
H_2SO_4[c]	2.26	2.44	2.55	2.62	2.65	2.67		
HNO_3	2.46	2.62	2.72	2.79	2.85	2.90		

[a] Added as $NaHCO_3$.

[b] Concentration 0.005 *mM* per cc.

[c] Concentration 0.025 *mM* per cc.

It will be noted that, on addition of one mole equivalent of borate, the time required for the liberation of two equivalents of HCl was increased from a period of less than 1 minute to about 97 minutes. In the presence of one equivalent of bicarbonate, this time was about 65 minutes, whereas in the presence of one-tenth equivalent of bicarbonate only 4 minutes were required. On the other hand, one equivalent of acetate increased the time required for the liberation of 2.5 equivalents of HCl from 8 minutes to 23 minutes; one equivalent of sulfate increased this time to 14 minutes; but under similar conditions, nitrate did not change the rate of the reaction. Thus it would appear that the salts of very weak acids, such as boric or carbonic, which are only slightly dissociated at this *p*H, act as strong inhibitors of the reaction, while the salts of stronger acids, such

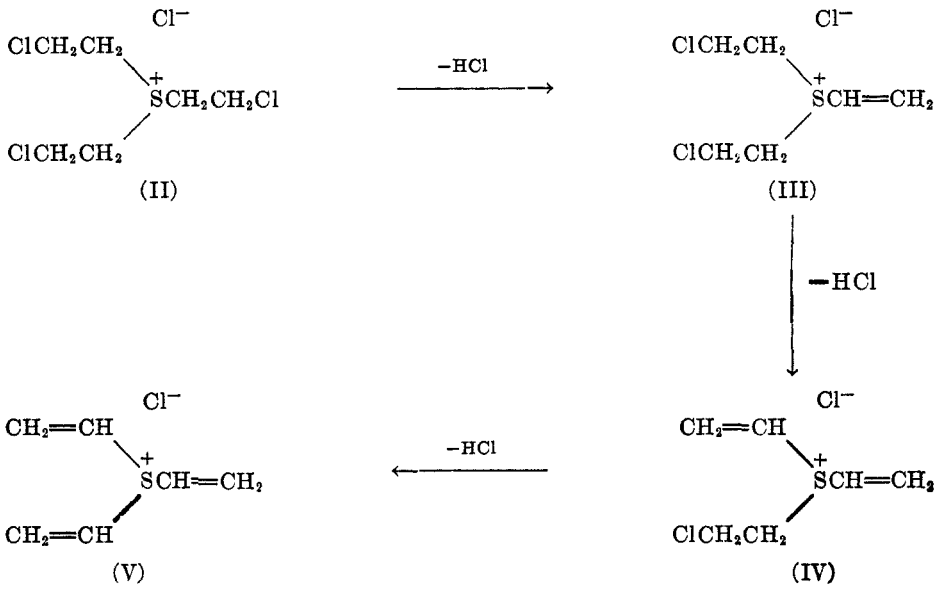


FIG. 1

as acetic, sulfuric or nitric, which are more completely dissociated, are weak inhibitors or show no inhibition at all.

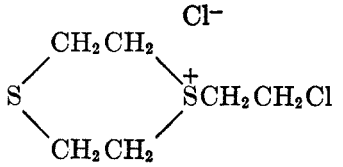
The mechanism of the hydrolysis of tris(β-chloroethyl)sulfonium chloride is given in Figure 1. The sequence of reactions given in the figure is supported by several lines of evidence. In the first place, the intermediate bis(β-chloroethyl)vinylsulfonium compound (III) was isolated as a picrylsulfonate from a bicarbonate-buffered reaction mixture aged for 10 minutes. Furthermore, the final product, the trivinylsulfonium salt (V), was isolated as a picrylsulfonate from a reaction mixture aged for 96 hours. Additional support for the reaction sequence given in Figure 1 was provided by a study of the reaction of II with thiosulfate. It was found that II reacts with thiosulfate in bicarbonate solution. However, the extent of thiosulfate consumption did not decrease concomitantly

with the liberation of HCl, and aged solutions of II still reacted with thiosulfate. These observations are accounted for by the fact that the final product of the reaction contains vinyl groups, and, therefore, also reacts with thiosulfate. In fact, trivinylsulfonium picrylsulfonate consumes almost two equivalents of thiosulfate within 16 hours.

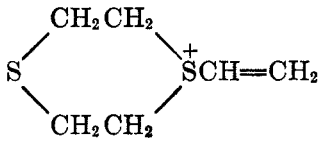
Three additional reactions of tris(β-chloroethyl)sulfonium chloride are of interest. In the presence of an excess of cysteine, three equivalents of SH groups disappear, but bis(cysteinylethyl)sulfide is formed. This compound has also been prepared by the reaction of H (5), or bis-β-[bis(β-hydroxyethyl)-sulfonium]ethylsulfide dichloride (1) with cysteine. When only two equivalents of cysteine are present, this product is not obtained. It would appear, therefore, that substitution of the three chlorine atoms of II by cysteine leads to the formation of an unstable sulfonium salt which decomposes to yield the sulfide. A somewhat analogous reaction must occur in the presence of an excess of pyridine, for here again a sulfide, bis(β-pyridiumethyl)sulfide, is formed. However, when treated with an alcoholic solution of NaOH, II yields tris(β-ethoxyethyl)-sulfonium chloride.

Preparation and properties of β-chloroethyl-1,4-dithiane sulfonium chloride and vinyl-1,4-dithiane sulfonium chloride. Since β-chloroethyl-1,4-dithiane sulfonium chloride (VI) contains only one β-chloroethyl group, it is well suited to a study of the properties of β-chloroethyl sulfonium compounds. It was prepared by chlorinating β-hydroxyethyl-1,4-dithiane sulfonium chloride with thionyl chloride.

The behavior of VI in aqueous solution is in many respects similar to that of tris(β-chloroethyl)sulfonium chloride. Thus when VI is dissolved in water, there is an initial fall in *p*H. If the *p*H is raised, HCl is liberated at a rate which is markedly dependent upon *p*H. It will be noted from Table III that at *p*H 5.0, 0.34 m. equiv. of HCl is liberated within 120 minutes, while at pH 7.5, 0.78 m. equiv. is liberated within 5 minutes. Furthermore, it will be noted from Table III that in the presence of one equivalent of bicarbonate, the rate of the formation of HCl is greatly decreased.



(VI)



(VII)

The product of the reaction of VI with water, the vinyl-1,4-dithiane sulfonium compound (VII), has been isolated as a picrylsulfonate from a bicarbonate-buffered reaction mixture. As will be described later, the vinyl compound (VII) was also obtained, as a chloride, by treatment of the zinc chloride double salt of S,S′-endoethylene-1,4-dithiane sulfonium dichloride with silver carbonate.

The β-chloroethyl and vinylsulfonium salts VI and VII both react with thiosulfate to form the β-thiosulfonatoethyl-1,4-dithiane sulfonium inner salt

(VIII) (Figure 2). The rate of the reaction of VI and VII with thiosulfate in aqueous solution at *p*H 7.5 is given in Columns 2 and 4 respectively of Table IV.

TABLE III

INFLUENCE OF *p*H AND BICARBONATE UPON THE REACTION OF β-CHLOROETHYL-1,4-DITHIANE SULFONIUM CHLORIDE (VI) WITH WATER

The procedure was similar to that given in Table I.

Temperature, 25°; concentration of VI, 0.05 *M*.

TIME, MIN.	*p*H 5.0		*p*H 7.5			
	no $NaHCO_3$		no $NaHCO_3$		+ $NaHCO_3$ (0.05 *M*)	
	H^+ liber. per *mM* of VI, M.EQUIV.	Cl^- liber. per *mM* of VI, M.EQUIV.	H^+ liber. per *mM* of VI, M.EQUIV.	Cl^- liber. per *mM* of VI, M.EQUIV.	H^+ liber. per *mM* of VI, M.EQUIV.	Cl^- liber. per *mM* of VI, M.EQUIV.
2	0.11		0.74		0.01	
5	.16	0.15	.79	0.77	.03	0.04
10			.82	.80	.08	.10
15	.20	.21	.85	.83		
30	.23	.25	.90	.88	.25	.25
60	.28	.28	.93	.94	.42	.46
120	.33	.34			.53	.54
180					.55	.56

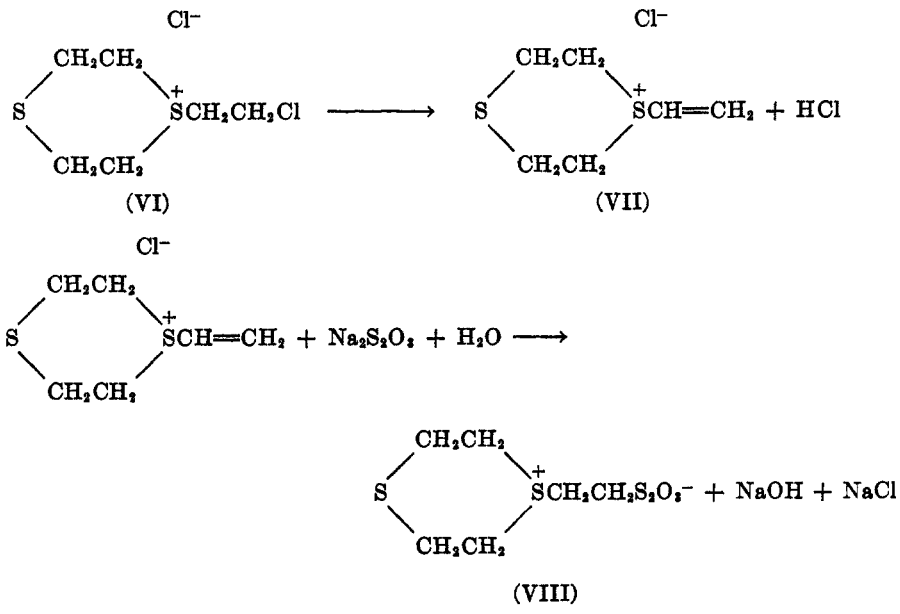


FIG. 2

β-Hydroxyethyl-1,4-dithiane sulfonium chloride, on the other hand, does not react with thiosulfate under these conditions.

Data presented above indicated that the rate of the elimination of HCl from VI is markedly influenced by bicarbonate. The results presented in Column 3 of Table IV show that the rate of the reaction of VI with thiosulfate is also reduced by bicarbonate. In the absence of bicarbonate; 0.39 m. equiv. of thiosulfate was consumed per *mM* of VI within 1 hour; while in the presence of one equivalent of bicarbonate, only 0.10 m. equiv. of thiosulfate was consumed.

In marked contrast, the rate of the reaction of VII with thiosulfate is not changed by the addition of bicarbonate (Columns 4 and 5 of Table IV). It will also be noted from Table IV that the rate of reaction of the vinyl group with thiosulfate is considerably faster than that of the β-chloroethyl group. Furthermore, when the vinyl group reacts with thiosulfate, OH^- is liberated at the same rate as thiosulfate is consumed. A comparison of the data of Table IV with

TABLE IV

INFLUENCE OF BICARBONATE UPON THE REACTION OF β-CHLOROETHYL-1,4-DITHIANE SULFONIUM CHLORIDE (VI) AND OF VINYL-1,4-DITHIANE SULFONIUM CHLORIDE (VII) WITH THIOSULFATE

Concentration of reactants per cc. at start of reaction: Columns 2 and 4, 0.05 *mM* of Sulfonium Chloride (VI or VII); 0.10 *mM* of $Na_2S_2O_3$. Columns 3, 5, and 6, 0.05 *mM* of Sulfonium Chloride (VI or VII); 0.10 *mM* of $Na_2S_2O_3$; 0.05 *mM* of $NaHCO_3$.

Temperature, 25°. The OH^- liberation (Column 6) was followed by continuous electrometric titration with HCl. The *p*H was maintained at about 7.5.

TIME, MIN.	THIOSULFATE CONSUMED PER *mM* OF VI		THIOSULFATE CONSUMED PER *mM* OF VII		OH^- FORMED PER *mM* OF VII
1.	M.EQUIV. 2.[a]	M.EQUIV. 3.	M.EQUIV. 4.	M.EQUIV. 5.	M.EQUIV. 6.
10	0.04	0.01	0.24	0.23	0.23
30	.18	.04	.48	.49	.49
60	.39	.10	.73	.74	.74
150	.64	.30	1.02	1.00	1.02
300	.73	.51			
1380	1.01	1.00			

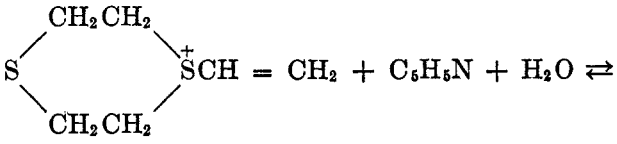
[a] 0.35 m.equiv. of NaOH per *mM* of VI were added at start to raise the *p*H to 7.7.

those of Table I shows that the rate of thiosulfate consumption by either the β-chloroethyl or vinyl group is much slower than the elimination of HCl from the chloroethyl group under similar conditions. This result indicates that loss of HCl with the formation of a reactive vinyl group is the first step in the reaction of β-chloroethyl sulfonium compounds with such groups as thiosulfate. Additional evidence for the formation of a vinyl group during the first stages of the reaction with thiosulfate lies in the fact that the *p*H of a reaction mixture containing VI and thiosulfate rapidly fell from 6.5 to about 3.5 as soon as the sulfonium salt was added. To raise the *p*H to 7.7, 0.35 m. equiv. of NaOH per *mM* of sulfonium salt was added, after which the *p*H again slowly fell to about 6.5. A *p*H of about 6.5 to 7.0 was maintained by the reaction mixture for at least 300 minutes, and then the *p*H rose to about 9.0 as the thiosulfate was consumed.

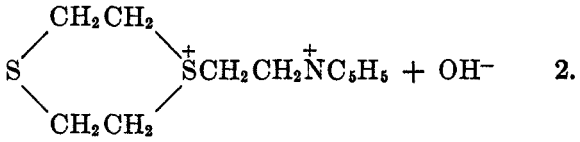
The fact that $NaHCO_3$ inhibits the reaction of β-chloroethyl-1,4-dithiane sulfonium chloride with thiosulfate, but does not inhibit the reaction of the vinyl compound with thiosulfate, is explained by the results presented above. Since a vinyl group must be formed prior to reaction with thiosulfate, the effect of $NaHCO_3$ is to reduce the rate of the formation of vinyl groups, but not the rate of reaction of vinyl groups once they are formed. The over-all effect, therefore, is a retardation of thiosulfate consumption. The mechanism of the reaction of VI and VII with thiosulfate is given in Figure 2.

It will be noted from Table IV that at *p*H 7.5 the reaction of VII with thiosulfate proceeds to completion. It has been found, however, that at a higher *p*H (8.5–9.0) the reaction appears to stop 15% short of completion. Moreover, when solutions of the isolated inner salt VIII are maintained at alkaline *pH* values, gradual decomposition occurs with the liberation of groups titratable with iodine. Thus after exposure of VIII for 100 hours to a *p*H of 8.0, 0.22 m. equiv. of iodine was consumed. After 100 hours at *p*H 8.5, 0.38 m. equiv. of iodine was consumed, while if the *p*H of exposure was raised to 9.0, 0.94 m. equiv. of iodine was consumed.

The β-chloroethyl and vinyl sulfonium salts (VI) and (VII) both react readily with pyridine to form the β-pyridiniumethyl-1,4-dithiane sulfonium salt (IX) which has been obtained as a dichloride and as a dipicrylsulfonate. The reaction may be represented by Equation 2.



(VII)



(IX) 2.

As can be seen from Equation 2, one equivalent of OH^- is liberated for each vinyl group which combines with pyridine. The rate and extent of the reaction were therefore followed by continuous electrometric titration with acid. The results given in Column 2 of Table V, show that the reaction starts at a rapid rate, 0.20 m. equiv. of OH^- being formed within 9 minutes. Subsequently, the reaction stops completely when only 28% of the theoretically possible amount of OH^- has been formed. On the basis of these data, it was suspected that the reaction between VII and pyridine was reversible, and that equilibrium had been attained when the forward reaction had gone 28% to completion.

In order to prove the reversible nature of the reaction, the decomposition of IX was studied. The pyridinium derivative (IX) was synthesized by treating a mixture of pyridine and pyridine hydrochloride with VII in ethanol-acetone.

The same product was also obtained from pyridine and VI in methanol. It was found that IX decomposes rapidly in aqueous solution, liberating within 10 minutes 66% of the theoretical quantity of H^+ (Column 3 of Table V). The equilibrium reached by the reverse reaction is, therefore, almost the same as that attained by the forward reaction, a strong indication that the reaction is reversible.

It follows from the foregoing that IX, in the course of its decomposition, should give rise to a reactive group (probably a vinyl group) and, therefore, should act as an alkylating agent. Indeed, it has been found that IX consumes thiosulfate at *p*H 7.5 and 25°. During this reaction, a small amount of crystal-

TABLE V

REACTION OF VINYL-1,4-DITHIANE SULFONIUM CHLORIDE (VII) WITH PYRIDINE AND OF β-PYRIDINIUMETHYL-1,4-DITHIANE SULFONIUM DICHLORIDE (IX) WITH WATER

Concentration of reactants per cc. at start of reaction: Column 2, 0.10 *mM* of VII; 0.20 *mM* of pyridine. Column 3, 0.105 *mM* of IX; 0.105 *mM* of pyridine.

Temperature, 25°. The OH^- or H^+ formation was followed electrometrically by adding HCl or NaOH (0.5 *N*) to maintain the *p*H at 7.3 to 7.5. The initial concentration of reactants for the experiment given in Column 3 was chosen so that the final volume was the same as that in the experiment recorded in Column 2.

TIME, MIN. 1.	OH^- LIBERATED PER *mM* OF VII, M.EQUIV. 2.	H^+ LIBERATED PER *mM* OF IX, M.EQUIV. 3.
1	0.05	0.32
2	.06	.55
3	.10	.62
4	.12	.64
5	.14	.65
6	.16	
8	.19	
10	.22	.66
12	.24	
14	.25	
16	.27	
20	.28	.66
30	.28	.66
60	.28	.66

line solid began to separate from the reaction mixture after about 4 hours. This product was identified as the inner salt (VIII) described above.

It has also been found that the rate of the transformation of IX into the vinyl compound is much more rapid than is the rate of the reaction of the sulfonium dichloride with thiosulfate. It is clear, therefore, that the major part of the thiosulfate consumption is attributable to a reaction involving the intermediate vinyl compound.

Additional evidence for the fact that IX can act as an alkylating agent is furnished by a study of the reaction of this substance with alanine. It has been found that the pyridinium compound reacts slowly with alanine, 0.99 m.

equiv. of amino nitrogen disappearing per *mM* of pyridinium salt within 48 hours. During the reaction with alanine, a small amount of dithiane separated after 24 hours, indicating partial decomposition of one of the sulfonium salts present in the reaction mixture.

Preparation and properties of S,S'-endoethylene-1,4-dithiane disulfonium dichloride. The synthesis of S,S'-endoethylene-1,4-dithiane disulfonium dichloride (X) involved the reaction of thiodiglycol with concentrated hydro-

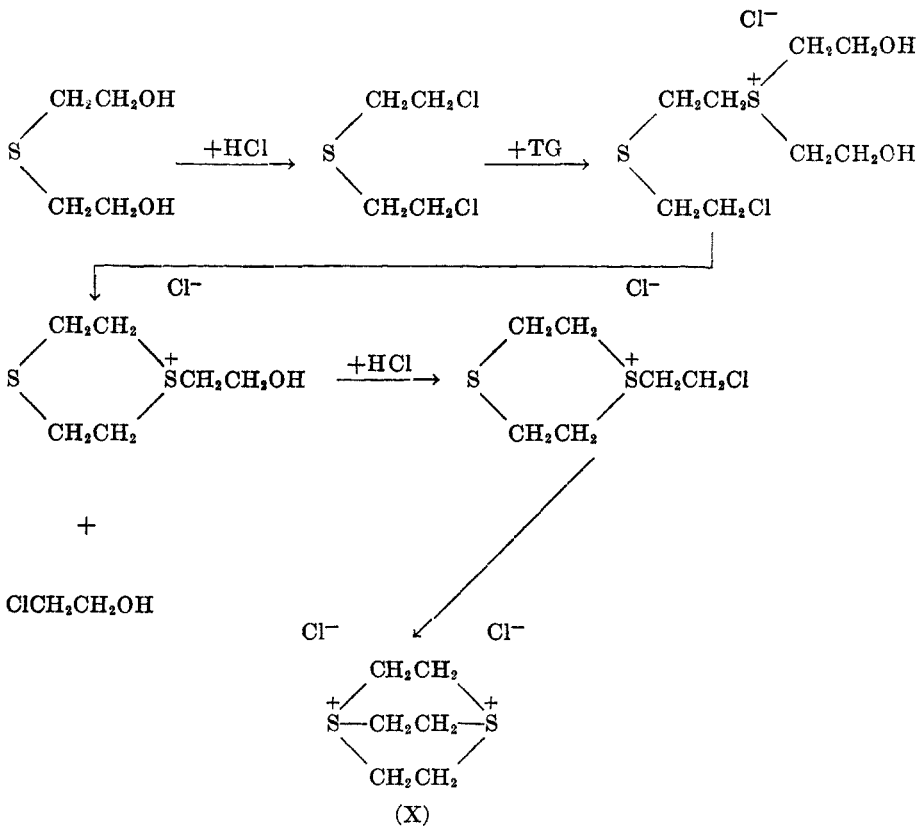


FIG. 3

chloric acid at 100°. The compound was isolated and analyzed as a double salt of zinc chloride and has also been analyzed as a dipicrylsulfonate.

Figure 3 is intended to indicate the general types of reaction which might lead to the formation of X. Possible variations of this general reaction sequence are obvious.

Davies and Oxford (6) have described the isolation of β-hydroxyethyl-1,4-dithiane sulfonium chloride from the reaction of H with 2 to 6 volumes of boiling water.

Upon treatment with silver carbonate, X is transformed into VII. The re-

action is analogous to a Hofmann degradation, only one sulfonium group being degraded under these conditions.

The relationship between chemical reactivity and toxicity of sulfonium salts. As a result of the chemical investigations detailed in this and a previous paper of this series (1), it has become possible to correlate the chemical reactivity of several sulfonium salts with their toxicity. The toxicity of a group of sulfonium salts is given in Table VI.

It can be seen from Table VI that those sulfonium salts which contain a reactive side chain capable of undergoing alkylation reactions are, in general, toxic. The most toxic compound in the table is XI, which is the only substance

TABLE VI

THE TOXICITY OF SEVERAL SULFONIUM SALTS

The approximate LD_{50} was determined in each case by intraperitoneal injection of graded doses into sets of three mice.

SUBSTANCE	APPROXIMATE LD_{50}
	mg./kg.
β - Chloroethyl - β - [bis(β - hydroxyethyl)sulfonium]ethylsulfide chloride (XI)	1.2[a]
Bis - β - [bis(β - hydroxyethyl)sulfonium]ethylsulfide dichloride (XII)	50–100[b]
β - Hydroxyethyl - β - [bis(β - hydroxyethyl)sulfonium]ethylsulfide chloride (XIIa)	86[a]
Tris(β-chloroethyl)sulfonium chloride (II)	80
β-Chloroethyl-1,4-dithiane sulfonium chloride (VI)	75
Vinyl-1,4-dithiane sulfonium chloride (VII)	75
β-Pyridiniumethyl-1,4-dithiane sulfonium dichloride (IX)	125
β-Hydroxyethyl-1,4-dithiane sulfonium chloride (XIII)	175
β-Thiosulfonatoethyl-1,4-dithiane sulfonium inner salt (VIII)	460
Methyl-bis(β-hydroxyethyl)sulfonium chloride (XIV)	1700
Methionine methyl sulfonium iodide (XV)	2000
Tris(β-hydroxyethyl)sulfonium chloride (I)	2000

[a] Reported by Smith, *et al.* (8)

[b] Reported previously (1).

possessing a β-chloroethylsulfide moiety. It will be recalled that XI is a potent alkylating agent (1). Compounds II, VI, and VII, all of which are good alkylating agents, also possess marked toxicity. In general, it would appear that the substitution of a reactive β-chloroethyl (or vinyl) group for an unreactive β-hydroxyethyl group results in an increase in toxicity. Thus compound XII is less toxic than compound XI, compound I is much less toxic than compound II, and compound XIII is markedly less toxic than are compounds VI or VII. Similarly, β-pyridiniumethyl-1,4-dithiane sulfonium chloride (IX) is slightly more toxic than is the corresponding hydroxyethyl compound (XIII). It will be recalled that compound IX decomposes at *p*H 7.5 with the liberation of an

active alkylating group (probably a vinyl group). Compound VIII, on the other hand, which is relatively non-toxic compared to the substances listed above, appears to be relatively stable at *p*H's below 8.

In comparing the toxicity and chemical reactivity of various sulfonium salts, the presence of a reactive side chain (β-chloroethyl or vinyl group) is not the only factor to be considered. Attention must also be directed towards the stability of the sulfonium sulfur atom. The ability of the sulfonium group to react with thiosulfate and/or to liberate acid when heated in aqueous solution may be taken as an index of stability or chemical reactivity. Of the sulfonium salts which do not possess reactive side chains, compounds XII and XIIa are the most toxic. It has already been shown, however, that these substances react with thiosulfate and decompose readily when heated in aqueous solution. Compound XIII, which possesses moderate toxicity, does not react with thiosulfate, but decomposes readily on heating in alkaline solution to give 1,4-dithiane, which can be isolated from the reaction mixture. Compounds I, XIV, and XV are by far the least toxic, and are also the most stable. Compounds I and XIV do not liberate appreciable quantities of HCl on heating in aqueous solution at 100° for 1 hour. Compound XV liberates only 17% of the theoretically possible quantity of acid under these conditions. It may be mentioned that the stability of XV is in marked contrast to the lability of the sulfonium salt formed from H and methionine. It will be recalled that the latter compound decomposes readily on heating in aqueous solution (7).

Considering the data in Table VI as a whole, two facts emerge. The more innocuous sulfonium salts all possess a relatively stable sulfonium sulfur atom, and do not possess any reactive, alkylating side chains. The more toxic sulfonium salts, on the other hand, each contain either a reactive side chain, or a relatively unstable sulfonium sulfur atom, or both.

EXPERIMENTAL

Tris(β-chloroethyl)sulfonium chloride (II). Tris(β-hydroxyethyl)sulfonium chloride was prepared by the method of Davies and Oxford (6). It was chlorinated in a manner similar to that described by Ettel and Kohlik (2) except that the chlorination was carried out at 25°. The yield of II was 50% of theory. The compound was recrystallized from the minimum amount of absolute ethyl alcohol by the addition of anhydrous ether; m.p. 108–109°.

Anal. Calc'd for $C_6H_{12}Cl_4S$: C, 27.9; H, 4.7; S, 12.4; Cl, 55.0.
Found: C, 27.9; H, 4.8; S, 12.4; Cl, 55.2.

Tris(β-chloroethyl)sulfonium picrylsulfonate. To a solution containing 1.28 g. (5 *mM*) of tris(β-chloroethyl)sulfonium chloride in 50 cc. of water, was added slowly 50 cc. of a solution containing 1.76 g. (5 *mM*) of sodium picrylsulfonate. The solid product which separated immediately was collected and washed with water; yield 2.40 g., corresponding to 94% of theory. The salt was recrystallized by dissolving it in 50 cc. of dry acetone and adding 60 cc. of anhydrous ether; m.p. 154°.

Anal. Calc'd for $C_6H_{12}Cl_3S \cdot C_6H_2N_3O_9S$: C, 28.0; H, 2.7; N, 8.2; S, 12.5; Cl, 20.7.
Found: C, 27.8; H, 2.7; N, 8.2; S, 12.7; Cl, 21.0.

Bis(β-chloroethyl)vinylsulfonium picrylsulfonate. A reaction mixture containing 2.56 g. (10 *mM*) of II, 4.2 g. (50 *mM*) of $NaHCO_3$, and 0.40 g. (10 *mM*) of NaOH in 200 cc. of water was allowed to stand 10 minutes at 25°. Titration of an aliquot indicated that 1.20 m.equiv.

of Cl^- had been liberated per *mM* of sulfonium salt. The remaining portion (180 cc.) was immediately acidified with 45 cc. of *N* HCl and a solution of 3.16 g. (9 *mM*) of sodium picrylsulfonate in 50 cc. of water was then added. The reaction mixture was concentrated to 50 cc. under reduced pressure (bath temperature, 40°), allowed to stand at 4° for 4 hours, and filtered. The product was washed with cold water and dried; yield 3.49 g., corresponding to 73% of theory. It was recrystallized four times by the addition of 50 cc. of anhydrous ether to a solution of the substance in 50 cc. of dry acetone; m.p. 134°.

Anal. Calc'd for $C_6H_{11}Cl_2S \cdot C_6H_2N_3O_9S$: C, 30.1; H, 2.7; N, 8.8; S, 13.4; Cl, 14.8.
Found: C, 30.0; H, 2.9; N, 8.8; S, 13.4; Cl, 14.9.

Trivinylsulfonium picrylsulfonate. A reaction mixture containing 6.38 g. (25 *mM*) of II, 10.5 g. (125 *mM*) of $NaHCO_3$, and 1.0 g. (25 *mM*) of NaOH in 500 cc. of water was allowed to stand for 96 hours at 25°. Titration of an aliquot showed that 2.87 m.equiv. of Cl^- had been liberated per *mM* of sulfonium salt. The remaining portion was acidified with 48 cc. of 2.7 *N* HCl and a solution of 7.56 g. of sodium picrylsulfonate in 50 cc. of water was added. The reaction mixture was concentrated to 50 cc. under reduced pressure (bath temperature, 40°), allowed to stand at 4° for 4 hours, and filtered. The product was washed with cold water and dried; yield 7.4 g., corresponding to 74% of theory. It was twice recrystallized from methyl alcohol; m.p. 157°.

Anal. Calc'd for $C_6H_9S \cdot C_6H_2N_3O_9S$: C, 35.5; H, 2.7; N, 10.4; S, 15.8.
Found: C, 35.5; H, 2.8; N, 10.4; S, 15.6.

Reaction of tris(β-chloroethyl)sulfonium chloride (II) with cysteine. A reaction mixture was made up to contain 1.28 g. (5 *mM*) of II, 2.35 g. (15 *mM*) of cysteine hydrochloride, 0.8 g. (20 *mM*) of NaOH, and 1.26 g. (15 *mM*) of $NaHCO_3$ in 50 cc. of O_2-free water. The mixture was kept at 25° under N_2. A solid began to separate after 3 hours. After 24 hours, the bis(cysteinylethyl)sulfide was collected, washed with water, and dried; yield 1.10 g., corresponding to 61% of theory. The filtrate gave a negative nitroprusside test. The crude product was recrystallized by dissolving it in 30 cc. of concentrated ammonium hydroxide and allowing the ammonia to evaporate slowly.

Anal. Calc'd for $C_{10}H_{20}N_2O_4S_3$: C, 36.6; H, 6.1; N, 8.6; S, 29.3.
Found: C, 36.4; H, 6.1; N, 8.6; S, 29.4.

Reaction of tris(β-chloroethyl)sulfonium chloride (II) with pyridine. A reaction mixture was made up to contain 2.56 g. (10 *mM*) of II and 8.05 cc. (50 *mM*) of pyridine in 25 cc. of absolute ethyl alcohol. One drop of triethylamine was added and the reaction mixture was allowed to stand 4 days at room temperature. Anhydrous ether (60 cc.) was then added to the reaction mixture to induce crystallization. The crude product was collected after 4 hours at 4°. The yield of crude bis(β-pyridiniumethyl)sulfide dichloride was 1.40 g. corresponding to 50% of theory. Since the dichloride was not analytically pure, it was purified by conversion to the dipicrylsulfonate. The crude dichloride (1.04 g.) was dissolved in 25 cc. of water, and 2.0 cc. of a solution containing 3.00 g. of picrylsulfonic acid in 25 cc. of water was added; the reaction was filtered, and the rest of the picrylsulfonic acid solution was added. The picrylsulfonate was collected and recrystallized from 80% methyl cellosolve. The melting point of the bis(β-pyridiniumethyl)sulfide dipicrylsulfonate was 216–218°.

Anal. Calc'd for $C_{14}H_{18}N_2S \cdot 2C_6H_2N_3O_9S$: C, 37.6; H, 2.7; N, 13.5; S, 11.6.
Found: C, 37.7; H, 2.7; N, 13.6; S, 11.7.

Tris(β-ethoxyethyl)sulfonium picrylsulfonate. A solution containing 1.28 g. (29.5 *mM*) of sodium hydroxide in 75 cc. of absolute ethyl alcohol was added with stirring to 25 cc. of an alcoholic solution containing 2.58 g. (10 *mM*) of II. After 20 minutes, the sodium chloride was removed and the filtrate concentrated under reduced pressure at 40° to a thin sirup. Anhydrous ether (100 cc.) was slowly added to the sirup. After 48 hours, a small amount of additional sodium chloride was removed and the filtrate added to 50 cc. of an aqueous solution containing 3.65 g. (10 *mM*) of picrylsulfonic acid. An oil separated which crystallized as the ether was removed under reduced pressure. The yield of tris(β-ethoxyethyl)sulfonium picrylsulfonate was 4.06 g. corresponding to 76% of theory. The

product was recrystallized from 15 cc. of methyl alcohol by the addition of 50 cc. of water m.p. 62–64°.

Anal. Calc'd for $C_{12}H_{27}O_3S \cdot C_6H_2N_3O_9S$: C, 39.8; H, 5.4; N, 7.8; S, 11.8.
Found: C, 39.9; H, 5.4; N, 7.8; S, 11.6.

β-Chloroethyl-1,4-dithiane sulfonium chloride (VI). β-Hydroxyethyl-1,4-dithiane sulfonium chloride (6) (20.0 g., 0.1 *M*) was treated at 25° with 35.7 g. (0.3 mole) of thionyl chloride for 2 hours. The reaction mixture was kept at 50° for 1 hour. The excess thionyl chloride was removed by maintaining the mixture under reduced pressure at 40° for 3 hours. The crude product solidified as the thionyl chloride was removed. The product was suspended in 50 cc. of dry ether, collected by filtration, and washed with dry ether; yield 20.7 g., corresponding to 95% of theory. The crude product was recrystallized by dissolving it in 120 cc. of boiling absolute ethyl alcohol, cooling, and adding 100 cc. of dry ether; m.p. 144°.

Anal. Calc'd for $C_6H_{12}Cl_2S_2$: C, 32.9; H, 5.5; Cl, 32.3.
Found: C, 33.1; H, 5.5; Cl, 32.3.

Vinyl-1,4-dithiane sulfonium picrylsulfonate. β-Chloroethyl-1,4-dithiane sulfonium chloride (2.19 g., 10 *mM*) was dissolved in 200 cc. of a solution containing 0.4 g. (10 *mM*) of NaOH and 1.68 g. (20 *mM*) of $NaHCO_3$. The reaction mixture was allowed to stand at 25° for 24 hours, and 3.63 g (10 *mM*) of picrylsulfonic acid dissolved in 50 cc. of water was added. The mixture was concentrated under reduced pressure to 40 cc. Crystallization occurred during the concentration. The concentrate was cooled to 4° for 2 hours, filtered, and the product washed with water. The yield of vinyl-1,4-dithiane sulfonium picrylsulfonate was 3.92 g., corresponding to 85% of theory. The product was recrystallized by suspending it in 50 cc. of boiling methyl cellosolve, filtering, and adding 50 cc. of ether to the filtrate. The melting point was 154–155° and no depression was observed on admixture with a sample prepared from S,S′-endoethylene-1,4-dithiane sulfonium dichloride.

Anal. Calc'd for $C_6H_{11}S_2 \cdot C_6H_2N_3O_9S$: C, 32.8; H, 3.0; N, 9.6; S, 21.9.
Found: C, 32.9; H, 3.1; N, 9.5; S, 21.8.

β-Thiosulfonatoethyl-1,4-dithiane sulfonium inner salt (VIII). Vinyl-1,4-dithiane sulfonium chloride (3.66 g., 20 *mM*), 10.0 g. (40 *mM*) of sodium thiosulfate, and 3.4 g. (40 *mM*) of sodium bicarbonate were dissolved in 100 cc. of water and the solution was allowed to stand at room temperature for 24 hours. Crystals of the thiosulfate salt appeared after 15 minutes and gradually increased in amount. The reaction mixture was cooled at 0°, filtered, and the crystalline product was dried *in vacuo* over P_2O_5; yield 3.9 g. (75% of theory) of nearly pure product (C, 28.0; H, 4.7). It was recrystallized from hot water, washed with alcohol and ether, and dried as before. The melting point was 151–153° with decomposition.

Anal. Calc'd for $C_6H_{12}O_3S_4$: C, 27.7; H, 4.6; S, 49.2.
Found: C, 27.7; H, 4.6; S. 49.2.

The same product was obtained in a similar manner from a reaction mixture containing 2.19 g. (10 *mM*) of β-chloroethyl-1,4-dithiane sulfonium chloride, 5.0 g. (20 *mM*) of sodium thiosulfate, and 1.7 g. (20 *mM*) of sodium bicarbonate dissolved in 50 cc. of water. The yield was 2.03 g. corresponding to 78% of theory. The melting point showed no depression when this product was mixed with that prepared from the vinyl sulfonium salt.

Anal. Calc'd for $C_6H_{12}O_3S_4$: C, 27.7; H, 4.6; S, 49.2.
Found: C, 27.7; H, 4.7; S, 49.2.

Compound VIII also crystallized from a reaction mixture containing 1.63 g. (5 *mM*) of IX, 2.5 g. (10 *mM*) of sodium thiosulfate, and 1.7 g. (20 *mM*) of sodium bicarbonate in 50 cc. of water.

Anal. Calc'd for $C_6H_{12}O_3S_4$: C, 27.7; H, 4.6; S, 49.2.
Found: C, 27.6; H, 4.5; S, 49.1.

β-Pyridiniumethyl-1,4-dithiane sulfonium dichloride (IX). Vinyl-1,4-dithiane sulfonium chloride (3.65 g., 20 *mM*) was dissolved in 20 cc. of absolute alcohol and to this solution were added 2.64 g. (23 *mM*) of pyridine hydrochloride dissolved in 5 cc. of absolute alcohol and 1.6 cc. (20 *mM*) of pyridine. After standing at room temperature for 24 hours, the

reaction mixture contained a mass of crystalline material which was collected (1.52 g.) and recrystallized from absolute ethyl alcohol-ether; m.p. 150–152°. The reaction mixture, after standing for 10 more days at room temperature, deposited an additional 1.40 g. of IX. The total yield corresponds to 49% of theory. The substance was dried for analysis at 78° over P_2O_5 *in vacuo*.

Anal. Calc'd for $C_{11}H_{17}Cl_2NS_2$: C, 44.3; H, 5.7; N, 4.7; S, 21.5.
Found: C, 44.4; H, 5.7; N, 4.8; S, 21.5.

The anhydrous substance, when exposed to air at 23° and 32% humidity, showed an increase in weight of 8.3%. Calculated for 1.5 moles of H_2O, 8.3%.

The same product was obtained from β-chloroethyl-1,4-dithiane sulfonium chloride and pyridine. The sulfonium chloride (10.9 g., 50 *mM*) was dissolved in 35 cc. of absolute methyl alcohol and 12.1 cc. (150 *mM*) of pyridine was added. The reaction mixture was allowed to stand at room temperature for 48 hours; 25 cc. of dry ether then was added to induce crystallization. After standing at 4° for 4 hours, the product was collected and washed with dry ether; yield 9.24 g. After recrystallization from absolute ethyl alcohol and ether, it melted at 150–152°, no depression in mixture with a sample of the substance prepared from vinyl-1,4-dithiane sulfonium chloride. After standing for 5 more days at room temperature, the mother liquors deposited an additional 3.84 g. of IX. The product was dried over P_2O_5 at 78° *in vacuo* for analysis. The total yield corresponds to 88% of theory.

Anal. Calc'd for $C_{11}H_{17}Cl_2NS_2$: C, 44.3; H, 5.7; N, 4.7.
Found: C, 44.1; H, 5.6; N, 4.9.

S,S'-Endoethylene-1,4-dithiane disulfonium dichloride (*X*). A mixture of 200 g. of thiodiglycol (Kromfax), 225 g. of $ZnCl_2$, and 700 cc. of HCl was boiled under reflux for 24 hours. During the reaction, a crystalline precipitate separated, which was collected and recrystallized from hot water. The filtrate was refluxed for 48 hours longer; on cooling, a further crop of crystals was obtained; total yield of recrystallized material, 26 g. For analysis, the material was recrystallized once more from hot water.

Anal. Calc'd for $C_6H_{12}Cl_2S_2 \cdot ZnCl_2$: C, 20.3; H, 3.4; S, 18.1; Zn, 18.4; Cl, 39.8.
Found: C, 20.3; H, 3.5; S, 17.8; Zn, 18.4; Cl, 39.9.

For the preparation of the dipicrylsulfonate, 0.9 g. of the $ZnCl_2$ double salt was dissolved in 50 cc. of water and a solution of 4 g. of picrylsulfonic acid in a mixture of 50 cc. of water and 15 cc. of *N* HCl was added. The dipicrylsulfonate (1.8 g.) crystallized out in the form of yellow leaflets.

Anal. Calc'd for $C_6H_{12}S_2 \cdot 2C_6H_2N_3O_9S$: C, 29.5; H, 2.2; N, 11.4; S, 17.5.
Found: C, 29.95; H, 2.5; N, 11.1; S, 17.4.

Vinyl-1,4-dithiane sulfonium chloride (*VII*). The double salt X (7 g.) was dissolved in 100 cc. of water and stirred at room temperature with 25 g. of Ag_2CO_3. After 90 minutes, the reaction mixture was filtered and the filtrate (which was free of Cl^-) was acidified with HCl to Congo Red. On evaporation *in vacuo*, a colorless crystalline chloride was obtained. For purification it was repeatedly dissolved in cold absolute ethanol and reprecipitated by the addition of anhydrous ether.

Anal. Calc'd for $C_6H_{11}ClS_2$: C, 39.45; H, 6.0; Cl, 19.4.
Found: C, 39.1; H, 5.9; Cl, 19.2.

The chloride (7.3 g.) was dissolved in 200 cc. of water and 15 g. of picrylsulfonic acid was added. The picrylsulfonate crystallized at once. The yield was 17 g., corresponding to 95% of the theory.

Anal. Calc'd for $C_6H_{11}S_2 \cdot C_6H_2N_3O_9S$: C, 32.8; H, 3.0; N, 9.6; S, 21.9.
Found: C, 32.7; H, 3.0; N, 9.5; S, 21.8.

Methyl-bis(β-hydroxyethyl)sulfonium salts. The iodide was obtained by heating 6.1 g. of thiodiglycol with 35.5 g. of methyl iodide (5 equivalents) in a mixture of 50 cc. of methanol and 10 cc. of water for 20 hours. On evaporation *in vacuo*, the iodide was obtained as a yellowish brown liquid (Davies and Oxford, 6). The sulfonium compound was isolated in crystalline form as a salt of flavianic acid. For this purpose the iodide was dissolved in

20 cc. of water and a solution of 15.7 g. of flavianic acid in 20 cc. of water and 1 cc. of 3 *N* HCl was added. The methyl-bis(β-hydroxyethyl)sulfonium flavianate crystallized at once as microscopic needles; yield 19.6 g. or 83% of the theory. It was thoroughly washed with ether and recrystallized from water containing some HCl; yield 18.25 g.

Anal. Calc'd for $C_5H_{13}O_2S \cdot C_{10}H_5N_2O_8S$: C, 40.0; H, 4.0; N, 6.2; S, 14.2.
Found: C, 39.9; H, 4.1; N, 6.3; S, 14.4.

The flavianate was converted to the chloride by treatment, in aqueous solution, with one equivalent of arginine monohydrochloride. The arginine flavianate was removed at 0° and the filtrate, which contained traces of flavianic acid, was employed for toxicity and stability tests.

Methionine methyl sulfonium iodide. This compound was prepared by the procedure of Toennies (9).

The salt was recrystallized twice from the minimum amount of water with the addition of acetone; m.p. 168–169°.

Anal. Calc'd for $C_6H_{14}INO_2S$: C, 24.7; H, 4.8; N, 4.8; S, 11.0.
Found: C, 24.6; H, 4.8; N, 4.8; S, 11.1.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

CHEMICAL REACTIONS OF MUSTARD GAS AND RELATED COMPOUNDS.[1] VII. THE CHEMISTRY OF BIS(β-CHLOROETHYL)-SULFONE, DIVINYL SULFONE AND DIVINYL SULFOXIDE

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In the course of the past 25 years, much interest has centered on the chemistry of bis(β-chloroethyl)sulfone [mustard gas sulfone, to be referred to as H sulfone (I)]. The ease with which H sulfone reacts with sulfhydryl, phenolic hydroxyl, and amino groups was recognized by Helfrich and Reid (1), Cashmore and McCombie (2), and Lawson and Reid (3). In fact, the great chemical reactivity of H sulfone led Flury and Wieland (4) in 1921 to suggest that vesication by H was due to oxidation of H in the skin to the sulfone. No positive evidence has been adduced to support this hypothesis, and there appear to be theoretical grounds for questioning its validity (5). Moreover, the recent work, which has demonstrated the great chemical reactivity of H itself, has rendered the hypothesis of Flury and Wieland unnecessary. Nevertheless, H sulfone continues to receive much attention because of its vesicancy and toxicity, and its close chemical relationship to H.

Alexander and McCombie (6) reported that H sulfone readily splits out HCl to form divinyl sulfone (II) when treated with triethylamine in dry benzene. They found that divinyl sulfone was an extremely reactive substance, combining readily with sulfhydryl, phenolic hydroxyl, and amino groups to form β-substituted derivatives. Ford-Moore (7) studied further the reaction of H sulfone and divinyl sulfone with amino compounds and observed that the product of the reaction of these two sulfones with a given compound invariably was the same. Ford-Moore and Lidstone (8) found that divinyl sulfone was formed when an aqueous solution of H sulfone was heated with calcium carbonate, and Marshall and Williams (9) earlier had observed that H sulfone liberated Cl^- in aqueous phosphate solution (*p*H 7.3–7.7). Boursnell, Francis, and Wormall (10) noted that, on treatment of H sulfone with aqueous sodium bicarbonate, a product was formed which reacted more readily with the amino group of glycine than does H sulfone itself. They suggested that this intermediate product was divinyl sulfone. Price (11) showed by isolation that divinyl sulfone was formed from H sulfone in bicarbonate - buffered solution.

Reaction of H sulfone, H sulfoxide and divinyl sulfone with water. When H

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sulfone is dissolved in water, the *p*H falls slowly. After several hours, a *p*H of about 3.5–4.5 is attained by a saturated solution, and tests with silver nitrate then show a trace of Cl^-. As soon as the *p*H is raised by the addition of alkali, equivalent amounts of H^+ and Cl^- are liberated. Table I shows that this elimination of HCl is catalyzed by OH^-. At *p*H 6.5–7.0, 0.35 m.equiv. of HCl is liberated within 30 minutes, whereas, at *p*H 7.5–7.8, 1.06 m.equiv. of HCl is liberated within 3 minutes and 1.47 m.equiv. within 30 minutes. The rate of HCl liberation is greatly reduced by the addition of sodium bicarbonate. In the presence of one equivalent of bicarbonate at *p*H 7.5–7.8, only about 0.37 m.equiv. of HCl is liberated within 30 minutes.

In marked contrast to H and H sulfone, the non-vesicant bis(β-chloroethyl)-sulfoxide (H sulfoxide) liberated HCl only very slowly at physiological *p*H values.

TABLE I

INFLUENCE OF *p*H AND BICARBONATE UPON THE REACTION OF H SULFONE WITH WATER

The H sulfone (I) dissolved in methyl cellosolve (1 *mM* of I in 0.8 cc. of methyl cellosolve) was added to water. The initial concentration of I was 0.02 molar. The H^+ liberation was followed electrometrically by adding NaOH (0.5 *N*) to maintain the *p*H as indicated. The Cl^- liberation was determined argentometrically on aliquots of the reaction mixture. Temperature, 25°.

TIME, MIN.	*p*H 6.5–7.0		*p*H 7.5–7.8		
	No $NaHCO_3$		No $NaHCO_3$		+$NaHCO_3$ (0.02 M)
	H^+ liber. per *mM* I, M. EQUIV.	Cl^- liber. per *mM* I, M. EQUIV.	H^+ liber. per *mM* I, M. EQUIV.	Cl^- liber. per *mM* I, M. EQUIV.	Cl^- liber. per *mM* I, M. EQUIV.
3			1.04	1.07	
5			1.17	1.16	
10	0.27	0.27	1.26	1.26	
30	0.35	0.38	1.47	1.47	0.40
90	0.55	0.54	1.66	1.66	0.80
150			1.81	1.81	1.02
420					1.55

In the *p*H range 7–8, only about 0.02 m.equiv. of HCl is formed within 150 minutes. At higher pH values HCl is liberated more rapidly, 0.23 m.equiv. of HCl being formed at *p*H 9.5 within 150 minutes. It has also been found that the rate of HCl liberation is reduced by bicarbonate.

Divinyl sulfone appears to be relatively stable in aqueous solution. Since, as will be shown below, divinyl sulfone reacts readily with thiosulfate, the disappearance of reactive vinyl groups on aging the sulfone in aqueous bicarbonate at 25° and *p*H 8.4 was followed by determining the decrease in thiosulfate titer. It was found that the thiosulfate titer of aged divinyl sulfone solutions (0.05 *M*) decreased by about 15% in 22 hours, and by about 60% in 94 hours.

Reaction of H sulfone and divinyl sulfone with sulfhydryl compounds. Both H sulfone and divinyl sulfone react readily with thiosulfate at *p*H 7.5. The data in Table II show that the rate of the reaction of H sulfone is markedly decreased

by bicarbonate. In the absence of bicarbonate, 0.42 m.equiv. of thiosulfate was consumed per *mM* of H sulfone within 1 hour, while in the presence of 1 mole equivalent of sodium bicarbonate, only 0.20 m.equiv. of thiosulfate was consumed. In contrast, the rate of the reaction of divinyl sulfone with thiosulfate in not influenced by bicarbonate. Both in the presence and in the absence of bicarbonate, about 1.00 m.equiv. of sodium thiosulfate was consumed per *mM* of divinyl sulfone within 1 hour. In this reaction OH^- was liberated at the same rate as thiosulfate was consumed.

In the initial stages of the reaction of H sulfone with thiosulfate HCl accumulated, and 0.34 m.equiv. of NaOH was required during the first few minutes to

TABLE II

INFLUENCE OF BICARBONATE UPON THE REACTION OF H SULFONE (I) AND OF DIVINYL SULFONE (II) WITH THIOSULFATE

Concentration of reactants per cc. at start of reaction: Columns 2 and 4, 0.02 *mM* of I; 0.05 *mM* of $Na_2S_2O_3$. Columns 3, 5, and 6, 0.02 *mM* of II; 0.05 *mM* of $Na_2S_2O_3$; 0.02 *mM* of $NaHCO_3$.

Temperature, 25°; *p*H 7.4–7.6.

TIME, MIN.	THIOSULFATE CONSUMED PER *mM* OF:				OH^- FORMED PER *mM* OF II + $NaHCO_3$ M. EQUIV.
	I		II		
	No $NaHCO_3$, M. EQUIV.	+ $NaHCO_3$, M. EQUIV.	No $NaHCO_3$, M. EQUIV.	+ $NaHCO_3$, M. EQUIV.	
1.	2.[a]	3.	4.[b]	5.	6.
5	0.11	0.05	0.20	0.23	0.20
10	.16	.07	.39	.37	.35
30	.27	.12	.73	.71	.66
60	.42	.20	1.01	.99	1.01
120	.67	.39	1.28	1.29	1.33
180			1.43	1.54	1.54
240	1.04	.78	1.56	1.62	1.68
360	1.27	.99			

[a] 0.34 m.equiv. of NaOH per *mM* of I were added at the start to raise the *p*H to 7.5.

[b] The *p*H was held as nearly as possible at *p*H 7.5. However, since the solution was not buffered, the *p*H fluctuated between 4 and 10.

maintain the *p*H at 7.5. The accumulation of HCl shows that the reaction of H sulfone with groups such as thiosulfate must first involve the formation of a reactive vinyl group. The fact that bicarbonate inhibits the reaction of H sulfone with thiosulfate, but does not inhibit the reaction of divinyl sulfone with thiosulfate, is a clear indication that bicarbonate decreases the rate at which vinyl groups are formed, but does not alter the reactivity of the vinyl groups once they are present. The reaction of H sulfone with thiosulfate may, therefore, be represented by the reactions portrayed in Figure 1.

The "Bunte salt" (III) has been isolated from the reaction of divinyl sulfone with thiosulfate. In alkaline solutions III slowly liberates substances which consume iodine. After 24 hours at *p*H 8.7, the iodine consumption was 0.24

m.equiv., while after 48 hours, the iodine consumption was 0.32 m.equiv. Hence, it seems likely that the second reaction given in Figure 1 is reversed in strongly alkaline solutions.

Ford-Moore and Lidstone (8) report that the reaction of divinyl sulfone with thiophenol, which leads to the formation of bis(phenylthioethyl)sulfone, is catalyzed by nitrogenous bases. We have found that when divinyl sulfone and thiophenol were allowed to react in 55% aqueous methylcellosolve solution in the absence of a catalyst, the reaction was 73% complete within 90 minutes. However, the reaction was 99% complete within 7 minutes when a small amount (0.018 mole equivalent) of triethylamine was added. Aqueous sodium bicarbonate is equally as effective as catalyst as is triethylamine. When the triethylamine was previously neutralized to *p*H 7.0 with HCl, its catalytic effect was lost; the reaction was then only 77% complete within 90 minutes. Hence it would appear that this catalytic effect is not specific, but results from the fact that the reaction between thiophenol and divinyl sulfone is very sensitive to slight changes in *p*H.

In aqueous solution, the rate of the reaction of divinyl sulfone with the SH group of both cysteine[5] and β-mercaptoethanol is also markedly dependent upon

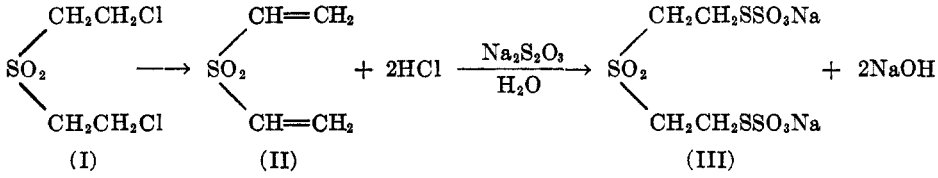


FIG. 1

the *p*H, increasing rapidly as the *p*H rises. At *p*H 4.4, 1.18 m.equiv. of the SH groups of cysteine reacted per *mM* of divinyl sulfone within 20 minutes, while at *p*H 5.1, 1.24 m.equiv. reacted within 3 minutes, and at *p*H 6.2, 2.0 m.equiv. reacted within 2 minutes. At *p*H 5.4, 1.00 m.equiv. of the SH groups of β-mercaptoethanol reacted per *mM* of divinyl sulfone within 5 minutes, while at *p*H 6.0 and 6.5, 1.46 and 1.96 m.equiv. respectively reacted within the same time. The product formed by the reaction of divinyl sulfone with β-mercaptoethanol, bis[β-(β-hydroxyethylthio)ethyl]sulfone has been prepared. In contrast to the "Bunte salt" of divinyl sulfone, this product did not liberate reducing substances at *p*H 8.5.

Reaction of divinyl sulfone with nitrogenous bases. Divinyl sulfone reacts readily with pyridine to form the bis(β-pyridiniumethyl) sulfone derivative (IV). Bis(β-pyridiniumethyl)sulfone dichloride was isolated from the reaction of divinyl sulfone with pyridine and pyridine hydrochloride in alcoholic solution. The rate and extent of the reaction of pyridine with divinyl sulfone were followed at *p*H 7.5 by continuous electrometric titration of the OH^- produced (Figure 2). The decomposition of the reaction product was followed under the same con-

[5] Ford-Moore (7) has shown that divinyl sulfone reacts with two equivalents of cysteine to form bis(cysteinylethyl)sulfone [$SO_2(C_2H_4SCH_2CH(NH_2)COOH)_2$].

ditions by continuous titration of the H^+ liberated when bis(β-pyridiniumethyl)-sulfone dichloride was dissolved in water. The data in Table III show that the reaction of divinyl sulfone with pyridine at *p*H 7.5 starts at a rapid rate, 1.15 m.equiv. of OH^- being formed within 5 minutes. Subsequently, the reaction stops completely when 1.48 m.equiv. of OH^- (74% of theory) have been formed. The reverse reaction, the decomposition of IV is also very rapid at the start, 0.40 m.equiv. of H^+ being formed within 1.5 minutes. The decomposition stops when 0.49 m.equiv. of H^+ (25% of theory) are liberated. Since essentially the same equilibrium point was reached by the reverse reaction as obtained by the forward reaction, the addition of pyridine to divinyl sulfone must proceed according to the reversible reaction sequences given in Figure 2.

Since OH^- is formed in the reaction of divinyl sulfone with pyridine, the position of the equilibrium will be determined by the *p*H of the solution. High *p*H values favor decomposition of IV, while lower *p*H values favor its formation. At low *p*H values, the forward reaction does not proceed because pyridine is then almost exclusively in the ionized form. When the experiment described

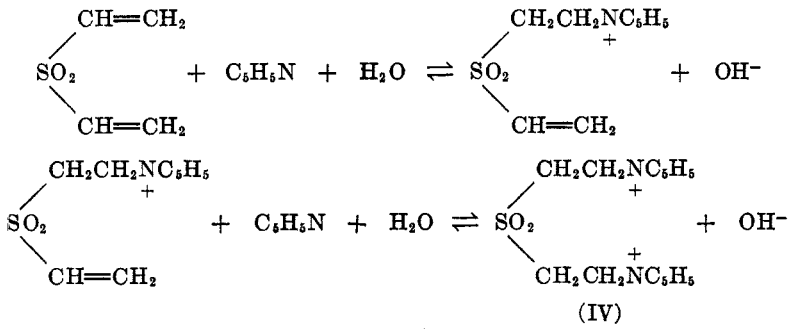


FIG. 2

in Column 2 of Table III was repeated, except that the *p*H was maintained at 6.5, equilibrium was established when 1.72 m.equiv. of OH^- had been liberated. At *p*H 7.5, this value was 1.48 m.equiv., and at *p*H 8.6 and 9.7 equilibrium was established when 0.83 and 0.17 m.equiv. respectively of OH^- had been liberated.

It follows from the reversible nature of the reaction of pyridine with divinyl sulfone that, in aqueous solution, IV should give rise to reactive vinyl groups. The validity of this conclusion is supported by the observation that the pyridinium salt reacts with cysteine, thiosulfate, and alanine. When a bicarbonate-buffered solution of bis(β-pyridiniumethyl)sulfone dichloride was treated with cysteine, the SH groups slowly disappeared. After about 10 minutes, a distinct odor of pyridine was detectable and 0.52 m.equiv. of cysteine had reacted. After about 2 hours, 1.21 m.equiv. of cysteine had reacted and a crystalline precipitate appeared. This precipitate increased in amount during the next few hours until, at the end of 20 hours, 2.04 m.equiv. of cysteine had reacted. The product was then filtered off and identified as the bis-cysteinyl derivative of divinyl sulfone (7).

For purposes of comparison, the reaction of bis(β-pyridiniumethyl)sulfide (12) with cysteine was investigated. In contrast to the sulfone, no reaction between the sulfide and cysteine occurred within 48 hours. It was also desirable to compare the stability of a β-pyridiniumethyl sulfonium salt. However, attempts to methylate bis(β-pyridiniumethyl)sulfide with methyl iodide were unsuccessful, only the diiodide of bis(β-pyridiniumethyl)sulfide being obtained. However, the alkylating properties of β-pyridiniumethyl-1,4-dithiane sulfonium chloride have been pointed out in the previous paper of this series (13).

TABLE III

REACTION OF DIVINYL SULFONE (II) WITH PYRIDINE AND OF BIS(β-PYRIDINIUMETHYL)-SULFONE DICHLORIDE (IV) WITH WATER

Concentration of reactants per cc. at start of reaction: 0.05 *mM* of II or IV; 0.20 *mM* of pyridine (Column 2); 0.10 *mM* of pyridine (Column 3).

The liberation of H^+ or OH^- was followed electrometrically by adding 0.5 *N* NaOH or HCl to maintain the *p*H at about 7.5. In the experiment given in Column 3 sufficient water was added to the reaction mixture to make the final volume the same as in the experiment reported in Column 2.

TIME, MINUTES 1.	OH^- PRODUCED PER *mM* OF II, M. EQUIV. 2.	H^+ PRODUCED PER *mM* OF IV, M. EQUIV. 3.
0.0	—	—
0.5	0.23	0.08
1.0	.38	
1.5	.51	.40
2.0	.68	.49
2.5	.79	
3.0	.92	.49
4.0	1.06	
5.0	1.15	.49
6.0	1.25	
7.0	1.34	
8.0	1.38	
9.0	1.41	
10.0	1.44	.49
11.0	1.46	
12.0	1.47	
14.0	1.48	
20.0	1.48	
180.0	1.48	.49

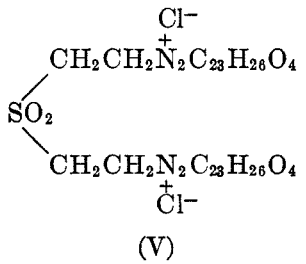
Additional evidence for the fact that bis(β-pyridiniumethyl)sulfone dichloride can act as an alkylating agent is furnished by its reaction with alanine. When a solution of IV (0.05 *M*) was treated at 25° with alanine (0.20 *M*), in the presence of bicarbonate (0.20 *M*) amino groups slowly disappeared. The disappearance of amino groups was 0.46 m.equiv. in 4 hours, and 0.80 m.equiv. within 24 hours. Under similar conditions, consumption of amino nitrogen by divinyl sulfone ceased within 22 hours when about 0.9 to 0.95 m.equiv. of alanine had reacted, suggesting, as pointed out by Boursnell, Francis, and Wormall (10), that a substituted sulfonazan is formed.

Compound IV was also isolated as a picrylsulfonate after an aqueous bicarbonate-buffered reaction mixture containing pyridine and divinyl sulfone had stood for 2 hours. After 24 hours, β-pyridiniumethyl-β-hydroxyethylsulfone was isolated from a similar reaction mixture. Bis(β-pyridiniumethyl)sulfone dipicrylsulfonate slowly dissolves in aqueous thiosulfate solution with the consumption within 2 hours of 1.04 m.equiv., and within 24 hours of 1.78 m. equiv., of thiosulfate. A slight decrease in this thiosulfate consumption was noted after 48 hours, in agreement with the previously noted instability of the thiosulfate derivative of divinyl sulfone in alkaline solution. Similarly, β-pyridiniumethyl-β-hydroxyethylsulfone picrylsulfonate consumes 0.96 m.equiv. of thiosulfate within 24 hours.

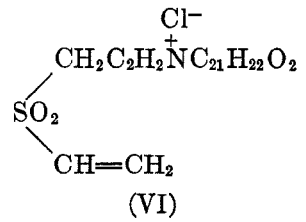
The extent of the reaction of divinyl sulfone with nicotinic acid and nicotinamide was followed electrometrically by continuous titration with acid under the same experimental conditions employed in the case of pyridine. Divinyl sulfone reacts slowly with nicotinamide at *p*H 7.5–8.0, the reaction ceasing after 14 minutes when only 0.079 m.equiv. of OH^- has been liberated. Thus, it would appear that equilibrium is established when only 4% of the theoretical quantity of OH^- is produced. When nicotinic acid is allowed to react with divinyl sulfone at *p*H 7.6–7.7, equilibrium is established when 1.14 m.equiv. of OH^- (57% of theory) are liberated.

Pyridine and its derivatives are not the only nitrogenous bases which react with divinyl sulfone. Attempts have been made to prepare the products of the reaction of divinyl sulfone with the following bases: ethyl-bis(β-chloroethyl)-amine, methyl-bis(β-chloroethyl)amine, tris(β-chloroethyl)amine, ethyldiethanolamine, methyldiethanolamine, diethanolamine, quinoline, nicotine, brucine, and strychnine. The experimental conditions were the same as or similar to those employed in the synthesis of the pyridine derivative. With the β-chloroethylamines and ethyldiethanolamine, the only crystalline compounds that could be isolated were the corresponding hydrochlorides. No crystalline products were obtained from the reaction with methyldiethanolamine, quinoline, and nicotine.

When brucine hydrochloride was treated with divinyl sulfone in alcohol, a crystalline derivative was obtained the elementary composition of which agreed with that of the expected structure (V). When strychnine hydrochloride was allowed to react with divinyl sulfone in aqueous methanol, a crystalline product (VI) was obtained.



(V)

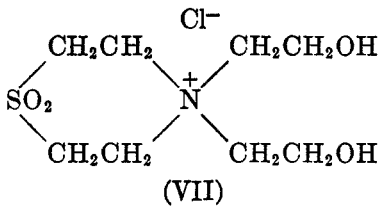


(VI)

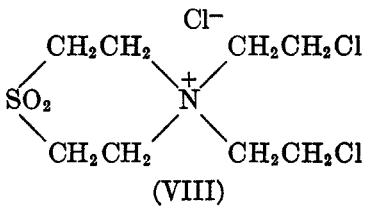
The brucine and strychnine derivatives of divinyl sulfone both were found to consume thiosulfate. The brucine derivative consumed 1.2 m.equiv., and the strychnine compound 0.65 m.equiv. of thiosulfate within 22 hours. In the case of V, the consumption of thiosulfate must be attributed to decomposition of the compound with the liberation of alkylating groups. The strychnine derivative (VI), however, still retains one vinyl group which might react with thiosulfate.

Diethanolamine hydrochloride reacts vigorously with divinyl sulfone in ethanol to form bis(β-hydroxyethyl)-1,4-thiazanium dioxide chloride (VII). The thiazanium chloride (VII) slowly liberates alkylating groups at *p*H 7.5 when treated with cysteine or thiosulfate. Within 3 hours, 0.92 *mM* of cysteine SH-groups had reacted with VII, while within 44 hours, 1.36 m.equiv. of cysteine SH-groups and 0.79 m.equiv. of thiosulfate had disappeared. The dicysteinyl derivative of divinyl sulfone was formed in the reaction of VII with cysteine.

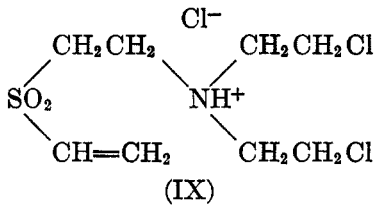
When VII was treated with thionyl chloride, a product was obtained the elementary analysis of which agrees with the expected chloro-substituted cyclic structure (VIII).



(VII)



(VIII)



(IX)

On dissolving the chlorinated product (0.02 *M*) in water, however, the *p*H falls to about 4.3, and when the solution is titrated in 80% alcohol to phenolphthalein, one equivalent of alkali is consumed. These findings suggest that the open chain isomer (IX) is present under these conditions. The product from the chlorination of VII will, therefore, be designated as β-[bis(β-chloroethyl)amino]-ethyl vinyl sulfone (IX), although its actual structure may be that represented either by VIII or by IX. The rapid reversible formation of vinyl groups from other quaternary ammonium compounds derived from divinyl sulfone would suggest that VIII would likewise readily be converted into IX.

Compound IX is of some interest since it is not only a monosubstituted derivative of divinyl sulfone, but is also a nitrogen mustard by virtue of the two β-chloroethyl groups attached to a tertiary nitrogen atom. The chlorinated product is unstable in bicarbonate-buffered solution. The data in Table IV show that Cl^- is liberated at a faster rate than H^+, indicating that hydrolysis of the chloroethyl groups proceeds through the formation of intermediate un-

TABLE IV

THE HYDROLYSIS OF β-[BIS(β-CHLOROETHYL)AMINO]ETHYL VINYL SULFONE (IX)

Concentration of reactants per cc.: 0.01 *mM* of IX; 0.10 *mM* of $NaHCO_3$.

Temperature, 25°; *p*H 8.1. The liberation of H^+ or Cl^- was followed in the manner already described (14).

TIME, MIN.	Cl^- LIBERATED PER *mM* OF IX, M.EQUIV.	H^+ LIBERATED PER *mM* OF IX, M.EQUIV.	$(Cl^-) - (H^+)$ M.EQUIV.
15	0.36	0.06	0.30
30	0.62	0.41	.21
60	0.94	0.71	.23
120	1.34	1.23	.11
240	1.48	1.36	.12
300	1.56	1.44	.12
420	1.66	1.54	.12
1440	1.76	1.73	.03
2880	1.80	1.77	.03

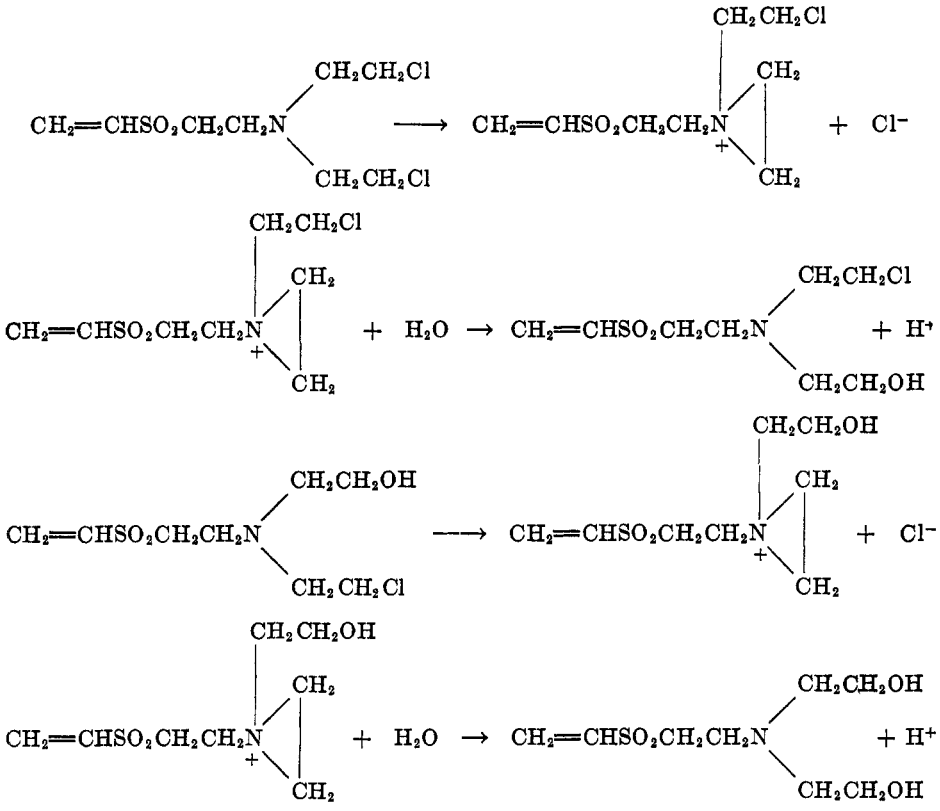


FIG. 3

stable ethylenimonium ions (Figure 3) (14). The data further indicate that the second ethylenimonium ion is more unstable than the first. Evidence for the

presence of a vinyl group in the end products of hydrolysis was gained throuhg the observation that a solution of IX, after aging for 2 days at *p*H 8.1, reacted with 0.46 m.equiv. of cysteine.

The chlorinated product (IX) readily reacts with thiosulfate, 1.32 m.equiv. of thiosulfate being consumed within 1 hour and 2.80 m.equiv. within 24 hours. The consumption of almost 3 equivalents of thiosulfate in 24 hours shows that the vinyl group and both chloroethyl groups have reacted with thiosulfate.

Ford-Moore and Lidstone (8) have reported that divinyl sulfone reacts with proline to give the crystalline betaine (X). The betaine (X) liberates alkylating groups slowly at *p*H 7.4, consuming 0.98 m.equiv. of cysteine SH-groups, and

TABLE V

THE TOXICITY OF MICE TO DERIVATIVES OF DIVINYL SULFONE

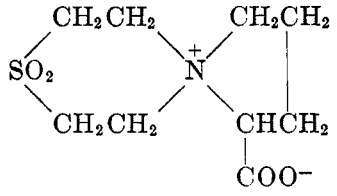
Intraperitoneal injection into sets of three mice.

COMPOUND[a]	APPROXIMATE LD_{50}
	mg./kg.
III	425
IV	200
V	80
VI	3.75
VII	875
IX	7.5[b]

[a] Bis[β-(β-hydroxyethylthio)ethyl]sulfone is non-toxic in doses of 1 g./kg. The betaine (X) is also non-toxic in doses of 1.5 g./kg.

[b] At doses below 50 mg./kg., death is delayed.

0.17 m.equiv. of thiosulfate, within 44 hours. The dicysteinyl derivative of divinyl sulfone was formed in the reaction with cysteine.

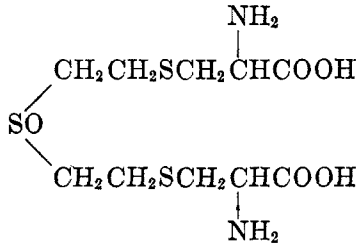


(X)

Toxicity of derivatives of divinyl sulfone. The toxicity of several derivatives of divinyl sulfone was determined by intraperitoneal injection of graded doses into sets of three mice. The results, presented in Table V, indicate that some of these compounds possess a noteworthy toxicity. This finding is not surprising in view of the ease with which many of the substances decompose under physiological conditions of *p*H and temperature to regenerate both the highly toxic divinyl sulfone, and the other component of the parent compound, which in some instances also possesses a high toxicity. It may be pointed out that chlorination of compound VII to yield IX results in over a 100-fold increase in toxicity.

Chemical reactions of divinyl sulfoxide. In contrast to H sulfone and divinyl sulfone, divinyl sulfoxide does not exhibit vesicant action. It seemed of interest, therefore, to study more closely the chemical reactions of divinyl sulfoxide, and to compare its behavior with that of divinyl sulfone.

Like divinyl sulfone, divinyl sulfoxide also reacts with the sulfhydryl group of cysteine and β-mercaptoethanol. However, these reactions are very much slower in the case of the sulfoxide than are the corresponding reactions of the sulfone. The rate of the reaction of the sulfoxide with SH groups is markedly dependent upon the *p*H of the solution. At *p*H 5.8, divinyl sulfoxide reacts within 40 minutes with only 0.43 m.equiv. of cysteine SH-groups, whereas, at *p*H 7.1, it reacts within 40 minutes with 1.05 m.equiv. and within 24 hours with 2.02 m.equiv. of cysteine SH-groups. The product formed in this reaction is bis(β-cysteinylethyl)sulfoxide (XI).



(XI)

Divinyl sulfoxide reacts with 0.06 m.equiv. of β-mercaptoethanol SH-groups within 1 hour at *p*H 5.7 and with 0.34 m.equiv. at *p*H 7.0; within 24 hours it reacts with 0.83 m.equiv. at *p*H 5.7 and with 2.04 m.equiv. at *p*H 7.0. The reaction of the sulfoxide with thiosulfate is also much slower than is that of the sulfone. Within 96 hours, divinyl sulfoxide reacts with only 0.39 m.equiv. of thiosulfate, whereas, under similar conditions, divinyl sulfone reacts with 1.90 m.equiv. of thiosulfate within 5 hours.

The data presented in Table VI show that divinyl sulfoxide also reacts with pyridine with the liberation of OH^-. However, the rate and extent of the reaction of the sulfoxide is much less than was that of the sulfone. From Table VI it would appear that at *p*H 7.5, only 0.277 m.equiv. of OH^- are liberated within 480 minutes and that equilibrium conditions are not then attained. Under comparable conditions, divinyl sulfone liberated 1.48 m.equiv. of OH^- and reached equilibrium within 14 minutes. At higher *p*H values, less OH^- is liberated by both the sulfoxide and the sulfone.

The data in Table VI suggest that the reaction of divinyl sulfoxide with pyridine, like that of divinyl sulfone, involves the addition of pyridine to the double bonds, that the reaction is reversible, and that the position of the equilibrium is influenced by the *p*H of the reaction mixture. However, definite proof for all of these contentions must await the isolation and investigation of the reaction products. Attempts to prepare bis(β-pyridiniumethyl)sulfoxide dichloride by a procedure analogous to that used to prepare the corresponding

sulfone were unsuccessful. From Table VI it would appear, however, that in the case of the sulfoxide, the equilibrium has been displaced rather far to the left, thus possibly explaining our failure to obtain the pyridinium sulfoxide.

Discussion. The experiments reported in this communication, coupled with those given in the previous paper of this series (13), indicate a striking similarity in behavior between β-substituted sulfones and β-substituted sulfonium salts. It has been demonstrated that two β-chloroethyl sulfonium salts and H sulfone all lose HCl by elimination with the formation of reactive vinyl groups. This

TABLE VI

INFLUENCE OF *p*H ON THE REACTION OF DIVINYL SULFOXIDE WITH PYRIDINE

Concentration of reactants per cc. at start of reaction: 0.05 *mM* of divinyl sulfoxide; 0.20 *mM* of pyridine.

Temperature, 25°.

The OH^- formation was followed electrometrically by adding HCl (0.1 *N* in Column 2; 0.05 *N* in Columns 3 and 4) to maintain the *p*H at the desired value.

TIME, MINUTES	OH^- PRODUCED PER *mM* OF DIVINYL SULFOXIDE AT		
1.	*p*H 7.5, M.EQUIV. 2.	*p*H 8.6, M.EQUIV. 3.	*p*H 9.7, M.EQUIV. 4.
24	0.012	0.021	0.011
48	.033	.041	.017
72	.051	.056	.021
96	.070	.072	.024
120	.086	.085	.025
144	.103	.098	.026
168	.118	.109	.026
192	.133	.119	.026
216	.150	.128	.026
240	.163	.136	.026
264	.178	.144	.026
288	.187	.152	.026
312	.200	.158	.026
336	.213	.164	
360	.224	.171	
384	.237	.175	
408	.247	.179	
432	.257	.183	
456	.266	.187	
480	.277		

elimination reaction in the case of both the sulfonium salts and H sulfone is influenced in a similar manner by changes in *p*H and by the presence of salts. Thus, the rate of elimination of HCl is markedly dependent upon *p*H, being very rapid at alkaline *p*H values, and slowing up as the *p*H falls; at acid *p*H values HCl is not formed at all. Moreover, the rate of elimination of HCl is strongly inhibited by bicarbonate.

The sulfonium salts and H sulfone appear to react readily with a number of substances to form β-substituted derivatives. It has been demonstrated, however, that chemical reaction is, in all cases, preceded by the elimination of HCl

and the formation of reactive vinyl groups. There is, in addition, a striking similarity in the behavior of the vinyl sulfonium groups and vinyl sulfone groups thus formed. This similarity is exemplified by a comparison of the properties of vinyl-1,4-dithiane sulfonium chloride with those of divinyl sulfone. Both substances react readily with pyridine in aqueous solution at *p*H 7.5 to form β-pyridinium derivatives. In both cases the reaction is reversible, and the speed of attainment of equilibrium, as well as the position of the equilibrium, is similarly influenced by *p*H. Furthermore, the pyridinium derivatives in both cases are unstable, and decompose with the formation of reactive alkylating groups which combine readily with SH groups or the amino group of alanine.

A further similarity between the properties of vinyl-1,4-dithiane sulfonium chloride and divinyl sulfone resides in the behavior of the two substances towards thiosulfate. Both react with thiosulfate at *p*H 6–8, the rate of the reaction increasing with rising *p*H and being unaffected by bicarbonate. At moderately alkaline *p*H values (*p*H 8.5–9.5), however, both thiosulfate derivatives decompose with the liberation of substances titratable with iodine.

Finally, Bartlett (15) has shown that acetic acid is eliminated from diacetylthiodiglycol methylsulfonium picrylsulfonate and also from diacetylthiodiglycol sulfone by treatment with bicarbonate solution, and that, in both cases, the resulting products consume thiosulfate.

The ready decomposition of sulfones (or sulfonium compounds) which contain a quaternary nitrogen atom in the β-position to the sulfur atom is of interest and may be compared with the usual decomposition of quaternary ammonium compounds described by Hofmann and familiarly known as the Hofmann degradation or exhaustive methylation. In the Hofmann degradation, a quaternary ammonium base decomposes under the influence of heat with scission of one of the C-N bonds and the resulting formation of a tertiary amine, an ethylenic group and water. On the other hand, the decomposition of the β-quaternary derivatives of sulfones (or sulfonium salts) occurs in aqueous solution at *p*H values near neutrality and proceeds spontaneously at room temperature with the formation of a tertiary amine, an ethylenic group and a hydrogen ion. In contrast to the Hofmann degradation, the decomposition of these sulfone (and sulfonium) derivatives is a reversible reaction and the extent of the decomposition is influenced by the *p*H.

For the general problem of vesication, it is of some interest that derivatives of divinyl sulfone (and consequently of H sulfone as well) are far more unstable than are similar derivatives of H. It is also of interest that the sulfone compounds decompose to yield reactive alkylating groups. It seems not unlikely, therefore, that *in vivo* the products of the reaction of divinyl sulfone with cellular constituents would undergo a similar decomposition. Should such a decomposition occur, it would become possible for one molecule of sulfone to react in succession with several functional groups in a cell. The sulfone residue might be handed on, so to speak, from one group to another, until it finally either reacted with some tissue component with which it formed a stable compound or was removed by the circulation

The question also may be raised as to whether the reactivity of oxidized H derivatives may play a role in the mechanism of the physiological action of H. In order to provide an experimental basis for this speculation, it is necessary to determine whether animal tissues contain enzyme systems capable of oxidizing the sulfide sulfur of H derivatives. Such an oxidation process might convert stable H residues attached to tissue constituents into unstable and reactive sulfoxide or sulfone residues. From a calculation of the energy necessary, Sugden (5) has concluded that the oxidation of H to H sulfone is unlikely to occur *in vivo*. No information has come to our attention concerning the energy required for the oxidation of H derivatives, however.

The authors would like to express their thanks to Miss Jean Grantham who assisted in carrying out many of the experiments, and to Doctor Adalbert Elek who performed the numerous microanalyses reported in this paper.

EXPERIMENTAL

Preparation of divinyl sulfone "Bunte salt" (III). Divinyl sulfone (2 cc., 20 *mM*) was added to 100 cc. of an aqueous solution containing 19.9 g. of $Na_2S_2O_3 \cdot 5H_2O$ (80 *mM*) and 1.3 g. of $NaHCO_3$ (16 *mM*). In order to prevent a rise in *p*H, CO_2 was continuously bubbled into the reaction mixture for 20 hours. The bicarbonate present in the reaction mixture was neutralized with the equivalent amount of 2 *N* HCl (28 cc.), and the solution was concentrated to dryness *in vacuo*. Last traces of water were removed by repeated concentration with absolute alcohol. The dry residue was extracted with four 100-cc. portions of hot absolute alcohol. The combined extracts were concentrated to about 50 cc. and ether was added. The crude "Bunte salt" which precipitated was recrystallized twice from absolute alcohol-ether and dried to constant weight in air; yield, 2.9 g.

Anal. Calc'd for $C_4H_8Na_2O_8S_5 \cdot 2H_2O$: C, 11.3; H, 2.8; S, 37.6; Na, 10.9; H_2O, 8.5.
Found: C, 11.3; H, 2.8; S, 37.4; Na, 11.1; H_2O, 8.4.

Bis-[β-(β-hydroxyethylthio)ethyl]sulfone. Divinyl sulfone (20 *mM*) and β-mercaptoethanol (41 *mM*) were mixed. No reaction took place until one drop of triethylamine was added, at which time a violent reaction ensued with the evolution of much heat. The mixture solidified on cooling. The solid product was recrystallized three times from absolute ethanol; yield 3.9 g.; m.p. 79–83° with sintering at 78°.

Anal. Calc'd for $C_8H_{18}O_4S_3$: C, 35. 1; H, 6.6; S, 35.05.
Found: C, 35.1; H, 6.5; S, 35.0.

Reaction of divinyl sulfone with sulfhydryl groups. The disappearance of the SH group of thiophenol was followed at 22° in a reaction mixture containing 0.049 *mM* of thiophenol, 0.028 *mM* of divinyl sulfone, and 0.0005 *mM* of added base (triethylamine, or $NaHCO_3$) per cc. The solvent was 55 % aqueous methylcellosolve. The SH consumption was followed by titration with 0.1 *N* iodine solution. The titration vessel was cooled in an ice-bath during the titration.

The rate of the reaction with cysteine and β-mercaptoethanol was followed at 25° in an aqueous reaction mixture containing 0.20 *mM* of the sulfhydryl compound and 0.05 *mM* of divinyl sulfone per cc. The solution of the sulfhydryl compound was first adjusted to the desired *p*H by adding aqueous $NaHCO_3$ solution. Ten-cc. aliquots were withdrawn and 0.05 cc. of divinyl sulfone added. After shaking to dissolve the sulfone, the reaction was quenched at the desired time by the addition of 1 cc. of *N* HCl, and the unreacted SH groups titrated as before. Parallel controls containing no divinyl sulfone were run.

Bis-(β-pyridiniumethyl)sulfone dichloride. Pyridine hydrochloride (12 g.) was dissolved in 25 cc. of absolute ethanol. To this solution were added 6 cc. of pyridine, 100 cc. of acetone, 2 drops of triethylamine, and 6 cc. of divinyl sulfone. After standing 24 hours at room temperature, the reaction mixture contained a mass of needle-like crystals. The

product (yield 5.3 g.) was recrystallized twice from methanol and acetone. The reaction mixture, on standing for 4 more days at room temperature, deposited an additional 5.6 g. of bis(β-pyridiniumethyl)sulfone dichloride.

The reaction product obtained in the manner outlined above contains about 1% of moisture even after drying at room temperature for several days over P_2O_5 *in vacuo*. The anhydrous substance, obtained by drying at 78° over P_2O_5 *in vacuo*, is hygroscopic. On drying in air at 23° and 32% relative humidity, however, the stable monohydrate is obtained; m.p 235° (dec.).

Anal. Calc'd for $C_{14}H_{18}Cl_2N_2O_2S \cdot H_2O$: C, 45.8; H, 5.5; S, 8.7; Cl^-, 19.3; H_2O, 4.9.
Found: C, 45.5; H, 5.4; S, 8.6; Cl^-, 19.0; H_2O, 5.0.

The same compound was obtained when bis(β-pyridiniumethyl)sulfide was oxidized with excess peracetic acid, thus confirming the structure of the product obtained from divinyl sulfone. Bis(β-pyridiniumethyl)sulfide dichloride [2.4 g., 7.6 *mM* (12)] was dissolved in 75 cc. of water containing 15 *mM* of peracetic acid. After standing at room temperature for 18 hours, the solution was extracted three times with ether to remove any excess peracetic acid. The aqueous layer was concentrated under reduced pressure, alcohol was added and the mixture was again concentrated. After repetition of this process, the residue crystallized upon the addition of anhydrous ethanol. It was recrystallized from 50 cc. of this solvent and dried to constant weight in air; yield 1.45 g.

Anal. Calc'd for $C_{14}H_{18}Cl_2N_2O_2S \cdot H_2O$: C, 45.8; H, 5.5; Cl^-, 19.3; H_2O, 4.9.
Found: C, 45.55; H, 5.55; Cl^-, 19.0; H_2O, 5.0.

Reaction of bis(β-pyridiniumethyl)sulfone dichloride with cysteine. Cysteine HCl (315 mg.) was dissolved in 8 cc. of 0.5 *N* $NaHCO_3$. To this solution were added 2 cc. of water and 184 mg. of bis(β-pyridiniumethyl)sulfone dichloride. The reaction mixture was kept at 25° under N_2 for 24 hours. The mixture was brought to *p*H 4 with HCl, and placed at 0°. The crystalline bis(cysteinylethyl)sulfone was filtered off; yield 157 mg., corresponding to 87% of theory.

Anal. Calc'd for $C_{10}H_{20}N_2O_6S_3$: C, 33.3; H, 5.6; NH_2-N, 7.8.
Found: C, 33.0; H, 5.5; NH_2-N, 7.9.

Bis(β-pyridiniumethyl)sulfone dipicrylsulfonate. A reaction mixture (500 cc.) was prepared containing 2.28 cc. (20 *mM*) of divinyl sulfone, 4.85 cc. (60 *mM*) of pyridine, and 7.56 g. (90 *mM*) of sodium bicarbonate. The *p*H of the solution rose from 8.3 to 8.9 within 10 minutes after dissolving the divinyl sulfone. The reaction mixture was allowed to stand for 2 hours at 25°, and a solution of 14.6 g. (40 *mM*) of picrylsulfonic acid in 100 cc. of water was then added. The mixture was cooled in an ice-bath for 1 hour, and the dipicrylsulfonate which had crystallized was collected and washed with cold water. The yield was 10.90 g., corresponding to 63% of theory. After one recrystallization from 90% methylcellosolve, the melting point was 208–210°.

Anal. Calc'd for $C_{14}H_{18}N_2O_2S \cdot 2C_6H_2N_3O_9S$: C, 36.2; H, 2.6; N, 13.0; S, 11.1.
Found: C, 36.4; H, 2.7; N, 13.1; S, 10.9.

The thiosulfate consumption of this product was measured at 25° in a solution containing 0.005 *mM* of the dipicrylsulfonate, 0.015 *mM* of $Na_2S_2O_3$, and 0.020 *mM* of $NaHCO_3$ per cc.

β-Pyridiniumethyl-β-hydroxyethylsulfone picrylsulfonate. This compound was isolated from a reaction mixture similar in composition to that employed in the preparation of bis(β-pyridiniumethyl)sulfone dipicrylsulfonate. The reaction mixture was allowed to remain at 25° for 24 hours before adding the picrylsulfonic acid. Subsequently, the mixture was concentrated under reduced pressure to about 200 cc. and cooled to 0° for 1 hour. The product crystallized during the concentration and cooling, yield 6.80 g., corresponding to 67% of theory. For recrystallization the compound was dissolved in 95% acetone and precipitated with ether; m.p. 189–190°.

Anal. Calc'd for $C_9H_{14}NO_3S \cdot C_6H_2N_3O_9S$: C, 35.4; H, 3.2; N, 11.0; S, 12.6.
Found: C, 35.4; H, 3.3; N, 11.0; S, 12.5.

The thiosulfate consumption of this producet was measured in the manner described for bis(β-pyridiniumethyl)sulfone dipicrylsulfonate.

Reaction of brucine hydrochloride with divinyl sulfone. Anhydrous brucine (3.9 g., 10 *mM*) was suspended in 5 cc. of methanol and brought into solution by the addition of 0.75 cc. of water. To this solution there was added 10 cc.of an aqueous ethanol solution (*ca.* 25%) containing 10 *mM* of HCl, 0.5 cc. (5.0 *mM*) of divinyl sulfone, and a drop of triethylamine. Crystals of the brucine derivative appeared within a half hour. After 5 hours at room temperature, the product was filtered, washed with 50% ethanol and dried in air; yield 3.6 g.; m.p. 173–175°.

Anal. Calc'd for $C_{50}H_{60}Cl_2N_4O_{10}S \cdot 4H_2O$: C, 57.1; H, 6.5; N, 5.3; S, 3.05; Cl^-, 6.7; H_2O, 6.9.

Found: C, 57.2; H, 6.6; N, 5.4; S, 3.0;Cl^-, 6.7; H_2O, 7.1.

The thiosulfate consumption of the brucine derivative was determined by shaking at room temperature a reaction mixture containing per cc.: 0.005 *mM* of the brucine compound, 0.02 *mM* of $Na_2S_2O_3$, and 0.04 *mM* of $NaHCO_3$. The unreacted $Na_2S_2O_3$ was determined after 22 hours.

Reaction of strychnine hydrochloride with divinyl sulfone. Strychnine (1 g., 3 *mM*) was added to a mixture of 40 cc. of methanol and 15 cc. of water containing 2.8 *mM* of HCl. To this solution, 1.0 cc. (10 *mM*) of divinyl sulfone was added. After 6 weeks, the crystalline product was filtered, thoroughly washed with alcohol and ether and dried over P_2O_5; yield 0.90 g.

The compound was recrystallized from hot aqueous methanol and digested in chloroform to remove any traces of strychnine. For analysis, it was dried at 100° *in vacuo* over P_2O_5. For the water determination, the substance was dried at 146° *in vacuo* over P_2O_5.

Anal. Calc'd for $C_{25}H_{29}N_2O_4S \cdot 1/2\ H_2O$: C, 60.3; H, 6.1; N, 5.6; S, 6.4; Cl^-, 7.1; H_2O, 1.8.

Found: C, 60.15; H, 6.46; N, 5.6; S, 6.3; Cl^-, 6.9; H_2O, 2.2.

The thiosulfate consumption was determined by titrating the thiosulfate unreacted after 22 hours in a reaction mixture containing per cc.: 0.05 *mM* of the strychnine derivative and 0.01 *mM* of $Na_2S_2O_3$.

Bis(β-hydroxyethyl)-1,4-thiazanium dioxide chloride (VII). Divinyl sulfone (5.0 cc., 50 *mM*) and a few drops of triethylamine were added to a solution of 16.5 g. (157 *mM*) of diethanolamine in 25 cc. of 4 *N* ethanolic HCl. The reaction mixture became warm and crystals appeared. After 2 days, 20 cc. of acetone was added to the reaction mixture and the crystalline product was filtered and washed with alcohol; yield 7.7 g. (60% of theory); m.p. 200°.

Anal. Calc'd for $C_8H_{18}ClNO_4S$: C, 37.0; H, 7.0; S, 12.3; Cl^-, 13.7.

Found: C, 36.8; H, 6.9; S, 12.3; Cl^-, 13.8.

The reaction of VII with cysteine and thiosulfate was followed at 25° by titrating the unreacted reducing substances with iodine in a reaction mixture containing per cc.: 0.05 *mM* of VII, 0.20 *mM* of cysteine or $Na_2S_2O_3$, and 0.20 *mM* of $NaHCO_3$.

β-[Bis(β-chloroethyl)amino]ethyl vinyl sulfone hydrochloride (IX). To 3 g. (11.5 *mM*) of VII, was added 15 cc. of thionyl chloride. After standing for 1 day at room temperature, the reaction mixture was evaporated under reduced pressure to remove excess thionyl chloride; the crystalline residue was washed with dry ether and recrystallized from methanol-ether; yield 3 g. (88% of theory).

Anal. Calc'd for $C_8H_{16}Cl_3NO_2S$: C, 32.4; H, 5.4; N, 4.7; S, 10.8; Cl^-, 11.95.

Found: C, 32.4; H, 5.7; N, 4.5; S, 10.7; Cl^-, 11.85.

The reaction of IX with thiosulfate was followed in a manner similar to that employed in the case of VII except that the reaction mixture contained per cc.: 0.05 *mM* of IX, 0.40 *mM* of $Na_2S_2O_3$, and 0.40 *mM* of $NaHCO_3$. The *p*H was maintained at 7.4 by bubbling CO_2 into the reaction mixture.

Reaction of divinyl sulfone with proline. To 4.6 g. (40 *mM*) of *l*-proline dissolved in 50 cc. of absolute methanol and 40 cc. of absolute ethanol, were added 4 cc. (40 *mM*) of divinyl sulfone and 3 drops of triethylamine. The mixture was allowed to stand at room temperature for 3 days and placed at 0° for 4 hours. The crystalline material was filtered off and recrystallized by solution in 4 cc. of water and precipitation with 50 cc. of hot absolute ethanol; yield 4.2 g. The substance was air dried for analysis.

Anal. Calc'd for $C_9H_{15}NO_4S$: C, 46.3; H, 6.5; N, 6.05.
Found: C, 46.1; H, 6.5; N, 6.0.

Ford-Moore reports the betaine (X) to contain water of crystallization. The substance prepared by us was anhydrous, however.

The reaction of X with cysteine at 25° and *p*H 7.4 was followed as described above using a reaction mixture containing per cc.: 0.05 *mM* of X, 0.20 *mM* of cysteine, and 0.20 *mM* of $NaHCO_3$. For the reaction with thiosulfate, a reaction mixture containing 0.10 *mM* of X, 0.20 *mM* of $Na_2S_2O_3$, and 0.40 *mM* of $NaHCO_3$ per cc. was employed.

Reaction of divinyl sulfoxide with sulfhydryl groups. The divinyl sulfoxide used in these studies was prepared by the method of Alexander and McCombie (4). Its reaction with cysteine, β-mercaptoethanol, and thiosulfate was carried out under the same experimental conditions employed in the case of divinyl sulfone.

Bis(β-cysteinylethyl)sulfoxide (XI). Divinyl sulfoxide (0.47 cc., 5.0 *mM*) was added to 100 cc. of a solution containing 3.14 g. (20 *mM*) of cysteine hydrochloride and 3.12 g. (37.5 *mM*) of $NaHCO_3$. The reaction mixture was allowed to stand under N_2 for 48 hours. Bis-(β-cysteinylethyl)sulfoxide separated from the reaction mixture, was washed with water, and dried. The mother liquors were acidified to *p*H 4.0 with *N* HCl (16 cc.) and concentrated under reduced pressure to 30 cc. The concentrate was cooled to 4° for 12 hours, and a second crop of the product was collected. The total yield was 0.76 g., corresponding to 44% of theory. The crude product was recrystallized for analysis by dissolving in concentrated ammonium hydroxide and allowing the ammonia to volatilize slowly.

Anal. Calc'd for $C_{10}H_{20}N_2O_5S_3$: C, 34.9; H, 5.9; S, 28.0.
Found: C, 35.3; H, 5.8; S, 28.4.

Reaction of divinyl sulfoxide with alanine. The reaction of divinyl sulfoxide with alanine at 25° was followed by measuring the decrease in amino nitrogen by the Van Slyke nitrous acid method in a reaction mixture containing 0.05 *mM* of divinyl sulfoxide, 0.15 *mM* of alanine, and 0.20 *mM* of $NaHCO_3$ per cc.

NEW YORK, N. Y.

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[a] Unpublished data obtained in Great Britain.
[b] Unpublished data obtained in the United States.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

THE PREPARATION OF 1,3-DIAMINO-2-METHYLAMINOPROPANE AND 1,3-DIAMINO-2-AMINOMETHYLPROPANE[1]

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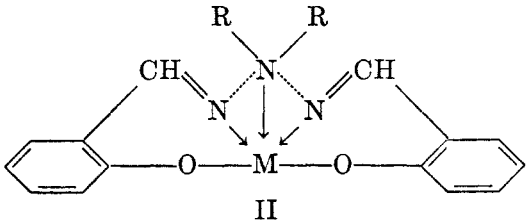
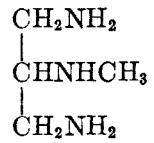
In a study of metallic chelate compounds related to those of salicylaldehyde ethylenediimine (I), one of the modifications in the structure of I which was studied was that resulting from the use of polyamines other than ethylenediamine. It was of particular interest to prepare Schiff's bases similar to I but in which a third coordinating group was present to form a fifth coordination bond with the metal in the final complex (II); *e.g.:*



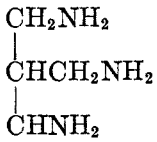
II

In II the dotted lines represent the remainder of the organic part of a triamine, and M represents the metal atom.

Among the substances tested in this way are two new triamines, 1,3-diamino-2-methylaminopropane (III) and 1,3-diamino-2-aminomethylpropane (IV).



III



IV

In III, the methylated amino group in the center of the chain was necessary to direct the condensation with salicylaldehyde to the formation of a single symmetrical Schiff's base; if 1,2,3-triaminopropane had been used a mixture of two Schiff's bases would probably have been formed. In the case of IV, Schiff's base formation with salicylaldehyde and any two of the three amino groups will give a symmetrical diimine.

1,3-Diamino-2-methylaminopropane (III) was prepared by treating 1,3-diacetaminoacetone with nitromethane in the presence of hydrogen and platinum oxide, according to a procedure devised by Emerson (1) for use with other carbonyl compounds.

1,3-Diamino-2-aminomethylpropane (IV) was prepared by the degradation of

[1]The work described in this paper was carried out as part of a program of research under Division 11, Section 1, of the National Defense Research Committee, under a contract with the University of California.

methanetriacetic acid, both the Curtius and the Schmidt-von Braun procedures being tried. In neither case was the yield of desired product good, numerous by-products being formed. Structures have been suggested for two of these (one is strictly speaking an intermediate and not a useless side product); these results are described in the experimental part. Due to the exigencies of the program under which this work was carried out a complete investigation of all of the products from these reactions could not be made.

EXPERIMENTAL

Bis-isonitrosoacetone. The method of Pechmann (2) was used, our yields being comparable to those reported by him and considerably better than those obtained by Dey (3).

A solution of 150 g. of crude acetonedicarboxylic acid (4) in 275 ml. of water was cooled in an ice-salt bath. A solution of 100 g. of sodium nitrite in 200 ml. of water was added slowly, with stirring, keeping the reaction mixture below 0°. The solid was filtered immediately, after previous cooling to −5°, and washed with small portions of ice-water. An additional amount was obtained by adding 200 ml. of cold 6 *N* nitric acid to the filtrate. The white product was washed with four small portions of ice-water and dried over sulfuric acid in a vacuum desiccator. It weighed 59 g. (51%) and decomposed at 133°.

Diaminoacetone dihydrochloride. The procedure of Koessler and Hanke (5) was used, a yield of 75 g. (60%) of the dihydrochloride being obtained from 91 g. of bis-isonitrosoacetone.

Diacetylaminoacetone. The procedure of Franchimont and Friedmann (6) was followed, crude diaminoacetone dihydrochloride being used. The purified (from ethanol as white plates) diacetaminoacetone, obtained in 39% yield, melted at 195–198°. Higher yields could probably be obtained starting with pure dihydrochloride [*cf.* Mann (7)].

Tribenzoyl-2-methylamino-1,3-diaminopropane. A solution of 5.0 g. of diacetaminoacetone, 3 g. of nitromethane, and 0.1 g. of Adams' catalyst in a mixture of 6 ml. of acetic acid and 150 ml. of ethanol was shaken for two hours under 2–3 atmospheres of hydrogen. The solution was filtered, made basic with sodium hydroxide and the alcohol removed by distillation. The residue was made strongly acid by the addition of 40 ml. of 12 *N* hydrochloric acid, and heated for 30 minutes at 100°, and evaporated to dryness in a vacuum. The residual salt was dissolved in 50 ml. of water and benzoylated with excess benzoyl chloride and 6 *N* sodium hydroxide. The oily benzoyl derivative crystallized upon the addition of ether. Recrystallized from aqueous alcohol, it formed coarse white prisms (7.2 g.; 59%) m.p. 156–156.5°.

Anal. Calc'd for $C_{25}H_{23}N_3O_3$: C, 72.3; H, 6.1.
Found: C, 72.4; H, 5.9.

1,3-Diamino-2-methylaminopropane trihydrochloride. A suspension of 37.5 g. of the benzoyl derivative in 300 ml. of conc'd hydrochloric acid was boiled under reflux in a stream of gaseous hydrogen chloride. The solid gradually dissolved, and after 8 hours the solution was cooled. The benzoic acid which separated was removed and the filtrate was diluted somewhat and extracted thoroughly with ether. Evaporation of the aqueous solution to dryness yielded 13 g. of a white, non-hygroscopic powder. After drying over phosphorus pentoxide at 100° and 20 mm. it was analyzed for chlorine:

Anal. Calc'd for $C_4H_{16}Cl_3N_3$: Cl, 42.7. Found: Cl, 43.2, 43.5.

The hydrochloride was dissolved in alcohol and precipitated by the addition of ether. It was obtained as a white, crystalline powder, m.p. 178°.

Anal. Calc'd for $C_4H_{16}Cl_3N_3$: C, 22.6; H, 7.6.
Found: C, 22.3; H, 7.5.

Treatment of the trihydrochloride with benzoyl chloride and alkali gave the tribenzoyl derivative, identical with the compound described above.

1,3-Diamino-2-aminomethylpropane

I. The Curtius degradation of methanetriacetic acid. Methanetriacetic acid was prepared

according to the method of Kohler and Reid (8), from dimethyl glutaconate and cyanoacetic ester. It was esterified in 80% yield by the usual procedure, using methanol and sulfuric acid.

The degradation of the acid through the hydrazide and azide was carried out along the lines of the procedure used by Curtius and Hesse (9) for preparing 1,2,3-triaminopropane from tricarballylic acid.

Methanetriacethydrazide. A solution of 8.8 g. of trimethyl methanetriacetate in a mixture of 20 ml. of absolute alcohol and 6.8 g. of 85% hydrazine hydrate was refluxed for 16 hours. Solid began to separate immediately and increased in amount as the reaction proceeded. The mixture was cooled and the solid was collected, washed with alcohol, and dried in a vacuum desiccator over sulfuric acid. The yield was 8.3 g. of a product sufficiently pure for conversion into the hydrochloride.

The trihydrazide crystallized from aqueous alcohol as rosettes of colorless needles; m.p. 246°, with gas evolution.

Anal. Calc'd for $C_7H_{16}O_3N_6$: C, 36.20; H, 6.94; N, 36.19.
Found: C, 36.48; H, 7.08; N, 35.20.

Methanetriacethydrazide trihydrochloride. A suspension of 15.3 g. of the trihydrazide in 75 ml. of water was cooled in an ice-bath and saturated with hydrogen chloride. The hydrazide first dissolved completely and as saturation proceeded crystals began to appear in the solution. After 30 minutes at 0°, 700 ml. of ethanol was added, and after allowing the mixture to stand at 0° for another 30 minutes it was filtered. The product (22.5 g., quantitative yield) was converted into the azide without further purification.

A sample purified by the addition of alcohol to a saturated aqueous solution of the hydrochloride, discarding the first crop of crystals, melted at 204° with gas evolution.

Anal. Calc'd for $C_7H_{19}Cl_3N_6O_3$: C, 24.60; H, 5.61.
Found: C, 24.64; H, 5.83.

Methanetriacetazide. To a solution of 14.7 g. of the trihydrazide trihydrochloride in 50 ml. of water was added 200 ml. of ether and, with stirring and cooling in an ice-bath, a solution of 8.92 g. of sodium nitrite in 15 ml. of water. After the addition was completed (7 minutes), stirring was continued for 15 minutes longer, with continued cooling. The ether layer was separated and the aqueous portion extracted with two 100-ml. portions of ether. The combined ether solutions were shaken with anhydrous calcium chloride (at 0°), filtered from the drying agent and used immediately.

A small portion of the ether solution was evaporated in a stream of air, leaving a viscous, colorless oil. This substance exploded with a loud report when warmed in a flame.

The reaction of methanetriacetazide with absolute alcohol. (A) A dry ether solution of the triazide from 14.7 g. of the trihydrazide hydrochloride was added to 200 ml. of absolute alcohol contained in a flask arranged for distillation. The ether was removed at a bath temperature of 50–60° over a period of two hours, nitrogen being evolved during this time. The bath temperature was then slowly raised to 90° and most of the alcohol distilled off, and final traces of volatile materials were removed by heating at 70° under a pressure of 2 mm. A viscous, brown-yellow oil remained, wt. 5.2 g. Upon shaking this oil with ether most of it crystallized. The solid was separated and recrystallized from alcohol-ether, from which it formed colorless needles, m.p. 110–111.5° (1.7 g.). A portion purified for analysis melted at 113.5–114.5°.

Anal. Calc'd for $C_{21}H_{40}N_6O_9$: C, 48.45; H, 7.74.
Found: C, 47.99, 47.93, 47.80; H, 7.41, 7.72, 7.83.

The analytical figures correspond best to the compound $CO[NHCH_2CH(CH_2NHCOOC_2H_5)_2]_2$.

(B) The viscous oil from which the compound, m.p. 113.5–114.5°, was isolated, was hydrolyzed directly in subsequent runs. The total of this oil resulting from two runs of 19.8 g. and 14.1 g. of triazide was refluxed for 20 hours with 200 ml. of concentrated hydrochloric acid. After filtration from a trace of tar the solution was evaporated to dryness *in vacuo*. A total of 10.7 g. of light-colored crystals was obtained. Recrystallized (charcoal) from water-ethanol, this yielded 4.7 g. of pure triamine trihydrochlorice.

The purified 1,3-diamino-2-aminomethylpropane *trihydrochloride* formed colorless needles, m.p. over 300°.

Anal. Calc'd for $C_4H_{16}Cl_3N_3$: C, 22.60; H, 7.59.
Found: C, 22.46; H, 7.62.

The *picrate* formed orange-yellow needles from water, which were apparently those of a trihydrate. Upon heating, the color changed from orange-yellow to pale yellow as the temperature was raised above 110°. A fresh sample placed in a bath at 150° melted, then solidified and remelted at 224°.

Anal. Calc'd (for trihydrate) $C_{22}H_{22}N_{10}O_{21}\cdot 3H_2O$: C, 32.35; H, 3.45.
Found: C, 32.40; H, 3.18.

Tris(benzoylaminomethyl)methane. The tribenzoate formed colorless needles, m.p. 221.5–222°. It showed no depression in m.p. when mixed with a sample (analyzed) prepared from triamine obtained by the Schmidt-von Braun method (see below).

II. The Schmidt-von Braun degradation of methanetriacetic acid. The procedure was patterned after that used by Buchman, *et al.* (10), with *cis-* and *trans*-1,2-cyclobutanecarboxylic acids. The principal products obtained were the dibenzoate of 1,3-diaminopropane-2-acetic acid, and the tribenzoate of the desired triamine. Small amounts of other substances, not identified, were also isolated.

The reaction of methanetriacetic acid with hydrazoic acid. Into a 500-ml., 3-necked flask, equipped with a dropping-funnel, stirrer, and thermometer, was placed 25 g. of methanetriacetic acid. Fifty ml. of concentrated sulfuric acid was added slowly, keeping the temperature below 40°. A solution of hydrazoic acid in chloroform was prepared from 45 g. of sodium azide; it contained 23.2 g. of hydrazoic acid (by titration). This solution was added over a period of three hours, maintaining the temperature at 35–40° by intermittent cooling with an ice-bath. Gas evolution began almost at once. Stirring was continued at 40° for twenty hours, at the end of which gas evolution had ceased. The reaction mixture was cooled to 0°, poured onto ice and, after separating a small amount of solid, the chloroform layer separated and discarded. The aqueous phase was freed of chloroform and hydrazoic acid by steam distillation and refluxed further for twenty-two hours.

The reaction mixture was made basic by the addition of 155 g. of potassium hydroxide (inorganic salts were removed by filtration) and to the solution was slowly added, with stirring, 83.5 g. of benzoyl chloride. The mixture was heated to 90° over forty-five minutes, cooled, and the whole shaken well with 400 ml. of ether. A white, ether-insoluble material was collected (4.5 g.) and the ether layer separated and dried over magnesium sulfate. A further portion of ether-insoluble material separated (1.0 g.). Concentration of the ether solution to 100 ml. and cooling yielded 5.7 g. of crystalline material.

Recrystallization of these combined crops from absolute alcohol yielded a total of 5.3 g. of pure tris(benzoylaminomethyl)methane, m.p. 222–222.5°.

Anal. Calc'd for $C_{25}H_{25}N_3O_3$: C, 72.57; H, 6.07.
Found: C, 72.53; H, 6.12.

Also isolated from this solution were two unidentified substances:

(A) Long, colorless needles, m.p. 240–241°.
Found: C, 70.09, 70.52; H, 5.26, 5.24.

(B) Colorless needles from alcohol, m.p. 161.5–162°.
Found: C, 69.48; H, 4 79.

Acidification of the alkaline aqueous layer yielded a yellowish, oily solid which, when shaken with ether, yielded 19.0 g. of white crystalline material. This contained some inorganic salts, and from it was isolated by crystallization from absolute alcohol 12.0 g. of colorless needles, m.p. 161.5–162°.

Anal. Calc'd for $(C_6H_5NHCH_2)_2CH\ CH_2COOH$: C, 67.07; H, 5.92.
Found: C, 66.97; H, 5.87.

The tribenzoyl derivative of the desired triamine could be hydrolyzed to the triamine trihydrochloride in theoretical yield by heating it with conc'd hydrochloric acid in a sealed tube at 150°.

SUMMARY

The preparation of 1,3-diamino-2-methylaminopropane and 1,3-diamino-2-aminomethylpropane has been described.

LOS ANGELES 24, CALIF.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

THE SYNTHESIS OF SOME INTERMEDIATES FOR USE IN THE PREPARATION OF ANALOGS OF SALICYLALDEHYDE ETHYLENEDIIMINE COBALT ("SALCOMINE")[1]

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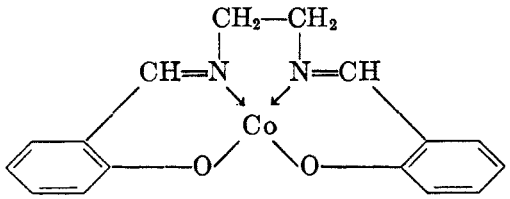
As part of a study having for its object the examination of the oxygen-carrying properties of chelate compounds of the type exemplified by salicylaldehyde ethylenediimine cobalt ("Salcomine") (I)



I

a large number of substances were prepared and tested in an effort to determine the structural requirements for activity and to discover chelates with oxygen-carrying properties superior to those of I. Among the practical improvements sought were (a) greater stability than Salcomine in repeated passage through the cycle of oxygenation and deoxygenation; (b) greater oxygen capacity (over the capacity of one atom of oxygen per mole of chelate possessed by Salcomine); and (c) increased rates of oxygenation and deoxygenation under conveniently attainable temperature and pressure conditions.

In pursuing these objectives modifications were made in the structure of I by using polyamines other than ethylenediamine, using substituted salicylaldehydes or other substances of related structures, and using other metals in place of cobalt. Most of the substances used in preparing the many analogs of I studied were well-known compounds, many of them prepared in this laboratory by established methods.[2] In a number of cases, however, compounds hitherto unreported were required. The syntheses of a number of these are described in this paper.

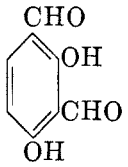
One of the ends sought in this work was to increase the proportion of metal in the complexes and thus to increase the percentage yield of oxygen obtained when these substances are used as reversible oxygen carriers. One of the possible means to this end was to use in place of salicylaldehyde compounds containing two *o*-hydroxyaldehyde groupings per benzene nucleus. Only one such com-

[1] The work described in this paper was carried out as part of a program of research under Division 11, Section 1, of the National Defense Research Committee, under a contract between the Office of Scientific Research and Development and the University of California.

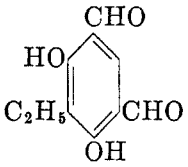
[2] All of the final chelate compounds were prepared and tested in other laboratories, with which we collaborated. Presumably much of this work will be reported elsewhere.

pound, resorcinol-2,4-dialdehyde (II) has been described previously (1, 2), and another representative of this class of compounds has been prepared in the present work. The new compound, 2,4-dihydroxy-3-ethylisophthalaldehyde (III) differs from I in that it possesses a symmetrical, and not vicinal, arrangement of the hydroxyl and aldehyde functions.

2,4-Dihydroxy-3-ethylisophthalaldehyde was prepared by the formylation of 2-ethylresorcinol, chloromethylation of the dimethyl ether of the latter, conversion of the chloromethyl group to a formyl group (by two methods), and finally demethylation.



II



III

While it would have been desirable to prepare the more immediate analog of II, lacking the ethyl group, the presence of a group at the 3-position was necessary to direct the entering chloromethyl group to the 5-position in 2,4-dimethoxy-3-ethylbenzaldehyde. The ethyl group was chosen because of the ready availability of 2-ethylresorcinol (3, 4).

In preparing II for tests of chelates derived from it, it was found impossible to duplicate the yield of 25% reported by Shoesmith and Haldane (1). After a study of the condensation of resorcinol and diphenylformamidine it was found possible to obtain reproducible yields of 14%, but no higher yield was obtained in any of numerous experiments.

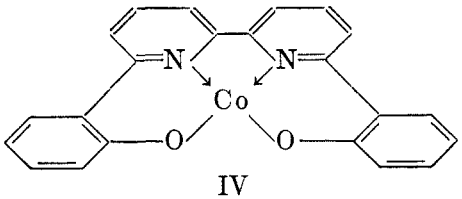
Since the degradation of Salcomine, when it is used as a reversible oxygen carrier, takes place at least in part as a result of oxidative attack on the salicylaldehyde nucleus, it was hoped that the use of a heterocyclic *o*-hydroxyaldehyde would permit the formation of an active but more stable cobalt complex. Experiments along this line were carried far enough to indicate that complexes containing such heterocyclic substances were devoid of oxygen-carrying activity.

Because of the limitations imposed by the exigencies of the program only a limited number of the possible avenues of approach to compounds of the type sought could be explored. Two methods were examined, and led to a sufficient number of substances for testing as chelates with ethylenediamine and cobalt. In view of the lack of oxygen-carrying ability in the compounds studied in these preliminary tests, the work was not extended further.

The most direct approach to the preparation of heterocyclic *o*-hydroxyaldehydes appeared to be the use of the Reimer-Tiemann reaction with suitable hydroxy compounds. Conrad and Limpach (5) have reported the preparation of 3-formyl-4-hydroxyquinaldine by this method, and in the present work this method was extended to the preparation of other 3-formyl-4-hydroxyquinaldines. Attempts to introduce a formyl group by this procedure into 4-hydroxypyridine and 4-hydroxy-2,6-dimethylpyrimidine were unsuccessful.

A second method investigated was the MacFayden-Stevens reaction (6, 7) starting from heterocyclic *o*-hydroxycarboxylic acids. This method proved of value in one case, and by its means was prepared 2-hydroxy-3-formyl-4,6-dimethylpyridine. An attempt to prepare in this way a 4-hydroxy-5-formyl-2-methylpyrimidine failed.

A number of compounds were prepared in which the role of the Schiff's-base nitrogen atoms in I was filled by the nitrogen atoms of heterocyclic nuclei. The substances chosen for study were 2-*o*-hydroxyphenylpyridine, 2-*o*-hydroxyphenylquinoline, 1-*o*-hydroxyphenylisoquinoline and 6,6′-bis-(*o*-hydroxyphenyl)-2,2′-dipyridine (IV). The latter compound was of special interest because the cobalt complex prepared from it closely resembles I in its molecular architecture.

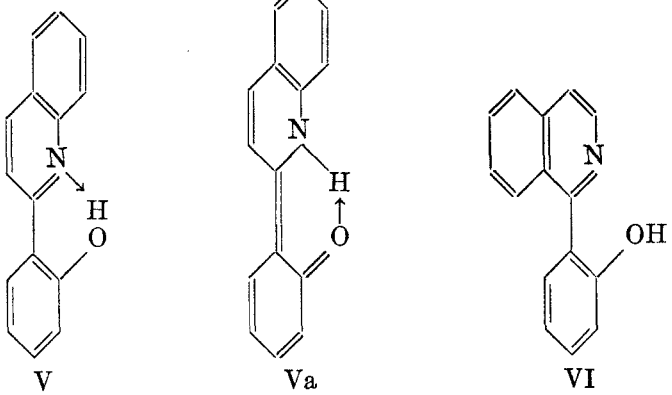


IV

This close resemblance is strikingly shown by the close similarity between molecular models (Stuart) of I and IV.

All of these substances were prepared by the addition of *o*-methoxyphenyllithium to the appropriate nitrogen heterocycle, followed by oxidation of the first-formed dihydro compound with nitrobenzene and demethylation with hydrobromic acid.

It is interesting to note that while 2-*o*-hydroxyphenylquinoline (V) is yellow, 1-*o*-hydroxyphenylisoquinoline (VI) is a colorless compound. Since the color of the first can be ascribed to the participation of resonance forms arising from Va, the isoquinoline derivative is probably inhibited from undergoing this kind of resonance by the steric interference of the 8-position of the heterocyclic nucleus.



V Va VI

An additional observation made in the course of these studies is worthy of comment. When phenyllithium was added to pyridine and to quinoline under

mild conditions and the products isolated without an intermediate oxidation by nitrobenzene, attempts to prepare picrates of the dihydro compounds thus prepared resulted in the production of picrates of the fully aromatic compounds; and the solutions in which picrate formation was taking place acquired intense red colorations during the course of the reactions. Treatment of the previously aromatized (by nitrobenzene) compounds with picric acid yielded the same picrates as were produced from the dihydro compounds, but no unusual colorations appeared in the solutions. Bergmann, Blum-Bergmann, and v. Christiani (8) reported that the reaction of phenyllithium with isoquinoline yielded what they considered to be 1-phenylisoquinoline, m.p. 80°, which formed a picrate, m.p. 165°. Ziegler and Zeiser (9), on the other hand, treated the product from the reaction of phenyllithium and isoquinoline with nitrobenzene and obtained what was probably 1-phenylisoquinoline, m.p. 97°. It appears likely that Bergmann's compound, m.p. 80°, was 1-phenyl-1,2-dihydroisoquinoline, and that his picrate was that of 1-phenylisoquinoline.

EXPERIMENTAL

Resorcinol-2,4-dialdehyde. The following experiments are typical of a number that were run in attempts to obtain the yield of 25% reported for this compound (1). Method B was found to give yields of 14% in larger runs than the one described.

A. A mixture of 5.0 g. of resorcinol and 9 g. of diphenylformamidine was heated to 175° for 15 minutes. The melt was cooled somewhat and poured into 50 ml. of 6 *N* sodium hydroxide and the mixture steam distilled until no more aniline came over. The residue was acidified and steam distillation was resumed until no more solid came over. The resinous residual material was removed, boiled for 10 minutes with 6 *N* sodium hydroxide, acidified and again subjected to steam distillation. The solid product in the distillate was collected and dried. The yield was 0.65 g. (9%) of nearly pure dialdehyde.

B. After the fusion of 5.0 g. of resorcinol and 9.0 g. of diphenylformamidine as described above, 100 ml. of alcohol was added to the cooled melt and the mixture boiled for several minutes. The insoluble residue (a), the material which separated from the solution on cooling (b), and the material precipitated by dilution of the filtrate (c) were separately boiled with 50 ml. of 6 *N* sodium hydroxide, acidified, and steam distilled.

Dialdehyde was obtained from (c) only, 1.17 g. (14%) being isolated from the steam distillate. The compound crystallized from dilute alcohol as soft, yellowish-white needles, m.p. 127–128° [reported (1), 126°].

Anal. Calc'd for $C_8H_6O_4$: C, 57.9; H, 3.6.
Found: C, 57.8; H, 3.8.

2-Ethylresorcinol was prepared by the method described by Russell (3, 4).

2-Ethyl-4-resorcylaldehyde. A stirred mixture of 10.2 g. of 2-ethylresorcinol, 12.0 g. of zinc cyanide, and 150 ml. of dry ether was saturated with dry hydrogen chloride. The gas stream was discontinued 30 minutes after saturation, the ether layer decanted, and the solid residue boiled with 150 ml. of water. Sufficient alcohol was added to the hot solution to bring about complete solution, and on cooling a first crop of 4.8 g. of product separated. An additional 5.3 g. was obtained from the mother liquor. The total yield (10.1 g.) was 75% of material melting at 118.5–120° [reported (10) 115–118°]. Yields of 74–80% were obtained in other runs.

2-Ethyl-4-resorcylaldehyde dimethyl ether. To a well-stirred solution of 4.5 g. of 2-ethyl-4-resorcylaldehyde in 25 ml. of methanol were added alternately in small portions a solution of 50 g. of potassium hydroxide in 300 ml. of water, and 60 ml. of dimethyl sulfate. Refluxing was maintained during the addition. After acidification, the methanol was removed

by distillation and the residue extracted with ether and the ether solution washed with dilute alkali. Removal of the ether left 4.1 g. (81%) of the dimethyl ether, m.p. 58–59.5°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2; OCH_3, 32.0.
Found: C, 67.6; H, 7.4; OCH_3, 31.8.

In another run, there was also isolated the monomethyl ether, 3-ethyl-4-methoxysalicylaldehyde, m.p. 47–48°, from petroleum ether.

Anal. Calc'd for $C_{10}H_{12}O_3$: OCH_3, 17.2. Found: OCH_3, 16.9.

2,4-Dimethoxy-3-ethyl-5-chloromethylbenzaldehyde. A mixture of 13.5 g. of 2-ethyl-4-resorcylaldehyde dimethyl ether, 27 ml. of 40% formalin and 10 g. of zinc chloride was stirred vigorously while hydrogen chloride was passed in. Sufficient external heat was applied to keep the mixture refluxing. After 90 minutes the mixture was poured onto ice and the oil which separated taken up in ether. The solution was washed thoroughly with sodium bicarbonate solution and water, dried, and the ether removed. Distillation of the residual oil gave 14.4 g. (92%) of material boiling at 166–166.5°/4 mm., which solidified on standing. A sample recrystallized from dilute alcohol formed stout white needles, m.p. 49–50°.

Anal. Calc'd for $C_{12}H_{15}ClO_3$: C, 59.4; H. 6.2; OCH_3, 25.6.
Found: C, 59.2; H, 6.5; OCH_3, 25.4.

4,6-Dimethoxy-5-ethylisophthalaldehyde. (A) A mixture of 14.5 g. of the chloromethyl compound, 21 g. of hexamethylenetetramine, 150 ml. of alcohol, and 50 ml. of water was refluxed for 3 hours. The alcohol was evaporated, 50 ml. of 6 *N* sulfuric acid added, and the mixture extracted with ether. From the ether extract there was obtained, after recrystallization from dilute alcohol and then from ligroin, 4.7 g. (35%) of the dialdehyde, m.p. 96–97°.

(B) The chloromethyl compound (23.0 g.) was converted to the acetoxymethyl derivative by refluxing it for 18 hours with 25 g. of anhydrous potassium acetate in 140 ml. of glacial acetic acid. The solvent was removed under reduced pressure, the residue mixed with water and neutralized with potassium carbonate and the acetoxymethyl aldehyde extracted with ether. Removal of the ether left 25 g. of crude acetoxymethyl compound, which was converted directly into the carbinol by treatment for 30 min. with 200 ml. of methanol containing about 0.05 mole of sodium methoxide. There was obtained 21.5 g. of the crude carbinol.

The carbinol was added slowly to 250 ml. of concentrated nitric acid (11). The temperature rose to 50°; after 15 minutes the solution was poured into 750 ml. of ice-water. The solid which separated was collected, washed with sodium bicarbonate solution and with water. Ether extraction of the aqueous solution afforded an additional amount. The dialdehyde (9.4 g.; 45%) was crystallized from alcohol; m.p. 95–96°.

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.4; OCH_3, 27.9.
Found: C, 64.8; H, 6.5; OCH_3, 27.8.

4,6-Dihydroxy-5-ethylisophthalaldehyde. A mixture of 12.0 g. of 4,6-dimethoxy-5-ethylisophthalaldehyde, 40 ml. of 48% hydrobromic acid, and 40 ml. of water was boiled under reflux for 4 hours. The solution was poured onto ice, made alkaline, and washed with ether to remove undemethylated material, then acidified and the oil which separated taken up in ether. The crude material, obtained on removal of the ether, was purified by sublimation at 145–150°/3–4 mm. The product formed nearly colorless prisms, m.p. 104–106°; yield, 7.0 g. (67%).

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.9; H, 5.3; OCH_3, 0.00
Found: C, 61.5; H, 5.3; OCH_3, 0.2.

3-Cyano-4,6-dimethyl-2-pyridone was prepared by he method of Bardhan (12).

Ethyl, 4-6-dimethyl-2-pyridone-3-carboxylate was prepared according to Simonsen and Naik (13). The yields in this reaction left much to be desired, and it was deemed preferable to proceed to the hydrazide through the hydrolysis of 3-cyano-4,6-dimethyl-2-pyridone to the amide (14), followed by treatment of the amide with hydrazine as detailed below.

4,6-Dimethyl-2-pyridone-3-carboxhydrazide. (A) From the ester: A solution of 4.35 g. of ethyl 4,6-dimethyl-2-pyridone-3-carboxylate in 5 ml. of 85% hydrazine hydrate was refluxed for three hours. A clear solution resulted when the solution was first heated to

150°, but after about one and one-half hours a precipitate began to appear. To the cooled reaction mixture was added 10 ml. of absolute alcohol, the lumps were crushed and the solid collected. The mother liquor was distilled with xylene until the water was removed, the solid residue collected and washed with absolute alcohol.

The total yield was 3.5 g. (86%). The hydrazide crystallized from absolute alcohol as soft, white needles, m.p. 239–240°.

Anal. Calc'd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12.
Found: C, 53.18; H, 6.22.

(B) From the amide: The direct replacement of $-NH_2$ by $-NHNH_2$ was found to occur satisfactorily. Although it was difficult to prepare pure hydrazide by this method it was found easy to prepare a pure sample of the benzenesulfonyl derivative of the hydrazide from a sample contaminated with amide.

A solution of 30.0 g. of 4,6-dimethyl-2-pyridone-3-carboxamide in 50 ml. of alcohol and 15 ml. of 85% hydrazine hydrate was heated in an oil-bath, allowing the alcohol to distil off. After the addition of another 10 ml. of hydrazine hydrate the solution was heated for an hour at 140–150°. The mixture was cooled and the product collected and recrystallized from alcohol. There was obtained 15.0 g. of hydrazide suitable for conversion into the benzenesulfonyl derivative.

Benzenesulfonyl 4,6-dimethyl-2-pyridone-3-carboxhydrazide. To a solution of 1.10 g. of the hydrazide in 25 ml. of warm pyridine was added 0.85 ml. of benzenesulfonyl chloride. A crystalline precipitate formed at once. The mixture was heated until a clear solution resulted and water was added until crystallization began. The product which separated on cooling was collected and dried. It weighed 1.82 g. (92%); it showed no definite melting point, decomposing at about 285° to a brown tar.

3-Formyl-4,6-dimethyl-2-pyridone. A suspension of 30.0 g. of the benzenesulfonylhydrazide in 700 ml. of ethylene glycol was heated to 160° with stirring. Twenty-six g. of dry sodium carbonate was added all at once, keeping the temperature at 160–165°. The solution turned orange and a brisk effervescence took place. After 2–3 minutes the evolution of gas had ceased; water was added cautiously until the temperature had fallen to 120° and then enough more to make a total volume of two liters. The filtered solution was extracted thoroughly with chloroform. Evaporation of the chloroform left a red-brown crystalline solid which was recrystallized from water (charcoal) to yield 8.0 g. (56%) of the desired aldehyde as bright yellow prisms, m.p. 210° (dec.).

Anal. Calc'd for $C_8H_9NO_2$: C, 63.6; H, 6.00.
Found: C, 63.7; H, 6.2.

The compound readily formed a brick-red 2,4-dinitrophenylhydrazone, a yellow phenylhydrazine and a colorless semicarbazone. None of these was characterized.

Ethyl 2-methyl-4-hydroxypyrimidine-5-carboxylate was prepared in improved yield by modifying the procedure of Todd and Bergel (15).

A solution of 7.6 g. of sodium in 250 ml. of absolute alcohol was cooled to 0° and to it was added with stirring 31.0 g. of acetamidine hydrochloride. After a few minutes 71 g. of ethyl ethoxymethylenemalonate (16) was added and stirring was continued at 0° for three hours. A cooled solution of 7.6 g. of sodium in 250 ml. of alcohol was added and the solution was allowed to come to room temperature slowly and to stand overnight. The alcohol was removed by distillation (finally under reduced pressure) and the pale yellow, solid residue was dissolved in water. The solution was filtered, extracted with ether (ether discarded) and acidified with about 20 ml. of glacial acetic acid. Extraction of the aqueous solution with chloroform yielded 47.7 g. (86%) of the ester, which forms soft, white needles from acetone, m.p. 190.5–191.5° [reported (15), 191°].

2-Methyl-4-hydroxpyrimidine-5-carboxyhydrazide. A mixture of 15.0 g. of the ester, 70 ml. of water, and 10 ml. of 85% hydrazine hydrate was boiled under reflux for two hours. The cooled solution was acidified with acetic acid, cooled in ice, and the crystalline product ollected. There was obtained 10.3 g. (83%) of shining yellow leaflets. A sample recrystallized from water melted with decomposition at 242–243°.

Anal. Calc'd for $C_6H_8N_4O_2$: C, 42.8; H, 4.8.
Found: C, 42.7; H, 5.0.

The hydrazide readily formed a crystalline benzal derivative when treated with benzaldehyde in aqueous solution.

Benzenesulfonyl 2-methyl-4-hydroxypyrimidine-5-carboxhydrazide. To a suspension of 27.0 g. of the hydrazide in 100 ml. of warm pyridine was added slowly and with stirring, 30 g. of benzenesulfonyl chloride. The solution was poured onto ice and the solid collected and recrystallized from acetic acid. There was obtaned 41.4 g. of nearly colorless material (84%). The compound had no definite m.p., decomposing on heating.

Anal. Calc'd for $C_{12}H_{12}N_4O_4S$: C, 46.7; H, 3.9.
Found: C, 46.7; H, 4.2.

Attempt to prepare 2-methyl-4-hydroxypyrimidine-5-aldehyde. To a solution of 4.0 g. of the benzenesulfonyl hydrazide in 50 ml. of ethylene glycol, heated to 155°, was added, all at once, 3.0 g. of dry sodium carbonate. After the brisk effervescence had subsided (about 3 min.) the solution was cautiously diluted with water to 200 ml., cooled, and acidified with 3.5 ml. of glacial acetic acid. A crystalline precipitate of the benzenesulfonyl hydrazide separated; this was removed, and attempts made to isolate the aldehyde from the orange filtrate. No aldehyde could be obtained; its presence at least in small amount in the solution was indicated by the formation of a red precipitate when dinitrophenylhydrazine reagent was added to a portion of the solution. A repetition of the experiment led to no better result.

Substituted 3-formyl-4-hydroxyquinaldines. These were prepared by the Reimer-Tiemann formylation of the correspondng 4-hydroxyquinaldines according to the procedure employed by Conrad and Limpach (5). The hydroxyquinaldines were prepared by cyclizing the appropriate methyl N-substituted-β-aminocrotonates by the method of Limpach (17).

3-Formyl-4-hydroxyquinaldine, previously described by Conrad and Limpach (5), was obtained in 58% yield, m.p. 278–280° (dec.) [reported, 273° (dec.)]

4-Hydroxy-6-methylquinaldine was prepared by the addition of 20 g. of methyl β-*p*-toluidinocrotonate to 100 ml. of white paraffin oil (Standard Oil Co., No. 7) heated to 255–260°. The solution was stirred for 20 minutes (crystallization of the product began after 5 min.), cooled, diluted with petroleum ether, and filtered. The product (13 g., 70%) melted at 280–282° (dec.). [Reported (5), 274–275°.]

Anal. Calc'd for $C_{11}H_{11}NO$: C, 76.3; H, 6.4.
Found: C, 76.1; H, 6.3.

3-Formyl-4-hydroxy-6-methylquinaldine. A mixture of 13.5 g. of 4-hydroxy-6-methylquinaldine, 10 g. of sodium hydroxide, 100 ml. of 80% ethanol, and 30 ml. of chloroform was refluxed, with stirring, for two days. The salt was removed by filtration and the filtrate acidified with dilute acetic acid. The product (5.0 g., 35%) was crystallized from glacial acetic acid, forming orange needles, m.p. 300° (dec.).

Anal. Calc'd for $C_{12}H_{11}NO_2$: C, 71.7; H, 5.5.
Found: C, 71.4; H, 5.5.

The compound gave an orange-red crystalline 2,4-dinitrophenylhydrazone almost insoluble in boiling glacial acetic acid.

3-Formyl-4-hydroxy-7,8-benzoquinaldine. The 4-hydroxy-7,8-benzoquinaldine prepared, as described above for the 6-methyl derivative, from methyl β-(α-naphthylamino)crotonate, was formylated by refluxing 48 g. of it for 24 hours in a mixture of 50 g. of sodium hydroxide, 500 ml. of 90% ethanol, and 125 ml. of chloroform. After the recovery of 30 g. of starting material there was obtained 8.0 g. of the aldehyde which formed tan-yellow needles from glacial acetic acid, m.p. 308° (dec.).

Anal. Calc'd for $C_{15}H_{11}NO_2$: C, 76.0; H, 4.7.
Found: C, 75.8; H 4.8.

4-Hydroxy-6-bromo- and -8-chloro-quinaldines were formylated in the same way, but gave unsatisfactory yields of products difficult to purify. Both products gave the characteristic orange-red, insoluble (in hot glacial acetic acid) 2,4-dinitrophenylhydrazones, but work on

these substances was discontinued before the aldehydes were fully purified and characterized.

The Reimer-Tiemann reaction with 4-hydroxypyridine and 2,6-dimethyl-4-hydroxypyrimidine. Treatment of 4-hydroxypyridine (18) with sodium hydroxide and chloroform failed to yield the desired aldehyde. Some starting material and small amounts of oily materials were isolated.

Treatment of 5.0 g. of 2,6-dimethyl-4-hydroxypyrimidine with 20 g. of sodium hydroxide in 25 ml. of water and 12 g. of chloroform on the steam-bath for four hours, followed by neutralization and extraction with chloroform resulted in the recovery of starting material only.

o-Methoxyphenyllithium was prepared according to the directions of Gilman, Zoellner, and Selby (19).

2-o-Methoxyphenyl-1,2-dihydroquinoline. To an ether solution of *o*-methoxyphenyllithium prepared from 18.9 g. of *o*-bromoanisole and 1.4 g. of lithium was added, dropwise and with stirring, a solution of 12.9 g. of redistilled quinoline in 30 ml. of ether. The ether boiled and a yellow solid separated. After 15 minutes' stirring, water was added cautiously and the mixture stirred for an hour at 0°. After separation of the ether layer and drying it over sodium sulfate the solvent was evaporated. The residual orange syrup crystallized on scratching. The yield was 16 g. (68% based on the lithium used). After recrystallization from aqueous ethanol it melted at 86–88°.

Anal. Calc'd for $C_{16}H_{15}NO$: C, 81.1; H, 6.4.
Found: C, 80.9; H, 6.4.

The compound liquefied on standing, partially after one month, completely after four.

2-o-Hydroxyphenylquinoline. A solution of 15 g. of the dihydro compound in 50 ml. of nitrobenzene was refluxed for an hour and poured into dilute hydrochloric acid. The product, isolated from the acid solution, was distilled as a viscous yellow oil, b.p. 196°/2 mm., and without further treatment refluxed for 24 hours with a solution of 25 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid. The resulting solution was neutralized with sodium carbonate yielding a yellow solid, m.p., after crystallization from 80% alcohol as yellow needles, 114–115.5°. The yield of purified product was 6.0 g. Döbner (20) reports yellow needles, m.p. 115°.

1-o-Hydroxyphenylisoquinoline. To the organolithium compound prepared from 21.8 g. of *o*-bromoanisole and 1.6 g. of lithium was added 15 g. of isoquinoline. Isolation, oxidation, and demethylation of the product were carried out as described above without extensive purification or examination of the intermediate compounds. The yield of purified 1-*o*-hydroxyphenylisoquinoline, obtained as colorless prisms from ethanol, was 5.8 g.; m.p. 167–168°.

Anal. Calc'd for $C_{15}H_{11}NO$: C, 81.4; H, 5.0.
Found: C, 81.1; H, 5.2.

The *picrate* formed clusters of yellow needles, m.p. 182–183° (after apparent dehydration at 100–105°).

Anal. Calc'd for $C_{21}H_{14}N_4O_8$: C, 56.0; H, 3.1.
Found: C, 55.9; H, 3.2.

2-o-Hydroxyphenylpyridine. By the same procedure, from 21.8 g. of *o*-bromoanisole and 15 g. of pyridine, was obtained 2.0 g. of *o*-hydroxyphenylpyridine. Much resinous material was obtained in the first step. The final product was a liquid, b.p. 135–145°/2 mm., which could not be crystallized. It was converted to its yellow picrate (m.p. 176–178°, with previous sintering) for analysis:

Anal. Calc'd for $C_{17}H_{12}N_4O_8$: C, 51.0; H, 3.0.
Found: C, 50.7; H, 3.2.

2,2'-Dipyridine. A modification of the method of Wilbaut and Overhoff (21) was used.

A suspension of 21 g. of copper powder in 200 ml. of cymene was stirred at 175–180° while 104 g. of 2-bromopyridine was added dropwise over one hour. Two additional portions of 21 g. each of copper powder were added during the addition of the bromopyridine. After heating for a further 2.5 hours the mixture was cooled and acidified with dilute HCl and

the cymene removed by steam distillation. The residual solution was made strongly basic and the dipyridine collected by steam distillation. The distillate was saturated with salt and extracted continuously with ether. Removal of the ether and distillation of the residue yeilded 31.5 g. of 2,2′-dipyridine, b.p. 147°/16 mm.

6,6′-Diphenyl-2,2′-dipyridine. This was prepared as a trial run before the use of *o*-methoxyphenyllithium was attempted.

An ether solution of phenyllithium prepared from 7 g. of bromobenzene and 0.56 g. of lithium was treated with a solution of 3.0 g. of 2,2′-dipyridine in 50 ml. of benzene. The solution became deep red and a red precipitate appeared. The ether was removed by distillation and the residual benzene solution refluxed for four hours with stirring. Water was added and after separation of the orange benzene solution, the latter was added to 5 ml. of nitrobenzene. This solution was heated on the steam-bath for a few minutes, when it became deep red in color. The volatile material was removed with steam and from the last portions of the steam distillate colorless crystals separated. This material (0.5 g.) was recrystallized from cellosolve, from which it formed colorless flakes, m.p. 176–178°. It gave no color with ferrous iron.

Anal. Calc'd for $C_{22}H_{16}N_2$: C, 85.7; H, 5.2.
Found: C, 85.4; H, 5.4.

6,6′-Bis-(o-methoxyphenyl)-2,2′-dipyridine. To an ice-cold ether solution of *o*-methoxyphenyllithium, prepared from 16.5 g. of *o*-bromoanisole and 1.1 g. of lithium, was added very slowly and with vigorous stirring a solution of 6.5 g. of 2,2′-dipyridine in 100 ml. of ether. The resulting brown solution was stirred overnight at 0°, after which ice and 10 ml. of nitrobenzene were added. The ether layer was separated, the ether evaporated and the residue distilled. The portion boiling at 130–250°/3 mm. was collected and redistilled, after which there was obtained 5.3 g., b.p. 190–195°/2 mm. No attempt was made to purify this further, a dipicrate being prepared for analysis; it formed fine yellow needles (from cellosolve), m.p. 211–212°.

Anal. Calc'd for $C_{36}H_{26}N_8O_{16}$: OCH_3, 7.51. Found: OCH_3, 7.39.

6,6′-Bis-(o-hydroxyphenyl)-2,2′-dipyridine. A solution of 14.0 g. of the methoxy compound in 250 ml. of 48% hydrobromic acid was refluxed overnight, poured onto ice, and neutralized with sodium carbonate. The amorphous solid was separated and crystallized from methanol. The pure compound (6.8 g.) formed clusters of yellow needles, m.p. 102.5–103.5°.

Anal. Calc'd for $C_{22}H_{16}N_2O_2$: C, 77.6; H, 4.7.
Found: C, 77.5; H, 4.9.

The *dipicrate*, recrystallized from cellosolve, formed a yellow powder, m.p. 193.5–195°.

Anal. Calc'd for $C_{34}H_{22}N_8O_{16}$: C, 51.1; H, 2.8.
Found: C, 51.1; H, 2.9.

Experiments on dehydrogenation of 2-phenyl-1,2-dihydropyridine derivatives. A. The product (25% yield) from the reaction of phenyllithium with pyridine in ether (carried out at the boiling point of ether) was a yellow oil; this formed a picrate, m.p. 172–174°, with the formation of an intense red coloration in the course of the reaction with picric acid.

B. When the hydrolysis of the pyridine-phenyllithium reaction mixture was followed by the immediate addition of nitrobenzene and completion of the dehydrogenation by a short period of heating on the steam-bath, a 60% yield of 2-phenylpyridine, b.p. 100–105°/2 mm., was obtained. This formed a picrate identical with that described in A, but during its formation, no unusual color appeared in the reaction mixture.

C. The reaction of phenyllithium with quinoline in ether (at room temperature) produced first a brown color and, after 15 minutes, a yellow precipitate. Hydrolysis, separation of the ether layer, and distillation of the product yielded a yellow oil (45% yield), b.p. 175–185°/4 mm. The picrate formed with the appearance of an intense red color in the solution; m.p. 188–190° (orange plates from cellosolve).

D. After the addition of quinoline to phenyllithium and hydrolysis of the reaction mixture, the ether layer was separated, added to 25 ml. of nitrobenzene, and warmed on the

steam-cone until the ether had evaporated. The product (78% yield) obtained by removal of the nitrobenzene and distillation, crystallized immediately. It formed clusters of yellow needles from methanol, m.p. 78–81°. The picrate formed without the appearance of the red coloration described in B; m.p. 190–191°. It showed no depression on mixing with the picrate described under B.

SUMMARY

A number of new compounds have been prepared for use in studies on metal chelates similar to salicylaldehyde ethylenediimine cobalt ("Salcomine"). Among these have been (a) aromatic and heterocyclic *o*-hydroxyaldehydes intended to replace salicylaldehyde, and (b) derivatives of 2-*o*-hydroxyphenylpyridine, intended to fill the role of salicylaldehyde ethylenediimine, in such complexes.

LOS ANGELES 24, CALIF.

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DERIVATIVES OF 2-PYRIDONE

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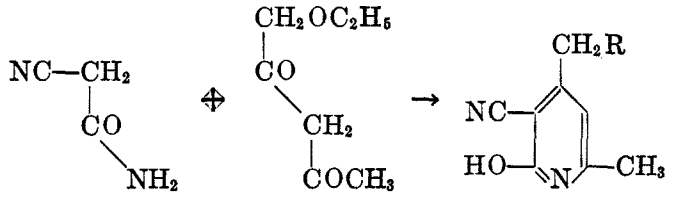
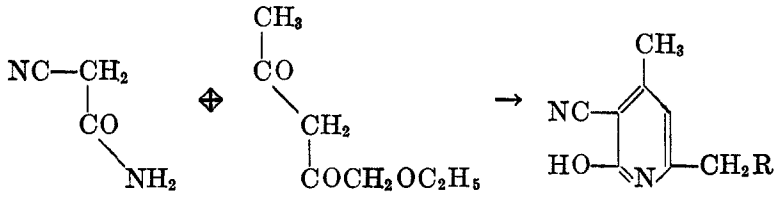
The chemistry of the 2-pyridones has long been a subject of great interest in the preparation of pharmaceuticals, and it has gained still greater prominence since the advent of Vitamin B_6. In the synthesis of 2-pyridones the pyridine ring system is frequently synthesized from suitable aliphatic compounds.

In the case of Vitamin B_6, the most convenient procedure consists in the reaction of cyanoacetamide (I) and ethoxyacetylacetone (II) leading to the formation of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (IIIa).[1]



I II IIIa R = OC_2H_5; IIIb R = OCH_3; IIIc R = H

The condensation is effected in the presence of an amine such as piperidine. Theoretically the condensation can also occur in an alternative way illustrated by the equation:

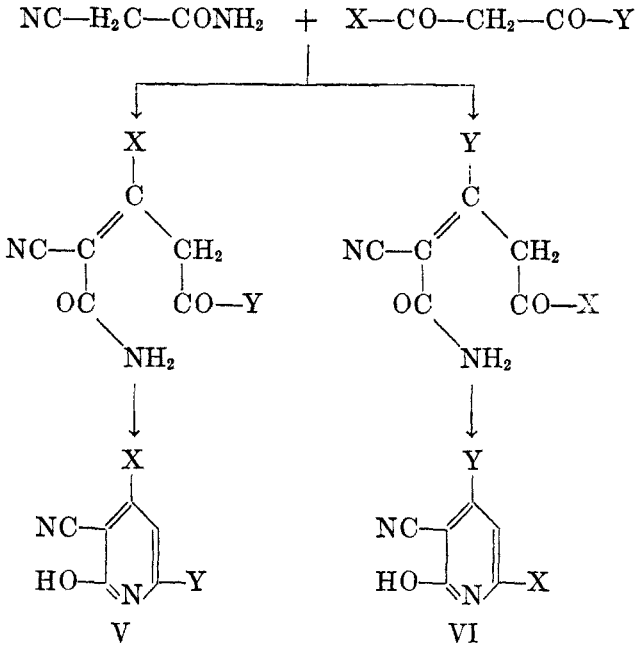


I II IVa R = OC_2H_5; IVb R = OCH_3

The mechanism of the reaction has been studied by Bardhan (1) with cyanoacetamide and several 1,3-diketones. He produced evidence that the formation

[1]For convenience, the formulas of the various pyridine derivatives are written in the aromatic form.

of the pyridine derivatives proceeds through unsaturated intermediates as illustrated by the scheme



He postulated that the relative reactivity of the respective carbonyl groups will determine the proportion of V and VI in the condensation product. The predominant isomer will have formula V if the carbonyl group adjacent to group X is more reactive and formula VI, if the more reactive carbonyl group is adjacent to Y. In the reaction of ethoxyacetylacetone with cyanoacetamide, both possible compounds IIIa and IVa are formed. Compound IIIa is isolated in about 75% yield, whereas compound IVa[2] is obtained in about 15% yield. If instead of ethoxyacetylacetone the lower homolog methoxyacetylacetone is used, the isomers IIIb and IVb are obtained in similar relative amounts.

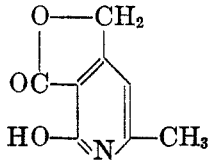
For the purpose of the synthesis of Vitamin B_6 the isomer IVa is a useless by-product. Since it is formed in considerable amounts, it seemed worth while to study its properties and reactions with the aim of obtaining useful derivatives. As a logical approach a study of the saponification and elimination of the cyano group was undertaken.

The behavior of the cyano group in compounds of the type of IIIa and IVa has not been investigated in detail. Harris, Stiller, and Folkers (2) found that compound IIIa is converted into the lactone VII by treatment with strong hydrochloric or sulfuric acid. It is therefore evident that the cyano group and the ethoxyl group are both attacked by acids.

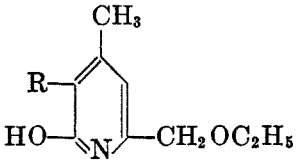
If the isomeric pyridone IVa is subjected to the action of mineral acids, no lactone can be formed. This reaction offers therefore the opportunity to study the relative susceptibility of the cyano group and the ethoxymethyl group to acid treatment. Refluxing compound IVa for five hours with 50% sulfuric acid gives

a mixture of compounds. As products of the reaction are found the acid VIIIa and the pyridone VIIIb, the former in about 5%, the latter in about 25% yield. A considerable quantity of the starting material, about 30%, is recovered unchanged. A further amount is completely broken down, apparently with splitting of the ethoxyl group.

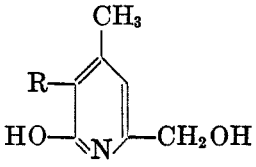
Fuming sulfuric acid reacts differently. At 5–10° the cyano group is largely unaffected, but the ethoxyl group is cleaved to give IXa. If, however, the reaction is carried out at 100°, the cyano group also undergoes saponification and the amide IXb is formed. Because this amide is rather soluble and difficult to isolate, it was converted by nitrous acid into the corresponding acid IXc which is easily isolated.



VII



VIIIa R = COOH
VIIIb R = H



IXa R = CN
IXb R = $CONH_2$
IXc R = COOH
IXd R = H

The results thus obtained are interesting because they illustrate that depending upon temperature and water content, sulfuric acid exerts a selective action on the cyano and ethoxyl groups in the same compound. However, acid treatment did not solve our original problem of converting the compound IVa into a uniform derivative with high yield.

We therefore resorted to the investigation of the action of alkali on the compound. The prospects of success were, however, not too great. Saponification of nitrile groups with alkalies is in general more difficult than with acids. In compounds of the type discussed here, the resistance of the cyano group is even more pronounced. The compound IIIc which is closely related to compounds IIIa and IVa having instead of the ethoxymethyl group a simple methyl group, has been subjected to the action of alkali by Moir (3). He found that even such drastic treatment as fusion with potash merely converted the cyano group into the amide group, yielding compound Xa. Since the ethoxymethyl group is less likely to survive such a treatment than a methyl group, fusion of either compound IIIa or IVa with alkali is obviously not too promising.

Compounds of the same type as IIIc, having a carboxyl group or a carbamyl group in place of the cyano group when subjected to alkaline treatment are not decarboxylated according to the results reported in the literature: Neither the amide Xa nor the ethyl ester Xb were decarboxylated with strong alkalies by Simonsen and Nayak (4) and by Knoevenagel and Cremer (5). These authors obtained only the corresponding free acid Xc.

In spite of these discouraging results we subjected compound IVa to the action of alkali for the following reasons. If the compound is written in the isomeric form XI, it can be regarded as a β-keto nitrile. Such nitriles when saponified give β-keto acids, which like acetoacetic acid, are known to undergo readily "ke-

TABLE I

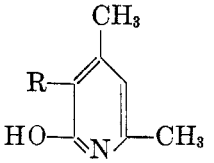
ALKOXYMETHYL-2-PYRIDONES

2-PYRIDONE DERIVATIVE	STRUCTURAL FORMULA	STARTING MATERIAL	REACTION TIME, HRS.	CRYSTAL'N SOLVENT	YIELD, %	M.P. °C	EMPIRICAL FORMULA	ANAL., %					
								Carbon		Hydrogen		Nitrogen	
								Calc'd	Found	Calc'd	Found	Calc'd	Found
4-Ethoxymethyl-6-methyl.....	XIIb	IIIa	24	Ethyl acetate	97	111–112	$C_9H_{13}NO_2$	64.65	64.72	7.84	7.72	8.38	8.55
4-Ethoxymethyl-6-methyl.....	XIIb	[a]	24	Ethyl acetate	92	109–110	$C_9H_{13}NO_2$						
4-Methyl-6-ethoxymethyl.....	XIIIb	IVa	36	Water	89	98–99	$C_9H_{13}NO_2$	Identical with material obtained in Part IIA					
4-Methoxymethyl-6-methyl...	XIIIb	IIIb	24	Ethyl acetate	88	129	$C_8H_{11}NO_2$					9.14	8.80
4-Methyl-6-methoxymethyl...	XIVb	IVb	24	Ethyl acetate	70	92	$C_8H_{11}NO_2$	62.72	62.41	7.24	7.19	9.14	9.19
4-Benzyloxymethyl-6-methyl..	XVb	XVa	28	Butanol	83	208–210	$C_{15}H_{14}N_2O_2$	70.85	70.87	5.55	5.88	11.02	11.08
4,6-Dimethyl.....		IIIc	41		74	172–173[b]	C_7H_9NO						
4-Hydroxymethyl-6-methyl...	XVIb	VII	8	Ethyl alcohol	42	213–214	$C_7H_9NO_2$	60.42	60.90	6.52	6.41	10.07	10.20
4-Methyl-6-hydroxymethyl...	IXd	IXa	24	Ethyl alcohol	37	224	$C_7H_9NO_2$	60.42	60.04	6.52	6.41	10.07	10.18

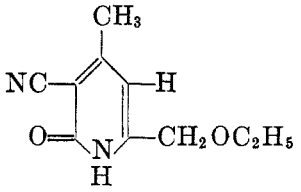
[a] 3-Carbamyl-4-ethoxymethyl-6-methyl-2-pyridone, prepared according to Schnider (7).

[b] This melting point is that of the unpurified product. Moir (3) reported the m.p. 177–179° (corr.).

tonic" cleavage not only with acids but also with dilute alkalies. Under proper conditions IVa should react similarly.



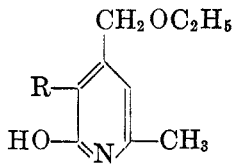
Xa R=$CONH_2$
Xb R=$COOC_2H_5$
Xc R=COOH



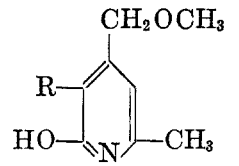
XI

Dilute aqueous alkali, at room temperature as well as at the boiling point, scarcely attacks the compound IVa. It is recovered practically quantitatively, even when boiled for several hours. If, however, the temperature is raised above 100°, by heating in an autoclave, saponification is achieved. If the compound is heated with dilute alkali at 150–170° for three to five hours, the acid VIIIa is formed. Continued heating for periods of 24 to 36 hours effects complete decarboxylation, yielding compound VIIIb. Both reactions proceed with excellent yields, and in spite of the high temperature practically no decomposition occurs. This reaction therefore is much superior to acid treatment, and fulfills the requirements for the technical problem confronting us.

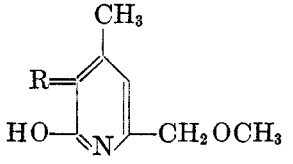
The success with compound IVa led to the investigation of the behavior of other 2-pyridones in the same reaction. The intermediate in the Vitamin B_6 synthesis, compound IIIa, likewise is saponified or decarboxylated under these conditions affording compounds XIIa and XIIb respectively. The corresponding methyl ethers IIIb and IVb are converted into the compounds, XIIIa and XIIIb, and XIVa and XIVb respectively. The benzyl ether XVa gives the pyridone XVb. The lactone VII is converted first into the acid XVIa and then into the compound XVIb. In this particular case, the acid XVIa is, however, more easily prepared by heating the lactone VII for a short time with dilute alkali at 100°. The nitrile IXa when heated for 20 hours with 5% sodium hydroxide at 160–170° yields compound IXd.



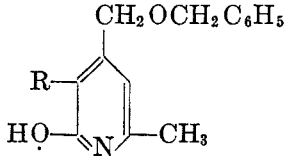
XIIa R=COOH
XIIb R=H



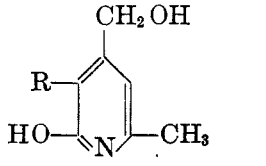
XIIIa R=COOH
XIIIb R=H



XIVa R=COOH
XIVb R=H



XVa R=CN
XVb R=H



XVIa R=COOH
XVIb R=H

With the compounds XVIb and IXd the yield is lower, because the hydroxymethyl groups are less resistent to the hot alkali than the corresponding alkoxyl groups in the other compounds.

The reaction proceeds equally well with all other functional derivatives of the carboxylic group. Thus, esters and amides react in the same way, yielding the free carboxylic acids or the decarboxylated derivatives in high yields when treated in the described manner.

The compounds obtained represent a new class of 2-pyridone derivatives which are easily accessible. They offer several opportunities for the preparation of derivatives which are at present under investigation.

We wish to thank Dr. Al Steyermark for the microanalyses recorded in the experimental part of this communication.

EXPERIMENTAL[3]

Part I. Preparation of 3-Cyano-2-Pyridones

Reaction of cyanoacetamide with alkoxy-1,3-diketones. A. *With ethoxyacetylacetone.* The condensation was carried out as described by Harris, Stiller, and Folkers (2) who reported however, only the compound IIIa, 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone. By acidification and concentration of the mother liquors about 15% of the isomeric 3-cyano-4-methyl-6-ethoxymethyl-2-pyridone (IVa), m.p. 130°, can also be obtained.[2]

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58.
Found: C, 62.23; H, 6.29; N, 14.71.

B. *With methoxyacetylacetone.* Bruce and Coover (6) describe this condensation in detail. In our laboratory similar conditions gave not only the 3-cyano-4-methoxymethyl-6-methyl-2-pyridone (IIIb) described by them, but also the isomeric 3-cyano-4-methyl-6-methoxymethyl-2-pyridone (IVb), m.p. 152°, which was isolated from the mother liquors and crystallized from ethyl acetate.

Anal. Calc'd for $C_9H_{10}N_2O_2$: N, 15.72. Found: N, 15.49.

C. *With benzyloxyacetylacetone.* 1. *Ethyl benzyloxyacetate.* Twenty-three grams of sodium was stirred at room temperature in 500 g. of benzyl alcohol for 20 hours. To the solution 123 g. of ethyl chloroacetate was slowly added. The mixture was then warmed for several hours at 80°. After cooling, it was extracted with water to remove inorganic salt and then fractionated. At 205–207°/12 mm. ethyl benzyloxyacetate distilled as an oil.

2. *Benzyloxyacetylacetone.* Seven grams of sodium was pulverized in 100 cc. of xylene and 18 cc. of absolute alcohol was added slowly with stirring. After completion of the formation of sodium alcoholate, a mixture of 56 g. of ethyl benzyloxyacetate and 20 cc. of dry acetone was added with stirring. The mixture was stirred for 15 hours at room temperature. It was extracted with water and dilute sodium hydroxide. The combined extracts were acidified with dilute HCl and extracted with ether. The ether extract was dried over Na_2SO_4, evaporated, and the residue distilled in a high vacuum. Benzyloxyacetylacetone was obtained as a yellow oil of b.p. 115–120°/0.05 mm.; yield 40 g.

3. *3-Cyano-4-benzyloxymethyl-6-methyl-2-pyridone* (*XVa*). Thirty-three grams of benzyloxyacetylacetone, 18 g. of cyanoacetamide and 10 cc. of piperidine were dissolved in 100 cc. of alcohol. The mixture was stirred at room temperature for several hours and then warmed to 50°. After cooling, water and dilute HCl were added. The crystals were

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[2]This compound was first isolated by Dr. O. Schnider of the Hoffmann-La Roche laboratories in Basle, Switzerland. (Private communication.)

[3]All melting points are uncorrected.

scarely soluble in alcohol. They were purified by recrystallization from butanol; m.p. 208–210°; yield 25 g.

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02.
Found: C, 70.87; H, 5.88; N, 11.08.

Part II. Action of Sulfuric Acid on 3-Cyano-4-methyl-6-ethoxymethyl-2-pyridone (IVa)

A. *Treatment of IVa with 50% sulfuric acid.* A mixture of 250 g. of IVa and 1250 cc. of 50% (by weight) sulfuric acid was refluxed for 5 hours and poured into 3700 g. of cracked ice. After the ice had melted, the precipitate was filtered and stirred with dilute sodium bicarbonate solution. The undissolved unchanged starting material was separated by filtration and dried; weight 82 g. Acidification of the filtrate with hydrochloric acid gave 9.9 g. of crude 3-carboxy-4-methyl-6-ethoxymethyl-2-pyridone (VIIIa) which was crystallized from water. The pure compound melted at 177–179°.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63.
Found: C, 56.89; H, 6.11; N, 6.81.

The sulfuric acid filtrate was treated with powdered sodium carbonate until *p*H 8.0 was reached. The resulting precipitate was filtered, digested with 250 cc. of boiling ethyl acetate, and filtered hot. On cooling, the filtrate gave 60 g. of crude 4-methyl-6-ethoxymethyl-2-pyridone (VIIIb). On crystallization from water the pure substance, m.p. 101–102°, was obtained.

Anal. Calc'd for $C_9H_{13}NO_2 \cdot \frac{1}{2}H_2O$: C, 61.34; H, 8.01; N, 7.95.
Found: C, 61.41; H, 7.97; N, 8.42.

B. *Treatment of IVa with cold fuming sulfuric acid.* To 170 g. of fuming sulfuric acid (15% SO_3), cooled in an ice-bath, 30 g. of IVa was added with stirring at 5–10° in 25 minutes. The mixture was removed from the ice-bath, stirred for 1.5 hours, and poured into a mixture of 200 g. of ice and 300 cc. of water. The mixture was filtered and the filtrate allowed to stand overnight. The solution was warmed on the water-bath for one hour and then allowed to crystallize. The yield of 3-cyano-4-methyl-6-hydroxymethyl-2-pyridone (IXa) amounted to 21 g. After crystallization from water it melted at 224–227° d.

Anal. Calc'd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07.
Found: C, 59.06; H, 4.79; N, 16.68.

C. *Treatment of IVa with hot fuming sulfuric acid.* To 165 g. of fuming sulfuric acid (15% SO_3), 30 g. of IVa was added with stirring so that the temperature did not exceed 100°. The mixture was then heated at 95–100° for 30 minutes and poured into 200 g. of ice. A solution of 9.9 g. of sodium nitrite was introduced with stirring at 5–15° during 45 minutes. The solution was then heated at 95° until gas evolution ceased. On dilution with 400 cc. of water, 15 g. of crude 3-carboxy-4-methyl-6-hydroxymethyl-2-pyridone (IXc) was obtained. The pure compound, m.p. 223–224° d., was obtained by crystallization from water.

Anal. Calc'd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65; neutral equivalent 183.
Found: C, 53.13; H, 5.05; N, 7.75; neutral equivalent 184.

Part III. Preparation of 3-Carboxy-2-pyridones

A. These compounds are generally prepared by heating in an autoclave at about 170° from 3 to 5 hours a mixture of 1 part sodium hydroxide, 2 parts of a 3-cyano-2-pyridone, and 7 parts of water. The solution is acidified with cooling with hydrochloric acid until precipitation is complete. The precipitate is stirred with a saturated aqueous solution of sodium bicarbonate and filtered to remove the insoluble unchanged starting material. The filtrate is then acidified with hydrochloric acid to give the crude 3-carboxy-2-pyridone which may be crystallized from alcohol or purified by crystallization of the sodium salt.

B. *3-Carboxy-4-methyl-6-ethoxymethyl-2-pyridone (VIIIa).* This compound was obtained after subjecting 40 g. of the 3-cyano compound (IVa) to the above alkaline treatment (Part IIIA) for 5 hours. The crude acid was dissolved in 200 cc. of 4% sodium hydroxide solution, and 1300 cc. of acetone was then added; yield 33 g. of the crystal-

line sodium salt. Acidification of a solution of the sodium salt gave the free acid (VIIIa) m.p. 176–177°. It gave no depression in melting point when mixed with the product obtained by treatment of IVa with 50% sulfuric acid (Part IIA).

C. *3-Carboxy-4-ethoxymethyl-6-methyl-2-pyridone (XIIa).* The ester, m.p. 132° was first prepared in poor yield by the reaction of ethyl cyanoacetate and ethoxyacetylacetone in the presence of piperidine. On saponification it gave the acid (XIIa), which melted at 218–219° after crystallization from alcohol.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.21; N, 6.63.
Found: C, 57.01; H, 6.03; N, 6.47.

The same acid was obtained in much better yield by subjecting 40 g. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (IIIa) to the alkaline treatment in Part IIIA for 3 hours and 10 minutes; yield of crude product 31 g., m.p. 208–216°. After one crystallization from alcohol the product melted at 214–216°. It was identified by a neutral equivalent determination and by a mixed melting point with the product from the reaction of ethyl cyanoacetate and ethoxyacetylacetone.

Anal. Calc'd for $C_{10}H_{13}NO_4$: Neutral equivalent, 211. Found: Neutral equivalent, 216.

D. *3-Carboxy-4-methoxymethyl-6-methyl-2-pyridone (XIIIa).* When 60 g. of the 3-cyano compound (IIIb) was subjected to the alkaline treatment for 4 hours and 10 minutes, a yield of 49 g. of the 3-carboxy compound (XIIIa), m.p. 219–220° d., was obtained. Crystallization from alcohol gave the pure acid, m.p. 222–223° d.

Anal. Calc'd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62.
Found: C, 54.80; H, 5.60.

E. *3-Carboxy-4-methyl-6-methoxymethyl-2-pyridone (XIVa).* From 5.8 g. of 3-cyano-4-methyl-6-methoxymethyl-2-pyridone (IVb) there was obtained 5.0 g. of the crude 3-carboxy compound (XIVa) after 5 hours of the alkaline treatment described in Part IIIA. The compound was purified by crystallization from alcohol, m.p. 200–201°.

Anal. Calc'd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62.
Found: C, 54.54; H, 5.32.

F. *3-Carboxy-4-hydroxymethyl-6-methyl-2-pyridone (XVIa).* A mixture of 10 g. of the lactone (VII) and 100 cc. of 5% sodium hydroxide was boiled for a few minutes after solution had occurred. The solution was cooled in an ice-bath and slowly acidified with dilute hydrochloric acid. The precipitate was washed thoroughly with water and dried in a desiccator at room temperature; yield 10.7 g. The acid is soluble in sodium bicarbonate solution in contrast to the lactone which is insoluble in this reagent. When a sample was introduced into a melting point block at 250°, it melted with effervescence, resolidified and then melted again at about 300° with decomposition. This behavior varies with the rate of heating.

Anal. Calc'd for $C_8H_9NO_4$: Neutral equivalent, 186. Found: Neutral equivalent, 183.

Part IV. Elimination of the Cyano group or other Carboxylic Functional groups from the 3-position of 2-pyridones

The preparation of 4-methyl-6-ethoxymethyl-2-pyridone (VIIIb) from the 3-cyano compound illustrates the general procedure for the preparation of all the compounds in Table I. With but two exceptions the 3-cyano compound was used as a starting material. The exceptions are the use of 3-carbamyl-4-ethoxymethyl-6-methyl-2-pyridone as a starting material for the preparation of 4-ethoxymethyl-6-methyl-2-pyridone (XIIb) and the use of the lactone VII for the preparation of 4-hydroxymethyl-6-methyl-2-pyridone (XVIb).

4-Methyl-6-ethoxymethyl-2-pyridone (VIIIb). A mixture of 90 g. of 3-cyano-4-methyl-6-ethoxymethyl-2-pyridone (IVa), 45 g. of sodium hydroxide, and 315 cc. of water was heated in an autoclave at 170° for 36 hours. The mixture was cooled, acidified to *p*H 6–7, and filtered. A yield of 73 g. of 4-methyl-6-ethoxymethyl-2-pyridone (VIIIb), m.p. 98–99°, was thus obtained. Its identity was established by a mixed melting point with the substance obtained by treatment of (IVa) with 50% sulfuric acid (Part IIA).

Alternatively the decarboxylated product can be extracted from the neutral reaction mixture with chloroform. The residue after distillation of the chloroform is then crystallized from the appropriate solvent.

SUMMARY

Condensation of cyanoacetamide with alkoxyacetylacetones occurs in two ways, yielding 4-alkoxymethyl-6-methyl-3-cyano-2-pryidones and 4-methyl-6-alkoxymethyl-3-cyano-2-pyridones. A method is described whereby these compounds are saponified or decarboxylated in high yields.

NUTLEY, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

SOME OBSERVATIONS ON THE STRUCTURE OF LIMONIN

T. A. GEISSMAN AND VSEVOLOD TULAGIN

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Limonin, first isolated from *Citrus* spp. (1) and since recognized in several other plants (2, 3, 4), is a member of a fairly large but relatively little-studied group of substances known generally as "bitter principles." These substances appear to form a well-defined class of naturally-occurring, nitrogen-free materials, possessing certain characteristics in common although being rather divergent in molecular size and perhaps in fundamental structure. The most common characteristic of these substances, besides their bitter taste, is that they are lactones. Where information is available it appears that the bitter principles possess complex alicyclic structures, or heterocyclic structures involving oxygen atoms in ether or acetal linkages. The presence of mobile ether linkages would be in accord with the ease with which isomerization (and in some cases degradation) of the molecules of many of these substances can be brought about by the action of acids. Indeed, this fact may bear some relationship to the observation that isomeric or closely similar bitter principles are frequently found associated in the same plant. For example, limonin has been reported to occur along with isolimonin (5), obacunoic acid (6), dictamnolide (6), obacunone (7), and dictamnolic acid (7). The bitter substances, with some exceptions, give acetone upon fusion with alkali and possess neither methoxyl, methylenedioxyl, nor acetyl groups.

Interest in the structure of liminon is heightened by the fact that it probably is concerned in the development of a bitter taste in expressed Navel orange juice, a problem of considerable economic importance to the citrus industry. It is to be hoped that precise information on the structures of limonin and of isolimonin, which is isolated along with limonin from citrus fruits, will be of value in solving the problem of producing stable, palatable Navel orange juice.

Up to the time the present work was begun the available information on the structure of limonin was scanty. Since the isolation of the bitter principle in 1841 (1) it has been investigated in a number of laboratories (2, 5, 8, 9, 10, 11, 12, 13, 14). The results of these investigations can be summarized briefly as follows:

Limonin is a dilactone having the composition $C_{26}H_{30}O_8$. It dissolves in concentrated sulfuric acid with the formation of a red-brown solution from which limonin cannot be recovered on dilution. It shows no indication of possessing a (reactive) carboxyl group or hydroxyl groups, and does not react with bromine in chloroform in the cold. Limonin does not react with Tollens' reagent nor does it give a positive Legal test. When oxidized with manganese dioxide in the presence of sulfuric acid it yields benzenepentacarboxylic acid. Upon fusion with alkali under very drastic conditions, followed by selenium dehydrogenation of the products of this treatment, 1,2,5-trimethylnaphthalene is formed. This hydrocarbon was also obtained by the zinc-dust distillation of columbin (15). Among the products of alkali fusion not subsequently treated with selenium was

isophthalic acid. Limonin has been shown to be different from columbin (9), a bitter principle which it closely resembles, and identical with obaculactone, evodin, and dictamnolactone (13).

The results of the catalytic hydrogenation of limonin gave early promise of useful results, but a more recent reexamination of this method of attack has cast some doubt upon the validity of some of the previously reported results. Koller and Czerny (5) reported the isolation of "hexahydrolimonic acid" and "tetrahydrolimonin," the latter substance probably being the same as one later obtained by Feist (11). Schechter and Haller (16) were unable to duplicate these findings.[1] In view of these conflicting reports the hydrogenation of limonin was not adopted as the first point of departure in the present work.

Our first efforts were directed at the stepwise degradation of limonin by oxidative means. Limonin is quite resistant to many oxidizing agents, but once oxidation starts it tends to proceed rapidly to the formation of fragmentary oxidation products. It was expected that if the lactone linkages could be opened to hydroxy esters, the hydroxyl groups might serve as points of attack. When limonin is warmed with dilute alkali it dissolves, and upon acidification the lactone groups are immediately reconstituted, limonin being the only recoverable substance. This is in contrast to the behavior of columbin, which can be transformed into an hydroxy acid by similar treatment (17). The remarkable stability of the lactone linkages in limonin is further shown by the fact that it has been found impossible to convert the compound into an ester by any of a number of procedures, including the use of dimethyl sulfate or methyl *p*-toluenesulfonate and alkali under a variety of conditions and the use of diazomethane with ether extracts from rapidly-extracted, freshly-acidified solutions of limonin.

Limonin is oxidized to a non-separable mixture of the fragmentary products of extreme degradation by hot, dilute nitric acid, chromic anhydride in acetic acid, hot alkaline potassium permanganate, and acidic hydrogen peroxide. It is stable to cold, alkaline hydrogen peroxide and is not materially affected by being refluxed overnight in nitrobenzene solution. The use of eight to ten equivalents of potassium manganate, however, has led to a partial oxidation product of limonin, limonilic acid. This substance contains a lactone group and is a carboxylic acid. Aqueous solutions of limonilic acid are not bitter. Analyses of limonilic acid and its methyl ester, along with neutral and saponification equivalents and a molecular weight determination, agree with the formula $C_{25}H_{28}O_9$ for the acid. This corresponds to a loss of a methyl or methylene group. Since limonin has $(\alpha)_D^{25}$ $-123°$ and limonilic acid has $(\alpha)_D^{25}$ $+109°$ it is probable that the oxidative attack has taken place at an asymmetric center.

Limonilic acid is inert towards hydroxylamine and 2,4-dinitrophenylhydrazine, forms no acetate when treated with acetic anhydride and sodium acetate, and yields no iodoform with iodine and alkali. Upon fusion with alkali, limonilic acid yields about 0.6 mole of acetone. Since limonin when treated in the same

[1] The formation of "hexahydrolimoninic acid" by the treatment of limonin with boiling, dilute hydrochloric acid, reported by Higby (12), must be regarded as doubtful since from Higby's description it is evident that he was dealing with an amorphous substance, and since it is difficult to see how this treatment could bring about so extensive a reduction of the molecule.

way yields about 0.88 mole of acetone it is probable that the grouping which gives rise to acetone in the case of limonin is still present in limonilic acid, and that both substances possess one acetone-producing side chain. Limonilic acid is no more prone to yield crystalline derivatives than is limonin, and shows the same sensitivity towards mineral acids and to further oxidation. Because of these facts

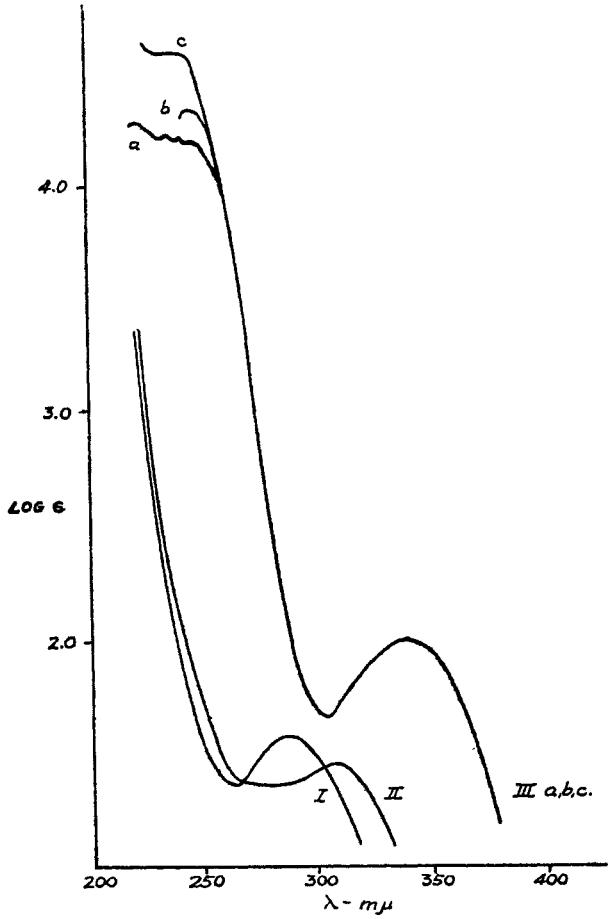


FIG. 1. Absorption Spectra of Limonin, Limonilic Acid, and Citrolin.
I. Limonin (in alcohol)
II. Limonilic Acid (in alcohol)
III. Citrolin (a) in alcohol)
(b) in chloroform
(c) in ether

and the difficulty of obtaining large amounts of limonin for study, attention was turned to an examination of other methods of treatment of limonin in the hope that more tractable degradation products might be found.

Because the use of hydriodic acid has been found to yield valuable information in studies on the nature of picrotoxin (18, 19, 20), its action on limonin has been studied. The treatment of limonin with hydriodic acid in boiling acetic acid

has yielded two reduction products, one (citrolin) having the composition $C_{26}H_{28-30}O_6$ and the other (desoxolimonin) having the probable composition $C_{26}H_{30}O_7$. Desoxolimonin has been obtained in very small amount only and has not been studied in detail.

Citrolin appears to undergo ready decomposition even in dilute alkaline solution. Treatment with hot 0.25 *N* potassium hydroxide for one hour causes the formation of dark-colored substances, and upon acidification of the solution neither citrolin nor any other definite products can be isolated. Titration of the alkaline solution is difficult because of an indefinite end-point and saponification values of approximately 280 are obtained. The most striking characteristic of citrolin is the ease with which acetone is split off upon treatment with dilute alkali. Acetone was readily detectable in the solution resulting from the treatment with 0.25 *N* alkali just described. No acetone is formed when limonin is treated in a similar fashion. This observation might indicate that the reduction with hydriodic acid has resulted in an attack upon the linkage responsible for the production of acetone.

Attempts to isolate definite products from the mixture resulting from the treatment of citrolin with alcoholic alkali were unsuccessful. An indication was obtained, however, that among the substances produced may be a phenolic or enolic substance.

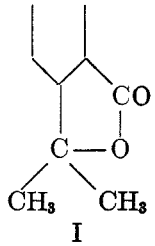
In an attempt to obtain information about the carbon skeleton of limonin, a sample of the bitter principle was heated with hydriodic acid in a sealed tube at 200°. This treatment yielded a colorless, viscous oil. This was treated with selenium in an attempt to bring about dehydrogenation to identifiable aromatic substances but the resulting tarry material could not be induced to yield a picrate.

The absorption spectra of limonin, limonilic acid, and citrolin are shown in Fig. 1.

A supplemental observation, while leading to no definite conclusions, is worthy of mention. Citrolin is oxidized with cold, dilute nitric acid to yield a very small amount of a crystalline oxidation product. Due to the poor yields obtained in this reaction the compound was not examined further.

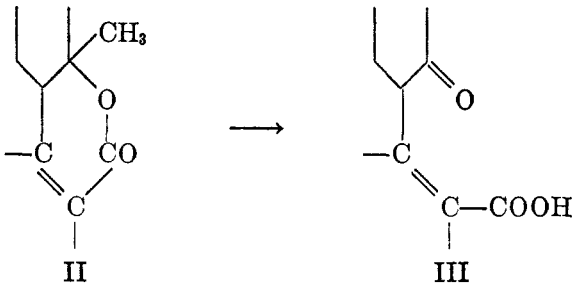
DISCUSSION

The evidence so far available indicates that limonin does not possess a bilaterally symmetrical structure. The formation of but one mole of acetone upon alkali fusion and the formation by oxidation of a lactone-carboxylic acid which also gives a mole of acetone support this conclusion. The great stability of the lactone groups in limonin, coupled with the formation of but one mole of acetone by alkali fusion, leads one to suggest that one of the lactone groupings is



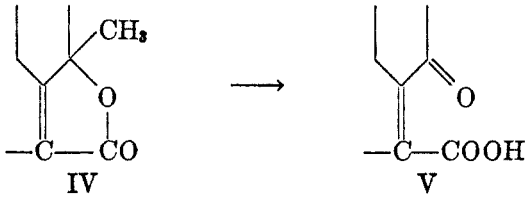
I

and that the other is not identically constituted. This second lactone group is the one which disappears in the formation of limonilic acid, and since in this transformation a carbon atom is lost, it is suggested that the original lactone linkage possesses the partial structure II shown in the following equations, which show the possible course of the reactions involved in the oxidation process:



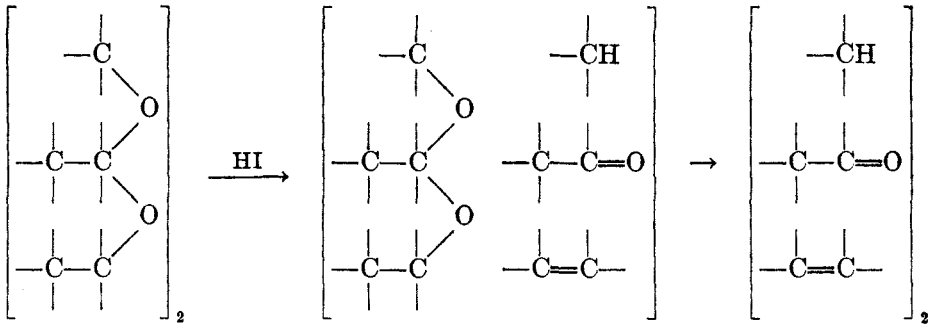
II III

The center of optical asymmetry lost in this step is evident from this equation. The inertness of the carboxyl group which it is supposed is formed in this reaction may be due to the kind and number of substituents present on the adjacent carbon atoms. That the lactone grouping II cannot be replaced by IV is indicated by the fact that limonilic acid does not have an absorption spectrum which would be expected of the resulting acid V, which is an α,β-unsaturated ketone (21).



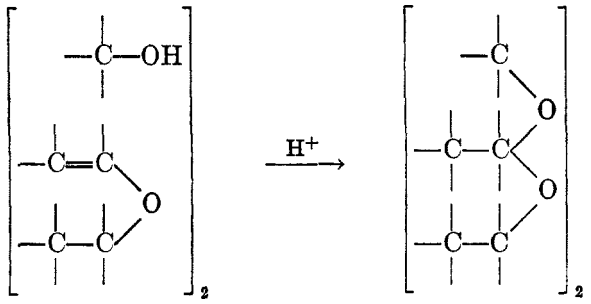
IV V

The formation of citrolin and desoxolimonin can be explained by the following partial structures, of which VI represents another part of the limonin molecule.



Limonin Desoxolimonin Citrolin
VI VII VIII

The reported presence of two hydroxyl groups in isolimonin (5), coupled with the fact that isolimonin is readily isomerized to limonin by acids, is in accord with the suggestion that limonin contains the grouping shown in VI. These observations would be in accord with the suggestion that isolimonin may contain the groupings represented in IX:



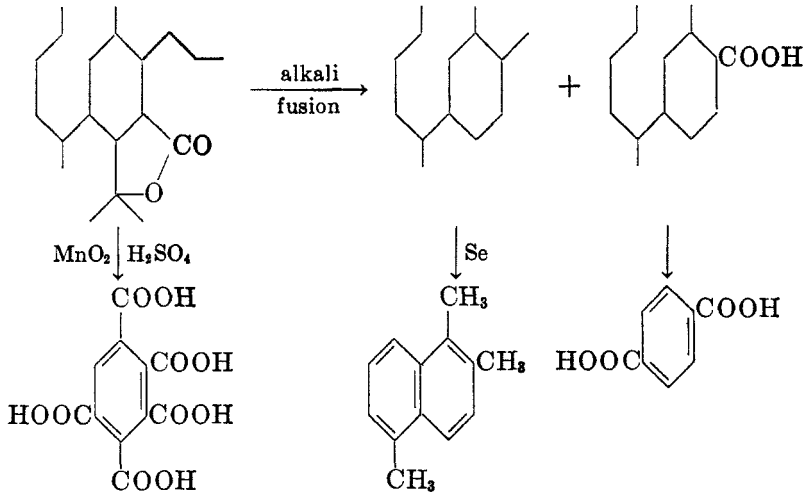
Isolimonin Limonin

IX

If the above structures represent portions of the limonin molecule it can be seen that the completely reduced skeleton of limonin would have the composition $C_{26}H_{46}$. This differs by eight hydrogen atoms from the paraffinic $C_{26}H_{54}$, indicating that limonin may possess four rings on four double bonds, or some combination of these.

The absorption spectra of limonin and of limonilic acid, showing a sharp increase at about 240 mμ which continues indefinitely into the short ultraviolet, are characteristic of these of α,β-unsaturated acids and esters (22). The fact that limonin, although showing unsaturation to catalytic hydrogenation, does not react with perphthalic acid, is in accord with the α,β-unsaturated lactone structure. The peaks in the spectrum of citrolin at about 245 mμ are reminiscent of those in the spectra of styrene and indene and may indicate that aromatization of a ring has occurred during the treatment with hydriodic acid. It should be mentioned that picrotoxin derivatives, which possess certain structural features similar to those suggested for limonin, can undergo aromatization under similar treatment (23).

The source of 1,2,5-trimethylnaphthalene, benzenepentacarboxylic acid, and isophthalic acid, all obtained by earlier workers by the use of degradation methods mentioned above, could be a partial structure such as the following, which includes the lactone ring shown in I:



The above suggestions are tentative only, and rest upon an experimental foundation which is still a narrow one. Further work, such as C-methyl determination, possibly ozonization, a reexamination of the hydrogenation of limonin and further degradation studies on citrolin will doubtless furnish further useful data to clarify the still obscure picture.

EXPERIMENTAL

The isolation of limonin. In a 5-gallon crock was placed about 10 lbs. of dried orange pulp (stock-feed material), which was covered with water. Steam was passed in for several hours. The pulp swelled to fill the crock, and occasionally more water was added to keep the mixture fluid. The hot mash was pressed out in a fruit press and reextracted in the same way. The cooled water extract was stirred thoroughly with two gallons of benzene, using a "Lightning" mixer, and the resulting emulsion broken with the aid of sulfuric acid and methanol. After a second extraction with benzene, the benzene solutions were evaporated as far as possible on a steam-cone, at atmospheric pressure and then at 22 mm. The residue was treated with 100 ml. of glacial acetic acid which was then removed under reduced pressure. This treatment removed essential oils whose presence made crystallization of the product difficult. The residue was dissolved in glacial acetic acid and allowed to crystallize. The thick, black suspension was filtered and the dark crystalline material washed with acetic acid until it was pale brown in color. It can be purified further by recrystallization from acetic acid or from acetone-methanol.

Limonin crystallizes from acetic acid with a molecule of acetic acid (24), forming crisp, white needles. It melts with decomposition at about 302–305° (corr.), depending somewhat upon the heating rate. The melting point of the solvated material is the same, the acetic acid evidently being lost during the heating.

Limonin gives a deep red-brown color in concentrated sulfuric acid. Tests for the methylenedioxyl group were negative. The change in titer of a chloroform solution of limonin and perphthalic acid was the same as that of a blank containing no limonin. Tests for other functional groups with the usual carbonyl reagents and with acylating reagents were negative, unchanged limonin being recovered, occasionally accompanied by very small amounts of oily materials.

Attempts to methylate limonin. I. A solution of 1.10 g. of limonin in 20 ml. of 6 *N* sodium hydroxide was filtered into a separatory funnel containing 100 ml. of ice-cold ether. The funnel was cooled in ice, 30 ml. of ice-cold 6 *N* sulfuric acid was added, the whole vigorously shaken, and the ether layer separated and added immediately to an ether solution of diazomethane (excess). After allowing the solution to stand overnight the excess diazomethane was decomposed with acetic acid and the solvents evaporated. The residue was shaken with cold, dilute sodium hydroxide and benzene. Nothing was recovered from the benzene; from the aqueous solution was recovered 0.80 g. of limonin upon acidification.

II. A solution of 1.0 g. of limonin in the theoretical amount of alkali was covered with 100 ml. of a diazomethane solution in ether, the whole being contained in a 3-necked flask fitted with a stirrer and dropping-funnel. While the mixture was stirred, dilute hydrochloric acid was introduced at the bottom of the aqueous layer. At the conclusion of the experiment there was present in the aqueous layer an ether-insoluble precipitate. This proved to be limonin. Nothing was obtained when the ether layer was evaporated.

III. A cooled solution of 0.51 g. of limonin in an equivalent amount of alcoholic alkali was treated with 2 ml. of acetic acid and the solution poured immediately into an excess of diazomethane in ether. From the solution limonin (0.43 g.) was obtained along with about 50 mg. of a non-crystallizable, dark-colored oil.

IV, etc. Attempts to methylate limonin by treatment with dimethyl sulfate in alcoholic alkali, keeping dimethyl sufate in excess in some experiments and alkali in excess in others failed to yield any recoverable material but limonin. Similar experiments with methyl

p-toluenesulfonate gave similar results. When the reagents were added in such a way as to keep the solution as nearly neutral as possible no better results were obtained.

The oxidation of limonin. I. A solution of 0.50 g. of limonin in 100 ml. of 1 *N* alkali was treated with 1 g. of sodium peroxide. After an hour the solution was heated to boiling and acidified. The precipitate which formed was limonin.

II. A solution of 0.50 g. of limonin in 100 ml. of 2 *N* alkali was treated with 15 ml. of 30% hydrogen peroxide. After 24 hours the solution was heated to boiling and acidified. Limonin was recovered.

III. Limonin was largely unaffected when 0.5 g. was allowed to stand overnight with 6 ml. of 30% hydrogen peroxide containing, first, one small drop of concentrated sulfuric acid and, later, 3 ml. of concentrated sulfuric acid. The solution after removal of unreacted limonin, yielded a small amount of water-soluble, dark-colored material which could not be purified further.

IV. Treatment of limonin with chromic anhydride in glacial acetic acid solution results in a rapid oxidation. The products of these experiments were water-soluble amorphous materials which resisted attempts at crystallization or purification.

V. A solution of 0.50 g. of limonin in 20 ml. of glacial acetic acid containing 2 ml. of concentrated nitric acid was refluxed for thirty minutes. Nitrogen oxides were evolved copiously. The solution was buffered with sodium acetate, evaporated to 5 ml., diluted with 25 ml. of water and extracted with ether. Evaporation of the ether left a considerable residue which was soluble in most of the common solvents with the exception of benzene and ligroin. In the absence of solvents it formed a glass. It dissolved in sodium bicarbonate solution with the evolution of carbon dioxide. The material could not be crystallized nor purified.

VI. *Limonilic acid.* To a solution of 3.16 g. of limonin in 100 ml. of 6 *N* sodium hydroxide was added 100 ml. of a solution 0.03 molar in potassium manganate and 6 *N* in sodium hydroxide (9 equivalents of potassium manganate). The solution was maintained at about 50° for an hour, during which the green color disappeared and a precipitate of manganese dioxide formed. The mixture was filtered and the filtrate acidified with hydrochloric acid, heated to boiling and allowed to cool, and kept at 5° overnight. The granular precipitate was collected and dried; it weighed 1.88 g. after recrystallization from methanol-water. Limonilic acid melts at about 292–293° (dec.) (uncorr.) when introduced into a bath preheated to that temperature. A mixture of limonin and limonilic acid melted at 255–260°.

Anal. Calc'd for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97.

Found: C, 63.65; H, 5.84; $(\alpha)_D^{25}$ +109° (in acetone).

When limonilic acid is titrated rapidly to the first end-point with thymol blue an equivalent weight of about 450 is found. The end-point fades, however; and if excess alkali is added and the excess back-titrated with standard acid a neutral equivalent of 237 is obtained. Calc'd for $C_{25}H_{28}O_9$: eq. wt. 236 (one lactone, one carboxyl).

Limonilic acid is soluble in sodium bicarbonate solution. It gives a red-brown color in concentrated sulfuric acid similar to that shown by limonin. It is not readily affected by bromine in carbon tetrachloride nor by potassium permanganate in acetone in the cold. On treatment with hot, dilute mineral acids it decomposes to brown, amorphous products. It did not yield carbonyl derivatives with hydroxylamine nor with 2,4-dinitrophenylhydrazine and was recovered unchanged after treatment of its solution in 1 *N* alkali with iodine. Treatment of 0.30 g. of limonilic acid with a mixture of acetic anhydride, sodium acetate, and acetic acid (20 minutes reflux) resulted in the eventual recovery of 0.28 g. of limonilic acid.

Methyl limonilate. A solution of 0.55 g. of limonilic acid in 30 ml. of ethanol was treated in small portions with 100 ml. of a solution of excess diazomethane in ether. After 30 minutes the excess diazomethane was decomposed with acetic acid, the ether solution washed with sodium bicarbonate solution, dried, and evaporated at 22 mm. The residual material was taken up in 30 ml. of acetone and treated with 11 ml. of 0.1 *N* sodium hydroxide. This

solution was poured into water and ether, the ether layer discarded and the aqueous layer acidified and then treated with excess sodium bicarbonate. Extraction of the resulting suspension with benzene and evaporation of the benzene solution yielded a solid which was crystallized from a mixture of 1 ml. of acetone and 4 ml. of methanol. After recrystallization from methanol the ester melted at 217–218° (uncorr.) with no decomposition.

Anal. Calc'd for $C_{26}H_{30}O_9$: C, 64.19; H, 6.22; mol. wt., 486.5.
Found: C, 64.23; H, 6.39; mol. wt. (Rast), 488.

Hydrolysis of limonin with acid. Treatment of limonin with boiling 50% hydrobromic acid in acetic acid resulted in the formation of a dark green, opaque solution from which no definite substance could be isolated. With hot, dilute hydrochloric acid in acetic acid some limonin was recovered.

Pyrolysis of limonin. A sample of 35 mg. (0.074 millimole) of limonin was heated in an evacuated, sealed ampule at 250–280° for 3 hours. The gas which formed was analyzed in a Blacet-Leighton micro gas analysis apparatus and was found to contain 0.021 millimole of carbon dioxide. Some limonin was recovered unchanged (about 50%) when another sample of 0.51 g. was heated for 3 hours at 290–300°. These results indicate that a mole of carbon dioxide is formed per mole of limonin; but because of the difficulty in recovering crystalline limonin from the tarry pyrolysis products this is subject to some uncertainty.

Alkali fusion of limonin and limonilic acid. About 50 mg. of limonin or limonilic acid was treated with 2 ml. of 75% potassium hydroxide solution and heated gradually to 350–360°. The distillate was condensed in a small bulb cooled in an ice-salt mixture.

To the distillate were added 1 ml. of alcohol, 1 ml. of a 10% solution of salicylaldehyde in alcohol, and 2 ml. of 10% ethanolic potassium hydroxide. This solution was heated at 100° for exactly one hour, cooled in ice, and the color measured at 550 mμ on a Beckman Photoelectric Spectrophotometer. The amount of acetone was calculated from a curve prepared by treating known amounts of acetone in the same way. The recovery of acetone by distillation from solutions containing known amounts was 90–95%.

Limonin:

45.7 mg. gave 0.085 millimole of acetone = 0.87 mole/mole limonin
51.3 mg. gave 0.097 millimole of acetone = 0.88 mole/mole limonin

Limonilic acid:

74.4 mg. gave 0.086 millimole of acetone = 0.54 mole/mole limonilic acid
55.5 mg. gave 0.070 millimole of acetone = 0.60 mole/mole limonilic acid

Hydriodic acid reduction of limonin: Citrolin. To a solution of 50 ml. of constant-boiling hydriodic acid in 80 ml. of glacial acetic acid was added 3.0 g. of limonin. The mixture was warmed to 60° until solution was complete. After the addition of 0.5 g. of red phosphorus the mixture was refluxed for 2 hours, then filtered through asbestos, diluted to 600 ml. with boiling water containing enough sodium bisulfite to reduce the excess iodine, clarified by filtration through "Supercel," and the filtrate allowed to cool. The material which separated was combined with a further amount obtained by extracting the dilute acetic acid filtrates with benzene and the whole dissolved in 40 ml. of acetone. An equal volume of methanol was added and the solution concentrated by distillation until crystallization began. After cooling, the solid was collected and recrystallized again in the same way. The yield was usually 500–600 mg. of long silky white needles which melted at 305° (uncorr.). It has $(\alpha)_D^{25}$ −120° (in acetone).

Anal. Calc'd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47; mol. wt., 436.5.
Calc'd for $C_{26}H_{30}O_6$: C, 71.37; H, 6.68; mol. wt. 438.5.
Found: C, 71.68; H, 6.81; mol. wt. (Rast), 426, 443.

Desoxolimonin. By evaporating the mother liquors from the crystallization of citrolin and extracting the residue with an amount of methanol just insufficient for complete solution, 50–60 mg. of another material was obtained. This material had the same m.p. as citrolin (305°, uncorr.), but a mixture of the two showed a large depression (m.p. 260–270°, uncorr.).

Anal. Calc'd for $C_{26}H_{30}O_7$: C, 68.70; H, 6.65.
Calc'd for $C_{26}H_{28}O_7$: C, 69.01; H, 6.24.
Found: C, 68.83; H, 6.57.

When 0.94 g. of citrolin was shaken for 20 hours with a solution of 20 ml. of concentrated nitric acid in 80 ml. of water, and the resulting clear solution neutralized with sodium bicarbonate and extracted continuously with ether, there was obtained a small amount of material which crystallized readily from acetic acid. Only about 5 mg. was obtained. It was not investigated further.

Saponification of citrolin. A solution of 0.50 g. of citrolin in 20 ml. of 10% ethanolic potassium hydroxide was refluxed for an hour. The solution became a deep greenish-brown. A few ml. of the solution was distilled off and was found to give a strong positive test for acetone. No definite products could be isolated, but a small amount of crude material, obtained by saturating the solution with carbon dioxide and extracting successively with ethyl acetate, benzene, and ether, rapidly decolorized bromine and gave a colored precipitate with ferric chloride.

Complete reduction of limonin. Two grams of limonin was heated in a sealed tube with 3 ml. of constant-boiling hydriodic acid at 200° for 24 hours. The contents of the tube were shaken with ether and an aqueous solution of sodium bisulfite. The colorless ether solution was evaporated, yielding about 2 g. of a colorless, viscous oil. This oil did not decolorize bromine in carbon tetrachloride and appeared to be insoluble in cold, concentrated sulfuric acid, but dissolved in cold, fuming sulfuric acid with a dark red-brown color. The oily material was heated at 330–350° for 48 hours with 3 g. of selenium. The product of this reaction was a yellow-brown tar which could not be purified and which could not be induced to yield a picrate.

SUMMARY

Three crystalline degradation products of limonin have been isolated, one, *limonilic acid*, by oxidation with potassium manganate, and two, *citrolin* and *desoxolimonin*, by hydriodic acid reduction.

On the basis of these observations and those reported by previous workers, proposals are made concerning certain structural features of the limonin molecule.

Los Angeles, Calif.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

1,2-CYCLOHEXANEDIONEDIOXIME

T. A. GEISSMAN AND MAURICE J. SCHLATTER

Received April 22, 1946

Rauh, Smith, Banks, and Diehl (1) recently described the preparation of 1,2-cyclohexanedionedioxime (Nioxime) by two different methods, but recorded their failure to prepare this compound by the method of Jaeger and van Dijk (2), in which 1,2-cyclohexanedionemonoxime is prepared by the reaction of sodium nitrite with 2-carboethoxycyclohexanone.

During the course of some recently concluded work[1] we have had occasion to prepare samples of 1,2-cyclohexanedione-monoxime and -dioxime for the purpose of examining certain metallic complexes derived from them as possible reversible oxygen carriers. In our hands the method of Jaeger and his co-workers proved entirely satisfactory when the precaution was taken to exclude air from the reaction mixture during the reaction of 2-carboethoxycyclohexanone with alkali and sodium nitrite. The crude monoxime, obtained in 89% yield, could be converted into dioxime in 60% yield. The latter yield is less than one might expect and may indicate that the crude monoxime is quite impure. However, it is to be noted that Rauh, *et al.*, report a yield of only 70% of the dioxime from the diketone, and a yield of only 41% from sodium 2-isonitrosocyclohexanone, even when a purity of but 80% is assumed for the latter.

Since our purpose was only to prepare samples of these compounds, we made no intensive study of the procedure with the object of finding the optimum conditions for these reactions.

EXPERIMENTAL

1,2-Cyclohexanedionemonoxime. A solution of 11.0 g. of sodium hydroxide in 200 ml. of water was added slowly to 42.5 g. of 2-carboethoxycyclohexanone in a narrow-mouthed bottle. A solution of 17.2 g. of sodium nitrite in 50 ml. of water was added and the bottle was tightly sealed[2] and shaken mechanically for 48 hours at room temperature. The pale yellow solution was cooled to 0° and a small excess of cold 6 *N* sulfuric acid (100 ml.) was added with shaking. A considerable amount of gas was evolved. The solution was allowed to stand for 30 minutes and then extracted with ten 50-ml. portions of ether. The ether solution was dried over magnesium sulfate (20 minutes, with shaking) and the solvent removed at 40°, the last traces being removed by raising the temperature to 70° and reducing the pressure to 20 mm. for five minutes. The pale yellow oil which remained weighed 28.5 g. (89%).[3]

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[1] This work was carried out as part of a program of research under Division 11, Section 1 of the National Defense Research Committee, under a contract with the University of California.

[2] In five runs in which air was not carefully excluded very poor yields of dark-colored products were obtained. These products appeared to decompose partially (with gas evolution) on standing overnight at room temperature.

[3] Jaeger and Bijerk (3) and Treibs and Dinelli (4) report that the monoxime cannot be crystallized, nor distilled without decomposition.

1,2-Cyclohexanedionedioxime. A hydroxylamine solution was prepared by adding to a solution of 23.2 g. of hydroxylamine hydrochloride in 50 ml. of water a solution of the theoretical quantity of sodium methoxide in 150 ml. of methanol. This solution was added to 28.5 g. of crude 1,2-cyclohexanedionemonoxime and the mixture allowed to stand at room temperature for 24 hours and then in the ice-chest for several hours. The first crop of dioxime weighed 11.7 g., and from the mother liquors was obtained an additional 9.4 g. (total, 21.1 g.; 60%, assuming pure monoxime). The dioxime melted at 187–190° (dec.), and after recrystallization at 189–190°.

SUMMARY

The procedure of Jaeger and van Dijk has been found to be satisfactory for the preparation of 1,2-cyclohexanedionemonoxime.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

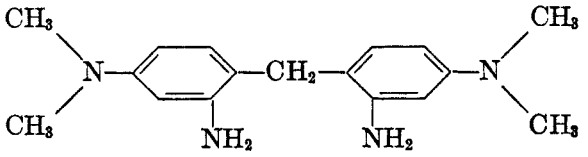
PREPARATION OF POLYAMINO SUBSTITUTED DIPHENYLMETHANES[1]

JOHN H. BILLMAN, DONALD G. THOMAS, M. HEDRICK, G. SCHROTENBOER, DAVID K. BARNES, J. NEMEC, P. TRIX, ELIZABETH CLELAND

Received May 31, 1946

It has been known for a long time that acridine compounds possess antimalarial activity. The outstanding example of this type of compound is Atabrine which has sufficient activity to make it a good substitute for quinine. However, Atabrine like all other acridine derivatives is appreciably toxic. It is therefore important to continue the search for other quinine substitutes having fewer undesirable physiological side reactions. One approach to this problem is the synthesis of compounds closely related to Atabrine but not having the acridine nucleus.

It was found by Small (1) that 2,2′-diamino-4,4′-bisdimethylaminodiphenylmethane (I) and 2,2′-diamino-4,4′-bisdiethylaminodiphenylmethane (II) possess antimalarial activity in avian malaria.



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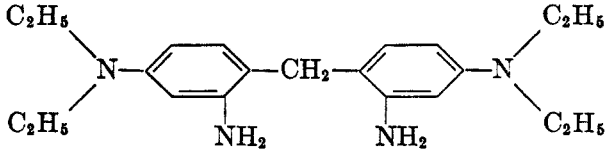
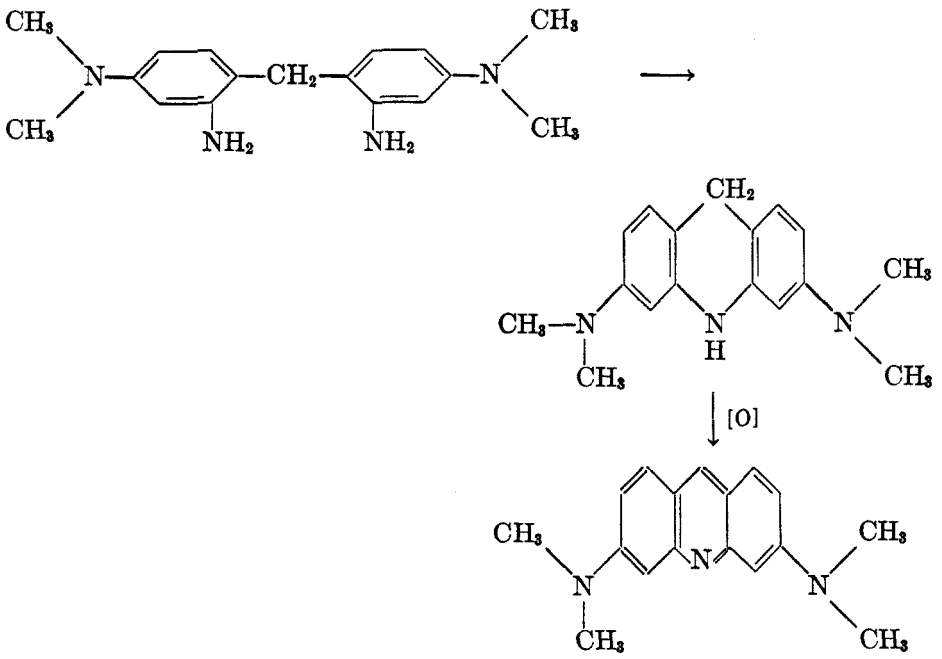


II

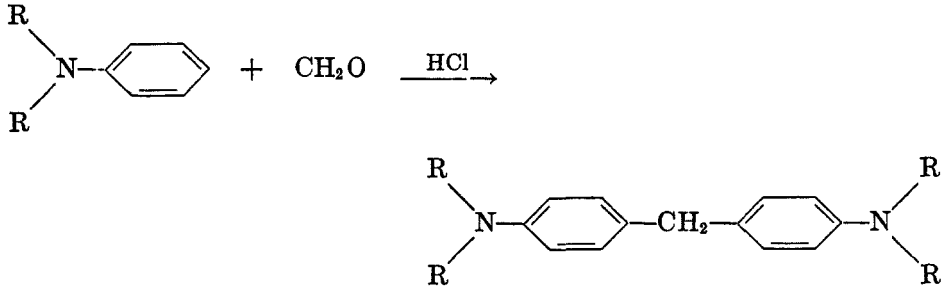
These compounds may be thought of as precursors to the acridines and thus be related to Atabrine since it has been shown by Biehringer (2) that compounds of this type may be deaminated to produce dihydroacridines which are readily oxidized by oxygen or ferric chloride to acridines.

[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Indiana University at Bloomington, Indiana.

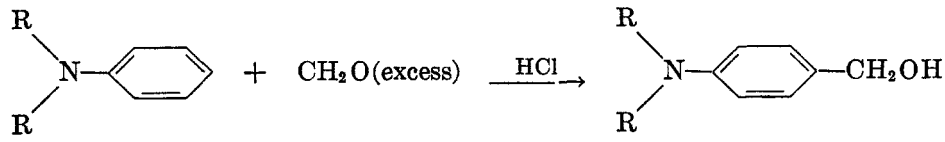


In view of these facts it was decided to prepare a number of chloro-, alkoxyl,- and alkyl-substituted polyaminodiphenylmethanes in order to see whether or not they would be more active and less toxic than the acridines.

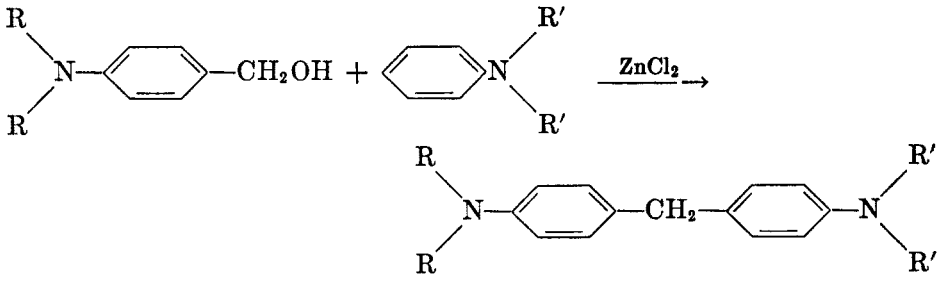
To prepare the symmetrically substituted diaminodiphenylmethanes the appropriate aniline derivatives were allowed to react with the calculated amount of formaldehyde.



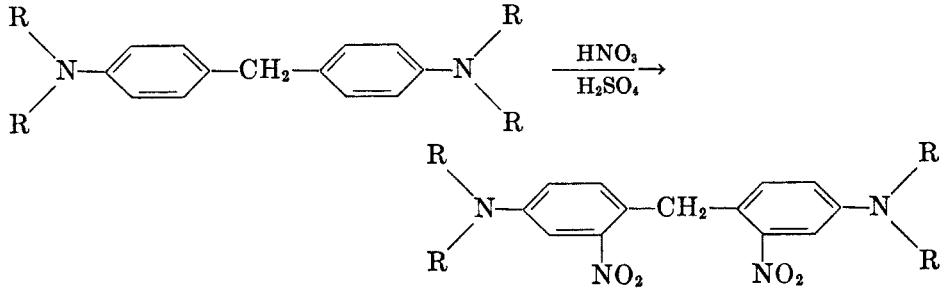
In the case of the unsymmetrically substituted diaminodiphenylmethanes it was necessary first to treat one of the substituted anilines with an excess of formaldehyde to obtain a benzyl alcohol.



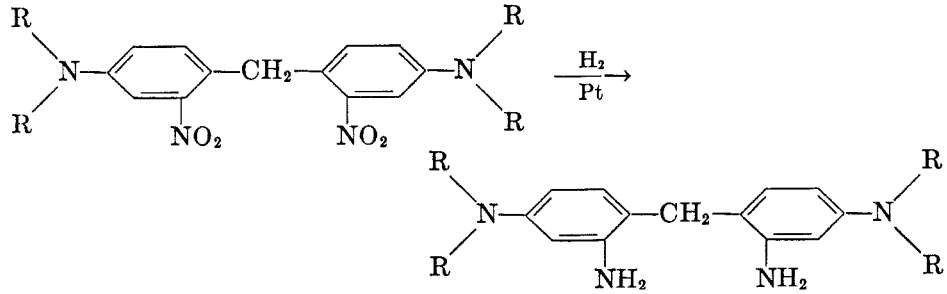
The benzyl alcohols thus formed were then allowed to react with another substituted aniline to produec the desired unsymmertical diaminodiphenylmethane derivative.



The tetraaminodiphenylmethanes were prepared by first nitrating the corresponding diaminodiphenylmethane with a sulfuric acid-nitric acid mixture to the dinitro derivative. According to previous workers these nitro groups enter the 2,2′ positions (2, 3). When half the calculated amount of nitric acid was used a mononitro derivative was formed.



The reduction of the dinitro compounds by the usual chemical methods was in general unsatisfactory for the yields were low or the nitro groups failed to reduce. Catalytic hydrogenation worked very well even with the compounds containing halogen atoms, provided that absolute ethyl alcohol was used as the solvent. It was found that water considerably reduced the rate of reduction of the dinitro compounds. This is in agreement with some observations made by Adams and co-workers (4) on the reduction of some simple mononitro compounds except that the effect of the presence of water on the reduction of the dinitro compounds was much more pronounced. Even a small percentage of water would add hours rather than minutes to the reduction time.



The compounds prepared are shown in Tables I, II, and III of the Experimental.

TABLE I

DIAMINODIPHENYLMETHANES

	M.P. OR B.P., °C., UNCORR.	CALC'D	FOUND
2,2'-Dichloro-4,4'-bis-(diethylamino)-diphenylmethane	68–69	N 7.38	7.37
3-Chloro-4,5'-bis-(dimethylamino)-2'-methoxydiphenylmethane*	104 (dec.)	N 3.96	4.00
3'-Chloro-4-dimethylamino-5'-diethylamino-2-methoxydiphenymethane	95	N 3.81	4.14
3,3'-Dichloro-4,4'-bis-(dimethylamino)-diphenylmethane·2HCl	70–73	Cl^- 17.92	17.87
3-Chloro-4-dimethylamine-4'-diethylamino-diphenylmethane*	115	N 3.97	4.30
3-Chloro-4-dimethylamino-4'-di-*n*-propylaminodiphenylmethane*	220 (dec.)	N 3.81	3.41
3-Chloro-4-dimethylamino-4'-di-*n*-butylaminodiphenylmethane*	220 (dec.)	N 3.68	3.71
3-Chloro-4-dimethylamino-5'-amino-2'-methoxydiphenylmethane·2HCl·$4H_2O$	172–174	Cl^- 16.3	16.2
3-Chloro-4-dimethylamino-2'-methyl-5'-aminodiphenylmethane·2HCl·$3H_2O$	174–176 (dec.)	Cl^- 17.6	17.4
4,4'-Bis-(methyl-*n*-propylamino)diphenylmethane	291–296/40 mm.		
2,4'-Bis-(dimethylamino)-5-methyldiphenylmethane	85–86		
2,2'-Dichloro-4,4'-bis-(dimethylamino)-diphenylmethane	98–99	[b]	
2,2'-Bis-(dimethylamino)-5,5'-dimethyldiphenylmethane		[a]	
3-Chloro-4,4'-bis-(dimethylamino)-diphenylmethane		[b]	
4,4'-Bis-(methylethylamino)diphenylmethane	253–255/18 mm.	[c]	
3,3'-Dichloro-6,6'-bis-(dimethylamino)-diphenylmethane		[b]	
2,4'-Bis-(dimethylamino)-5-chlorodiphenylmethane	159–160	N 9.70	9.69

* Prepared as a salt of 1,1'methylene-bis-(2-hydroxy-3-naphthoic acid). The melting points are for the salts.

[a] Previously prepared by Braun and Kruber, *Ber.*, **45**, 2977 (1912).

[b] Previously prepaed by Braun and Kruber, *Ber.*, **46**, 3460 (1913).

[c] Previously prepared by Frohlich, *Ber.*, **44**, 1062 (1911).

Acknowledgment: We wish to thank Dr. Lyndon Small of The National Institute of Health, Bethesda, Maryland, for suggesting this problem.

EXPERIMENTAL

N,N-Dialkylanilines. These compounds were synthesized by treating the desired aniline with a trialkyl orthophosphate similar to the procedure previously described (5).

3-Chloro-4-dimethylaminobenzyl alcohol. 3-Chloro-4-dimethylaminobenzyl alcohol was prepared by the procedure of Braun and Kruber (6). A yield of 71.9 g. of the benzyl alcohol was obtained from 146.6 g. of *o*-chlorodiethylaniline. The other benzyl alcohols used in this work were prepared by a similar procedure.

TABLE II

NITRO-DIAMINODIPHENYLMETHANES

	M.P., °C. (UNCORR.)	CALC'D	FOUND
2,2′-Dinitro-4,4′-bis-(diethylamino)-diphenylmethane	119–120	[a]	
2,2′-Dinitro-4,4′-bis-(methyl-*n*-propylamino)diphenylmethane	83		
2,4′-Dinitro-2′,4-bis-(diethylamino)-5-methyldiphenylmethane		11.94	11.90
2,2′-Dinitro-4,4′-bis-(diethylamino)-6,6′-dimethyldiphenylmethane	118–119	N 13.07	12.76
2,2′-Dinitro-6,6′-dichloro-4,4′-bis-(dimethylamino)diphenylmethane	157–157.5	Cl 17.19	17.24
2,2′-Bis-(dimethylamino)-4,4′-dinitro-5,5′-dimethyldiphenylmethane	107–108	[b]	
3-Chloro-4,4′-bis-(dimethylamino)-6,6′-dinitrodiphenylmethane	183		
2,2′-Dinitro-4,4′-bis-(methylethylamino)-diphenylmethane	101–102	N 15.05	14.74
3-Chloro-4-dimethylamino-2′-methyl-5′-nitrodiphenylmethane	86–87		
2,2′-Dinitro-4,4′-bis-(dimethylamino)-diphenylmethane		[c]	
2,2′-Dinitro-6,6′-dichloro-4,4′-bis-(diethylamino)diphenylmethane	77	N 11.94	11.90
4,4′-Dinitro-5,5′-dichloro-2,2′-bis-(dimethylamino)diphenylmethane	120–122	Cl 17.19	17.68
2-Nitro-6,6′-dichloro-4,4′-bis-(dimethylamino)diphenylmethane	95–98	Cl 19.29	19.62

[a] Previously prepared by Epstein, *Chem. Zentr.*, **74**, I, 798 (1903).

[b] Previously prepared by Braun, Kruber and Aust, *Ber.*, **46**, 3056 (1913).

[c] Previously prepared by Pinnow, *Ber.*, **27**, 3162 (1894).

Diaminodiphenylmethanes. Method A. The symmetrically substituted diaminodiphenylmethanes were synthesized by allowing two moles of the desired N,N-dialkylaniline to react with approximately nine-tenths of a mole of formaldehyde. A typical example of this method is illustrated by the preparation of 2,2′-dichloro-4,4′-bis-diethylaminodiphenylmethane.

Method B. The unsymmetrically substituted diaminodiphenylmethanes were prepared by allowing an aminobenzyl alcohol to react with an N,N-dialkylaniline. The preparation of 3-chloro-4-dimethylamino-4′-di-*n*-butylaminodiphenylmethane serves to illustrate the procedure used.

2,2'-Dichloro-4,4'-bis-diethylaminodiphenylmethane. To 100 g. (0.545 mole) of *m*-chlorodiethylaniline in a 500-cc. round-bottomed flask was added 68 g. of concentrated hydrochloric acid with stirring and cooling. To this solution was added 17.1 g. of 40% formaldehyde (8.8 g. or 83% of the theoretical amount) and it was allowed to stand for twelve hours. The solution was refluxed for five hours, allowed to stand for forty hours at room temperature, then poured upon 300 g. of ice and made basic with cold sodium hydroxide solution (60 g. of sodium hydroxide in 300 cc. of water). The product separated as an oil. The basic

TABLE III

TETRA-AMINODIPHENYLMETHANES

	M.P., °C. (UNCORR.)	CALC'D	FOUND
2,2'-Diamino-4,4'-bis-(methyl-*n*-propylamino)diphenylmethane tetrahydrochloride		N 11.52	11.49
2,2'-Diamino-4,4'-bis-(diethylamino)-6,6'-dimethyldiphenylmethane trihydrochloride	180 (dec.)	Cl 22.30	22.30
2,2'-Diamino-4,4'-bis-(dimethylamino)-6,6'-dichlorodiphenylmethane dihydrochloride	(dec.)	Cl 33.29	33.21
2,2'-Bis-(dimethylamino)-4,4'-diamino-5,5'-dimethyldiphenylmethane trihydrochloride	[a]	Cl 25.22	25.12
3-Chloro-4,4'-bis-(dimethylamino)-6,6'-diaminodiphenylmethane	134	N 17.57	17.59
2,2'-Diamino-4,4'-bis-(methylethylamino)-diphenylmethane, salt with 1,1'-methylene-bis-(2-hydroxy-3-naphthoic acid)	210 (dec.)	N 5.14	4.76
2,2'-Dichloro-4,4'-bis-(diethylamino)-6,6'-diaminodiphenylmethane trihydrochloride tetrahydrate	193–195 (dec.)	Cl^- 18.00	17.99
2,4'-Bis-(dimethylamino)-4,2'-diamino-5-methyldiphenylmethane		[b]	
2,2',4,4'-Tetra(diethylamino)diphenylmethane tetrahydrochloride	180–193	Cl 23.75	23.60
2,2'-Bis-(acetylamino)-4,4'-bis-(dimethylamino)diphenylmethane	231	N 15.21	15.00
2,2'-Diamino-4,4'-bis-(dimethylamino)-diphenylmethane		[c]	

[a] Previously prepared as the free base by Braun, Kruber and Aust., *Ber.*, **46**, 3056 (1913).
[b] Previously prepared by Braun, Kruber, and Aust, *Ber.*, **46**, 3056 (1913).
[c] Previously prepared by Biehringer, *J. prakt. Chem.*, [2], **54**, 242 (1899).

mixture was steam-distilled to remove the unchanged *m*-chlorodiethylaniline and then extracted with benzene. The benzene was removed by distillation and the residue was distilled under diminished pressure. The first fraction, which weighed 9 g., distilled at 95–100° (1.5–2 mm.). The main fraction of 61.8 g., which distilled at 240–250° (1.5–2 mm.), was 2,2'-dichloro-4,4'-bis-diethylaminodiphenylmethane. Crystals were obtained from alcohol which melted at 68–69°. Twenty-five and three-tenths grams of unchanged *m*-chlorodiethylaniline was recovered. The yield, based on the amount of *m*-chlorodiethylaniline which reacted, was 80.3%.

Anal. Calc'd for $C_{21}H_{28}Cl_2N_2$: N, 7.38. Found: N, 7.37.

2,2'-Dichloro-4,4'-bis-diethylamino-6,6'-dinitrodiphenylmethane. To 120 g. of concentrated sulfuric acid was added slowly 21.0 g. (0.055 mole) of 2,2'-dichloro-4,4'-bis-diethylaminodiphenylmethane. To this solution in a flask surrounded by a water-bath at room temperature was added with vigorous stirring a mixture of 11.4 g. (0.128 mole) of concentrated nitric acid and 11.4 g. of concentrated sulfuric acid. The addition required about an hour and during this time the water-bath became somewhat warmer. The orange solution was allowed to stand at room temperature for twenty-four hours, poured upon cracked ice and neutralized with a saturated sodium carbonate solution. The gummy material which separated was collected on a filter and washed thoroughly with water to remove the inorganic salts. The residue was recrystallized twice from hot alcohol; after the second recrystallization, 8.3 g. (32%) of the pure, orange 2,2'-dichloro-4,4'-bis-diethylamino-6,6'-dinitrodiphenylmethane was obtained which melted at 77°.

Anal. Calc'd for $C_{21}H_{26}Cl_2N_4O_4$: N, 11.94. Found: N, 11.90.

A similar procedure was used for the preparation of all of the dinitro compounds with the exception that some of the reactions were carried out at 0° instead of room temperature.

2,2'-Dichloro-4,4'-bis-diethylamino-6,6'-diaminodiphenylmethane trihydrochloride tetrahydrate. Three grams (0.064 mole) of 2,2'-dichloro-4,4'-bis-diethylamino-6,6'-dinitrodiphenylmethane was dissolved in 100 cc. of absolute alcohol and 0.057 g. of platimum oxide catalyst was added. Reduction was carried out at 25° and with an initial pressure of hydrogen of about forty pounds. The theoretical amount of hydrogen was used in about four hours. The solution was filtered by gravity into a warm flask containing low-boiling petroleum ether. The vapors of petroleum ether displaced the oxygen in the flask and thus prevented darkening of the amine. Most of the alcohol and petroleum ether were removed under reduced pressure. Low-boiling petroleum ether was added to the concentrated alcoholic solution and the solution cooled, but the amine oiled out of solution and could not be obtained crystalline.

After all the alcohol and petroleum ether had been removed, 100 cc. of dry benzene was added and dry hydrogen chloride passed into the solution for one or two minutes. A pink hydrochloride precipitated and was removed by filtration. Traces of solvent were removed under reduced pressure in a vacuum desiccator. A yield of 2.8 g. (79.8%) of 2,2'-dichloro-4,4'-bis-diethylamino-6,6'-diaminodiphenylmethane trihydrochloride trihydrate was obtained which melted with decomposition at 193–195°.

Anal. Calc'd for $C_{21}H_{41}Cl_5N_4O_4$: Cl (ionizable), 18.00. Found: Cl, 17.99.

3-Chloro-4-dimethylamino-4'-di-n-butylaminodiphenylmethane. To 25.0 g. (0.135 mole) of 3-chloro-4-dimethylaminobenzyl alcohol was added 52.0 g. (0.254 mole) of di-*n*-butylaniline and 40 g. of fused zinc chloride. After heating and stirring the mixture at 180° for nine and one-half hours, the viscous mass was poured into cold water. Excess sodium hydroxide was added to the solution and the mixture heated to boiling to dissolve the zinc hydroxide which precipitated when the complex was decomposed with base. The oily layer containing the product and unreacted starting material was removed from the water layer by extraction with benzene. The benzene solution was dried and distilled under reduced pressure. Twenty-one grams of di-*n*-butylaniline was recovered. The yield of 3-chloro-4-dimethylamino-4'-di-*n*-butylaminodiphenylmethane which distilled at 235–242°/3 mm., was 34.8 g. or 69.2% on the basis or the benzyl alcohol used.

To 10.325 g. (0.0277 mole) of this diamine was added about 10 cc. of concentrated hydrochloric acid. The solution was diluted and heated to boiling at which time a dilute ammonium hydroxide solution was added dropwise until a drop produced a point of lasting turbidity.

To 10.758 g. (0.0277 mole) of 1,1'-methylene-bis-(2-hydroxy-3-naphthoic acid) was added an excess of dilute ammonium hydroxide. The solution was made neutral by boiling until all of the excess ammonia was expelled.

When the above solutions were cool, and each had been diluted to about 400 cc. with distilled water, they were mixed with vigorous stirring. The precipitate which formed was

filtered off and washed well with water. After drying the precipitate over phosphorus pentoxide the product weighed 20.1 g. This is a 95% yield of the 1,1′-methylene-bis(2-hydroxy-3-naphthoic acid) salt of 3-chloro-4-dimethylamino-4′-di-*n*-butylaminodiphenylmethane.

Anal. Calc'd for $C_{43}H_{49}ClN_4O_6$: N, 3.68. Found: N, 3.71.

SUMMARY

A series of 31 new di-, tri-, and tetra-amino substituted diphenylmethanes have been prepared. All of the tetra-amino diphenylmethanes and some of the diaminodiphenylmethanes were submitted for testing of their antimalarial activity.

BLOOMINGTON, IND.

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(5) THOMAS, BILLMAN, AND DAVIS, *J. Am. Chem. Soc.*, **68**, 895 (1946).
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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE VAPOR-PHASE CHLORINATION OF ALIPHATIC KETONES

NORMAN RABJOHN[1] AND EDGAR R. ROGIER

Received May 31, 1946

The preparation of chlorinated aliphatic ketones has been accomplished usually in the liquid phase in the presence of metallic carbonates. This procedure is time-consuming, and often does not lead to satisfactory yields of the desired compounds. The recent patent literature (1, 2, 3, 4) has indicated that ketones can be chlorinated successfully in the vapor phase. Previously, Akashi (5) had reported the vapor-phase chlorination of a number of aliphatic compounds in the presence of nickel chloride. Justoni (6) has apparently[2] carried out a critical examination of the various methods for the chlorination of ketones. Aside from the latter work, no study has been made of the chlorination of ketones in the vapor state.

The present investigation was concerned with the vapor-phase chlorination at atmospheric pressure of a limited number of aliphatic ketones in order to determine its value as a preparative method, and to identify the resulting products. It was also hoped that some idea might be gained of the preferential position taken by a chlorine atom upon entering a ketone molecule.

The chlorinations were accomplished simply by passing a stream of dry chlorine into the vapors of the ketone by means of the apparatus described in the Experimental part. The products of the reaction were collected, separated by fractional distillation and identified. The following chart summarizes the ketones which have been chlorinated, the products isolated and the approximate proportions of each obtained.

$$CH_3COC(CH_3)_3 \xrightarrow{Cl_2} \begin{cases} ClCH_2COC(CH_3)_3 & (85\%) \\ Cl_2CHCOC(CH_3)_3 & (8\%) \\ ClCH_2COC(CH_3)_2(CH_2Cl) & (7\%) \end{cases}$$

$$CH_3COCH_2CH_3 \xrightarrow{Cl_2} \begin{cases} CH_3COCHClCH_3 & (62\%) \\ ClCH_2COCH_2CH_3 & (21\%) \\ ClCH_2COCHClCH_3 & (17\%) \end{cases}$$

$$CH_3COCH(CH_3)_2 \xrightarrow{Cl_2} \begin{cases} CH_3COCCl(CH_3)_2 & (58\%) \\ ClCH_2COCCl(CH_3)_2 & (27\%) \\ ? & (15\%) \end{cases}$$

$$C_6H_5COCH_3 \xrightarrow{Cl_2} C_6H_5COCH_2Cl + C_6H_5COCHCl_2 \text{ (Mixture)}$$

Pinacolone was readily chlorinated in the vapor phase to give a high yield of a monochlorinated product (1-chloro-3,3-dimethyl-2-butanone) and small amounts of the two dichlorinated products indicated. The results are interesting since

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[2] After our study had been completed, an abstract (6) of Justoni's investigation appeared. As yet, it has not been possible to obtain the original article.

they are quite different from those of Hill and Kropa (7) for liquid-phase chlorination. These authors found that 1-chloro-3,3-dimethyl-2-butanone could be prepared only with difficulty in low yield. In agreement with Fittig (8) they observed that the principal product of the reaction was 1,1-dichloro-3,3-dimethyl-2-butanone. The vapor-phase chlorination of pinacolone affords only a few per cent of this material. It is also of interest that another dichloro compound (1,4-dichloro-3,3-dimethyl-2-butanone) resulted from the latter reaction. In this case a methyl group has been attacked which is removed from the influence of the carbonyl group.

The products of the vapor-phase chlorination of methyl ethyl ketone are similar to those obtained in the liquid phase. Vladesco (9) has reported that 3-chloro-2-butanone and 1,3-dichloro-2-butanone can be isolated from the reaction of chlorine on methyl ethyl ketone. In the presence of calcium carbonate Kling (10) obtained a mixture consisting of about 80% of 3-chloro-2-butanone and 20% of 1-chloro-2-butanone. Blaise (11) has shown that an aqueous solution of methyl ethyl ketone produces 1,1-dichloro-2-butanone, 1,3-dichloro-2-butanone and 3,3-dichloro-2-butanone when treated with chlorine at 60°. The fact that only one dichloro ketone (1,3-dichloro-2-butanone) was isolated from vapor-phase chlorination may be attributed in part, at least, to the rapid removal of the reaction products from the zone of reaction.

Aside from the work of Justoni (6) the direct chlorination of methyl isopropyl ketone apparently has not been attempted. The vapor-phase chlorination of this ketone led to a mixture of products which could not be separated cleanly. It was possible to identify 3-chloro-3-methyl-2-butanone and 1,3-dichloro-3-methyl-2-butanone. A higher-boiling fraction, which was not characterized, appeared to be a dichloro ketone. The ratio of mono- to di-chlorination was approximately 1:1.

Lapworth (12) originally suggested that reactions of chlorine and bromine with compounds containing a carbonyl group are preceded in all cases by enolization. The latter process is slow compared with the rapid addition of the halogen to the enol. Meyer (13) has pointed out that enolization is catalyzed by acids to a greater degree in non-ionizing then in ionizing media. It would appear that the vapor-phase system satisfies this condition ideally.

Bartlett and co-workers (14) have made a study of the relative rates of formation of the enols which can arise in a series of optically active secondary butyl ketones. They found, contrary to the general impression, that under acid catalytic conditions tertiary hydrogen atoms are less active as regards rate of enolization than either primary or secondary hydrogen atoms. This is directly opposite to the results they had obtained previously with menthone, and they concluded that there is no simple relationship between alkyl substitution and rate of competitive enolization.

The relative proportions of the products obtained from the vapor-phase chlorination of the ketones studied give a qualitative picture that seems to agree with Bartlett's results. In the case of pinacolone, where the only *alpha* hydrogen atoms are primary, a high yield of the expected monochlorinated product resulted.

Acetone exhibits (4) a similar behavior when chlorinated in the vapor state. Only a few per cent of symmetrical dichloroacetone has been isolated from the high-boiling residues left after removing the monochloroacetone. This demonstrates the relative difficulty of substituting a second hydrogen atom by means of vapor-phase chlorination. It appears that in pinacolone a *beta* hydrogen atom can be replaced as readily as a second *alpha* hydrogen.

Methyl ethyl ketone offers both primary and secondary *alpha* hydrogen atoms for attack by a chlorine atom. As was expected the secondary hydrogen was substituted much more readily than the primary. The ratio of chlorinated products isolated was approximately 3:1. In the case of methyl isopropyl ke-

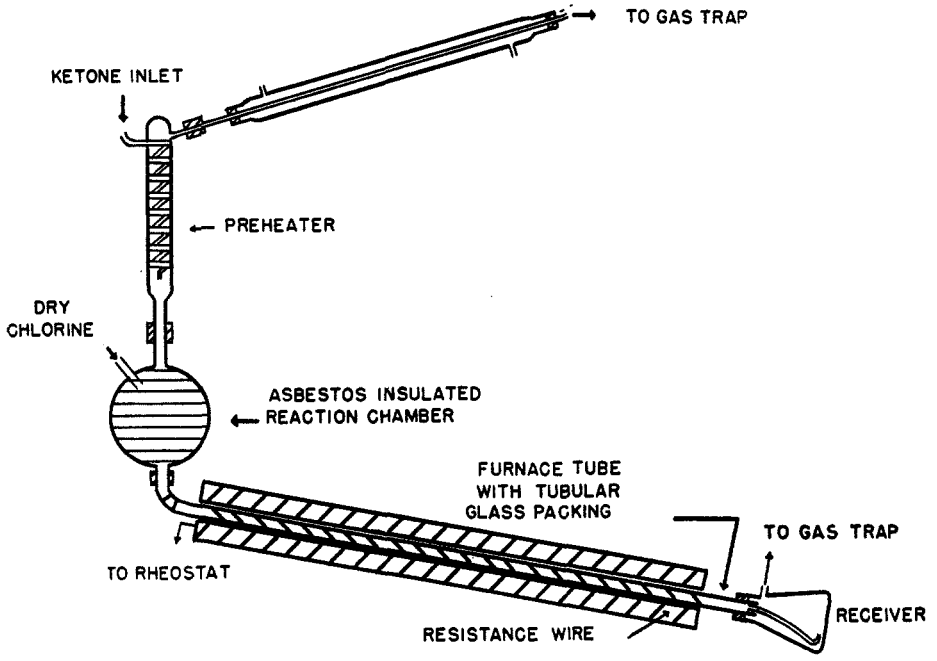

FIG. I. VAPOR PHASE CHLORINATION APPARATUS

tone, where primary and tertiary *alpha* hydrogens are in competition, the latter is more readily substituted. However, the yield of monochlorinated ketone was not as high as might have been anticipated. Since no 1-chloro-3,3-dimethyl-2-butanone, but a considerable quantity of 1,3-dichloro-3,3-dimethyl-2-butanone, was obtained it is difficult to attempt to compare the relative ease of substitution here. It might be argued, from the apparent difficulty with which dichlorination occurs that a primary *alpha* hydrogen was replaced prior to a tertiary in the formation of 1,3-dichloro-3,3-dimethyl-2-butanone.

EXPERIMENTAL

General procedure for vapor-phase chlorination. The chlorinations were performed in the apparatus shown in the accompanying diagram. Commercial chlorine was bubbled

through concentrated sulfuric acid before entering the reaction chamber. The furnace tube was maintained at a temperature sufficiently above the boiling point of the unchlorinated ketone so that gentle refluxing occurred in the preheater. The addition of the ketone was adjusted so that it equaled the flow of chlorinated products from the liquid-sealed trap. The combination of the ketone and chlorine produced a vigorous exothermic reaction.

Chlorination of pinacolone. The chlorination of 300 g. of pinacolone (b.p. 103–107°) yielded 357 g. of chlorinated ketones. Distillation[3] of the mixture gave the following fractions:

FRACTION	B.P. (15 MM.), °C	WGT. (G.)
1	29–69	9.0
2	69–72	13.4
3	72–74	46.7
4	74–76	92.2
5	75–76	47.3
6	76–78	47.0
7	78–79	24.2
8	79–84	25.8
9	84–110	7.4
10	110–113	6.6
11	113–119	4.3

Fractions 1, 4, 8, and 10 were redistilled and identified.

Fraction 1; pinacolone: b.p. 106–107°. The 2,4-dinitrophenylhydrazone (m.p. 125–126°) of this material showed no depression of the melting point when mixed with a known sample of pinacolone 2,4-dinitrophenylhydrazone.

Fraction 4; 1-chloro-3,3-dimethyl-2-butanone: A colorless, highly lachrymatory liquid which turned red upon standing for several months; b.p. 75–76°/15 mm.; n_D^{20} 1.4422. Hill and Kropa (7) have reported the boiling point of this material as 60.5°/7 mm. The 2,4-dinitrophenylhydrazone of this compound crystallized in orange-yellow prisms from alcohol; m.p. 143–144°.

Anal. Calc'd for $C_{12}H_{15}ClN_4O_4$: C, 45.79; H, 4.84.
Found: C, 45.90; H, 4.94.

Oxidation of a sample of the chloro ketone with sodium hypobromite solution yielded an acid which melted at 33–34°. The *p*-bromophenacyl ester of this acid (m.p. 77–78°) caused no depression in the melting point of a known sample of *p*-bromophenacyl pivalate.

Fraction 8; 1,1-dichloro-3,3-dimethyl-2-butanone. This material solidified in the receiver of the fractionating apparatus and crystallized from dilute alcohol in long, colorless needles; m.p. 50–51° [Fittig (8) gave the melting point as 51°]. The 2,4-dinitrophenylhydrazone formed with difficulty. It was crystallized from alcohol and obtained in the form of orange needles; m.p. 185–186° (decomp.).

Anal. Calc'd for $C_{12}H_{14}Cl_2N_4O_4$: C, 41.27; H, 4.04.
Found: C, 41.28; H, 3.86.

Oxidation of a portion of the dichloro ketone with sodium hypochlorite solution gave pivalic acid; *p*-bromophenacyl ester (m.p. 77–78°).

Fraction 10; 1,4-dichloro-3,3-dimethyl-2-butanone: A colorless, lachrymatory liquid which turned black upon standing for several days; b.p. 111–112°/15 mm.; n_D^{20} 1.4758.

Anal. Calc'd for $C_6H_{10}Cl_2O$: Cl, 41.9. Found: Cl, 41.6.

The 2,4-dinitrophenylhydrazone of this compound was crystallized from alcohol; m.p. 118–119°.

Anal. Calc'd for $C_{12}H_{14}Cl_2N_4O_4$: C, 41.27; H, 4.04.
Found: C, 41.59; H, 4.16.

[3] All fractionations were carried out with a column packed with glass helices and having about a 12 plate rating.

The dichloro ketone was treated with sodium hypobromite solution and yielded β-chloropivalic acid. The amide of this acid was prepared and crystallized from water in colorless plates; m.p. 108–109°. A mixed melting point with a known sample of this amide, prepared according to the method of Kharasch (15), showed no depression.

Chlorination of methyl ethyl ketone.[4] One kilogram of redistilled methyl ethyl ketone (b.p. 77–78°) was passed through the chlorinator and 1241 g. of a crude product was obtained. It was fractionated as follows:

FRACTION	B.P., °C	WGT. (G.)
1	65–103	404
2	103–111	33
3	111–113	467
4	113–133	29
5	133–140	156
6	140–160	20
7	70–75 (30 mm.)	128

Fractions 3, 5 and 7 were redistilled and identified.

Fraction 3; 3-chloro-2-butanone: A colorless, highly lachrymatory liquid which turned yellow upon standing; b.p. 112–113°; n_D^{20} 1.4171 [Kling (10) has given the boiling point as 114–117°]. The semicarbazone of this compound was prepared by the method of Curd and Robertson (16). It melted at 138–139°. By heating a small quantity of the chloro ketone with aniline at 100°, as described by Vladesco (9), 2,3-dimethylindole was obtained; m.p. 106–107°.

Fraction 5; 1-chloro-2-butanone: A colorless, lachrymatory liquid which turned pink upon standing; b.p. 137–138°; n_D^{20} 1.4372. Levene and Haller (17) have given this boiling point as 138.8–139.2°/755 mm. Phthaliminomethyl ethyl ketone was prepared from the chloro ketone by the method of Kolshorn (18). It was obtained in the form of long, white needles after crystallization from water; m.p. 107–108°.

Anal. Calc'd for $C_{12}H_{11}NO_2$: C, 66.35; H, 5.10.
Found: C, 66.58; H, 4.94.

Fraction 7; 1,3-dichloro-2-butanone: A colorless, extremely lachrymatory liquid which turned violet and then black upon standing; b.p. 166–167°; n_D^{20} 1.4650 [Blaise (11) has reported the boiling point to be 165°]. Oxidation of a sample of this material with sodium hypobromite gave α-chloropropionic acid; b.p. 184–185°. This was identified by conversion to the phenylhydrazine salt according to the procedure of Stempel and Schaffel (19). A mixed melting point with the corresponding salt of a known sample of α-chloropropionic acid gave no depression.

Chlorination of methyl isopropyl ketone. The ketone was prepared by the directions of Whitmore, Evers, and Rothrock (20). The chlorination was carried out with 240 g. of ketone; yield, 316 g. of crude product. On distillation, the following fractions were obtained.

FRACTION	B.P. (15 MM.) °C	WGT. (G.)
1	29–30	61
2	30–56	28
3	56–58	71
4	58–65	21
5	65–72	25
6	72–73	34
7	73–98	12
8	98–99	18

Fractions 1, 3, and 6 were redistilled and identified.

[4] This experiment was performed by Mr. Calvin Wolf.

Fraction 1; methyl isopropyl ketone. The boiling point and refractive index of this material were identical with those of methyl isopropyl ketone.

Fraction 3; 3-chloro-3-methyl-2-butanone: A colorless, highly lachrymatory liquid; b.p. 145–146°; n_D^{20} 1.4390. Treatment of 8 g. of this ketone with 200 cc. of 17% sodium hypochlorite solution gave a solid, chlorine-free acid. It was crystallized from petroleum ether; m.p. 78–80°. A mixed melting point with a known sample of α-hydroxyisobutyric acid was not depressed. The 2,4-dinitrophenylhydrazone of this ketone crystallized in orange colored needles from alcohol; m.p. 115–116°.

Anal. Calc'd for $C_{11}H_{13}ClN_4O_4$: N, 18.62. Found: N, 18.25.

Fraction 6; 1,3-dichloro-3-methyl-2-butanone: A colorless, lachrymatory liquid; b.p. 164–165°; n_D^{20} 1.4600.

Anal. Calc'd for $C_5H_8Cl_2O$: C, 38.70; H, 5.20; Cl, 45.7.
Found: C, 38.60; H, 5.58; Cl, 45.0.

Chlorination of acetophenone. Three hundred grams of acetophenone, b.p. 197–199°, was chlorinated in the previously described manner. The product weighed 316 g. and was distilled through a 500 cc. modified Claisen flask. The following fractions were obtained;

FRACTION	B.P. (20 MM.), °C	WGT. (G.)
1	95–133	51
2	133–134	137
3	136–137	90

Fraction 1 consisted largely of unchanged acetophenone.

Fractions 2 and 3 would not crystallize at room temperature but solidified in an ice-chest. A portion of fraction 2 was crystallized from petroleum ether and gave colorless prisms which melted at 55–56°. The melting point of phenacyl chloride has been reported to be 59° (21). Oxidation of a sample of fraction 2 by means of sodium hypobromite yielded only benzoic acid.

ACKNOWLEDGMENT

The authors wish to thank Dr. Nelson J. Leonard for his assistance during part of this work. They are also indebted to Miss Theta Spoor for the microanalytical data reported in this paper.

SUMMARY

Several aliphatic ketones have been chlorinated in the vapor phase and the products of the reaction identified. The method affords a relatively simple means of obtaining a number of chloro-substituted ketones.

URBANA, ILL.

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[CONTRIBUTION FROM THE VENABLE LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

ACYLOINS. I. REACTION OF ACYLOIN ENOLATES WITH PRIMARY ALKYL HALIDES

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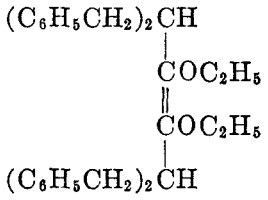
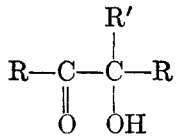
The available data concerning the reaction of alkyl halides with intermediates in the acyloin condensation indicate that, depending upon the conditions, alkylation of the so-called acyloin enolates may result in the formation of either of two types of products. Kharasch and co-workers (1) have noted the occurrence of dissociation plus carbon-alkylation in liquid ammonia solution, obtaining, for example, a 32% yield of ethyl isopropyl ketone in addition to 28% of isobutyroin upon hydrolysis of a mixture which resulted from the reaction of ethyl bromide with the condensation product of sodium and ethyl isobutyrate. An instance of oxygen-alkylation has, on the other hand, been described by Scheibler and Emden (2) in reporting that the formation of 2,3-diethoxy-1,1,4,4-tetrabenzyl-2-butene (I) occurred when the product from the reaction of potassium with ethyl α,α-dibenzyl acetate was treated with ethyl bromide in ethyl ether.



I

Thus, it may be inferred that the diether of the corresponding enediol normally results from the alkylation of an acyloin enolate in solvents of low dissociating power, particularly since such a conclusion would appear to be supported by the analogy in Bachmann's observation (3) of the conversion of benzil-disodium to the dimethyl ether of α,α'-stilbenediol by methyl iodide, as well as by reports (4) of similar transformations of other metal derivatives of aromatic α-diketones.

In the investigation described in the present writing, acyloin enolates derived from esters of lower aliphatic acids were alkylated with primary alkyl halides, the solvent employed being either toluene or ethyl ether. No evidence of the formation of enediol ethers was obtained. Instead, the product in each case was an



II

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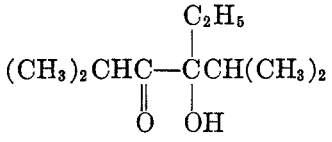
α-hydroxy ketone, the structure of which is represented by the general formula II where R designates the hydrocarbon residue of the aliphatic acid and R′ the primary alkyl group appended during the displacement. The yields of these materials were nearly the same as those obtained in the preparation of the corresponding acyloins. Moreover, the degree of alkylation was apparently not affected by an excess of the alkyl halide.

The first reaction studied was that of ethyl iodide with the isobutyroin intermediate. Upon separation of the resulting mixture, after hydrolysis, only traces of isobutyroin and diisobutyryl were isolated. The principal product was a colorless and, seemingly, pure liquid fraction, the boiling point of which was higher than that of the acyloin. Reactions of this substance with classification reagents revealed the probability of its containing active hydrogen and a carbonyl group; however, tests for unsaturation or an acyloin structure were negative. The Zeisel determination denoted the absence of ethoxyl groups, whereas the molecular weight and the carbon and hydrogen analysis were in agreement with the molecular formula $C_{10}H_{20}O_2$.

It was therefore apparent that this compound was produced from a single carbon-alkylation. Furthermore, inasmuch as the product was not an unsymmetrical acyloin, the attachment must have occurred at the carbon of an antecedent carbonyl group. The only probable structure conforming to these requisites would be that of 2,5-dimethyl-4-ethyl-4-hydroxy-3-hexanone (III). Comparison of the physical properties of the material obtained in this alkylation reaction



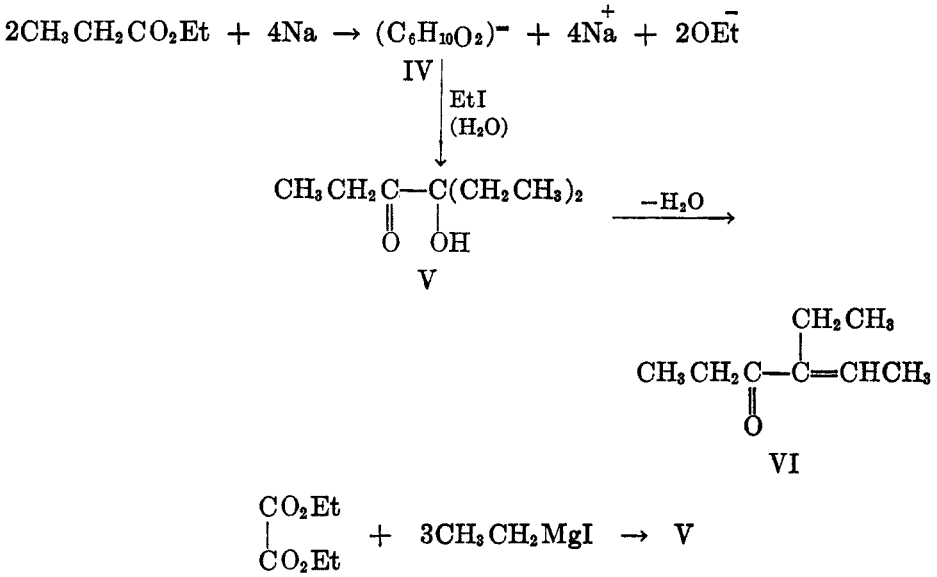
III

with those of III as prepared by the reaction of diisobutyryl with ethylmagnesium iodide[2] served to indicate that this assumption was correct.

The formation of 4-ethyl-4-hydroxy-3-hexanone (V) upon alkylation of the propionoin intermediate with ethyl iodide and the dehydration of V to 4-ethyl-4-hexene-3-one (VI) afforded conclusive evidence regarding the course of this alkylation reaction. Both compounds have been previously described (5), and the identity of V, thus obtained, with a sample prepared by the reaction of ethyl magnesium iodide with ethyl oxalate (6) was established by determination of mixed melting points of the semicarbazones.

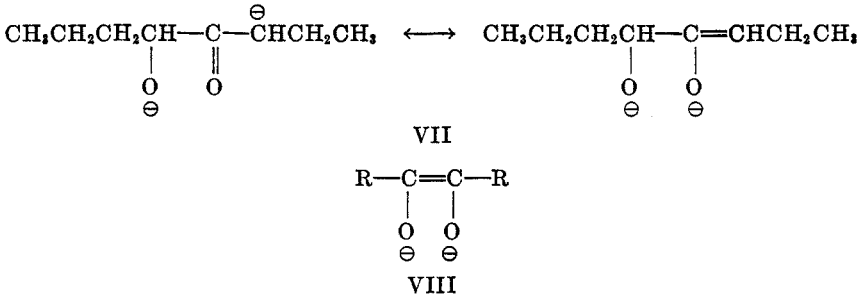
In extending this alkylation by primary alkyl halides to the reaction of the butyroin intermediate with ethyl iodide and of the valeroin intermediate with *n*-butyl bromide, the results achieved were entirely analogous to those obtained

[2] It has been shown by Bouveault, *Bull. soc. chim.*, (3) **35**, 654 (1906), that, because of the proximity effect, the addition reaction of the Grignard reagent with diisobutyryl involves only one carbonyl group. This comparison was therefore accepted as indicating a proof of structure by synthesis.



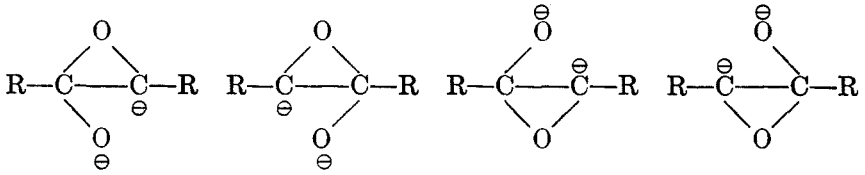
with the isobutyroin and propionoin enolates, and the structures assigned to the products were, respectively, those of 5-ethyl-5-hydroxy-4-octanone and 6-butyl-6-hydroxy-5-decanone. Thus, it appears that this reaction may be general in its application to the purely aliphatic acyloin enolates, although the complete establishment of its scope will necessitate its expansion to other members of the series.

Since there was no indication that the reaction involves other than an ionic process, discussion of the mechanism will for the present be limited to consideration of the probably anonic intermediate, represented in the case of propionoin by the non-committal formula IV. The anion VII has been suggested by Woodward and Blout (7) in describing the condensation of the butyroin intermediate with ethyl acetate because of the general inadequacy of the older dienolate structure (VIII).



It is possible that structures analogous to VII are involved in this reaction with alkyl halides, although such a process would require a rearrangement, inasmuch as the product from the expected alkylation of this form would be otherwise an unsymmetrical acyloin.

Another possible structure for the reacting species in the alkylation is represented by IX. The present data do not constitute a basis for a choice between this form and that of VII. However, it is suggested, in view of the fact that analogs of VII cannot be formulated for systems without enolizable hydrogen, that resonance contributions of the type IX account for the stabilization of anions of aliphatic acyloins such as pivaloin which possess no α-hydrogen.



IX

The investigation of the reaction of the pivaloin intermediate as well as that of other acyloin enolates, with alkyl halides has been temporarily interrupted. The authors look forward to its continuation at the earliest opportunity.

EXPERIMENTAL

All boiling and melting points are corrected.

The fractionating columns employed for the separations described in this section, as well as for the purification of the esters and alkyl halides used as starting materials, were provided with means for adiabatic control and were packed with $\frac{3}{16}$-inch glass helices. The dimensions of the packed sections were either 10 mm. x 45 cm. or 10 mm. x 60 cm. and the still-heads were of the total-condensation variable take-off type.

Preparation of the acyloin intermediates in ethyl ether. The method of Snell and McElvain (8) was modified for the preparation of these substances in ethyl ether, particular care being taken to add the ester to the sodium very slowly in order to minimize the occurrence of secondary reactions which result from the presence of an excess of the former reactant in the mixture.

The following procedure was found to give the best yields either in the subsequent alkylation reactions or upon hydrolysis to the acyloin: Sodium (46 g., 2.0 g. atoms) was very finely powdered in 300 ml. of dry xylene in a 2-l. three-necked flask, equipped with an efficient wire stirrer and a reflux condenser. After decanting the xylene from the powdered metal and washing it thoroughly with absolute ethyl ether, the sodium was suspended in 600 ml. of absolute ethyl ether, the mixture heated to the boiling point on a steam-bath and 1.0 mole of the appropriate ester gradually added, with stirring, over a period of six to eight hours. At the end of the addition the heating and stirring were continued for twelve to fourteen hours. The condensation was then practically complete, only a very small amount of unreacted sodium remaining in the mixture.

Diisobutyryl. Isobutyroin (144 g., 1.0 mole) was dehydrogenated in the liquid phase at 280° over copper chromite catalyst (4 g.) with ethylene as the hydrogen acceptor (9). A high-pressure hydrogenation vessel having an approximate volume of 0.3 l. was employed for the reaction and the initial pressure of the ethylene was adjusted to 51.5 atm. at 28°. The reaction period was thirty hours. After removal of the catalyst the resulting mixture was subjected to fractional distillation, the yellow material boiling at 146–148° (atmospheric pressure) being collected as diisobutyryl; yield 38.2 g. (27%). Lower yields were obtained when the dehydrogenation was carried out over shorter periods.

Alkylation of the acyloin intermediates with ethyl iodide in ethyl ether. Excepting where otherwise noted, all of these reactions were carried out as follows: To the acyloin intermediate in ethyl ether, as formed from the reaction of 1.0 mole of ester, was added 156 g.

(1.0 mole) of freshly-distilled ethyl iodide in one portion. The reaction mixture was then refluxed, with stirring, for twenty-four hours. At the end of this period the mixture was decomposed by the gradual addition of 225 ml. of distilled water and the ether layer separated. The ether solution was washed successively with two 100-ml. portions of distilled water, 100 ml. of 5% hydrochloric acid, and 100 ml. of 5% aqueous potassium bicarbonate and dried over sodium sulfate. The products were then isolated from this solution by fractional distillation.

Tests with classification reagents. Tests with the following reagents, which were carried out according to standard procedures, were negative: (a) alkaline potassium permanganate solution, (b) bromine-carbon tetrachloride solution, (c) Fehling's solution. The reaction of sodium with the materials under investigation was slow at room temperature; upon warming the mixtures the evolution of hydrogen was vigorous.

No evidence of reaction was observed upon treatment of III with either phenylhydrazine or 2,4-dinitrophenylhydrazine. However, all of these α-hydroxy ketones, upon prolonged heating with a solution of semicarbazide hydrochloride and sodium acetate in dilute ethanol, gave high-melting, crystalline products which were not characterized, but which were probably the substituted 4,5-dihydro-3(2)-*as*-triazones resulting from cyclization of the semicarbazones. Attempts to isolate the intermediary semicarbazones were unsuccessful excepting in the case of V.

2,5-Dimethyl-4-ethyl-4-hydroxy-3-hexanone (III). (*a*) *From the reaction of the isobutyroin intermediate with ethyl iodide.* After removal of the solvent by ordinary distillation, the following fractions were obtained from the mixture which resulted from the alkylation of the isobutyroin enolate according to the foregoing general procedure:

FRACTION	BOILING POINT		WEIGHT, G.
	°C.	Mm.	
1	to 109	32.5	trace
2	110–11.5	34–35.5	72.0
	Residue		4.9

Fraction 3 represented an 83.7% yield of 2,5-dimethyl-4-ethyl-4-hydroxy-3-hexanone; b.p. 71.5–72° (4 mm.); n_D^{25} 1.4388; d_4^{25} 0.9072 M_D calc'd 49.92; found 49.93.

Anal. Calc'd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70; mol. wt., 172.26.

Found: C, 69.63; H, 11.75; mol. wt., 171.2 (ebulliometrically in carbon tetrachloride); OC_2H_5 (Zeisel determination), 0.0.

(*b*) *From diisobutyryl.* To the Grignard reagent prepared from 8.5 g. (0.35 g. atom) of magnesium turnings and 56 g. (0.36 mole) of ethyl iodide in 150 ml. of ethyl ether was gradually added, over a period of two hours, a solution of 35.5 g. (0.25 mole) of diisobutyryl in 100 ml. of ethyl ether. Upon completion of the addition, the mixture was refluxed for 1.5 hours. The resulting mixture was then hydrolyzed by the addition of a solution of 25 g. of ammonium chloride in 75 ml. of distilled water. The ether solution was decanted from the aqueous mixture, washed twice with 50-ml. portions of water and dried over anhydrous sodium sulfate. After removal of the ether, distillation of the residue gave the following fractions:

FRACTION	BOILING POINT		WEIGHT, G.
	°C.	Mm.	
1	65–88.5	35	5.7
2	88.5–91	35	5.8
3	91–108.5	35–33.5	1.9
4	108.5–110	33.5–34	13.1

Fractions 1 and 2 were yellow in color and consisted, principally, of isobutyroin resulting from the reduction of diisobutyryl. Fraction 4, which was colorless, represented a 30% yield of 2,5-dimethyl-4-ethyl-4-hydroxy-3-hexanone (based on diisobutyryl); b.p. 70.5–71° (3.5 mm.); n_D^{25} 1.4386.

Anal. Calc'd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70.
Found: C, 69.87; H, 12.14.

4-Ethyl-4-hydroxy-3-hexanone (V). (*a*) *From the reaction of the propionoin intermediate with ethyl iodide.* This alkylation of the propionoin intermediate in ethyl ether by the foregoing general procedure gave 42.3 g. (58.8%) of 4-ethyl-4-hydroxy-3-hexanone; b.p. 88–89° (34.5 mm.).

(*b*) *From the reaction of ethylmagnesium iodide with ethyl oxalate.* The experimental details of this synthesis of V have not been previously reported; hence, they are included here. To the Grignard reagent prepared from 58.3 g. (2.4 g. atoms) of magnesium turnings and 382 g. (2.45 moles) of ethyl iodide in 800 ml. of ethyl ether was gradually added, with stirring, a solution of 111 g. (0.76 mole) of ethyl oxalate in 500 ml. of ethyl ether, during a period of one hour. After refluxing the resulting mixture for ½ hour, decomposition was effected by the gradual addition of 25% aqueous ammonium chloride. The ether solution was then decanted from the aqueous mixture, washed with distilled water and dried over sodium sulfate. The mixture was separated by fractional distillation, the yield of 4-ethyl-4-hydroxy-3-hexanone boiling at 176–177.5° (742 mm.) being 59.6 g. (54.3%) (based on ethyl oxalate). A fraction boiling at 94–95.5° (4 mm.) weighed 9.4 g. and represented a 7.1% yield of 3,4-diethyl-3,4-hexanediol.

The *semicarbazone* of V was prepared by refluxing a mixture of 2.9 g. of the ketone, 2.8 g. of semicarbazide hydrochloride, 3.5 g. of sodium acetate, 5 ml. of 95% ethanol and 7 ml. of distilled water for two hours. At the end of this time the mixture was cooled and 20 ml. of water added in order to complete the precipitation of the semicarbazone. The weight of the crude derivative was 2.8 g.; m.p. 172–175°. Two grams of this product was recrystallized from 65 ml. of boiling water and the material thus obtained recrystallized again from 55 ml. of boiling water. The recovery of the pure white semicarbazone was 1.4 g. (dried at 80°); m.p. 177–177.5° [reported m.p. (5) 178°]. No deviation from this m.p. was observed for mixtures of the semicarbazone of V obtained in *a* with that of the product obtained in *b*.

The *dehydration of V* was carried out in the following manner: To 12.0 g. (0.083 mole) of V, obtained from the alkylation of the propionoin intermediate, was added 10 ml. of syrupy phosphoric acid (85%) and the mixture refluxed for three hours. The resulting mixture was then slowly distilled in an ordinary distillation apparatus until no more organic material appeared in the distillate. Fractional distillation of the upper layer of this distillate gave 1.9 g. (18%) of *4-ethyl-4-hexene-3-one* (VI); b.p. 167–170°. The semicarbazone of this product, after two recrystallizations from 20% aqueous ethanol, melted at 177.5–178° [reported m.p. (5) 178°].

5-Ethyl-5-hydroxy-4-octanone. Alkylation of the butyroin enolate, prepated in ethyl ether, with ethyl iodide by the foregoing general procedure gave 47.1 g. (54.7%) of 5-ethyl-5-hydroxy-4-octanone; b.p. 112–113.5° (32 mm.), 74.5–75° (3 mm.); n_D^{25} 1.4336; d^{25} 0.8927; M_D calc'd 49.92, found 50.21.

Anal. Calc'd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70.
Found: C, 69.38; H, 11.28.

6-Butyl-6-hydroxy-5-decanone. The preparation of the valeroin enolate in ethyl ether was unsatisfactory. The consistency of this intermediate was such that the sodium particles adhered together, virtually stopping the normal condensation by the time half of the ester has been added. Accordingly, this product was prepared in boiling toluene by a modification of the procedure described by Hansley (10). To 1 liter of dry toluene in a 2-l. three-necked flask, provided with a wire stirrer and a reflux condenser, was added 23 g. (1.0 g. atom) of sodium and the reaction mixture heated to the b.p. in an oil-bath. To this mixture was then gradually added 65 g. (0.05 mole) of ethyl *n*-valerate, with rapid stirring, over a period of 1.5 hours. During this time the mixture was kept boiling gently by maintaining the bath temperature at 105–110°. The stirring was then continued at this tempera-

ture for two hours in order to complete the reaction. The resulting mixture was allowed to cool to 85°, and 137 g. (1.0 mole) of *n*-butyl bromide added in one portion. Stirring was then continued for sixteen hours while heating on a steam-bath at approximately 85°. The warm reaction mixture was hydrolyzed by the addition of 200 ml. of distilled water and the toluene layer separated, washed twice with 200-ml. portions of distilled water, once with 100 ml. of 5% hydrochloric acid and finally with 100 ml. of 5% aqueous potassium bicarbonate. The resulting solution was fractionally distilled, water being removed as the azeotrope. The principal fraction, boiling at 104.5–105° (1.0 mm.), weighed 27.6 g. and represented a 48.4% yield of 6-butyl-6-hydroxy-5-decanone; n_D^{25} 1.4428; d_4^{25} 0.8775; M_D calc'd 68.39, found 68.96.

Anal. Calc'd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36.
Found: C, 73.36; H, 12.66.

The forerun boiling above the b.p. of toluene in the above separation was negligible, and the high-boiling residue, which could not be distilled under these conditions, appeared to be typical of that ordinarily obtained in the preparation of acyloins.

SUMMARY

The reaction of acyloin enolates with primary alkyl halides, in either ethyl ether or toluene, was examined for four of the acyloins above acetoin. Instead of the production of enediol ethers under these conditions, the formation of α,α-dialkyl-α-hydroxy ketones, resulting from a single alkylation at the carbon of a prior carbonyl group, was observed to occur.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MARYLAND]

SYNTHETIC ANTIMALARIALS. SOME β-DIALKYLAMINOETHANOLS AND α-ALKYLAMINOBORNEOLS[1]

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The present paper presents an extension of earlier work (1) in these laboratories, and is part of an extensive investigation of aryl dialkylaminoalkanols initiated at the National Institute of Health (2).

The preparation of the compounds described herein follows in general the methods of earlier work (1, 2). The two monoalkylaminoborneols were synthesized by reductive alkylamination of "camphor quinone" and subsequent reduction of the remaining carbonyl group by the Meerwein-Ponndorf method.

The compounds prepared and submitted for testing are α-(4-biphenyl)-β-diethylaminoethanol hydrobromide (SN-5371-13), α-(4-biphenyl)-β-di-*n*-butylaminoethanol hydrobromide (SN 5372-13), α-(4′-bromo-4-biphenyl)-β-diethylaminoethanol hydrobromide (SN 6989-13), α-(4′-bromo-4-biphenyl)-β-di-*n*-butylaminoethanol hydrochloride (SN 5881-4), N-ethyl-α-aminoborneol hydrochloride (SN 9025-4), and N-*n*-butyl-α-aminoborneol hydrochloride (SN 8600-4).[2]

The structures of the biphenyl-substituted compounds are clear from their method of preparation and earlier work on *p*-phenylphenacyl bromide (3). The structures of the alkylaminoborneols are apparent from the work of Rupe and di Vignano (4).

EXPERIMENTAL[3]

α-(4-Biphenyl)-β-diethylaminoethanol hydrobromide (SN-5371-13). Reduction of 12.5 g. of 4-biphenyl diethylaminomethyl ketone hydrochloride, prepared from *p*-phenylphenacyl bromide by a method quite similar to that described earlier (1), and purified by recrystallization from alcohol-ether, was accomplished with 15 g. of aluminum isopropoxide in 100 ml. of anhydrous 2-propanol. The mixture was boiled and the acetone formed was removed through a three-foot helix-packed column; when a negative test for acetone was obtained in a small test portion of the distillate, the reaction was considered complete. The remaining solvent was removed under diminished pressure and the residue was taken up in 10% hydrochloric acid. The acid solution was then made strongly basic and the organic base was extracted with ether. After the ether solution had been thoroughly dried, the hydrobromide of SN-5371 was precipitated by means of dry hydrogen bromide. The crude salt was recrystallized from alcohol-ether; after one recrystallization, the salt melted at 139–140°; the yield in the reduction was 55%.

Anal. Calc'd for $C_{18}H_{24}BrNO$: C, 61.9; H, 6.93.
Found: C, 61.9; H, 6.77.

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[1] This work was carried out under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

[2] See "Antimalarial Drugs, 1941–1945", F. Y. Wiselogle, Editor, in press. The Survey Number (SN) identifies the drug in the Survey Office and in the monograph.

[3] Semi-micro analyses by J. Daniel Draper of this laboratory.

α-(4-Biphenyl)-β-di-n-butylaminoethanol hydrobromide (SN-5372-13). The preparation of this substance was carried out by the method described directly above. From 23.0 g. of crude amino ketone hydrochloride was obtained 14.5 g. of twice recrystallized hydrobromide (61.5%). SN-5372-13 melts at 110.4–111.3°.

Anal. Calc'd for $C_{22}H_{32}BrNO$: C, 65.01; H, 7.95; Br, 19.66.
Found: C, 64.9; H, 7.94; Br. 19.58.

α-(4'-Bromo-4-biphenyl)-β-diethylaminoethanol hydrobromide (SN-6989-13). The hydrochloride of SN-6989 is sufficiently sparingly soluble in aqueous hydrochloric acid so that it can be separated by filtration after the residue from the reduction of the amino ketone has been poured into cold hydrochloric acid; otherwise the preparation of SN-6989 from 4-(4'-bromophenyl)phenacyl bromide followed the scheme earlier described. The hydrochloride was converted into base, taken up in ether, and precipitated by means of dry hydrogen bromide from the dried ether solution. After recrystallization from alcohol-ether to constant melting point, the hydrobromide melted at 193–195°. The over-all yield from the substituted phenacyl bromide was 55%.

Anal. Calc'd for $C_{18}H_{23}Br_2NO$: C, 50.34; H, 5.36; Br (ionic), 19.06.
Found: C, 50.33, 50.76; H, 5.60, 5.55; Br (ionic), 18.81, 18.85.

α-(4'-Bromo-4-biphenyl)-β-di-n-butylaminoethanol hydrochloride (SN-5881-4). This substance was obtained from the corresponding phenacyl bromide in the usual way. The product melts at 171.6–172.4°; the over-all yield from the bromide was 58%.

Anal. Calc'd for $C_{22}H_{31}BrClNO$: C, 60.00; H, 7.04.
Found: C, 60.06, 59.32; H, 6.55, 6.48.

N-n-Butyl-α-aminocamphor hydrohloride (4). A mixture of 30 g. of "camphor quinone" and 14.6 g. of *n*-butylamine in 60 ml. of absolute alcohol was boiled under reflux for 2 hours and then hydrogenated in the presence of Raney nickel at about 40–60 p.s.i. gauge pressure. After separation of the catalyst by filtration, the solution was evaporated to remove the alcohol, and the residue was taken up in dry ether. Dry hydrogen chloride precipitated the amine salt; the yield was 44 g. of hydrochloride which melted at 257–260° (95%). Recrystallization of the crude substance from alcohol-ether yielded a product whose melting point was 272–273°.

N-n-Butyl-α-aminoborneol hydrochloride (SN-8600-4). Reduction of 34 g. of the above hydrochloride in a mixture of 120 g. of aluminum isopropoxide and 500 ml. of dry 2-propanol yielded 27 g. (78.5%) of N-*n*-butyl-α-aminoborneol hydrochloride after the crude product had been once recrystallized from 80% alcohol. The hydrochloride melted at 313–314°. The crude hydrochloride crystallized from the reduction mixture after the latter had been poured into aqueous hydrochloric acid.

Anal. Calc'd for $C_{14}H_{28}ClNO$: C, 64.14; H, 10.69.
Found: C, 64.37, 64.35; H, 10.63, 10.71.

N-Ethyl-α-aminocamphor. The hydrochloride of this amine (4) was obtained by a method like that described above for the corresponding N-*n*-butyl derivative; 34 g. of hydrochloride, m.p. 255–256° after recrystallization from alcohol-ether, was obtained from 41 g. of "camphor quinone" (60%). The salt was converted to free base, taken up in ether, and used in the next step, after removal of the ether, without further purification.

N-Ethyl-α-aminoborneol hydrochloride (SN-9025-4). From 17 g. of the amine described directly above was obtained 12 g. (60%) of once-recrystallized hydrochloride (alcohol-ether). N-Ethyl-α-aminoborneol hydrochloride melts with decomposition in a sealed capillary at 369–370°.

Anal. Calc'd for $C_{12}H_{24}ClNO$: C, 61.7; H, 10.0.
Found: C, 61.8; H, 10.0.

SUMMARY

The preparation of four α-aryl-β-dialkylaminoethanols and two N-alkyl-α-aminoborneols has been described.

In five of the six cases studied, the final Meerwein-Ponndorf reduction was advantageously carried out on a salt of the amino ketone.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF SCHERING CORPORATION]

PREPARATION OF ARYL ALIPHATIC ACIDS BY THE MODIFIED WILLGERODT REACTION

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Recently there has been described from these laboratories (1) a simplified procedure for carrying out the Willgerodt rearrangement of aryl methyl ketones to the aryl acetic acids using morpholine and sulfur in place of the conventional ammonium polysulfide. In the course of other investigations we have had the opportunity to apply this modification of the Willgerodt reaction to a number of ketones not previously studied. In the meantime, the reaction has been used successfully by other investigators (2) with slight modification.

We have now established that the reaction is much more general than previously reported. Under the proper conditions amino and hydroxy substituted aryl-aliphatic ketones can be converted into the corresponding aryl-aliphatic acids in yields ranging from 40–60%. Halogenated aryl ketones give the corresponding acetic acids in yields of 50%. In addition, ketones such as phenyl *n*-propyl and phenyl *n*-butyl ketones react to give the ω-phenyl aliphatic acids in yields of 36% and 14% respectively.

With carboxy or carbalkoxy substituted ketones, an interesting series of reactions takes place. When such ketones are heated with sulfur and an excess of morpholine, the keto group undergoes the normal Willgerodt rearrangement to the thioacetmorpholide with the simultaneous aminolysis of the carboxy or carbalkoxy group to the morpholide. For example, *o*-acetyl benzoic acid and its ethyl ester gave under such conditions the dimorpholide of *o*-carboxy phenylthioacetic acid. With the isomeric *m*- and *p*-acetylphenylacetic acids and their esters, amide formation, although observed, is not complete. In addition, it was established that with excesses of sulfur, the morpholide could be further converted into the morpholide of the corresponding thioacid. However, in spite of the apparent diversity of reactions which occur, the conversion of carboxy or carbalkoxy aryl ketones into the corresponding acids proceeds in good yields.

Several heterocyclic ketones were also studied. In the case of 3-pyridyl methyl ketone and 2-phenyl quinoline-4-methyl ketone, the preparation of the thioacetmorpholide proceeded normally. However, α-thienyl methyl ketone on treatment with sulfur and morpholine gave a black tarry mass from which none of the thiomorpholide could be isolated, and on saponification none of the expected 2-thienyl acetic acid was obtained.

From the readily accessible mono- and di-acetyldiphenyls, *p*-xenylacetic acid and the *p*,*p*′-diphenyldiacetic acid have been obtained in over-all yields of 80–85%. These two acids have previously been prepared by the chloromethylation of diphenyl and conversion of the chloride to the nitrile followed by hydrolysis. Such reactions give, at best, exceedingly poor over-all yields.

In general, the morpholine-sulfur modification of the Willgerodt reaction is applicable to any aromatic-aliphatic ketone except those ketones substituted by groups which are attacked under the conditions of this reaction.

EXPERIMENTAL

p-Xenylacetic acid. A mixture of 78.4 g. (0.4 m.) of *p*-phenylacetophenone, 20.5 g. (0.64 m.) of sulfur, and 125 cc. of morpholine was refluxed for 6–8 hours. A large excess of morpholine was used in this and subsequent preparations since it was found desirable to have the reaction mixture fluid during the reflux period. Toluene and xylene were unsatisfactory solvents. While the mixture was still hot, it was poured into 500 cc. of methyl alcohol, cooled, filtered, and washed with a small volume of cold methyl alcohol, yield 112 g. (94%), m.p. 137–139°.[1a] This material was sufficiently pure for hydrolysis to *p*-xenylacetic acid. Recrystallized for anaylsis from ethyl alcohol, m.p. 142–143°.

Anal. Calc'd for $C_{18}H_{19}NOS$: N, 4.71. Found: N, 4.72.

One hundred twelve grams of the crude thioacetmorpholide was refluxed for eight hours with 750 cc. of 70% ethyl alcohol and 150 cc. of 50% NaOH. The alcohol was then removed by evaporation, water added to the residue, and after neutralizing with HCl and treating with charcoal, the solution was filtered. The filtrate, on acidification, gave 76 g. (95%) of *p*-xenylacetic acid, m.p. 155–159°. Recrystallized from acetic acid, m.p. 164–165°, literature m.p. 153° (3).

Anal. Calc'd for $C_{14}H_{12}O_2$: C, 79.21; H, 5.66.
Found: C, 79.12; H, 5.94.

Replacing morpholine by piperidine in the above reaction gives rise to the piperidide of *p*-xenylthioacetic acid,[1b] m.p. 131–132° after recrystallization from alcohol.

Anal. Calc'd for $C_{19}H_{21}NS$: N, 4.74. Found: N, 4.86.

p,p'-Diphenyldiacetic acid. A mixture of 47.6 g. (0.2 m.) of *p,p'-diacetyldiphenyl* (4), 20.5 g. (0.64 m.) of sulfur, and 150 cc. of morpholine was refluxed for 8–10 hours. The bis-thioacetmorpholide[1c] was isolated by pouring the reaction mixture into alcohol, yield 78 g. (88.5%), m.p. 225–227°. Recrystallized from benzene and petroleum ether, m.p. 228–229°.

Anal. Calc'd for $C_{24}H_{28}N_2O_2S_2$: C, 65.47; H, 6.41.
Found: C, 64.96; H, 6.50.

Seventy-two grams of the crude bis-thioacetmorpholide was refluxed with 750 cc. of 70% alcohol and 100 cc. of 50% NaOH for approximately 12 hours. The reaction mixture was worked up as described for *p*-xenylacetic acid, the crude *p,p'*-diphenyldiacetic acid being recrystallized from acetic acid, yield 38 g. (86%), m.p. 280–282°, literature m.p. 270–273° (5). Recrystallized from acetic acid for analysis, m.p. 282–284°.

Anal. Calc'd for $C_{16}H_{14}O_4$: C, 71.08; H, 5.22.
Found: C, 70.82; H, 5.54.

p-Phenylenediacetic acid. A mixture of 82.4 g. (0.4 m.) of ethyl *p*-acetylphenylacetate[2] (6), 20.5 g. (0.64 m.) of sulfur, and 150 cc. morpholine was refluxed for six hours, then poured into 500 cc. of ethyl alcohol. The reaction product could not be crystallized and was hydrolyzed by refluxing with alcoholic alkali for six hours. The alcohol was then evaporated and the *p*-phenylenediacetic acid isolated using the procedure described for *p*-xenylacetic acid, yield 60 g., m.p. 220–230°. Recrystallized from dilute ethanol, yield 53.5 g. (70%), m.p. 253–254°; literature m.p. 236°, 240–241°, and 244°.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; N.E., 97.
Found: C, 61.77; H, 5.37; N.E., 98.

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[1] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these drugs will be given in a forthcoming monograph; 1a, SN-13,097; 1b, SN-13,098; 1c, SN-13,096; 1d, SN-13,099; 1e, SN-13,095; 1f, SN-13,656.

[2] The free acid can be used in this preparation and gives approximately the same yield.

m-Phenylenediacetic acid. A mixture of 197 g. of crude ethyl *m*-acetylphenylacetate[2] (6), 50 g. of sulfur, and 250 cc. of morpholine was refluxed for eight hours. The thioacetmorpholide did not crystallize from alcohol and was directly hydrolyzed by refluxing for 8–10 hrs. with 1000 cc. of 70% alcohol and 200 cc. of 50% sodium hydroxide. The reaction product was worked up and 120 g. of *m*-phenylenediacetic acid was obtained, m.p. 166–167°. The ethyl ester was prepared in the usual manner and distilled, yield 145 g., b.p. 145–150°/1 mm. The distillate partially solidified, and the liquid and solid fractions were separated by filtration. The solid fraction, amounting to 25 g., was saponified and identified as *p*-phenylenediacetic acid, m.p. and mixed m.p. 253–254°. The liquid fraction was saponified yielding *m*-phenylenediacetic acid, m.p. 171.5–172°, literature 170°.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; N.E., 97.

Found: C, 61.74; H, 5.26; N.E., 97.8.

Homophthalic acid. Refluxed for five hours 16.4 g. (0.1 m.) of *o*-acetylbenzoic acid (7), 4.8 g. (0.16 m.) of sulfur, and 20 cc. of morpholine. After cooling, the somewhat viscous solution was slowly poured into a mixture of ice and sulfuric acid. The solid product so obtained was filtered and recrystallized from dilute alcohol, yield 5 g. (15.5%),[3] m.p. 160–164°. Recrystallized for analysis from dilute alcohol, m.p. 163.5–164°. The compound so obtained is the dimorpholide of *o*-carboxyphenylthioacetic acid.[1d]

Anal. Calc'd for $C_{17}H_{22}N_2O_3S$: C, 61.06; H, 6.64; N, 8.38.

Found: C, 61.16; H, 6.76; N, 8.51.

The above described dimorpholide was also obtained from ethyl *o*-acetylbenzoate by refluxing for six hours 23 g. of ester, 5 g. of sulfur, and 40 cc. of morpholine. The reaction mixture, while still warm, was diluted with ethyl alcohol, and after the addition of ice, the dimorpholide crystallized out, yield 26 g., m.p. 163.5–164.5°. Mixed melting point with product obtained from the free acid showed no depression.

Ten grams of the dimorpholide was saponified with 80 cc. of 10% alcoholic sodium hydroxide. The alcoholic solution was then diluted with an equal volume of water, the alcohol evaporated and the aqueous solution acidified. The crude homophthalic acid was filtered and then recrystallized from water, yield 3.5 g. (65%), m.p. 176–177°, literature 175–177°.

Hydrocinnamic acid. A mixture of 26.8 g. (0.2 m.) of propiophenone, 10.2 g. (0.32 m.) sulfur, and 23 g. (0.26 m.) of morpholine was refluxed for six hours. The reaction product was poured into 200 cc. of 10% alcoholic sodium hydroxide and refluxed for 6–8 hrs. After removing the alcohol, the alkaline solution was diluted with water, acidified with hydrochloric acid to Congo Red paper and extracted twice with ether. The ether extracts were washed with water, dried, and after removing the ether, the residue was distilled, yield 19.5 g. (65%); b.p. 125–129°/6 mm.; m.p. 46–47°.

γ-Phenylbutyric acid. A mixture of 74 g. (0.5 m.) of phenyl *n*-propyl ketone, 25.6 g. (0.8 m.) of sulfur, and 75 cc. of morpholine was refluxed for 15 hours. The oily reaction product was saponified and worked up by ether extraction. The ether residue was recrystallized from water, yield 30 g. (36%), m.p. 47–49°. Recrystallized again from water, m.p. 50–51°, literature 51°. Neutral equivalent 164; found 164.6.

Δ-Phenylvaleric acid. A mixture of 81 g. (0.5 m.) of phenyl *n*-butyl ketone, 25.6 g. (0.8 m.) of sulfur, and 75 cc. morpholine was treated as described for the phenyl *n*-propyl ketone. The ether residue was recrystallized from water, yield 12 g. (14%), m.p. 58–59°, literature 57–58°. Neutral equivalent 178; found 179.

p-Methoxyphenylacetic acid. Four hundred twenty grams (2.8 m.) of *p*-methoxyacetophenone, 135 g. (4.2 m.) of sulfur, and 298 g. (3.5 m.) of morpholine were refluxed for five hours. The reaction mixture was slowly poured into water, allowing the first addition to crystallize before the bulk of the mixture was added. The crude yellow solid was filtered, thoroughly ground up with water, filtered, and air-dried, yield 676 g. (96%), m.p. 64–67.5°. Recrystallized for analysis from dilute methanol, m.p. 71–72°.

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[3] This represents the yield obtained when the theoretical amount of morpholine is used. In an experiment using 50 cc. of morpholine, the yield was 65%.

Anal. Calc'd for $C_{13}H_{17}NO_2S$: N, 5.58; S, 12.75.
Found: N, 5.65; S, 12.45.

To 4 liters of 10% alcoholic sodium hydroxide, 502 g. (2 m.) of the crude thioacetmorpholide was added and the mixture refluxed for 10 hours. After removing most of the alcohol, one liter of water was added to the distillation residue and the alkaline solution strongly acidified with HCl. The resulting solution was cooled and then thoroughly extracted with ether. The ether extracts were combined, evaporated, and the residue recrystallized from water, yield 260 g. (78%), m.p. 83–85°, literature 85°. The aqueous filtrates should be extracted with ether since *p*-methoxyphenylacetic acid is quite soluble in water.

p-Methoxyhydrocinnamic acid. Eighty-two grams (0.5 m.) of *p*-methoxypropiophenone, 25.6 g. (0.8 m.) of sulfur, and 75 cc. of morpholine were refluxed for 8 hours. The oily thioacetmorpholide was added to 500 cc. of 10% alcoholic sodium hydroxide and the mixture refluxed six hours. The alcoholic solution was diluted with 250 cc. of water, the alcohol evaporated, and the resulting solution acidified and extracted with ether. After removing the ether, the residue was recrystallized from benzene-petroleum ether, yield 56 g. (62%); m.p. 98–100°. Recrystallized again, m.p. 101–102°, in agreement with the literature.

p-Hydroxyphenylacetic acid. A mixture of 27.8 g. (0.2 m.) of *p*-hydroxyacetophenone, 10.2 g. (0.32 m.) of sulfur, and 35 cc. of morpholine was refluxed for six hours. The reaction product was poured into 200 cc. of 10% alcoholic sodium hydroxide and refluxed for six hours. The resulting alcoholic solution was diluted with an equal volume of water and the alcohol evaporated. The aqueous solution was acidified, cooled, and thoroughly extracted with ether. The ether was evaporated and the residue recrystallized from benzene, yield 12.6 g. (42%), m.p. 144–147°. A second recrystallization raised the m.p. to 147–149°, literature 148°.

p-Hydroxyhydrocinnamic acid. Thirty grams (0.2 m.) of *p*-hydroxypropiophenone, 10.2 g. sulfur, and 35 cc. of morpholine were refluxed for eight hours. The crude reaction product was saponified with 200 cc. of 10% alcoholic sodium hydroxide and worked up as described for the *p*-hydroxyacetophenenone. The ether residue was recrystallized from benzene-petroleum ether, yield 8.8 g. (26.8%), m.p. 126–127°, literature 128°.

p-Chlorophenylacetic acid. A mixture of 38.5 g. (0.25 m.) of *p*-chloroacetophenone, 12.8 g. (0.4 m.) of sulfur, and 30 cc. of morpholine was refluxed for eight hours. The crude product was saponified and poured into water. After evaporating the alcohol, the residue was acidified, cooled, and filtered, yield 28 g., m.p. 90–94°. Recrystallized from water, yield 20 g. (47%), m.p. 100–101°. A second recrystallization gave 18..6 g. of pure *p*-chlorophenylacetic acid melting at 102–104°; literature 104°; 105–106°.

p-Bromophenylacetic acid. The procedure as described for the chloro compound, was employed 50 g. (0.25 m.) of *p*-bromoacetophenone, yield 25 g. (51%), m.p. 106–109° after recrystallization from water; recrystallized again, m.p. 112–113°, literature 114–115°.

p-Aminophenylacetic acid. Thirty-three grams (0.25 m.) of *p*-aminoacetophenone, 12.8 g. (0.4 m.) of sulfur, and 35 cc. of morpholine was refluxed for eight hours. The oily reaction product was saponified, poured into water, and the alcohol removed. The aqueous solution was then acidified with acetic acid, cooled thoroughly and filtered, yield 30 g., m.p. 170–186° dec. It was recrystallized twice from water, yield 16.5 g. (43.8%), m.p. 194–196° dec., literature 199–200°.

Methyl 3-pyridylacetate. One hundred twenty-one grams (1.0 m.) of 3-pyridyl methyl ketone (8), 52 g. (1.6 m.) of sulfur, and 150 g. of morpholine were refluxed for six hours. The reaction mixture was then poured into ice, and after standing overnight the crude solid was filtered, yield 141 g. (65.5%), m.p. 72–76°. It was recrystallized from benzene and petroleum ether, m.p. 78.5–79.5°.

Anal. Calc'd for $C_{11}H_{14}N_2OS$: C, 59.44; H, 6.35.
Found: C, 59.30; H, 6.40.

Twenty-two and two-tenths grams (0.1 m.) of the thioacetmorpholide[1e] was refluxed with 100 cc. of 50% alcohol and 20 cc. of 50% sodium hydroxide. The reaction mixture was evaporated to dryness under reduced pressure. The residue was taken up in 150 cc. of methyl

alcohol, and, after saturating the alcoholic solution with dry HCl, it was concentrated to dryness. The residue was then extracted in a Soxhlet with methyl alcohol, and after removing the methyl alcohol the methyl 3-pyridylacetate was distilled, yield 8 g., b.p. 85°/2 mm.

2-Phenylquinoline-4-thioacetmorpholide.[11] To 4.5 g. of sodium dust was added 100 cc. of anhydrous ether and 12 cc. of absolute ethyl alcohol. After the formation of the sodium ethoxide was complete, 17.5 g. of absolute ethyl acetate and 34 g. of ethyl 2-phenylcinchoninate was added dropwise. The mixture was refluxed for 20 hours, poured into water and extracted with ether to remove unreacted esters. The alkaline solution was acidified with HCl, the mixture refluxed for two hours and then made alkaline and extracted with ether. The ether was evaporated and the crude 2-phenylquinoline 4-methyl ketone was recrystallized from aqueous alcohol, yield 12.5 g., m.p. 76–78°. Recrystallized for analysis, m.p. 77–78°.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.67. Found: N, 5.93.

A mixture of 9.5 g. of the ketone, 2 g. of sulfur, and 10 cc. of morpholine was refluxed for five hours. The cooled reaction mixture was poured into methyl alcohol and the crude solid product was recrystallized from alcohol, yield 8.6 g., m.p. 191–192°. Recrystallized for analysis, m.p. 193–194°.

Anal. Calc'd for $C_{21}H_{20}N_2OS$: N, 8.04. Found: N, 8.27.

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The authors wish to express their appreciation to Miss Hilda Hankin, Mrs. Anna Klingsberg, and Mr. Peter Hirschler for their technical assistance.

SUMMARY

1. The morpholine-sulfur modification of the Willgerodt reaction has been applied to the synthesis of halogen, hydroxy, and amino substituted aryl acetic acids.

2. Carboxy and carbalkoxy methyl ketones react normally to give carboxy arylacetic acids.

3. Several heterocyclic ketones were studied; the pyridyl and quinolyl methyl ketones reacting normally, whereas α-thienyl methyl ketone yielded only tarry products.

BLOOMFIELD, N. J.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF NOTRE DAME AND COLUMBIA UNIVERSITY; THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH; AND THE RESEARCH LABORATORIES OF MERCK AND COMPANY]

SYNTHESIS OF ETHYL QUININATE[1]

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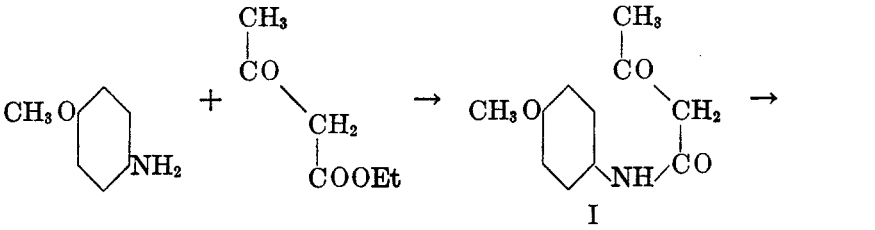
Early in 1942, when the advent of war had made an intensive search for new antimalarials imperative, one of the most promising fields of study appeared to be that of the 6-methoxy-4-quinolyl carbinols. For this work we needed relatively large amounts of quininic acid, which of course could no longer be made by the usual procedure of oxidation of quinine.

There were recorded in the literature, however, four different syntheses of quininic acid, each starting from *p*-anisidine, and it was hoped that at least one of these might prove adaptable to large-scale work. Inasmuch as it involved an expensive iodine oxidation, and the over-all yield was found by Ainley and King (1) to be very low, the synthesis developed by Kaufmann (2) was not deemed suitable. It was considered that the syntheses of Halberkann (3) and Thielepape (4) held some promise. The latter two have been investigated in detail by Buchman, who will publish his results elsewhere.

The fourth method, developed by Rabe *et al.* (5) and improved upon by Ainley and King (1), was thought likely to be the most promising for large-scale work. Special attention has therefore been devoted to the problem of increasing the yields in the seven steps involved in this synthesis, which are as follows:



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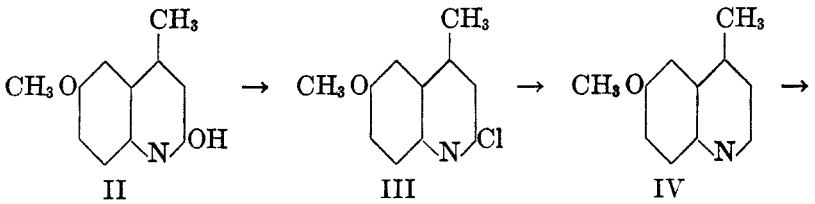
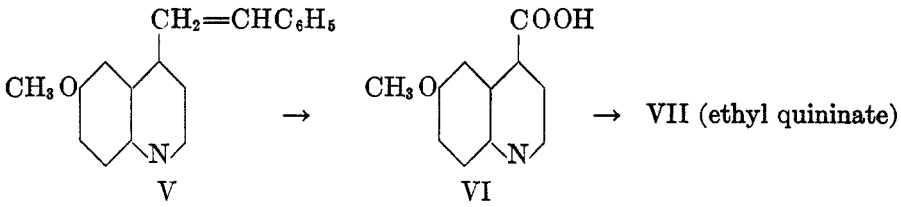


II III IV

[1]The work reported here was done in part under contracts recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Notre Dame and Columbia University.



This synthesis was reinvestigated on a laboratory scale by a group at the University of Notre Dame,[2] and the procedures they developed were further modified and then adapted to pilot-plant scale by workers at Columbia University and the Research Laboratories of Merck and Company.[3] Simultaneously and quite independently, two of us (R. S. T. and M. A. C.) at Mellon Institute devoted some attention to improvements in the methods and later agreed to joint publication. As a result of these studies, many important details not mentioned by the earlier workers (1, 5) have been observed, the procedures have been so modified as to simplify the experimental work or improve the yields (or both), and all the operations have been performed on a much larger scale than previously. The present paper embodies the most important results obtained by the various groups mentioned above.

In the preparation of *p*-acetoacetanisidide, I, it has been found possible either to lessen the proportion of acetoacetic ester recommended by Ainley and King (1) without lowering their yield (81%), or to retain their proportions and raise the yield to 93%. If one takes into consideration the recovery of unchanged starting materials, the yield is practically quantitative. The ring-closure step (I → II) could be carried out on a much larger scale (up to 1 kg. in the laboratory) without appreciable diminution in yield (75–80%), and the isolation and purification of the product was simplified considerably.

Ainley and King (1) reported a 98.5% yield for the preparation of the 2-chloro compound (III) but none of the workers in the present group has been able to duplicate this yield. Furthermore, it has been found that the temperature (130–140°) recommended by Ainley and King is too high, the reaction being smoother at lower temperature (110–120°). In addition, better methods of isolation and purification have been developed.

The 2-chloro compound (III) can be converted to 6-methoxylepidine (IV) by reduction or by catalytic hydrogenation. Ainley and King had hydrogenated the chloro compound in glacial acetic acid-sodium acetate solution over palladized charcoal; in the present work it was discovered that the hydrogenation could be

[2]The authors acknowledge some technical assistance rendered by Dr. James F. Kerwin, Dr. Eldred E. Young, and Mr. James M. Constantin.

[3]We wish to thank Merck and Company for their generosity in placing their facilities at our disposal without charge.

[4]After the present work had been completed, Campbell and Schaffner (6) described a modified Doebner-Miller synthesis whereby 6-methoxylepidine could be obtained from *p*-anisidine in 52% yield in one step. If large amounts of this lepidine derivative should be needed in the future, this one-step preparation may supplant the four-step synthesis described here.

carried out equally well in warm alcoholic potassium hydroxide in the presence of Raney nickel, and that the lepidine was then more easily isolated. However, it was also found that the reduction of III to IV could be brought about by zinc and acetic acid, a much simpler procedure. The yield by both methods was almost quantitative[4] (95–98%).

6-Methoxy-4-styrylquinoline (V) was prepared essentially according to Rabe (5), except that the water formed in the reaction was continuously removed by distillation, and a procedure was developed for avoiding isolation of the styrylquinoline acid sulfate. It was found that the crude styryl compound could be used direct'y for oxidation, thus avoiding the tedious recrystallization from ligroin. Since Bulach (7) had found that acetic anhydride facilitates condensation between quinaldine and *p*-nitrobenzaldehyde to yield the corresponding styryl derivative, it was of interest to learn whether it is as efficient as zinc chloride in the present condensation. It was found that it gives a yield (41%) inferior to that obtained with zinc chloride.

The styryl compound was oxidized to quininic acid in 50% pyridine, as described by Ainley and King (1), and in acetone. The yield was about the same in either solvent, but the use of acetone greatly facilitated isolation of the product. Quininic acid was then esterified with ethanol in the presence of sulfuric acid; it was found easier to purify the ester (VII) by crystallization than by distillation.

In Table I the results of the present work are compared with those of the earlier workers, from which it may be seen that the highest laboratory yields we have obtained considerably exceed those of Ainley and King, our over-all yield being some 63% greater. Routine laboratory preparations and pilot plant preparations gave somewhat lower yields, but it is expected that further refinements in the industrial technique for step VI → VII will make ethyl quininate available at a not-too-exorbitant cost.

Since Rabe did not give the yield of I, but intimated that it was the same as that of Limpach (8) (90%), and for V gave only the yield of crude sulfate, the over-all yield we have calculated for his work is a liberal approximation.

EXPERIMENTAL

p-Acetoacetanisidide (I), SN 6788,[5] *Procedure A* (Mellon). Ethyl acetoacetate (1015 ml., 8 moles *reagent* grade) was placed in a 3-necked, 2-liter flask provided with thermometer and mechanical stirrer, and having one neck open. The ester was heated to 160–165° (bath temp., 175–176°) and *p*-anisidine (246 g., 2 moles) added in portions with stirring during 45 minutes; the mixture was kept at this temperature a further 30 minutes, allowed to cool, kept overnight in the refrigerator, and filtered. The air-dried crystals (426 g.) were stirred with pentane (500 ml.) to remove adhering ethyl acetoacetate, filtered, washed with pentane (50 ml.), air-dried, and then dried at 60°; weight, 370 g. (Unchanged ester was recovered by evaporating the pentane filtrate plus washings to dryness.)

The mother liquor of the first crop was evaporated to dryness under reduced pressure (bath at 110°), and the crystalline residue freed from *p*-anisidine as follows: It was dissolved

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[5]The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these drugs will be tabulated in a forthcoming monograph.

in chloroform (430 ml.) and 430 ml. of hexane was added, the solution nucleated, and kept overnight in the refrigerator. The second crop weighed 16 g., making the total yield of I, 386 g. (93%); m.p. 116–117°. Limpach (8) reported a yield of 90%. This material is pure enough for the next step.

For analysis, it was recrystallized by dissolving 20 g. in 100 ml. of chloroform, filtering, adding 100 ml. of hexane in portions, and cooling the mixture for several hours. The colorless crystals so obtained (14.8 g.) melted at 118–119°, in agreement with the value given by Ainley and King (1). Others have reported the melting point as 115–116° (9).

Anal.[6] Calc'd for $C_{11}H_{13}NO_3$: C, 63.73; H, 6.3; N, 6.76.
Found: C, 63.85; H, 6.3; N, 7.24.

Procedure B (Notre Dame). Yields of 80–85% may be obtained when a smaller excess of acetoacetic ester is used; it was found convenient to add *p*-anisidine in the molten state. In a typical experiment, 500 ml. of acetoacetic ester (*practical* grade) was heated to 165°, 200 g. of molten *p*-anisidine (*practical*) was added from an electrically-heated dropping-funnel, with mechanical stirring, during 45 minutes and then treated as in procedure A, giving 236 g. of cream-colored crystals, m.p. 118–119°. A second crop was obtained by concentration of the mother liquor, making the total yield 80–85%.

2-Hydroxy-6-methoxylepidine (II), SN 6846, Procedure A (Mellon). Concentrated sulfuric acid (*d*, 1.84; 137.5 ml.) was added, *without cooling*, to 250 g. of dry, recrystallized *p*-

TABLE I

YIELDS IN THE SYNTHESIS OF ETHYL QUININATE

WORKER	I	II	III	IV	V	VI	VII	OVER-ALL, I–VII
Rabe.....	90 (?)	*ca.* 100	75	90	100 (?)	—	80	*ca.* 50 (?)
Ainley & King.....	81	80	98.5	97.5	81	84.5	82	34.9
Present:								
Lab.—highest.....	93 (100)	83	94	98	94	95	90	57 (61.5)
Lab.—average....	80–85	75–80	75–85	90–98	85–90	70–85	80–90	
Pilot plant.....	—	78	85–90	87	84	—	53	

methoxyacetoacetanilide in a two-necked flask (thermometer). The flask containing the mixture (temp. 60°) was then attached to a reflux condenser ("Drierite" tube) and placed in a glycerol bath at room temperature. The bath temperature was raised, during 105 minutes, until the reaction temperature reached 100° (bath temp. 92°). The exothermic reaction continued for 90 minutes, the reaction temperature being kept at, or slightly below, 100°; reaction product then started to crystallize. The reaction temperature was now maintained at 95° during 2 hours (bath temp. 98°), giving a yellow, almost solid mass which was cooled to 60°, removed from the flask, and kept overnight under 2.5 liters of water. It was stirred until free from lumps, filtered, washed with three 500-ml. portions of water, resuspended in water (1 liter), stirred, and kept overnight at room temperature. It was then filtered off, air-dried, dried at 60° (72 hours) and 110° (20 hours); yield 181.5 g. (79.5%); m.p. 267–268° (Al block). This material was pure enough to be used for the next step.

When 50-g. portions of anisidide were treated as above, the yield was somewhat greater (83%; m.p., 270–273°). [Rabe (5) reported an "almost quantitative" yield of impure material (m.p. 253°) having an incorrect analysis some 2% deficient in carbon; and Ainley and King (1) obtained an 80% yield of impure material (m.p. not recorded) containing "traces of unchanged" anisidide.]

[6]All analyses were performed by Dr. Carl Tiedcke, New York, N. Y. for R.S.T. and M.A.C.

It was recrystallized as follows: 10 g. was dissolved in 40 ml. of boiling glacial acetic acid (reflux), the hot solution filtered, 120 ml. of water added in portions to the filtrate, and the suspension of colorless crystals kept overnight in the refrigerator. The product was dried as above; yield 9 g.; m.p. 273–275° (Al block). Rabe (5) gave m.p. 253°; Kermack and Muir (10), m.p. 255°; Monti and Verona (11), m.p. 268°; Ainley and King (1), m.p. 268–270°; Backeberg (12), m.p. 272°.

Anal. Calc'd for $C_{11}H_{11}NO_2$: N, 7.41. Found: N, 7.50.

Procedure B (Columbia, Merck). Finely powdered I (1000 g.) was added portionwise during 45 minutes to 700 ml. of concentrated sulfuric acid in a 3-necked, 3-liter flask fitted with a thermometer and mechanical stirrer, the temperature being kept below 35°. The mixture was then warmed on a hot-water bath until the vigorous gas evolution was well under way (the temperature at which this began varied from 65° to 95°); the water-bath was replaced by an ice-bath and the temperature of the reaction mixture kept at 100° by external cooling. When the reaction had subsided the mixture was kept at 95–100° for two hours and then poured into ice-water (4 kg.). The solid was washed twice with 2-liter portions of water, suspended in 1.5 liters of ice-water, and treated with ammonium hydroxide until the mixture was basic to litmus. The yield of light gray product suitable for use in the next step was about 75%. Unless the acid was completely removed the material darkened on drying and had to be recrystallized.

2-Chloro-6-methoxylepidine (III), Procedure A (Mellon). The method of Ainley and King (1) was modified to avoid "the initial vigorous reaction," and the proportion of phosphorus oxychloride employed was diminished by one-third. It was found that the product must be entirely freed from acid, as otherwise its solubilities are considerably changed.

To 2-hydroxy-4-methyl-6-methoxyquinoline (200 g.; dried at 110°) in a 1-liter flask (ground-glass joint) was added 400 ml. of phosphorus oxychloride and the suspension heated under reflux ("Drierite" tube) in a glycerol bath, the temperature of which was raised from 25° to 90° during 30 minutes. Gentle evolution of hydrogen chloride then began and the hydroxy compound started to dissolve. During the next 20 minutes the bath temperature was raised to 108°, whereupon gentle refluxing commenced; after 10 minutes at this temperature, all the hydroxy compound had dissolved and the chloro compound started to crystallize out. The bath temperature was slowly raised to 120° during the next 30 minutes and then the mixture was allowed to cool; it was evaporated to dryness (ground-glass joints) under diminished pressure (bath temp. 60°), some 180 ml. of phosphorus oxychloride being recovered.

The solid product was now added in portions, with stirring, to a mixture of 2 liters of chopped ice with one liter of water, giving yellowish crystals which were filtered off (filtrate A), washed with three 250-ml. portions of water, stirred into a paste with 250 ml. of water, and a saturated aqueous solution of sodium bicarbonate added with stirring until effervescence ceased; this neutralization of traces of acid is important. The suspension was filtered (filtrate B) and the solid washed with three 250-ml. portions of water, air-dried, and dried at 60° (48 hours); yield 197.2 g.; m.p. 145–147°. (This material is pure enough to be used in the next step.)

Filtrates A and B were united, and sodium bicarbonate was added to neutrality, giving a second crop which was washed and dried as above; wt. 4.9 g; m.p. 139–140°; total yield 202.1 g. (92%). The preparation was repeated several times, but the yield recorded by Ainley and King (1) (98.5% of material having m.p. 142–144°) could not be duplicated.

It was recrystallized as follows: 10 g. was dissolved in 68 ml. of glacial acetic acid under reflux, on a boiling-water bath. Water (34.5 ml.) was then added in 5-ml. portions through the top of the condenser, the solution cooled to room temperature, kept overnight in the refrigerator and the colorless crystals filtered off, washed with water, and dried as above and at 110° (45 minutes); yield 8.3 g.; m.p. 146–148°.

The substance (10 g.) was also recrystallized from boiling absolute ethanol (130 ml.) giving 9.2 g. of long, colorless needles having a silky sheen; m.p. 146°. Rabe (5) described the substance as "yellowish needles"; m.p. 145°.

Anal. Calc'd for $C_{11}H_{10}ClNO$: C, 63.60; H, 4.9; N, 6.75; Cl, 17.08.
Found: C, 63.24; H, 4.8; N, 6.39; Cl, 16.98.

Procedure B (Notre Dame, Columbia). It was found that the chloro compound could be isolated directly from the cold reaction mixture by filtration, while most of the tarry by-products remained in solution in the phosphorus oxychloride.

A mixture of dry 2-hydroxy-6-methoxylepidine (150 g.) and 450 ml. of phosphorus oxychloride ("purified" grade) was heated under reflux until the bath temperature reached 110°. When the inside temperature reached 100° boiling began, and the temperature rose rapidly to 105°; there was rapid refluxing and a copious evolution of gas. Occasionally it was necessary to lower the oil-bath for a few moments. After the initial vigorous reaction had subsided, the mixture was heated as in procedure A, cooled in ice, filtered through a sintered glass funnel, and the solid pressed as dry as possible. The solid was added gradually, with stirring, to a mixture of ice and water, filtered, washed thoroughly with ice-water, and finally with a small amount of boiling ethanol. The product obtained (156 g.; 94%) was a light gray, slightly impure solid, m.p. 142–145°, which could usually be dechlorinated without purification. Occasionally, however, it poisoned the catalyst, and had to be recrystallized.

Recrystallization of large amounts was difficult and troublesome, but several methods were found to be fairly satisfactory; (a) A ratio of 40 ml. of 40% sulfuric acid to 10 g. of compound, with 1 g. of decolorizing carbon, was used. The recrystallized material was washed thoroughly with water and dried; recovery of product (m.p. 142–145°) was 78%; (b) ten grams of crude chloro compound in 175 ml. of 95% alcohol was treated with 1–2 g. of Norit. The recovery, including a second crop, was 78–80% of material melting at 142–145° after sintering at 139°.

Using larger amounts of 2-hydroxy-6-methoxylepidine, the reaction gave poorer yields. Thus, when 420 g. of II and 1260 ml. of phosphorus oxychloride were caused to react as described in B, and the product isolated as described in A, the yield of crude III was 70–80%. Crystallization from 95% alcohol or 40% sulfuric acid diminished the yield of product suitable for hydrogenation to 54–62%.

6-Methoxylepidine (IV), SN 2736, Procedure A[7] (Notre Dame, Columbia). Conversion of III to IV can be effected conveniently by catalytic hydrogenolysis using Raney nickel, and the amount of chloro compound hydrogenated at one time is limited only by the capacity of the apparatus available. The reaction can be carried out at room temperature but is more rapid at 45–65°.

A mixture of 15.6 g. of III, 135 ml. of absolute alcohol, 6 g. of potassium hydroxide pellets (*reagent* grade), and 6 g. of alcohol-washed Raney nickel was shaken with hydrogen at 60 lb./sq. in. at 45–65°. Hydrogen absorption was complete in two hours. The products from several such experiments were then combined.

The clear solution obtained after removal of the catalyst (IV is much more soluble in alcohol than III) was evaporated under reduced pressure, and the resulting oil poured into water and chilled. The crystalline hydrate of IV was collected, washed with cold water, pressed, and air-dried (one to two days). The yield of material melting at 51–53° (sintering at 48°) was 94%. It was used in the next step without purification.

In a larger-scale run, 1086 g. of III was hydrogenated at room temperature and 40 lbs./sq. in. in 26 hours to give an 88% yield of IV.

Procedure B (Mellon). The following method may be used without modification for larger quantities. One hundred grams of III was dissolved in 675 ml. of glacial acetic acid plus 75 ml. of water at 70°, under reflux, with mechanical stirring. Granulated zinc (50 g., No. 30 mesh) was added in one portion, and stirring was continued during 6 hours at 70°. The hot solution was then filtered, and the unreacted zinc (11.1 g.) was washed with four 25-ml. portions of water, which were added to the main filtrate. This was evaporated to dry-

[7]Since this work was completed, a similar method has been reported by Kleiman and Weinhouse, *J. Org. Chem.*, **10**, 562 (1945).

ness under reduced pressure, and the product shaken with 1 liter of 8 *N* sodium hydroxide solution plus 600 ml. of chloroform. The aqueous layer was re-extracted with four 100-ml. portions of chloroform, the combined chloroform extracts dried with anhydrous sodium sulfate, filtered, and evaporated to dryness, giving a brown sirup (81.7 g., 98%) which crystallized on standing at room temperature. It was purified by distillation; b.p. 96–97° at 0.1 mm. (bath temp. 110–116°); colorless crystals, m.p. 31–32°. This is anhydrous 6-methoxylepidine.

6-Methoxy-4-styryl quinoline (V), SN 6845, Procedure A (Notre Dame, Columbia). One hundred grams of 6-methoxylepidine hydrate (IV), 540 g. of dry benzaldehyde (E.K. Practical, purified shortly before use by shaking with sodium carbonate solution), and 36 g. of fused zinc chloride were placed in a 2-liter flask fitted with a short still-head and condenser set for downward distillation. The flask was heated[8] in an oil-bath at 185–190° until no more water distilled over; this required about five hours. The mixture was cooled to room temperature, and the product isolated as described by Rabe (5). The crude air-dried sulfate weighed 188 g. (theoretical yield).

(Mellon) Anhydrous IV (10 g.) gave 24 g. of crude acid sulfate which was purified by washing with absolute alcohol (125 ml.) and recrystallizing the washed product (20 g.) from absolute alcohol (600 ml.). The material was obtained as golden-yellow crystals (14.6 g.), m.p. 249–250°. Although this salt has been described before (5) there is no indication in the literature whether it is the acid or normal sulfate. Analysis showed it to be the acid sulfate.

Anal. Calc'd for $C_{18}H_{15}NO \cdot H_2SO_4$: N, 3.90; S, 8.93.
Found: N, 3.83; S, 8.95.

The crude sulfate was transformed to free base by shaking with excess 20% sodium hydroxide and extracting with ether (chloroform has some advantages as the extractant). Usually the product was obtained as a greenish solid, sometimes as an oil. Purification of the styryl compound from ligroin was tedious and attended by considerable loss but the crude material could be used in the next step. The yield was usually about 85–90%, but occasionally fell to 65%. When 10-g. portions of anhydrous IV were treated as described by Rabe, the yield of styryl base was 13.7 g. (94%) (R.S.T. and M.A.C.).

Procedure B (Mellon). The method was improved by omitting isolation of the acid sulfate, giving 6-methoxy-4-styrylquinoline directly. Distilled anhydrous 6-methoxylepidine (20 g.) was condensed with benzaldehyde as described above, the cooled reaction mixture dissolved in 150 ml. of chloroform and extracted with two 100-ml. portions of 8 *N* sodium hydroxide solution. The chloroform solution was dried and evaporated to dryness under diminished pressure, giving 127 g. of a greenish-brown liquid which was freed from benzaldehyde (89 g.) by distillation at 20 mm.; a second fraction (5 g. of yellow, somewhat viscous liquid, probably containing 6-methoxylepidine) distilled at 94–98° at 0.05 mm. (bath temp. 124–180°). The dark green still residue (33.5 g.) was dissolved in 150 ml. of chloroform and extracted with 75 ml. of 8 *N* sodium hydroxide solution, washed with water, dried, and evaporated to dryness; yield 27.2 g. For purification, this was dissolved in 408 ml. of boiling heptane under reflux, the hot solution decanted through a fluted filter to remove a trace of insoluble gum, and the filtrate allowed to cool to room temperature; a further small amount of dark-colored gum separated. The yellow heptane solution was decanted, nucleated, and kept overnight in the refrigerator, giving a first crop (10.6 g.) of yellow crystals; m.p. 59–60° (free base). Further crops were isolated from the mother liquor, and by retreatment of the gum.

It was recrystallized as follows: 10 g. was dissolved in 100 ml. of dry ether, 200 ml. of pentane was added, and the mixture filtered, nucleated, and kept overnight in the refrigerator, giving a first crop (6.3 g.) of extremely pale yellow crystals, m.p. 63–64°. Again recrystallized, it had m.p. 64–65°. [Rabe (5) gives m.p. 75°, possibly a misprint.]

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.72; H, 5.8; N, 5.36.
Found: C, 82.51; H, 5.8; N, 5.36.

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[8]When the reaction was carried out at 140° for 19 hours, the yield was only 20%.

Condensation of 6-methoxylepidine with benzaldehyde in acetic anhydride (Columbia, Merck). A solution of 10 g. of 6-methoxylepidine hydrate, 6.0 g. of benzaldehyde, and 43.2 g. of acetic anhydride was boiled under reflux for 4 hours, the mixture evaporated to dryness under reduced pressure, the residue mixed with 5 *N* sulfuric acid, and the styryl sulfate isolated as described above. The yield was only 41% of the theoretical.

Quininic acid (VI) Procedure A. By proceeding essentially as described by Ainley and King (1), using 50% pyridine as solvent *and* for washing the manganese oxides, the highest yield of acid was 95% (Mellon), while the average yield was 70–85%. The variations in yield were probably due to variations in purity of the crude styryl base used. In larger runs (180 g. of styryl compound) the time of reacting was increased to 6 hours. There was no indication that the use of stoichiometric amounts of permanganate gave better yields than the use of the ratio prescribed by Ainley and King (1).

Procedure B (Columbia). When the above procedure was followed, but using acetone as solvent instead of 50% pyridine, the yield of quininic acid was about the same (75–85%). Acetone has certain advantages as the solvent: (a) The manganese dioxide is more easily removed; when 50% pyridine is used a difficultly-filterable sludge is obtained; (b) the acetone is more readily removed from the product than is the pyridine-water mixture; and (c) acetone is considerably cheaper than pyridine.

Ethyl quininate (VII) (Columbia). The procedure of Ainley and King was followed, but the ester was purified by crystallization instead of by distillation. A solution of the crude, dry ester (101 g. from 94.5 g. of quininic acid) in hot 90–110° ligroin (450 ml.) was stirred with Norit, the mixture filtered, and the Norit rinsed with 50 ml. of hot solvent. When the filtrate was cooled slowly to 4° there precipitated 83.6 g. of light cream-colored ester, m.p. 66–67.5°. Concentration of the filtrate gave a second crop (6.0 g.) with the same melting point. The yield was 84%; if this is corrected for the 5 g. of quininic acid recovered from the ammoniacal washings, the yield is raised to 90%.

Pilot-plant runs (Merck and Co.). The *p*-acetoacetanisidide (I) was prepared by U.S. Industrial Chemicals, Inc., at our request. The product supplied by them was gray-white in color, and melted at 115–116°; it was suitable for use without purification.

In the ring-closure reaction (I → II) a 57-lb. run was carried through, using procedure B. The reaction was performed in a 10-gallon Pfaudler jacketed reactor, fitted for steam or brine, and having an efficient agitator. The yield of light gray II, m.p. 259–266° (dec.), which was thoroughly washed and dried but not recrystallized, was 78%.

When 15–20 lb. batches of II were converted to III by the B procedure (with isolation by procedure A), the yield of unrecrystallized III was 85–90%. The chlorination was carried out in a stainless steel reaction vessel provided with hot or cold jacket, and the mixture was stirred during the reaction with an "anchor" type stirrer. Recrystallization of the crude product from 95% alcohol led to a poor recovery (62.2%), making the yield of pure III about 54%.

The chlorine was removed from III by catalytic hydrogenolysis over Raney nickel, as described in Procedure A, using 12–15.5 lb. batches of III. The reactor was stainless steel and was equipped with a very vigorous agitator. The conversion of III to 6-methoxylepidine monohydrate (IV) gave an average yield of 87.3%.

The 6-methoxylepidine was condensed with benzaldehyde, as described in Procedure A, using 10–12 lb. batches of IV. In one case the yield of crude styryl compound (V) was 78%; in another, 89%. The reactions were carried out in a stainless steel oil-heated still provided with a stainless steel stirrer, and a slow stream of nitrogen was passed through the hot solution for the entire 6.5-hour reaction period. No rubber or neoprene gaskets could be used because they were attacked by the benzaldehyde vapors. The free styryl base was liberated as described in Procedure A, as much ether as possible was removed, and then a current of nitrogen under reduced pressure was pulled through the residue at 100° for one hour, in order to remove all volatile material. The crude residue was used, without purification, in the oxidation step.

The large-scale oxidation work was carried out before the acetone procedure (Procedure

B) had been developed and, consequently, 50% pyridine was used as solvent. When a 27-lb. batch of styryl compound was used, the reaction time was nine hours; the manganese dioxide sludge was removed through a small filter press, and the filter cake was slurried twice with 20 to 25 gallon portions of water to ensure complete removal of the quininic acid. The quininic acid, dried to constant weight at 40–50° under reduced pressure, was obtained in 103% yield. This material showed a neutralization equivalent of 232, whereas the calculated value is 210.

Large-scale esterification of the quininic acid (VI → VII) (22.27 lbs. of quininic acid and 18 gallons of absolute alcohol) gave but a poor yield of ester (53%, corrected for recovered quininic acid).

SUMMARY

Simplified and improved procedures for the preparation of ethyl quininate from *p*-anisidine are described. The over-all yield has been increased some 63%.

Methods of purifying the intermediates are given and their correct melting points are recorded.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

SYNTHESIS OF 1-AMINOPHENAZINES AND CONVERSION OF THEM TO POTENTIAL ANTIMALARIALS[1]

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During the course of a systematic exploration of various derivatives of heterocyclic nuclei as possible antimalarials, the close relationship between derivatives of 1-aminophenazine and the highly active 8-aminoquinolines suggested that the phenazine system possibly would be worthy of investigation. A properly substituted phenazine also bears some resemblance to the nucleus of Quinacrine. In the present communication, we wish to report the development of a satisfactory general synthesis for 1-aminophenazines and the condensation of representative members of this group with 3-diethylaminopropyl chloride.

Of the derivatives of phenazine previously reported, only a few carry a substituent in the 1-position. These include the hydroxy, methoxy, methyl, chloro, and amino derivatives, as well as the carboxylic acid and its amide. All such derivatives have been obtained heretofore in poor yields and with considerable difficulty. The general method used (1, 2) except for the preparation of the acid and the 1-amino derivative, involved condensation of a 3-substituted 1,2-benzoquinone with *o*-phenylenediamine. The only previously described synthesis of 1-aminophenazine itself is that of Kehrman and Prunier (3). In this, 1,3-diaminophenazine was prepared because of inability to synthesize the intermediate 3-amino-1,2-benzoquinone, and the 3-amino group was removed selectively by diazotization. Wohl and Lange (4) were unsuccessful in obtaining 1-aminophenazine by fusing *o*-nitroaniline, aniline, and zinc chloride together. The product was 2-aminophenazine. Nitration of phenazine itself yields only the 1,3-dinitro derivative, which could not be reduced (5). 1-Nitrophenazine has been obtained as a by-product of the decarboxylation of 2,6-dinitrodiphenylamine-4-carboxylic acid (6), but the method appears to have no preparative value. Even the recent interest caused by the discovery that certain natural bacterial products, such as pyocyanine and chlororafin, are simple 1-substituted phenazine derivatives has failed to stimulate the development of a convenient synthesis for these compounds.

Of other general syntheses of phenazines, that involving intramolecular ring closure of a 2-aminodiphenylamine appeared to be worthy of further study in connection with the present problem. Such diphenylamine derivatives have been closed to phenazines by the action of lead dioxide (7) and more recently the method has been used for the synthesis of some simply substituted phenazines (8), although in poor yield. A modification of the original procedure, introduced by Kehrman and Havas (5), involves heating a mixture of 2-nitrodiphenylamine

[1] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

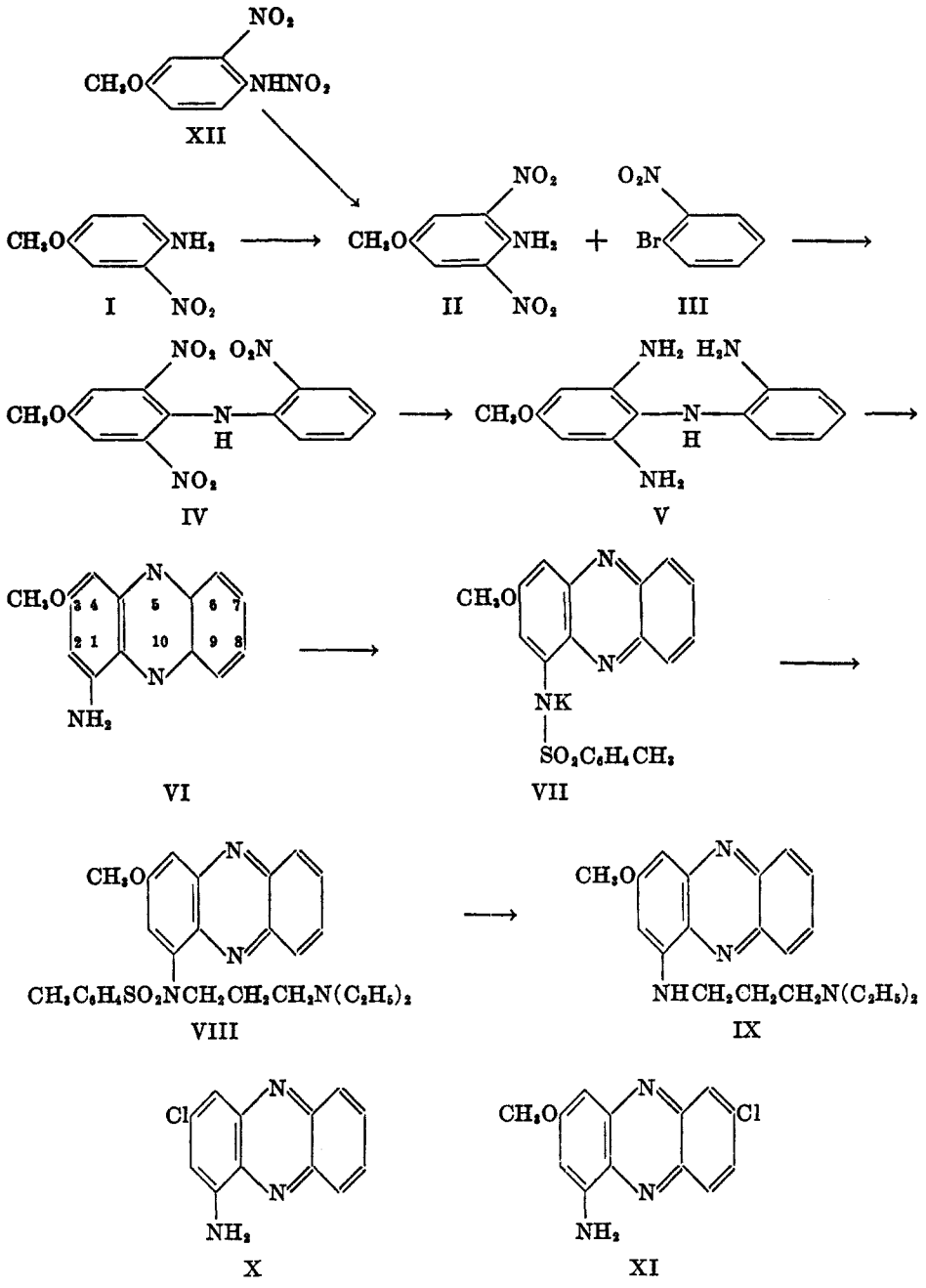
and 2-aminodiphenylamine to obtain phenazine in good yield. The method failed when applied to the synthesis of substituted phenazines (8). Eckert and Steiner (9) found that when 2,2′-dinitrodiphenylamine was reduced with stannous chloride and hydrochloric acid, the product was a quinhydrone type complex of phenazine and dihydrophenazine which was readily converted to phenazine by oxidizing agents. Tomlinson (10) isolated 2,2′-diaminodiphenylamine from the products of the reduction of 2,2′-dinitrodiphenylamine with zinc dust and acetic acid. The former on treatment with ferric chloride in dilute hydrochloric acid solution gave a quantitative yield of phenazine.

In adapting the general method of Eckert and Steiner to the present case, the assumption was made that a third amino group ortho to the diphenylamine linkage would remain unaffected during the relatively mild conditions under which the ring closure proceeded. This assumption proved to be correct. When 2,6,2′-trinitro-4-methoxydiphenylamine (IV) was reduced catalytically and the resulting triamine (V) was oxidized in hydrochloric acid solution with ferric chloride, 1-amino-3-methoxyphenazine (VI) was obtained in good yield. In a similar manner, 1-amino-3-chlorophenazine (X) and 1-amino-3-methoxy-7-chlorophenazine (XI) were prepared.

The requisite intermediate for the synthesis of 1-amino-3-methoxyphenazine, 2,6,2′-trinitro-4-methoxydiphenylamine (IV) was prepared from 3,5-dinitro-4-aminoanisole (II) by condensation with *o*-nitrobromobenzene (III). The usual procedure (9, 10) of fusing the reactants at 180° with potassium carbonate and copper powder or cuprous chloride resulted in poor yields and often in fume-offs. Because of the high melting point of the product, the reaction mixture soon solidified, which prevented complete reaction. When dry nitrobenzene was used as a solvent, no appreciable reaction occurred. However, in the presence of wet nitrobenzene, the reaction proceeded to the extent of 50% at the reflux temperature in ten minutes. A longer heating period did not increase the yield. Further, because of the insolubility of the product, the tedious steam distillation for removal of the nitrobenzene could be dispensed with, and the reaction mixture was merely diluted with alcohol. In the syntheses of 2,6,2′-trinitro-4-chlorodiphenylamine and 2,6,2′-trinitro-4-methoxy-4′-chlorodiphenylamine the yields were somewhat lower.

A curious change in crystalline form was noted when 2,6,2′-trinitro-4-methoxydiphenylamine (IV) was heated to 160°. The substance, which normally crystallizes as orange needles, changed to a light yellow. The yellow form on recrystallization separated as orange needles even when seeded with the yellow crystals. Similar changes have been noted with other dinitrophenylamines and picrylanilines (11, 12).

Since a considerable amount of 3,5-dinitro-4-aminoanisole (II) was required in the present work, and since 3-nitro-4-aminoanisole (I) was readily available, the conversion of the latter to the former in good yield was investigated. The method of Macciotta (13) involving rearrangement of 2-nitro-4-methoxyphenylnitramine (XII) led to a poor yield of the desired product. Direct nitration of 3-nitro-4-aminoanisole under special conditions resulted in a good yield of



the dinitro compound. By the same procedure 2,6-dinitro-4-chloroaniline was obtained from 2-nitro-4-chloroaniline, although the yield was somewhat lower. The method was unsuccessful when applied to *o*-nitroaniline.

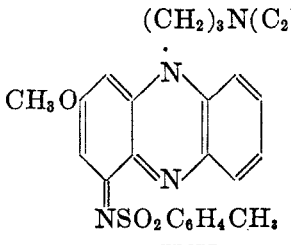
Prior to the development of the above direct nitration method, nitration of benzene sulfon-*p*-anisidide was investigated. Reverdin (14) has described the formation of 2-nitro- and 2,6-dinitro-4-methoxybenzene sulfonanilide without giving experimental details. By varying the experimental conditions under which the nitration was carried out, it has been possible to produce three compounds at will. Two of these were identical with the mononitro and dinitro compounds described by Reverdin. The third, which crystallized from the hot reaction mixture, proved to be a molecular compound of the mononitro- and dinitro-sulfonanilides.

Reduction of the trinitrodiphenylamines with either stannous chloride or zinc dust and acetic acid by methods which are reported to be successful in the cases of simpler diphenylamines (9, 10) resulted in a vigorous reaction, but no product could be isolated. However, reduction with hydrogen and platinum oxide gave satisfactory yields of the triaminodiphenylamines. As a general rule, these were not isolated prior to the ring closure. The chlorine atom, when present, was not removed during the reduction. Apparently some ring closure to the phenazines took place during the reduction as evidenced by the presence of an odor of ammonia in the reaction mixture. The free triaminodiphenylamines are colorless crystalline solids which are remarkably stable in the solid state. Solutions of them, however, rapidly turn dark on exposure to the air.

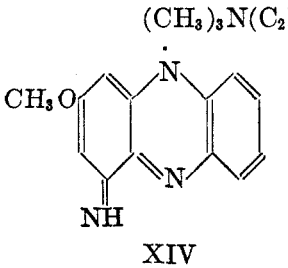
The triaminodiphenylamines in solution directly as obtained from the catalytic reduction were oxidized to the phenazines with ferric chloride in hydrochloric acid solution (10). The phenazine monohydrochlorides were dark blue and the free bases were red crystalline compounds.

3-Diethylaminopropylchloride was condensed with the 1-aminophenazines by the method of Gawron and Spoerri (15) to yield the final drugs (typical reaction VI–IX). The hydrochlorides of the drugs were blue and readily soluble in water. The concentrated blue aqueous solutions of the hydrochlorides turned red on dilution. In two cases the free bases were obtained as red, crystalline, low-melting solids.

A resonating form of the ion, VII, carries the negative charge on the ring nitrogen atom 5. This brings into consideration an alternate interpretation of the reaction of VII with diethylaminopropyl chloride, in which case the product would possess the structure, XIII, and the hydrolysis product that of XIV



XIII



XIV

While no direct proof can be advanced in favor of the structures VIII and IX we favor the latter, by analogy with the recorded behavior of 2-aminopyridine when it is alkylated as a negative ion in the presence of sodamide. Thus Tschitschibabin, Konowalowa, and Konowalowa (16) found that reaction of 2-aminopyridine with methyl iodide results in the formation of 2-aminopyridinium methiodide, while in the presence of one equivalent of sodamide, the sodium salt of 2-aminopyridine is formed, which on reaction with methyl iodide leads to the exclusive formation of 2-methylaminopyridine. Whitmore and co-workers (17) prepared 2-aminoalkylaminopyridines by the reaction of 2-aminopyridine with an appropriate aminoalkyl halide in the presence of one equivalent of sodamide. In one representative case, the structure of the product was shown to be identical with that obtained by reaction of 2-bromopyridine with the aminoalkylamine. Since an obvious analogy exists between 2-aminopyridine and the aminophenazines here described, we assume that the alkylation reactions take a similar course in the two series.

EXPERIMENTAL

All melting points are corrected.

3,5-Dinitro-4-aminoanisole (II). Two hundred grams of 3-nitro-4-aminoanisole (technical material from National Aniline Division of Allied Chemical & Dye Corporation) was added rapidly with stirring to 900 ml. of nitric acid (*d* 1.4) at room temperature. The temperature rose to 33° and was held at 30–35° by occasional outside cooling. Red crystals of the product soon began to separate. After one hour the mixture was cooled in ice, filtered, and the precipitate was washed first with dilute nitric acid (1 vol. nitric acid, *d* 1.4: 2 vols. water) and then repeatedly with water. The yield of material, melting at 161–163°, which was pure as obtained, was 70–80%. The identity of the substance was confirmed by mixed melting point with an authentic sample prepared according to Reverdin (14).

2-Nitro-4-methoxybenzenesulfonanilide. To a solution of 20 g. of benzenesulfon-*p*-anisidide in 100 ml. of 95% alcohol was added 10 ml. of nitric acid (*d* 1.4) and the mixture was heated just below the boiling point for one hour. On cooling, the mononitro compound, melting at 85°, separated. Reverdin (14) reports the material melting at 87°. On hydrolysis, 3-nitro-4-aminoanisole, melting at 123°, was obtained.

When the above procedure was repeated using 20 ml. of nitric acid and heating the mixture for an hour and a half, long pale yellow needles separated from the hot solution, and on cooling, 18 g. of material melting at 129–131° was obtained. The melting point was not changed by recrystallization from alcohol. On hydrolysis of this substance, a mixture of 3-nitro- and 3,5-dinitro-4-aminoanisole was obtained. That the material melting at 129–131° was a molecular compound was shown by its formation when equimolar amounts of the mono- and di-nitro derivatives were recrystallized from alcohol. The 2,6-dinitro-4-methoxybenzenesulfonanilide was prepared according to King and Beer (18) and melted at 176°.

Anal. Calc'd for $C_{26}H_{23}N_5O_{12}S_2$: C, 47.2; H, 3.5.
Found: C, 47.5; H, 3.5.

2-Nitro-4-methoxyphenylnitramine (XII) and its rearrangement to 3,5-dinitro-4-aminoanisole. The general method of Orton (19) was used. To a suspension of 45 g. of 3-nitro-4-aminoanisole in 400 ml. of glacial acetic acid was added a mixture of 48 ml. of nitric acid (*d* 1.52), previously decolorized by addition of urea, and 50 ml. of acetic anhydride over one hour during which the mixture was chilled in ice. The mixture was stirred for an additional hour, poured onto ice and the precipitate was stirred at room temperature with 3% sodium carbonate solution. The insoluble material was filtered off. Acidification of

the carbonate solution with 2 *N* hydrochloric acid gave 15.5 g. of a red solid. Without further purification this was added slowly with stirring to 150 ml. of ice-cold sulfuric acid. The solution became warm and a small amount of oxides of nitrogen was evolved. After standing one hour at room temperature, the mixture was poured onto ice and the dark red precipitate was recrystallized from glacial acetic acid. The yield of material which melted at 160–162° was 17%. The substance showed no depression in melting point when mixed with the dinitro derivative prepared by the method of Reverdin (14).

2,6,2'-Trinitro-4-methoxydiphenylamine. In a 500 ml. 3-necked flask equipped with a thermometer, mechanical stirrer, and a short air condenser was placed 30.3 g. of *o*-bromonitrobenzene, 31.5 g. of 3,5-dinitro-4-aminoanisole, 30 g. of anhydrous potassium carbonate, 2 g. of freshly reduced copper powder, 90 ml. of nitrobenzene, and 1 ml. of water. The mixture was rapidly heated to 210° and maintained at gentle reflux with vigorous stirring for fifteen minutes. After cooling, alcohol was added and the mixture was chilled in an ice-bath and filtered. The solid thus removed was suspended in 10% hydrochloric acid, filtered off and the insoluble material was washed thoroughly with water, dried, and recrystallized from dioxane-alcohol. The product crystallized as orange needles which melted at 209–211°. The yield was 24 g. (48%).

Anal. Calc'd for $C_{13}H_{10}N_4O_7$: C, 46.7; H, 3.0.
Found: C, 46.8; H, 3.0.

The same substance was also obtained in 37% yield when an intimate mixture of 9 g. of 3,5-dinitro-4-aminoanisole, 10 g. of *o*-bromonitrobenzene, 15 g. of anhydrous sodium carbonate, and 0.5 g. of cuprous chloride was heated in an oil-bath at 180° for seven hours (9). Towards the end of the heating period, the mass solidified almost completely. It was cooled, broken up, boiled with water. After drying, the material was crystallized from benzene and then from glacial acetic acid. The mother liquors contained considerable unreacted dinitroaminoanisole.

2,6,2'-Triamino-4-methoxydiphenylamine (*V*). A suspension of 25 g. of 2,6,2'-trinitro-4-methoxydiphenylamine in 200 ml. of alcohol was shaken with 200 mg. of Adams platinum oxide catalyst under about 35 lb. hydrogen pressure. As the reduction proceeded, the mixture warmed up, but the rate of hydrogen uptake slowed down towards the end of the reduction. A colorless precipitate of the triaminomethoxydiphenylamine separated. As is indicated below, it is not necessary to isolate the pure triamine for the preparation of 1-amino-3-methoxyphenazine. Pure 2,6,2'-triamino-4-methoxydiphenylamine was obtained by filtering off the crude reduction product and recrystallizing it from alcohol (decolorizing carbon) under a nitrogen atmosphere. The triaminodiphenylamine forms colorless needles which become slightly pink on long standing and melt at 168–170°.

Anal. Calc'd for $C_{13}H_{16}N_4O$: C, 63.9; H, 6.6.
Found: C, 63.9; H, 6.5.

The triaminodiphenylamine dissolved readily in acetic anhydride with considerable evolution of heat. On cooling, a tetraacetyl derivative crystallized in small plates and melted at 245–247°.

Anal. Calc'd for $C_{21}H_{24}N_4O_8$: C, 61.2; H, 5.9; N, 13.6.
Found: C, 61.4; H, 5.8; N, 13.6.

1-Amino-3-methoxyphenazine (*VI*). Crude crystalline 2,6,2'-triamino-4-methoxydiphenylamine was dissolved in dilute hydrochloric acid and to the solution an excess of aqueous ferric chloride solution was added at room temperature. There was a slight rise in temperature and deep blue crystals began to separate almost immediately. After standing overnight at room temperature and then chilling in ice, the crystalline material was filtered off and washed with 2% hydrochloric acid. The yield of 1-amino-3-methoxyphenazine hydrochloride melting at 217–220° was almost quantitative. The substance is almost insoluble in cold water, but fairly soluble in boiling water from which it can be recrystallized. When pure, it melts at 220–223°. The crude hydrochloride was used for the next step.

Anal. Calc'd for $C_{13}H_{11}N_3O \cdot HCl$: C, 59.7; H, 4.6.
Found: C, 59.6; H, 4.6.

It was not necessary to isolate the triaminomethoxydiphenylamine prior to preparing the phenazine. When the reduction mixture was acidified with hydrochloric acid, filtered from the catalyst, and then treated with ferric chloride, a 71.5% yield of the phenazine hydrochloride was obtained.

1-Amino-3-methoxyphenazine, liberated from the hydrochloride melted at 174–175° after sublimation at 150° and 1 mm. The sublimed material crystallized from heptane as reddish needles of the same melting point.

Anal. Calc'd for $C_{13}H_{11}N_3O$: C, 69.3; H, 4.9; N, 18.7.
Found: C, 69.5; H, 4.9; N, 18.7.

The *acetyl derivative* was obtained by warming a solution of the phenazine in acetic anhydride for a few minutes on the steam-bath. After recrystallization from heptane, it formed yellow needles which melted at 190–191°.

Anal. Calc'd for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9.
Found: C, 67.5; H, 4.8.

1-p-Toluenesulfonamido-3-methoxyphenazine (VII). To a solution of 5 g. of crude 1-amino-3-methoxyphenazine hydrochloride (warming was necessary to effect solution) in 15 ml. of dry pyridine was added 4 g. of *p*-toluenesulfonylchloride. The solution became very hot and in some experiments the pyridine boiled. A crystalline precipitate separated almost immediately. The reaction was completed by warming the mixture on the steam-bath for ten minutes. After cooling, the dark mixture was diluted with 30 ml. of alcohol, filtered, and the insoluble material was washed with alcohol. After recrystallization from dioxane, 4 g. of yellow plates melting at 201–202° was obtained. The substance is insoluble in alcohol and readily soluble in benzene.

Anal. Calc'd for $C_{20}H_{17}N_3O_3S$: C, 63.3; H, 4.5.
Found: C, 63.6; H, 4.5.

N-p-Toluenesulfonyl-1-(3-diethylaminopropylamino)-3-methoxyphenazine (VIII). To a solution of 13.5 g. of 1-*p*-toluene sulfonamido-3-methoxyphenazine in 300 ml. of hot dioxane was added a filtered solution of 2.5 g. (1 equiv.) of potassium hydroxide in 25 ml. of alcohol. The mixture turned deep red and almost immediately a crystalline orange-red precipitate of the potassium salt began to separate. After cooling, the potassium salt was filtered off and washed with ether. It was insoluble in water, alcohol, and dioxane, and soluble in pyridine. It did not melt at 330°. To a suspension of the potassium salt obtained as above in 250 ml. of absolute alcohol was added 6 g. of freshly distilled 3-diethylaminopropylchloride and the mixture was refluxed for two hours, when the solid material went into solution. After refluxing for an additional hour, the alcohol was removed under reduced pressure and the residue was recrystallized twice from heptane, giving 14 g. (80%) of pale yellow silky needles which melted at 112–114°. The substance is soluble in dilute mineral acids and is reprecipitated unchanged by base. It is very soluble in alcohol.

Anal. Calc'd for $C_{27}H_{32}N_4O_3S$: C, 65.8; H, 6.6.
Found: C, 65.7; H, 6.5.

1-(3-Diethylaminopropylamino)-3-methoxyphenazine (IX). The above *p*-toluenesulfonamido derivative (10 g.) was added with stirring to 30 ml. of sulfuric acid (sp. gr. 1.84) at room temperature. The solid dissolved with evolution of heat. Hydrolysis was completed by warming the mixture for ten minutes on the steam-bath, after which it was poured onto cracked ice. The resulting deep blue solution was made alkaline with potassium hydroxide. The red oil which separated was extracted with three portions of benzene under nitrogen. After drying the combined benzene extracts with calcium chloride and removal of the solvent under nitrogen, the residue was dissolved in acetone. To the acetone solution a dilute ethereal solution of hydrogen chloride was added. The dihydrochloride of 1-(3-diethylaminopropylamino)-3-methoxyphenazine separated as a blue crystalline powder. The yield of analytically pure material obtained directly and melting at 193.5–194° was 8 g. (96%). The hydrochloride can be obtained directly by adding ethereal hy-

drogen chloride to the dried benzene extracts of the base. It then separates as an oil which crystallizes on rubbing under acetone. It is fairly soluble in alcohol, from which it can be recrystallized, and readily soluble in water. Its blue concentrated aqueous solution turns red on dilution; on addition of more acid the blue color returns.

Anal. Calc'd for $C_{20}H_{26}N_4O \cdot 2HCl$: C, 58.4; H, 6.9.
Found: C, 58.1; H, 7.0.

The free base, obtained as a red oil from the hydrochloride, slowly crystallized as red needles which melted at 41–43°. It is insoluble in water and readily soluble in the common organic solvents.

Anal. Calc'd for $C_{20}H_{26}N_4O$: C, 71.0; H, 7.7.
Found: C, 70.8; H, 7.8.

2,6,2'-Trinitro-4-methoxy-4'-chlorodiphenylamine. A mixture of 21.3 g. of 3,5-dinitro-4-aminoanisole, 23.6 g. of 2-bromo-5-chloronitrobenzene prepared by the general method of Gibson and Johnson (20), 20 g. of anhydrous potassium carbonate, 2 g. of freshly reduced copper powder, 70 ml. of nitrobenzene, and 5 drops of water was heated at 210° with stirring for fifteen minutes. After cooling, the mixture was diluted with alcohol and filtered. The solid was suspended in 10% hydrochloric acid, filtered again, and dried. This crude product invariably contained some unreacted dinitroanisidine which was removed by extraction with 500 ml. of boiling alcohol, in which the diphenylamine derivative was substantially insoluble. The residue was then recrystallized from a mixture of dioxane and alcohol, yielding 12–14 g. (35–38%) of yellow needles melting at 202–204°.

Anal. Calc'd for $C_{13}H_9ClN_4O_7$: C, 42.4; H, 2.5.
Found: C, 42.4; H, 2.6.

2,6,2'-Triamino-4-methoxy-4'-chlorodiphenylamine. The above trinitro compound (30 g.) was shaken under 30 lb. pressure of hydrogen with 0.2 g. of Adams platinum oxide catalyst. At first the reduction was very rapid and considerable heat was evolved. However, toward the end the reaction slowed down and two portions of fresh catalyst were added. The deep red solution was filtered from the catalyst and chilled in ice, yielding 1.5 g. of pure 2,6,2'-triamino-4-methoxy-4'-chlorodiphenylamine as reddish plates which melted at 137–139°. A negative silver test for chloride ion in the filtrate showed that the chlorine had not been removed during the reduction.

Anal. Calc'd for $C_{13}H_{15}ClN_4O$: C, 56.0; H, 5.4.
Found: C, 55.8; H, 5.1.

1-Amino-3-methoxy-7-chlorophenazine. The filtrate from the above crystalline material was acidified with hydrochloric acid and ferric chloride solution was added as in the preceding case. The blue phenazine hydrochloride began to separate almost immediately. The yield of crude hydrochloride, melting at 203–205°, was 71%. It was used directly for the next step. The free base, liberated from the hydrochloride crystallized as red needles from heptane and melted at 187–190°.

Anal. Calc'd for $C_{13}H_{10}ClN_3O$: C, 60.1; H, 3.9.
Found: C, 59.8; H, 3.9.

The *acetyl derivative* formed yellow needles from heptane and melted at 199–202°.

Anal. Calc'd for $C_{15}H_{12}ClN_3O_2$: C, 59.7; H, 4.0.
Found: C, 59.6; H, 3.9.

1-Benzenesulfonamido-3-methoxy-7-chlorophenazine. To a warm solution of 5 g. of the crude hydrochloride of 1-amino-3-methoxy-7-chlorophenazine in 15 ml. of dry pyridine was added 5 g. of benzenesulfonyl chloride. The reaction was completed by heating the mixture on the steam-bath for fifteen minutes. After cooling, alcohol was added and the sulfonamide was filtered off and recrystallized from dioxane. It formed golden yellow plates and melted at 247-250°. The yield was 4 g. (60%).

Anal. Calc'd for $C_{19}H_{14}ClN_3O_3S$: C, 57.1; H, 3.5.
Found: C, 56.9; H, 3.5.

N - Benzenesulfonyl - 1 - (3 - diethylaminopropylamino) - 3 - methoxy - 7 - chlorophenazine. This was prepared as in the preceding case. The crude product after removal of the alcohol

was extracted with boiling heptane and the small insoluble fraction was discarded. Recrystallization of the material which separated from the cooled heptane extracts once more from the same solvent, gave 57% of the product which melted at 148–149°.

Anal. Calc'd for $C_{26}H_{29}ClN_4O_3S$: C, 60.9; H, 5.7.
Found: C, 60.6; H, 5.6.

1-(3-Diethylaminopropylamino)-3-methoxy-7-chlorophenazine. The benzenesulfonyl group in the above substance was removed in almost quantitative yield by hydrolysis with sulfuric acid as in the preceding case. The phenazine separated as a red oil which was extracted with benzene under nitrogen. Addition of dry hydrogen chloride to the dried benzene solution of the base precipitated an oily hydrochloride which crystallized on addition of alcohol. After air drying, the substance melted at 158–160° and furnished analytical figures corresponding to the dihydrochloride dihydrate.

Anal. Calc'd for $C_{20}H_{25}ClN_4O \cdot 2HCl \cdot 2H_2O$: C, 49.9; H, 6.5.
Found: C, 50.1; H, 6.6.

On drying at room temperature *in vacuo*, the weight loss was 8.4% (calc'd 8.1%) and the anhydrous dihydrochloride resulted.

Anal. Calc'd for $C_{20}H_{25}ClN_4O \cdot 2HCl$: C, 53.9; H, 6.1.
Found: C, 54.3; H, 6.1.

When dried at 78° *in vacuo* over phosphorus pentoxide, the dihydrochloride dihydrate lost all its water and one molecule of hydrogen chloride per two molecules of salt. (Weight loss calc'd: 11.3%; found: 11.4%).

Anal. Calc'd for $(C_{20}H_{25}ClN_4O)_2 \cdot 3HCl$: C, 56.2; H, 6.3.
Found: C, 56.2; H, 6.2.

All three of the hydrochlorides melted at the same temperature even in sealed tubes, indicating that transition to the stable form occurred during heating.

2,6-Dinitro-4-chloroaniline. Two hundred grams of 2-nitro-4-chloroaniline was added rapidly with stirring to 900 ml. of nitric acid (*d* 1.4). The temperature was held between 30° and 35°. Yellow needles of the dinitro compound soon began to separate. After one hour, the mixture was chilled in ice and the solid was filtered off, washed once with nitric acid (1:1), and then with water until free from acid. After drying at 70°, the yield of material melting at 147–148° was 134 g. (56%). 2,6-Dinitro-4-chloroaniline, prepared from 2,6-dinitro-1,4-dichlorobenzene, is reported as melting at 145–146°.

2,6,2'-Trinitro-4-chlorodiphenylamine. 2,6-Dinitro-4-chloroaniline was condensed with *o*-bromonitrobenzene as in the preceding examples. The reaction mixture was considerably darker and the yield was lower than in the other cases. The diphenylamine derivative (yield 24%) formed golden needles which melted at 212–213°.

Anal. Calc'd for $C_{12}H_7ClN_4O_6$: C, 42.6; H, 2.1.
Found: C, 42.5; H, 2.0.

When an intimate mixture of 10.8 g. of 2,6-dinitro-4-chloroaniline, 10.1 g. of *o*-bromonitrobenzene, 10 g. of anhydrous potassium carbonate, and 1 g. of copper powder was heated in a Wood's metal-bath, the mixture turned very dark and gentle gas evolution began at an inside temperature of 180°. At 190° the rate of gas evolution increased and the heat applied was sharply decreased. Within ten minutes an explosion accompanied by a flash of flame and heavy green smoke occurred. The residue was completely carbonized.

2,6,2'-Triamino-4-chlorodiphenylamine. The above trinitro compound (25 g.) was reduced as before with platinum oxide in alcohol. Fresh catalyst had to be added twice and the hydrogen absorption stopped when 95% of the theoretical amount was absorbed. A sample of the dark red solution gave a negative test with silver nitrate, showing that the chlorine substituent remained intact. The presence of a strong odor of ammonia in the solution indicated that some ring closure had taken place. On chilling the alcoholic solution, 4 g. of the triaminodiphenylamine crystallized. After recrystallization from alcohol, it formed colorless needles which melted at 183–185°.

Anal. Calc'd for $C_{12}H_{13}ClN_4$: C, 58.0; H, 5.3.
Found: C, 58.3; H, 5.1.

The tetraacetyl derivative, prepared by dissolving the amine in acetic anhydride and then cooling the solution, crystallized as small colorless plates which melted at 222–224°.

Anal. Calc'd for $C_{20}H_{21}ClN_4O_4$: C, 57.6; H, 5.1.
Found: C, 57.8; H, 5.3.

1-Amino-3-chlorophenazine (*X*). The filtrate from the above crystalline triaminodiphenylamine was acidified with hydrochloric acid and oxidized with ferric chloride as above. The dark blue phenazine hydrochloride separated almost immediately. Since the salt was appreciably soluble in dilute alcohol, the reaction mixture, after standing overnight, was buffered with sodium acetate solution, on which the brick red 1-amino-3-chlorophenazine (15 g.) separated. As thus obtained, it melted indefinitely at 189–197° with softening at 150°. It was readily purified by sublimation *in vacuo*. After crystallization of the sublimate from dilute alcohol or heptane, the phenazine formed red needles which melted at 202–204°.

Anal. Calc'd for $C_{12}H_8ClN_3$: C, 62.8; H, 3.5.
Found: C, 63.0; H, 3.4.

The *acetyl derivative* crystallized from heptane as yellow needles melting at 196–197°.

Anal. Calc'd for $C_{14}H_{10}ClN_3O$: C, 61.9; H, 3.7.
Found: C, 61.9; H, 3.5.

1-Benzenesulfonamido-3-chlorophenazine. This was prepared from the crude aminophenazine in pyridine as before in 50% yield. The substance formed yellow plates which melted at 230–232°, from dioxane.

Anal. Calc'd for $C_{18}H_{12}ClN_3O_2S$: C, 58.5; H, 3.3.
Found: C, 58.7; H, 3.2.

N-Benzenesulfonyl-1-(3-diethylaminopropylamino)-3-chlorophenazine. The pink potassium salt of 1-benzene sulfonamido-3-chlorophenazine which crystallized on addition of one equivalent of alcoholic potassium hydroxide solution to a hot solution of the sulfonamide in dioxane was refluxed with one equivalent of 3-diethylaminopropyl chloride in absolute alcohol. After sixteen hours boiling, some unchanged potassium salt was present; an additional half an equivalent of diethylaminopropyl chloride was added and refluxing was continued for six hours more. The residue after removal of the alcohol was extracted with boiling heptane. The combined heptane extracts, from which nothing crystallized, were concentrated to dryness, leaving an oil which crystallized on scratching. After recrystallization from petroleum ether (30–50°) 43% of material melting at 76–78° was obtained.

Anal. Calc'd for $C_{25}H_{27}ClN_4O_2S$: C, 62.2; H, 5.6.
Found: C, 61.9; H, 5.5.

1-(3-Diethylaminopropylamino)-3-chlorophenazine. The benzenesulfonyl group in the above substance was removed as in the preceding cases. The blue dihydrochloride of the base melted at 200–203°.

Anal. Calc'd for $C_{19}H_{25}Cl_3N_4$: C, 54.9; H, 6.1.
Found: C, 55.0; H, 6.1.

The free base was obtained as an oil which crystallized on rubbing, and melted at 52–54°.

Anal. Calc'd for $C_{19}H_{23}ClN_4$: C, 66.5; H, 6.8.
Found: C, 66.3; H, 6.8.

The microanalyses reported were done by Miss Lois May and Mr. W. Sashek.

SUMMARY

1. A general synthesis for 1-aminophenazine derivatives has been developed.

2. Three representative dialkylaminoalkyl-1-aminophenazines have been prepared for evaluation as antimalarials.

3. An improved synthesis of 3,5-dinitro-4-aminoanisole has been developed.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

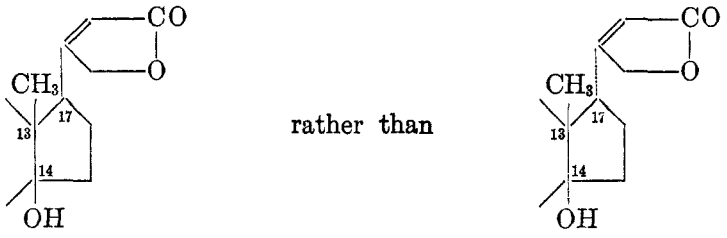
INVESTIGATIONS ON STEROIDS. IX. SOME NEW POLYHYDROXY-ETIOCHOLANIC ACIDS[1]

MAXIMILIAN EHRENSTEIN AND ALDA RUTH JOHNSON

Received July 28, 1946

In a previous publication (1) 3,5,14-trihydroxyestrane-10,17-dicarboxylic acid served as an intermediate in the preparation of compounds structurally related to hormones of the pregnane series. The dicarboxylic acid was prepared from strophanthidin (I) according to procedures known from the literature. The stepwise degradation of the unsaturated lactone ring is a time-consuming and uneconomical procedure which, in addition, is associated with an undesired inversion of the configuration at carbon atom 17.

Doubts have recently arisen regarding the presently accepted stereochemical structure of strophanthidin.[2] Ruzicka (2) states for instance that certain reactions of strophanthidin are not in agreement with the configuration of a derivative of 3(α),5-dihydroxycoprostane. Very recent work from the same laboratory (3) supports the assumption that in the normal, naturally-occurring, sterids the side chain at carbon atom 17 is attached in β-position.[2a] According to this postulation, the part of ring D in the cardiac aglycons has to be formulated



Because of these uncertainties regarding the configuration of strophanthidin, no stereochemical relationships will be indicated in the chemical structures of this publication though certain aspects of configuration will be discussed.

A number of years ago Steiger and Reichstein (4) published a new approach to the problem of degrading the unsaturated lactone ring of cardiac aglycons. By treating the diacetate of digoxigenin with less than the stoichiometrically

[1]Aided by a joint grant from the Smith, Kline, and French Laboratories and Sharp & Dohme, Inc. in Philadelphia. Additional support was provided through a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

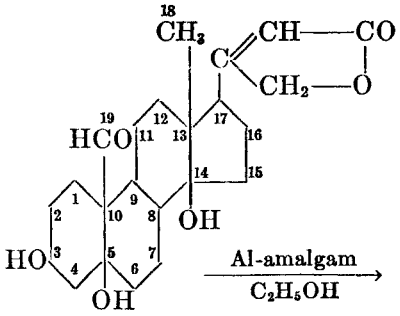
[2]For conventional stereochemical structure *cf. e.g.* (1, p. 436, formula I)

[2a] In this country, Gallagher and Long (12) had previously arrived at the same conclusion. While this paper was in press, Reichstein's laboratory (13) also reported data supporting this configuration at carbon atom 17.

required amount of potassium permanganate in a solution of acetone they were able to remove three carbon atoms of the unsaturated lactone ring in one operation, and thus succeeded in obtaining a 3,12-diacetoxy-14-hydroxyetiocholanic acid. The neutral fraction of this oxidation consisted almost exclusively of unchanged crystalline starting material. It did not appear promising to apply the same method to strophanthidin acetate because the formation of an additional carboxyl group at carbon atom 10 would complicate the separation of the reaction products. The question arose, however, whether this type of oxidation could be successfully applied to strophanthidol diacetate (III). Strophanthidin (I) can be reduced to strophanthidol (II) either with aluminum isopropoxide and isopropyl alcohol (Meerwein-Ponndorf reaction) or by the action of aluminum amalgam in a solution of 95% alcohol (5, 6). We found that the latter method furnishes very satisfactory results provided a suitable brand of aluminum is available for the preparation of the aluminum amalgam. From the recrystallized strophanthidol the 3,19-diacetate (III) can be obtained in good yields. Whereas the melting point of pure strophanthidol is uncharacteristic, that of the diacetate is well defined(191–192°).

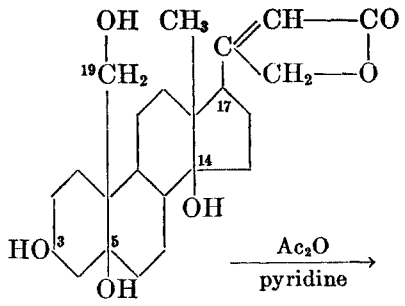
When strophanthidol 3,19-diacetate was treated in acetone solution with three moles of potassium permanganate, furnishing the equivalent of 4.5 atoms of oxygen, a fair amount of an amorphous acid oxidation product was obtained which represented the crude 3,19-diacetoxy-5,14-dihydroxyetiocholanic acid (IV).[3] The neutral oxidation product, likewise amorphous, consisted only partly of unchanged starting material (III), as was proved by chromatographic separation. It was found that a purification of this amorphous neutral material is not necessary. When it was subjected to a renewed oxidation with potassium permanganate, more of the crude 3,19-diacetoxy-5,14-dihydroxyetiocholanic acid could be secured, although in a somewhat smaller yield. Saponification of the crude diacetoxy acid (IV) yielded the crystalline 3,5,14,19-tetrahydroxyetiocholanic acid (V), melting at 217-218.5°. By means of diazomethane it was converted into the crystalline methyl 3,5,14,19-tetrahydroxyetiocholanate (VI) whose melting point was at 168–169°. The non-crystalline part of the product resulting from the saponification of the crude IV was likewise subjected to treatment with diazomethane which yielded, after chromatographic purification of the reaction product, a certain amount of pure crystalline VI. An attempt was made to secure the diacetoxy acid (IV) in a crystalline form. For this purpose pure 3,5,14,19-tetrahydroxyetiocholanic acid (V) was subjected to acetylation which obviously furnished the pure 3,19-diacetoxy-5,14-dihydroxyetiocholanic acid (IV). It resisted all attempts at crystallization. When this compound was treated with diazomethane the likewise amorphous methyl 3,19-diacetoxy-5,14-dihydroxyetiocholanate (VII) resulted.

[3] In a conversation with Professor T. Reichstein in Atlantic City on March 14, 1946, the senior author disclosed the essential findings described in this paper. Professor Reichstein mentioned that he had found strophanthidol to be the aglycon of a new cardiac glycoside from Strophanthus Kombé (cymarol, hydrolyzable to strophanthidol and cymarose). He has also subjected strophanthidol diacetate to an oxidation with potassium permanganate.



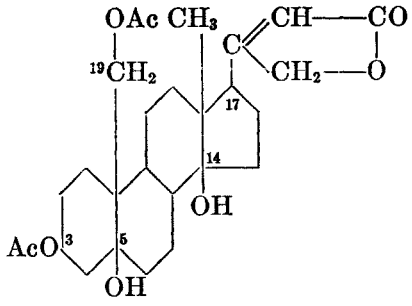
I. Strophanthidin

Al-amalgam
C_2H_5OH

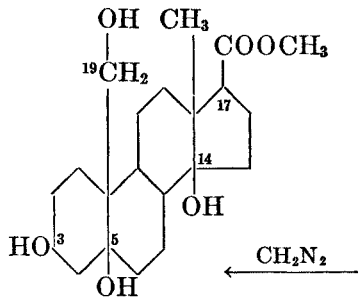


II. Strophanthidol

Ac_2O
pyridine

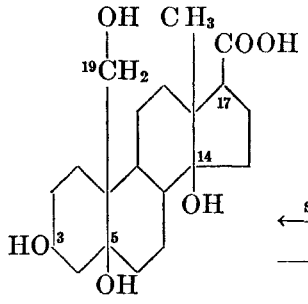


III. Strophanthidol 3,19-diacetate



VI. Methyl 3,5,14,19-tetrahydroxyetiocholanate

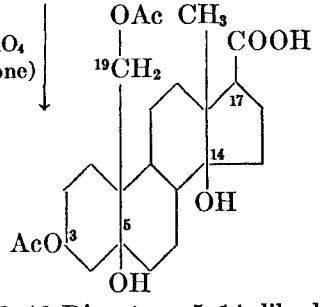
CH_2N_2



V. 3,5,14,19-Tetrahydroxyetiocholanic acid

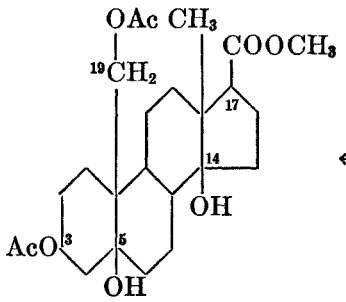
saponific.
Ac_2O
pyridine

$KMnO_4$
(acetone)



IV. 3,19-Diacetoxy-5,14-dihydroxyetiocholanic acid

CH_2N_2



VII. Methyl 3,19-diacetoxy-5,14-dihydroxyetiocholanate

Since the conclusion of this work two publications have appeared in which digitoxigenin acetate (7) and gitoxigenin diacetate (8) were subjected to the same oxidation procedure. The yields of the resulting etio acids seem to differ, depending on the structure of the aglycon.

The next object of this investigation was the elimination of the tertiary hydroxyl group at carbon atom 14 by dehydration and subsequent hydrogenation of the resulting double bond. In our last publication (1) an example of such a selective dehydration was presented.[4] Depending on the method used, two different dehydration products were obtained, the one probably being a $\Delta^{8,14}$and the other a Δ^{14}-compound. As is known, a double bond in $\Delta^{8,14}$-position is resistant to catalytic hydrogenation, whereas a double bond in Δ^{14}-position can easily be saturated. Since it was our aim to obtain the double bond in the reducible, *i.e.* in the Δ^{14}-position, we selected the same method which we had formerly utilized in an analogous instance (1).[4] Hence 3,5,14,19-tetrahydroxyetiocholanic acid (V) was treated with alcoholic hydrogen chloride. The two experiments described in the experimental part differ only in that the second experiment was carried out under slightly more vigorous conditions than the first. Using this procedure V is not only dehydrated but also largely transformed into ethyl esters and possibly also to a minor extent into lactones. Approximately 85% of the reaction product consisted of neutral material. This is in contrast to the example of our previous publication in which, under the same experimental conditions, the carboxyl group at carbon atom 17 remained largely intact. Such a different behavior can only be explained on the basis of the difference in the stereochemical configuration of the carboxyl group in the two compounds. Whereas in the previous instance the carboxyl group is attached to carbon atom 17 in the iso position, it is fairly certain that in the present example we are dealing with a normal configuration.

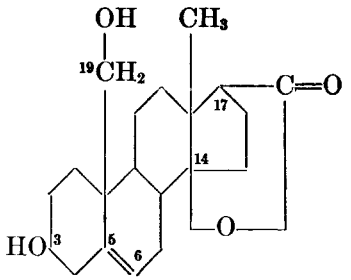
The reaction product consisted mainly of non-crystalline material. A very small amount of a crystalline neutral substance could be secured, whose melting point was between 90 and 100°. Its solution in chloroform gives a yellow color with tetranitromethane and the analysis is in agreement with the empirical formula $C_{20}H_{28}O_4$. The substance may therefore represent the unsaturated lactone X. The final structure cannot be given without further investigation. In particular, attempts at hydrogenation and saponification will be undertaken as soon as a sufficient amount of this substance has accumulated.

The first of the two dehydration experiments was carried out under rather mild conditions and from this another crystalline substance was secured in small amounts from the neutral fraction. It proved to be a simple esterification product of the starting material. Immediately after recrystallization the melting point of this ethyl 3,5,14,19-tetrahydroxyetiocholanate (VIII) is 186–188.5°.[5]

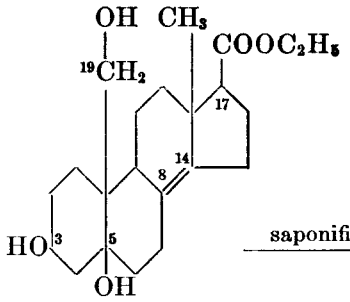
In a preliminary dehydration experiment the neutral reaction product had been subjected to a chromatographic separation. A very small amount of

[4] 3,5,14-Trihydroxyestrane-10,17-dicarboxylic acid was dehydrated to Δ^{14}-estrene-3,5-diol-10,17-dicarboxylic acid.

[5] For variations of this melting point *cf.* experimental part.

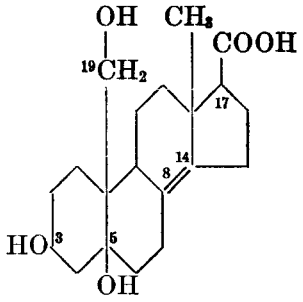


X. Lactone $C_{20}H_{28}O_4$?

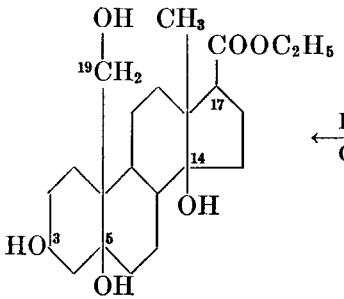


XI. Ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate

saponific.

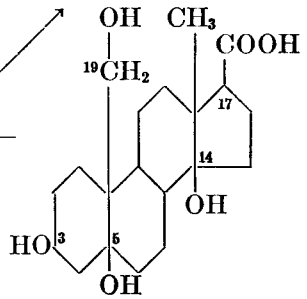


XII. 3,5,19-Trihydroxy-$\Delta^{8,14}$-etiocholenic acid



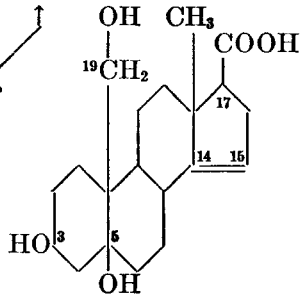
VIII. Ethyl 3,5,14,19-tetrahydroxy-etiocholanate

Neutral Products (85%)
C_2H_5OH + HCl

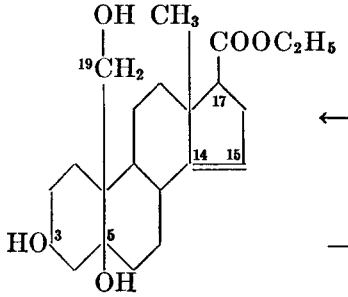


V. 3,5,14,19-Tetrahydroxy-etiocholanic acid

Acid Products (15%) ?
C_2H_5OH + HCl

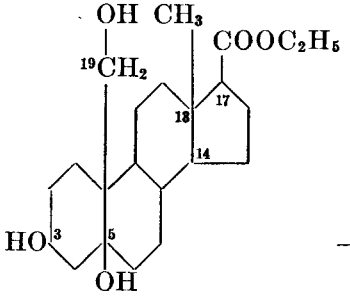


XIII. 3,5,19-Trihydroxy-Δ^{14}-etiocholenic acid



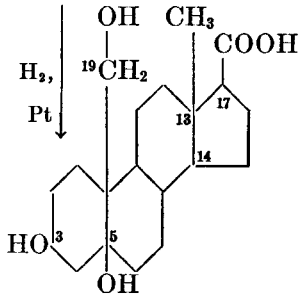
IX. Ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate

H_2, Pt



XV. Ethyl 3,5,19-trihydroxy-etiocholanate

saponific



XIV. 3,5,19-Trihydroxy-etiocholanic acid

another crystalline substance, melting at 187–192°, was isolated. Its structure is probably that of ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI). The compound will be discussed more fully below. The main product of the neutral fraction of the dehydration is ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX) which remained amorphous even after chromatographic purification.[5a]

No purification of the acid fractions of the dehydration products was carried out. The amorphous acid material was subjected directly to catalytic hydrogenation. After the identification of the hydrogenation products, conclusions were drawn as to the composition of the original acid fraction of the dehydration, as will be discussed below.

Usually, after the isolation of the crystalline substance which possibly represents the lactone X the dehydrated material was separated into neutral and acid fractions.[6] As mentioned, we were able in one instance[7] to isolate from the neutral fraction a certain amount of crystalline ethyl 3,5,14,19-tetrahydroxyetiocholanate (VIII) which was separated by filtration. Otherwise, the crude neutral and acid fractions were subjected directly to catalytic hydrogenation.

The main reaction product of the neutral fraction was in each instance the crystalline ethyl 3,5,19-trihydroxyetiocholanate (XV), the purest sample of which melted at 188–190°. It must have resulted from the amorphous ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX). In the saturated compound the hydrogen atom at carbon atom 14 can be assumed to possess the normal con-

[5a] (Addition to proof, October 29, 1946.) On repeating the dehydration experiments under conditions resembling those of Expt. II (*cf.* expt. part), treatment of the neutral material with acetone yielded substantial quantities of flat prismatic crystals. The melting points of recrystallized samples from three experiments were 187–189°, 189–191° and 190–191.5°. In a solution of chloroform, all substances gave a distinct yellow color with tetranitromethane. There were pronounced depressions of the melting points when the samples were mixed with compounds VIII or XI. The material is probably the crystalline modification of ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX). Oddly enough there was no depression of the melting point when mixed with an authentic sample of compound XV. $[\alpha]_D^{22}$ + 48.9° (20.0 mg. in 2.0 cc. of chloroform; second sample).

Anal. Calc'd for $C_{22}H_{34}O_5$: C, 69.79; H, 9.06
Found: C, 69.68, 69.64, 69.66; H, 8.98, 9.03, 9.08.

The noncrystalline part was subjected to chromatographic adsorption. From some of the early eluates crystalline residues were obtained which, on recrystallization from ether, furnished needles; negative reaction with tetranitromethane; m.p. 205–208°; $[\alpha]_D^{22}$ + 64.8° (10.0 mg. in 2.0 cc. of chloroform); this substance is obviously pure ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI) (*cf.* expt. part; Expt. and Flow Sheet II).

Anal. Calc'd for $C_{22}H_{34}O_5$: C, 69.79; H, 9.06.
Found: C, 69.41, 69.79; H, 9.05, 8.99.

The residues obtained from some of the late eluates were recrystallized from acetone; long flat prisms; positive reaction with tetranitromethane; m.p. 184–186°. There was no depression of the melting point with the compound believed to be the crystalline modification of IX.

[6] In one experiment the crude dehydration product was hydrogenated without previous separation into neutral and acid fractions. In this instance the separation was performed after the hydrogenation; *cf.* experimental part, C, Exp. I.2.

[7] *Cf.* experimental part, C, Exp. I.1.

figuration, *i.e.* "trans" to the methyl group at carbon atom 13.[8] A fair amount of moderately pure XV can usually be obtained by direct crystallization.[9] Additional quantities of this substance can be secured by subjecting the residue obtained from the mother liquor to a separation by chromatographic adsorption. This procedure provided at the same time some other compounds in a pure crystalline form.

From some of the first eluates of the chromatogram there was isolated a small amount of a substance which probably represents ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI); the highest melting point observed was 185°, though it is possible that it was not that of a completely pure sample. The formation of a certain amount of such a compound during the process of dehydration appears plausible. It is understandable that such a compound goes through the process of catalytic hydrogenation unchanged. It is furthermore not surprising that a solution of this substance in chloroform does not give a yellow color with tetranitromethane in spite of the presence of the double bond. It should be pointed out that the fractions of the chromatogram from which this substance was obtained contain some other material which still has to be identified. In particular one would have to examine these fractions for the presence of the hydrogenation product of the substance which has been tentatively assigned formula X. From several of the following eluates there was isolated XV, which has been discussed above. Near the last eluate of the chromatogram it was usually possible to identify a small amount of ethyl 3,5,14,19-tetrahydroxy-etiocholanate (VIII).

Saponification[10] of the main hydrogenation product, XV, furnished the free 3,5,19-trihydroxyetiocholanic acid (XIV) which melts at 259–260°. Esterification of the latter compound by means of diazomethane yielded methyl 3,5,19-trihydroxyetiocholanate (XVII) with the melting point 220–222.5°. By means of acetylation, XV was transformed into ethyl 3,19-diacetoxy-5-hydroxy-etiocholanate (XVII) whose melting point is 108–109.5°.

The saponification of ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI) yielded 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII), melting at 286–288°,

[8] In our last publication (1) Δ^{14}-estrene-3,5-diol-10,17-dicarboxylic acid (with the carboxyl group at C_{17} in iso position) was hydrogenated to estrane-3,5-diol-10,17-dicarboxylic acid. In the latter compound the hydrogen atom at carbon atom 14 had been assigned the normal configuration, *i.e.* "trans" to the methyl group at carbon atom 13. According to observations made in Ruzicka's laboratory (3) it appears possible that only with the normal Δ^{14}-unsaturated etio acids does hydrogenation lead to a normal configuration at carbon atom 14 (rings C/D trans), whereas with the carboxyl group at C_{17} in the iso position, a compound with the hydrogen atom at C_{14} in the epi position (rings C/D cis) results. It is possible, therefore, that the assumption made in our previous publication (1) will have to be revised.

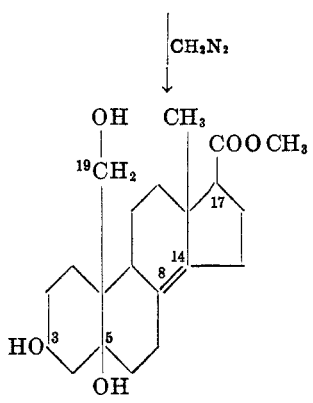
[9] *Cf.* in particular experimental part, C, exp. II. In this instance the over-all yield of this substance (XIII) from 3,5,14,19-tetrahydroxyetiocholanic acid (V) was at least 30%.

[10] The saponification was carried out with potassium hydroxide in methanol. The neutral reaction product was found to be a mixture of the ethyl and methyl esters, a sign that transesterification had taken place.

which in turn, by treatment with diazomethane, was converted into methyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XVI) with the melting point 270–274°.

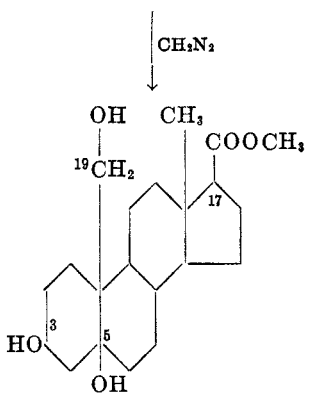
The acid dehydration products were identified by implication. The resinous acid material was subjected to catalytic hydrogenation. In each such instance

XII;



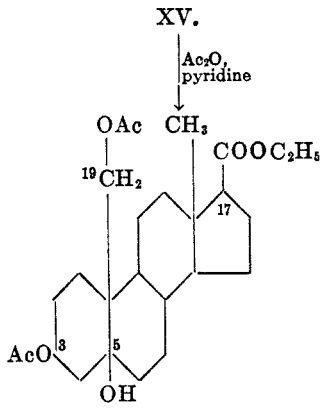
XVI. Methyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate

XIV.



XVII. Methyl 3,5,19-trihydroxy-etiocholanate

XV.



XVIII. Ethyl 3,19-diacetoxy-5-hydroxyetiocholanate

it was possible to isolate a certain amount of 3,5,19-trihydroxyetiocholanic acid (XIV) which can only have resulted from 3,5,19-trihydroxy-Δ^{14}-etiocholenic acid (XIII). The material contained in the mother liquor of compound XIV was transformed into the methyl ester with diazomethane. The resulting product was subjected to chromatographic adsorption which yielded a small amount of a substance which was apparently identical with XVI. Hence it is fairly certain that a small quantity of 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII) was present in the acid dehydration product. As was pointed out before it should be inert to catalytic hydrogenation.

As is known, certain steroids with a hydroxyl group at carbon atom 14 are dehydrated to Δ^{14}-unsaturated compounds by pyridine-phosphorus oxychloride at room temperature (7, 8) whereas others are inert under these experimental conditions (9). When ethyl 3,19-diacetoxy-5-hydroxyetiocholanate (XVIII) was treated according to this procedure at room temperature for a period of twenty hours, a fair amount of unchanged starting material could be recovered and there was no indication of the formation of unsaturated material (tested with tetranitromethane).[11] This indicates that under these experimental conditions the tertiary hydroxyl group at carbon atom 5 appears to be inert. The question arises therefore, whether methyl 3,19-diacetoxy-5,14-dihydroxy-etiocholanate (VII), when treated under these mild conditions, will yield to a selective dehydration with the formation of methyl 3,19-diacetoxy-5-hydroxy-Δ^{14}-etiocholenate. Treatment at a higher temperature may possibly involve the tertiary hydroxyl groups both at carbon atoms 5 and 14. Experiments along these lines will be undertaken. The compounds described in this publication will serve as intermediates for further chemical transformations.

EXPERIMENTAL

The melting points were determined with the Fisher-Johns melting point apparatus. The readings are sufficiently near the true melting points so that no corrections have been made. The microanalyses were carried out by Mr. William Saschek, Department of Biochemistry, Columbia University, New York.

A. *Preparation of strophanthidol 3,19-diacetate (III).* The procedures used were essentially those of Rabald and Kraus (5, 6).

Strophanthidin (I). Hydrolysis of k-strophanthin with 0.5% hydrochloric acid (10) furnished the crude strophanthidin which was recrystallized from aqueous methanol. The melting points of the recrystallized, frequently somewhat brownish, material were usually between 145 and 160°. On heating above the melting point, solidification occurred and eventually renewed melting at a temperature above 200°. The yields of strophanthidin, expressed as per cent fractions of the invested strophanthin (*i.e.* not theoretical yields) were as follows; from about 1170 g. of Strophanthin Penick U.S.P.XI: crude 26.6%, recrystallized 24.5%; from about 270 g. of Strophanthin Merck U.S.P.XII: crude 42.6%, recrystallized 30.2%. Two samples of strophanthin which had not been standardized according to pharmacopoeial requirements were kindly provided by S. B. Penick & Co. and furnished the following yields of strophanthidin; crude 40.8%, recrystallized 36.0% and crude 43.9%, recrystallized 36.6% respectively.

Strophanthidol (II). The reduction of strophanthidin (I) was carried out with active aluminum amalgam which was prepared as follows:[12] The surface of 10 g. of Aluminum Metal, Foil (thickness approx. 0.025 mm.) of the J. T. Baker Chemical Co. was thoroughly cleansed with petroleum ether and cut into pieces of about 2 x 2 cm. To the aluminum was added enough 2% sodium hydroxide to cover the whole metal (about 100 cc.). As soon as a lively evolution of hydrogen had set in, the alkali solution was decanted and the aluminum washed quickly and repeatedly with water. Thereupon 100 cc. of a solution of 0.5% mercuric chloride was allowed to act upon the aluminum for a period of two minutes. The metal was then washed quickly and repeatedly with water and eventually with 95% alcohol.

[11] Because of the negative result of this experiment it is not recorded in the experimental part.

[12] Cf. also Houben-Weyl, 3rd. edit. II, 256. Weygand, Organic Preparations, Interscience Publishers, p. 9.

To the still moist aluminum amalgam was added at once a solution of 10 g. of recryst. strophanthidin in 380 cc. of 95% alcohol. A lively reaction set in immediately and it was sometimes necessary to cool the reaction mixture for a moment. The mixture was allowed to stand at room temperature for a period of several days during which there was added a total of 30 cc. of water in installments of 5 cc. each. Usually after about four days the aluminum had almost completely disintegrated, save for a few shreds of metal. The grey sludge of aluminum hydroxide was filtered by suction and subsequently extracted by refluxing it three times for one hour each with 400 cc. of 95% alcohol. The combined colorless alcoholic solutions were concentrated to a smaller volume *in vacuo*, which caused the separation of white crystals. After the filtration of the latter and renewed concentration, etc., more crystalline crops could be secured. The crystalline material usually totalled about 9.0–9.2 g. From the final mother liquor there was obtained a dry residue weighing 0.5–0.6 g. The melting points of the various crystalline fractions were usually between 135 and 150°, occasionally slightly higher. The combined crystalline fractions were recrystalized by dissolving them in about 200 parts of ethyl acetate and concentrating to a smaller volume in a partial vacuum. Several crops of large colorless transparent prisms were obtained. The melting points of the major parts of the crystalline material were between 140 and 155°. Lower-melting crops of several experiments were pooled and the melting points raised by renewed crystallization from ethyl acetate. The total yield of such purified strophanthidol (II), obtained in 25 reduction experiments (starting material: 250 g. of recryst. strophanthidin) was 212 g. The Legal test, with alcohol as a solvent (11), was positive.

Anal. Calc'd for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43.

$C_{23}H_{34}O_6 + \frac{1}{2}CH_3COOC_2H_5$: C, 66.62; H, 8.50.

Found: C, 66.32; H, 8.55.

Strophanthidol 3,19-diacetate (III). To a solution of 5.145 g. of purified strophanthidol in 20.6 cc. of pyridine was added 10.3 cc. of acetic anhydride and the mixture allowed to stand at room temperature for 24 hours. After pouring it into 103 cc. of water and permitting the precipitate to stand overnight, the diacetate separated in white platelets. They were filtered, washed with water and dried; wt: 3.81 g. The filtrate was extracted with 250 cc. of ethyl acetate and the latter phase washed neutral by treating it twice with 60 cc. of *N* hydrochloric acid, once with 60 cc. of *N* sodium bicarbonate solution and twice with 60 cc. of water. After drying overnight with sodium sulfate and removal of the solvent, a dry residue of 1.77 g. was obtained.

The crystalline material (3.81) g.) was recrystallized by dissolving it in about 25 cc. of acetone and gradually adding to this solution petroleum ether over a period of several hours. Too rapid addition produces an oily separation. After standing overnight, the crystals were filtered and washed with an acetone-petroleum ether mixture (3:7). The filtrate was concentrated to a smaller volume on a water-bath and the addition of petroleum ether continued. First crop; wt. 2.432 g.; m.p. 186–183°. Second crop; wt. 1.094 g.; m.p. 187–188.5°. Third crop; wt. 0.237 g.; m.p. 162–166°.

Similar treatment of the residue from the ethyl acetate extraction (1.77 g.) furnished crystalline material; wt. 0.734 g.; m.p. 184–186°. It should be pointed out, that in several experiments of this type the residue from the ethyl acetate extract did not yield crystals when subjected to the same handling. Such resinous material can be partially transformed into pure crystalline diacetate by chromatographing its solution in benzene over a column of aluminum oxide. The adsorbed material is eluted by washing with benzene, benzene-ether, ether, various ratios of ether-acetone, acetone, and various ratios of acetone-methanol. The crystalline diacetate can be secured from the ether-acetone eluates by bringing them to dryness and recrystallizing the residues from acetone-petroleum ether.

Altogether 202.7 g. of purified strophanthidol were subjected to acetylation in small lots (30 experiments). A total of 178.2 g. of crystalline fractions was obtained, more than 90% of which consisted of strophanthidol diacetate (III) with melting points above 185°. Since only a small sample of resinous acetylation product has been subjected to chromatographic separation, similar treatment of the remainder of such material should increase the above yield substantially.

The optical rotations and microanalyses are recorded for two crystalline samples melting at 185–188° and 191–192° respectively. $[\alpha]_D^{26.5}$ +49.4° (30.0 mg. in 2.0 cc. of chloroform), $[\alpha]_D^{26.5}$ +54.7° (30.0 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{27}H_{38}O_8$: C, 66.08; H, 7.81.
Found: C, 66.11, 66.02; H, 7.95, 7.80.

B. *Preparation of 3,5,14,19-tetrahydroxyetiocholanic acid (V) and derivatives. Crude 3,19-diacetoxy-5,14-dihydroxyetiocholanic acid (IV).* Strophanthidol diacetate (III) was oxidized in a solution of acetone with three moles of potassium permanganate. To 5.0 g. of III dissolved in 294 cc. of purest dry acetone was added 4.84 g. of finely ground potassium permanganate. The mixture was shaken in a bottle with glass stopper for about two hours, after which the permanganate color had completely disappeared. The reaction mixtures originating from three oxidations of a total of 16.1 g. of III were transferred into a distilling flask and the acetone removed from the brown suspension by distilling first in a partial and eventually in a full vacuum. To the residue was added about 50 cc. of water to produce a sludge which was transferred into a separatory funnel. It was then acidified to Congo paper by slowly adding about 100 cc. of approx. 10% sulfuric acid. The brown suspension was extracted once with 200 cc. of ether and seven times with 150 cc. of ether. The ether extracts were eventually combined (combined ether extracts). Thereafter the brown suspension was extracted twice with 150 cc. of ethyl acetate and six times with 100 cc. of ethyl acetate. The ethyl acetate extracts were eventually combined (combined ethyl acetate extracts).

The combined ether and ethyl acetate extracts were each separated into acid and neutral material as follows:

A. Combined ether extracts. They were extracted with 50 cc. and 25 cc. of a 5% solution of sodium carbonate and then washed three times with 10 cc. of water. The ether phase (neutral ether) was dried with sodium sulfate overnight, filtered, and eventually brought completely to dryness *in vacuo*. The residue was a brittle foam; weight after drying in a vacuum desiccator, 5.976 g. The above mentioned carbonate phases and aqueous washings were combined. This solution was made acid to Congo paper by slowly adding to it in a separatory funnel about 40 cc. of 10% sulfuric acid, which caused a sticky precipitate to appear. The suspension was thoroughly extracted with 200 cc., 150 cc., and five times with 100 cc. of ether.[12a] These ether extracts were combined, washed eight times with 8 cc. of water and finally dried overnight with sodium sulfate. The ether phase (acid ether) was then filtered, concentrated, and eventually brought completely to dryness in a vacuum. The residue was a brittle foam; weight after drying in a vacuum desiccator over KOH, 7.1872 g.

B. Combined ethyl acetate extracts. They were extracted with 30 cc. and 15 cc. of a solution of 5% sodium carbonate and subsequently washed three times with 10 cc. of water. The ethyl acetate phase (neutral ethyl acetate) was dried with sodium sulfate, filtered and eventually brought completely to dryness *in vacuo*. The residue was a brittle foam; weight after drying in a vacuum desiccator over KOH, 0.558 g. The above mentioned carbonate phases and aqueous washings were combined. The resulting solution was acidified to Congo paper by slowing adding to it in a separatory funnel about 35 cc. of 10% sulfuric acid. The acidified material was very thoroughly extracted five times with 100 cc. of ethyl acetate. The combined ethyl acetate extracts were washed twice with 8 cc. of water and six times with 5 cc. of water and eventually dried with sodium sulfate. The ethyl acetate phase (acid ethyl acetate) was filtered, concentrated, and finally brought to dryness *in vacuo;* weight after drying over KOH in a vacuum desiccator, 0.227 g. The acid material as obtained from the ether extract or the ethyl acetate extract resisted all attempts at crystallization.

The pooled neutral material as recovered from the oxidation likewise resisted all attempts at crystallization. A sample of 100 mg. was subjected to chromatographic adsorp-

[12a] In some experiments a subsequent extraction was carried out with 75–100 cc. of ethyl acetate. The residues obtained from these extracts weighed slightly over 1% of the material invested in the oxidations.

tion. For this purpose it was dissolved in a mixture of 10 cc. of benzene and 1.5 cc. of petroleum ether which was filtered through a column of 4.0 g. of aluminum oxide (Brockmann). The column was washed successively with 15-cc. portions of benzene, benzene, benzene-ether (1:1), ether, ether-acetone (1:1), acetone, acetone, methanol. The residues obtained from the ether-acetone and the first acetone eluate represented the main fractions weighing 36.0 mg. and 8.5 mg. respectively. They were combined (44.5 mg.) and dissolved in acetone to which petroleum ether was added gradually. On seeding with strophanthidol diacetate (III), crystallization began at once. The crystalline material had the melting point of 185–188° and there was no depression of the melting point when admixed to an authentic sample of III.

The pooled crude neutral material, as recovered from various experiments, was subjected to reoxidations with varying ratios of potassium permanganate. When treated with the same ratio (ratio 1) of the oxidant as the original III, the color of the permanganate disappeared only very slowly, and hence shaking had to be extended overnight. When the amount of the permanganate was cut down to two-thirds or one-half of the ratio of the original oxidation, the color disappeared within 4 to 5 hours or 2½ hours respectively. From the following tabulation (Tables A and B) of yields it can be concluded that in the reoxidation experiments optimal yields of acid material are obtained when the amount of permanganate s cut down to about two-thirds of the ratio of the oxidation of III.

Tabulation of yields

(Figures in parentheses are the numbers of oxidations into which each experiment was divided. The ratio of $KMnO_4$ used in the original experiment is taken as 1. The yields are expressed as per cent of the invested starting material. In all experiments at least $\frac{9}{10}$ of the acid material was obtained from the ether fraction.)

A. Oxidation of Strophanthidol Diacetate (III)

Experiment no.	I	II	III	IV
Invested g	16.1 (3)	15.59 (3)	15.56 (3)	15.83 (3)
Ratio of $KMnO_4$	1	1	1	1
Total acid %	46.0	48	52	48.6
Total neutral %	40.6	35	36	41.6
Total recovered %	86.6	83	88	90.2

B. Reoxidation of Neutral Material

(recovered from oxidation of strophanthidol diacetate)

Experiment no.	I	II	III
Invested g	0.94 (1)	12.04 (2)	12.20 (2)
Ratio of $KMnO_4$	1	⅔	½
Total acid %	21.7	35	29
Total neutral %	31.5	49	56
Total recovered %	53.2	84	85

3,5,14,19-Tetrahydroxyetiocholanic acid (V). To a solution of 3.0 g. of the above acid (from ether extract) in 15 cc. of methanol was added a solution of 4.5 g. of potassium hydroxide in 60 cc. of methanol and the mixture then refluxed on a water-bath for a period of thirty minutes. After the addition of 150 cc. of water the solution was immediately concentrated *in vacuo* (45–50°) to a volume of about 65 cc. The solution was cooled with ice and made acid to Congo paper by slowly adding 7.5 cc. of conc'd hydrochloric acid which caused a precipitate to appear. The reaction mixture was thoroughly extracted eight times, each

time with 100 cc. of ethyl acetate. It was found that more numerous extractions will increase the yield of the saponification product too slightly to be practical. The combined ethyl acetate extracts were washed eight times with 5–6 cc. of water and then dried with sodium sulfate. After filtering, the solution was concentrated to a small volume (about 40–45 cc.) *in vacuo* (40–50°). In this concentration the deacetylated acid apparently forms a supersaturated solution. The reaction product separated in a microcrystalline form by heating the solution briefly on a water-bath and scratching the walls of the container. After standing at room temperature overnight, the almost white microcrystalline material was filtered and thoroughly washed with ethyl acetate; yield 1.42 g.; m.p. 208–210° (subseq. effervescence). On concentrating, the filtrate occasionally furnished small amounts of further crystalline material. In the present instance the filtrate was brought to dryness *in vacuo* (40–50°) and furnished a brittle foam which weighed 0.89 g. after drying over KOH in a vacuum desiccator. This amorphous material still contains some of V, because on esterifying it with diazomethane and subjecting the reaction product to chromatographic adsorption, an appreciable amount of the crystalline methyl ester of the acid (VI) can be obtained. The preparation of the methyl ester from the crystalline as well as amorphous acid will be described below. The yields of the crystalline acid were approximately the same in thirteen different saponification experiments; a total of 35.52 g. of acid ether extract furnished 16.36 g. of crystalline V. It made no difference whether the starting material (acid ether extract) had originated from an oxidation of strophanthidol diacetate (III) or from a reoxidation of "neutral material". The melting points were sometimes slightly lower than recorded above. It should be pointed out that several attempts to saponify acid ethyl acetate extracts furnished only resinous products. Although it was not tried, it is considered possible that some crystalline methyl ester of the 3,5,14,19-tetrahydroxyetiocholanic acid (VI) could be obtained from such saponified material by treatment with diazomethane and subsequent chromatographic purification.

For analysis the crystalline acid as obtained from ethyl acetate was recrystallized by dissolving it (reflux) in the required amount of acetone and concentrating to a smaller volume on a water-bath. On subsequent standing at room temperature the separation of glistening platelets began rather early. They were filtered after standing overnight. The melting point of the recrystallized V was 217–218.5° (subseq. effervescence). $[\alpha]_D^{23.5}$ +38.9° (15.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{20}H_{32}O_6$: C, 65.17; H, 8.76.
Found: C, 65.31, 65.04; H, 8.50, 8.47.

Methyl 3,5,14,19-tetrahydroxyetiocholanate (VI). a. From cryst. 3,5,14,19-tetrahydroxyetiocholanic acid (V). About 0.12 g. of pure acid (V) which had been recrystallized from acetone was dissolved (reflux) in the required amount of acetone (14 cc.) and the solution concentrated to about two-thirds of this volume on a water-bath. To this solution was added at 0° an amount of an ethereal solution of diazomethane sufficient to produce a persistent yellow color. After brief standing at room temperature the excess of diazomethane was evaporated on a water-bath and the solution then brought to dryness *in vacuo* (40–45°) The residue was a brittle foam which was transferred into a separatory funnel by means of a total of 40 cc. of ether. The ether solution was washed successively with 3 cc. of *N* hydrochloric acid, 3 cc. of water, 3 cc. of a solution of 5% sodium carbonate, and three times with 3 cc. of water. After drying with sodium sulfate, the solution was filtered and brought to dryness, eventually *in vacuo*. The residue was a colorless resin which became almost completely crystalline after a few days standing in a vacuum desiccator; yield 0.091 g. This material was recrystallized by dissolving it in acetone and slowly adding at room temperature some petroleum ether. The separation of spear-shaped crystals began very soon. The crystalline material was filtered on the following day; yield 0.053 g.; m.p. 168–169°. More crystalline ester could be secured from the mother liquor. $[\alpha]_D^{23.5}$ +59.6° (20.0 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{21}H_{34}O_6$: C, 65.92; H, 8.96.
Found: C, 65.87; H, 8.86.

b. From amorphous acid (v. supra). To a solution of 2.46 g. of amorphous acid (non-crystalline fraction, obtained by saponifying "acid ether extract") in 20.0 cc. of acetone was added at 0° an excess of an ethereal solution of diazomethane. The reaction mixture was kept in ice for about 3 minutes and then at room temperature for 15 more minutes. Thereafter the excess of the diazomethane was removed on a water-bath and the solution brought to dryness *in vacuo* (40–50°). The residue was a foamy mass which proved to be very sparingly soluble in ether. It was dissolved in 15 cc. of acetone and this solution poured in a separatory funnel into 750 cc. of ether. The resulting solution was washed successively twice with 15 cc. of *N* hydrochloric acid, once with 10 cc. of water, once with 15 cc. of a solution of 5% sodium carbonate, and four times with 8 cc. of water. After drying with sodium sulfate and filtering, the solution was brought completely to dryness, first on a water-bath, eventually *in vacuo*. The residue was a brittle foam; wt: 1.857 g. This residue was subjected to chromatographic adsorption for which purpose it was dissolved in a mixture of 180 cc. of benzene and 20 cc. of petroleum ether. The solution was filtered through a column (diam. 1.8 cm.) of 55 g. of aluminum oxide (standardized acc. to Brockmann, Merck & Co., Rahway). The original solution was passed through within six hours, the following eluate within five hours and all other eluates within about thirty minutes each.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE G.	APPEARANCE OF RESIDUE
1	180 cc. benzene + 20 cc. petr. ether (original solution)	0.0092	Colorless grease
2	200 cc. benzene	.0673	Colorless resin
3	150 cc. benzene + 50 cc. ether	.1339	Colorless, partly foamy resin
4	50 cc. benzene + 150 cc. ether	.1426	Colorless, partly foamy resin
5	200 cc. ether	.0141	Slightly yellowish grease
6	150 cc. ether + 50 cc. acetone	.0132	Yellow resin
7	50 cc. ether + 150 cc. acetone	.0244	Slightly yellow resin
8	200 cc. acetone	.0823	Yellow resin
9	199.5 cc. acetone + 0.5 cc. methanol	.1715	Slightly yellow resin
10	198 cc. acetone + 2 cc. methanol	.2712	Colorless resin, partly cryst
11	195 cc. acetone + 5 cc. methanol	.3184	Colorless brittle foam
12	180 cc. acetone + 20 cc. methanol	.3302	Colorless brittle foam
13	150 cc. acetone + 50 cc. methanol	.1174	Colorless brittle foam
14	200 cc. methanol	.1512	Slightly yellowish mass
Total		1.8469	

The residues of fractions 8 to 12 were selected for examination. They were separately dissolved in small amounts of acetone and petroleum ether was added gradually to these solutions. Fraction 8 yielded only oily material. Fraction 9 yielded two crystalline fractions: 9a. 0.0417 g., m.p. 169–171°; 9b. 0.0016 g., m.p. 166–169°. Fraction 10 also yielded two crystalline fractions: 10a. 0.1240 g., m.p. 168–170°; 10b. 0.0154 g., m.p. 169–171°. Fraction 11 likewise yielded two crystalline fractions: 11a. 0.1535 g., m.p. 163–165°; 11b. 0.0123 g., m.p. 167–170°. All these crystalline fractions (total: 0.3485 g.) did not give a depression of the melting point when mixed with the analytical sample of the methyl ester (*v. supra*). From fraction 12 only traces of crystals were obtained; the major part of the material came out oily. It is believed that the yield of crystalline ester can be increased by combining the non-crystalline parts of fractions 9–11 and all of fraction 12 and subjecting this material to a renewed chromatographic separation.

3,19-Diacetoxy-5,14-dihydroxyetiocholanic acid (IV). To a solution of 50 mg. of pure crystalline 3,5,14,19-tetrahydroxyetiocholanic acid (V) in 0.4 cc. of pyridine was added 0.2 cc. of acetic anhydride and the mixture allowed to stand at room temperature overnight. It was then brought to dryness *in vacuo* (50°), the viscous residue taken up in 15 cc. of ether and this solution shaken with 4 cc. of *N* hydrochloric acid and a few times with 2 cc. of water. After extracting the ether solution twice with a few cc. of a cold solution of 5% sodium carbonate, the combined carbonate phases were immediately made acid to Congo paper by adding cold *N* hydrochloric acid. After thoroughly extracting with ether, washing the combined ether phases a few times with water, and drying with sodium sulfate, the ether solution was brought to dryness, leaving 32.7 mg. of a colorless resin. All attempts at crystallization failed.

Methyl 3,19-diacetoxy-5,14-dihydroxyetiocholanate (VII). The above resinous IV was treated in an ethereal solution with diazomethane and the reaction product was isolated in the usual way. The yield was 27 mg. of a colorless resin. This material was dissolved in a mixture of benzene and petroleum ether and chromatographed over 1.0 g. of alumina. The adsorbate was successively eluted with 5-cc. portions of benzene-petroleum ether (benzene content gradually increasing), benzene, benzene-ether (ether content gradually increasing), ether, ether-acetone (1:1), acetone, acetone-methanol (methanol content gradually increasing), and methanol. All residues obtained from these eluates were resinous. The main fraction (10 mg.) was secured from the ether-acetone phase. It resisted all attempts at crystallization.

C. *Dehydration of 3,5,14,19-tetrahydroxyetiocholanic acid (V) and subsequent hydrogenation of the unsaturated reaction product; preparation of 3,5,19-trihydroxyetiocholanic acid (XIV) and 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII) and their derivatives.* The dehydration was carried out by the action of a 0.1 *N* solution of hydrogen chloride in absolute alcohol. This process transforms at the same time about 85–90% of the acid material into the ethyl ester. Separation into acid and neutral fractions was carried out either before or after the hydrogenation. For the sake of clarity the experiments will be described with the aid of flow sheets.

Experiment I (Flow Sheet I). A total of 2.5088 g. of crystalline V was dissolved in 240 cc. of 0.1 *N* hydrogen chloride in absolute alcohol. This solution was kept at room temperature for a period of 35 minutes, after which a slow distillation was begun at atmospheric pressure and under anhydrous conditions. The bath temperature was kept between 103 and 105° throughout the whole distillation which was carried out over a period of 95 minutes. The residue was 75–80 cc. of a light golden solution, to which was added 50 cc. of water and the distillation then continued *in vacuo* (45–47°) until a distinct turbidity appeared. The latter was brought into solution by briefly heating on a water-bath and the solution was then allowed to stand at room temperature overnight which caused the separation of some oily material and also macrocrystalline needles. The crystals were partly imbedded in the oil and hence frequent leaching with aqueous alcohol (1:1) was necessary to obtain them in a colorless form; dry weight: 42.7 mg.; m.p. about 97–99.5°. This substance, which is possibly the lactone X, proved to be essentially insoluble in a solution of sodium carbonate. A solution in chloroform gave with tetranitromethane a distinct yellow color, indicating its unsaturated character. Its recrystallization proved to be difficult.[13] All decantates and filtrates were combined and the alcohol completely removed *in vacuo*. This produced a light yellow precipitate which was taken up with 175 cc. of ether. The aqueous phase was thereafter extracted four times with 75-cc. portions of ether. The combined ether extracts were washed six times, each with 5 cc. of water. After the drying of the solution with sodium sulfate and filtering, the ether was removed, eventually *in vacuo*. The residue was a brittle foam; weight after drying, 2.3531 g. For further experiments this material was divided into two parts.

1. *Experiments with first part of the crude dehydration product.* A solution of 1.2273 g. of the crude product in 140 cc. of ether was separated into neutral and acid material as follows.

[13] For microanalysis *cf.* second dehydration experiment.

It was extracted successively with 10 cc. and 5 cc. of 5% sodium carbonate and then five times with 2-cc. portions of water. The ether solution was dried with sodium sulfate, filtered and brought completely to dryness. The neutral residue was a colorless brittle foam; dry weight: 1.0177 g. The above mentioned carbonate phases and aqueous washings were combined and made acid to Congo by the addition (ice-cooling) of 2.5 cc. of conc'd hydrochloric acid, which produced a cheesy precipitate. It was extracted successively with 100 cc., 50 cc., and three times with 40-cc. portions of ether. The combined ether extracts were washed six times each with 3 cc. of water and then dried with sodium sulfate. After filtering, the solution was brought completely to dryness. The acid residue was a slightly yellowish brittle foam; dry weight 0.1865 g. It was kept for further experiments.

Treatment of the neutral residue (1.0177 g.) with about 5 cc. of ether yielded a clear yellowish solution to which some petroleum ether was added very slowly over the period of a whole day. Very gradually some hard white crystalline material deposited on the walls, which increased on standing overnight. The crystals were filtered the following day and washed with ether containing petroleum ether; dry weight 0.0724 g.; m.p. about 164–169.5°. These crystals were identified as ethyl 3,5,14,19-tetrahydroxyetiocholanate (VIII) (*v. infra*). To the mother liquor was added more petroleum ether over a period of several hours which resulted in the separation of only resinous material. This precipitate was not isolated but brought to dryness together with the supernatant solution. The residue (wt. 0.9473 g.) was a brittle foam, consisting probably mainly of ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX); $[\alpha]_D^{23.5}$ +46.4° (20.0 mg. in 2.0 cc. of chloroform). In a solution of chloroform the substance gave a yellow color with tetranitromethane. The analytical figures indicate the presence of a certain amount of VIII.

Anal. Calc'd for $C_{22}H_{34}O_5$: C, 69.79; H, 9.06.
Found: C, 68.97; H, 9.01.

Ethyl 3,5,14,19-tetrahydroxyetiocholanate (VIII). The crystalline material mentioned above (wt. 72.4 mg.; m.p. 164–169.5°) was dissolved in acetone. The solution was concentrated to a small volume on a water-bath and then some petroleum ether added at room temperature. The separation of sheaves of spear-shaped crystals began at once. The substance was filtered the following day; wt. 44.2 mg.; m.p. 186–188.5°; $[\alpha]_D^{23.5}$ +45.7° (20.0 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{22}H_{36}O_6$: C, 66.62; H, 9.16.
Found: C, 66.22; H, 8.98.

When the filtrate was concentrated and petroleum ether was added, a second crop of crystalline material was obtained; wt. 6.2 mg.; m.p. 184.5–187.5°. It should be mentioned that the two samples gave melting points about ten degrees lower after having been kept in as desiccator for a period of several weeks.

Hydrogenation. A suspension of 350 mg. of platinum oxide in 4.5 cc. of glacial acetic acid was reduced and after the addition of a solution of 0.8505 g. of the previously mentioned amorphous unsaturated ethyl ester in 10 cc. of glacial acetic acid, shaking was continued at room temperature (23°) for a period of 3½ hours. The total hydrogen absorption was 55.2 cc.; of this amount about 50 cc. was absorbed during the first hour. Calc'd for ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX), 54.5 cc. (23°). The solution was filtered from the catalyst and quickly brought to dryness *in vacuo* (45–50°). To the syrupy residue 5 cc. of water was added at once. After standing overnight the material was extracted twice with 60-cc. portions of ethyl acetate. The combined extracts were washed neutral by treating them three times with 3-cc. portions of a solution of 5% sodium carbonate and six times with 2.5 cc. of water each. After drying with sodium sulfate and filtering, the solution was brought to dryness. The residue was 0.8278 g. of a resin, a part of which was purified by chromatographic adsorption. For this purpose 0.6937 g. of the residue was dissolved in 70 cc. of ether. The solution was filtered through a column (diam. 20 mm.) of 19 g. of aluminum oxide. The original solution was passed through within one hour and the following eluates within 25 minutes each.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE G.	APPEARANCE OF RESIDUE
1	70 cc. ether (original solution)	0.0201	Resinous
2	40 cc. ether + 30 cc. acetone	.0912	Slightly yellow, partly cryst.
3	20 cc. ether + 50 cc. acetone	.0103	Yellow, crystalline
4	70 cc. acetone	.0402	Microcrystalline
5	70 cc. acetone + 0.2 cc. methanol	.0451	Partly cryst. resin
6	70 cc. acetone + 0.3 cc. methanol	.0689	Crystalline
7	70 cc. acetone + 0.5 cc. methanol	.0733	Crystalline
8	69 cc. acetone + 1 cc. methanol	.0775	Crystalline
9	68 cc. acetone + 2 cc. methanol	.0895	Partly cryst. resin
10	65 cc. acetone + 5 cc. methanol	.0958	Resinous
11	50 cc. acetone + 20 cc. methanol	.0407	Brittle foam
12	70 cc. methanol	.0235	Amorphous
Total		.6761	

The residues of the eluates were separately dissolved in acetone to which, in some instances, petroleum ether was added to induce crystallization.

Fractions 2 to 4. No uniform crystalline substance could be secured from fraction 3. Fractions 2 and 4 furnished a total of 9.2 mg. (2.9 mg. and 6.3 mg. respectively) of needle-shaped crystals melting at 189–194°. Fraction 2 furnished an additional crop of 6.9 mg. of somewhat less pure material, melting at 184–188°. These substances (total 16.1 mg.) were identified as ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI). They gave no depressions of the melting points when mixed with authentic samples of this substance (*v. infra.*).

Fraction 5. The crystalline material (total 10.2 mg.) obviously represented a mixture.

Fractions 6 to 10. Four fractions of needle-shaped crystals, totalling 0.1255 g., had melting points between 178 and 182°. Two fractions (total 0.0457 g.) of almost the same purity had melting points between 175 and 178°. By mixed melting points all these fractions were identified as ethyl 3,5,19-trihydroxyetiocholanate (XV) (*v. infra.*). The total yield of this substance was therefore 0.1712 g. The yield can perhaps be somewhat increased by subjecting the material contained in the mother liquors of these fractions to a renewed chromatographic separation.

Fraction 11. No crystalline material could be obtained.

2. *Experiments with second part of the crude dehydration product.* Chronologically these experiments preceded those carried out with the first part of the crude dehydration product. In retrospect the following procedure appears less convenient than the one described above. It is recorded because it yielded a number of chemically pure compounds which served as reference samples. The product was subjected to a catalytic hydrogenation without subjecting it first to a separation into acid and neutral material.

A suspension of 455 mg. of platinum oxide in 7 cc. of glacial acetic acid was reduced and after the addition of a solution of 1.1258 g. of the crude dehydration product in 12 cc. of glacial acetic acid, shaking was continued at room temperature (23°) for a period of 3½ hours, when the hydrogenation came to a standstill. The total hydrogen absorption was 65.8 cc. of which 62.5 cc. were absorbed during the first 1½ hours. Calc'd for ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX), 72.3 cc. (23°). As may be concluded from the preceding experiment, the deficiency of the hydrogen absorption is probably mainly attributable to the presence of a fair amount of VIII. The solution was filtered from the platinum and concentrated *in vacuo* (about 52°) to a slightly turbid colorless syrup to which 5 cc. of water was added immediately. The following day the sticky material was taken up in 100 cc. of ethyl acetate and this solution washed with 6 cc. and with two 2-cc. portions of water. There-

after it was separated into neutral and acid material by extracting it successively with 10 cc. and 5 cc. of 5% sodium carbonate and then five times with 2-cc. portions of water. The ethyl acetate solution was dried with sodium sulfate, filtered, and brought to dryness, eventually *in vacuo*. The neutral residue was a white, largely crystalline cake; weight 0.962 g. The above-mentioned carbonate phases and aqueous washings were combined and made acid to Congo by adding 2.5 cc. of conc'd hydrochloric acid (ice-cooling), which caused a cheesy precipitate. It was thoroughly extracted with 75 cc., 50 cc., and three times with 40-cc. portions of ethyl acetate. The combined ethyl acetate extracts were washed six times each with 2 cc. of water and finally dried with sodium sulfate. After filtering, the solution was brought to dryness. The acid residue was a colorless resin; weight 0.1831 g.

By treating the neutral residue (0.962 g.) with ether, altogether 0.603 g. of crystals and 0.318 g. of resinous material (brittle foam) was obtained. The crystalline fraction was subjected to numerous crystallizations from which, however, no uniform substances could be obtained; altogether 0.512 g. of non-uniform crystalline material and 0.082 g. of an amorphous product (brittle foam) resulted. The crystalline material (0.512 g.) was subjected to an elaborate purification by chromatographic adsorption. It was dissolved in 60 cc. of benzene and this solution passed through a column (diam. 19 mm.) of 15 g. of aluminum oxide within a period of three hours. The following four eluates were passed through within an hour each and the rest within about 35 minutes each.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE G.	APPEARANCE OF RESIDUE
1	60 cc.benzene (original solution)	0.0006	Greasy
2	45 cc. benzene + 15 cc. ether	.0020	Resinous
3	15 cc. benzene + 45 cc. ether	.0073	Partly cryst. resin
4	60 cc. ether	.0161	Pt. cryst. yellowish resin
5	40 cc. ether + 20 cc. acetone	.0127	Yellowish crystals
6	20 cc. ether + 40 cc. acetone	.0067	Resinous
7	60 cc. acetone	.0102	Crystalline
8	60 cc. acetone + 0.15 cc. methanol	.0275	Crystalline
9	60 cc. acetone + 0.20 cc. methanol	.0444	Crystalline
10	60 cc. acetone + 0.30 cc. methanol	.0414	Large crystals
11	60 cc. acetone + 0.50 cc. methanol	.0464	Large crystals
12	58 cc. acetone + 2 cc. methanol	.1134	Crystalline
13	55 cc. acetone + 5 cc. methanol	.0944	Brittle foam
14	45 cc. acetone + 15 cc. methanol	.0409	Resinous
15	60 cc. methanol	.0235	Essentially crystalline
Total		.4878	

The residues of the above chromatographic fractionation were subjected to a thorough examination:

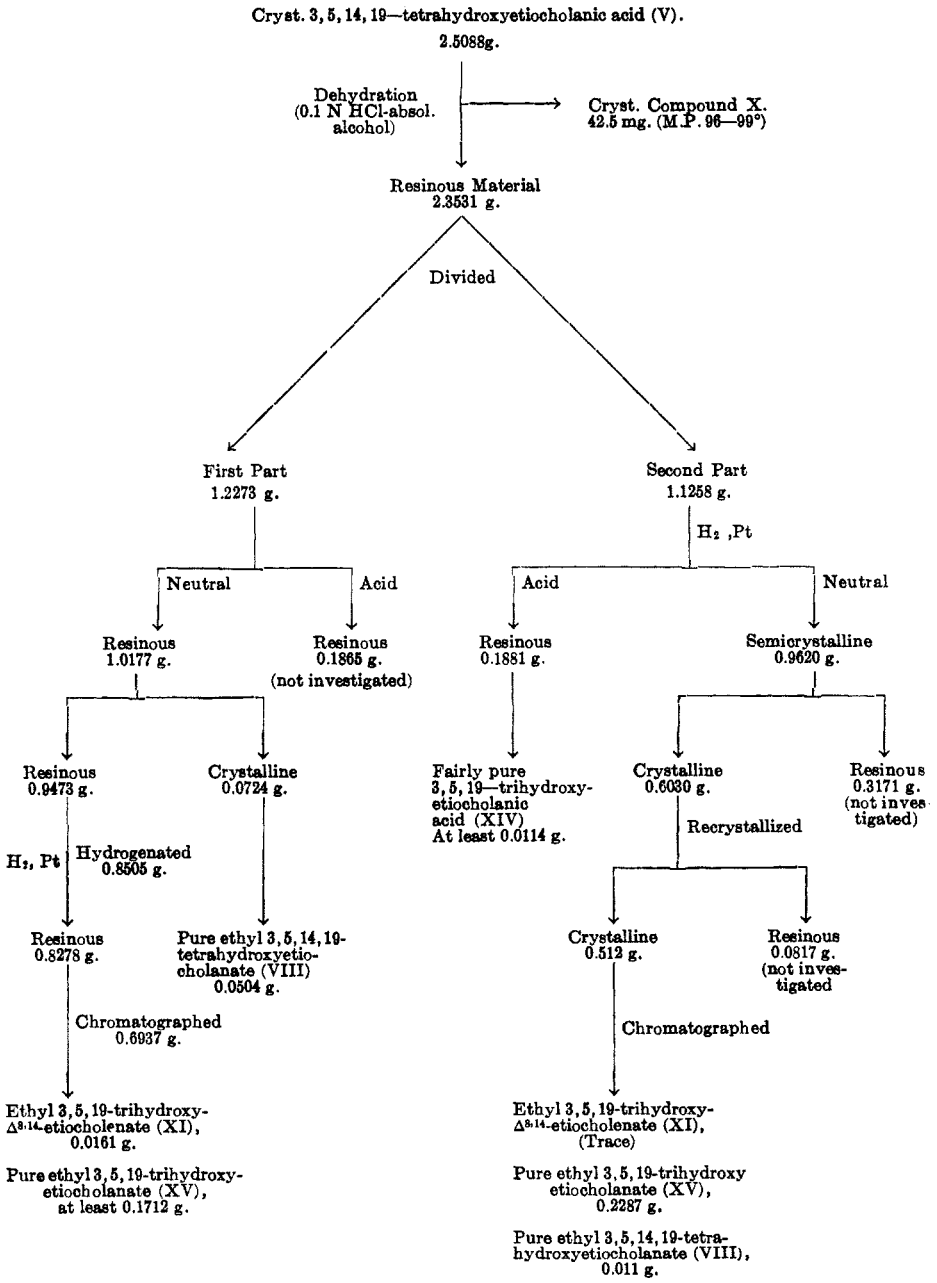
Fractions 4 and 5. These residues were combined and dissolved in a very small volume of acetone to which a little petroleum ether was added. After standing for a few days some stout, slightly yellowish prismatic crystals had separated; wt. 3.9 mg.; m.p. 174–176°. This substance was obviously identical with ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI) to be described in a subsequent experiment.

Anal. Calc'd for $C_{22}H_{34}O_5$: C, 69.79; H, 9.06.
Found: C, 69.72; H, 9.06.

Ethyl 3,5,19-trihydroxyetiocholanate (XV). Fractions 8 to 11. The residues were separately dissolved in acetone and concentrated to a small volume on a water-bath. Long,

flat, rather stout prismatic crystals separated on standing at room temperature, sometimes after the addition of a little petroleum ether. After filtering, additional crystalline separa-

FLOW SHEET (EXPERIMENT I)



tions were obtained by analogous treatment of the concentrated mother liquors. Nine crystalline fractions, totalling 0.1228 g., represented identical material, with melting points

above 185°. The carbon-hydrogen determinations were carried out with the first crops obtained from fractions 10 (25 mg.; m.p. 188–190°) and 11 (27 mg.; m.p. 188.5–190°) respectively. The optical rotation refers to the first crop derived from fraction 11. $[\alpha]^{24.5}_{D}$ +62.9° (20.0 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{22}H_{36}O_5$: C, 69.42; H, 9.54.
Found: C, 69.43, 69.26; H, 9.57, 9.82.

Fractions 12 and 13. When the residues were separately recrystallized from acetone (the addition of petroleum ether produced mixtures) one crop of crystalline material was secured in each instance; weights 0.0516 g. and 0.0170 g. respectively; m.p. 184–187° and 184–189.5° respectively. These substances were identical with ethyl 3,5,19-trihydroxyetiocholanate (XV).

Material obtained from the mother liquors of fractions 8–11 (0.0369 g.) and fractions 12–13 (0.1395 g.) was combined and subjected to a renewed chromatographic separation. Such treatment yielded a number of crystalline fractions totalling 0.0373 g., with melting points above 185°. This material was likewise identical with XV. The total yields of pure samples of this substance, as derived from the original chromatogram, was therefore 0.2287 g.

Fraction 14. When the residue was recrystallized from a small volume of acetone to which an equal amount of petroleum ether was added, about 11 milligrams separated as crystalline scales; m.p. 186–189°. There was no depression of the melting point when mixed with an authentic sample of ethyl 3,5,14,19-tetrahydroxyetiocholanate (XVIII). The analysis was further proof for the identity.

Anal. Calc'd for $C_{22}H_{36}O_6$: C, 66.62; H, 9.16.
Found: C, 66.39; H, 9.24.

The acid part of the hydrogenation product (0.1881 g.) was dissolved in a little acetone. Crystalline material separated on standing overnight; wt. 11.4 mg.; m.p. 240–247° (melting to light brown liquid, subseq. effervescence); no depression of melting point when mixed with authentic sample (*v. infra.*) of 3,5,19-trihydroxyetiocholanic acid (XIV). A second crystalline crop separated from the mother liquor: wt. 26.0 mg.; m.p. between 210 and 230° (melting to yellow liquid; subseq. effervescence).

Experiment II (Flow Sheet II). Since the first dehydration experiment had yielded a certain amount of VIII, indicating that the reaction had not gone to completion, it was decided to perform the dehydration under slightly more vigorous conditions. A total of 1.2716 g. of recrystallized V was dissolved in 130 cc. of 0.1 *N* hydrogen chloride in absolute alcohol. It was kept at 87° (reflux) for one hour. It was then distilled at atmospheric pressure at a slow rate (bath temp. 92–95°) for a period of ninety minutes and finally at a more rapid rate (bath temp. gradually raised to 100°) for a period of 45 minutes. To the residue, representing approximately 40 cc. of a yellowish solution, was added 30 cc. of water and the distillation was then continued *in vacuo* (45–50°) until a distinct turbidity appeared. The turbidity was brought into solution by briefly heating on a water-bath and the solution then allowed to stand at room temperature overnight which caused the separation of some resinous material and also of yellowish needles.

Compound $C_{20}H_{28}O_4$ (Lactone X ?). The crystals were separated from the resin by frequent leaching with aqueous alcohol (1:1); pale yellow needles; dry weight 45.8 mg.; m.p. 91–93°. A solution of this substance in chloroform gave with tetranitromethane a distinct yellow color.

Anal. Calc'd for $C_{20}H_{28}O_4$: C, 72.24; H, 8.49.
Found: C, 72.68, 72.60; H, 8.37, 8.35.

From the mother liquor the alcohol was completely removed *in vacuo*. This produced an oily precipitate which was taken up with 100 cc. of ether. The aqueous phase was thereafter extracted five times with 50-cc. portions of ether. The combined ether extracts were washed five times with 3-cc. portions of water, extracted successively with 10 cc. and 5 cc. of 5% sodium carbonate and finally washed seven times with 3 cc. of water. The ether solution was dried with sodium sulfate, filtered, and brought to dryness. The neutral residue was a colorless brittle foam; weight 1.085 g. To a solution of this neutral material in 4 cc. of

ether, petroleum ether was added very gradually (*cf.* Expt. I.1). Only a resinous precipitate was obtained, indicating that probably no appreciable amount of VIII was present. This precipitate was brought to dryness together with the supernatant solution. The above carbonate phases and final aqueous washings were combined and acidified to Congo by adding 2.5 cc. of conc'd hydrochloric acid. The acid material was isolated by extracting once with 100 cc. and five times with 40-cc. portions of ether. The combined ether extracts were washed five times with 3 cc. of water and then dried with sodium sulfate. After filtering and bringing to dryness, the acid residue was obtained as a slightly yellow resin; weight 0.1186 g. The neutral and acid residues were separately subjected to catalytic hydrogenation.

Hydrogenation of neutral residue. A suspension of 450 mg. of platinum oxide in 7 cc. of glacial acetic acid was reduced and after the addition of a solution of 1.080 g. of the neutral residue in 12 cc. of glacial acetic acid, shaking was continued at room temperature (26°) for a period of about 3½ hours. The total hydrogen absorption was 68.7 cc.; calc'd for ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX), 69.8 cc. The solution was filtered from the catalyst and immediately brought to dryness *in vacuo* (45–50°). To the syrupy residue 5 cc. of water was added at once. The following day the wax-like, semi-crystalline material was taken up in 100 cc. of ethyl acetate. The latter solution was separated from the water and washed neutral by treating it successively with 5 cc. and 2 cc. of 5% sodium carbonate and finally five times with 2-cc. portions of water. After drying with sodium sulfate, the ethyl acetate solution was brought completely to dryness *in vacuo;* weight of the resinous residue, 1.0404 g. The residue was dissolved in a small volume of acetone and this solution seeded with an authentic sample of ethyl 3,5,19-trihydroxyetiocholanate (XV) (*v.* Exp. I. 2.). Separation of stout prismatic crystals began immediately. They were filtered the following day and identified as moderately pure XV; yield 0.3474 g.; m.p. about 170–175°; mixed m.p. with pure authentic sample, 177°.

Anal. Calc'd for $C_{22}H_{36}O_5$: C, 69.42; H, 9.54.
Found: C, 69.40; H, 9.30.

From the filtrate 0.0368 g. of definitely impure crystalline material (m.p. 155–158°) was obtained. The final mother liquor was brought completely to dryness; weight of the resinous residue, 0.5740 g. This residue was subjected to chromatographic adsorption, for which it was dissolved in 60 cc. of ether. The solution was filtered through a column (diam. 20 mm.) of 16 g. of aluminum oxide within a period of 80 minutes. The eluates were passed through, each within 25–40 minutes.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE G.	APPEARANCE OF RESIDUE
1	60 cc. ether (original solution)	0.0693	Resinous
2	40 cc. ether + 20 cc. acetone	.1382	Partly cryst. resin
3	20 cc. ether + 40 cc. acetone	.0251	Crystalline
4	60 cc. acetone	.0338	Crystalline
5	60 cc. acetone + 0.15 cc. methanol	.0255	Partly cryst. resin
6	60 cc. acetone + 0.20 cc. methanol	.0097	Crystalline
7	60 cc. acetone + 0.30 cc. methanol	.0065	Resinous
8	60 cc. acetone + 0.40 cc. methanol	.0117	Partly cryst. resin
9	60 cc. acetone + 0.50 cc. methanol	.0288	Crystalline
10	59 cc. acetone + 1 cc. methanol	.0461	Crystalline
11	58 cc. acetone + 2 cc. methanol	.0640	Foamy glass
12	55 cc. acetone + 5 cc. methanol	.0647	Foamy glass
13	45 cc. acetone + 15 cc. methanol	.0293	Foamy glass
14	60 cc. methanol	.0153	Semi-crystalline
Total		.5680	

The residues of the above chromatographic fractionation were separately recrystallized. Fractions 1–5 definitely represented mixtures, but no attempt was made at this time to subject them to a systematic purification.

Ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI). When fractions 2, 3, and 4 were recrystallized from acetone, a number of crystalline crops (dagger-shaped crystals) were obtained with melting points between 185 and 190° (the substances melted first around 170° and then solidified to remelt at the stated temperature); total yield 42 mg. A sample in chloroform gave with tetranitromethane no yellow color. There were several crystalline crops with melting points below 100°. The major part of the material contained in fractions 2–4 remained resinous. The analysis was performed with a crystalline sample melting at 185°. This melting point is not claimed to be that of an entirely pure sample. The mixed melting point with ethyl 3,5,19-trihydroxyetiocholanate (XV) was 156°.

Anal. Calc'd for $C_{22}H_{34}O_5$: C, 69.79; H, 9.06.
Found: C, 69.40; H, 8.85.

When the residues of fractions 9 and 10 were recrystallized from acetone, a total of only 40.8 mg. of crystalline material (transparent rod-shaped crystals) with melting points between 170 and 180° was obtained. These crops represented moderately pure XV, as was also established by mixed melting point with an authentic sample.

Anal. Calc'd for $C_{22}H_{36}O_5$: C, 69.42; H, 9.54.
Found: C, 69.27; H, 9.54.

On recrystallizing the residue of fraction 11 from acetone, several crystalline crops with melting points below 150° were obtained. They obviously represented mixtures.

When the residue of fraction 12 was recrystallized from acetone, 17.2 mg. of flaky white crystals were obtained; m.p. 175–180°. There was no depression of the melting point when mixed with an authentic sample of ethyl 3,5,14,19-tetrahydroxyetiocholanate (VIII). According to the analysis, the substance was not quite pure.

Anal. Calc'd for $C_{22}H_{36}O_6$: C, 66.62; H, 9.16.
Found: C, 67.55; H, 9.24.

A second crop was obtained by adding a little petroleum ether to the mother liquor; wt. 11.2 mg.; m.p. 169–174°. This material was obviously less pure.

No uniform crystalline material could be secured from the residue of fraction 13.

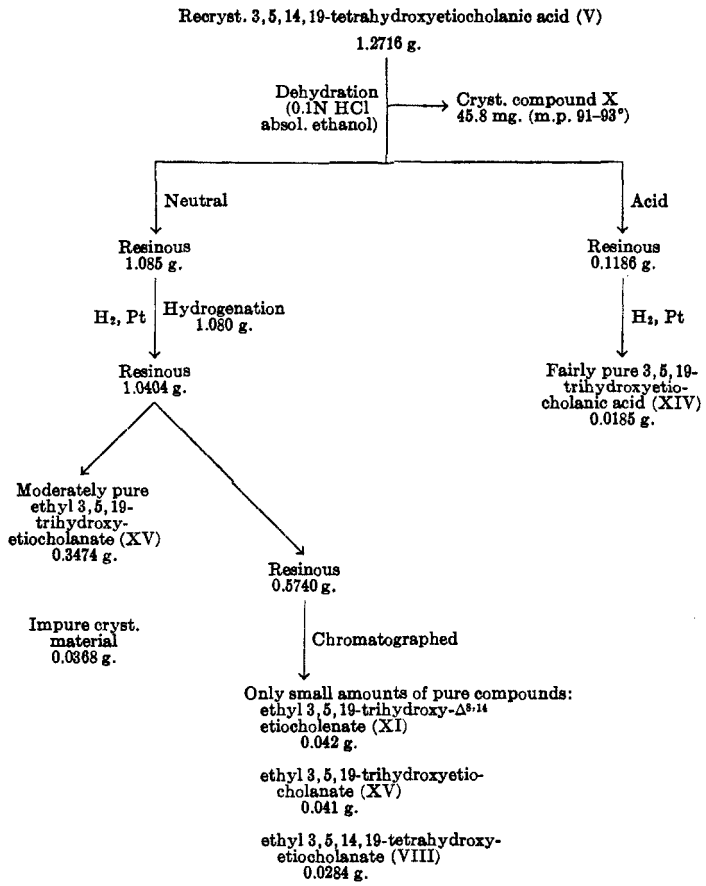
Hydrogenation of acid residue. Platinum oxide (50 mg.) in glacial acetic acid (3 cc.) was reduced and a solution of the acid residue (0.1186 g.) in 4 cc. of glacial acetic acid was added and the shaking with hydrogen continued for a period of three hours. The total absorption of hydrogen was 8.9 cc. (26°); calc'd for 3,5,19-trihydroxy-Δ^{14}-etiocholenic acid (XIII), 8.3 cc. Immediately thereafter the solution was filtered from the catalyst and brought to dryness *in vacuo*. To the resinous residue was added 3 cc. of water. By kneading the resinous material on the following day repeatedly with 0.5-cc. portions of water it eventually became crumbly and filterable; dry weight after filtering, 0.094 g. By recrystallizing this material from acetone or acetone-petroleum ether, three crystalline crops totalling 25.9 mg. were obtained; the melting points were between 230 and 255°. The mother liquor, on being brought to dryness, yielded 66.9 mg. of a resin. The combined three crystalline crops were recrystallized from acetone. The pure acid crystallized in white, broad, flat needles; wt. 12.7 mg.; m.p. 250–252°. There was no depression of the melting point when mixed with an authentic sample of 3,5,19-trihydroxyetiocholanic acid (XIV) (*v. infra.*).

Anal. Calc'd for $C_{20}H_{32}O_5$: C, 68.13; H, 9.16.
Found: C, 67.93; H, 9.03.

From the mother liquor 5.8 mg. of crystalline material, melting at 245–252°, was obtained.

A solution in ether of the resinous part (66.9 mg.) of the hydrogenation product was treated with an excess of diazomethane. The weight of the resinous reaction product was 69.5 mg. Its chromatographic purification was inconclusive. No methyl 3,5,19-trihydroxyetiocholanate (XVII) could be isolated. About 5 mg. of crystalline material was secured which probably represents, though in an impure form, methyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XVI).

FLOW SHEET II (EXPERIMENT II)



3,5,19-Trihydroxyetiocholanic acid (XIV). To a solution of 86.8 mg. of purest ethyl 3,5,19-trihydroxyetiocholanate (XV) (from Expt. I.2) in 2.5 cc. of methanol was added 0.17 g. of potassium hydroxide dissolved in 1.0 cc. of methanol. The mixture was refluxed on a water-bath for two hours. After the addition of 2 cc. of water the solution was brought almost to dryness *in vacuo* and the residue taken up in 5–6 cc. of water. The suspended crystalline material was extracted by shaking with 10 cc. of ether. The ether phase was washed three times with 1-cc. portions of water. After drying with sodium sulfate and filtering, the ether solution was brought to dryness; weight of the crystalline neutral residue, 29.5 mg.

The combined alkaline solution and aqueous washings were made acid to Congo by the addition of 1 cc. of conc'd hydrochloric acid (ice-cooling), which produced an emulsion from which a fine white precipitate separated soon. It was extracted with 10 cc. of ether to which, because of the insolubility of the precipitate, 10 cc. of ethyl acetate had to be added. It had to be subsequently extracted five times each with 10 cc. of ethyl acetate to bring all of the white material into solution. The aqueous phase was then extracted once more with 10 cc. of ethyl acetate. The combined extracts were washed once with 2 cc. and four times with 1-cc. portions of water. After drying with sodium sulfate the solution was brought to dryness *in vacuo* and the residue dried in a vacuum desiccator over potassium hydroxide; weight of the crystalline acid residue, 53.8 mg. This material was dissolved in the required amount (10–11 cc.) of acetone and the solution concentrated

to a smaller volume (about 2 cc.) on a water-bath when suddenly crystallization set in. The substance crystallized in bunches of flat spear-shaped crystals. It was filtered after a few hours standing at room temperature. Additional crops of rather pure material were obtained by concentrating the mother liquor; yields: Crop 1, wt. 28.2 mg.; m.p. 259–260°. Crop 2, wt. 15.1 mg.; m.p. 256.5–258°. Crop 3, wt. 1.8 mg.; m.p. 254–256°. All these crops melted to a light-brown liquid and there was subsequent effervescence. The determination of the optical rotation and the microanalysis were performed with the first crop. $[\alpha]_D^{25}$ + 69.5° (8.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{20}H_{32}O_5$: C, 68.13; H, 9.16.
Found: C, 67.66; H, 9.18.

A solution of the neutral crystalline residue (29.5 mg.) in ether was concentrated on a water-bath until crystallization set in. The stout, ruler-shaped crystals were filtered the following day (crop 1, wt. 17.7 mg.; m.p. 208–211°). This material obviously represented a mixture of the ethyl and methyl esters of 3,5,19-trihydroxyetiocholanic acid (XV and XVII). Additional crystalline material was obtained by concentrating the filtrate on a water bath (crop 2, wt. 4.8 mg.; m.p. 222.5–224°). On bringing the final mother liquor to dryness, a crystalline residue (6.1 mg.) was obtained. The second crop represented pure XVII. There was no depression of the melting point when it was mixed with an authentic sample of that compound (*v. infra.*). The results of the microanalysis were likewise in agreement with this conclusion.

Anal. Calc'd for $C_{21}H_{34}O_5$: C, 68.80; H, 9.36.
Found: C, 68.89; H, 9.24.

Methyl 3,5,19-trihydroxyetiocholanate (XVII). To a solution of 26.6 mg. of 3,5,19-trihydroxyetiocholanic acid (XIV) in 5 cc. of acetone was added at 0° a slight excess of an ethereal solution of diazomethane. After standing at room temperature for a period of twenty minutes, the excess of the diazomethane was removed on a water-bath and the resulting colorless solution brought to dryness *in vacuo*. The crystalline residue was dissolved in 15 cc. of ether and this solution washed neutral by treating it successively with 1 cc. of *N* hydrochloric acid, 1 cc. of water, 1 cc. of 5% sodium carbonate, and three times with 1-cc. portions of water. After drying with sodium sulfate the solution was brought to a small volume on a water-bath. Crystallization set in spontaneously; characteristic hexagonal platelets. The material was filtered after some standing at room temperature; weight 15.2 mg.; m.p. 220–222.5°. $[\alpha]_D^{23.5}$+61.3° (8.0 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{21}H_{34}O_5$: C, 68.80; H, 9.36.
Found: C, 68.75; H, 9.34.

A second crop of a similar looking crystalline product was secured by concentrating of the mother liquor; weight 3.8 mg.; m.p. 218–220.5°.

Ethyl 3,19-diacetoxy-5-hydroxyetiocholanate (XVIII). To a solution of 108 mg. of pure ethyl 3,5,19-trihydroxyetiocholanate (XV) (from Expt. I.2) in 0.4 cc. of pyridine was added 0.4 cc. of acetic anhydride and the mixture allowed to stand at room temperature for a period of 22 hours. It was then concentrated *in vacuo* (65°) to a viscous, colorless oil which was taken up in 25 cc. of ether. This solution was washed neutral by shaking it successively twice with 2-cc. portions of *N* hydrochloric acid, twice with 2 cc. of 5% sodium carbonate, and five times with 1 cc. of water each. After drying with sodium sulfate, the solution was brought to dryness. The residue was a colorless resin which partly crystallized overnight in an evacuated desiccator; weight, 127.5 mg. On adding a little ether, some white crystalline material separated which was filtered after brief standing; weight of this first crop, 39.0 mg.; m.p. 108–109.5°. $[\alpha]_D^{23.5}$+60.3° (20.0 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{26}H_{40}O_7$: C, 67.20; H, 8.68.
Found: C, 67.26; H, 8.66.

By concentrating the filtrate to a smaller volume several additional crops of crystalline material were obtained; crop 2, wt. 31.3 mg.; m.p. 107–108°; crop 3, wt. 22.4 mg.; m.p. 03–105°; crop 4, wt. 12.4 mg.; m.p. 97–101.5°.

3,5,19-Trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII). To a solution of 34.9 mg. of ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI) (*cf.* Expt. II) in 1 cc. of methanol was added 70 mg. of potassium hydroxide, dissolved in 1 cc. of methanol. The mixture was refluxed for two hours and then kept at room temperature for about 30 minutes, 3 cc. of water was added, and the solution concentrated *in vacuo* to a volume of about 1 cc. After the addition of 3 cc. of water the turbid solution was extracted four times with 5-cc. portions of ether. The combined ether phases were washed three times with 1.5 cc. of water, dried with sodium sulfate, and finally brought to dryness; weight of the crystalline neutral residue, 4.1 mg.

The combined aqueous phases were made acid to Congo by the addition of 0.5 cc. of conc'd hydrochloric acid (ice-cooling). This produced a turbidity from which a white, apparently crystalline precipitate separated promptly. It was extracted seven times with 5-cc. portions of ethyl acetate. The combined extracts were washed five times each with 1 cc. of water, dried with sodium sulfate, brought completely to dryness and then kept in a vacuum desiccator over potassium hydroxide; weight of the crystalline acid residue, 27.6 mg. This residue was dissolved in 10 cc. of acetone and the solution concentrated on a water-bath to a volume of about 3 cc. The white, scaly microcrystalline material was filtered after a few hours' standing at room temperature. Additional crops of fairly pure material were obtained by concentrating the mother liquor. Yields: Crop 1, wt. 6.6 mg.; m.p. 286–288°. Crop 2, wt. 5.4 mg.; m.p. 285.5–287.5°. Crop 3, wt. 2.9 mg.; m.p. 281–283°. Crop 4, wt. 0.6 mg.; m.p. 283–286°. All these crystalline crops melted to a dark brown liquid. The final mother liquor was brought to dryness *in vacuo*; weight of the crystalline residue, 8.9 mg. The microanalysis was performed with the first crop and the optical rotation was determined with the second crop. The error of the latter determination is possibly larger than usual, because the scanty solubility of this substance afforded a solution of a very low concentration. $[\alpha]_D^{29.5}+77.3°$ (3.6 mg. in 2.0 cc. of acetone)

Anal. Calc'd for $C_{20}H_{30}O_5$: C, 68.52; H, 8.63.
Found: C, 68.11; H, 8.56.

Methyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XVI). A solution of 8.9 mg. of 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII) in 6 cc. of acetone was concentrated to about two-thirds of this volume on a water-bath. To this was added at 0° an excess of an ethereal solution of diazomethane. The reaction mixture was allowed to stand cold for about 10 minutes and at room temperature for about 25 minutes. The solution was brought to dryness *in vacuo* and the white residue taken up in 45 cc. of ether. The ether solution was washed neutral by treating it successively with 1 cc. of *N* hydrochloric acid, 1 cc. of water, 1 cc. of 5% sodium carbonate, and three 1-cc. portions of water. After drying with sodium sulfate and bringing to dryness, the ether solution yielded 9.8 mg. of a white crystalline residue. It was treated with some acetone and the white crystalline material then separated by filtration; microscopic flat short needles; wt. 4.9 mg.; m.p. 270–274° (brown sq.).

Anal. Calc'd for $C_{21}H_{32}O_5$: C, 69.18; H, 8.83.
Found: C, 69.03; H, 8.75.

The filtrate was brought to dryness *in vacuo* and yielded 3.3 mg. of a white crystalline residue.

The methylation was also carried out with the crystalline residue obtained from the final mother liquor of 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII) (8.9 mg.; *cf.* preceding expt.). Worked up the same way as described above there was obtained 1.3 mg. of microscopic needles; m.p. 272–276° (brown liq.). When the filtrate was brought to dryness, 6.9 mg. of a resinous residue was obtained.

SUMMARY

1. Strophanthidol (II) and its diacetate (III) were prepared from strophanthidin (I) according to procedures published in the literature. Supplementary observations are recorded.

2. Strophanthidol diacetate (III) was oxidized to the 3,19-diacetoxy-5,14-dihydroxyetiocholanic acid (IV) which in turn was saponified to 3,5,14,19-tetrahydroxyetiocholanic acid (V). The methyl esters of the latter two compounds are described (VII and VI respectively).

3. Treatment of 3,5,14,19-tetrahydroxyetiocholanic acid (V) with alcoholic hydrogen chloride yielded predominantly neutral substances.

The main reaction product of the neutral fraction was ethyl 3,5,19-trihydroxy-Δ^{14}-etiocholenate (IX) which in turn was hydrogenated to ethyl 3,5,19-trihydroxyetiocholanate (XV). The latter compound furnished by acetylation ethyl 3,19-diacetoxy-5-hydroxyetiocholanate (XVIII) and by saponification 3,5,19-trihydroxyetiocholanic acid (XIV). The methyl ester (XVII) of this acid was prepared.

Minor neutral products of the reaction with alcoholic hydrogen chloride were ethyl 3,5,14,19-tetrahydroxyetiocholanate (VIII), an unsaturated compound of the possible empirical formula $C_{20}H_{28}O_4$ (X?), and ethyl 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate (XI). The latter compound resists catalytic hydrogenation. It was saponified to 3,5,19-trihydroxy $\Delta^{8,14}$-etiocholenic acid (XII) which in turn was transformed into its methyl ester (XVI).

It was concluded that the acid products of the reaction with alcoholic hydrogen chloride contained 3,5,19-trihydroxy-Δ^{14}-etiocholenic acid (XIII) and possibly also 3,5,19-trihydroxy-$\Delta^{8,14}$-etiocholenic acid (XII). Among the hydrogenation products of the whole acid fraction there was identified 3,5,19-trihydroxyetiocholanic acid (XIV) which can only have originated from the unsaturated acid XIII.

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ERRATA

Price, Leonard, and Curtin, "2-Amino-4-methyl-6-methoxymethylpyrimidine, some Derivatives and Related Compounds." *J. Org. Chem.*, **10**, 318 (1945)

Page 320, Legend for Fig. 1, the third curve, 4-amino-5-methylpyridine, should read 4-amino-5-methylpyrimidine.

Page 321, Analysis for 2-(N^4acetylsulfanilamido)-4-methyl-6-methoxymethylpyrimidine should read:

Anal. Calc'd for $C_{15}H_{18}N_4O_4S$: C, 51.41; H, 5.18; N, 15.98.
Found: C, 51.76; H, 5.75; N, 15.55.