[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF SCHERING CORPORATION]

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI. PART II. THE DISPLACEMENT OF GROUPS BY HYDROGEN

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In continuation of previous work in this laboratory on the reduction of carbonyl compounds by a nickel-aluminum alloy in alkaline solution (1), the displacement by hydrogen of methoxyl, halogen, and sulfonic acid groups from several benzenoid compounds was observed. This paper presents the results of our studies on this displacement reaction.

The hydrogenolysis of sulfonic acid groups in the naphthalene series (2) and of halogens in many aliphatic and aromatic compounds has been observed during reductions with zinc and acid (3, 4). Several isolated instances of the displacement of other groups, such as the methoxyl groups (5) and the —C=OR (6) have been reported in the course of the Clemmensen reduction. Catalytic reduction, particularly at high pressures, often brings about hydrogenolysis (7).

When treated with nickel-aluminum alloy and aqueous alkali,[1] halogen and sulfonic acid groups (Tables I and II), are displaced by hydrogen, the displacement of these groups being apparently independent of their number, their position, or the presence of other groups.

All halogen-containing compounds which we have studied (Table I), be they aliphatic, aromatic, alicyclic, or heterocyclic, quantitatively exchanged their halogen for hydrogen.[2]

Up to the present time the reductive displacement of sulfonic acid groups has been limited, in general, to the *alpha*-naphthalenesulfonic acids, only a few instances of a similar displacement being observed for the *beta* compounds (2). With our reduction method, sulfonic acid groups are displaced from *alpha*- and *beta*-naphthalenesulfonic acids, as well as from the benzenesulfonic acids. The low yields in some cases are quite likely due to a poisoning of the nickel catalyst by the sulfite or sulfide formed during the reaction.

Two organometallic compounds were investigated, arsanilic acid and phenylmercuric acetate, the former yielding aniline and the latter diphenyl.

[1] The reduction of the compounds given in the tables of this paper was carried out according to the procedure previously described (1). The yields of the reduction products are calculated to the starting material and represent products purified by recrystallization or distillation. Ten grams of substance were used in those reductions in which only one product was obtained, whereas, twenty-five grams were used in those reductions where two or more products were formed.

[2] In Table I are given only those halogen compounds whose reduction product has been identified. Halogen compounds belonging to the aliphatic, alicyclic and heterocyclic classes are given in another publication which describes the application of this reduction procedure to the quantitative determination of halogens in organic compounds. See *Ind. Eng. Chem. Anal. Ed.*, **15**, 576 (1943).

Of the compounds studied, only halogen and sulfonic acid groups are displaced by hydrogen from monosubstituted benzene derivatives. In disubstituted benzene compounds, not only were halogen and sulfonic acid groups displaced, but alkoxyl groups as well. Whether or not an alkoxyl group will be displaced by hydrogen depends upon the nature and position of the other substituent.

When subjected to this reduction procedure, *p*-anisidine (I) and *o*- (II), *m*- (III), and *p*-cresyl methyl ether (IV) were recovered unchanged. When the *ortho-para*-directing methyl or amino group in compounds I to IV is replaced by the *meta*-directing carboxyl group, quantitative displacement of the methoxyl

TABLE I

HALOGEN COMPOUNDS

COMPOUND	REDUCTION PRODUCT	% YIELD
1. Bromobenzene[a]	Benzene	100[b]
2. *m*-Chlorobenzoic acid	Benzoic acid	100
3. *p*-Chloronitrobenzene[a]	Aniline	65
4. *p*-Chlorobenzaldehyde	Toluene	60
5. 5-Chloro-2-hydroxybenzaldehyde	*o*-Cresol	75
6. *p*-Bromoacetophenone[a]	Ethylbenzene	67
7. β-(*p*-Chlorobenzoyl)propionic acid	γ-Phenylbutyric acid	70

[a] 25 cc. of alcohol used as solvent.

[b] The yield of benzene is based on the quantitative recovery of bromine as silver bromide.

TABLE II

SULFONIC ACIDS

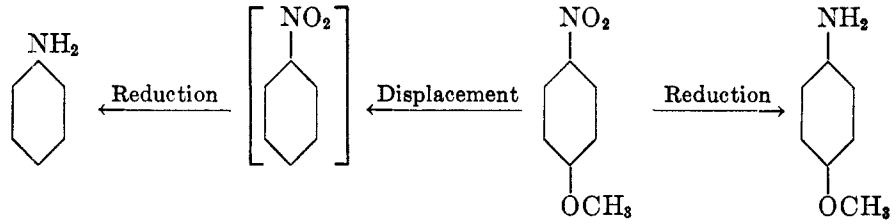
COMPOUND	REDUCTION PRODUCT	% YIELD
1. Benzenesulfonic acid	Benzene	10[a]
2. *o*-Sulfobenzoic acid	Benzoic acid	40
3. *m*-Sulfobenzoic acid	Benzoic acid	50
4. Naphthalene-β-sulfonic acid	Naphthalene	40
5. 2-Naphthol-6-sulfonic acid	β-Naphthol	30
6. 2-Naphthol-3,6-disulfonic acid	β-Naphthol	30

[a] The poor recovery of benzene is very probably due to the entrainment of the vapors by the hydrogen liberated from the alloy.

group takes place in *o*- and *p*-methoxybenzoic acid. However, the *m*-methoxybenzoic acid is recovered unchanged. In none of our experiments has the displacement of a *meta*- substituted methoxyl group been observed.

A similar displacement of the methoxyl group took place in compounds with other *meta*-directing groups, such as $-NO_2$, —CHO, and $-COCH_3$. In addition to the displacement reaction, the *meta*-orienting groups in these compounds are themselves capable of reduction (1) to the *ortho-para*-orienting amino or alkyl groups. In a compound containing such a reducible substituent, elimination of the methoxyl group can occur only before the reduction has converted the *meta*-directing into an *ortho-para*-directing group. For example, in the reduc-

tion of *p*-nitroanisole, a 20% yield of aniline and a 70% yield of *p*-anisidine was obtained. The aniline must result from an initial displacement of the methoxyl



group followed by the reduction of the nitrobenzene thus formed, whereas the *p*-anisidine arises from the initial reduction of the nitro group. The two possible reduction products were also obtained in varying amounts from *p*-methoxybenzyl alcohol and from *o*- and *p*-methoxybenzaldehyde. While only ethylbenzene was isolated from the reduction of *p*-methoxyacetophenone, it is quite possible that *p*-methoxyethylbenzene was also formed in small amounts.

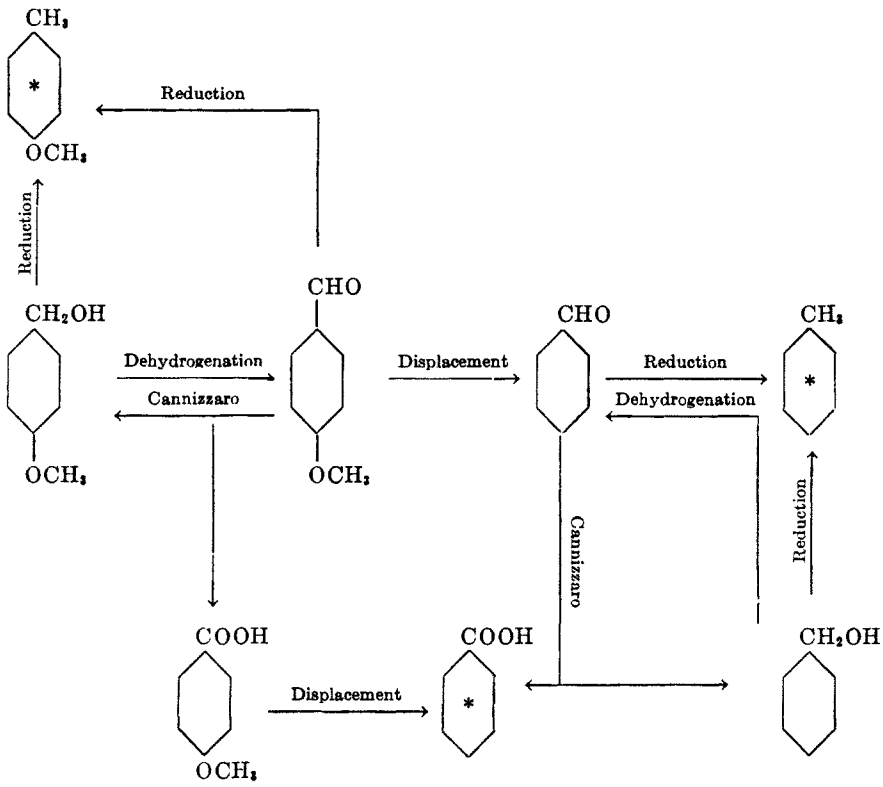
A third reaction product, benzoic acid, was isolated from the reduction of *p*-methoxybenzyl alcohol and *p*-methoxybenzaldehyde. A reinvestigation of the reduction products of benzyl alcohol and benzaldehyde also revealed the presence of benzoic acid in both cases. In the alkaline environment, part of the benzaldehyde and its substituted derivatives may undergo a Cannizzaro conversion to the corresponding alcohols and acids. The formation of benzoic acid from the benzyl alcohols can be explained by assuming an initial dehydrogenation of the alcohols to the aldehydes, followed by a displacement or Cannizzaro reaction. It is in agreement with this explanation that with *p*-methoxybenzyl alcohol, displacement of the methoxyl group was observed, notwithstanding the fact that the CH_2OH group is essentially an *ortho-para*-directing group. It is probable that the displacement of the methoxyl group does not occur in the original compound but in the *p*-methoxybenzaldehyde and the *p*-methoxybenzoic acid with their *meta*-directing groups in *para* position to the methoxyl group.

There are, then, several reactions possible in the reduction of the benzyl alcohols and benzaldehydes. The scheme shown on top of page 4 illustrates the probable course of the reaction, the asterisks indicating the compounds actually isolated in the case of *p*-methoxybenzyl alcohol.

The displacement reaction is not restricted to the methoxyl group, a similar loss of the alkoxyl group occurring in *p*-ethoxybenzaldehyde, and in *p*-ethoxy-, *p*-propoxy-, *p*-isopropoxy-, and *p*-butoxybenzoic acids. The yields of benzoic acid varied from 10% with *p*-ethoxybenzoic acid to 60% with *p*-propoxybenzoic acid, despite the fact that twice the usual amount of alloy and alkali was used in these reductions.

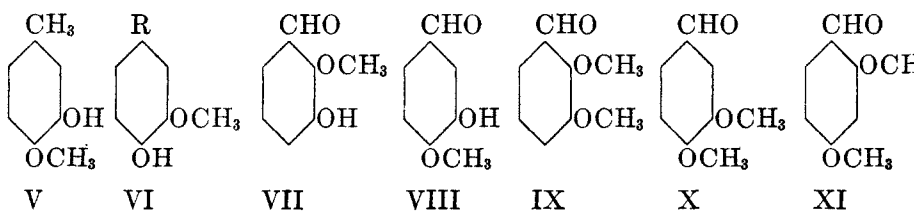
Benzyloxyl compounds are split in the same manner as observed with other reduction methods, *o*-benzyloxybenzoic acid yielding toluene and salicylic acid. *o*-Methylthiolbenzoic acid, however, behaves as the oxygen analog, giving only benzoic acid.

The introduction of a hydroxyl or methoxyl group as the third group in the



disubstituted benzene derivatives alters considerably the course of the displacement reaction. The most striking change in the displacement reaction is that in many cases displacement of *meta*-orienting groups was observed, a reaction for which no parallel could be found in the literature. It compares, however, with observations made by others, who have shown that carbonyl groups are displaceable by hydrogen, halogen, and nitro groups (8, 9, 10, compare also 11).

In the trisubstituted compounds (VI to XI) displacement of the aldehyde group by hydrogen occurred, notwithstanding the diversified position relationships of the hydroxyl and methoxyl groups to the aldehyde group. Although the only product isolated in the reduction of these aldehydes was guaiacol or dimethoxybenzene, it is evident from an inspection of the formulas (VI to XI)



R=CH_2OH, CHO, $COCH_3$

that other reduction products may be formed. For example, in isovanillin (VIII) small amounts of *meta*-cresol and 3-hydroxy-4-methoxytoluene (V) may have been formed, but, in the presence of large amounts of guaiacol, detection of these compounds is difficult and was not considered within the scope of this investigation.

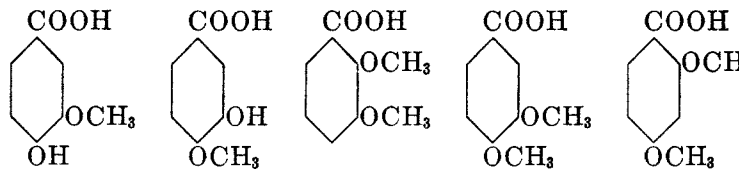
TABLE III

DISUBSTITUTED BENZENE DERIVATIVES

COMPOUND	REDUCTION PRODUCT	% YIELD
1. *o*-Methoxybenzaldehyde	1. *o*-Cresyl methyl ether	45
	2. Toluene	15
	3. Benzoic acid	20
2. *o*-Methoxybenzoic acid	Benzoic acid	100
3. *o*-Methylthiolbenzoic acid	Benzoic acid	75
4. *o*-Benzyloxybenzoic acid	Salicylic acid	75
5. Diphenyl ether	Recovered unchanged	
6. *p*-Methoxybenzyl alcohol[a]	1. *p*-Cresyl methyl ether	50
	2. Toluene	15
	3. Benzoic acid	20
7. *p*-Methoxybenzaldehyde[a]	1. *p*-Cresyl methyl ether[c]	30
	2. Toluene	45
8. *p*-Nitroanisole[a]	1. *p*-Anisidine	70
	2. Aniline	20
9. *p*-Anisic acid	Benzoic acid	100
10. *p*-Ethoxybenzaldehyde[a]	1. Benzoic acid	40
	2. *p*-Ethoxytoluene	15
	3. Toluene	25
11. *p*-Ethoxybenzoic acid[b]	Benzoic acid	10
12. *p*-Methoxyacetophenone[a]	Ethylbenzene	50
13. β-(*p*-Methoxybenzoyl)propionic acid	γ-Phenylbutyric acid	65
14. *p*-Isopropoxybenzoic acid[b]	Benzoic acid	30
15. *p*-Propoxybenzoic acid[b]	Benzoic acid	60
16. *p*-Butoxybenzoic acid[b]	Benzoic acid	40
17. *p*-Methoxyphenylacetic acid	Recovered unchanged	
18. *p*-Methoxycinnamic acid	*p*-Methoxyhydrocinnamic acid	95
19. *m*-Methoxybenzaldehyde[a]	*m*-Cresyl methyl ether[c]	55
20. *m*-Methoxybenzoic acid	Recovered unchanged	
21. *p*-Dimethylaminobenzaldehyde[a]	*p*-Dimethyltoluidine[c]	70

[a] 25 cc. of alcohol used as solvent. [b] Recovered from the reduction mixture, *p*-ethoxybenzoic acid 90%, *p*-isopropoxybenzoic 60%, *p*-propoxybenzoic acid 25%, *p*-butoxybenzoic acid 60%. [c] These aldehydes were reduced before we were aware of the presence of benzoic acid in the aqueous phase.

The reduction of the acids (XII to XVI) corresponding to the aldehydes (VI to XI) illustrates the complex nature of these reactions. While vanillic acid (XII) was recovered unchanged, isovanillic acid (XIII) yielded *m*-hydroxybenzoic acid. However, it was necessary to use about five times the normal amount of alloy and alkali in order to bring about this conversion. That the methoxyl group was displaced in isovanillic acid suggests the possibility of a



XII XIII XIV XV XVI

similar cleavage in isovanillin, but the rate of its displacement is apparently much slower than that of the aldehyde group. The acids (XIV to XVI), when

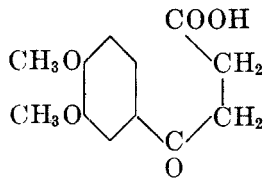
TABLE IV

TRISUBSTITUTED BENZENE DERIVATIVES

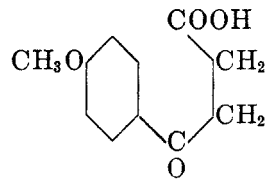
COMPOUND	REDUCTION PRODUCT	% YIELD
1. 2,3-Dimethoxybenzaldehyde[a]	Veratrole	70
2. 2,3-Dimethoxybenzoic acid[b]	Recovered unchanged	
3. 3,4-Dimethoxybenzaldehyde[a]	Veratrole	75
4. 3,4-Dimethoxybenzoic acid[b]	Recovered unchanged	
5. β-(3,4-Dimethoxybenzoyl) propionic acid	γ-(3,4-dimethoxyphenyl)butyrolactone[c]	70
6. 3,4,5-Trimethoxybenzoic acid	Recovered unchanged	
7. 2,4-Dimethoxybenzaldehyde[a]	Resorcinol dimethyl ether	45
8. 2,4-Dimethoxyacetophenone[a]	Resorcinol dimethyl ether[d]	15
9. 2,4-Dimethoxybenzoic acid[e]	Recovered unchanged	
10. 3-Methoxy-4-hydroxytoluene	Recovered unchanged	
11. Vanillyl alcohol	Guaiacol	60
12. Vanillin	Guaiacol	70
13. Isovanillin	Guaiacol	70
14. 3-Ethoxy-4-hydroxybenzaldehyde	*o*-Ethoxyphenol	75
15. 3-Methoxy-2-hydroxybenzaldehyde	Guaiacol	75
16. 3-Methoxy-4-hydroxyacetophenone	Guaiacol	70
17. Vanillic acid	Recovered unchanged	
18. Isovanillic acid	*m*-Hydroxybenzoic acid[f]	50

[a] 25 cc. of alcohol used as solvent. [b] The reduction of these acids with 5 times the normal amount of nickel-aluminum alloy did not yield any *m*-methoxybenzoic acid. [c] M.p. 116–117°; Calc'd. for $C_{12}H_{14}O_4$: C, 64.87; H, 6.36. Found: C, 65.25; H, 6.40. [d] Residue from the distillation (60%) gave the dinitrophenylhydrazone of the original compound. [e] This acid was quantitatively recovered on treatment with alloy and alkali at 125° for 5 hours. [f] Further treatment with alloy and alkali converted 90% of the isovanillic acid to *m*-hydroxybenzoic acid.

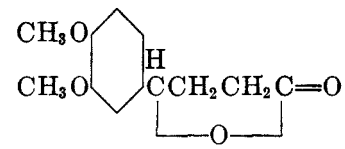
treated in the same manner as isovanillic acid, did not undergo any displacement of the methoxyl groups. As in the case of 3,4-dimethoxybenzoic acid (XV) β-(3,4-dimethoxybenzoyl)propionic acid (XVII) did not undergo any displacement of the *p*-methoxyl group, despite the fact that β-(*p*-methoxybenzoyl)propionic acid (XVIII) gave a 65% yield of γ-phenylbutyric acid. From the reduction of XVII γ-(3,4-dimethoxyphenyl)butyrolactone (XIX) was obtained in



XVII



XVIII



XIX

70% yield in addition to a small amount of intractable oil. The behavior of these acids (XIV to XVII) is somewhat surprising in view of the fact that all four have a methoxyl group in either the *ortho* and/or *para* position to a *meta*-directing group. No change occurred in 2,4-dimethoxybenzoic acid (XVI) even after heating under pressure with nickel-aluminum alloy and alkali at 125° for 5 hours.

The reduction of 3,4,5-trimethoxybenzoic acid was also studied to determine whether the presence of three methoxyl groups might bring about the displacement of the carboxyl group. However, neither the carboxyl nor any one of the methoxyl groups was displaced.

SUMMARY

1. Treatment of compounds containing halogen, sulfonic acid, alkoxyl, carbonyl, and metallic groups with nickel-aluminum alloy and aqueous alkali has resulted in the displacement of these groups by hydrogen.

2. The displacement of halogen and sulfonic acid groups has been found to be independent of the structure of the compound.

3. Alkoxyl groups are displaced from disubstituted benzene derivatives when they are *ortho* or *para* to a *meta*-directing group.

4. In trisubstituted benzene derivatives of the general formula $RC_6H_3R'R''$, where R is a *meta*-directing group other than carboxyl, R′ is either a hydroxyl or alkoxyl group, and R″ is an alkoxyl group, displacement of the *meta*-directing groups by hydrogen was observed, this displacement being independent of the position relationship of the three groups.

BLOOMFIELD, N. J.

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[CONTRIBUTION NO. 286 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

XANTHYDROL AS A REAGENT FOR THE IDENTIFICATION OF SULFONAMIDES

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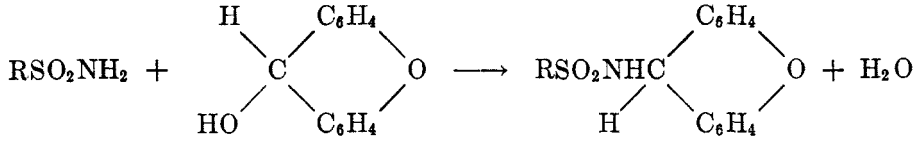
The most general method for the identification of sulfonamides consists of their hydrolysis with acid or alkali (1). This method has the disadvantage of being both laborious and not too satisfactory with respect to the isolation and characterization of the hydrolysis products. Much more desirable would be a non-hydrolytic procedure which operates directly on the sulfonamide group present. Some progress in this direction has been reported by Evans and Dehn (2), who condensed unsubstituted sulfonamides with phthalyl chloride. Work has also been reported on a similar condensation between alkyl halides and sulfonamides (3), although this was directed towards alkyl halide rather than sulfonamide identification.

The use of xanthydrol for the preparation of amide derivatives (4) naturally suggests its possible utility with sulfonamides. Two such derivatives are known. In 1935, Wood (5) reported condensing xanthydrol with *p*-toluenesulfonamide and with sulfanilamide. (He also secured the bis derivative of sulfuryl diamide.) No experimental details were given.

The reaction between sulfonamides and xanthydrol may be expressed by the equation



The condensation requires an acid medium, acetic acid being satisfactory. This is in agreement with the earlier work of Fosse (6) and Adriani (7) on xanthydrol condensations.

The N-xanthylsulfonamides, also in line with their work, form only with unsubstituted amides. The derivatives so prepared are crystalline, easily formed and purified compounds, suitable for use in identification work. A very simple general procedure, requiring only one-quarter gram of sulfonamide, has been developed and applied successfully to twelve benzenoid sulfonamides and one imide. It failed where the alkyl groups on the ring were branched.

In Table I are listed the melting points and analyses of the N-xanthylsulfonamides which have been prepared.

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[2] Taken from the thesis of Victor S. Frank submitted in partial fulfilment of the requirements for the degree of Bachelor of Science at M. I. T. Present address Dewey and Almy Chemical Co., Cambridge, Mass.

The following benzenoid sulfonamides failed to give xanthyl derivatives: 2,4,6-triethylbenzenesulfonamide, *p*-t-butyl-, *p*-t-amyl- and the *p*-cymenebenzenesulfonamides, N-ethyl-*p*-toluenesulfonamide. Two compounds, 4-sec-butyl-, and 2-methyl-4-isopropyl-benzenesulfonamides, gave exceedingly poor yields of products. It will be observed that all of these sulfonamides, except the triethyl and the N-ethyl, have branched chain alkyl substituents. It would appear that such groups, even *para* to the sulfonamide group, block the xanthydrol condensation. It was not expected that the N-ethyl compound would condense,

TABLE I

N-XANTHYL-*n*-ALKLYBENZENESULFONAMIDES

-BENENESULFONAMIDE-1	N-XANTHYL DERIVATIVE			
	M.P.°C[a]	% Nitrogen[b]		
		Calc'd	Found	
—	200–200.5	4.16	4.28	4.35
2-Me-	182–183.5	3.99	4.03	4.10
4-Me-	197–197.5[c,d,g]	3.99	4.46	4.47
4-Et-	195.5–197[c,e]	3.84	3.95	4.15
4-*n*-Pr-	199–200.5[d,e]	3.69	3.92	3.95
4-*n*-Bu-	185–186.5	3.56	3.88	3.95
4-*n*-Am-	164.5–165	3.44	3.54	3.64
3,4-di-Me-	189–190[f]	3.84	3.98	3.99
2,4-di-Me-	187–188.5[f]	3.84	3.85	3.94
2,5-di-Me-	175–176	3.84	3.72	3.92
2,4,6-tri-Me-	203–204	3.69	3.85	4.08
4-NH_2-	207–208[h]	5.26 (di)	5.46	5.55
Saccharin[i]	198–199[i]	3.86	4.20	4.33

[a] All melting points are uncorrected and were determined on a copper block with standard 360° melting point thermometer as described in Morton, "Laboratory Technique in Organic Chemistry," 1st Ed., McGraw-Hill, New York, **1933**, pp. 32–33. [b] Nitrogen analyses were semi-micro and were performed by Malcolm L. Brown, whom we wish to thank for his cooperation. [c] Mixed melting point of these derivatives was 185–191°. [d] Mixed melting point of these derivatives was 183–192°. [e] Mixed melting point of these derivatives was 187–189°. [f] Mixed melting point of these derivatives was 163–167°. [g] Melting point reported by Wood (5) was 198°. [h] Melting point reported by Wood (5) was 209°. [i] Melting point reported by Fabre (8) was 199–200°. [j] Saccharin gave lower yields than did the sulfonamides though still enough to work with.

since most of the earlier work has shown that a free amide group is required. However, equally as surprising as the recalcitrance of the branched alkyl compounds was the failure of triethylbenzenesulfonamide to condense. The analogous mesitylene compound worked beautifully, and so did ethylbenzene, but not the triethyl. (Yields on all of the xanthylbenzenesulfonamides except saccharin, which fell to 50% amounted to 80–90%.) Deviations from the standard procedure involving as much as 2 hours heating or 2 weeks standing at room temperature all failed to produce a product.

The failure of 2,4,6-triethylbenzenesulfonamide to condense may be analogous to the like behavior of picramide (7). The failure of N-ethylbenzenesulfonamide to condense offers evidence against the likelihood of C-xanthyl (*i.e.* ring substituted) derivatives, except in cases such as aniline or sulfanilamide, where the ring is activated by the amino group.

The inhibiting effect of the branched alkyl groups is perhaps suggested by the fact that larger *n*-alkyl groups seem to slow down the rate of condensation somewhat, since in a given time, the yields from benzenesulfonamide itself are about 10% greater than those from *p*-*n*-amylbenzenesulfonamide.

EXPERIMENTAL

Xanthydrol. The xanthydrol used was obtained by the sodium-amalgam reduction of xanthone, (9), kindly supplied by the General Chemical Company. Eastman xanthydrol was also used, but was somewhat less satisfactory than the freshly prepared product [*cf.* Phillips and Pitt (4)].

The saccharin, sulfanilamide, and the benzene- and toluene-sulfonamides were Eastman products. All other sulfonamides used were obtained through the courtesy of Professor E. H. Huntress (10) from those prepared by Dr. J. S. Autenrieth as a portion of his doctorate thesis (M.I.T., 1941).

Preparation of N-xanthylalkylbenzenesulfonamides. One-quarter gram of xanthydrol was dissolved in 10 cc. of glacial acetic acid with 0.25 gram of the sulfonamide. This solution was shaken at room temperature for 2–3 minutes and allowed to stand for 90 minutes. The product was filtered and recrystallized from dioxane-water (3:1). One recrystallization was usually sufficient. The products were dried, at room temperature, at the water-pump for about one-half hour.

For recrystallization dioxane-water (3:1) was found to be most generally satisfactory. Cold alcohol does not dissolve the xanthyl derivatives to a very high degree, but dissolves the reactants, so it is useful for washing the products. Dioxane mixed with either acetone (1:1) or alcohol (1:1) is also a useful mixed solvent.

The products were not dried at elevated temperatures since it was found that 80°-drying caused a lowering of the melting points of 2–8°.

The reaction mixture may be heated, but the condensation time saved is not great, and the product becomes more difficult to purify.

3,N¹-Dixanthylsulfanilamide. The analyses in Table I give evidence for a dixanthyl derivative (the mono has a calculated N content of 7.95%). This probably means that a second xanthyl group has gone onto the ring, since aniline is reported to give a C-xanthyl derivative (7). The amino group of the sulfanilamide was shown to be intact by a positive test with nitrous acid.[3] It is believed then, using conventional orientation, that this dixanthyl derivative is probably 3,N¹-dixanthyl sulfanilamide.

SUMMARY

A very simple procedure has been developed for the direct preparation of N-xanthyl derivatives of sulfonamides using xanthydrol as a reagent. No prior hydrolysis is required. Data are given for twelve sulfonamides and saccharin.

[3] That is, diazotization to give nitrogen-test 2.23, Mulliken-Huntress Manual, "Identification of Organic Compounds", 1937, p. 137; Shriner and Fuson, "Systematic Identification of Organic Compounds", 2nd Ed., p. 50.

Seven sulfonamides, five with branched alkyl substituents, failed to condense satisfactorily. The N-xanthyl derivatives are crystalline, easily formed and purified compounds, well suited for the characterization of sulfonamides.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF JOHNS HOPKINS UNIVERSITY]

THE ETHYLATION OF BENZENE. THE COURSE OF THE REACTION[1]

E. M. MARKS, J. M. ALMAND, AND E. EMMET REID

Received August 7, 1943

From the preparative standpoint the ethylation of benzene has been well taken care of by a long line of investigators. Ethylated benzenes may be obtained readily and in good yields by introducing the appropriate amounts of ethylene into benzene in the presence of aluminum chloride. The same may be accomplished, though much less economically, with ethyl chloride. It has been tacitly assumed that the proportions of the products depend only on the amounts of the reactants put in; we find that this is far from being the case.

The purpose of the present investigation was to throw light on the mechanism of the reaction by a quantitative study of the alteration of its course by changes of the conditions. This required accuracy of an entirely different order in the determination of the products. In every run the two layers were separated and the hydrocarbons in each determined by fractionation in stills which gave results reproducible to within 1%. The percentage of the symmetrical isomer was determined in each of the triethylbenzene fractions. For preparation purposes the composition of the top layer, which is usually about nine-tenths of the product, is important. The lower catalytic layer can be used over again. Incidentally, from the data given, favorable conditions for obtaining any desired ethylated benzenes can be selected.

The normal course of the ethylation. Before studying the effects of changes in the reaction conditions, it was necessary to obtain a comprehensive picture of the formation and disappearance of the various ethylated benzenes, as ethylene is added under what may be called normal conditions, 268 cc. of ethylene per minute per mole of benzene, stirring at 7,500 r.p.m., 75°, and 13 moles of benzene to 1 of aluminum chloride. After a run is well started the absorption of ethylene is complete but at first some escapes and carries benzene with it. Hence the ethylene-benzene ratio has been calculated from the products. The results of runs in which from 1 to 5 moles of ethylene were added are in Table I. The line "E" shows the percentage distribution of the ethylene. The lines "T" and "B" give the molar percentages of the various ethylated benzenes in the top and bottom layers. The last column, "Sym.", shows the percentage of the 1,3,5-triethylbenzene in the tri-fraction, the remainder being the unsymmetrical. The results are shown in Fig. 1, which was constructed by drawing smooth curves through the known points and correcting these by trial so that at any point the moles of the products will add up to 100% and the moles of ethylene in them will equal the moles introduced. The result is an approximation, but the general picture is substantially correct for this set of conditions. The maxima for the various ethylation products correspond roughly to the amounts of ethylene put in but are at very different heights. The remarkable

[1] Taken from dissertations of E. M. Marks and J. M. Almand.

thing is the large amount of the hexaethyl that is formed in the early stages of the ethylation. Of the first mole of ethylene 18% goes to form hexa- and only 27% to the mono-ethyl. The early appearance of the hexaethyl has been noted

TABLE I

DISTRIBUTION OF ETHYLENE WHEN VARIOUS AMOUNTS ARE INTRODUCED INTO 1 MOLE OF BENZENE AND THE COMPOSITIONS OF THE TOP AND BOTTOM LAYERS IN MOLE-PERCENTAGES. ALSO THE PERCENTAGE OF THE 1,3,5-ISOMER IN THE TRIETHYL FRACTION

NO.	MOLES C_2H_4		BENZENE	MONO-	DI-	TRI-	TETRA-	PENTA-	HEXA-	SYM.
1	1.03	E		27	24	12	8	11	18	
		T	50	27	12	3	1	2	3	4
		B	16	14	8	15	10	3	7	75
2	2.14	E		9	45	28	13	2	3	
		T	2	19	51	18	8	1	1	61
		B	—	25	26	42	1	1	5	95
3	3.17	E		0.3	9	56	25	4	6	
		T	—	1	15	60	20	2	2	58
		B	—	—	—	57	21	7	15	70
4	4.22	E		—	1	17	37	27	18	
		T	—	—	1	24	41	22	12	56
		B	—	—	—	—	28	45	27	—
5	5.29	E		—	—	—	11	39	50	
		T	—	—	—	—	15	43	42	—
		B	—	—	—	—	4	29	67	—

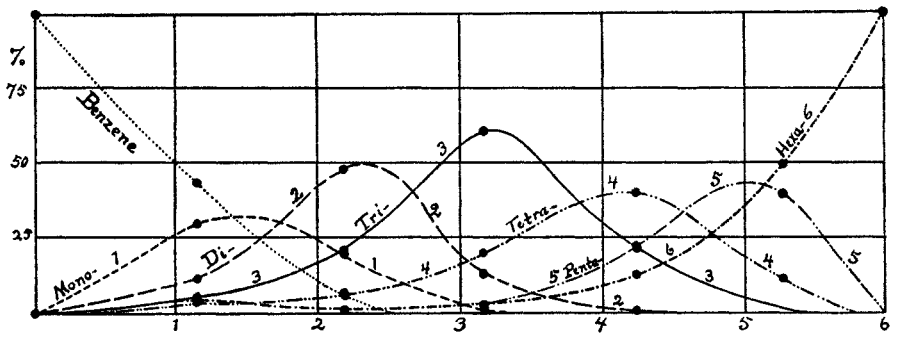

FIG. 1. MOLES OF ETHYLENE INTRODUCED. MOLE PERCENTAGES OF ETHYLATION PRODUCTS PRESENT AT DIFFERENT STAGES OF ETHYLATION

previously. It actually decreases during the introduction of the second and third moles of ethylene.

Benzene-aluminum chloride ratio. There has been a wide variation in the

benzene-aluminum chloride ratio in ethylation experiments by various authors. Balsohn (1) used 14:1, while 1.4:1 has been recommended for the preparation of 1,3,5-triethylbenzene (2). In Table II are the results of runs in which this ratio was varied from 4 moles of benzene to 1 of aluminum chloride to 23:1, 3 moles of ethylene being added in each. The runs in which this ratio is less than 10 show little difference. More aluminum chloride produces more triethyl- with a higher percentage of the 1,3,5-isomer and less of the di- and penta-ethyl.

Temperature effect. In Table III are data for two runs at a temperature lower than usual and for two at a higher. Since the reaction does not start well at

TABLE II

EFFECTS OF VARYING THE BENZENE-ALUMINUM CHLORIDE RATIO. DISTRIBUTION OF 3 MOLES OF ETHYLENE AND THE COMPOSITIONS OF THE TOP AND BOTTOM LAYERS. ALSO THE PERCENTAGE OF THE 1,3,5-ISOMER IN THE TRIETHYL FRACTION

NO.	$C_6H_6/AlCl_3$		BENZENE	MONO-	DI-	TRI-	TETRA-	PENTA-	HEXA-	SYM.
6	4	E		0.1	5	60	30	1.4	3.5	
		T	0.4	0.6	10	63	24	1	1	65
		B	—	—	1	64	29	1	5	75
7	6.3	E		0.1	5	63	27	1	3.8	
		T	0.6	0.4	9	67	22	1	0.4	62
		B	—	—	5	67	20	1	7	77
8	9	E		0.1	6	60	28	2.5	3.2	
		T	0.8	0.5	11	65	22	1	0.2	58
		B	—	—	1	56	24	5	14	71
9	18	E		0.2	9	52	29	4	6	
		T	0.3	0.8	16	56	23	2	2	48
		B	—	—	—	50	24	9	17	67
10	20	E		0.4	10	51	27	6	5	
		T	0.5	1.5	17	54	21	4	2	48
		B	—	—	—	53	25	8	13	—
11	23	E		0.2	9	45	28	12	5	
		T	0.3	0.9	17	50	22	8	2	48
		B	—	—	—	43	23	10	14	—

the lower temperature and since benzene boils below the higher, all of these were started as usual and the temperatures adjusted as soon as circumstances would permit. The distribution of the ethylene is shown in Figs. 2 and 3. The results at 95° are much like those at 75°, the usual temperature, but those at 55° are markedly different, there being less tri- and much more hexaethyl.

The effect of water. A small amount of water has a remarkable accelerating effect on the absorption of ethylene in the early stages of the reaction as is shown in Fig. 4. With 0.2% the rate starts to fall off at 1.5 mole, with 0.5% at 1.1 and with 1% at 0.9 mole while with 2% the absorption starts well but soon ceases

TABLE III

EFFECT OF TEMPERATURE. DISTRIBUTION OF THE ETHYLENE AND THE COMPOSITIONS OF THE TOP AND BOTTOM LAYERS

NO.	TEMP., °C	MOLES C_2H_4		BENZENE	MONO-	DI-	TRI-	TETRA-	PENTA-	HEXA-	SYM.
12	55	2.09	E		9	28	27	9	11	16	
			T	21	20	30	15	5	5	4	15
			B	—	11	25	44	1	6	13	64
13	95	2.17	E		8	45	41	3	0.3	3	
			T	2	17	51	28	2	0.1	0	65
			B	—	16	33	39	0.3	0.4	11	90
14	55	3.03	E		2	17	31	12	14	24	
			T	8	8	30	27	10	7	10	15
			B	—	1	7	50	1	16	25	59
15	95	3.22	E		0.1	6	59	28	3	4	
			T	0.1	0.4	11	64	23	1	0.5	62
			B	—	—	—	55	17	7	20	62

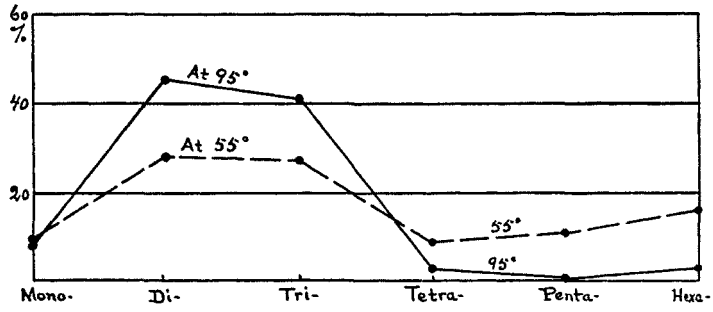

FIG. 2. TEMPERATURE EFFECT. PERCENTAGE DISTRIBUTION OF ETHYLENE WHEN TWO MOLES ARE INTRODUCED AT TWO DIFFERENT TEMPERATURES

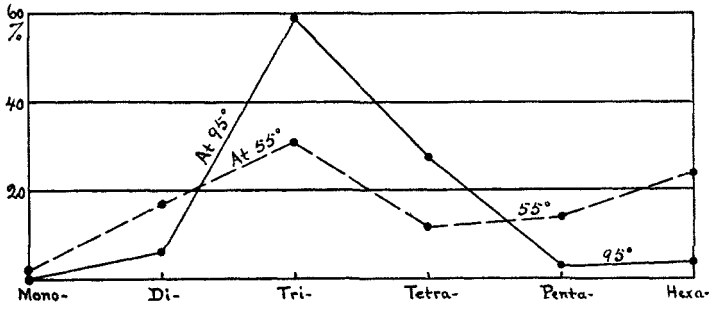

FIG. 3. TEMPERATURE EFFECT. PERCENTAGE DISTRIBUTION OF ETHYLENE WHEN THREE MOLES ARE INTRODUCED AT TWO DIFFERENT TEMPERATURES

entirely. The ethylene was admitted as fast as it was absorbed instead of at the usual constant rate. Runs had to be made changing other conditions to

get at the reason for the abnormal results of Runs 18 and 19 which showed large amounts of hexa- and small amounts of tri-ethyl. The results are in Table IV and some are plotted in Fig. 5. With reference to the distribution of the ethylene these two-mole runs fall into two classes, the normal in which over 40% of the ethylene appears in the diethyl and only 2–4% in the hexaethyl and those in which about 20% is in the di- and 37–50% in the hexa-ethyl.

Speed of ethylation. A run was made with the benzene-aluminum chloride ratio 6.3 and stirring at 12,000 r.p.m. After 1.7 moles of ethylene had been added, the absorption was at the rate of 1622 cc., or 0.07 mole, per minute per mole of benzene, or 18 volumes to one of the original benzene. This is double the rate previously attained, and about 20 times the rate used by Smith and Guss with ethyl chloride (3).

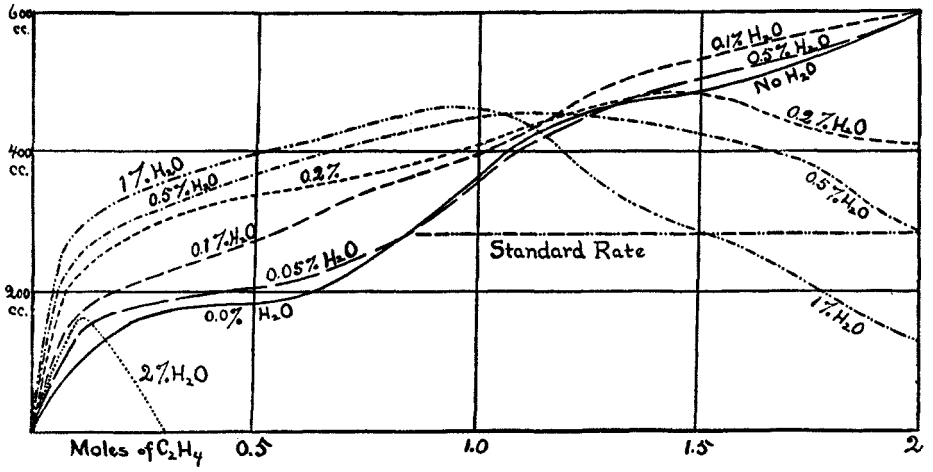

FIG. 4. EFFECT OF WATER. RATES OF ABSORPTION OF ETHYLENE IN THE PRESENCE OF DIFFERENT AMOUNTS OF WATER

Discussion of results. Taken as a whole, the results give strong support to the view that a part of the benzene is alkylated completely, and that then the hexaethyl is broken down largely to 1,3,5-triethylbenzene. If the ethylene is introduced at a moderate rate the tearing down of the highly alkylated products may keep pace with their building up and the results will be such as are represented in Fig. 1. It is possible that the proportions there shown would have been altered somewhat if the stirring and heating had been prolonged after all of the ethylene was in. When the amount of catalyst is small, the temperature low, or the ethylene is crowded in, the redistribution lags behind; more of the hexa- remains and less of the 1,3,5-triethyl is formed. When the conditions of the ethylation are considered this seems reasonable. The ethylation is concentrated on the hydrocarbons that are present in the heavy catalytic layer. If the amount of this is small or if diffusion between it and the top layer is poor the ethylene will not be distributed.

TABLE IV

EFFECTS OF WATER AND OF OTHER VARIABLES. DISTRIBUTION OF THE ETHYLENE AND THE COMPOSITIONS OF THE TOP AND BOTTOM LAYERS

NO.	WATER	C_6H_6/$AlCl_3$	RATE	C_2H_4 MOLES		BENZENE	MONO-	DI-	TRI-	TETRA-	PENTA-	HEXA-	SYM.
16	0.0	13	[a]	2.23	E		8	44	35	7	2	4	
					T	1	18	51	24	4	1	1	47
					B	—	10	29	47	1	3	10	70
17	0.05	13	[a]	2.15	E		9	44	36	5	2	4	
					T	2	20	49	24	3	1	1	52
					B	—	11	31	44	1	5	8	84
18	0.10	13	[a]	2.16	E		11	22	19	8	3	37	
					T	19	26	23	13	5	1	13	5
					B	—	12	37	24	1	4	22	72
19	0.20	13	[a]	2.36	E		11	19	14	11	3	42	
					T	15	27	22	11	7	1	17	3
					B	—	15	30	20	1	9	25	82
20	0.50	13	[a]	2.50	E		10	22	19	11	1	37	
					T	9	27	27	14	7	1	15	6
					B	—	13	33	34	1	2	17	77
21	0.20	13	1[c]	2.20	E		8	44	38	4	3	3	
					T	1	17	52	26	2	1	1	52
					B	12	13	23	43	2	1	6	85
22	0.0	13	2.1	2.52	E		10	19	15	4	2	50	
					T	14	25	24	12	3	1	21	3
					B	—	19	31	23	—	9	18	78
23	0.0	6.3	2.1	2.21	E		7	45	44	1	1	2	
					T	1	15	51	30	1	1	1	60
					B	—	13	30	48	1	2	6	75
24[b]	0.0	13	2.1	2.17	E		8	44	39	4	2	3	
					T	2	17	50	27	2	1	1	54
					B	6	18	23	43	2	1	7	79

[a] The ethylene was added as fast as it was taken up.

[b] The stirring was raised to 12,000 r.p.m.

[c] 1 = 268 cc. per mole per minute.

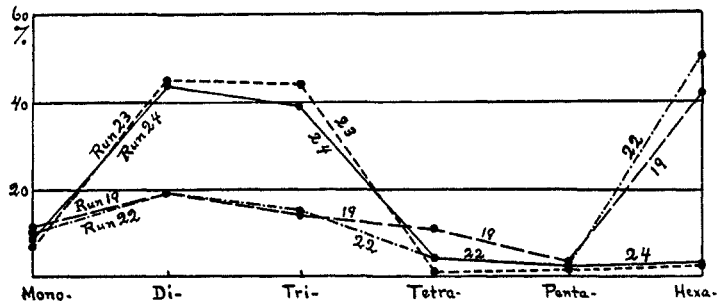

FIG. 5. DISTRIBUTION OF ETHYLENE WHEN TWO MOLES ARE INTRODUCED UNDER DIFFERENT CONDITIONS

The remarkably high hexa- and low 1,3,5-triethyl- found in Runs 18, 19, and 20 were at first attributed to the influence of the water but the normal results of Run 21 with water present indicate that the cause was rather the crowding in of the ethylene. In Run 22 the initial ethylene absorption was speeded up with hydrogen chloride, and results obtained similar to those of Run 19. The high rate of ethylene introduction was taken care of in Run 23 by doubling the amount of aluminum chloride and in Run 24 by increasing the rate of stirring. The distribution of the ethylene is dependent on the diffusion between the two layers and the diffusion, in turn, is proportional to the area of

TABLE V

THE MOLE PERCENTAGES OF HEXA-, 1,3,5-TRI-, AND 1,2,4-TRIETHYL. ALSO *r*, THE RATIO OF THE CONCENTRATION OF THE 1,3,5-TRIETHYL IN THE BOTTOM LAYER TO THAT IN THE TOP

NO. RUN	HEXA-	1,3,5-	1,2,4-	*r*
Two moles of ethylene				
23	0.9	20	12	2.0
24	1.2	16	12	2.3
21	1.2	15	13	2.7
17	1.2	14	12	3.0
16	1.4	13	13	2.9
18	13	1.5	12	26
20	15	2.0	14	31
19	18	1.2	10	50
22	21	1.2	12	50
Three moles of ethylene				
8	1.7	38	26	1.1
6	1.9	44	21	1.1
7	2.0	43	23	1.3
15	2.0	39	24	0.9
10	2.4	27	27	1.4
11	2.8	25	25	1.2
3	3.0	35	24	1.1
9	3.0	28	28	1.3
14	12.2	7	24	7.4

the interface. Breaking the catalytic layer up into smaller droplets has the same effect as increasing its amount.

In Table V the results of two-mole runs are grouped together, arranged according to the amounts of hexaethyl present. In each run the triethyl is divided into its symmetrical and unsymmetrical parts and the ratio of these in the two layers is shown. The same is done for the three-mole runs. During the addition of the third mole of ethylene there is opportunity for the redistribution of the alkyls in the products already formed. Hence these runs should not differ as much as those with two. This is found to be true.

The total amount of the triethyl decreases from top to bottom in each part of the table but the amount of the unsymmetrical is markedly constant, regardless of the conditions. With 2 moles of ethylene the unsymmetrical is between 10% and 13% while the 1,3,5-isomer varies from 1.2% to 20%. Under conditions which do not favor redistribution, the symmetrical is relatively scarce and is concentrated in the bottom layer. With 3 moles of ethylene the results are similar but not so striking.

A high yield of 1,3,5-triethylbenzene may be obtained by passing in 3 moles of ethylene with even a low amount of aluminum chloride provided the temperature is high or the agitation vigorous. A triethyl fraction containing better than 95% of the unsymmetrical isomer may be obtained by taking the top layer of a low-temperature run in which the ethylene absorption rate is kept at the maximum.

SUMMARY

1. It has been found that the conditions of the ethylation of benzene, temperature, rate of introduction of ethylene, speed of stirring, and amount of aluminum chloride catalyst, greatly influence the proportions of the products.

2. These effects have been studied so as to throw light on the mechanism of the reaction.

3. The results appear to show that a part of the benzene is carried to the hexaethyl and that this is then dealkylated to a sort of equilibrium mixture containing much of the symmetrical triethylbenzene.

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[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE TRANSAMINATION REACTION. THE EFFECT OF VARIOUS NUCLEAR SUBSTITUTED PHENYLAMINOACETIC ACIDS ON THE COURSE OF THE REACTION[1]

EDWARD K. HARVILL[2] AND ROBERT M. HERBST[2]

Received August 14, 1943

The results of previous transamination studies in chemical systems were explained by the assumption of the formation of a Schiff base-like intermediate as the initial stage of the interaction of *alpha*-amino acids with *alpha*-keto acids (1, 2). This was followed by the elimination of carbon dioxide, generally accompanied by the shift of the carbon-nitrogen double bond from the ketonic side of the Schiff base to the amino acid side. Hydrolysis then produced a new amino acid and an aldehyde. In certain reactions two aldehydes were formed, necessitating the assumption that the intermediate Schiff base could be decarboxylated to a lesser extent and hydrolyzed without shift of the carbon-nitrogen double bond, thus regenerating the original amino acid and forming the aldehyde derived from the keto acid.

In the reaction between pyruvic acid and α-aminophenylacetic acid, carbon dioxide, alanine, and only one aldehyde, benzaldehyde were formed. On the other hand, pyruvic acid and α-amino-*p*-methoxyphenylacetic acid produced, in addition to carbon dioxide and alanine, two aldehydes, anisaldehyde and acetaldehyde. In general, it has been observed that carbon dioxide evolution is much more rapid in transaminations with arylaminoacetic acids than with aliphatic amino acids.

$$\begin{matrix} p\text{-}CH_3OC_6H_4CH(NH_2)COOH \\ + \\ CH_3COCOOH \end{matrix} \longrightarrow \begin{cases} \xrightarrow{(I)} p\text{-}CH_3OC_6H_4CHO + CO_2 + CH_3CH(NH_2)COOH \\ \xrightarrow{(II)} CH_3CHO + CO_2 + p\text{-}CH_3OC_6H_4CH(NH_2)COOH \end{cases}$$

It was of interest to determine the effect of nuclear substituents in the arylaminoacetic acids on the speed and course of the reaction. For this purpose the reactions between pyruvic acid and *o*-chloro-, *o*-methoxy-, *o*-hydroxy-, *p*-chloro-, *p*-methoxy-, and *p*-hydroxy-phenylaminoacetic acids as well as furylaminoacetic acid were studied. Phenylaminoacetic acid was included in the series for comparison purposes.

In Figures 1 and 2 the rates of carbon dioxide evolution in the various systems are represented graphically. It will be observed that carbon dioxide was evolved more rapidly in transaminations with the *ortho* substituted arylaminoacetic acids than with the *para* substituted compounds. In the *para* substituted series, as in the *ortho* series, the rate of carbon dioxide formation fell in the well defined sequence: Cl > CH_3O > OH

[1] Abstracted from a thesis presented by Edward K. Harvill to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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A similar sequence was found by Shoppee (3, 4, 5) in determining the mobility of methyleneazomethine systems which involved a reversible prototropic change of various substituted Schiff bases. These results were interpreted in accordance with the ideas of Ingold and his collaborators (6, 7) by assuming that an electron recession from the side chain caused the ionization of a proton from the *alpha* carbon atom with the formation of an electromeric ion in which the anionic charge was distributed between the *alpha* and *gamma* carbon atoms. The position taken up by the proton on recombination with the electromeric ion is deter-

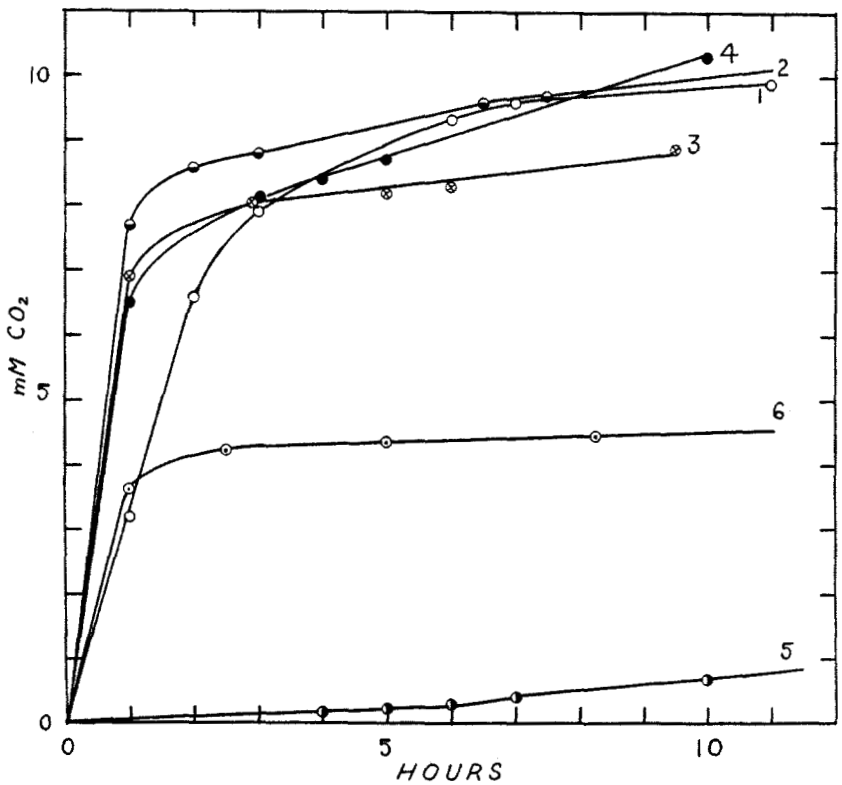
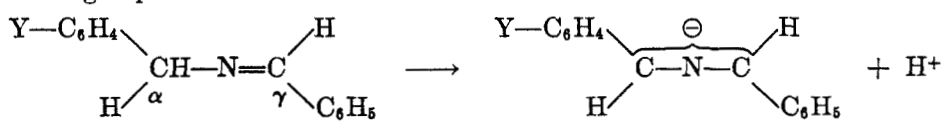


Figure 1. Carbon dioxide evolution from 30 mM pyruvic acid and 10 mM of (1) phenylaminoacetic acid, (2) *o*-chlorophenylaminoacetic acid, (3) *o*-methoxyphenylaminoacetic acid, (4) *o*-hydroxyphenylaminoacetic acid, (5) pyruvic acid alone, and (6) furylaminoacetic acid.

mined by the electron distribution, which in turn depends in part upon the nature of the group Y.



Shoppee found that the effect of nuclear substitutions in either the *meta* or *para* position varied with the electron attracting power of the substituted phenyl

group and could be correlated with the dipole moment. The effect of the substituents fell into the order

$$NO_2 > Cl > I > OMe > Me > NMe_2.$$

Transamination reactions appear to involve methyleneazomethine systems similar to those studied by Ingold. Knoop and Martius' (8) synthesis of an imino dicarboxylic acid by the catalytic hydrogenation of a solution of arginine and pyruvic acid favors the assumption of a Schiff base-like intermediate.

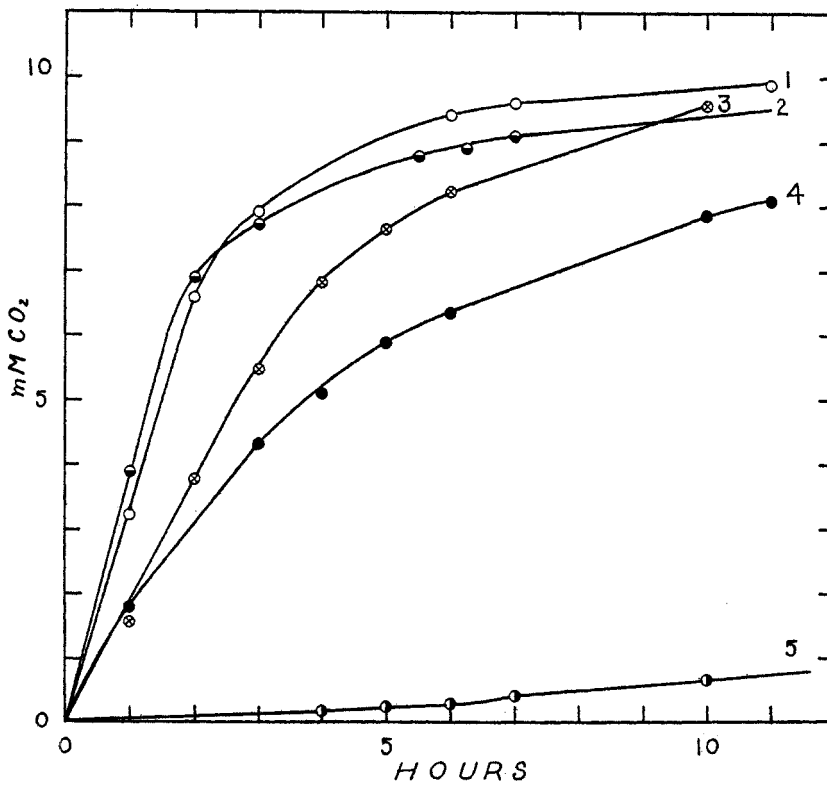
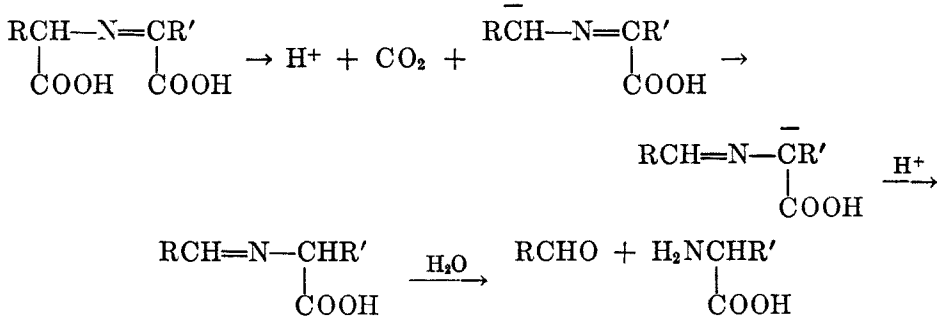


Figure 2. Carbon dioxide evolution from 30 mM pyruvic acid and 10 mM of (1) phenylaminoacetic acid, (2) *p*-chlorophenylaminoacetic acid, (3) *p*-methoxyphenylaminoacetic acid, (4) *p*-hydroxyphenylaminoacetic acid, and (5) pyruvic acid alone.

Brewer and Herbst (9) have shown that the reaction between ethyl pyruvate and ethyl aminophenylacetate is catalyzed by sodium ethoxide and that mineral acids cause a marked decrease in the speed of the reaction. Their reaction appears to be closely analogous to the true prototropic systems of Ingold and Shoppee in that it depends upon the dissociation of a proton from the intermediate Schiff base.

However, transamination reactions in which the carboxyl groups of both the *alpha*-amino acid and the *alpha*-keto acid are free differ from the true methylene-

azomethine systems. The reactions are unidirectional and proceed with the evolution of carbon dioxide. The presence of mineral acids has little effect on the reactions, whereas the addition of alkali inhibits them almost completely (1). These systems appear to involve an electrotropic change as shown by Herbst and Rittenberg (10), rather than a prototropic change in which proton transfer is necessary. They suggested that the reaction involved the decarboxylation of the intermediate Schiff base-like compound with a simultaneous shift of the double bond to form an electrotropic carbonium ion. The process was completed by the addition of a proton from the medium to the carbonium ion and hydrolysis of the resulting Schiff base.



Since decarboxylation is presumed to occur simultaneously with a shift of the double bond from the *beta, gamma* to the *alpha, beta* position, the rate of evolution of carbon dioxide may be considered a measure of the electrotropic change.

Although the mechanism of transamination differs from that of the methylene-azomethine systems studied by Shoppee, our results show that similar factors will influence the rates of reaction in both cases. In both systems reaction is facilitated by the withdrawal of electrons from the side chain, the greater the electron attracting effect of the group Y-C_6H_4- the more rapid is the conversion. The effects of the various substituents in the benzene ring upon the rate of decarboxylation fall into the sequence determined by Shoppee.

Relatively little work has been done with regard to the effect of *ortho* substituents in the benzene ring on the rate of side-chain reactions of this type. In the cases here reported all the *ortho* substituents were more effective than the *para* substituents in promoting decarboxylation. This was not surprising since the *ortho* substituents are closer to the seat of the reaction than the *para* substituents which transmit their electronic effects through a system of conjugated double bonds. For the entire series studied carbon dioxide evolution was facilitated by the groups in the following order:

$$o\text{-Cl} > o\text{-CH}_3\text{O} > o\text{-OH} > p\text{-Cl} > p\text{-CH}_3\text{O} > p\text{-OH}.$$

The simplicity of the method recommends it for further use in studying the electronic effects of various groups and allows a direct comparison not only of aryl but also alkyl groups, a possibility not realized in the reversible methylene-azomethine systems.

Although the effects of various substituents in the benzene ring on the rate of the reaction were significant, their influence on the course of the reaction was inconsistent. When R was *o*-methoxyphenyl, *p*-methoxyphenyl, *p*-hydroxyphenyl, and furyl, two aldehydes were formed in addition to alanine and carbon dioxide. When R was *o*-chlorophenyl, *p*-chlorophenyl, and *o*-hydroxyphenyl, only the aromatic aldehyde was formed in addition to alanine and carbon dioxide. Acetaldehyde is not formed in an aqueous solution of pyruvic acid under the experimental conditions. Furthermore, the fact that acetaldehyde is formed only in a few of our systems shows that the reaction between alanine and pyruvic acid is too slow to account for its formation in these reactions. In all the reactions scheme I was followed predominantly. The aromatic aldehydes were isolated in yields of 46–80% whereas the maximum yield (15%) of acetaldehyde was obtained in the reaction with furylaminoacetic acid. When R was a substituted phenyl group the highest yield of acetaldehyde was 6.5%.

The formation of acetaldehyde can be explained by decarboxylation and hydrolysis of the Schiff base without shift of the double bond and unaccompanied by an electron shift. Benzoylformic acid and alanine have been reported (2) to produce only a trace of benzaldehyde and carbon dioxide. In this case the initial intermediate is stable since the double bond is conjugated with the benzene ring and the formation of benzaldehyde probably is due to the slow decomposition of the postulated intermediate Schiff base.

EXPERIMENTAL

Transamination reactions. The apparatus described in a previous paper (2) was used in all the transamination reactions.

In all the experiments 10 mM of amino acid and 100 cc. of water were placed in the reaction flask and the system was connected. Nitrogen gas washed with 40% potassium hydroxide and concentrated sulfuric acid was passed through a capillary tube and into the reaction flask at a constant rate of 1.78 liters per hour. The amino acid solution was kept at a gentle boil and 30 mM of pyruvic acid was added through the addition tube. The reaction was considered to start with the addition of pyruvic acid and the rate was followed by weighing periodically the absorption tube charged with 40% potassium hydroxide and concentrated sulfuric acid to determine the carbon dioxide formed. The rates of carbon dioxide evolution are shown in Figures 1 and 2.

Upon the completion of the reaction, the volatile aldehydes absorbed by the bisulfite trap were estimated quantitatively by titrating the excess and bound bisulfite with standard iodine solution (11). The titrated solution was then distilled into a solution of dimedon (dimethyldihydroresorcinol). The dimedon derivatives were identified by melting points and by mixed melting points with authentic specimens.

The reaction mixture was extracted with ether to remove aromatic aldehydes. The ether layer was washed first with 5% sodium carbonate to remove pyruvic acid, then with water, dried over anhydrous sodium sulphate and evaporated. The residual aldehyde was characterized as a derivative whose identity was confirmed by its melting point and mixed melting point with an authentic specimen.

The reaction mixture was then extracted continuously with ether for 48–72 hours to remove pyruvic acid. The water solution was evaporated almost to dryness and the alanine was precipitated by the addition of alcohol. It was characterized by conversion into α-phenylureidopropionic acid whose identity was established by its melting point and mixed melting point with an authentic specimen.

The results of these reactions are recorded in Table I.

Hydantoins. The hydantoins were prepared by a method essentially that of Bucherer and Lieb (12) by heating the appropriate aldehyde, potassium cyanide, and ammonium carbonate in aqueous alcoholic solution.

5-(*o*-Hydroxyphenyl)hydantoin could not be prepared by the above general procedure. With salicylaldehyde only a red gummy substance was secured from which no definite product could be isolated. Hydrolysis of 10 g. of 5-(*o*-methoxyphenyl)hydantoin with 30 cc. of hydriodic acid (sp. gr. 1.5) by boiling under reflux for 3 to 5 hours gave on cooling 5.2 g. (56% yield) of the 5-(*o*-hydroxyphenyl)hydantoin. Recrystallization from water gave a product melting at 240–244° with decomposition.

5-Furylhydantoin melting at 101° was invariably obtained from furfural. A sample of the hydantoin stored for about one month in a clear glass bottle at room temperature was found to melt at 147°. The two forms are interconvertible. Several recrystallizations of

TABLE I

PRODUCTS OF THE REACTION BETWEEN PYRUVIC ACID AND α-ARYLAMINOACETIC ACIDS[a]

30 mM Pyruvic acid; 10 mM Amino acid; 100 cc. of Water

R		ACETALDEHYDE, YIELD, mM[b]	ALANINE, YIELD, mM[c]	RCHO			
				YIELD, mM	ISOLATED AS	M.P., °C	REF.
R_1	*p*-Methoxyphenyl	0.19[c]	8.9	6.5	*p*-Nitrophenylhydrazone	160 dec.	14a
R_2	*o*-Methoxyphenyl	0.65[c]	5.7	7.3	2,4-Dinitrophenylhydrazone	249–250	14b
R_3	*p*-Chlorophenyl	None	9.6	4.6	Phenylhydrazone	126–127	15b
R_4	*o*-Chlorophenyl	None	8.6	7.6	Phenylhydrazone	84	15a
R_5	*p*-Hydroxyphenyl	0.35[d]	6.9	5.2	Phenylhydrazone	178 dec.	15b
R_6	*o*-Hydroxyphenyl	None	9.2	8.0	2,4-Dinitrophenylhydrazone	248–252 dec.	14c
R_7	Furyl	1.51[e]	[f]	[f]			

[a] See Figures 1 and 2 for carbon dioxide evolution.

[b] Acetaldehyde determined quantitatively by titration of the bisulfite trap.

[c] Identified as the dimedon derivative m.p. 138–140°.

[d] Identified as acetaldehyde *p*-nitrophenylhydrazone m.p. 126–127°.

[e] Identified as α-phenylureidopropionic acid, m.p. 168–169° with decomposition.

[f] Only a resinous brown product could be isolated from the reaction mixture.

one form from water inoculating each time with the other form effected conversion to the seeding form. The furylhydantoins turn pink in the presence of light, the lower-melting form changing more rapidly than the higher. The higher-melting form is stable on storage. When kept at 30° for five days the melting point of the lower-melting form had changed from 101° to 142–144°. The higher-melting form showed no change of melting point under the same conditions. Only the form melting at 147° has been previously reported (13).

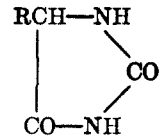
The melting points, yields, and analyses of the hydantoins are recorded in Table II.

Amino acids. The amino acids were prepared by the hydrolysis of the hydantoins with barium hydroxide.

The *para* substituted phenylaminoacetic acids were more insoluble in water than the corresponding *ortho* substituted compounds. Recrystallization of the *p*-methoxy- and *p*-hydroxy-phenylaminoacetic acids from water gave compounds that melted with decomposition. Recrystallization of the same compounds from dilute alcohol gave products that sublimed. The sublimation point was much lower than the melting point.

TABLE II

5-ARYLHYDANTOINS



R[i]	FORMULA	M.P., °C[a]	YIELD, %	NITROGEN, %	
				Calc'd	Found
R_1	$C_{10}H_{10}N_2O_3$	195[d]	70	13.59	13.74
R_2	$C_{10}H_{10}N_2O_3$	189[e]	99	13.59	13.67
				58.25[b]	58.46[b]
				4.86[c]	4.82[c]
R_3	$C_9H_7ClN_2O_2$	191	69	13.33	13.24
R_4	$C_9H_7ClN_2O_2$	175–176[f]	63	13.33	13.38
R_5	$C_9H_8N_2O_3$	269–270 dec.[g]	75	14.58	14.43
R_6	$C_9H_8N_2O_3$	240–244 dec.		14.58	14.43
				56.25[b]	56.28[b]
				4.17[c]	4.31[c]
R_7	$C_7H_6N_2O_2$	101[h]	65	16.85	16.79
		147			16.76

[a] All melting points corrected.

[b] Percentage carbon.

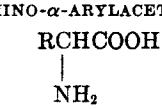
[c] Percentage hydrogen.

[d–h] Henze and Speer, *J. Am. Chem. Soc.*, **64**, 523 (1942) give melting points 191.5°, [e] 186–187°, [f] 176°, [g] 263° dec., [h] 147°.

[i] See Table I.

TABLE III

α-AMINO-α-ARYLACETIC ACIDS



R[j]	FORMULA	M.P., °C[a]	YIELD, %	NITROGEN, %	
				Calc'd	Found
R_1	$C_9H_{11}NO_3$	248–285 dec.[d]	51	7.72	7.70
		230 sub.			7.67
R_2	$C_9H_{11}NO_3 + H_2O$	161–162	74	7.02	7.02
				54.27[b]	54.39[b]
				6.53[c]	6.48[c]
R_3	$C_8H_8ClNO_2$	261–262 dec.	47	7.56	7.72
R_4	$C_8H_8ClNO_2$	219.5	77	7.56	7.67
R_5	$C_8H_9NO_3$	240–241 dec.[e]	41	8.38	8.44
		229 sub.			8.28
R_6	$C_8H_9NO_3$	194–195 dec.	35	8.38	8.32
R_7	$C_6H_7NO_3$	212–213 dec.	52	9.93	9.86

[a] All melting points corrected.

[b] Percentage carbon.

[c] Percentage hydrogen.

[d] Tieman and Kohler, *Ber.*, **14**, 1979 (1881) give 225° sub.

[e] Fromherz, *Z. physiol. Chem.*, **70**, 353 (1910) gives 225° sub.

[f] See Table I.

TABLE IV

α-PHENYLUREIDO-α-ARYLACETIC ACIDS

RCHCOOH
|
NHCONHC$_6$H$_5$

R[f]	FORMULA	M.P., °C[a]	NITROGEN, %	
			Calc'd	Found
R_1	$C_{16}H_{16}N_2O_4$	196 dec.[d]	9.33	9.44
R_2	$C_{16}H_{16}N_2O_4$	186.2	9.33	9.21
			64.00[b]	64.00[b]
			5.32[c]	4.97[c]
R_3	$C_{15}H_{13}ClN_2O_3$	185.5	9.21	9.00
R_4	$C_{15}H_{13}ClN_2O_3$	177–179	9.21	9.19
R_5	$C_{15}H_{14}N_2O_4$	192 dec.[e]	9.79	9.96
R_7	$C_{13}H_{12}N_2O_4$	147 dec.	10.76	10.75

[a] All melting points corrected.
[b] Percentage carbon.
[c] Percentage hydrogen.
[d] Tieman and Kohler, *Ber.*, **14**, 1979 (1881), give melting points "about 198°".
[e] Fromherz, *Z. physiol. Chem.*, **70**, 353 (1910), gives m.p. 193°.
[f] See Table I.

TABLE V

5-ARYL-3-PHENYLHYDANTOINS

RCH—NH
| \
| CO
| /
CO—NC$_6$H$_5$

R[e]	FORMULA	M.P., °C[a]	NITROGEN, %	
			Calc'd	Found
R_1	$C_{16}H_{14}N_2O_3$	179	9.92	9.73
R_2	$C_{16}H_{14}N_2O_3$	134	9.92	9.79
			68.08[b]	68.05[b]
			4.96[c]	5.19[c]
R_3	$C_{15}H_{11}ClN_2O_2$	167–168	9.79	9.94
R_4	$C_{15}H_{11}ClN_2O_2$	187.5	9.79	9.88
R_5	$C_{15}H_{12}N_2O_3$	171 and 201[d]	10.44	10.26
R_6	$C_{15}H_{12}N_2O_3$	224–225	10.44	10.21

[a] All melting points corrected.
[b] Percentage carbon.
[c] Percentage hydrogen.
[d] Melts at 171°. Solidifies immediately and then melts at 201°. After cooling it remelts at 201°.
[e] See Table I.

α-Amino-*o*-methoxyphenylacetic acid was found to crystallize with a molecule of water and melted at 161–162°. Attempts to secure the anhydrous form were unsuccessful. Upon drying at sufficiently high temperature, even under reduced pressure, to remove the water, d ep seated decomposition of the compound took place.

The copper salt of α-amino-*o*-methoxyphenylacetic acid was obtained in the form of light blue needles.

Anal. Calc'd for $(C_9H_{10}O_3N)_2Cu + 2H_2O$: Cu, 13.83. Found: Cu, 13.74, 13.70.

Decomposition of the salt with hydrogen sulphide led to the original acid as shown by nitrogen analysis and mixed melting point with the original material.

Only the aminohydroxyphenylacetic acids gave a coloration with ferric chloride. α-Amino-*p*-hydroxyphenylacetic acid gave a pale violet coloration with ferric chloride, while α-amino-*o*-hydroxyphenylacetic acid gave a deep blue coloration.

The melting points, yields and analyses of the amino acids are recorded in Table III.

α-Phenylureido acids. The α-phenylureido acids were prepared from the amino acid by the usual treatment with phenyl isocyanate in alkaline solution.

α-Amino-*o*-hydroxyphenylacetic acid formed 3-phenyl-5-(*o*-hydroxyphenyl)hydantoin directly. Acidification of the alkaline reaction mixture produced a gelatinous substance that was extremely difficult to filter. On standing several days in the acid solution, the material became crystalline, m.p. 224–225°. Boiling the gelatinous precipitate with hydrochloric acid caused immediate precipitation of the hydantoin.

The melting points and analyses of the phenylureido acids are recorded in Table IV.

5-Aryl-3-phenylhydantoins. The phenylureides were converted to the hydantoins by boiling with hydrochloric acid.

5-Furyl-3-phenylhydantoin could not be prepared. Phenylureidofurylacetic acid decomposed to a gummy mass when heated with hydrochloric acid.

5-(*p*-Hydroxyphenyl)-3-phenylhydantoin melted at 171°, solidified almost instantaneously, and then melted again at 201°. After solidifying it melted again at 201°.

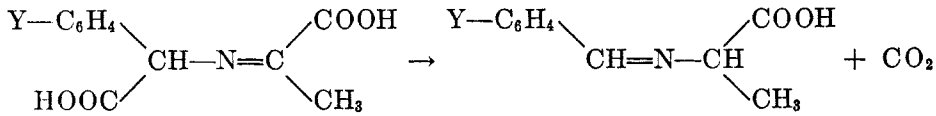
The melting points and analyses of the 5-aryl-3-phenyl hydantoins are recorded in Table V.

SUMMARY

1. In the reaction between pyruvic acid and α-amino-*p*-hydroxyphenyl-, -*p*-methoxyphenyl-, and -*o*-methoxyphenyl-acetic acids both acetaldehyde and an aromatic aldehyde are formed in addition to alanine and carbon dioxide.

2. In the reaction between pyruvic acid and α-amino-*p*-chlorophenyl-, -*o*-chlorophenyl-, and -*o*-hydroxyphenyl-acetic acids only an aromatic aldehyde is formed together with alanine and carbon dioxide.

3. In the system



the rate of carbon dioxide formation is greater the greater the dipole moment of YC_6H_4. The effect of the same group is enhanced by shifting it from the *para*- to the *ortho* position.

4. In their effect upon the rate of carbon dioxide formation the groups studied fall into the order

$$o\text{-Cl} > o\text{-CH}_3\text{O} > o\text{-OH} > p\text{-Cl} > p\text{-CH}_3\text{O} > p\text{-OH}.$$

5. *o*-Chlorophenyl, *p*-chlorophenyl, *o*-methoxyphenyl, *p*-methoxyphenyl, *o*-hydroxyphenyl, *p*-hydroxyphenyl, and furyl aminoacetic acids have been prepared by the hydrolysis of the corresponding hydantoins. They have been characterized as the substituted *alpha*-phenylureidoacetic acids and substituted 3,5-diphenylhydantoins.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

SOME REACTIONS OF NITRILES AS ACID ANAMMONIDES[1]

EDWARD L. HÖLLJES, JR. AND E. C. WAGNER

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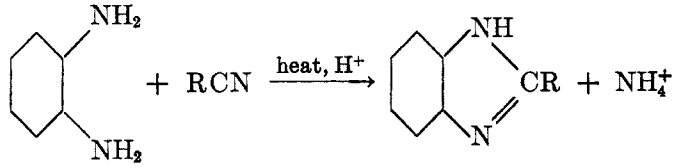
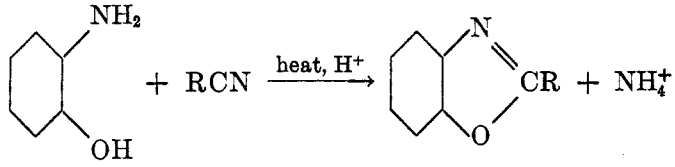
Structurally the nitriles may be regarded as nitrogen system "anhydrides" of the amidines (ammono-acids), though Franklin's term "anammonides" more properly suggests the relationship involved. There are no exact oxygen-system counterparts of the nitriles recognizable from formal structural considerations, and this may render functional analogies not immediately obvious. The reactions of nitriles include some which suggest a functional similarity between nitriles and carboxylic acid anhydrides. Examples (1) include the reactions of nitriles with water, alcohols, hydrogen sulfide, mercaptans, ammonia, and amines; the reaction of acetic anhydride with potassium hydroxide and that of benzonitrile with potassium amide, to yield respectively potassium acetate and potassium ammonobenzoate (potassium benzamidine) (2), are analogous. Other reactions of nitriles indicate a functional similarity of nitriles to aldehydes and ketones. Examples (1) include analogous condensations with hydroxylamine, hydrazine, alkali-metal bisulfite, condensations of the aldol type, and the cyanohydrin reaction.

The analogy between nitriles (considered as ammono-acid "anhydrides" or acid anammonides) and acid anhydrides has now been extended by the demonstration that three well known ring closures of the Ladenburg type, familiarly effected by action of acid anhydrides, acids, amides, esters, or substituted amidines (3), can be effected also by action of nitriles. The essential reactions are the following:

I. Formation of the imidazole ring:

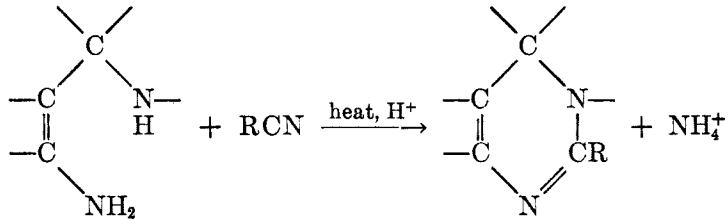


II. Formation of the oxazole ring:



[1] This paper is constructed from the dissertation submitted by Edward L. Hölljes, Jr. to the Graduate School of the University of Pennsylvania in partial satisfaction of the requirements for the degree of Doctor of Philosophy, June 1943.

III. Formation of the pyrimidine ring:



It was found that these reactions proceed only in presence of acid (the acidity of *o*-aminophenol suffices to promote a slow reaction), and that they proceed under anhydrous conditions, a fact which excludes the cyclical operation of water to generate *in situ* the corresponding amide or acid, to whose presence the ring closure could be attributed. Evidence was obtained to indicate the series of reactions through which the ring closure occurs, the initial step being the addition of proton to the nitrile to form the reactive cation: $RCN + H^+ \rightleftharpoons [RC{=}NH \leftrightarrow RC{\equiv}NH]^+$. The reaction in each of the three types studied appears to involve hydrogen ion catalysis. Discussion of the experimental findings follows.

I. FORMATION OF THE IMIDAZOLE RING

The Ladenburg ring closure, using *o*-diamines and acids (4, 12), acid anhydrides (5), or acyl halides (6), to form benzimidazoles, naphthimidazoles, etc., was recently extended into the nitrogen system by use of amidines as the acidic reactants (3). The relationships among acids, acid anhydrides, amidines, and nitriles, the first three of which can be used interchangeably in the Ladenburg reaction, are such as to suggest that nitriles can likewise effect the ring closure (*cf.* 16, 29). In preliminary experiments it became apparent that the desired reaction took place only in presence of acid. When *o*-phenylenediamine and benzonitrile were heated under reflux for twenty-four hours, or for six hours in a sealed tube at 200°, there was no evidence that a reaction had occurred. Substitution of the hydrochloride of *o*-phenylenediamine for the base led (by either procedure) to formation of 2-phenylbenzimidazole in good yield. The reaction was extended by use of other nitriles, both aliphatic and aromatic, the reactants being heated in sealed tubes. Yields of the corresponding 2-substituted benzimidazoles ranged from 27% to 72%. Results are summarized in Table I.

Experiments with benzonitrile, in which the quantities of acid present were varied (by use of *o*-phenylenediamine and its hydrochloride in suitable proportions), showed that reaction occurred with moderate rapidity when the acid present was at least equivalent to the nitrile. With less acid the reaction occurred, but at a decreased rate. In absence of acid no isolable amount of 2-phenylbenzimidazole was formed. The results on which these conclusions are based appear in Table II. The acid, which is indispensable to the success of the reaction, must be distributed among the bases present, but as a result of thermal dissociation and proton sharing among the nitrogen atoms it is available throughout the reaction, and hence functions cyclically. When the molar ratio of acid

to nitrile is unity, the former is progressively combined as ammonium chloride, which itself is mildly effective in promoting the reaction. An experiment with equivalent quantities of *o*-phenylenediamine, benzonitrile, and ammonium

TABLE I

FORMATION OF 2-SUBSTITUTED BENZIMIDAZOLES FROM *o*-PHENYLENEDIAMINE HYDROCHLORIDE AND NITRILES[a]

NITRILE	PRODUCT	YIELD		YIELD PURE, %	M.P., °C.
		Crude, g.	Pure, g.		
HCN[b]	Benzimidazole	0.22	0.14	5.9	170.5
CH_3CN	2-Methylbenzimidazole (7)	1.10	0.72	27.3	173.6
CH_3CH_2CN	2-Ethylbenzimidazole (7)	1.72	1.03	58.8	172
n-C_3H_7CN	2-*n*-Propylbenzimidazole (7)	3.15	2.27	71.0	157–159
n-C_4H_9CN	2-*n*-Butylbenzimidazole (7)	2.43	1.65	47.4	150
n-$C_5H_{11}CN$	2-*n*-Amylbenzimidazole (7)	2.65	1.88	50.0	162
C_6H_5CN	2-Phenylbenzimidazole (4)	2.85	2.80	72.4	287–288
p-$CH_3C_6H_5CN$	2-*p*-Tolylbenzimidazole (8)	3.01	2.95	70.9	266–269

[a] 0.02 mole of each reactant; 2 hours at 200° in sealed tube.

[b] KCN 0.01 mole and *o*-phenylenediamine hydrochloride 0.01 mole. The reaction mixture was extracted with 50 cc. of hot water containing 5 cc. of conc'd hydrochloric acid. The filtered extract was made alkaline with ammonium hydroxide, concentrated to 30 cc., and chilled for 2 hours. The benzimidazole was crystallized from water. The result of this experiment is not decisive, as the presence of hydrolysis products (e.g., formate) in the potassium cyanide might account for the small yield of benzimidazole.

TABLE II

EFFECTS OF AMOUNT OF ACID AND TIME OF HEATING UPON FORMATION OF 2-PHENYLBENZIMIDAZOLE FROM BENZONITRILE AND *o*-PHENYLENEDIAMINE

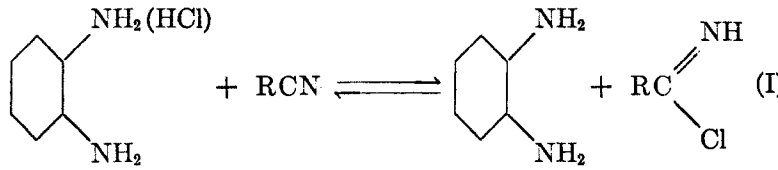
ACID	MOLAR RATIO ACID: C_6H_5CN	TIME AT 200°, HRS.	YIELD 2-PHENYLBENZIMIDAZOLE, %
None	0	2	0.0
None	0	6	0.0
Phenol	20	6	21
NH_4Cl	1	4	58
HCl[a]	0.2	2	26.6
HCl	0.2	4	59.8
HCl	0.2	6	64.8
HCl	1	2	74.2
HCl	2	2	72.4
HCl	2	4	66.5

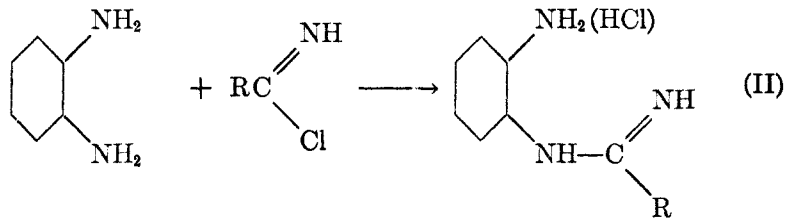
[a] Hydrochloric acid introduced as *o*-phenylenediamine hydrochloride.

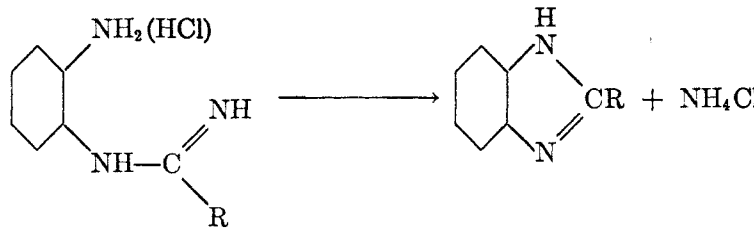
chloride, heated for four hours at 200°, yielded 58% of 2-phenylbenzimidazole. Even phenol was found to induce the reaction feebly, a yield of 21% of 2-phenylbenzimidazole resulting when *o*-phenylenediamine and benzonitrile were heated

in presence of excess phenol but in absence of other acid. It seems permissible to conclude that the imidazole ring closure by action of nitrile is a case of general acid catalysis.

The course of the reaction. The facts that nitriles cause ring closure only in presence of acid, and that acids such as hydrogen chloride and hydrogen bromide unite additively with nitriles under anhydrous conditions to yield highly reactive ammonoacyl halides, suggest at once a plausible reaction course, indicated by equations 1, 2, 3, and 4:

1. 

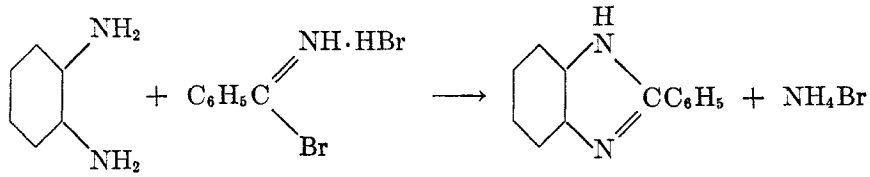
2. 

3. 

4. $NH_4Cl \rightleftharpoons NH_3 + HCl$

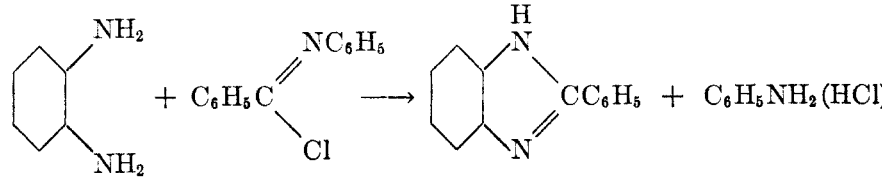
The results of experiments to test the validity of equations 2 and 3, together with other observations discussed below, leave little doubt as to the correctness of the suggested mechanism.

The ability of an ammono-acyl chloride (1) to effect the ring closure with *o*-phenylenediamine (equations 2 and 3) was shown by use of benziminobromide hydrobromide; after a brief heating up to 100° the yield of 2-phenylbenzimidazole was 56%:

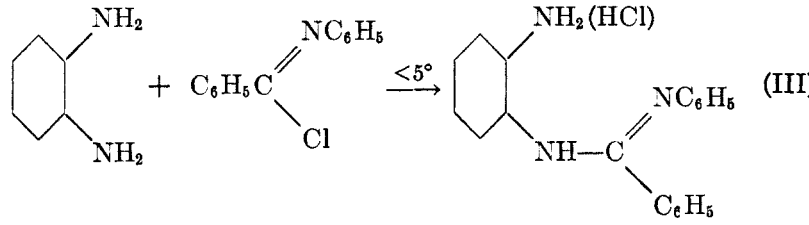
5. 

To avoid uncertainty due to the ambiguous structure of benziminobromide hydrobromide, similar experiments were conducted using N-phenylbenzimino-

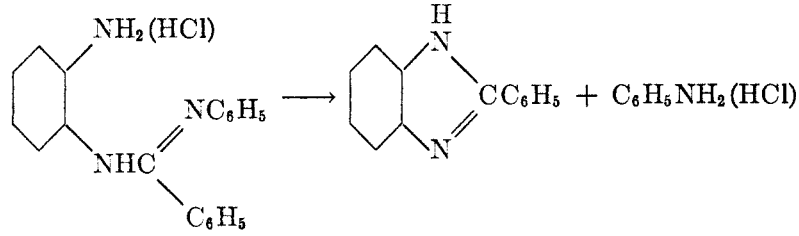
chloride, which does not form a hydrochloride, and is more satisfactorily stored and handled than the simpler imino halide. It was found to react readily with *o*-phenylenediamine on warming briefly at 100°, yielding 57% of 2-phenylbenzimidazole:

6. 

A reaction essentially identical with that represented by equation 2 (formation of an intermediate of type II) was effected separately by allowing *o*-phenylenediamine and N-phenylbenziminochloride to react at low temperature. The yield of N-phenyl-N′-*o*-aminophenylbenzamidine hydrochloride was 68% (equation 7). The corresponding base was isolated and identified by complete elementary analysis.

7. 

The ring closure represented by equation 3 was effected separately by heating the substituted amidine, corresponding to III, which resulted in quantitative conversion to 2-phenylbenzimidazole and aniline. The hydrochloride of III was converted into the same products almost completely on standing for two weeks at room temperature (equation 8).

8. 

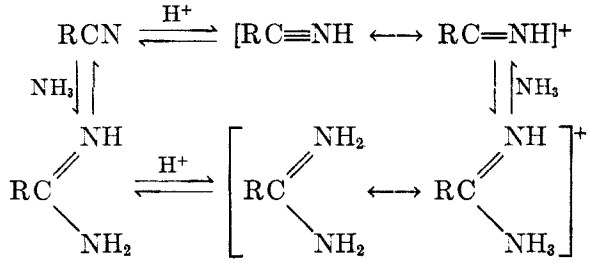
The final step (equation 4) is of importance when the ratio of acid to nitrile is less than unity, and then serves to supply acid to complete the reaction. Thermal dissociation of ammonium chloride is sensible at 200° (11), and the ability of this salt to promote formation of 2-phenylbenzimidazole from *o*-phenylenediamine and benzonitrile at this temperature was shown by the result of the experiment mentioned earlier.

The reaction course represented by equations 1, 2, 3, and 4 is thus supported by the separate realization of each of the last three steps, which in the over-all

reaction would be contingent upon occurrence of the first step, for which there is no direct evidence. It is noteworthy that the over-all reaction requires relatively severe conditions and is not rapid, whereas reactions 2 and 3 proceed rapidly even under mild conditions. It appears that the formation of the iminochloride is the rate-determining step, and that it does not occur readily under the experimental conditions employed. The equilibria involved, with the feebly basic nitrile in competition with *o*-phenylenediamine, and also with ammonia liberated by the ring closure, for the protons which promote the reaction, must be decidedly unfavorable to the formation of the ammono-acyl ion. It is obvious that the reactivity of this ion would operate against its survival, so that isolation of the iminochloride as the product of step 1 under reaction conditions is scarcely to be expected.

When *o*-phenylenediamine and N-phenylbenziminochloride (10) were brought into reaction in boiling ligroin (70–90°) the results were somewhat different than those reported above for other conditions. The products were 2-phenylbenzimidazole and N,N′-diphenylbenzamidine (13), the latter produced by interaction of part of the iminochloride with the aniline liberated during the ring closure. The survival of the benzamidine under these mild conditions, and its failure to survive in reactions at higher temperatures, may be attributed to the ability of the benzamidine to react at 200° to effect ring closure, as shown previously (3) for certain formamidines and acetamidines. Experiments showed that *o*-phenylenediamine dihydrochloride and diphenylbenzamidine, when heated at 200°, reacted to give 2-phenylbenzimidazole (46%), but that in absence of acid no isolable amount of 2-phenylbenzimidazole was formed.[2]

The analogies recognizable among acids (or anhydrides), amidines, and nitriles, including the abilities of all three types to yield benzimidazoles from *o*-phenylenediamine, suggest that the three reactions may proceed by a single essential reaction involving hydrogen ion catalysis. With respect to the nitrogen system compounds (amidines and nitriles) the essential relationships may be summarized in the scheme:



[2] The influence of acid upon such ring closures by amidines requires clarification by further work, for evidence now available is conflicting. Formamidines appear to react satisfactorily without addition of acid (3), a fact attributable to the acidic character of these amidines. Acetamidines, in absence of added acid, failed to react in two attempts to close the pyrimidine ring (3), but a diaryl acetamidine and *o*-phenylenediamine reacted in absence of acid to yield 2-methylbenzimidazole (64%). The results mentioned above indicate that benzamidines are unreactive in absence of acid.

These equilibria represent the ion $RC{=}\overset{+}{N}H$ to be the reactive intermediate which can be formed from either amidine or nitrile in presence of proton, and the tentative view that this ion is involved in ring closures effected by both amidines and nitriles appears to be consistent with the fact that of the three entities—amidine, nitrile, $RC{=}\overset{+}{N}H$—the last is by far the most reactive.

II. FORMATION OF THE OXAZOLE RING

The formation of benzoxazoles from *o*-aminophenols has been effected by use of acid anhydrides (14, 15), amidines (3), and amides (17, 18, 19). Similar reactions using nitriles were reported by Wheeler (16) and by Skraup (18, 19) the formation of benzoxazoles requiring prolonged heating (up to forty-eight hours) at reflux temperatures. In the present study it was found that the

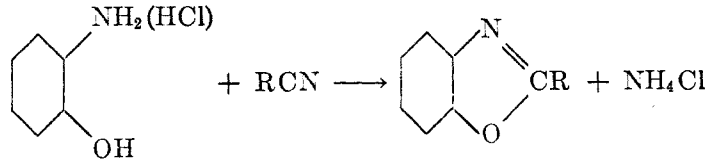
TABLE III

FORMATION OF 2-SUBSTITUTED BENZOXAZOLES FROM *o*-AMINOPHENOL HYDROCHLORIDE AND NITRILES[a]

NITRILE	PRODUCT	M.P., °C.	B.P., °C.	YIELD		ANALYSIS, N	
				g.	%	calc'd	found
CH_3CN	2-Methylbenzoxazole (14)		59–60 12 mm.	0.89	33.5		
C_2H_5CN	2-Ethylbenzoxazole (19)		75–76 2 mm.	1.80	61.2	9.52	9.46 9.33
n-C_4H_9CN	2-*n*-Butylbenzoxazole		68–70 20 mm.	1.74	49.7	7.99	7.80 7.87
n-$C_5H_{11}CN$	2-*n*-Amylbenzoxazole		114–114.5 2 mm.	1.99	52.6	7.40	7.25 7.29
C_6H_5CN	2-Phenylbenzoxazole (18)	102.5–103.5		2.97	70.5		
p-$CH_3C_6H_4CN$	2-*p*-Tolylbenzoxazole (18)	114		3.01	72.0		

[a] 0.02 mole of each reactant; 2 hours at 200° in sealed tube.

required reaction time could be decreased by heating in sealed tubes, and that the reactions were greatly accelerated by presence of acid. Thus benzonitrile and *o*-aminophenol on refluxing for twenty-four hours gave 2-phenylbenzoxazole in 54% yield. By heating in a sealed tube at 200° the yield was 51% in nine hours. A mixture of *o*-aminophenol hydrochloride and benzonitrile gave a yield of 72% in two hours. This improved procedure (equation 9) was employed in the preparation of a series of 2-substituted benzoxazoles; results are summarized in Table III.

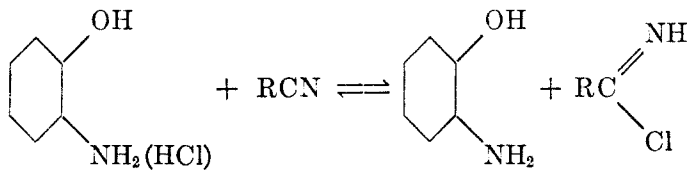
9. 

Furonitrile (α) and 2,6-dimethoxybenzonitrile failed to yield benzoxazoles either in presence or absence of hydrogen chloride. The reaction mixtures became resinous and sticky, and no product was isolable by the usual procedure. It is probable that furonitrile polymerized, and that the reaction with dimethoxybenzonitrile was at some point sterically obstructed.

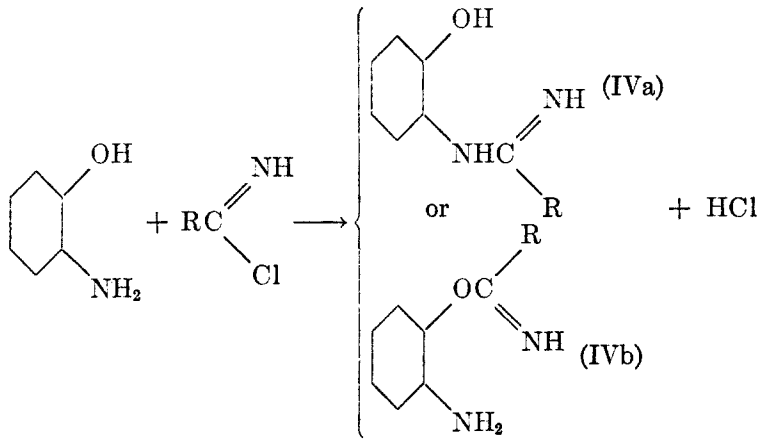
The effect of acid upon the reaction of *o*-aminophenol with benzonitrile was studied experimentally as in section I. In absence of acid (sealed tube at 200°) the yields were about 6% after two hours, 24.6% after four hours, and 51% after nine hours. In presence of hydrogen chloride equivalent to the nitrile the yields were over 70% after two hours. The occurrence of ring closure in absence of added acid (though at a retarded rate) contrasts with the results obtained with *o*-phenylenediamine (section I). The possibility that reaction may have been due to presence of a trace of water operating cyclically to cause ring closure *via* hydration products of the nitrile was excluded by the result of an experiment conducted under anhydrous conditions, a 24% yield of 2-phenylbenzoxazole being obtained. It therefore appears that *o*-aminophenol is sufficiently acidic to promote the reaction, though less effectively than hydrogen chloride.

The course of the reaction. A reaction course similar to that discussed in section I for the imidazole ring closure (equations 1, 2, 3, 4) is suggested, *viz.*,

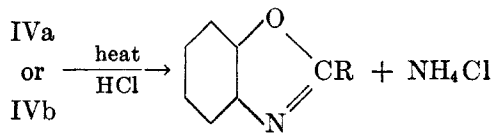
10.



11.

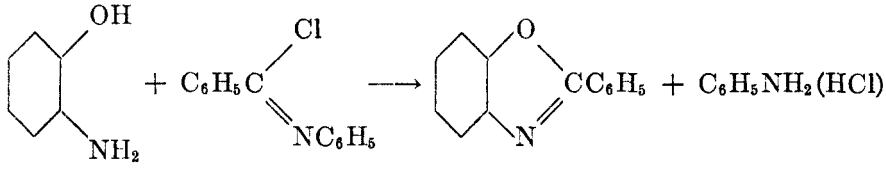


12.

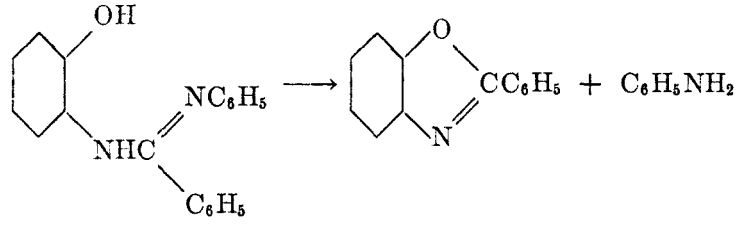


13. $$NH_4Cl \rightleftharpoons NH_3 + HCl$$

In these equations the anion may be Cl^- or $o\text{-}NH_2C_6H_4O^-$. The eligibility of an iminochloride to serve as an intermediate was shown experimentally: when *o*-aminophenol and N-phenylbenziminochloride were warmed briefly at 100°, 2-phenylbenzoxazole was formed in a yield of 58% (equation 14).

14. 

The intermediate IVa or IVb was obtained as a compound $C_{19}H_{16}N_2O$ by interaction of *o*-aminophenol and N-phenylbenziminochloride at low temperature (5°). Evidence discussed below indicates the compound to be IVa (phenyl-*o*-hydroxyphenylbenzamidine) rather than IVb (*o*-aminophenylbenziminophenyl ester). It was found to undergo rapid and practically quantitative conversion to 2-phenylbenzoxazole on heating (94% after thirty minutes at 100°), and gradual conversion at room temperature (equation 15).

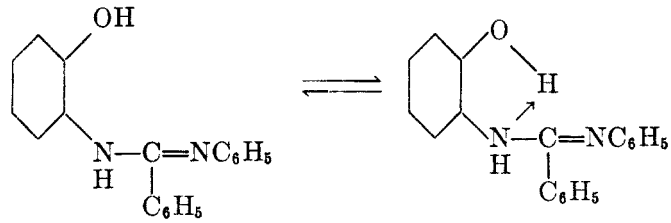
15. 

The identity of the compound $C_{19}H_{16}N_2O$. The formula is consistent with either structure IVa or IVb. Comparison of the solubilities of the similarly related compounds N,N′-diphenylbenzamidine and N-phenylbenziminophenyl ether (20) yielded no significant observation. The application of chemical tests, or of synthetic procedures to prepare IVa or IVb, was seriously restricted by the readiness with which the compound underwent ring closure. The diazotization and coupling test (21), and also the ferric chloride test (22), gave results which were not typical and which were therefore ambiguous.

The compound failed to condense with benzaldehyde, and this result, indicating absence of an amino group, appears to exclude formula IVb, since benzaldehyde reacts readily with both *o*-aminophenol (23) and *o*-phenylenediamine (24).

Collateral evidence which supports formula IVa is the fact that the formation of the compound by interaction of *o*-aminophenol and N-phenylbenziminochloride is actually a nitrogen-system benzoylation analogous to benzoylation by benzoyl chloride, which itself attacks the amino group of *o*-aminophenol preferentially (27), yielding N-*o*-hydroxyphenylbenzamide (*o*-benzaminophenol) and not *o*-aminophenyl benzoate. Further it is noteworthy that reduction of *o*-nitrophenyl benzoate yields hydroxyphenylbenzamide rather than the expected *o*-aminophenyl benzoate (40), the structural change suggesting the stability of the amide (corresponding to IVa) to be greater than that of the ester (corresponding to IVb).

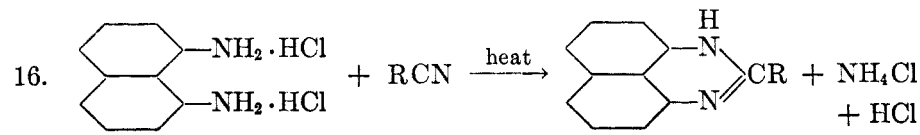
The foregoing evidence justifies a preference for structure IVa. Efforts were made to demonstrate the presence of the hydroxyl group of this structure by methylation with diazomethane, but the results were negative. It would be somewhat arbitrary to conclude that no hydroxyl group is present, since it is known that ortho-substituents may interfere with or prevent methylation of phenolic groups by diazomethane. Thus, diazomethane converts salicylic acid to methyl salicylate (25) and methyl 2,3,4-trihydroxybenzoate to methyl 3,4-dimethoxysalicylate (26), in both cases without methylation of the ortho-hydroxyl group. This impairment of the normal reactivity of hydroxyl may be attributed to chelation, and a similar obliteration of hydroxylic function might occur in structure IVa:



A like explanation, based on structure IVb, could be offered for the failure of the compound to react with benzaldehyde, but in this case the assumed chelation is improbable, as it would involve nitrogen in the role of hydrogen donor, *i.e.*, as more "acidic" than oxygen. Consideration of all the evidence thus leads to a fairly certain conclusion that the intermediate in question is phenyl-*o*-hydroxyphenylbenzamidine (structure IVa).

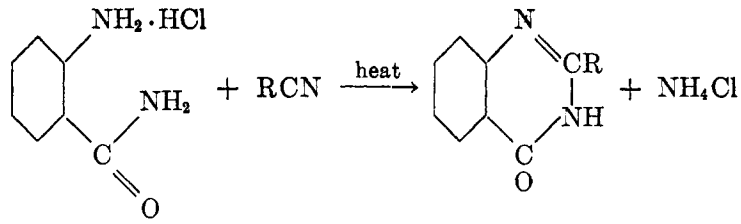
III. FORMATION OF THE PYRIMIDINE RING

Conversion of 1,8-diaminonaphthalene to 2-substituted perimidines. This ring closure, previously effected by use of acids or acid anhydrides (28) and of diphenylformamidine (3), has now been effected similarly by means of nitriles:

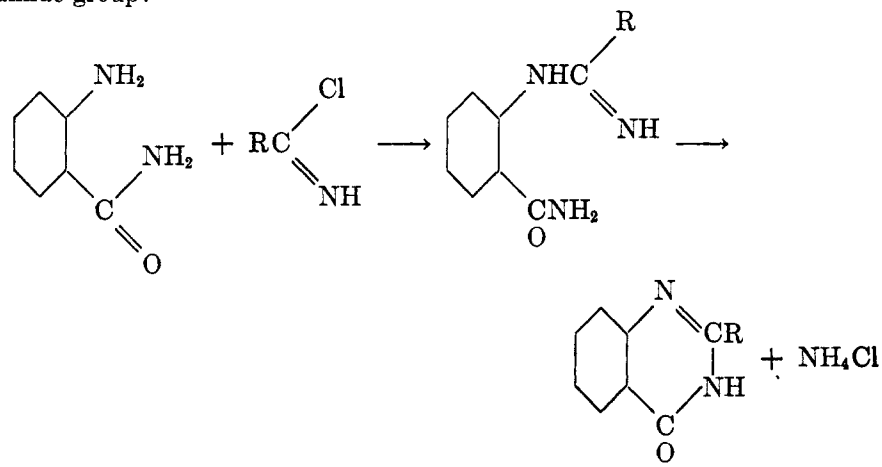


The reactions involved appear to be essentially the same as those of the imidazole ring closure.

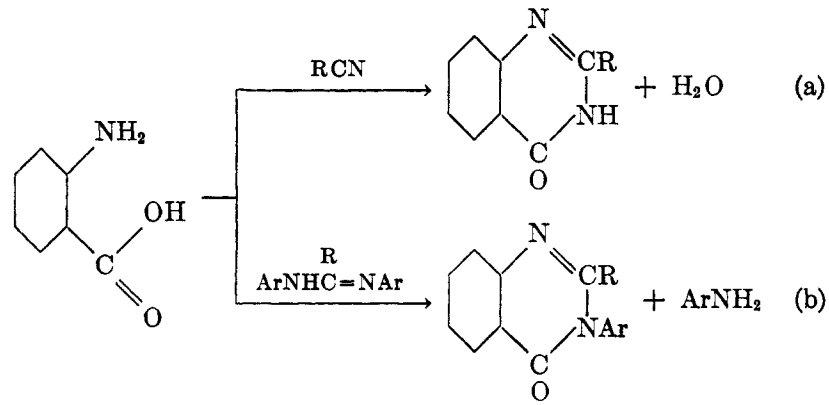
Conversion of anthranilamide to 2-substituted-4-keto-3,4-dihydroquinazolines. It was found that this closure of the pyrimidine ring occurred by interaction of anthranilamide with acetic anhydride, butyric acid, or benzoic acid, or by interaction of anthranilamide hydrochloride with acetonitrile, butyronitrile, or benzonitrile. In both series the products were the corresponding 2-substituted quinazolones [methyl, *n*-propyl (29), phenyl (30)], and in the nitrile reactions the by-product was ammonium chloride:

17. 

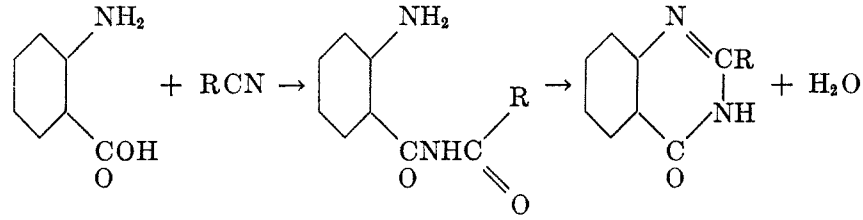
An experiment with anthranilamide and acetonitrile in absence of added acid yielded a little of the quinazolone, indicating the ability of anthranilamide (as a weak acid) to catalyze the reaction feebly. A reaction course similar to that proposed for imidazole ring closure seems probable, with the initial ammonoacylation (corresponding to equation 2) affecting the *o*-amino group rather than the amide group:

18. 

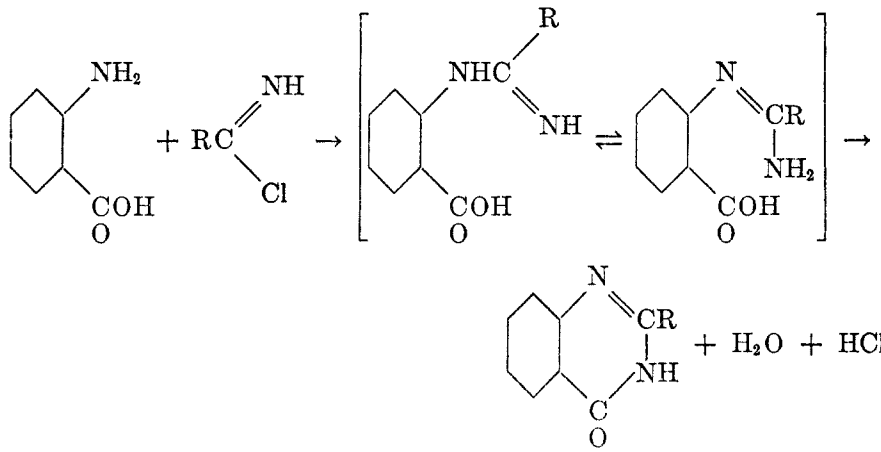
A somewhat similar preparation of 2-substituted quinazolones from anthranilic acid and nitriles was reported by Bogert and Gotthelf (31). In this reaction, the nitrile nitrogen becomes incorporated into the ring, and is not eliminated as ammonia as in the reaction with anthranilamide; the synthesis therefore resembles that of 3-substituted quinazolones from anthranilic acid or ester and disubstituted amidines (32), and of quinazolones by interaction of anthranilic acid and amides [the Niementowski reaction (32)]:

19. 

Here the nitrile and the amidine appear to function similarly, the former as an acid anammonide, the latter as ammono-acid, and both contributing carbon and nitrogen to the ring. The mechanism suggested by Bogert and Hand (29) for reaction 19a postulates primary formation of a mixed imide by addition:

20. 

The proof offered by Bogert and Hand cannot be questioned here, but it may be mentioned that Colby and Dodge (33) reported the formation of such imides to require higher temperatures and longer periods of heating than sufficed for Bogert and Hand's reaction. It is suggested that this reaction, like those considered previously, may involve initial ammonoacylation by nitrile in presence of acid.



EXPERIMENTAL

Most of the starting materials were obtained from the Eastman Kodak Company. Tolunitrile was prepared from *p*-toluidine (34), 2,6-dimethoxybenzonitrile from *m*-dinitrobenzene (35), 1,8-diaminonaphthalene by hydrogenation of 1,8-dinitronaphthalene (3), and anthranilamide from ammonium hydroxide and isatoic anhydride (36), the latter made from anthranilic acid and phosgene (37). Anthranilamide hydrochloride was obtained in 80–90% yields by dissolving the amide in the minimal 6 *N* hydrochloric acid and then adding excess of the concentrated acid.

Carbon and hydrogen were determined by semimicro combustion (38) and nitrogen by semimicro Kjeldahl analysis (39). Melting points of specimens of 2-phenylbenzimidazole were determined by use of a copper block melting point apparatus.

I. Formation of the imidazole ring

Preparation of 2-substituted benzimidazoles. General procedure. Equivalent amounts (generally 0.02 mole) of *o*-phenylenediamine dihydrochloride and nitrile were heated in a

sealed tube at 200° for two hours. The reaction mass was dissolved in dilute hydrochloric acid, using for 2-alkylbenzimidazoles 35 cc. to 100 cc. of water containing 5 cc. of concentrated hydrochloric acid (the volume required became progressively greater as the size of the alkyl group increased), and for 2-arylbenzimidazoles 300 cc. of water containing 10 cc. of concentrated hydrochloric acid, followed by heating for an hour, the volume of solution being kept near 300 cc. by addition of water as needed. The solution was filtered to remove any particles of glass or carbonaceous debris, and the filtrate was treated by one of the following procedures.

To isolate phenyl- or *p*-tolyl-benzimidazole as *hydrochloride* the solution was treated with 20 cc. of concentrated hydrochloric acid and the mixture was chilled for an hour. The precipitated salt was removed by filtration, and was recrystallized from hot water after decolorization by Norit.

To isolate the 2-substituted benzimidazole as *base* the acid solution was made alkaline with ammonium hydroxide, using 10 cc. of strong ammonia water for the alkylbenzimidazoles and 15 cc. for the arylbenzimidazoles. The precipitated base was recrystallized from dilute ethanol. Results of experiments in which eight nitriles were used appear in Table I.

In a blank experiment, made to exclude the possibility that all or some of the substituted benzimidazole was formed during the isolation procedure by action of acid (15, 41) produced by hydrolysis of the nitrile, a mixture of 0.02 mole each of *o*-phenylenediamine dihydrochloride and each nitrile was treated by the isolation procedure only, with omission of the heating in a sealed tube. No benzimidazole could be detected.

Influence of acid. Seven attempts to bring into reaction *o*-phenylenediamine and benzonitrile in absence of acid, by heating together 0.02 mole of each under reflux for twenty-four hours or by heating in sealed tubes at 200° for six hours, all failed to yield isolable 2-phenylbenzimidazole. The mixtures were leached with hot water containing hydrochloric acid, and the extracts were submitted to steam distillation to remove benzonitrile. The unchanged *o*-phenylenediamine, recovered as hydrochloride from the liquid in the distilling flask, weighed from 2.41 g. to 2.68 g. (83–90%). Similar experiments in which acetonitrile was used likewise failed.

The effects of various proportions of acid in promoting the reaction of *o*-phenylenediamine and benzonitrile (0.02 mole of each) was studied in a series of experiments in which the amounts of acid were adjusted by use of suitable proportions of *o*-phenylenediamine and of its hydrochloride. In separate experiments there were used as the sole source of acid, ammonium chloride (0.02 mole), and phenol (0.42 mole). The isolation procedures were substantially the same as the operations outlined in the general procedure. The results of the foregoing experiments appear in Table II.

Formation of 2-phenylbenzimidazole from o-phenylenediamine and benziminobromide hydrobromide (equation 5). Benziminobromide hydrobromide was prepared by a procedure based upon that of Engler, (9). Hydrogen bromide, generated by allowing bromine to drop into boiling tetralin, was passed through a solution of 10 g. of benzonitrile in 10 cc. of ether chilled in an ice-bath. After thirty minutes the dense precipitate was removed by rapid filtration, washed quickly with 15 cc. of ice-cold ether, and immediately transferred to a dry bottle. The yield was about 60%. The product was white and crystalline, and upon exposure to the air it fumed actively, necessitating rapid handling.

A mixture of 5.30 g. (0.02 mole) of benziminobromide hydrobromide and 2.16 g. (0.02 mole) of *o*-phenylenediamine in a sealed tube was heated until the temperature reached 100°, when the furnace was allowed to cool. The isolation procedure yielded 2.16 g. (56%) of 2-phenylbenzimidazole.

Formation of 2-phenylbenzimidazole from o-phenylenediamine and N-phenylbenziminochloride (equation 6). N-Phenylbenzimino chloride was prepared by a modification of the method of Wallach (10). Benzanilide was dried by fusion, the melt was allowed to solidify and was ground to a fine powder. The dry benzanilide (50 g.) was placed in a flask fitted with a calcium chloride tube, 51 g. of phosphorus pentachloride was introduced, and the flask was shaken vigorously for five minutes and was then allowed to stand several hours.

A reflux condenser was attached, and the mixture was heated gently on a steam-cone. Hydrogen chloride was evolved and the mixture gradually liquefied. It was transferred to a 200-cc. modified Claisen flask and was fractionated under reduced pressure. Phosphorus oxychloride distilled below 100°, and the residue of phenylbenziminochloride distilled at 146° at 3 mm. Yields in several runs ranged from 80% to 90%. The product melted at 37°.

A mixture of 0.02 mole each of *o*-phenylenediamine and N-phenylbenziminochloride in a sealed tube was heated until the temperature reached 100°, when the furnace was allowed to cool. The 2-phenylbenzimidazole obtained weighed 2.21 g. (57%).

Formation of N-phenyl-N'-o-aminophenylbenzamidine (equation 7). A solution of 3.50 g. (0.016 mole) of N-phenylbenziminochloride in 40 cc. of chloroform was chilled below 5° and was added to a similarly chilled solution of 1.82 g. (0.0169 mole) of *o*-phenylenediamine in 80 cc. of chloroform. The flask was shaken during about 20 minutes; a bright yellow precipitate appeared. The mixture was kept below 5° for an hour, and the solid was removed by filtration. The yield of 3.60 g. corresponded to 68% of N-phenyl-N'-*o*-aminophenylbenzamidine monohydrochloride. The base was isolated by treatment of an ice-cooled alcoholic solution of the hydrochloride with a half-saturated aqueous solution of sodium carbonate. The precipitated product was collected on a filter, washed with ice-water, and dried in the air. In this manner 2.0 g. of hydrochloride yielded 1.14 g. (65%) of light yellow-brown base, which softened at 126–140°, and was meanwhile converted into a white solid with evolution of vapor having the odor of aniline. The white solid melted at 284–287°, and by mixed melting point test was identified as 2-phenylbenzimidazole, into which the phenyl-*o*-aminophenylbenzamidine was converted by heat.

Anal. Calc'd for $C_{19}H_{17}N_3$: C, 79.44; H, 5.77; N, 14.63.
Found: C, 79.54, 79.62; H, 5.92, 5.99; N, 14.34, 14.37.

Hydrochloride: Calc'd for $C_{19}H_{18}ClN_3$: N, 12.99. Found: N, 12.84, 12.91.

Formation of 2-phenylbenzimidazole from N-phenyl-N'-o-aminophenylbenzamidine (equation 8). (a) N-Phenyl-N'-*o*-aminophenylbenzamidine (1.00 g.) in a small distilling flask was heated at 190–220° in an oil-bath. A reaction occurred, with distillation of aniline, which was collected in 3 *N* hydrochloric acid. When bubbling of the heated mass ceased, and all volatile material had distilled, the residue of crude 2-phenylbenzimidazole (0.694 g.; 103%; m.p. 283–289°) was identified by mixed melting point test. The distillate liquid was evaporated to dryness, leaving 0.432 g. (95%) of aniline hydrochloride.

(b) N-Phenyl-N'-*o*-aminophenylbenzamidine hydrochloride (2.5 g.) was allowed to stand at room temperature for 2 weeks. The mass was extracted with 25 cc. of water, and the residue of 2-phenylbenzimidazole was dried. It weighed 1.60 g. (95%), melted at 283–289°, and was identified by mixed melting point test. The aqueous extract yielded 0.94 g. of aniline hydrochloride (83%).

Interaction of N-phenylbenziminochloride and o-phenylenediamine at intermediate temperature. A solution of 6.47 g. (0.03 mole) of N-phenylbenziminochloride in 40 cc. of 70–90° ligroin was added by drops during an hour to a suspension of 3.24 g. (0.03 mole) of *o*-phenylenediamine in 50 cc. of boiling ligroin, after which refluxing was continued for 4 hours. The chilled mixture deposited 8.41 g. of an orange-yellow powder, of which 5.0 g. was dissolved in the least alcohol, and the solution was shaken with an equal volume of saturated potassium carbonate solution. The water layer was withdrawn and discarded, and the alcohol layer was treated with 25 cc. of cold water. After 10 minutes the precipitate was removed (4.31 g.). This material was a mixture of N,N'-diphenylbenzamidine and 2-phenylbenzimidazole, which were isolated (with considerable loss of each) by the following procedure based upon the greater solubility of 2-phenylbenzimidazole in dilute alcohol. Three grams of the mixture was dissolved in the least 95% ethanol, and water was added until about half of the solid was precipitated. This was removed and treated further as outlined in (a); the filtrate was treated as given in (b).

(a) The residue (1.4 g.) insoluble in dilute alcohol was dissolved in ethanol and about one-half was reprecipitated by addition of water. The solid (0.6 g.) melted at 144–146°.

After recrystallization from dilute alcohol the compound (0.4 g.) melted at 144–146°. A mixture with diphenylbenzamidine made from N-phenylbenziminochloride and aniline (13) melted at 143–145°.

(b) The filtrate was treated with water until no further precipitation occurred. The solid was dissolved in alcohol, and about one-half was reprecipitated by water. This material was removed and discarded. The filtrate was treated with water to precipitate completely the dissolved base, which weighed 0.3 g. and melted at 286–288°. A mixture with 2-phenylbenzimidazole melted at 285–290°.

Formation of 2-phenylbenzimidazole from o-*phenylenediamine hydrochloride and N,N'-diphenylbenzamidine.* From 0.34 g. (0.003 mole) of *o*-phenylenediamine hydrochloride and 0.34 g. (0.0013 mole) of diphenylbenzamidine heated in a sealed tube at 200° for 3.5 hours there was obtained by the general procedure 0.11 g. (46%) of 2-phenylbenzimidazole. Under the same conditions 0.12 g. of *o*-phenylenediamine (base) and 0.30 g. of diphenylbenzamidine yielded no isolable 2-phenylbenzimidazole, and half of the diphenylbenzamidine was recovered.

II. Formation of the oxazole ring

Preparation of 2-substituted benzoxazoles. General procedure. Equivalent amounts (generally 0.02 mole) of *o*-aminophenol or its hydrochloride and nitrile were heated together in a sealed tube at 190–210° for 5 hours. The material in the tube was leached with 100 cc. of ether, and the filtered ether extract was washed with three 30-cc. portions of 4 *N* sodium hydroxide solution. The ether layer was filtered, dried with calcium chloride, and freed of ether by distillation. The residue if an oil (alkylbenzoxazole) was distilled under reduced pressure from a modified Claisen flask; if a solid (arylbenzoxazole) it was crystallized from dilute alcohol. Results, for six nitriles, are summarized in Table III. In experiments using furonitrile or 2,6-dimethoxybenzonitrile the sticky and resinous reaction mixtures yielded no substituted benoxazole when treated by the isolation procedure outlined above.

Reaction under anhydrous conditions. An experiment was performed using *o*-aminophenol which had been dried at 60° for 72 hours and a tube which had been dried at 110° for 72 hours. The benzonitrile had been kept for a week in contact with anhydrous magnesium sulfate, and was distilled directly into the tube, which was sealed immediately. The experiment was completed as outlined below. The yield of 2-phenylbenzoxazole was 24.6%.

Influence of acid. In these experiments the amounts of hydrogen chloride present (introduced as *o*-aminophenol hydrochloride) varied from zero to one equivalent. The general procedure was followed, except that after distillation of the ether the residue was treated with 3 cc. of conc'd hydrochloric acid, and the solution was poured into 200 cc. of cold water. The precipitated product was removed by filtration; it was in all cases substantially pure, melting at 100–102°. Results are collected in Table IV.

Formation of 2-phenylbenzoxazole from o-*aminophenol and N-phenylbenziminochloride (equation 14).* A mixture of 2.16 g. (0.01 mole) of N-phenylbenziminochloride and 1.09 g. (0.01 mole) of *o*-aminophenol in a sealed tube was heated to 100° after which the furnace was allowed to cool. The product was extracted in 50 cc. of ether, and the filtered solution was washed with two 20-cc. portions of *N* hydrochloric acid and then dried over calcium chloride. The ether was removed by distillation, and the residue was crystallized from dilute alcohol. The yield of 2-phenylbenzoxazole was 1.12 g. (58%), and its melting point was 103°.

*Formation of N-phenyl-N'-*o-*hydroxyphenylbenzamidine (equation 11).* A chilled solution of 2.16 g. (0.01 mole) of phenylbenziminochloride in 20 cc. of chloroform was added during 10 minutes to a stirred solution of 1.09 g. (0.01 mole) of *o*-aminophenol in 50 cc. of chloroform chilled in an ice-bath. The suspension was stirred for 20 minutes without cooling and was then returned to the ice-bath and stirred for an hour. The solid product, removed by filtration and air dried, weighed 2.68 g. (82% calculated as phenyl-*o*-hydroxyphenylben-

zamidine monohydrochloride). To obtain the base an ice-cold solution of 2.0 g. of the hydrochloride in the least alcohol was treated with an equal volume of a chilled saturated solution of sodium bicarbonate.[3] After 15 minutes in the ice-bath the mixture was filtered. The precipitate was shaken with ice-water in a flask (to remove sodium bicarbonate) and the residue was collected on a filter. The product, obtained as pale yellow needles, weighed 1.28 g. (72%), and melted indefinitely and with decomposition between 80° and 90°. It was found to be soluble in alcohol and ether, slightly soluble in ligroin, almost insoluble in benzene, and slowly soluble in 6 *N* hydrochloric acid.

Anal. Calc'd for $C_{19}H_{16}N_2O$: C, 79.17; H, 5.55; N, 9.72.
Found: C, 79.21, 79.03; H, 5.22, 5.52; N, 9.69, 9.69.

Hydrochloride. Calc'd for $C_{19}H_{17}ClN_2O$: N, 8.62. Found: N, 8.67, 8.62.

The picrate melted at 134° corr.

Experiments to test the structure of compound IV ($C_{19}H_{16}N_2O$). The diazotization and coupling test (21) gave a brown precipitate, permitting no conclusion, since both diphenylbenzamidine and N-phenylbenziminophenyl ester behaved similarly. In the ferric chloride test (22) an orange-brown coloration developed slowly; both diphenylbenzamidine and N-phenylbenziminophenyl ester responded negatively.

To a solution of 0.3 g. of compound IV in 10 cc. of ether was added 1 cc. of benzaldehyde, and the solution was allowed to stand in the refrigerator for 72 hours. No precipitate appeared and upon removal of the solvent the starting material was recovered, and was identified as the picrate. A similar result was obtained when the reaction was attempted in alcohol.

TABLE IV

EFFECTS OF AMOUNT OF ACID AND TIME OF HEATING UPON FORMATION OF 2-PHENYLBENZOXAZOLE FROM *o*-AMINOPHENOL AND BENZONITRILE

MOLAR RATIO HCl:PhCN[a]	TIME AT 200°, HRS.	YIELD 2-PHENYLBENZOXAZOLE, %
0	2	3.3, 9.5
0	4	24.6[b]
0	9	51.0
1	2	70.5
		76.2

[a] Hydrochloric acid introduced as *o*-aminophenol hydrochloride.

[b] Experiment under anhydrous conditions.

When 10 cc. of an ether solution of diazomethane (42) was added to a solution of IV in 10 cc. of ether no evolution of gas occurred either at 5° or upon standing at room temperature for 2 hours. Removal of ether and diazomethane left behind the unchanged starting compound, identified as its picrate.

Formation of 2-phenylbenzoxazole from N-phenyl-N'-o-hydroxyphenylbenzamidine (equation 15). One gram of IV was heated for 30 minutes in an oil-bath at 100°. The residue was taken up in 1 cc. of cold conc'd hydrochloric acid and the solution was poured into 100 cc. of water. After an hour the precipitate was removed. The yield was 0.64 g. (94%), the m.p. was 102°, and a mixture with 2-phenylbenzoxazole had the same m.p.

III. Formation of the perimidine ring

Preparation of 2-substituted perimidines from 1,8-diaminonaphthalene and nitriles (equation 16). A mixture of 2.31 g. (0.01 mole) of 1,8-diaminonaphthalene hydrochloride and

[3] When dilute sodium bicarbonate solution was used, the product was gummy. Stronger bases, such as sodium carbonate and ammonium hydroxide, caused discoloration and apparent decomposition.

0.01 mole of nitrile in a sealed tube was heated at 200° for 4 hours. The reaction mass was extracted with 100 cc. of water containing 5 cc. of conc'd hydrochloric acid by heating for about 45 minutes. Norit was added, the digestion was continued for 15 minutes, and the mixture was filtered hot. To the filtrate (volume about 75 cc.) 10 cc. of conc'd hydrochloric acid was added, and after chilling for an hour the mixture was filtered. The solid was dissolved in the least hot water, the Norit treatment repeated, and the filtrate treated with 10 cc. of conc'd hydrochloric acid. After chilling the mixture for 30 minutes the precipitate of 2-substituted perimidine hydrochloride was collected on a filter. The corresponding bases all showed the dull olive-green colors and the unsatisfactory melting points which characterize this group of compounds. The products were characterized further by analysis of their hydrochlorides.

2-Methylperimidine hydrochloride: yield 1.02 g. (46.7%); N, calc'd, 12.82; found, 12.81, 12.81, 12.68.

2-*n*-Propylperimidine hydrochloride: yield 0.91 g. (37.0%); N, calc'd, 11.37; found, 11.10, 11.18.

Blank experiments, similar to those outlined following the general procedure of section I, were performed and yielded no isolable perimidine.

Preparation of 2-substituted 4-ketodihydroquinazolines. (a) *From anthranilamide and carboxylic acids or anhydrides.* A mixture of 3.45 g. (0.02 mole) of anthranilamide hydrochloride and acetic anhydride, butyric acid, or benzoic acid (0.1 mole) was heated for 3 hours at 200° in an oil-bath. The reaction mixture was extracted with 30 cc. of water by heating for 15 minutes. The solution was made slightly alkaline with ammonium hydroxide, and the mixture was chilled overnight and was filtered. The solid product was recrystallized from dilute alcohol. 2-Methyl-3,4-dihydroquinazolone-4 (29): yield 1.16 g. (36.2%); m.p. 239–241°. 2-*n*-Propyl-3,4-dihydroquinazolone-4 (29): yield 1.20 g. (31.9%); m.p. 200–202°. 2-Phenyl-3,4-dihydroquinazolone-4 (30): yield 0.80 g. (18.0%); m.p. 217–219°.

(b) *From anthranilamide and nitriles.* A mixture of 3.45 g. (0.02 mole) of anthranilamide hydrochloride and 0.02 mole of acetonitrile, *n*-butyronitrile or benzonitrile was heated in a sealed tube for 2 hours at 200°. The reaction mass was treated with 100 cc. of benzene, which was refluxed for 30 minutes and then filtered hot. The residue from the benzene extraction was ammonium chloride (0.95–1.00 g.; 89–95%). The benzene solution was concentrated to 25 cc., chilled for 24 hours, and the precipitated quinazolone was removed by filtration. The crude product was recrystallized from dilute alcohol, after decolorization with Norit. 2-Methyl-3,4-dihydroquinazolone-4: yield 0.63 g. (19.7%); m.p. 238–240°. 2-*n*-Propyl-3,4-dihydroquinazolone-4: yield 0.83 g. (22.6%); m.p. 200–201°. 2-Phenyl-3,4-dihydroquinazolone: yield 0.82 g. (18.5%); m.p. 220–223°.

An experiment in which anthranilamide (1.36 g.; 0.01 mole) and acetonitrile (0.5 g.; 0.012 mole) were heated (in absence of acid) yielded less than 0.1 g. (below 6%) of 2-methyldihydroquinazolone.

The three products obtained by methods (a) and (b) were identified by mixed melting point tests.

SUMMARY

Certain heterocyclic ring closures were effected by interaction of 1,2- or 1,3-diamino compounds, or of *o*-aminophenol, and nitriles, the processes being essentially identical with conventional ring closures of the Ladenburg type as effected (at lower temperatures) by means of carboxylic acids or their anhydrides. The cases studied comprise the formation of 2-alkyl or 2-aryl benzimidazoles from *o*-phenylenediamine, of 2-alkyl or 2-aryl benzoxazoles from *o*-aminophenol, of 2-substituted perimidines from 1,8-diaminonaphthalene, and of 2-substituted

dihydroquinazolones from anthranilamide, *viz.*, closures of the imidazole, oxazole, and pyrimidine rings by means of nitriles.

In these reactions the nitrile carbon is incorporated into the ring; the nitrile nitrogen is finally present as ammonium salt or ammonia.

The reactions require presence of acid, and appear to be catalyzed by hydrogen ion. Reaction occurs slowly in absence of added acid if one of the reactants is acidic in character (*e.g.*, *o*-aminophenol), but is markedly promoted by the presence of a strong acid, which may be introduced as a salt of the amino compound used.

The course of the closure of the imidazole ring and that of the oxazole ring have been established with a considerable degree of probability for the cases in which hydrogen chloride is the catalyst. It appears that the iminochloride forms first (by additive union of nitrile and acid) and reacts with an amino group to yield the substituted amidine (an ammono-acyl compound), which undergoes ring closure as do the analogous aquo-acyl compounds of the oxygen system. The first step is relatively slow, and requires the use of high temperature and extended reaction periods. The subsequent steps, each realized separately, proceed rapidly and almost quantitatively. The acid is rendered available for another cycle by the thermal dissociation of ammonium chloride which is the by-product.

PHILADELPHIA, PA.

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A NEW CLASS OF SUBSTANTIVE AZO DYES

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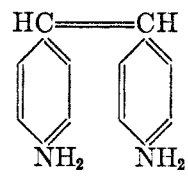
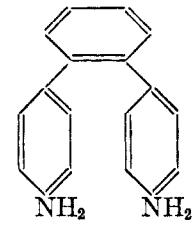
In the preceding paper on *o*-terphenyl (1), mention was made of azo dyes obtainable from 4′,4″-diamino-*o*-terphenyl (I). Like the example given with β-naphthol, some are monazo dyes, but it is possible to couple two molecules of certain dye intermediates so that the products are disazo dyes. If the structure of these dyes is examined critically, a great resemblance to dyes derived from 4,4′-diamino-*cis*-stilbene (II) is noticed. The *o*-terphenyl derivatives can be considered as stilbenes in which a benzene ring has taken the place of the ethylene linkage.



II



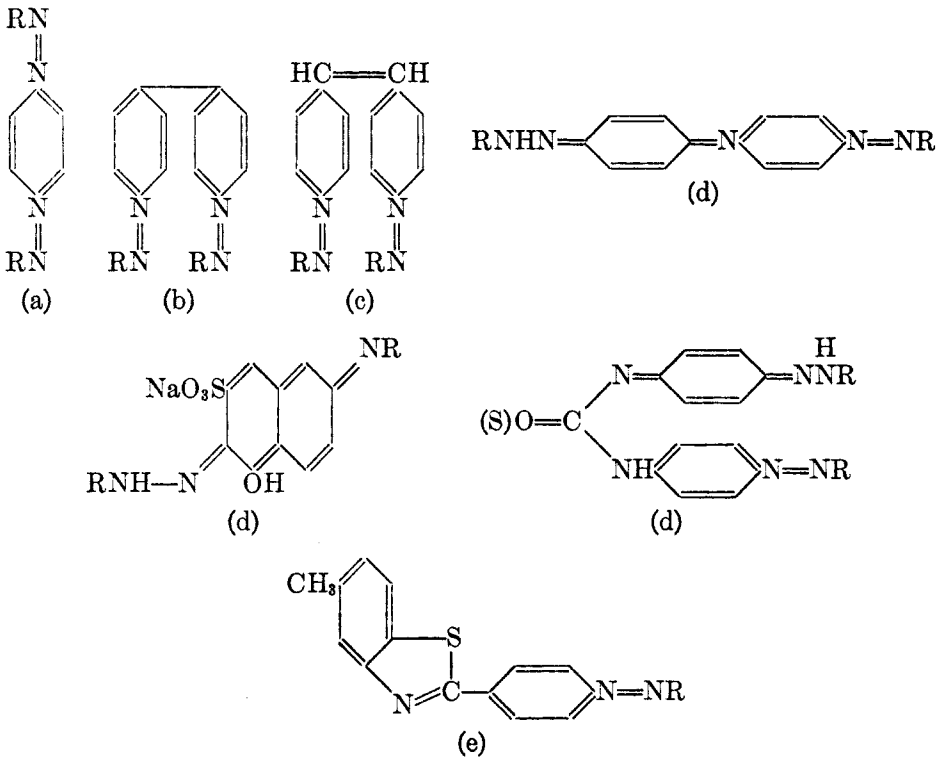
I

From this viewpoint, *o*-terphenyl disazo dyes should be substantive to cotton; they are.

If *p*-phenylenediamine is considered to be the parent substance of substantive dyes, then benzidine is the first benzolog, and diamino-*o*-terphenyl is a higher benzolog. From this point of view, 4,4′-diamino-*p*-terphenyl, which is also a benzolog, should give a substantive dye; it does. A new group of substantive dyes has thus been discovered to be added to the small number previously known.

Substantive dyes are characterized by the presence of an elongated conjugated system of multiple linkages usually terminating in nitrogen, oxygen, or sulfur. For convenience they may be subdivided as follows: (a) dyes derived from *para*-diamines or the diaminonaphthalenes; (b) the benzidine group, which includes the disazo dyes made from benzidine, benzidine sulfone, 2,7-diaminofluorene, 2,7-diaminocarbazole, 2,7-diaminophenanthraquinone, and the like, in which compounds the azo groups are on aromatic rings, and *para* to a *single* bond connecting the two rings; (c) the stilbene colors, in which the azo linkages are *para* to a *double* bond; (d) dyes having a crossed-conjugated system—this includes the dyes from 4,4′-diaminodiphenylamine, J acid,[1] (2-amino-5-hydroxynaphthalene-7-sulfonic acid), and the amides; (e) the thiazole dyes, such as Primuline, which are essentially a special case of the *para*-diamines (a). The amides (which include ureas and thioureas) have the linkage —CONH—, and

[1] This group comprises J acid and its derivatives, such as the aminobenzoyl-J-acids, its imidazole, etc. This system is apparent when the hydrazone form is considered.



usually result from treatment of monazo dyes having a free amino group with phosgene, thiophosgene, or cyanuric chloride. Of course, a single dye may comprise structures belonging to more than one of these groups; such an accumulation may increase the substantivity, *e.g.*, the recently patented (2) anthraquinone direct dyes for cotton can be considered as derivatives of benzidine or *p*-phenylenediamine.

In this paper the term substantivity is used in its usual sense to mean that the dye colors cotton directly, so that it will not readily wash out when rinsed with water. Since substantivity is a relative term,[2] it is necessary to select some standard arbitrarily (3).

In examining the dyes derived from diamino-*o*-terphenyl, comparisons were made with a generally accepted direct dye, such as Congo Red, and a monazo acid dye, such as Ponceau G (4).

Of the many theories advanced over a long period of years to explain substantivity, all have been discarded for one reason or another except two[3]; according to the first, summarized by Hodgson (5), it was considered that substantive dyes were coplanar, and according to the second, advocated by Lenher and

[2] It has a close parallel in "octane rating" applied to gasoline.

[3] As recently as 1936, Ruggli and Lang [*Helv. Chim. Acta*, **19**, 996 (1936)] disposed of the idea that substantive dyes contained long straight chains, by comparing *cis* and *trans* isomers in the stilbene series. The *cis* isomer, which was not straight-chained, was the more substantive.

Smith (6), it was proposed that substantivity was related to particle size. Dyes derived from 4′,4″-diamino-*o*-terphenyl cannot possibly be coplanar, but they furnish additional support to the views of Lenher and Smith.

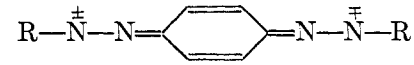
There seem to be two factors that contribute to substantivity, a crossed-conjugated system of multiple linkages,[4] and particle size. Multiple conjugation has been considered by many authors as one of the basic causes of substantivity. This concept is applicable to a number of cases, but cannot explain the substantivity of, say, J-acid or thiazole dyes. Multiple conjugation is only a special case of certain resonating systems; this should be remembered when writing

TABLE I

COLOR OF MONAZO DYES

	COUPLING COMPONENT	COLOR OF WOOL FABRIC
G acid	2-Hydroxynaphthalene-6,8-disulfonic acid	Orange
J acid urea	2-Amino-5-hydroxynaphthalene-7-sulfonic acid urea	Orange
Benzoyl J acid	2-Benzamido-5-hydroxynaphthalene-7-sulfonic acid	Red-orange
J acid	2-Amino-5-hydroxynaphthalene-7-sulfonic acid	Red-brown
2R acid	2-Amino-8-hydroxynaphthalene-3,6-disulfonic acid	Brownish-red
R acid	2-Hydroxynaphthalene-3,6-disulfonic acid	Pink
Epsilon acid	1-Hydroxynaphthalene-3,8-disulfonic acid	Pink
Acetyl H acid	1-Acetamino-8-hydroxynaphthalene-3,6-disulfonic acid	Bluish-pink
Chromotropic acid	1,8-Dihydroxynaphthalene-3,6-disulfonic acid	Red-violet
2S acid	1-Amino-8-hydroxynaphthalene-2,4-sulfonic acid	Brown-violet
H acid	1-Amino-8-hydroxynaphthalene-3,6-sulfonic acid	Dull violet
S acid	1,8-Dihydroxynaphthalene-4-sulfonic acid	Taupe
NW acid	1-Hydroxynaphthalene-4-sulfonic acid	Carmine
RG acid	1-Hydroxynaphthalene-3,6-disulfonic acid	Carmine

formulas (a)–(e) in the electronic resonance form, as, *e.g.*, the following for the phenylenediamine dyes.



The resonance conjugation of hetero atoms (in particular of N) which may not be recognizable as conjugation in the ordinary structural formulas seems to be the "common denominator" of all substantive dyes.

The considerations emphasize the structural factors involved in substantivity, but leave unexplained the well-established effect of the particle size. It is not

[4] It may be noted that such conjugated systems as stilbene can be written in a crossed-conjugated form. The converse is not necessarily true. (Branch and Calvin, "The Theory of Organic Chemistry", Prentice-Hall, Inc., New York, 1941, p. 114.)

unlikely that the electronic resonance form contributes to or causes the easily reversible agglomeration of the dye molecule to particles of roughly molecular dimension.[5]

So far, it has not been found possible to synthesize 4,4′-diamino-*m*-terphenyl. Direct nitration (7, 8), and reduction of the hydrocarbon gives 3-phenylbenzidine, dyes from which, of course, show a high degree of substantivity. Efforts to build up the *meta*-terphenyl ring system by coupling the three benzene rings, in the form of suitable derivatives, have been unsuccessful.

EXPERIMENTAL

Commercial *o*-terphenyl[6] after recrystallization was converted into the diamino derivative as previously described (1). To the solution was added 10 cc. of concentrated hydrochloric acid, and 5 g. of ice, and it was at once tetrazotized in the usual fashion. The tetrazo solution was added to an alkaline solution of the second component. The initial red-violet color slowly changed to a bluish-red. It was noted that coupling with two moles of the naphthol was very sluggish unless the solution was strongly alkaline. Thus, it was easy to obtain monazo dyes, which are described later.

For coupling with two equivalents of H acid, the tetrazo solution was added, dropwise, to a cold, stirred solution of 7 g. of pure H acid in 100 cc. of water containing 2 g. of potassium carbonate and 10 cc. of 40% sodium hydroxide solution. After 6 hrs. of stirring, the volume was reduced to 50 cc. under reduced pressure, and 300 cc. of acetone added. The resultant paste was triturated with absolute ethanol, and 8.6 g. of a fine powder obtained. This was extracted with 95% ethanol using a modified Soxhlet cup (10), until 80% had been removed. The residual dye still contained 10% of inorganic salts, its actual strength being 90.15%. It was analyzed, the results being corrected for ash content.

Anal. Calc'd for $C_{38}H_{24}N_6Na_4O_{14}S_4$: C, 40.8; H, 2.2; N, 7.5.
Found: C, 40.6; H, 2.0; N, 8.0.

Several monazo acid dyes were prepared from the diamino-*o*-terphenyl; they do not color cotton, but dye wool from an acid bath. The shades are given in Table I.

4,4′-Dinitro-*m*-terphenyl (7) was purified by a fractional crystallization from glacial acetic acid. Two contaminants were noted: (a) dinitro-*p*-terphenyl, which is the least soluble portion, and (b) a mononitro derivative of unknown structure, melting above 300°.

Anal. Calc'd for $C_{18}H_{13}NO_2$: N, 5.1. Found: N, 5.1.

It is presumably a polymeric condensation product, as has been described in the *meta* series.

The dinitro-*m*-terphenyl, m.p. 216°, was readily reduced by hydrogen in the presence of Raney nickel. After removal of the catalyst and solvent, the residual diamine was tetrazotized directly, and the filtered solution at once coupled with H acid in strongly alkaline solution. The dye solution was brought to *p*H 7–8 and the dyeing on cotton carried out in the presence of magnesium sulfate. It colors cotton a reddish-blue.

Qualitatively, this dye appears to have a greater degree of substantivity than the other isomeric terphenyl derivatives.

4′,4″-Dinitro-*p*-terphenyl (11) was separated from its by-products by treatment with stannous chloride in hydrochloric acid. The purified dinitro compound melts at 276°. While the isomeric *ortho* and *meta* dinitro derivatives are easily reduced, the *para* diamine

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[5] A paper by the junior author is now in preparation, in which is discussed the relation between substantivity, particle size, and crossed-conjugated systems.

[6] The latest specimen of Santowax O which we used was about 95% *o*-terphenyl, and did not require the distillation procedure (9) employed for cruder material; recrystallization alone gave a sufficiently pure product for the experimental work. We are indebted to Dr. R. L. Jenkins of the Monsanto Chemical Co. for a supply of this Santowax.

is formed only slowly; success was achieved by operating in dioxane solution at 110°, using a high-pressure bomb. After the catalyst had been filtered, the solution was tetrazotized, filtered from a little resinous material, and coupled with an alkaline solution of H acid; the color, initially red, soon becomes violet. It dyes cotton directly, in the presence of a little magnesium sulfate, and the color is only partially removed after several hours' boiling of a dyed specimen in 1% soap solution.

SUMMARY

A new class of substantive dyes derived from the *ortho* and *para* terphenyls has been described.

It has been suggested that there are two factors that contribute to substantivity, namely, a crossed-conjugated system of multiple linkages, and particle size.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

ISATOIC ANHYDRIDE. I. REACTIONS WITH PRIMARY AND SECONDARY AMINES AND WITH SOME AMIDES[1]

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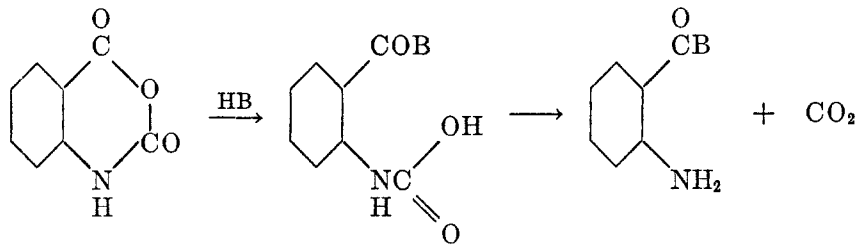
Isatoic anhydride is a convenient reagent for certain anthranoylations, serving instead of the unknown anthranoyl chloride and similarly to anthranil (1), which at present is not conveniently obtainable. Isatoic anhydride has been used recently in syntheses of substituted dihydroquinazolones (2) and tetrahydroquinazolones (3), but its usefulness in synthesis is limited because its chemistry has been studied only partially and in some directions not very successfully. This paper describes the initial work in the study of its preparation and reactions. The previously reported reactions with compounds containing reactive hydrogen atoms (ammonia, primary amines, alcohols, phenols) may be regarded as anthranoylations, in general:



B = —NH_2, —NHR, —NHAr, —OR, —OAr

The liberation of carbon dioxide is characteristic of these reactions, which are those of a cyclic mixed anhydride of a simple carboxylic acid and a carbamic acid.

The interaction of isatoic anhydride and ammonia or common primary amines (4, 7, 8) proceeds readily, but it was found that some primary and secondary amines react to liberate carbon dioxide but yield the expected amides in small amounts or not at all, the principal products being amorphous solids of refractory character and ill defined properties. For convenience these reactions and their products will be referred to as "abnormal". The nature of these materials, the manner of their formation, and procedures by which their formation to some extent may be controlled or avoided, are discussed below. Alcohols and phenols were reported to yield esters of anthranilic acid (4, 6, 9) but preliminary results have indicated that their reactions with isatoic anhydride may be in part abnormal. The reactions of isatoic anhydride with amides (acetamide, urea) were reported by Meyer (9) to be slow and to yield only amorphous and poorly defined products. This finding has been verified for acetamide, but both urea and ethyl

[1] This paper is constructed from the doctoral thesis submitted by Robert H. Clark to the Graduate School of the University of Pennsylvania, 1943.

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carbamate were found to yield also benzoylenurea. It was found possible to use isatoic anhydride in a simplified quinazolone synthesis, eliminating the necessity of preparing separately the intermediate substituted anthranilamide. These results are discussed later.

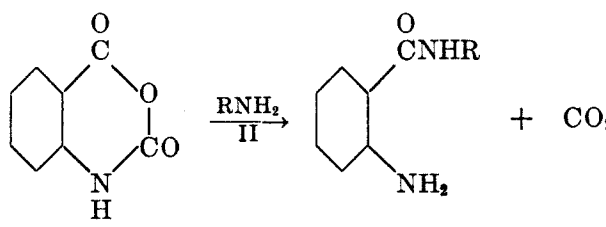
Isatoic anhydride is a minor by-product of the preparation of anthranilic acid from phthalimide (10), and has been prepared from anthranilic acid by action of either ethyl chlorocarbonate or phosgene. The chlorocarbonic ester method (5) proved to be only moderately satisfactory, requiring prolonged heating and producing isatoic anhydride in yields usually not above fifty per cent, accompanied by relatively large amounts of monoethyl isatoate or (and) diethyl isatoate. Erdmann's phosgene method (5), involving maintenance of relatively low acidity by occasional introduction of sodium carbonate, appears to be equally uncertain, and was abandoned when a final trial yielded almost wholly an amorphous product, not identified. A patented procedure (11) by which phosgene is passed into a strongly acid solution of anthranilic acid with no subsequent regulation of the increasing acidity, a favorable temperature being maintained by the rate at which phosgene is introduced, was found consistently to give good yields of substantially pure isatoic anhydride and no undesirable by-product. This method, in the form developed in the course of numerous trials, is described in the experimental section.

I. REACTIONS OF ISATOIC ANHYDRIDE WITH PRIMARY AMINES

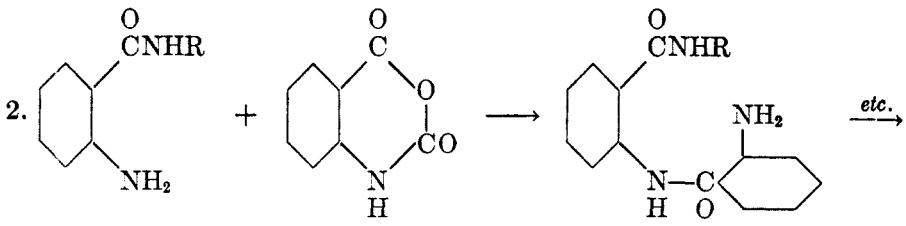
Strongly basic primary amines react readily with isatoic anhydride at low or moderate temperatures (room temperature to 130° in most cases), and some even in water solution. Aromatic primary amines with ortho substituents (*e.g.*, 2,6-dimethylaniline, mesidine) or with negative substituents in ortho or para positions (*e.g.*, *o*-bromoaniline, *o*- and *p*-nitroanilines, methyl and ethyl anthranilates) were found to react less readily and to yield largely or almost wholly the abnormal products. The essential results of the reactions of thirty-one primary amines are collected in Table I.

The *abnormal reaction* occurs with evolution of carbon dioxide in amounts that indicate the involvement of isatoic anhydride to be quantitative or nearly so. The probable course of the abnormal reaction becomes obvious when it is noted that the product formed by the normal reaction (equation 1) contains a free amino group, and is therefore capable of reaction with isatoic anhydride (equation 2):

1.

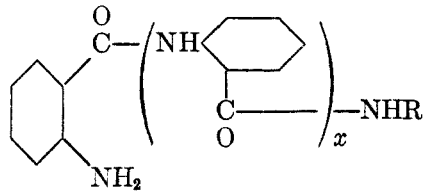


I III

2. 

III IV

If the reactivity of the amino-hydrogen of compound III approaches or exceeds that of the amino-hydrogen of compound II, then some or all of III will react with isatoic anhydride to form IV. This product likewise contains a free amino group, and if the reactivity of II is for any reason low the condensation may continue, yielding products representable by the general formula V.



V

The conditions which favor abnormal reaction probably prevail not beyond the second or third stage ($x = 1$ or 2). It may be concluded that mixtures of products result, and that the average value of x is not integral and is not large. Such molecules, because of their jagged structures and multipolar characters may well associate or aggregate to form macromolecular polyamides analogous to proteins, nylon, etc. The abnormal products show characteristics consistent with this view: they are amorphous, refractory, and practically insoluble in the common solvents, including acids and bases. In no case was it possible to isolate a single compound of type IV or V from the intractable mixtures obtained. This excluded identification of any abnormal product with an anthranoylanthranilamide of type IV synthesized from *o*-nitrobenzoyl chloride as described by Meyer (12), though the superficial properties of the two are unmistakably similar.

The essential correctness of the foregoing conception of the abnormal reaction was established by the following experimental findings. (A) The interaction of equivalent amounts of isatoic anhydride and *o*-bromoaniline yielded no isolable normal product, but when *o*-bromoaniline was used in large excess some N-(*o*-bromophenyl)anthranilamide was formed. It may be inferred that the excess of amine in part overcame the disadvantage inherent in a relatively high rate for reaction 2 as compared with reaction 1. (B) The interaction of equivalent amounts of isatoic anhydride and aniline is normal, but when two equivalents of isatoic anhydride were used the product was amorphous and entirely unlike anthranilanilide obtained from equivalent weights of the reactants. The amount of carbon dioxide evolved showed all the isatoic anhydride (two equiv-

alents) to have reacted. (C) When pure anthranilanilide (a normal product) was heated with an equivalent of isatoic anhydride the theoretical amount of carbon dioxide was disengaged and the abnormal product resulted. (D) Hydrolytic cleavage of the abnormal product obtained from isatoic anhydride and anthranilamide was effected by heating under pressure with concentrated hydrochloric acid. The hydrolytic products were anthranilic acid and ammonia, as required by a structure of type V, and the quantity of ammonia indicated the average value of x to be 2. From the evidence just reviewed it is concluded that the abnormal products are mixtures of polyanthranoylanthranilamides as represented by formula V.

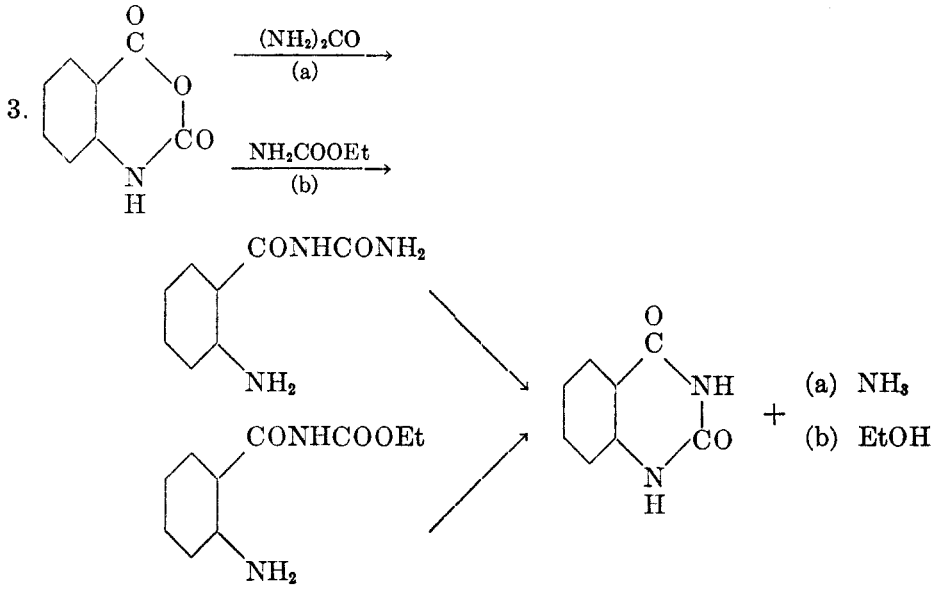
II. REACTIONS OF ISATOIC ANHYDRIDE WITH SECONDARY AMINES

The interaction of isatoic anhydride and secondary amines has not been studied previously. When equivalent amounts were heated together, reaction occurred and carbon dioxide was evolved, but the N,N-disubstituted anthranilamides which would be the normal products were obtained usually in small amounts or not at all, the reaction mixtures in most cases being resinous, gummy masses, from which no well-defined compounds could be isolated. It was found however that moderately good yields of normal products resulted when the secondary amines were maintained in considerable excess throughout the reaction, in order to impose a statistical disadvantage on the abnormal reaction (equation 2). This was done in each case by adding finely-divided solid isatoic anhydride slowly to a two- to five-fold excess of the amine while the mixture was kept at a temperature which ensured rapid reaction as indicated by prompt evolution of carbon dioxide. By this procedure normal condensations were effected using N-alkylanilines, but results with several strongly reactive secondary amines (*e.g.*, diethylamine) were not materially improved, the low yields of the normal products (which in these cases are liquids or low-melting solids) by either procedure being due apparently to difficulties in the isolations. Table II presents the essential results with secondary amines. The structures of the new compounds were established by independent synthesis of each compound by condensing with *o*-nitrobenzoyl chloride the amine represented and by reduction of the product (12, 13).

III. REACTIONS OF ISATOIC ANHYDRIDE WITH AMIDES (PRELIMINARY)

Acetamide and isatoic anhydride reacted slowly above 180° to yield an amorphous product with the characteristics of a mixture, confirming the result reported by Meyer and Bellmann (9). An abnormal condensation seems likely with acetamide, whose feebly basic amino group presumably cannot compete advantageously with the basic amino group of the first-formed product, so that interaction of this and isatoic anhydride occurs, yielding products of type V. In contrast with this behavior of acetamide it was found that urea and also ethyl carbamate reacted with isatoic anhydride to yield benzoylenurea, as well as considerable amorphous material. The formation of benzoylenurea was anticipated, for it was known to be obtainable by interaction of anthranilic acid and

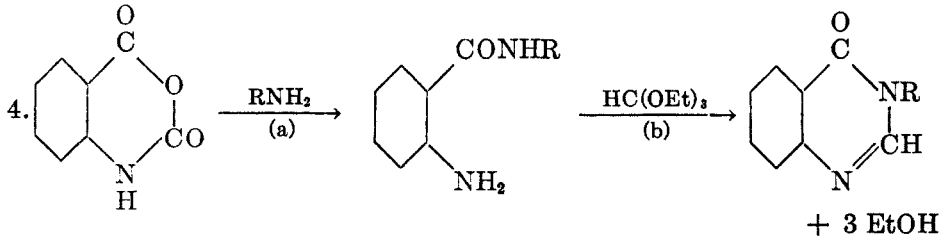
urea (14) and also ethyl carbamate (15). It is concluded that the initial reactions of these amides are normal, and that incidence of the abnormal reactions is in part excluded because of the ease of ring closure:



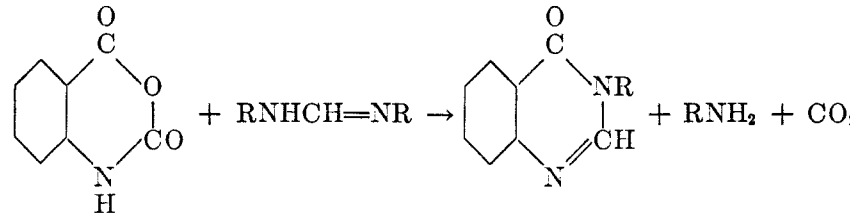
The formation of benzoylenurea from isatoic anhydride and urea may occur also by an alternate course, for the ammonia liberated during the ring closure would react with isatoic anhydride to form anthranilamide, which on heating with urea is known to yield benzoylenurea (16).

IV. THE SYNTHESIS OF 3-SUBSTITUTED-4-KETO-3,4-DIHYDROQUINAZOLINES

This synthesis, by interaction of isatoic anhydride, primary amines, and ethyl orthoformate, was found to be feasible, and constitutes a simplification of the conventional ring closure using the preformed substituted anthranilamide and orthoformic ester. The course of the reaction is not clear, as there may be involved primary interaction of isatoic anhydride and amine to form the substituted anthranilamide, followed by ring closure with orthoformic ester (equation 4), or (and) primary interaction of amine and orthoformic ester to yield the corresponding formamidine (17), which has been shown (2) to react with isatoic anhydride to form the quinazolone (equation 5):



5. (a) $2\,RNH_2 + HC(OEt)_3 \longrightarrow RNHCH{=}NR + 3\,EtOH$

(b)  $+ RNHCH{=}NR \rightarrow$ $+ RNH_2 + CO_2$

Reaction 5b, however, required temperatures 20° to 30° higher than sufficed for reactions 4a,b and also for reaction 4a and 4b when effected separately. The formation of dihydroquinazoline from isatoic anhydride, amine, and ethyl orthoformate therefore appears to follow the course represented by equations 4a, b.

An attempted quinazolone synthesis using ethyl orthoacetate instead of ethyl orthoformate was unsuccessful, as was an attempt to effect synthesis of a tetrahydroquinazolone by interaction of isatoic anhydride, aniline, and methylal (105° in sealed tube), the reaction proceeding only to the anthranilamide stage.

EXPERIMENTAL

Unqualified melting point values were obtained with a Fisher-Johns apparatus. Corrected values were determined in a Hershberg apparatus (22). Nitrogen analyses were made by a semimicro Kjeldahl procedure (23).

Preparation of isatoic anhydride (11). One mole (137 g.) of anthranilic acid was dissolved in a mixture of 150 g. (125 ml.) of conc'd hydrochloric acid and 1 liter of water. The solution was filtered into a three-liter three-necked flask fitted with a sealed mechanical stirrer, an inlet tube reaching to the bottom of the flask, and an outlet tube connected to a safety flask, followed by a Drechsel absorber charged with ammonium hydroxide. The mixture was stirred mechanically and phosgene was passed through an empty safety bottle and then into the solution of anthranilic acid at such rate (about two bubbles per second) that bubbles of gas escaped only slowly at the surface of the liquid (hood). The temperature rose, but was readily maintained near 50° by regulation of the rate at which the phosgene was introduced. The rate of absorption of phosgene was found to be increased as the rate of stirring was increased. Separation of isatoic anhydride began soon after the stream of phosgene was started. The process was continued during several (2 to 4) hours or until the absorption of phosgene was much decreased. The flask was disconnected and a stream of air bubbled through its contents to remove phosgene. The white solid was collected, washed several times with cold water, and dried at 110°. Yields from a number of runs ranged from 115 g. to 125 g. (71–77%) of material melting at 240–243°, pure enough for use. Further purification may be effected by crystallization from 95% ethanol (30 ml. per gram) or from hot dioxane (10 ml. per gram).

I. Reactions of isatoic anhydride with primary amines

A. Procedures (Cf. Table I). 1. *Aliphatic monoamines (ethyl, propyl, butyl, amyl).* Powdered isatoic anhydride (2.04 g.; 0.0125 mole) was added gradually to a solution of slightly more than an equivalent amount of amine in 10 ml. (or the minimal larger volume) of water. Evolution of carbon dioxide was spontaneous and vigorous. When action ceased the solid product was washed by decantation with three 25-ml. portions of cold water, dried, and crystallized from dilute alcohol or benzene, a second crop being obtained by concentration of the mother liquor.

2. *Aliphatic diamines (ethylenediamine and propylenediamine).* Powdered isatoic anhydride (8.15 g.; 0.05 mole) was added gradually to a solution of a slight excess of the di-

amine in 15 ml. of water. Reaction started upon warming the mixture gently, and became vigorous. The mixture was allowed to stand overnight. After partial drying it was crystallized from dioxane-water mixture, two crops being obtained.

3. *Cyclohexylamine.* Isatoic anhydride (4.08 g.; 0.025 mole) was sifted slowly into 4.94 g. (0.05 mole) of cyclohexylamine. Reaction occurred cold; the mixture was finally heated to 100° to complete the action. The hot mixture was treated with 15 ml. of alcohol and was chilled in ice. The crystalline product was recrystallized from 50% ethanol.

4. *Benzylamine* (5.6 g.; 0.05 mole) was poured upon 4.08 g. (0.025 mole) of isatoic anhydride. When the spontaneous reaction had subsided the mixture was heated to 165°. The brown, fluid mass solidified upon cooling. It was washed well with cold water on the filter, dried, and crystallized from benzene, a second crop being recovered from the mother liquor.

5. *Aromatic amines* (excepting *o*-bromoaniline, 2,6-dimethylaniline, mesidine, *o*- and *p*-nitroaniline, anthranilamide, and anthranilic esters; see later procedures). Isatoic anhydride (2.04–8.15 g.; 0.0125–0.05 mole) and a 3% excess of amine were heated to reaction temperature (50° to 130°) in a water-bath or oil-bath until evolution of carbon dioxide ceased. The solid residual mass was dissolved in hot benzene and two crops of crystals were isolated. The product from anthranilic acid was isolated by extraction in *N* sodium hydroxide solution and was reprecipitated by acetic acid. The products from (a) 2-aminopyridine, (b) 2-amino-3-methylthiazole (24) and (c) 2-amino-6-methylbenzothiazole (25) were crystallized respectively from (a) 40% ethanol, (b) 95% ethanol, and (c) benzene (twice) then alcohol (twice).

6. *Phenylhydrazine* (9) and isatoic anhydride in 95% ethanol reacted at 70°. On chilling the solution in an ice-salt bath, yellow crystals separated; a second crop was obtained from the filtrate.

7. *Hydroxylamine* (*9*). To a solution of 6.9 g. (0.10 mole) of hydroxylamine hydrochloride in 250 ml. of water was added an equivalent amount of sodium carbonate. To the solution was added 8.15 g. (0.05 mole) of isatoic anhydride; reaction was spontaneous. The mixture was allowed to stand overnight, and the solid product was crystallized from water at 40°, dried briefly in the air and then completely in a vacuum desiccator. This compound decomposed rapidly upon exposure to moist air.

8. *o-Bromoaniline.* Interaction of equivalent amounts of *o*-bromoaniline and isatoic anhydride yielded 90% or more of the theoretical carbon dioxide (collected and weighed in an Ascarite absorber), but the product was amorphous and obviously of the abnormal type. A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and two equivalents of *o*-bromoaniline (8.60 g.; 0.05 mole) heated at 130° gave off 90% of the theoretical carbon dioxide. Excess amine was removed by steam distillation. Extraction of the solid residue with 100 ml. of hot 1:1 alcohol left undissolved 0.9 g. of material melting 175–220°, not examined further. The alcohol solution was chilled, yielding 0.96 g. of material which softened slowly above 116°. Addition of water to the filtrate precipitated 1.97 g. of material melting near 106°. This was extracted four times with 1:1 hydrochloric acid, and the filtered extracts were made alkaline with ammonium hydroxide. The combined precipitates were crystallized from dilute ethanol, two crops of N-anthranoyl-*o*-bromoaniline being obtained.

9. *2,6-Dimethylaniline* and isatoic anhydride, the former in 5% excess, reacted slowly during four hours at 125–130°. Extraction of the mass with hot benzene left undissolved a gray material without definite melting point. No identifiable solid could be recovered from the benzene extract.

10. *Mesidine* (4.25 g.; 0.0315 mole) and isatoic anhydride (4.08 g.; 0.025 mole) reacted slowly at 125–130°, and in seven hours liberated 80% of the theoretical carbon dioxide. A small part of the mass dissolved in hot benzene; the residue (3.96 g.) melted indefinitely above 250°. No well defined product could be isolated from the benzene extract.

11. *Ethyl anthranilate.* A mixture of 8.30 g. (0.05 mole) of ethyl anthranilate and 8.15 g. (0.05 mole) of isatoic anhydride, heated at 140–150° until gas evolution ceased, yielded 93% of the theoretical carbon dioxide. The sticky reaction mixture was extracted with two 200-ml. portions of boiling 95% ethanol, most of the mass remaining undissolved as an

amorphous material without definite melting point. On cooling the combined alcohol extracts, 1.45 g. of crystalline material melting at 136–140° separated. This was crystallized from 95% ethanol in three portions, the first melting at 139–143°, and the second and third at 157–158°. The filtrate from the crude substance of m.p. 136–140° was heated nearly to boiling, and water was added to incipient turbidity. After treatment with Norit the mixture was filtered and the filtrate was chilled, causing separation of an oil which solidified on standing. It was broken up, dried in the air (2.06 g.; m.p. 50–70°) and crystallized from 60% alcohol in two crops melting at 93.5–94.5° corr. This compound was found to be the normal product, ethyl N-anthranoylanthranilate. For its identification, ethyl anthranoylanthranilate was made synthetically from *o*-nitrobenzoyl chloride and ethyl anthranilate, which condensed in presence of aqueous sodium hydroxide. The product was crystallized from dilute alcohol and was then reduced in alcohol solution in an Adams and Vorhees apparatus using Raney nickel catalyst. The resulting ethyl N-anthranoylanthranilate separated from the filtered liquid upon addition of water. It melted at 94–94.5°, corr. A mixture of this compound and the compound obtained from isatoic anhydride and ethyl anthranilate melted at 93.5–94.5°, corr. The product of m.p. 157–158° mentioned above, possibly dianthranoylanthranilic ester, could not be identified with a specimen of this compound made synthetically from ethyl N-anthranoylanthranilate by condensing with *o*-nitrobenzoyl chloride in presence of aqueous alkali and reduction of the resulting N-(*o*-nitrobenzoyl)anthranoylanthranilic ester (m.p. 161–162° after crystallization from 95% alcohol). The ethyl dianthranoylanthranilate melted at 121–122.5°, a value not changed by crystallization from 60% ethanol.

12. *Methyl anthranilate.* Equimolecular amounts (0.10 mole) of isatoic anhydride and methyl anthranilate were heated at 170° until gas evolution ceased. Extraction of the reaction mixture with 200 ml. of hot methanol left undissolved most of the solid, which did not melt up to 285°. The methanol extract was concentrated by slow evaporation, with occasional removal of the solid which separated in small amount; this material showed no definite m.p. Finally a crystalline compound separated: 1.20 g. (4.5%); m.p. 114.5–115.5° corr. Meyer (12) reported methyl N-anthranoylanthranilate, made *via* *o*-nitrobenzoyl chloride, to melt at 119°.

13. *Anthranilamide.* A mixture of 5.40 g. (0.0397 mole) of anthranilamide and 6.47 g. (0.0397 mole) of isatoic anhydride was heated at 105–108° for two hours and then at 130° for one hour. The reaction yielded 81% of the theoretical carbon dioxide. The brown, glassy reaction mixture dissolved almost wholly in hot alcohol. Concentration of the extract yielded 4.38 g. of solid material which softened and melted from 150° to 165°; it was examined as described in section B. No normal product was obtained.

14. o-*Nitroaniline and* p-*Nitroaniline.* A mixture of 1.75 g. (0.0127 mole) of nitroaniline and 2.04 g. (0.0125 mole) of isatoic anhydride was heated at 155–160° until the slow evolution of carbon dioxide appeared to cease. The mass was extracted with 140 ml. of boiling benzene. Concentration of the benzene extract yielded only some unchanged nitroaniline. The yellow amorphous materials not soluble in benzene weighed 1.50 g. and 1.42 g. respectively. That from *o*-nitroaniline did not melt up to 285°; that from *p*-nitroaniline softened around 230° (unchanged isatoic anhydride).

B. Abnormal reactions and products. 1. *Aniline and excess isatoic anhydride* (Cf. *Section A, Procedure 5*). A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and 1.16 g. (0.0125 mole) of aniline was heated at 110–120° until evolution of carbon dioxide ceased. The evolved carbon dioxide was 90% of the theoretical based on all the isatoic anhydride taken. The mass was extracted with 100 ml. of 95% ethanol, leaving undissolved 0.72 g. of amorphous material which melted at 250° and was found to be not isatoic anhydride. The alcohol extract upon concentration yielded 1.35 g. of a solid which melted from 180° to 195°. These products are abnormal; the m.p. of anthranilanilide is 125°.

2. *Conversion of normal to abnormal compound (Equation 2).* A mixture of 2.04 g. (0.0125 mole) of isatoic anhydride and 2.65 g. (0.0125 mole) of anthranilanilide was heated at 120° until no more carbon dioxide escaped; the carbon dioxide was 82% of the theoretical. The

TABLE I

REACTIONS OF ISATOIC ANHYDRIDE WITH PRIMARY AMINES

AMINE	PROCEDURE; TEMPERATURE °C.	REF.	M.P. °C.[c]	PRODUCT YIELD,[a,b] %	NITROGEN, (KJELDAHL)[d]	
					Calc'd, %	Found, %
Ethylamine	1; room	18	102–103 obs.	87.7	—	—
n-Propylamine	1; room	—	98.5–100	100	15.74	15.30, 15.36
n-Butylamine	1; room	—	83–84	83.6	14.58	14.32, 14.40
n-Amylamine	1; room	—	80.0–81.0	88.3	13.60	13.25, 13.30
Isoamylamine	1; room	—	69.0–70.0	91.4	13.60	13.35, 13.26
Ethylenediamine	2; room	19	242.0–243.0 obs.[e]	59.1	—	—
Propylenediamine	2; room	—	183.0–184.0[e]	50.2	17.95	17.81, 17.62
Cyclohexylamine	3; room, then 100	—	155.5–156.5	70.2	12.84	12.77, 12.92
Benzylamine	4; room, then 165	—	123.0–123.5	69.0	12.39	12.33, 12.42
Aniline	5; water-bath	8a	125.5–126.5	79.0	—	—
p-Toluidine	5; 85–90	20	150.0–151.0	83.2	—	—
p-Anisidine	5; 125–130	3	125.0–126.0	64.0	—	—
m-Bromoaniline	5; 120–130	—	147.5–149.0	60.5	9.63	9.54, 9.52
p-Bromoaniline	5; 120–130	3	148.0–149.0	70.0	—	—
m-Chloroaniline	5; 125–130	—	130.0–131.5	74.5	11.36	11.10, 11.35
p-Chloroaniline	5; 110–120	—	140.0–141.5	72.3	11.36	11.05, 11.28
2,4-Dimethylaniline	5; 120–130	20	137–138 obs.	56.9	—	—
Anthranilic acid	5; 50	21	205.5–206.5	54.0	—	—
2-Aminopyridine	5; 130	—	132.0–133.0	56.0	19.70	19.56, 19.66
2-Amino-4-methylthiazole	5; 100	—	117.5–118.5	68.8	18.01	17.76, 17.76
2-Amino-6-methylbenzothiazole	5; 130–140	—	186.0–187.0	20.4	14.80	14.48, 14.41
Phenylhydrazine	6; 70	9	172.0–173.0 obs.	78.6	—	—
Hydroxylamine	7; room	9	78 obs.	57.9	—	—
o-Bromoaniline	8; 130	—	115.5–116.0	9.6[f]	9.63	9.67, 9.69
2,6-Dimethylaniline	9; 125–130	—	—	[f]	—	—
Mesidine	10; 125–130	—	—	[f]	—	—
Ethyl anthranilate	11; 140–150	—	93.5–94.5	9.5[f]	Ident. by synthesis	
Methyl anthranilate	12; 170	12	114.5–115.5	4.5[f]	—	—
Anthranilamide	13; 130	—	—	[f]	—	—
o-Nitroaniline	14; 155–160	—	—	[f]	—	—
p-Nitroaniline	14; 155–160	—	—	[f]	—	—

[a] The products are the N-monosubstituted anthranilamides corresponding to the amines used.

[b] Only definite compounds (not abnormal products) are listed.

[c] Melting points are corrected unless designated "obs."

[d] Compounds for which analytical data are given have not been reported previously.

[e] This product is the *sym*-bis-anthranoyl diamine.

[f] Reaction largely abnormal.

reaction mixture was extracted with 100 ml. of boiling 95% ethanol, leaving undissolved 0.91 g. of material which melted 230–245° and was found to be not isatoic anhydride. The alcohol extract, when concentrated by evaporation, yielded in two crops 1.23 g. of amorphous material melting from 180° to 195°.

3. *Composition of abnormal product as shown by cleavage.* In these experiments the product of m.p. 150–165° obtained from anthranilamide and isatoic anhydride (Section A, procedure 13) was used. Attempts to decompose it by refluxing with aqueous hydrochloric acid were unsuccessful, and hydrolysis by aqueous alkali yielded some ammonia but no anthranilic acid or other identifiable product. Nearly complete cleavage resulted when 1.0 g. of substance was heated with 5 ml. of conc'd hydrochloric acid in a sealed tube at 125–135° for 4.5 hours. The clear liquid was evaporated to dryness; the yellow granular residue weighed 1.29 g. The presence of anthranilic acid was shown by dissolving 0.25 g. of the residue in 10 ml. of 5% sodium hydroxide solution and shaking with benzenesulfonyl chloride, filtering, acidifying to precipitate N-(benzenesulfonyl)anthranilic acid, which was crystallized from 50% ethanol. The m.p. was 212–214°, and a mixture of this compound and an authentic specimen of benzenesulfonylanthranilic acid melted at 211–212°. The quan-

TABLE II

REACTIONS OF ISATOIC ANHYDRIDE AND SECONDARY AMINES

AMINE	PROCEDURE	PRODUCT[a]			NITROGEN, (KJELDAHL)	
		B.P., °C.	M.P., °C.[b]	YIELD, %	Calc'd, %	Found, %
Diethylamine	1	147–148 (1 mm.)	70.0–70.5 obs.	28.7	14.58	14.42, 14.40
	2	158–160 (4 mm.)	70.0–70.5 obs.	31.6		
Di-*n*-propylamine	2	174–177 (4 mm.)	Oil	29.3		
			Picrate: 104–104.5		15.59	15.39, 15.28
Piperidine	1	160–163 (1–2 mm.)	73.0–74.0	63.3	13.73	13.50, 13.55
Methylaniline	2	—	127–127.5	41.0	12.39	12.00, 12.11
Ethylaniline	2	—	102.5–103	33.3	11.66	11.37, 11.41
n-Propylaniline	2	—	75.5–76.5	11.5[c]	11.02	10.79, 10.75

[a] The products are the N,N-disubstituted anthranilamides corresponding to the amines used. Excepting methylphenylanthranilamide they are new compounds.

[b] Melting points are corrected unless designated "obs."

[c] Evolved carbon dioxide was 90% of the theoretical.

tity of ammonia produced by the hydrolysis was determined by heating with strong sodium hydroxide solution 1.00 g. of the hydrolysis residue (equivalent to 0.78 g. of the original substance), distilling the ammonia into 50 ml. of 0.1 *N* hydrochloric acid and titrating the excess acid. The ammonia found (equivalent to 29.18 ml. of decinormal acid) was 0.0453 g. The amounts required by formula V when $x = 1, 2, 3$ are 0.0660 g., 0.0452 g., 0.0344 g. The substance examined had an average composition corresponding to the requirements of formula V when $x = 2$; the close agreement is fortuitous, since the material was not a single compound.

II. Reactions of isatoic anhydride with secondary amines

A. Procedures (Cf. *Table II*). 1. *Amine and isatoic anhydride in equivalent amounts.* The amine (diethylamine 3.65 g., 0.05 mole; piperidine 2.13 g., 0.025 mole) was dissolved in 10 ml. of 95% ethanol, and an equivalent amount of powdered isatoic anhydride was added. Reaction was vigorous at room temperature. When evolution of carbon dioxide ceased the reaction mixture was distilled fractionally under reduced pressure. Essential data for the two products appear in Table II.

2. *Amine in excess.* To the amine, taken in three to five times the theoretical amount (0.063 to 0.15 mole), referred to isatoic anhydride, was added gradually and in small portions, finely divided isatoic anhydride (0.0125 to 0.05 mole), the mixture in each case being kept at such temperature that prompt evolution of carbon dioxide followed each addition. Diethylamine and di-*n*-propylamine reacted without warming; the experiments with alkylanilines were run at 120–130°. To isolate the N,N-dialkylanthranilamides the mixtures were distilled *in vacuo*. Excess amine distilled first, after which the products passed over as 2° to 3° fractions. N,N-di-*n*-propylanthranilamide did not solidify, and for identification and analysis was converted into its 1:1picrate (m.p. 103–104°), made in alcohol solution. To isolate the alkylarylanthranilamides the mixtures were first subjected to steam distillation to remove excess amine. In each case the residue in the flask was treated with 25 ml. of 1:1 hydrochloric acid, and the mixture was extracted with benzene. The acid layer was chilled and made alkaline with ammonium hydroxide. The precipitated product (in the experiment with propylaniline oily at first) was crystallized from dilute alcohol. Essential data for individual compounds appear in Table II.

3. *Identification of products.* Of the compounds listed in Table II only N-methyl-N-phenylanthranilamide has been reported previously. All were identified by mixed m.p. tests using the same compounds made by independent syntheses by the method of Meyer (12) and Pictet and Gonset (13). *Procedure:* To 0.025–0.05 mole of secondary amine and 0.025–0.05 mole of *o*-nitrobenzoyl chloride was added slowly 20–50 ml. of 20% sodium hydroxide solution, and the mixture was shaken. The product which separated was washed with water, and was then dissolved in 40 ml. of 95% ethanol and hydrogenated in presence of Raney nickel in an Adams and Voorhees apparatus. The filtered solution was heated on a water-bath to remove alcohol, and the residue was distilled under reduced pressure. The main fraction solidified on cooling, excepting the one composed of N,N-dipropylanthranilamide, which was converted to its picrate (*cf.* procedure 2). The determined constants of the products so obtained from the several secondary amines are as follows: N-anthranoyldiethylamine, b.p. 144–146° (1 mm.); m.p. 69.5–71.0° corr.; N-anthranoyldi-*n*-propylamine, an oil, b.p. 154–156° (1 mm.); picrate, m.p. 104.0–104.5°; N-anthranoylpiperidine, m.p. 73.0–74.5° corr.; N-anthranoyl-N-methylaniline, m.p. 126.5–127.5° corr.; N-anthranoyl-N-methylaniline, m.p. 102.0–103.0° corr.; N-*o*-nitrobenzoyl-*n*-propylaniline, m.p. 92–92.5°; N-anthranoyl-*n*-propylaniline, m.p. 75.5–76.5° corr. Mixtures of the solid products with corresponding compounds made from secondary amines and isatoic anhydride showed no significant depressions in the like melting points of the single compounds.

III. Reactions of isatoic anhydride with amides

1. *Acetamide (9).* A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and 7.40 g. (0.125 mole) of acetamide was heated at 180–190° until the slow evolution of carbon dioxide ceased. The cooled mixture was extracted with 20 ml. of warm water to remove excess acetamide. The undissolved residue (2.25 g.) was amorphous and yellow. It softened slowly above 250° but showed no m.p.

2. *Ethyl carbamate; formation of benzoylenurea.* A mixture of 8.15 g. (0.05 mole) of isatoic anhydride and 22.3 g. (0.25 mole) of ethyl carbamate was heated under return condenser for two hours at 220–240°. The cooled mass was ground and extracted with 30 ml. of 95% ethanol; the undissolved residue weighed 10.92 g. Five grams of this material was dissolved in 50 ml. of warm 0.5 *N* sodium hydroxide solution and the solution was chilled. The precipitate (the disodium salt of benzoylenurea) was removed and dissolved in 75 ml. of hot water, and the solution was acidified with 1:1 sulfuric acid. The precipitated benzoylenurea was collected on a filter, washed with water, and crystallized from glacial acetic acid. The product (1.26 g.; 34%) did not melt at 280°. It was identified by conversion of the disodium salt to the N,N-dimethyl derivative by action of dimethyl sulfate. From 0.40 g. of the supposed benzoylenurea and excess dimethyl sulfate was obtained, by shaking the mixture which was kept somewhat alkaline by addition to sodium hydroxide solution at intervals, 0.44 g. of crystalline dimethylbenzoylenurea, m.p. 166°. A mixture of this com-

pound with an authenic specimen of dimethylbenzoylenurea melted at the same temperature.

3. *Urea; formation of benzoylenurea.* A mixture of 8.15 g. (0.05 mole) of isatoic anhydride and 15.0 g. (0.025 mole) of urea was heated at 140° (the lowest temperature at which gas evolution was noticeable) for two hours. Excess urea was removed from the cooled mixture by leaching with 35 ml. of warm water, leaving a yellow residue (5.16 g.). Of this material 1.5 g. was treated as described in 2 for isolation of benzoylenurea, of which 0.75 g. (31.8%) was obtained. It did not melt at 280°, and was identified as the dimethyl derivative (m.p. 167°) by mixed m.p. test (166–167°).

IV. Synthesis of 3-substituted-4-keto-3,4-dihydroquinazolines

A mixture of 0.025 mole each of aniline, *p*-toluidine or *p*-anisidine, isatoic anhydride, and ethyl orthoformate was heated under a return condenser for the periods and temperatures noted below; in each case alcohol began to reflux at about 80°. The alcohol was removed by distillation (3.1 ml.), and the solid crystalline residue was crystallized from alcohol. The data for each of these experiments are recorded herewith in the following sequence: the amine used, the duration of the heating, the temperature of heating, and with respect to the substituted dihydroquinazolone the solvent used for crystallization, the yield, and the m.p. Aniline; 6 hrs.; 120–125°; 1:1 ethanol; 72.1%; 136–136.5° (ref. 16). *p*-Toluidine; 1.5 hr.; 115–120°; 65% ethanol; 66%; 144–145° (ref. 16). *p*-Anisidine; 1.5 hr. 110°; 95% ethanol 72.2%; 194–195° (ref. 3). The compound obtained from *p*-toluidine was identical with 3-*p*-toyl-3,4-dihydroquinazolone-4 as made in 73.2% yield by heating N-anthranoyl-*p*-toluidine with ethyl orthoformate at 110° for four hours. The m.p. was 144–145°; a mixed m.p. test showed no depression.

Attempts to extend this synthesis by use of ethyl orthoacetate instead of ethyl orthoformate were unsuccessful. Equivalent amounts (0.025 mole) of amine (aniline, *p*-anisidine), isatoic anhydride, and ethyl orthoacetate were heated under return condenser at 110° for three hours. At about 70° gas was evolved, and at about 80° slow refluxing was in progress. The reaction mixtures were viscous, and yielded no substituted quinazolone.

An attempted analogous synthesis of a tetrahydroquinazolone was unsuccessful. A mixture of 4.08 g. (0.025 mole) of isatoic anhydride, 2.35 g. (0.0253 mole) of aniline and 4.0 ml. (an excess) of methylal was sealed in a tube and heated at 100–105° for two hours. The ether-soluble material weighed 3.12 g., and proved to be anthranilanilide (m.p. 119–120°).

SUMMARY

Studies of certain reactions of isatoic anhydride led to the following conclusions: 1. primary amines without obstructing substituents condense to yield the corresponding substituted anthranilamides with evolution of carbon dioxide; 2. when the normal condensation referred to is in some way retarded, isatoic anhydride reacts also with the free amino group of the substituted anthranilamide to form a dianthranoyl compound, and by successive repetitions of this reaction polyanthranoyl compounds result, obtained as amorphous mixtures (the abnormal reaction); 3. secondary amines condense normally but with an increased tendency to yield in part amorphous products; 4. the abnormal reaction can be limited to some extent by use of amine in excess, and especially by adding isatoic anhydride gradually to an excess of amine, the mixture being held at a temperature at which reaction is rapid; 5. the polyamide character of the abnormal products was demonstrated for polyanthranoylanthraniline and polyanthranoylanthranilamide by conversion of the normal to the abnormal product and by the results of cleavage; polyanthranoylanthranilamide appears to have an average

composition which approximates that of dianthranoylanthranilamide; 6. isatoic anhydride reacts with acetamide to form amorphous products, but condenses with urea or ethyl carbamate to yield also benzoylenurea; 7. interaction of isatoic anhydride, primary amine and ethyl orthoformate yields the corresponding 3-substituted 4-keto-3,4-dihydroquinazolines; under the same conditions the analogous reaction with ethyl orthoacetate does not occur.

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SOLUBILITIES OF HIGH MOLECULAR WEIGHT NORMAL ALIPHATIC NITRILES

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The solubility of a straight-chain aliphatic compound in an organic solvent is a function of both the polar group and the length of the hydrocarbon chain. Frequently somewhat unpredictable results are encountered due to association of the compound itself or of the compound with the solvent. Random solubility measurements show very little concerning the influence of these various factors. It is, therefore, important to determine the solubilities of a number of members of each homologous series in a variety of solvents before generalizations can be drawn safely. In previous investigations in this Laboratory the solubilities of the normal saturated aliphatic acids (1), the symmetrical normal aliphatic ketones (2), and the normal aliphatic amides, anilides, and N,N-diphenylamides (3) have been determined in a wide variety of organic solvents. This paper reports the solubilities of the normal aliphatic nitriles in sixteen organic solvents. It is planned to extend this investigation to include several other aliphatic series with the expectation that this work may permit of some evaluation of the influence of homology, specific functional groups, and other factors which affect the solubilities of aliphatic compounds in organic solvents.

EXPERIMENTAL

The nitriles used in this investigation were prepared from fatty acids[1] which had been highly purified by previously described methods (4). The nitriles were prepared by passing the corresponding acid over aluminum oxide in the presence of ammonia at 400° (5). They were washed free of acid, dried with potassium carbonate, and purified by fractionation *in vacuo* in a Stedman packed column. The stearonitrile was purified by several crystallizations from 95% ethanol. The freezing points of these nitriles are listed in Table I.

The solvents were of the best grade obtainable and were dried carefully and distilled twice before using. The ethanol was commercial "absolute" which was diluted to 95.0% by weight with conductivity water. Its concentration was determined by checking its density against known values (11).

Solution temperatures were determined by cooling 3–5 g. portions of solution in 1 x 15 cm. test tubes which were placed in an air-bath. The latter was immersed in an acetone-bath which was cooled with solid carbon dioxide. Temperatures within the samples were measured by means of a potentiometer with an iron-constantan thermocouple. A calibrated thermometer was used in setting the reference junction. As the nitriles crystallized from solution upon cooling, the temperature of the air-bath was raised gradually until the mixtures redissolved. Solution temperatures determined in this manner were reproducible within $\pm 0.1°$ and are, in general, considered accurate to at least $\pm 0.2°$. The temperatures below about $-25°$ are probably accurate to only $\pm 0.4°$.

RESULTS AND DISCUSSION

As in the case of the aliphatic ketones (2), the nitriles exhibit a marked correlation between their solubilities and the polarity of the solvents. In general, the

[1] The freezing points of these acids were 30.62° for capric, 43.77° for lauric, 54.15° for myristic, 62.30° for palmitic, and 69.28° for stearic acid.

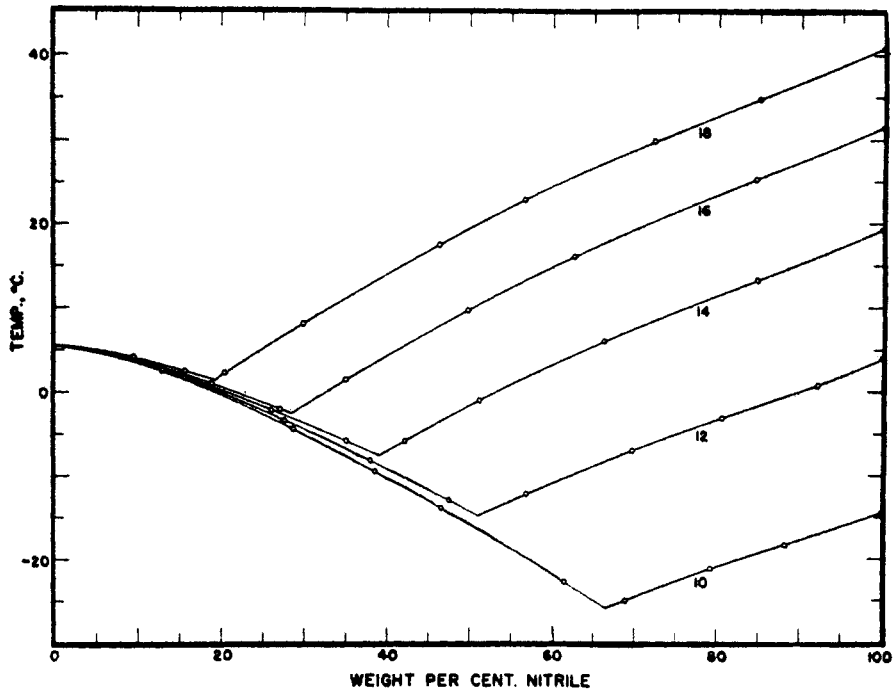

FIG. 1. SOLUBILITIES OF THE NITRILES IN BENZENE
The numbers refer to the number of carbon atoms in the compounds

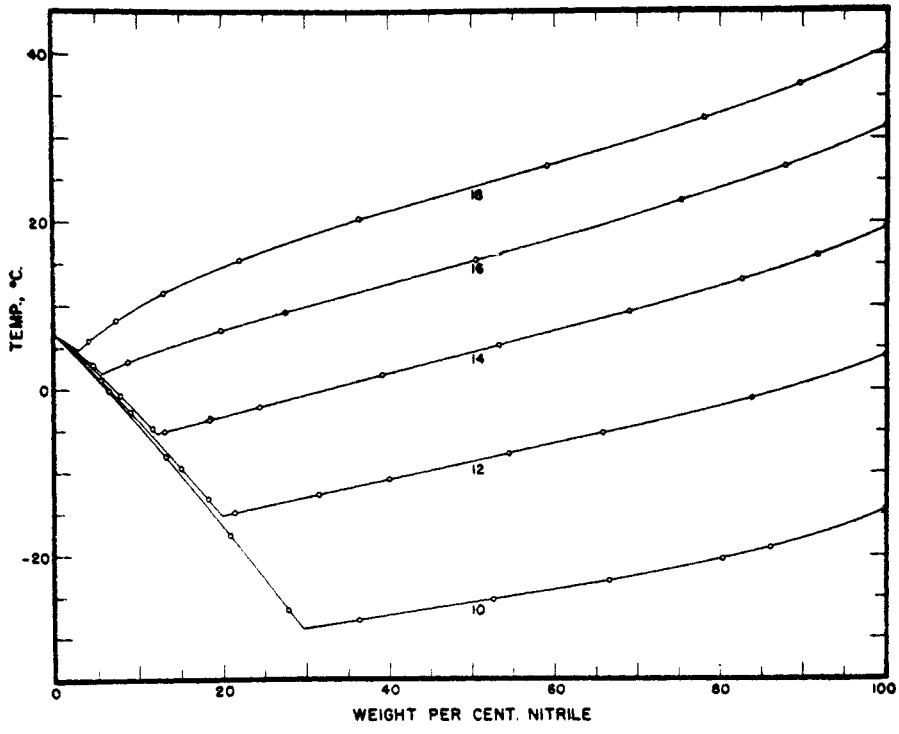

FIG. 2. SOLUBILITIES OF THE NITRILES IN CYCLOHEXANE

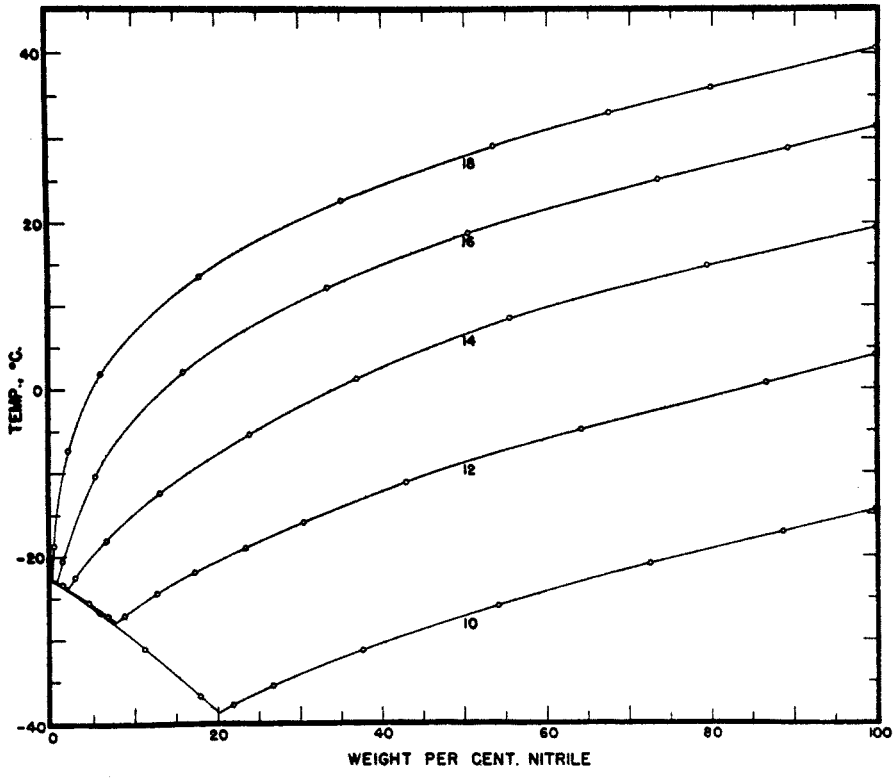

FIG. 3. SOLUBILITIES OF THE NITRILES IN TETRACHLOROMETHANE

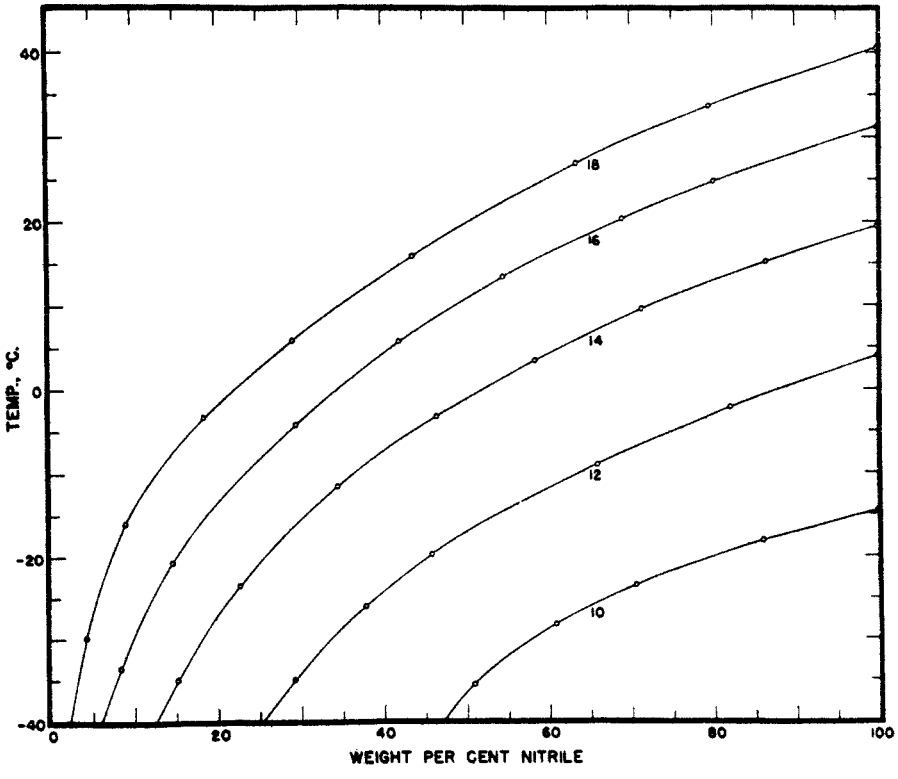

FIG. 4. SOLUBILITIES OF THE NITRILES IN TRICHLOROMETHANE

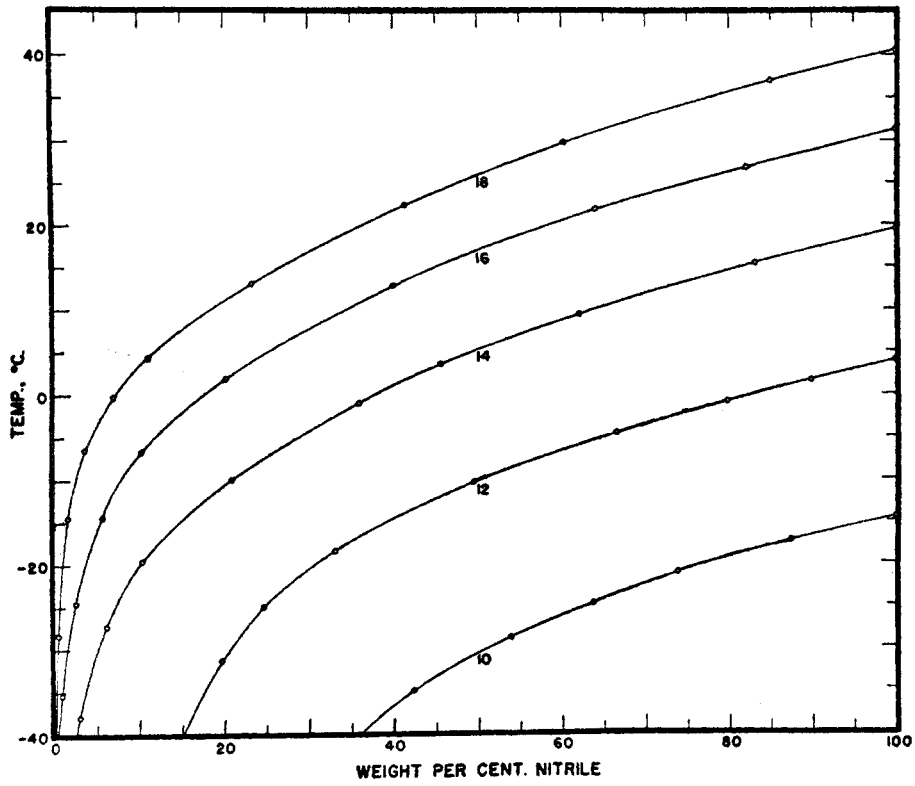

FIG. 5. SOLUBILITIES OF THE NITRILES IN ETHYL ETHER

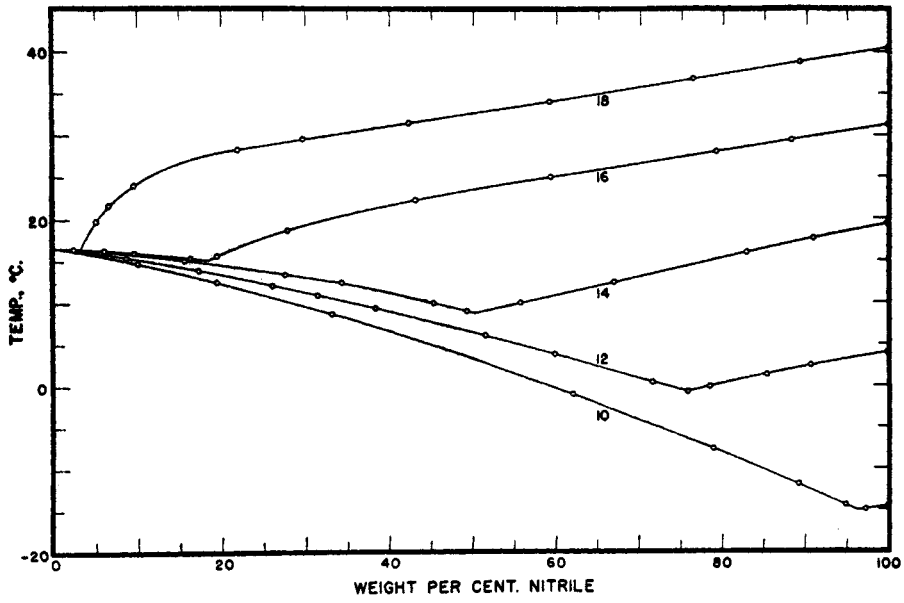

FIG. 6. SOLUBILITY CURVES OF THE NITRILES IN GLACIAL ACETIC ACID

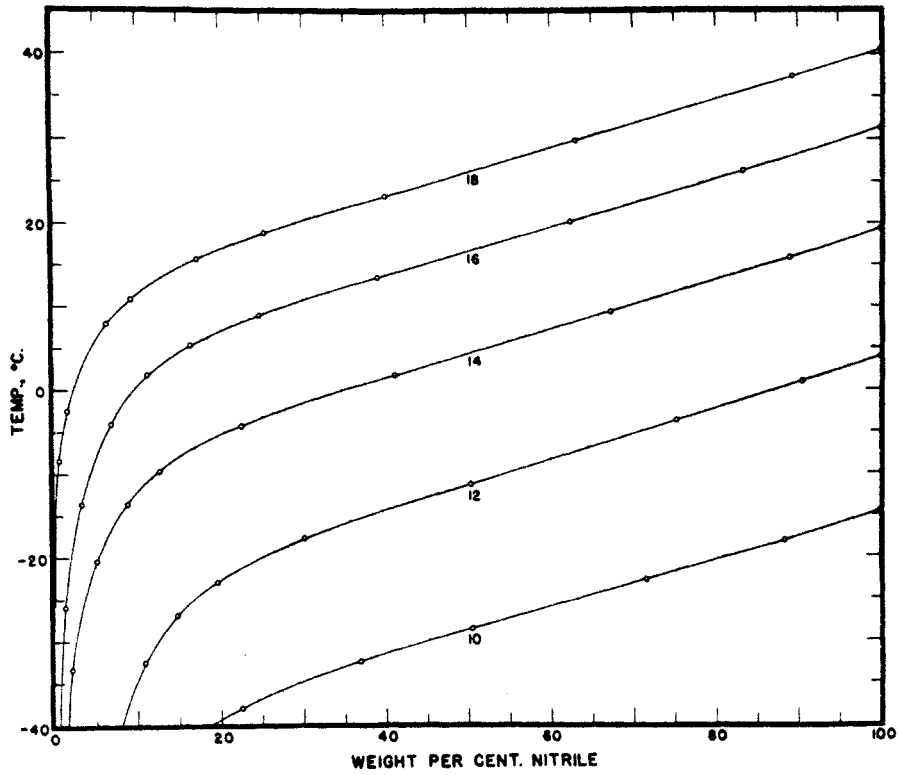

FIG. 7. SOLUBILITIES OF THE NITRILES IN ETHYL ACETATE

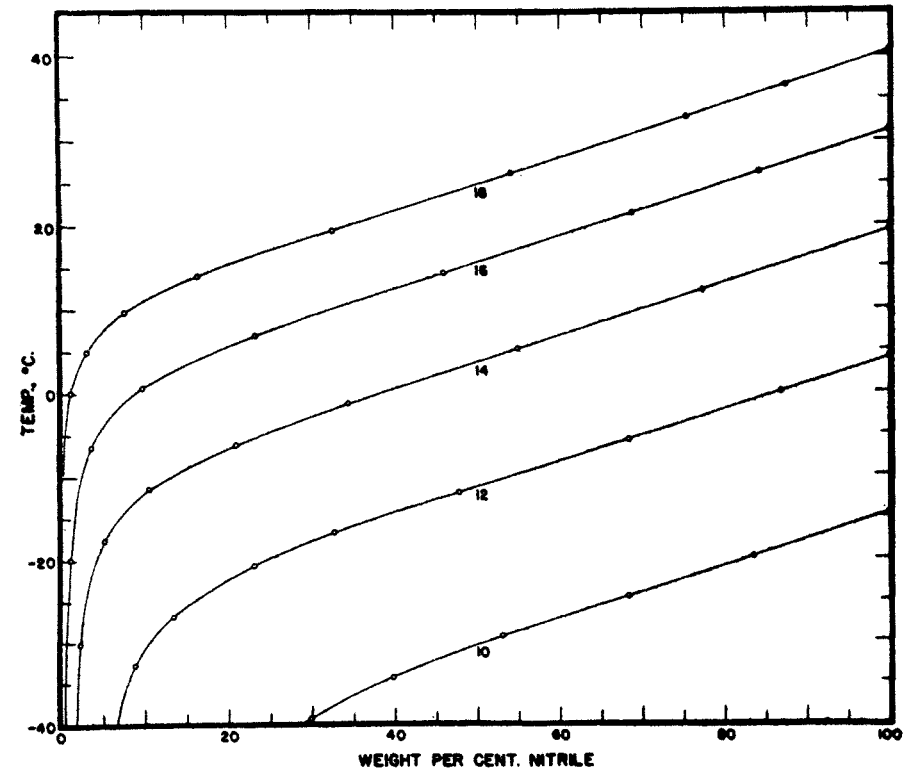

FIG. 8. SOLUBILITIES OF THE NITRILES IN ACETONE

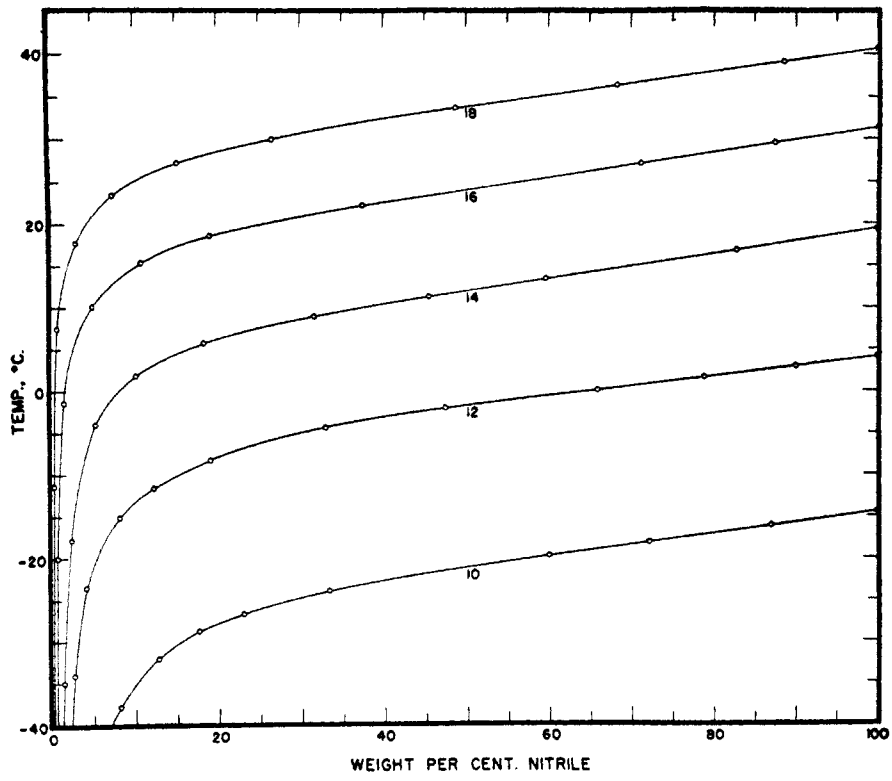

FIG. 9. SOLUBILITIES OF THE NITRILES IN 95% ETHANOL

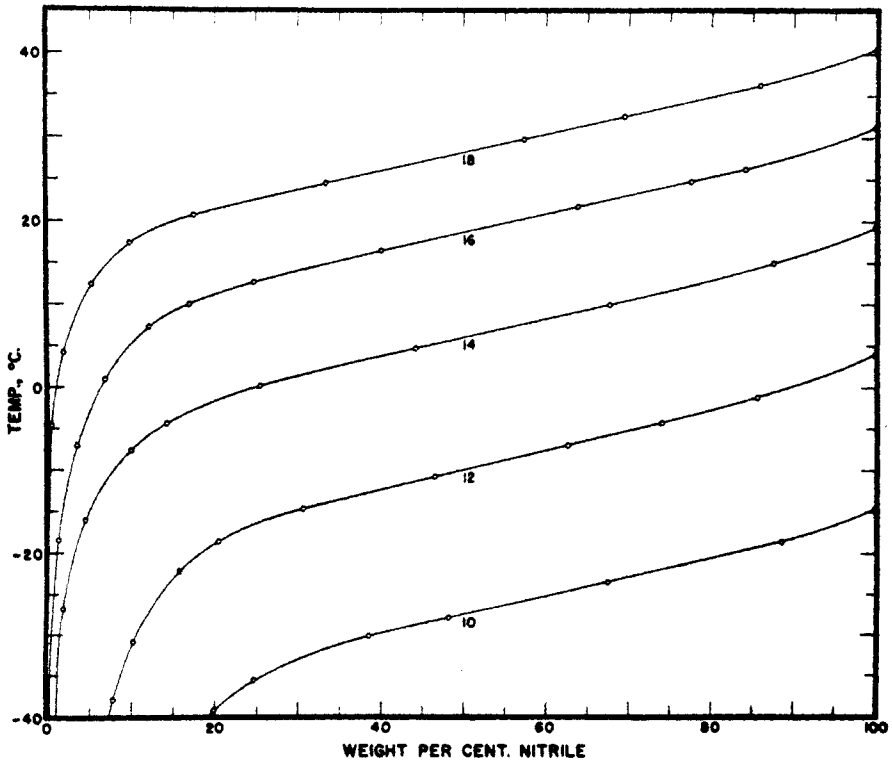

FIG. 10. SOLUBILITIES OF THE NITRILES IN NITROETHANE

solubilities decrease with increased polarity of the solvent. In any given solvent, the solubilities decrease regularly with increased molecular weight of the nitriles.

The aliphatic nitriles form simple eutectics with the non-polar solvents benzene, cyclohexane, and tetrachloromethane. The solubility curves of these systems are shown graphically in Figs. 1–3. The compositions and freezing points of the eutectics are listed in Table II.

The solubilities of the nitriles in benzene and cyclohexane are listed in Table III, and those in tetrachloromethane in Table IV.

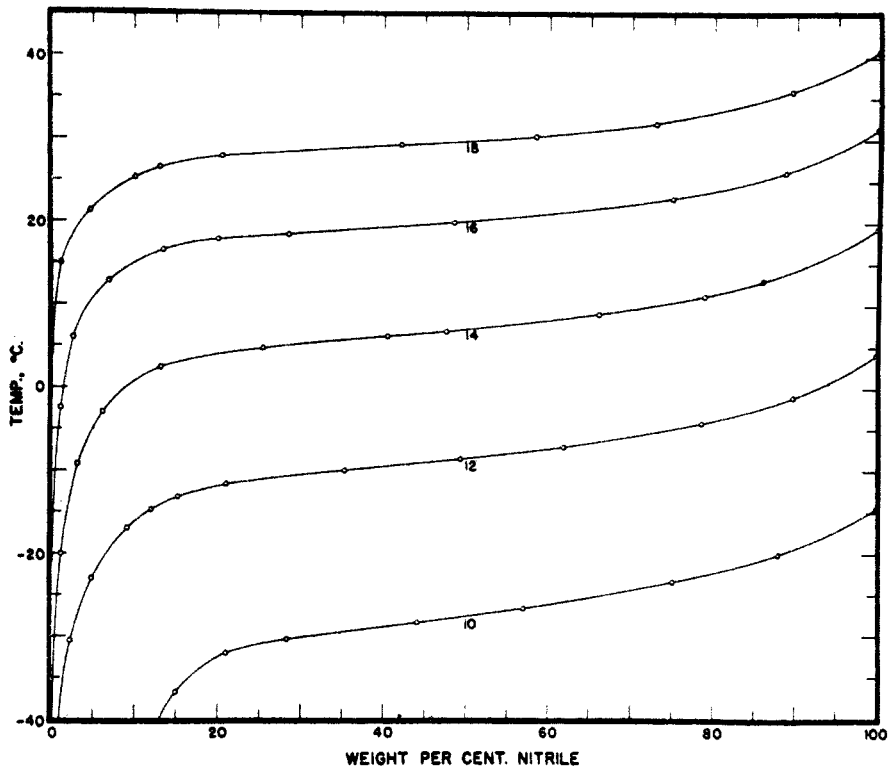

FIG. 11. SOLUBILITIES OF THE NITRILES IN ACETONITRILE

Of the three non-polar solvents investigated the nitriles are most soluble in benzene and least soluble in tetrachloromethane. In view of the fact that these solvents consist of symmetrical molecules whose low dielectric constants[2] are practically identical, it appears that the resonance of the benzene molecule is an important factor affecting the solubility of the nitriles.

[2] The dielectric constants (12) of the solvents used in this investigation are as follows at room temperature: benzene, 2.3; cyclohexane, 2.4; tetrachloromethane, 2.2; trichloromethane, 4.9; ethyl ether, 4.3; glacial acetic acid, 6.7; ethyl acetate, 6.2; butyl acetate, 5.0; acetone, 21; 2-butanone, 18; methanol, 33; 95% ethanol, 25; isopropanol, 26; *n*-butanol, 8; nitroethane, 30; and acetonitrile, 38.

TABLE I

FREEZING POINTS OF PURIFIED NITRILES

NO. OF C ATOMS	NITRILE	F.P., °C.	REF. (M.P., °C.)
10	Caprinitrile	−14.46	−17.9 (6)
12	Lauronitrile	+4.02	+4 (7, 8)
14	Myristonitrile	19.25	19 (7, 8)
16	Palmitonitrile	31.40	31 (7, 8)
			29 (9)
			30-31 (10)
18	Stearonitrile	40.88	41 (7, 8)

TABLE II

EUTECTICS FORMED BY NITRILES

SOLVENT		NO. OF C ATOMS				
		10	12	14	16	18
Benzene	Wt. % Nitrile	66.6	51.1	39.0	28.4	19.2
	F.P., °C.	−25.9	−14.8	−7.6	−2.6	+1.2
Cyclohexane	Wt. % Nitrile	29.7	19.9	12.1	5.6	2.8
	F.P., °C.	−28.8	−15.1	−5.2	+2.0	+4.8
Tetrachloro-methane	Wt. % Nitrile	20.2	7.9	2.1	0.7	≈0.1
	F.P., °C.	−38.9	−27.9	−23.8	−23.0	−22.8

TABLE III

SOLUBILITIES OF NITRILES IN BENZENE AND CYCLOHEXANE

NO. OF C ATOMS	GRAMS PER 100 G. BENZENE			GRAMS PER 100 G. CYCLOHEXANE		
	10.0°	20.0°	30.0°	10.0°	20.0°	30.0°
10	∞	∞	∞	∞	∞	∞
12	∞	∞	∞	∞	∞	∞
14	318	∞	∞	245	∞	∞
16	101	250	2750	43.2	198	2700
18	50	104	264	11.2	55	223

TABLE IV

SOLUBILITIES OF NITRILES IN TETRACHLOROMETHANE

NO. OF C ATOMS	GRAMS PER 100 G. TETRACHLOROMETHANE				
	−20.0°	0.0°	10.0°	20.0°	30.0°
10	320	∞	∞	∞	∞
12	24.0	515	∞	∞	∞
14	5.1	52	155	∞	∞
16	1.5	15.7	41.0	120	1725
18	0.2	5.2	15.1	41.2	130

TABLE V

SOLUBILITIES OF NITRILES IN TRICHLOROMETHANE

NO. OF C ATOMS	GRAMS PER 100 G. TRICHLOROMETHANE					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	90	395	∞	∞	∞	∞
12	35.1	84	720	∞	∞	∞
14	14.4	34.6	107	260	∞	∞
16	6.3	17.7	52	95	213	2300
18	2.3	7.8	28.2	53	102	233

TABLE VI

SOLUBILITIES OF NITRILES IN ETHYL ETHER

NO. OF C ATOMS	GRAMS PER 100 G. ETHYL ETHER					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	57	345	∞	∞	∞	∞
12	17.8	43.0	480	∞	∞	∞
14	2.6	11.0	60	175	∞	∞
16	0.4	3.6	21.0	52	139	1700
18	≈0.1	0.9	7.5	22.2	56	155

TABLE VII

SOLUBILITIES OF NITRILES IN GLACIAL ACETIC ACID

NO. OF C ATOMS	GRAMS PER 100 G. GLACIAL ACETIC ACID		EUTECTICS	
	20.0°	30.0°	WT.% NITRILE	F.P., °C.
10	∞	∞	96.5	−15.1
12	∞	∞	75.9	−0.7
14	∞	∞	50.4	+8.8
16	48.0	1075	18.4	15.2
18	5.4	47.6	3.1	16.4

TABLE VIII

SOLUBILITIES OF NITRILES IN ETHYL ACETATE

NO. OF C ATOMS	GRAMS PER 100 G. ETHYL ACETATE					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	23.6	442	∞	∞	∞	∞
12	8.7	33.2	690	∞	∞	∞
14	1.6	5.5	55	225	∞	∞
16	0.5	2.0	10.7	38.7	163	2400
18	—	≈0.1	2.3	9.2	40.3	175

TABLE IX

Solubilities of Nitriles in Butyl Acetate

No. of C atoms	Grams per 100 g. butyl acetate					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	28.8	390	∞	∞	∞	∞
12	11.3	24.3	560	∞	∞	∞
14	2.8	7.0	42.8	174	∞	∞
16	1.1	3.0	12.6	34.2	125	1850
18	≈0.2	0.4	3.2	11.7	38.8	142

TABLE X

Solubilities of Nitriles in Acetone

No. of C atoms	Grams per 100 g. acetone					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	40.8	478	∞	∞	∞	∞
12	7.3	32.6	660	∞	∞	∞
14	1.8	4.2	63	239	∞	∞
16	0.3	1.0	9.5	47.8	187	2450
18	—	≈0.1	1.0	8.8	53	197

TABLE XI

Solubilities of Nitriles in 2-Butanone

No. of C atoms	Grams per 100 g. 2-butanone					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	46.0	560	∞	∞	∞	∞
12	11.4	38.7	755	∞	∞	∞
14	3.5	10.0	76	272	∞	∞
16	1.2	3.1	16.4	60	205	2750
18	≈0.1	0.4	5.1	17.1	65	238

TABLE XII

Solubilities of Nitriles in Methanol

No. of C atoms	Grams per 100 g. methanol					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	7.6	170	∞	∞	∞	∞
12	2.0	5.1	163	∞	∞	∞
14	1.0	1.4	5.8	41.4	∞	∞
16	≈0.1	0.2	0.8	2.6	16.8	770
18	—	—	—	≈0.2	1.6	13.6

TABLE XIII

Solubilities of Nitriles in 95.0% Ethanol

No. of C atoms	Grams per 100 g. 95% ethanol					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	7.5	137	∞	∞	∞	∞
12	2.4	5.6	181	∞	∞	∞
14	1.2	2.2	8.7	59	∞	∞
16	0.6	0.7	1.7	5.1	33.3	1000
18	≈0.2	0.3	0.5	0.9	4.5	35.7

TABLE XIV

Solubilities of Nitriles in Isopropanol

No. of C atoms	Grams per 100 g. isopropanol					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	7.5	150	∞	∞	∞	∞
12	2.5	5.6	212	∞	∞	∞
14	1.5	2.3	9.7	67	∞	∞
16	0.6	1.0	2.2	7.2	40.8	1000
18	≈0.1	0.2	0.8	2.2	8.6	54

TABLE XV

Solubilities of Nitriles in *n*-Butanol

No. of C atoms	Grams per 100 g. *n*-butanol					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	7.8	156	∞	∞	∞	∞
12	2.9	6.8	233	∞	∞	∞
14	1.7	3.0	13.2	83	∞	∞
16	0.7	1.2	3.6	12.0	58	1175
18	≈0.2	0.5	1.4	3.8	16.2	83

TABLE XVI

Solubilities of Nitriles in Nitroethane

No. of C atoms	Grams per 100 g. nitroethane					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	23.6	455	∞	∞	∞	∞
12	7.9	22.1	830	∞	∞	∞
14	1.0	3.1	32.7	207	∞	∞
16	≈0.1	1.0	6.6	20.2	127	2850
18	—	≈0.1	0.8	3.9	17.8	137

The behavior of the nitriles in the slightly polar solvents is illustrated by the solubilities in trichloromethane (Fig. 4, Table V), ethyl ether (Fig. 5, Table VI), glacial acetic acid (Fig. 6, Table VII), ethyl acetate (Fig. 7, Table VIII), and butyl acetate (Table IX).

In general, the nitriles are less soluble in these slightly polar solvents than in the non-polar solvents. They are, however, considerably more soluble in trichloromethane than in tetrachloromethane at any given temperature. Evidently halogenation decreases the solubility of nitriles in the hydrocarbons. Contrary to the behavior of other long-chain compounds (2, 3), the nitriles are less soluble in butyl acetate than in ethyl acetate.

The solubilities of the nitriles in acetone are listed in Table X and shown graphically in Fig. 8, and those in 2-butanone are listed in Table XI.

The nitriles are less soluble in acetone than in 2-butanone. They are, however, more soluble in both of these solvents than in any of the less polar solvents, except in the lower concentration ranges.

TABLE XVII

SOLUBILITIES OF NITRILES IN ACETONITRILE

NO. OF C ATOMS	GRAMS PER 100 G. ACETONITRILE					
	−40.0°	−20.0°	0.0°	10.0°	20.0°	30.0°
10	15.6	730	∞	∞	∞	∞
12	0.9	6.9	1200	∞	∞	∞
14	≈0.1	1.1	9.6	258	∞	∞
16	—	≈0.1	1.3	4.6	94	4250
18	—	—	≈0.1	0.5	3.6	115

The solubilities of the nitriles in methanol, 95% ethanol, isopropanol, and *n*-butanol are listed in Tables XII–XV, respectively, and their behavior in these alcohols is illustrated by their solubility curves in 95% ethanol which are shown in Fig. 9.

The nitriles are less soluble in these four alcohols than in any of the preceding solvents. For example, lauronitrile is much less soluble in *n*-butanol than in ethyl acetate whose polarity is of the same order of magnitude as that of *n*-butanol. It is to be noted that the solubilities of the nitriles in these four alcohols differ relatively little at corresponding temperatures, in spite of the wide range of polarity of the alcohols.

The solubilities of the nitriles in nitroethane and in acetonitrile are listed in Tables XVI and XVII, and are shown graphically in Figs. 10 and 11, respectively.

The nitriles are less soluble in these two highly polar solvents than in any of the other solvents investigated, with the exception of the alcohols. They are less soluble in acetonitrile than in nitroethane. The initial slopes of the solubility curves in both acetonitrile and in nitroethane are much more abrupt than

in any of the other solvents studied. The shape of the solubility curves of the nitriles is characteristic of a wide variety of high molecular weight aliphatic compounds. This typical deviation from a linear relationship between temperature and concentration has been attributed to intermolecular association (12, 13) as indicated by the cryoscopic behavior of a number of long chain compounds in benzene. It should be borne in mind, however, that while this type of curve has frequently been obtained for compounds, shown by independent methods to be associated, it does not necessarily follow that all compounds exhibiting this type of curve are associated in solution. The high dipole moments of the nitriles (14) are indicative of a tendency towards association. Evidence of appreciable association of the nitriles due to hydrogen bonding has been reported (15). The nitrogen atom of the nitrile group has, however, been stated to be less active in this respect than that contained in the amine or the amide group. Molecular association is probably one of the factors influencing the slope of the temperature concentration curves of long-chain compounds. No conclusions, however, regarding the nature or the extent of this association should be drawn until further investigations of the behavior of long-chain compounds are available.

SUMMARY

The solubilities of caprinitrile, lauronitrile, myristonitrile, palmitonitrile, and stearonitrile have been determined in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl ether, glacial acetic acid, ethyl acetate, butyl acetate, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF GEORGIA]

SOME DERIVATIVES OF CHLORAL WITH AROMATIC AMINES[1]

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INTRODUCTION

The superiority of the chloral derivatives which have been introduced into medicine as substitutes for chloral hydrate is supposed to lie in their enhanced activity, lack of irritant properties, and improved taste. As a class, however, they are sometimes dismissed with the statement that their activity depends solely on the chloral which they liberate more or less rapidly after ingestion (1).

Although several derivatives of chloral with amides have found some use as hypnotics and sedatives (2, 3, 4), chloral has been combined with amines to give only three compounds for which therapeutic merit is claimed, namely: Hypnal, the addition compound of antipyrine and chloral (5), and the products of the reaction of chloral with Orthoform (6) and with Orthoform New (6), respectively. These three compounds represent in each instance the addition or "aldehyde ammonia" type of compound which results when an amine adds to chloral through its carbonyl group.

In addition to the "chloral amines", two other possible series of compounds from chloral and primary amines are the Schiff bases, $RN{=}CHCCl_3$, obtained by condensing a primary amine with chloral through the elimination of water; and the bis(arylamino)trichloromethylmethanes, $CCl_3CH(NHAr)_2$, obtained by condensing two molecules of an aromatic primary amine with one molecule of chloral through the elimination of one molecule of water.

The bis(arylamino)trichloromethylmethanes, commonly called condensation compounds, are of pharmacological interest for three reasons. (a) The introduction of halogen atoms in an organic molecule may enhance or even confer physiological activity by increasing its solubility in fats (7, 8). (b) The condensation compound of chloral and *p*-phenetidine is analogous to the local anesthetic, Phenacaine (9). (c) It has been reported that the accidental swallowing of a small amount of the derivative from chloral and *o*-toluidine produced a feeling of numbness over the entire body (10).

In view of the above, a series of the addition compounds, 2-trichloro-1-hydroxyethylarylamines, $CCl_3CH(OH)NHAr$, and a series of the condensation compounds, bis(arylamino)trichloromethylmethanes, $CCl_3CH(NHAr)_2$, have been prepared from chloral and some selected aromatic primary amines to be tested as analgesics and anesthetics.

Previous workers, notably Wheeler and his students (11), usually obtained the addition compounds by allowing equal molecular quantities of chloral and

[1] The funds used to defray the cost of this study were generously provided by the Advisory Faculty Council of the University Center in Georgia.

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the amine stand in inert solvents at temperatures ranging from 0 to 40°. Although the condensation compounds could sometimes be obtained under these mild conditions, they were usually prepared by refluxing chloral with the amine for several hours in benzene or toluene.

One Schiff base of chloral, that of chloral with *o*-aminobenzoic acid, is mentioned in the literature (12), but apparently this type of compound is rarely formed from the reaction of chloral with amines.

TABLE I

CONDENSATION COMPOUNDS $CCl_3CH(NHAr)_2$

Ar	FORMULA	YIELD, %	M.P., °C. (corr.)	NITROGEN, %	
				Calc'd	Found
o-C_6H_4COEt[a]	$C_{20}H_{21}Cl_3N_2O_2$	77	160	6.54	6.49
p-$C_6H_4CO_2Et$[b]	$C_{20}H_{21}Cl_3N_2O_4$	97	91.5	6.09	6.04
p-$C_6H_4CO_2Me$[c]	$C_{18}H_{17}Cl_3N_2O_4$	95	104	6.48	6.45
2-Naphthyl[d]	$C_{22}H_{17}Cl_3N_2$	88	116–118	6.73	6.60
m-$C_6H_4CH_3$[e]	$C_{16}H_{17}Cl_3N_2$	95	103.5	8.15	8.00
o-C_6H_4Cl[f]	$C_{14}H_{11}Cl_5N_2$	90	104	7.28	7.20
p-C_6H_4OEt[g]	$C_{18}H_{21}Cl_3N_2O_2$	65	91	6.93	6.86
C_6H_5CO-[h]	$C_{16}H_{13}Cl_3N_2O_2$	95	116	7.53	7.55

[a] From an equal mixture of toluene and ligroin. [b] From ligroin. [c] From an equal mixture of benzene and ligroin. [d] From heptane. [e] From isopropanol. [f] From an equal mixture of ligroin and cyclohexane. [g] From cyclohexane. [h] From benzene.

TABLE II

ADDITION COMPOUNDS $CCl_3CHOHNHAr$

Ar	FORMULA	YIELD %	M.P., °C. (corr.)	NITROGEN, %	
				Calc'd	Found
o-$C_6H_4CO_2Me$[a]	$C_{10}H_{10}Cl_3NO_3$	86	105	4.69	4.52
o-HOC_6H_3-*p*-CO_2Me[b]	$C_{10}H_{10}Cl_3NO_4$	93	155	4.45	4.40
p-C_6H_4COMe[c]	$C_{10}H_{10}Cl_3NO_2$	93	104.5	4.95	4.88

[a] From ligroin. [b] From glacial acetic acid. [c] From a mixture of 8 parts of heptane and 2 parts of benzene. Compound No. 2 has been prepared earlier in an impure state (6).

In contrast to most previous methods, it was found that the condensation compounds, and in a few instances the addition compounds, could be prepared in excellent yields directly from chloral hydrate and the amine, thus avoiding the use of the unstable chloral and the severe conditions which are usually employed for these reactions.

EXPERIMENTAL

One-tenth mole of the amine or its salt was added to 0.1 mole of glacial acetic acid contained in a 500-ml. Erlenmeyer flask. To this was added 0.1 mole of chloral hydrate previously dissolved in 100 ml. of distilled water containing 0.01 mole of sodium acetate. The mixture was mechanically shaken for 72 hours or less depending on the length of time re-

quired for the reaction. The crystalline product, which formed, was filtered off, washed by suction with distilled water and then recrystallized from the appropriate solvent.

The method was checked by treatment of chloral hydrate with *o*-toluidine (10), *p*-aminoacetophenone (13), ethylurethan (14) and several other amines and amides, the chloral addition compounds and/or the chloral condensation compounds of which are known, and in each instance the constants of the particular compound obtained were identical with those reported.

The method was then used to combine chloral hydrate with the following: (a) *o*-aminopropiophenone, (b) ethyl *p*-aminobenzoate, (c) methyl *p*-aminobenzoate, (d) β-naphthylamine, (e) *m*-toluidine, (f) *o*-chloroaniline, (g) *p*-phenetidine, and (h) benzamide. In each case the condensation compound was obtained, and these new compounds are listed in Table I.

Under identical conditions chloral hydrate reacted with the following amines: (a) methyl anthranilate, (b) Orthoform, and (c) *p*-aminoacetophenone respectively to yield the addition compound. These new compounds are listed in Table II.

DISCUSSION

Most of the aromatic amines and the amides, both aliphatic and aromatic, which have been tried with the method gave excellent yields of either the addition compound or the condensation compound with the latter predominating. The compounds can be isolated in a relatively pure state.

The somewhat anomalous reaction of chloral hydrate, which lacks unsaturation, with amines to give these addition and condensation compounds becomes more acceptable in view of the fact that the ammonia addition compound of acetaldehyde readily reacts with semicarbazide to give the same semicarbazide addition compound of acetaldehyde which is obtained when acetaldehyde reacts with semicarbazide (15).

In general it was found that equal molecular quantities of chloral hydrate and the amines reacted more readily and gave better yields regardless of whether the addition or condensation compound was obtained. It would appear, therefore, that the reaction always goes through the addition or "aldehyde ammonia" stage (11), and that the proportion of the reactants has little if any influence on the type of compound produced. Removal of one molecule of chloral hydrate from two molecules of the addition compound should give one molecule of the corresponding condensation compound; and, in fact, this was accomplished with the addition compounds listed in Table II by heating them at 75° in an oven.

The compounds listed in Tables I and II are fairly stable, easily-purified chloral derivatives, some of which can be dissolved in diluted acids.

In no instance was it possible to cause the addition compound to lose the elements of water to produce the —HC=N— linkage which characterizes Schiff bases. This is in agreement with the findings of others.

Some of the compounds described here have been turned over to Dr. Eugene L. Jackson of the Department of Pharmacology of the Medical School of Emory University for pharmacological testing.

ACKNOWLEDGMENT

The authors wish to thank Dr. Walter H. Hartung of the School of Pharmacy of the University of Maryland for the sample of *o*-aminopropiophenone which was used in this study.

SUMMARY

1. A method has been described for preparing a series of addition compounds and a series of condensation compounds of chloral with amines by the use of chloral hydrate.

2. Three new addition compounds of chloral with amines and eight new condensation compounds of chloral with amines have been prepared and purified for pharmacological testing.

3. The three new addition compounds have been converted to the corresponding condensation compounds by means of heat.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XIII. THE SYNTHESIS OF ALIPHATIC AMINO ALCOHOLS OF PHARMACOLOGICAL INTEREST (1)

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Barger and Dale (2) state that for compounds to produce a rise in blood pressure they must have the minimum skeleton Ar-C-C-N, where Ar is an aromatic nucleus. More recently, Gunn and Gurd (3) have shown that the cycle may be hydroaromatic, and they claim no important qualitative difference between β-cyclohexylethylamine and β-phenylethylamine. Hexahydropropadrin, or 1-cyclohexyl-2-aminopropan-1-ol, is also known to have pressor activity (4).

Physiologically active compounds with hydrogenated rings frequently retain their characteristic activity when the cycle is opened (5). Blicke and Zienty (6) found that the antispasmodic value of methyl-di-β-cyclohexylethylamine is altered only quantitatively by opening the ring in the 1,2 position to produce methyldioctylamine. Barger and Dale (2) observed that the physiological response of cyclohexylamine was slower in appearing and was more prolonged but otherwise resembled the pressor activity obtained with *n*-hexylamine.

Consequently, what will be the effect if the ring of hexahydropropadrin is opened at various places in the cycle? Pressor activity is known to exist in aliphatic amines (2, 7) beginning with *n*-butylamine, reaching the maximum with *n*-hexylamine and still apparent in the higher homologs. Dunker and Hartung (8) state that "the introduction of the hydroxyl leads to a decrease in toxicity and activity as compared to the non-hydroxylated amine".

Accordingly, it appeared desirable to prepare for pharmacological examination a series of aliphatic amino alcohols of general structure $RCHOHCHNH_2R'$, and consisting of eight or nine carbon atoms since, in the aromatic amino alcohols, activity is found in arylethanolamines and arylpropanolamines.

The open-chain amino alcohols were obtained by the reduction of the corresponding nitro alkanols. These intermediates were synthesized by the method of Vanderbilt and Hass (9). Of the ten nitro alcohols listed in Table I, Nos. 1, 2, 3, 9, and 10 have been previously reported (10).

Efforts to hydrogenate catalytically the aliphatic nitro alcohols with palladium were unsuccessful. Raney nickel in an acid medium (acetic and carbonic acids) at room temperature was satisfactory. In neutral medium no trace of the desired amino alkanol could be isolated; instead, most of the nitrogen could be accounted for in the form of primary and secondary amines with smaller alkyl groups, indicating that the nitro alkanol chain underwent fission, *e.g.*:

$$RCHOHCHNO_2R' \xrightarrow[\text{Raney nickel}]{\text{neutral solvent}} R'CH_2NH_2 + R'CH_2NHCH_2R$$

That the fission occurs with a partially hydrogenated product is indicated by allowing the nitro alcohol to stand at room temperature for seventy-two hours

with (a) the corresponding amino alcohol; (b) hydrochloric acid; (c) sodium hydroxide; (d) Raney nickel, whereupon the nitro alcohol remained unaffected, and by treating the amino alcohol with hydrogen at temperatures as high as 85°, and pressures as high as 300 pounds per square inch in the presence of Raney nickel, without decomposition.

Electrolytic reduction of 3-nitroheptan-4-ol was very successful.

TABLE I

NITRO ALCOHOLS SYNTHESIZED

COMPOUND	B.P., °C	YIELD, %	REFRACTIVE INDEX AT 22 °C.
1. 3-Nitroheptan-4-ol	122–123/18 mm.	70	
2. 2-Nitro-2-methylhexan-3-ol	122–123/21 mm.	58	
3. 5-Nitroöctan-4-ol	123–124/13 mm.	76	
4. 1-Nitro-3-ethylpentan-2-ol	109–111/26 mm.	51	1.4436
5. 2-Nitro-4-ethylhexan-3-ol	118–120/22 mm.	49	
6. 1-Nitroheptan-2-ol	118–120/24 mm.	55	
7. 2-Nitroöctan-3-ol	133–134/22 mm.	43	1.4524
8. 3-Nitrononan-4-ol	142–143/23 mm.	59	1.4515
9. 1-Nitroöctan-2-ol[a]	130–132/24 mm.	69	
10. 2-Nitrononan-3-ol	134–136/23 mm.	57	

[a] Cerf de Mauny (*Bull. soc. chim.*, **7**, 133 (1940); *Chem. Abstr.*, **34**, 5413 (1940)) gives the boiling point as 135°/10 mm.

TABLE II

AMINO ALCOHOLS SYNTHESIZED

COMPOUND	YIELD, %	B.P., °C.	METHOD*	BENZAMIDES		
				M.P., °C., corr.	NITROGEN ANAL. Calc'd %	NITROGEN ANAL. Found %
1. 2-Amino-4-ethylhexan-3-ol	69	110–112/27 mm.	A	151	5.62	5.68, 5.62
2. 3-Aminoheptan-4-ol	54	98–99 /20 mm.	B	145	5.95	5.91, 5.96
	75		C			
3. 1-Aminoöctan-2-ol	41	130–132/26 mm.	B	158	5.62	5.51, 5.59
4. 5-Aminoöctan-4-ol	66	118–119/26 mm.	A	149–150	5.62	5.47, 5.56
5. 3-Aminononan-4-ol	38	116–118/27 mm.	B	161	5.32	5.34, 5.39

* A—Catalytic reduction with Raney nickel and acetic acid.
B—Catalytic reduction with Raney nickel and carbonic acid.
C—Electrolytic reduction.

Table II contains information pertaining to the amino alcohols synthesized. Hass and Vanderbilt (11) have described previously 3-aminoheptan-4-ol and 5-aminoöctan-4-ol; the other three are unreported.

EXPERIMENTAL

Preparation of the nitro alcohols. The method used was essentially that of Vanderbilt and Hass (9). Immediately prior to use, these products were redistilled and a three-degree cut utilized.

When treated in the manner designed for the preparation of urethans (12), all of the nitro alkanols reacted with α-naphthylisocyanate to produce di-α-naphthylurea. Bickel and French (13) report a similar observation with other alcohols.

Reduction of the nitro alcohols. (*a*) *Catalytic hydrogenation, acetic acid medium.* Twelve grams of glacial acetic acid and 0.2 mole of nitro alcohol were dissolved in enough absolute alcohol to make 100 cc. One gram of Raney nickel was added and the mixture reduced at room temperature with an initial hydrogen pressure of at least 600 pounds per square inch. The pressure drop was theoretical. After the catalyst had been removed by filtration, the alcohol was allowed to evaporate spontaneously. The residue was extracted with 10% hydrochloric acid. After washing the acid extract with toluene, it was made strongly alkaline with 40% sodium hydroxide. The amino alcohol which separated was removed; the remaining aqueous portion was extracted with ether, and this ethereal solution was added to the unpurified amino alcohol. The solution was dried for 18 hours over anhydrous magnesium sulfate. Distillation at reduced pressure yielded the amino alcohol as a water-white liquid.

(*b*) *Catalytic hydrogenation, carbonic acid medium.* The use of solid carbon dioxide reported by Vanderbilt (14) results in the production of carbonic acid which combines with the amine as it is produced. Two-tenths mole of the nitro alkanol was dissolved in enough absolute alcohol to make 100 cc. and 1 g. of Raney nickel was added to this solution. Two hundred grams of solid carbon dioxide was placed in the bomb before sealing. After two hours the pressure became constant at 240 pounds per square inch and the system was assumed to be in thermal equilibrium. Hydrogen was admitted until the pressure rose at least an additional 600 pounds per square inch. After shaking for three hours, the pressure dropped approximately 70% of the theoretical decrease. Additional agitation of 24 hours failed to produce a further change. The nickel was removed, the alcohol evaporated at reduced pressure, and the product isolated as described above.

(*c*) *Electrolytic reduction.*[1] The reduction was carried out in a 1500 cc. beaker using a lead anode, separated from the cathode by a porous cup, and a lead cathode, 15 × 14 cm. The cathode plate was coated with spongy lead just before reduction by placing it in a hot, acidified suspension of lead chloride with a lead anode and passing a current through the cell until the cathode was covered with a gray coat of the spongy lead. The electrolyte consisted of 10% sulfuric acid, approximately one liter being used in the cathode compartment. The porous cup serving as the anode compartment was kept filled with the acid. Seventy-one grams of 3-nitroheptan-4-ol was added to the cathode compartment, the catholyte was continuously stirred, and a current of about 15–17 amperes and about 8 volts was passed through the cell. As the reduction took place, the nitroheptanol, which was suspended in the catholyte, went into solution. After several hours, 47 g. more nitroheptanol was added and reduction continued. Only a small amount of oily material remained at the end of the reduction. The reduction cell was cooled in a water-bath during the operation, the temperature remaining at 35°.

The catholyte was filtered and extracted with toluene. The catholyte was then made strongly alkaline with 40% sodium hydroxide and then solid sodium hydroxide was added. The oil which separated was collected and combined with ether extractions of the alkaline solution. The extract was dried over sodium hydroxide and then distilled.

Oxidation of 5-aminoöctan-4-ol. That the amino alcohols have the structure assigned is confirmed by the oxidation of 5-aminoöctan-4-ol. A sample weighing 5.872 g. was shaken for one hour with 3% solution of potassium permanganate acidified with sulfuric acid; the excess permanganate was reduced with sodium sulfite and the resultant mixture filtered. The filtrate was made alkaline with 10% sodium hydroxide and refiltered. This solution was then evaporated on a water-bath. The dry crystals thus obtained were dissolved in the

[1] The electrolytic reduction was carried out by Dr. Glenn E. Ullyot of the Research Laboratories, Smith, Kline, and French, Philadelphia, Pa., to whom the authors express thanks.

minimum amount of 50% sulfuric acid, and ether was used to extract 5.1 g. of butyric acid, whose identity was proved through the anilide (13).

This represented a 71% yield of butyric acid on the assumption that two molecules of butyric acid are produced from one molecule of the amino alcohol, and since the yield is greater than 50%, proves the assumption.

Preparation of the monobenzoyl derivatives of the amino alcohols. These compounds were synthesized by shaking calculated quantities of the amino alcohol and benzoyl chloride in excess 20% sodium hydroxide solution, and recrystallizing the resulting mass from toluene and then from 50% aqueous alcohol. The properties of the amides are included in Table II.

It was hoped that pharmacological data might be included in this paper, but because of present conditions such studies are being delayed.

CONCLUSIONS

1. In the preparation of open-chain amino alcohols of pharmacological interest, five new nitro alkanols were synthesized.

2. The electrolytic reduction of nitro alkanols gives good yields of corresponding amino alkanols.

3. Raney nickel, in the presence of carbonic or acetic acid, will catalyze the hydrogenation of the nitro alkanols to the corresponding amino alkanols.

4. When the reduction is carried out in neutral solvent, the carbon chain of the nitro alcohol undergoes fission of the alkane chain with the formation of primary and secondary amines. Evidence indicates that the fission takes place with some partially hydrogenated product.

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[CONTRIBUTION FROM THE NOYES LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

PREPARATION AND PROPERTIES OF SOME N-SUBSTITUTED SULFAMIC ACIDS[1]

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The recent development of processes for the production of sulfamic acid on a commercial basis has led to renewed interest and study, not only of the free acid, but of many of its inorganic and organic derivatives (1). From both a practical and a theoretical point of view these compounds hold considerable promise, but it is only through an elucidation of their chemical relationships as nitrogen analogs of sulfuric acid that potential applications will reveal themselves. A consideration of the properties and chemical reactions of sulfamic acid, NH_2SO_3H, leaves no doubt but that this substance may appropriately be designated as an aquo-ammono sulfuric acid. The N-substituted sulfamic acids, $RNHSO_3H$ and $RR'NSO_3H$, may in like manner be looked upon as the nitrogen analogs of the alkyl and aryl sulfuric acids, obtainable either by amination (addition of amine), or by the aminolysis (solvolysis by an amine) of sulfur trioxide, or of its derivatives, respectively. These relationships become apparent by reference to the schematic presentation outlined in Figure 1.

The N-substituted sulfamic acids and their derivatives, the salts, amides, halides, and esters represent a widely diversified class of compounds. Until recently (1) no attempt had been made to classify these compounds with respect to types and general methods of preparation. It was the discovery that the sodium salt of N-phenylsulfamic acid, $C_6H_5NHSO_3Na$, possessed very interesting antipyretic properties that led the authors to study the preparation of related compounds. To do so it became necessary to check carefully recorded methods of synthesis before the preparation of selected compounds for pharmacological evaluation could be undertaken. This study led, subsequently, to the remarkable discovery that salts of N-cyclohexylsulfamic acid stimulate profoundly the sense perception of sweetness. Related compounds were therefore synthesized to determine the effect of structure upon sweetness.

The present paper is divided into four parts: A. General methods for the preparation of N-substituted sulfamic acids; B. Preparation and properties of a selected number of N-substituted sulfamic acids; C. Effect of structure on the physiological properties; D. Effect of structure on sweetness.

A. GENERAL METHODS FOR THE PREPARATION OF N-SUBSTITUTED SULFAMIC ACIDS

Among the methods reported in the literature for the preparation of N-substituted sulfamic acids, the one involving the direct action of chlorosulfonic acid

[1] This paper is an abstract of a thesis submitted by M. Sveda in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry in the Graduate School of the University of Illinois, 1939.

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on an amine in an indifferent diluent was found to be best suited for the preparative work required in the experimental development of the present investigation. Both N-mono- and -disubstituted sulfamic acids can be prepared with the minimum of apparatus and effort. Until this work was initiated, no monoaliphatic amines had been treated with chlorosulfonic acid, but in this investigation the generality of the method was extended to include the utilization of these amines.

Alternative procedures were occasionally employed with varying success. From a perusal of the work of Seyewetz and Bloch (2) it was thought that monoarylsulfamic acids could be prepared easily by reducing an aromatic nitro compound with sodium hyposulfite. This method was used with scant success in this work, because of the difficulty encountered in the isolation of the desired product. It was, however, applied qualitatively for the first time to the preparation of an N-substituted cycloalkylsulfamic acid. Aminolysis of the pyridine-sulfur trioxide addition compound was successful in some instances. A few

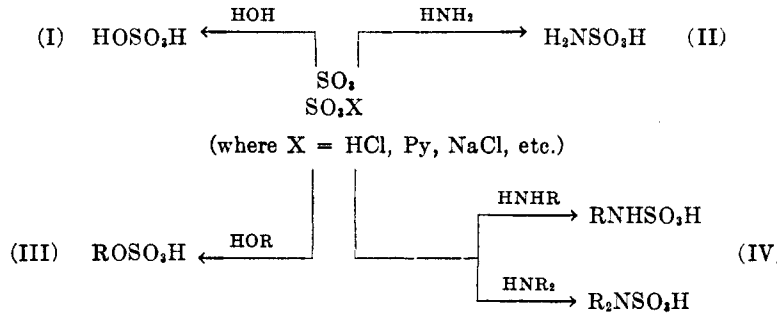

FIG. 1. SOLVATION AND SOLVOLYTIC PRODUCTS OF SULFUR TRIOXIDE AND OF COMPOUNDS RELATED TO SULFURIC ACID: (I) SULFURIC ACID, (II) SULFAMIC ACID, (III) ALKYLSULFURIC ACIDS, (IV) N-SUBSTITUTED SULFAMIC ACIDS.

amines were also treated with sodium chlorosulfonate with success. Traube (3) had subjected to aminolysis a product resulting from the interaction of sodium chloride and sulfur trioxide, but there is no previous record of the production of sulfamic acids from commercial sodium chlorosulfonate. A discussion of these four general procedures follows.

Aminolysis of chlorosulfonic acid. The aminolysis of chlorosulfonic acid is summed up by the following equation:

$$3\ RR'NH + ClSO_3H \rightarrow RR'NSO_3H \cdot HNRR' + RR'NH \cdot HCl$$

Three equivalents of amine are dissolved in several volumes of dry chloroform, and the resulting solution is placed in a three-necked round-bottomed flask fitted with a stoppered dropping-funnel, a thermometer, and an efficient mechanical stirrer. The flask is placed in an ice-salt mixture, and one equivalent of chlorosulfonic acid is added dropwise at such a rate as not to cause the temperature of the reaction mixture to rise above 0°. Several alternative methods are

then available for the actual isolation of particular sulfamates. If the resulting mixture of amine salts is soluble in the reaction medium, the solvent is removed by evaporation under reduced pressure; if the reaction products are insoluble in chloroform, simple filtration attains the same end.

If the free N-substituted sulfamic acid derived from the amine sulfamate formed in the reaction is stable, the amine sulfamate and amine hydrochloride can be separated by fractional crystallization from an aqueous solution. The restriction that the free sulfamic acid be stable is imposed, because amine hydrochlorides, especially those derived from weakly basic amines, render aqueous solutions acid. Furthermore, the presence of an excess of chlorosulfonic acid would, of course, produce the same result. This method of isolating the desired product is applicable only when the N-substituents of the sulfamic acids are entirely aliphatic in character. Moreover, since metallic sulfamates undergo metathetical reactions readily, amine sulfamates are rarely isolated.

The usual procedure for isolating sulfamates involves decomposition of the amine salts with an alkali hydroxide or carbonate, or with an alkaline earth hydroxide. If further metathetical reactions are contemplated, barium hydroxide is the ideal reagent, since it leads to the isolation of the barium sulfamate. The latter can be treated with a variety of soluble sulfates to produce other sulfamates by metathesis.

After treating the amine salts with the metallic hydroxide or carbonate, the liberated amine, if insoluble in water, is removed by extraction with chloroform or ether. If the amine is soluble in water, the former is removed by evaporating the entire solution to dryness under reduced pressure. Should an alkaline earth sulfamate be desired, the excess alkaline earth hydroxide is now removed by dissolving the dry mass in water, and passing in carbon dioxide. The alkaline earth sulfamate is then obtained by fractional crystallization from water.

When alkali hydroxides or carbonates are used to decompose the amine salts, the alkali sulfamates are recovered by the use of either of two general procedures: (a) After the liberated amine is removed, the alkali sulfamate can be separated from the alkali chloride by fractionation from water, the chloride usually being the more soluble. (b) Should the alkali sulfamate be sufficiently soluble in alcohol, the former can be separated from the alkali chloride by extraction of the dry mixture with the hot solvent.

Sodium N-phenylsulfamate by the aminolysis of chlorosulfonic acid. Reagents: 139.5 g. (1.5 moles) of aniline in one liter of $CHCl_3$; 58.3 g. (0.5 mole) of HSO_3Cl; 79.5 g. (0.75 mole) of Na_2CO_3. Yield 37.0 g., corresponding to 40% of the theoretical.

Anal. Calc'd for $C_6H_5NHSO_3Na$: N, 5.84. Found: N, 5.80.

After all of the chlorosulfonic acid had been added, the mixture of amine salts was removed by filtration and added to a solution of the sodium carbonate in 2.5 liters of water. Since the aniline which was liberated did not separate, it was removed by extraction with ether. The aqueous layer was evaporated to dryness on a steam-bath and the dry residue was extracted with absolute alcohol. The crude sodium phenylsulfamate was then purified by crystallization from 97% alcohol, since ethanol of that concentration was found to be a much better solvent for the salt than absolute alcohol.

Nitridation of sodium dithionite. The nitridation of sodium dithionite by nitro compounds to yield sulfamic acids can be represented by the following over-all equation:

$$ArNO_2 + Na_2S_2O_4 + H_2O \rightarrow ArNHSO_3Na + NaHSO_4$$

However, the mechanism of the reaction probably involves two steps:

$$ArNO_2 + Na_2S_2O_4 + H_2O \rightarrow ArNHOH + SO_2 + Na_2SO_4$$
$$ArNHOH + SO_2 + Na^+ \rightarrow ArNHSO_3Na + H^+$$

In addition, the presence of excess hydroxyl ion is necessary to prevent the solution from becoming acid, which would cause decomposition of the arylsulfamic acids. Tertiary sodium phosphate is used for this purpose.

To a solution of 150 g. (0.4 mole) of tertiary sodium phosphate dodecahydrate in 800 cc. of freshly boiled water, is added 760 g. (4.4 moles) of commercial sodium dithionite and 126 g. (1 mole) of nitrobenzene. Twelve hundred cc. of freshly boiled water is then added at a temperature of 50°, and the resulting mixture is agitated until complete solution of the sodium dithionite is effected. After standing at room temperature for 24 hours, the reaction mixture is cooled, and the crude product which precipitates is extracted with boiling absolute alcohol to obtain the sodium N-phenylsulfamate. In a typical experiment, 27.2 g. of sodium N-phenylsulfamate was obtained, corresponding to 15% of the theoretical.

The disadvantages of this method are immediately apparent from a glance at the large quantities of water-soluble salts, other than sodium phenylsulfamate, which are present in solution. Fractionation from water is patently impossible. Furthermore the desired salt is only slightly soluble in boiling absolute alcohol, and consequently the purification of any considerable amount of crude sodium phenylsulfamate is a long and tedious process.

Aminolysis of the pyridine-sulfur trioxide addition compound. The main disadvantage of the use of the pyridine-sulfur trioxide addition compound as an intermediate in the preparation of N-substituted sulfamic acids lies in the relative instability of the sulfonating agent after it is once formed. Since the pyridine-sulfur trioxide addition compound cannot be stored intact for more than a day or two, it must be prepared shortly before it is to be aminolyzed.

Once a quantity of the pyridine-sulfur trioxide[3] addition compound is on hand, the actual aminolysis is a simple task. For every mole of pyridine-sulfur trioxide that is to be used, approximately 2.5 moles of the particular amine is placed in a three-fold volume of ice-water. The reaction flask, fitted with an efficient stirrer, is surrounded by an ice-bath. After gradually sifting in the pyridine-sulfur trioxide addition compound, the reaction mixture is agitated until the former has disappeared. At least four hours are usually necessary to effect aminolysis.

Since organic sulfamic acids are usually isolated as metallic salts, a slight excess of the particular metallic hydroxide is then added. The liberated amines are removed by extraction or distillation, and the metallic sulfamate is purified by fractionation, in much the same manner as metallic sulfamates are isolated from the reaction mixture produced in the aminolysis of chlorosulfonic acid.

[3] Methods for preparation of the pyridine-sulfur trioxide addition compound and of related complexes will be published in Vol. II, Inorganic Syntheses.

Aminolysis of sodium chlorosulfonate. When the study of the aminolysis of sodium chlorosulfonate was first undertaken, the most obvious equation representing the facts was postulated as:

$$2\ RNH_2 + NaSO_3Cl \rightarrow RNHSO_3Na + RNH_2 \cdot HCl$$

It was hoped that the amine could be dissolved in, say, chloroform, and after the sodium chlorosulfonate was added, the reaction product could be removed by filtration. Then the particular sodium sulfamate could be obtained by fractional crystallization from aqueous solution. This would eliminate the addition of sodium hydroxide and much of the subsequent technique employed in the preparation of a metallic sulfamate by the aminolysis of chlorosulfonic acid.

That the above equation did not represent all of the facts was first suspected when cyclohexylamine was used to aminolyze sodium chlorosulfonate. Investigation showed that the amine salt was the product. There was, therefore, no alternative but to add sodium hydroxide to the filtered original reaction product. The resulting solution was then evaporated to dryness under reduced pressure to remove the liberated amine and the residue was recrystallized from water.

There are several possible explanations for the preferential production of the amine salt. The first is that the sodium chlorosulfonate acts as a donor of sulfur trioxide to the amine, thus:

$$2\ RNH_2 + NaSO_3Cl \rightarrow RNHSO_3H \cdot H_2NR + NaCl$$

The second is that the chlorine may be removed from sodium chlorosulfonate by aminolysis as originally postulated, but that since sodium chloride is undoubtedly the least soluble compound present in the reaction mixture, the sodium sulfamate and the amine hydrochloride react metathetically in the chloroform.

One other difficulty, inherent in this method, lies in the composition of the sodium chlorosulfonate. Since the final purification of the desired compound involves a separation of sodium chloride and the particular sodium sulfamate, the 30% sodium chloride originally present in commercial sodium chlorosulfonate must be regarded as an objectionable inert substance.

B. PREPARATION AND PROPERTIES OF SOME N-SUBSTITUTED SULFAMATES

Sodium N-phenylsulfamate. The preparation of this compound by several methods has already been described. In common with salts of other N-arylsulfamic acids, some of which are described below, acidification causes decomposition (hydrolysis) to occur with formation of the amine and sulfuric acid.

The subject compound was found to be soluble in liquid ammonia to yield a solution which would react with sodium to give a white precipitate presumably best represented by the formula $C_6H_5(Na)SO_3Na$. Filtration and treatment of the product with water gave a solution which still yielded a positive sulfamate test, indicating that no deep-seated change had taken place and that in all probability the original reaction with sodium in liquid ammonia had merely involved replacement of the imido hydrogen. This is not altogether unexpected in view of the fact that sulfamic acid behaves as a dibasic acid in liquid ammonia (4).

Sodium N-(p-ethoxyphenyl)sulfamate. Reagents: 51.4 g. (0.375 mole) of *p*-phenetidine in 300 cc. of $CHCl_3$; 14.6 g. (0.125 mole) of HSO_3Cl; 13.3 g. (0.125 mole) of Na_2CO_3 in 200 cc. of H_2O Yield, 13.5 g., corresponding to 45% of the theoretical.

Anal. Calc'd for $C_8H_{10}NNaO_4S$: N, 5.81. Found: N, 5.87.

The salt was purified by recrystallization from ethanol. It had previously been prepared by the reduction of *p*-ethoxynitrobenzene with sodium bisulfite (5).

Sodium N-(p-tolyl)sulfamate. Reagents: 107 g. (1.00 mole) of *p*-toluidine in one liter of CCl_4; 38.8 g. (0.33 mole) of HSO_3Cl; 47.0 g. (0.44 mole) of Na_2CO_3 in 300 cc. of H_2O. Yield, 30 g., corresponding to 45% of the theoretical.

Anal. Calc'd for $C_7H_8NNaO_3S$: N, 6.69. Found: N, 6.85.

The reaction product containing a mixture of sodium salts was extracted with alcohol and the desired compound purified by recrystallization from the same solvent. Sodium *p*-tolylsulfamate had already been prepared by reduction of *p*-nitrotoluene with sodium dithionite (2) and with sodium bisulfite (5).

Sodium N-methyl-N-phenylsulfamate. Reagents: 107 g. (one mole) of methylaniline in one liter of $CHCl_3$; 38.8 g. (0.33 mole) of HSO_3Cl; 42.4 g. (0.4 mole) of Na_2CO_3 in 350 cc. of H_2O. Yield, 57 g., corresponding to 82% of the theoretical.

Anal. Calc'd for $C_7H_8NNaO_3S$: N, 6.69. Found: N, 6.80.

The reaction products resulting from the interaction of the amine and chlorosulfonic acid were soluble in chloroform. The desired substance was recrystallized from absolute ethanol. Sodium N-methyl-N-phenylsulfamate may also be prepared by treatment of sodium N-phenylsulfamate in alkaline solution with dimethylsulfate (5, 6). The potassium and ammonium salts (7) had previously been prepared by a method essentially similar to that described by the authors.

Sodium N-benzylsulfamate. Reagents: 32.1 g. (0.3 mole) of benzylamine in 200 cc. of $CHCl_3$; 11.7 g. (0.1 mole) of HSO_3Cl; 10 g. (0.25 mole) of NaOH in 100 cc. of H_2O. Yield, 12.2 g., corresponding to 58.5% of theoretical.

Anal. Calc'd for $C_7H_8NNaO_3S$: N, 6.69. Found: N, 6.58.

The product prepared by the aminolysis of chlorosulfonic acid was purified by fractionation from alcohol. The same compound had previously been obtained by the alkaline hydrolysis of the benzyl ester of N-benzylsulfamic acid, which in turn had been prepared by interaction of benzyl chloride and silver sulfamate (8).

Sodium N-(β-phenylethyl)sulfamate. Reagents: 18.2 g. (0.15 mole) of β-phenylethylamine in 100 cc. of $CHCl_3$; 5.9 g. (0.05 mole) of HSO_3Cl in 25 cc. of $CHCl_3$; 5.0 g. (0.125 mole) of NaOH in 60 cc. of H_2O. Yield, 5.5 g., corresponding to 50% of the theoretical.

Anal. Calc'd for $C_8H_{10}NNaO_3S$: N, 6.28; Na, 10.3.
Found: N, 6.33; Na, 10.28.

Purification of this salt by recrystallization from water was found to be difficult because of excessive foaming of the solution. Consequently, 98% ethanol was employed for this purpose.

Sodium N-(γ-phenylpropyl)sulfamate. Reagents: 16.2 g. (0.12 mole) of γ-phenylpropylamine in 100 cc. of $CHCl_3$; 4.66 g. (0.04 mole) of HSO_3Cl in 15 cc. of $CHCl_3$; 5 g. (0.125 mole) of NaOH in 50 cc. of H_2O. Yield, 5.0 g., corresponding to 52% of the theoretical.

Anal. Calc'd for $C_9H_{12}NNaO_3S$: N, 5.90; Na, 9.72.
Found: N, 5.80; Na, 9.52.

The product resulting from the interaction of the amine and chlorosulfonic acid did not precipitate from chloroform solution. Removal of the solvent by evaporation under reduced pressure yielded a viscous mass which crystallized only on standing. The aqueous solution of the sodium salt also foamed copiously with the result that 90% alcohol was used to effect purification by recrystallization.

Sodium N-(n-hexyl)sulfamate. Reagents: 15.2 g. (0.15 mole) of *n*-hexylamine in 100 cc. of $CHCl_3$; 5.9 g. (0.05 mole) of HSO_3Cl in 25 cc. of $CHCl_3$; 5 g. (0.125 mole) of NaOH in 50 cc. of H_2O. Yield, 5.6 g., corresponding to 55% of the theoretical.

Anal. Calc'd for $C_6H_{14}NNaO_3S$: N, 6.90; Na, 11.3.
Found: N, 7.00; Na, 11.22.

The reaction products resulting from the interaction of *n*-hexylamine and chlorosulfonic acid were found to be soluble in chloroform. As in the case of the two previous salts derived

from β-phenylethylamine and γ-phenylpropylamine, aqueous solutions of the sodium salt of N-(*n*-hexyl)sulfamic acid foamed so markedly that recrystallization from water was impossible.[4] The product was therefore purified by recrystallization from 95% ethanol.

Cyclohexylammonium N-cyclohexylsulfamate. Reagents: 99 g. (1 mole) of cyclohexylamine in 300 cc. of $CHCl_3$; 38.8 g. (0.33 mole) of HSO_3Cl. Yield, 54 g. corresponding to 58% of the theoretical.

Anal. Calc'd for $C_{12}H_{26}N_2O_3S$: S, 11.52. Found: S, 11.76.

After all the chlorosulfonic acid had been added, the precipitated reaction product was fractionated from water until the desired compound was obtained free from chloride ion.

Sodium N-cyclohexylsulfamate. Reagents: 198 g. (2 moles) of $C_6H_{11}NH_2$ in one liter of $CHCl_3$; 78 g. (0.66 mole) of HSO_3Cl; 60 g. (1.5 moles) of NaOH in 900 cc. of H_2O. Yield, 102 g., corresponding to 77% of the theoretical.

Anal. Calc'd for $C_6H_{12}NNaO_3S$: N, 6.97. Found: N, 6.98.

The first fractions of sodium N-cyclohexylsulfamate, amounting to 90 g., were obtained from water. When it became difficult to obtain chloride-free material from water, the solution was evaporated to dryness and the residue extracted with 80% ethanol. Fractionation of the alcoholic filtrate yielded an additional 12 g. of sodium N-cyclohexylsulfamate.

The preparation of the sodium salt was also effected qualitatively by reaction of nitrocyclohexane with sodium dithionite in aqueous solution in the presence of tertiary sodium phosphate.

Barium-N-cyclohexylsulfamate. Reagents: 148.5 g. (1.5 mole) of $C_6H_{11}NH_2$ in 800 cc. of $CHCl_3$; 58.3 g. (0.5 mole) of HSO_3Cl; 175 g. (0.56 mole) of $Ba(OH)_2 \cdot 8H_2O$ in 1200 cc. of freshly boiled water. Yield, 79 g., corresponding to 57% of the theoretical.

Anal. Calc'd for $C_{12}H_{24}BaN_2S_2O_6 + 1.5\ H_2O$: Ba, 26.44; S, 12.31.
Found: Ba, 26.41, 26.39; S, 12.30, 12.35.

After addition of the mixture of amine salts to the aqueous barium hydroxide solution, extreme care had to be exercised to remove all of the liberated cyclohexylamine by evaporating the entire solution to dryness under reduced pressure. The amine is sufficiently basic to permit precipitation of barium carbonate by the addition of carbon dioxide to an aqueous solution of barium chloride containing free cyclohexylamine.

Ammonium N-cyclohexylsulfamate. Reagents: 1.32 g. (0.01 mole) of $(NH_4)_2SO_4$ in 15 cc. of H_2O; 5.21 g. (0.01 mole) of $Ba(SO_3NHC_6H_{11})_2 \cdot 1.5H_2O$ in 40 cc. of H_2O. Yield, 3.7 g., which is practically the theoretical.

Anal. Calc'd for $C_6H_{16}N_2O_3S$: S, 16.34. Found: S, 16.52.

Precipitated barium sulfate was removed by filtration and the product recovered by evaporation of the filtrate. The ammonium salt appears to sinter at about 208°, but does not melt even at 220°.

The ammonium salt was also prepared by metathesis in liquid ammonia from ammonium chloride and the barium salt. Interaction of equivalent quantities of these reactants takes place with precipitation of barium chloride, which is insoluble in liquid ammonia. The precipitated barium chloride is removed by filtration and the liquid ammonia solution is allowed to evaporate, leaving behind a residue of ammonium N-cyclohexylsulfamate.

Silver N-cyclohexylsulfamate. Reagents: 13.4 g. (0.067 mole) of $C_6H_{11}NHSO_3Na$ in 600 cc. of hot water; 11.3 g. (0.067 mole) of $AgNO_3$ in 150 cc. of hot water. Yield, 16 g., corresponding to 85% of the theoretical.

Anal. Calc'd for $C_6H_{12}AgNO_3S$: Ag, 37.69. Found: Ag, 37.67, 37.57.

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[4] It is interesting in this connection to refer again to the fact that the N-substituted sulfamic acids are the analogs of the alkyl sulfuric acids. Long-chain derivatives of the latter, in the form of their alkali salts, have found wide commercial application as surface active agents. The anions, SO_3NHR^- or $SO_3NRR'^-$, where R and R′ are high molecular weight alkyl or aralkyl radicals, possess the characteristically polar structure which imparts similar properties to salts of certain N-substituted sulfamic acids.

A slight amount of precipitate was formed when the reactants were mixed. After filtration through a sintered glass filter the silver salt precipitated from the cooled filtrate. It should be emphasized that solutions of the salt are especially sensitive towards dust and organic matter; also that preparation of the silver salt must be carried out in a darkened room because of its extraordinary sensitivity to light, when moist.

N-cyclohexylsulfamic acid. Reagents: 4.36 g. (0.0084 mole) of $Ba(SO_3NHC_6H_{11})_2 \cdot 1.5\,H_2O$ suspended in 50 cc. of water; 33.1 cc. of 0.505 *N* H_2SO_4. Yield, 2.8 g., which is practically the theoretical. The melting point was found to be 169–170° (uncorr).

Anal. Neutral equiv. Calc'd for $C_6H_{11}NHSO_3H$: 179.24. Found: 178.94.

The neutral equivalent was obtained by titrating a sample of the free acid with standard barium hydroxide by means of a Beckman *p*H meter. The end-point lay between *p*H 7.3–7.4, indicating that cyclohexylsulfamic acid is a fairly strong acid.

Cyclohexylsulfamic acid must be prepared cold, because the free acid is slowly hydrolyzed by hot water. After removal of the precipitated barium sulfate, the filtrate was concentrated under reduced pressure in order to obtain the desired compound.

Sodium N-dicyclohexylsulfamate. Reagents: 54.35 g. (0.3 mole) of dicyclohexylamine in 200 cc. of $CHCl_3$; 11.65 g. (0.1 mole) of HSO_3Cl; 8 g. (0.2 mole) of NaOH in 400 cc. of H_2O. Yield, 24.5 g., corresponding to 86% of the theoretical.

Anal. Calc'd for $C_{12}H_{22}NNaO_3S$: N, 4.95. Found: N, 4.89.

The reaction products resulting from the interaction of dicyclohexylamine and chlorosulfonic acid did not precipitate from chloroform. Evaporation of the solvent yielded a crystalline mass which, on treatment with aqueous sodium hydroxide was converted into the slightly soluble sodium salt. The sodium salt dissolved completely when the solution was heated to 50°, making it possible to separate the liberated dicyclohexylamine. Cooling of the aqueous solution gave the impure sodium salt which was purified by solution in cold ethanol and subsequent precipitation by the addition of a large quantity of ether.

N-dicyclohexylsulfamic acid. Reagents: 2.84 (0.01 mole) of sodium N-dicyclohexylsulfamate in 20 cc. of H_2O; 10 cc. of an aqueous solution containing one cc. of conc'd HCl. Yield, quantitative. Melting point, 161° (uncorr.).

Anal. Neutral equiv. Calc'd for $(C_6H_{11})_2NSO_3H$: 262.3. Found: 266.6

The neutral equivalent was obtained by dissolving a sample of the acid in an excess of standard sodium hydroxide and back-titrating with standard hydrochloric acid, using phenolphthalein as an indicator.

The preparation of the free acid is easily effected since the compound is practically insoluble in water at ordinary temperatures. Purification was effected by dissolving in chloroform and reprecipitating the desired compound by the addition of ether.

Sodium N-ethyl-N-cyclohexylsulfamate. Reagents: 38.1 g. (0.3 mole) of N-ethylcyclohexylamine in 200 cc. of $CHCl_3$; 11.65 g. (0.1 mole) of HSO_3Cl in 25 cc. of $CHCl_3$; 10 g. (0.25 mole) of NaOH in 150 cc. of H_2O. Yield, 19.5 g., corresponding to 85% of the theoretical.

Anal. Calc'd for $C_8H_{16}NNaO_3S$: N, 6.11. Found: N, 6.09.

Purification was effected by dissolving the crude sodium salt in absolute ethanol followed by addition of an excess of ether.

Sodium N-methyl-N-cyclohexylsulfamate. Reagents: 17 g. (0.15 mole) of N-methylcyclohexylamine in 100 cc. of $CHCl_3$; 5.9 g. (0.05 mole) of HSO_3Cl; 5 g. (0.125 mole) of NaOH in 200 cc. of H_2O. Yield, 8.0 g., corresponding to 75% of the theoretical.

Anal. Calc'd for $C_7H_{14}NNaO_3S$: N, 6.51. Found: N, 6.46.

Purification of the crude product was effected by crystallization from absolute alcohol.

Sodium N-(2-methylcyclohexyl)sulfamate. Reagents: 17 g. (0.15 mole) of 2-methylcyclohexylamine in 100 cc. of $CHCl_3$; 5.9 g. (0.05 mole) of HSO_3Cl in 25 cc. of $CHCl_3$; 5 g. (0.125 mole) of NaOH in 100 cc. of H_2O. Yield, 7.5 g., corresponding to 70% of the theoretical.

Anal. Calc'd for $C_7H_{14}NNaO_3S$: N, 6.51; Na, 10.69.
Found: N, 6.41; Na, 10.35.

Purification of the crude product was effected by recrystallization from absolute ethanol.

Sodium N-(ac-tetrahydronaphthyl)sulfamate. Reagents: 22.1 g. (0.15 mole) of ac-tetrahydro-β-naphthylamine in 100 cc. of $CHCl_3$; 5.9 g. (0.05 mole) of HSO_3Cl in 25 cc. of $CHCl_3$;

5 g. (0.125 mole) of NaOH in 175 cc. of H_2O. Yield, 5.3 g., corresponding to 43% of the theoretical.

Anal. Calc'd for $C_{10}H_{12}NNaO_3S$: N, 5.62; Na, 9.27;
Found: N, 5.50; Na, 9.20.

It was impossible to purify this salt by recrystallization from water, because the foaming properties of the aqueous solution prevented filtration without an undue loss of the froth by entrainment into the vacuum line. Ethanol was therefore employed as the recrystallizing solvent.

C. EFFECT OF STRUCTURE ON THE PHYSIOLOGICAL PROPERTIES OF N-SUBSTITUTED SULFAMATES[5]

The minimal effective antipyretic dose (hereafter designated as M.E.D.) for sodium phenylsulfamate was found to be 15 mg. per kg. on febrile rats. The compound was less effective than acetanilide, which has an M.E.D. of 12.5 mg. per kg. Since phenacetin is a more effective antipyretic than is acetanilide, it was only logical to prepare sodium *p*-ethoxyphenylsulfamate. Strangely enough, sodium *p*-ethoxyphenylsulfamate showed no antipyretic action at a dose of 34.9 mg. per kg. when used to treat febrile rats.

Since the substitution of a *p*-ethoxyl group into the phenyl nucleus destroyed the antipyretic properties of the molecule, the next variation was to introduce a simple alkyl group into the ring. Accordingly, sodium *p*-tolylsulfamate was prepared. The first pharmacological reports on this compound were very encouraging, for the M.E.D. was 10 mg. per kg., or 48.3 micromoles per kg., in contrast to the 15 mg. per kg., or 84.9 micromoles per kg. which had been found for sodium phenylsulfamate. However, another trial carried out one month later was anything but encouraging, for when the dosage was increased to 75 micromoles per kg., a marked *hyperthermia* resulted.

This sharp reversal in antipyretic action may be a characteristic of sodium *p*-tolylsulfamate. On the other hand, it must be borne in mind that one month separated the two tests. Arylsulfamates are extremely sensitive to hydrolysis, especially after incipient hydrolysis has once occurred. Since no special precautions were observed to protect the substance from contact with moisture of the atmosphere, the marked hyperthermia caused by the compound one month after the first tests may have been the result of decomposition products.

More significant, perhaps, than the mere antipyretic action of these compounds, was the duration of time over which the antipyretic action was apparent. Although sodium phenylsulfamate was not as effective mole for mole as was acetanilide, the action of the former was much more prolonged. The sulfamic acid grouping appeared to be acting as a dam, slowly releasing the antipyretic constituent, in this case, undoubtedly, aniline.

On the assumption that this was, indeed, the function of the sulfamic acid portion of the molecule, sodium (β-phenylethyl)sulfamate was prepared in the hope that this substance would also be effective for a longer period of time than β-phenylethylamine itself. If the sulfamic acid derivative of this amine exhibited a prolongation of the latter's characteristic effect, the next logical extension

[5] Based upon pharmacological studies carried out by C. L. Rose of the Lilly Research Laboratories, Indianapolis, Indiana.

would be a study of the sulfamic acid derivatives of adrenaline and ephedrine. Moreover, all previous work on other types of aralkyl amine derivatives had shown that the essential grouping was Ar—C—C—N, and that any variation from two in the number of carbon atoms separating the aryl group and the amino nitrogen resulted in a marked decrease in the pressor action. Therefore, the homologs, sodium benzylsulfamate, $C_6H_5CH_2NHSO_3Na$, and sodium (γ-phenylpropyl)sulfamate, $C_6H_5CH_2CH_2CH_2NHSO_3Na$, were also prepared, in order to determine whether this decrease in activity extended to the sulfamates. At the same time, sodium ac-tetrahydro-β-naphthylsulfamate, which was prepared primarily for determining the effect of structure on the sweetness of cyclohexylsulfamic acid derivatives, was also tested, because ac-tetrahydronaphthylamine was known to have a pressor action similar to that of β-phenylethylamine.

However, pharmacological data showed that sodium β-phenylethylsulfamate exhibited markedly less pressor action than did β-phenylethylamine itself. The homologs of sodium β-phenylethylsulfamate were, therefore, not tested.

A plausible explanation for the decrease in activity of these sulfamates is extremely easy to formulate. Sodium N-β-phenylethylsulfamate, and sodium N-ac-tetrahydro-β-naphthylsulfamate contain the aralkyl groups directly attached to the sulfamic acid grouping. They are, therefore, much less susceptible to hydrolysis, and the free amine which, in the last analysis, would cause the pressor action, is not readily liberated. On the other hand, the N-arylsulfamic acids which exhibited an antipyretic action are much more readily hydrolyzed to yield the corresponding amines.

D. EFFECT OF STRUCTURE ON THE SWEETNESS OF CYCLOHEXYLSULFAMIC ACID DERIVATIVES

The discovery of the remarkable extent to which salts of N-cyclohexylsulfamic acid stimulated the sense perception of sweetness lead to a study of various N-substituted sulfamic acids in order to determine which groups were responsible for this phenomenon.

From the fact that sodium N-phenylsulfamate possessed only a sweet aftertaste, it was obvious that if a ring attached directly to the nitrogen is essential, that ring must be reduced. In order to ascertain whether a ring is essential, sodium N-*n*-hexylsulfamate was prepared. The latter compound can be considered as sodium N-cyclohexylsulfamate in which the ring has undergone fission. The hexyl derivative was not sweet, again limiting the property of sweetness to a reduced ring.

The next step was to determine whether an N-cyclohexylsulfamic acid in which the ring was left intact could be modified in any manner which would destroy the characteristic sweet taste. Since free N-cyclohexylsulfamic acid possesses a lemon-sour sweetness, and the silver, sodium, ammonium, and cyclohexylammonium salts all had a marked sweetness, no further modifications of the salt-forming groups were attempted. This left only the hydrogen on the

nitrogen to be changed. Accordingly, the hydrogen was replaced, in turn, by the methyl, ethyl, and cyclohexyl groups. None of the resulting compounds was sweet, *viz.*, sodium N-methyl-N-cyclohexylsulfamate, sodium N-ethyl-N-cyclohexylsulfamate, and sodium N-dicyclohexylsulfamate.

It remained to be determined whether substituents on the cyclohexyl ring could be introduced without losing, qualitatively at least, the sweetness characteristic of N-cyclohexylsulfamic acid and its salts. Although the attempt to prepare sodium N-menthylsulfamate failed, sodium N-(2-methylcyclohexyl)sulfamate and sodium N-(ac-tetrahydro-β-naphthyl)sulfamate were found to be capable of existence. Both of these compounds were sweet, the former markedly so, and the latter only slightly. It should be pointed out that the latter is a cyclohexenyl derivative, and not strictly a ring substituted cyclohexylsulfamate.

TABLE I

COMPARISON OF SWEETNESS

COMPOUND	DILUTION IN WATER AT WHICH SWEETNESS IS EASILY PERCEPTIBLE
$C_6H_{11}NHSO_3Na$	1:10,000
$C_6H_{11}NHSO_3NH_4$	1: 5,000
o-$CH_3C_6H_{10}NHSO_3Na$	1: 2,500
saccharin	1:50,000
sugar	1:140

Thus the groups essential for sweetness were found to be: (a) a cyclohexyl ring, which may or may not be substituted, and (b) a free hydrogen on the nitrogen: (simple or substituted cyclohexyl ring)—N(H)—SO_3X, where X may be almost any salt-forming group.

It is of interest to note that the —C(H)—N(H)—SO_2— linkage occurs in both the cyclohexylsulfamic acid derivatives and in saccharin. However, it should also be pointed out that the two types of molecules have very little else in common.

Insofar as the actual determination of the extent to which a compound affects the sense perception of sweetness is concerned, the results are, at best, semi-quantitative. However, conservative estimates of the sweetness of several of these compounds are recorded in Table I.

In view of the remarkable sweetness of derivatives of cyclohexylsulfamic acid it was deemed advisable to carry out a number of feeding experiments on rabbits and rats to determine if any adverse physiological effects were produced. The authors are indebted to Professor H. E. Carter and Mr. J. R. Weisiger of the Department of Biochemistry of the University of Illinois for carrying out the experiments the results of which are summarized in the following report:

"1. In order to determine whether sodium cyclohexylsulfamate is altered in

any way by the animal body, it was administered orally, intraperitoneally, and intravenously to rabbits. The urine was collected for 12 hours and was analyzed as follows: Excess barium chloride was added to an aliquot portion of the urine. The precipitated barium sulfate was filtered. The filtrate was acidified with hydrochloric acid and sodium nitrite was added. Nitrous acid decomposes the cyclohexylsulfamic acid yielding sulfuric acid which precipitates in the presence of the excess barium chloride. The barium sulfate was filtered, dried, and weighed. Controls with normal urine gave no precipitate after the nitrous acid treatment. Analysis of normal rabbit urine to which varying amounts of the sulfamic acid had been added gave nearly theoretical recoveries (95–97%). The amounts of the sulfamic acid recovered in the urine after administration to rabbits varied from 80 to 90% of the amount given. The method of administration had no consistent effect on the amount recovered although the feeding gave slightly higher recoveries in four out of six experiments.

"2. In order to determine whether the substance has any marked toxic effects a group of fifteen white rats weighing 50–60 gm. were divided into five groups. All were given the ordinary stock ration. Group I was a control, receiving only the stock ration and daily intraperitoneal injections of 2.0 cc. of 5% sodium chloride solution. Groups II, III, IV, and V received respectively 0.01, 0.05, 0.1, and 0.5 gm. per day of the sodium salt dissolved in 2.0 cc. of water and administered by intraperitoneal injection. The growth of all the rats was followed for a two weeks' period. The amounts of food consumed and the weight gained by the controls and the experimental animals was identical. At the end of the experiment blood nonprotein nitrogen and blood hemoglobin values were determined. The values were all within the normal range.

"3. We were interested in the voluntary food consumption by rats of food containing varying amounts of the sodium salt. The rats always cleaned up 10 gm. of the stock ration daily. When 0.1 gm. of the sodium salt was added to the 10 gm. portion of stock ration the food consumption varied between 7 and 10 gm. When as much as 0.5 gm. of the sodium salt was added to 10 gm. of food the consumption dropped to 3–5 gm. per day.

"In other experiments the rats were given a choice between stock ration and stock ration containing 1 per cent of the sodium salt. In every case the rats consumed all the stock ration and very little or none of the sweetened food. However, these experiments are probably of no significance with respect to other species of animal."

ACKNOWLEDGMENTS

The authors consider it a privilege to acknowledge their indebtedness to the Eli Lilly Company for the financial support, in the form of a research fellowship, which made this study possible. Their thanks are also extended to personnel of the Lilly Research Laboratories, especially to Mr. H. A. Shonle for his very real interest in this problem and for his many helpful suggestions, and to Mr. C. L. Rose who supplied most of the pharmacological data. Appreciation is also expressed here for the help rendered by Professor H. E. Carter and Mr. J. R.

Weisiger of the University of Illinois in carrying out animal feeding experiments. Thanks are also due the Monsanto Chemical Company for making available many otherwise difficultly obtainable amines.

SUMMARY

1. Methods for the preparation of N-substituted sulfamic acids have been reviewed and subjected to a critical evaluation. The procedure involving aminolysis of chlorosulfonic acid is considered superior to those involving (a) reaction of amines with addition compounds of sulfur trioxide and with sodium chlorosulfonate and (b) nitridation of dithionites, such as the interaction of aliphatic and aromatic nitro compounds with sodium dithionite.

2. The chemical properties and pharmacological characteristics of a number of N-substituted sulfamic acids have been determined. Isolation of derivatives of the following compounds has been effected: (a) N-monosubstituted sulfamic acids, $RNHSO_3H$, where R = phenyl, *p*-ethoxyphenyl, *p*-tolyl, benzyl, β-phenylethyl, γ-phenylpropyl, *n*-hexyl, cyclohexyl, 2-methylcyclohexyl, ac-tetrahydronaphthyl; (b) N-disubstituted sulfamic acids, $RR'NSO_3H$, where R and R′ are, respectively, methyl and phenyl, cyclohexyl and cyclohexyl, ethyl and cyclohexyl, and methyl and cyclohexyl.

3. The extraordinary sweetness of certain N-substituted sulfamic acids is thus far limited to those containing as substituent (a) a cyclohexyl ring which may or may not be substituted on the ring and (b) a free hydrogen on the nitrogen atom, *viz.* $RNHSO_3X$, where X is almost any salt-forming group.

URBANA, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

SOLUBILITIES OF HIGH MOLECULAR WEIGHT NORMAL ALIPHATIC PRIMARY AMINES

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The solubility curves of long-chain aliphatic compounds in organic solvents show a characteristic deviation from a linear relationship between concentration and temperature. In low concentrations the solubility of these compounds increases relatively little with considerable increase in temperature, while at higher concentrations their solubility increases markedly with relatively little rise in temperature. Hence, the initial slope of a typical solubility curve is very steep, while at moderate dilutions the slope changes abruptly, giving a relatively flat curve at higher concentrations. This behavior is exhibited by the higher fatty acids (1, 2), ketones (3), nitriles (4), amine salts (5), and amides, anilides, and N,N-diphenylamides (6). In order to obtain more complete data concerning the effects of various polar groups upon the solubilities of aliphatic compounds, the previous investigations in this Laboratory have been extended to the normal aliphatic primary amines. This paper presents the solubilities of decylamine, dodecylamine, tetradecylamine, hexadecylamine, and octadecylamine in fourteen organic solvents.

EXPERIMENTAL

The amines were obtained by hydrogenation of the highly purified nitriles used in the previous solubility investigations (4). They were purified by two distillations *in vacuo* to remove all secondary amine. The freezing points of these amines are listed in Table I.

The solvents were those used for the previous solubility studies. They were freshly distilled and cooled without access to the atmosphere, to prevent contamination with carbon dioxide.

The solubilities of the amines were determined with the equipment and in the manner described in previous reports (4, 10). Precautions were taken to prevent exposure of the amines to carbon dioxide.

RESULTS AND DISCUSSION

The solubility curves of the primary amines are similar to those of the fatty acids, ketones, and nitriles. The amines, however, do not exhibit the marked correlation between solubility and polarity of the solvent which is so striking with the other compounds.

The primary amines form simple eutectics with the non-polar solvents benzene, cyclohexane, and tetrachloromethane. These eutectic systems are illustrated graphically by the benzene (Fig. 1) and tetrachloromethane (Fig. 2) diagrams. The compositions and freezing points of the eutectics are listed in Table II.

The solubilities of the amines in these non-polar solvents are listed in Tables III–V. In these solvents, the amines are most soluble in benzene and least soluble in tetrachloromethane.

The solubilities of the amines in the slightly polar solvents trichloromethane,

ethyl ether, ethyl acetate, and butyl acetate are listed in Tables VI–IX, respectively, and the solubility curves for the amines in trichloromethane are shown graphically in Fig. 3.

TABLE I

FREEZING POINTS OF PURIFIED AMINES

AMINE	NO. OF C ATOMS	F.P., °C.	LIT. M.P., °C.
Decylamine	10	16.11	—
Dodecylamine	12	28.32	25 (7) 27–28 (8, 9) 28.0 (F.P.) (10)
Tetradecylamine	14	38.19	37 (8, 9)
Hexadecylamine	16	46.77	45–46 (9, 11) 46 (12) 47 (13)
Octadecylamine	18	53.06	54–55 (9) 47 (13) 55–56 (14)

TABLE II

EUTECTICS FORMED BY THE AMINES

SOLVENT		NO. OF C ATOMS				
		10	12	14	16	18
Benzene	Wt. % amine	31.7	18.0	10.8	6.1	2.2
	F.P., °C.	−5.6	+0.2	3.0	4.6	5.2
Cyclohexane	Wt. % amine	12.8	8.3	5.5	2.7	1.0
	F.P., °C.	−10.5	−3.5	+0.8	4.0	5.6
Tetrachloro-methane	Wt. % amine	7.2	4.4	1.9	0.4	<0.1
	F.P., °C.	−25.8	−24.4	−23.4	−23.0	—

TABLE III

SOLUBILITIES OF AMINES IN BENZENE

NO. OF C ATOMS	G. PER 100 G. BENZENE				
	10.0°	20.0°	30.0°	40.0°	50.0°
10	395	∞	∞	∞	∞
12	72	277	∞	∞	∞
14	26.4	83	302	∞	∞
16	10.0	30.7	98	388	∞
18	4.2	14.8	52	173	1000

In general, the amines are more soluble in trichloromethane than in any other solvent investigated. It is apparent from the wide divergence of the solubilities in tetrachloromethane and in trichloromethane that further halogenation of the

TABLE IV

SOLUBILITIES OF AMINES IN CYCLOHEXANE

NO. OF C ATOMS	G. PER 100 G. CYCLOHEXANE				
	10.0°	20.0°	30.0°	40.0°	50.0°
10	318	∞	∞	∞	∞
12	57	230	∞	∞	∞
14	19.9	68	268	∞	∞
16	7.4	26.6	86	360	∞
18	2.8	13.2	42.9	144	940

TABLE V

SOLUBILITIES OF AMINES IN TETRACHLOROMETHANE

NO. OF C ATOMS	G. PER 100 G. TETRACHLOROMETHANE					
	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	10.5	57	∞	∞	∞	∞
12	5.5	19.8	148	∞	∞	∞
14	2.3	7.7	56	235	∞	∞
16	0.5	3.2	21.2	73	335	∞
18	<0.1	0.6	7.7	27.9	120	835

TABLE VI

SOLUBILITIES OF AMINES IN TRICHLOROMETHANE

NO. OF C ATOMS	G. PER 100 G. TRICHLOROMETHANE						
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	17.7	43.0	148	∞	∞	∞	∞
12	9.2	20.0	56	315	∞	∞	∞
14	4.5	11.2	29.5	110	308	∞	∞
16	2.4	6.6	17.0	56	117	378	∞
18	1.2	3.3	9.4	31.9	63	149	845

TABLE VII

SOLUBILITIES OF AMINES IN ETHYL ETHER

NO. OF C ATOMS	G. PER 100 G. ETHYL ETHER					
	−40.0°	−20.0°	0.0°	20.0°	30.0°	34.5°
10	1.4	12.1	86	∞	∞	∞
12	0.2	3.4	22.6	275	∞	∞
14	—	0.2	5.8	71	273	705
16	—	—	0.2	18.5	72	135
18	—	—	—	4.4	22.7	46.8

hydrocarbon results in a loss of solvent action. The behavior of the amines in ethyl acetate and in butyl acetate is unusual in that the solubilities are practically identical in these two solvents.

TABLE VIII

SOLUBILITIES OF AMINES IN ETHYL ACETATE

NO. OF C ATOMS	G. PER 100 G. ETHYL ACETATE					
	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	14.8	69	∞	∞	∞	∞
12	4.7	18.6	221	∞	∞	∞
14	1.7	7.8	57	233	∞	∞
16	0.3	3.2	19.7	63	295	∞
18	—	0.9	9.5	27.0	100	845

TABLE IX

SOLUBILITIES OF AMINES IN BUTYL ACETATE

NO. OF C ATOMS	G. PER 100 G. BUTYL ACETATE					
	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	13.3	69	∞	∞	∞	∞
12	4.4	23.0	221	∞	∞	∞
14	1.4	9.7	62	233	∞	∞
16	0.2	3.5	23.9	64	295	∞
18	—	1.0	11.4	30.4	100	845

TABLE X

SOLUBILITIES OF AMINES IN ACETONE

NO. OF C ATOMS	G. PER 100 G. ACETONE					
	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	6.6	54	∞	∞	∞	∞
12	0.3	8.1	266	∞	∞	∞
14	—	0.1	15.5	228	∞	∞
16	—	—	<0.1	4.7	445	∞
18	—	—	—	<0.1	3.7	17.0

TABLE XI

SOLUBILITIES OF AMINES IN 2-BUTANONE

NO. OF C ATOMS	G. PER 100 G. 2-BUTANONE					
	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	10.0	65	∞	∞	∞	∞
12	3.6	18.6	290	∞	∞	∞
14	0.2	2.8	48	285	∞	∞
16	—	—	8.3	48	580	∞
18	—	—	0.2	6.3	85	1975

The solubilities of the amines in acetone and in 2-butanone are listed in Tables X and XI, respectively, and the acetone curves are shown in Fig. 4.

TABLE XII

Solubilities of Amines in Methanol

No. of C atoms	g. per 100 g. methanol						
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	31.0	172	550	∞	∞	∞	∞
12	4.8	29.7	196	930	∞	∞	∞
14	≈0.2	2.8	62	292	770	∞	∞
16	—	0.2	6.1	116	256	785	∞
18	—	—	0.6	15.6	95	256	1440

TABLE XIII

Solubilities of Amines in 95% Ethanol

No. of C atoms	g. per 100 g. 95% ethanol						
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	8.5	91	350	∞	∞	∞	∞
12	2.0	14.1	115	660	∞	∞	∞
14	—	1.5	30.2	218	660	∞	∞
16	—	—	3.0	83	239	770	∞
18	—	—	0.1	7.2	75	280	1630

TABLE XIV

Solubilities of Amines in Isopropanol

No. of C atoms	g. per 100 g. isopropanol						
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	11.1	49.0	228	∞	∞	∞	∞
12	4.7	15.0	75	492	∞	∞	∞
14	0.6	3.7	25.1	154	458	∞	∞
16	—	0.4	7.3	68	169	580	∞
18	—	—	0.5	30.0	86	228	1330

TABLE XV

Solubilities of Amines in *n*-Butanol

No. of C atoms	g. per 100 g. *n*-butanol						
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	9.5	30.8	182	∞	∞	∞	∞
12	2.4	8.5	57	430	∞	∞	∞
14	0.2	2.4	16.5	130	405	∞	∞
16	—	<0.1	3.9	55	148	515	∞
18	—	—	0.4	22.7	75	208	1240

TABLE XVI

Solubilities of Amines in Acetonitrile

No. of C atoms	g. per 100 g. acetonitrile					
	−20.0°	0.0°	20.0°	30.0°	40.0°	50.0°
10	2.8	12.7	∞	∞	∞	∞
12	—	0.2	27.7	∞	∞	∞
14	—	—	1.8	14.9	∞	∞
16	—	—	0.2	1.3	14.8	∞
18	—	—	—	0.3	1.9	10.5

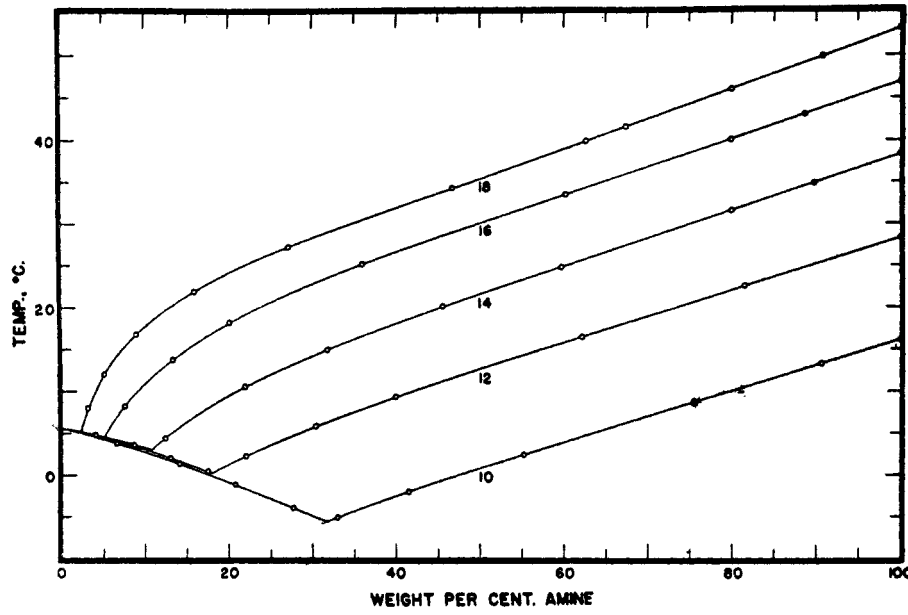

FIG. 1. SOLUBILITIES OF THE PRIMARY AMINES IN BENZENE
The numbers of the curves refer to the number of carbon atoms in the compounds

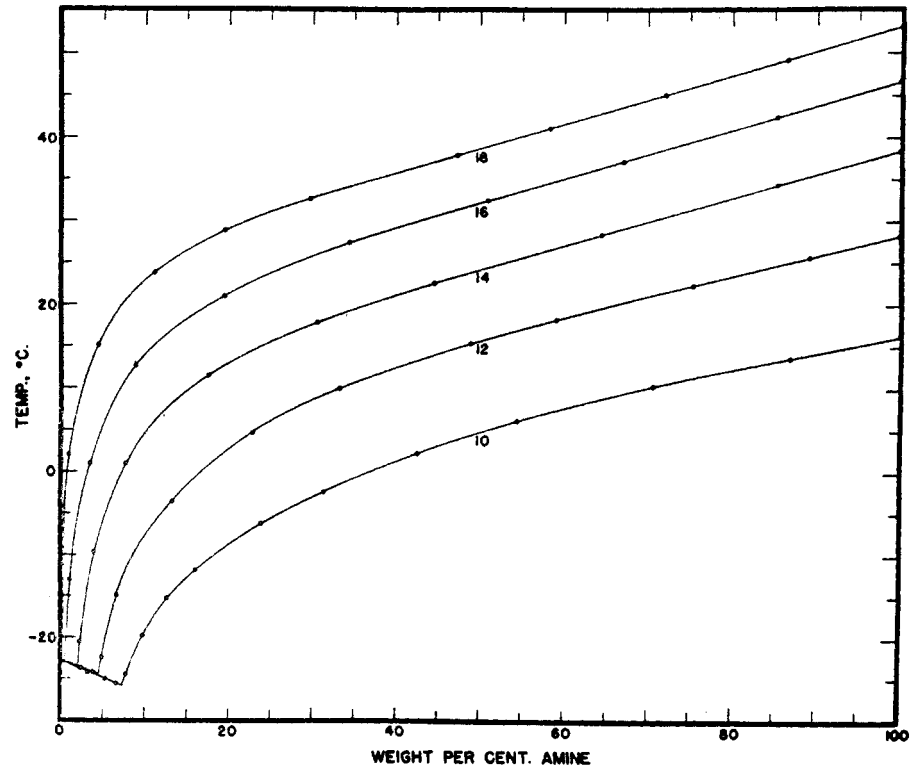

FIG. 2. SOLUBILITIES OF THE PRIMARY AMINES IN TETRACHLOROMETHANE

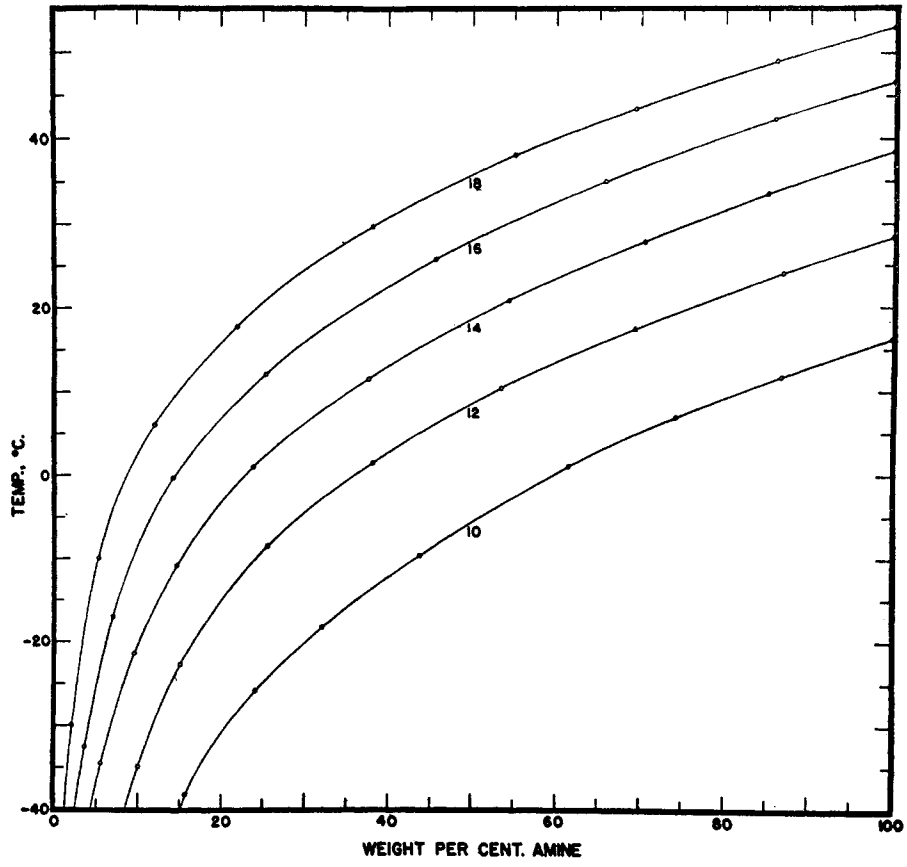

FIG. 3. SOLUBILITIES OF THE PRIMARY AMINES IN TRICHLOROMETHANE

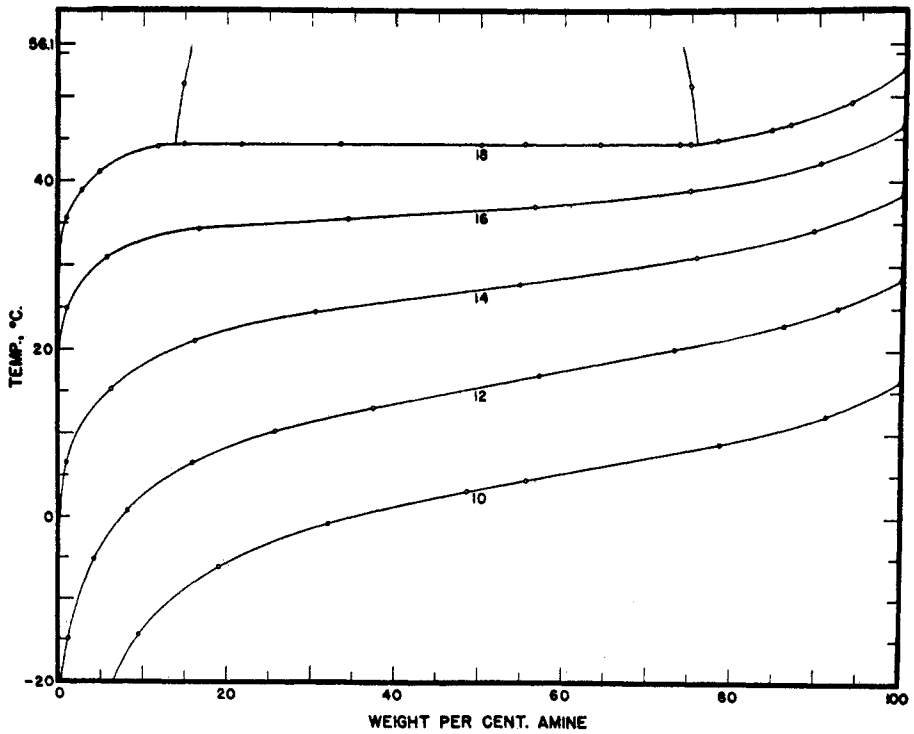

FIG. 4. SOLUBILITIES OF THE PRIMARY AMINES IN ACETONE

The amines are somewhat more soluble in 2-butanone than in acetone. It can be seen in Fig. 4 that the solubility of octadecylamine in acetone becomes so limited that a considerable region consisting of two immiscible solutions appears. Of the fatty acid derivatives investigated in the present series, octadecylamine is the only one which forms conjugate solutions with a solvent of a polarity as low as that of acetone.

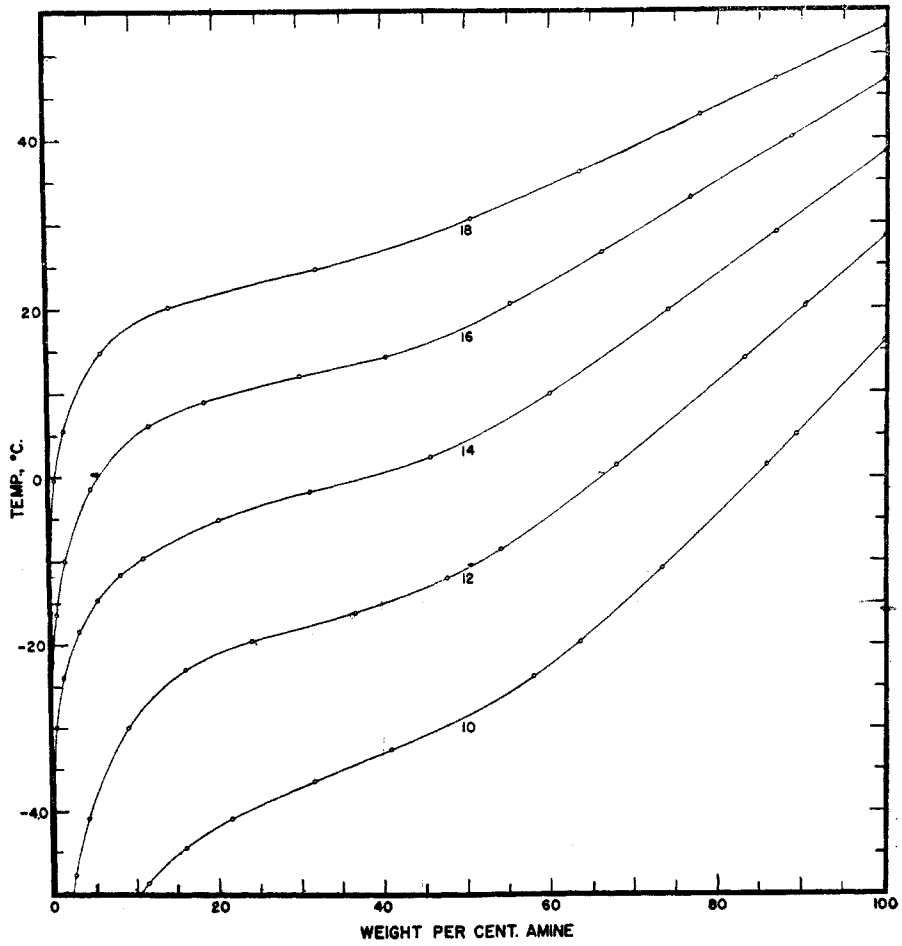

FIG. 5. SOLUBILITIES OF THE PRIMARY AMINES IN METHANOL

The solubilities of the amines in methanol, 95% ethanol, isopropanol, and *n*-butanol are listed in Tables XII–XV, respectively. The behavior of the amines in the alcohols is illustrated by the methanol curves (Fig. 5) and the *n*-butanol curves (Fig. 6).

The amines differ from the other fatty acid derivatives studied in this Laboratory in that they are considerably more soluble in the lower alcohols than in any of the other solvents investigated except trichloromethane. Most of other the

compounds are less soluble in the alcohols than in the other solvents except the highly polar solvents such as acetonitrile. The amines differ widely in their solubilities in the various alcohols, while the solubilities of other long-chain compounds do not differ greatly in these solvents.

The solubilities of the amines in acetonitrile are listed in Table XVI, and are shown graphically in Fig. 7.

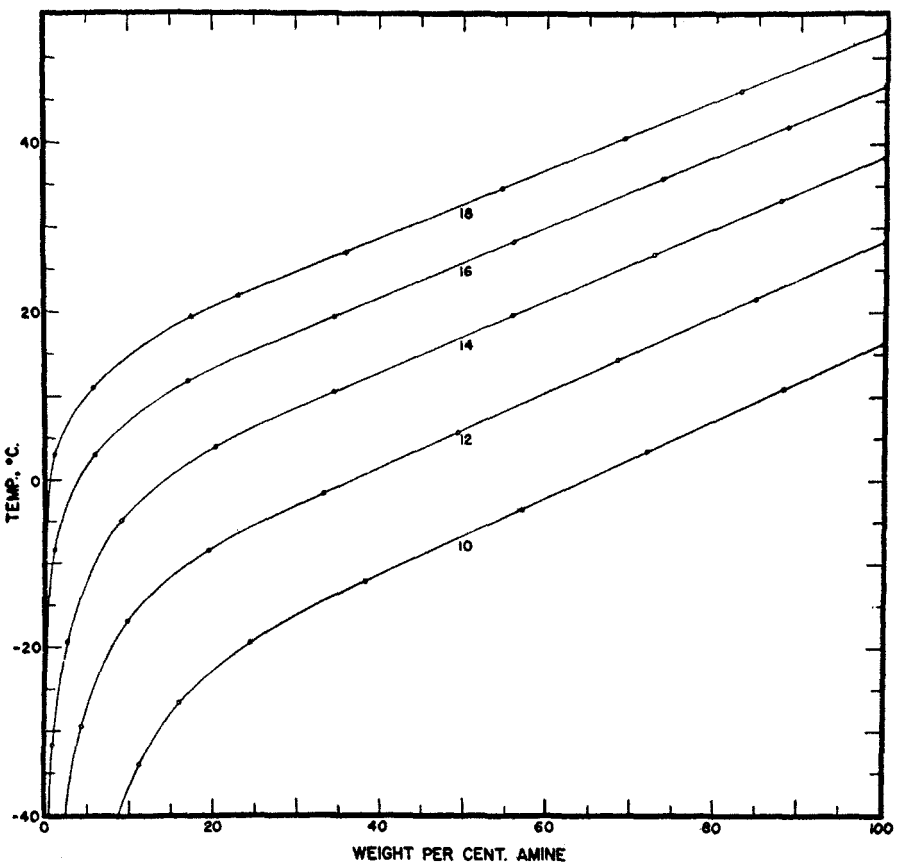

FIG. 6. SOLUBILITIES OF THE PRIMARY AMINES IN *n*-BUTANOL

The amines are less soluble in this highly polar solvent than in any other solvent studied and octadecylamine shows a region of immiscibility similar to that found in the octadecylamine-acetone system. In the acetonitrile system the entire immiscible region exists below the boiling point of the solvent and the upper limit of the region of conjugate solutions can, therefore, be located.

The solubility of the amines in nitroethane is indeterminable due to their reaction with this solvent.

The characteristic shape of the solubility curves of long-chain aliphatic compounds has been attributed to intermolecular association (1, 15). The mod-

erately high dipole moments of the amines (16) suggest the probability that these compounds are molecularly associated. Evidence that the amines are associated through hydrogen bonding has been reported (17). It has been observed however, that the amines do not give an abnormal freezing point depression in benzene or boiling point elevation in ethanol, which indicates that they are not associated in these solvents (18). Uutil more complete data concerning the

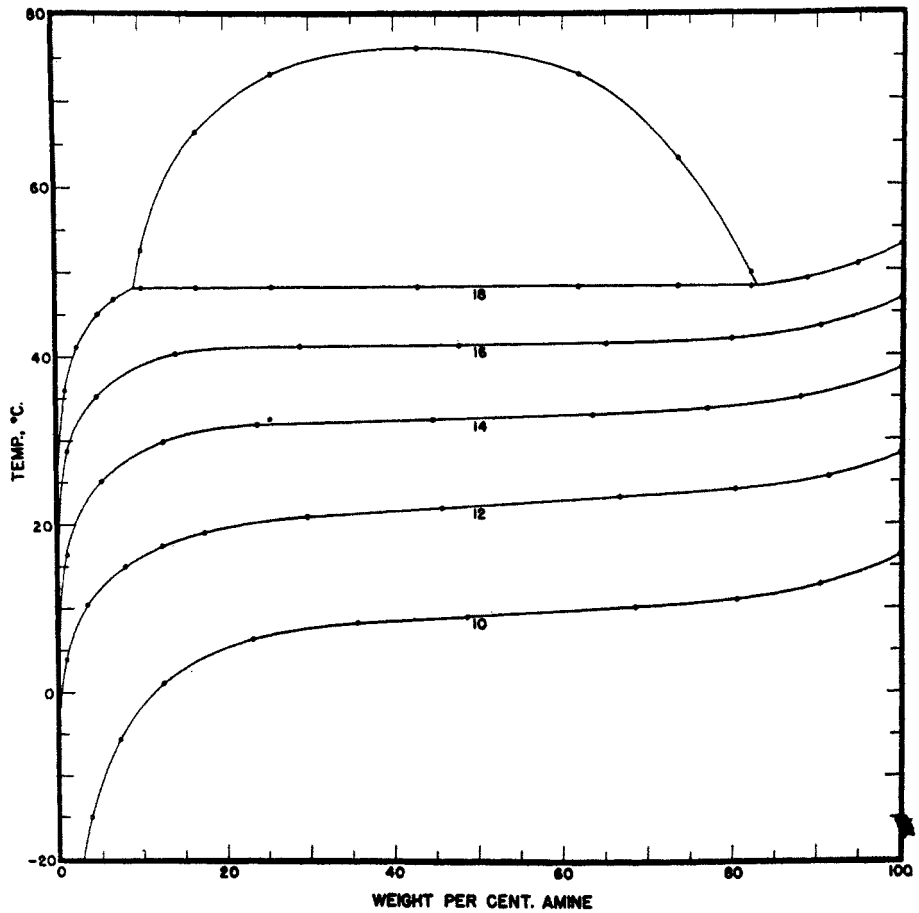

FIG. 7. SOLUBILITIES OF THE PRIMARY AMINES IN ACETONITRILE

behavior of long-chain compounds are available, no conclusions as to the effect of association upon solubility can be drawn.

SUMMARY

The solubilities of decylamine, dodecylamine, tetradecylamine, hexadecylamine, and octadecylamine have been determined in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl ether, ethyl acetate, butyl acetate,

acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, and acetonitrile.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE STABILIZATION OF POLYSULFONES TOWARD HEAT[1]

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When a polysulfone derived from an olefin and sulfur dioxide is heated to its melting or softening point, it tends to decompose with the liberation of sulfur dioxide (1). In a patent (2) it has been claimed that heating a polysulfone with an olefinic compound containing a negative group linked to one of the unsaturated carbon atoms, at a temperature not to exceed 100°, increases the stability of the polysulfone toward further heating. The compounds specifically mentioned as having this effect are vinyl acetate, chlorobutadiene, and acrylic esters. Wilder (3) has improved the heat stability of butenepolysulfones by treating them at 60–100° with such olefinic compounds as partially polymerized vinyl chloride, esters of acrylic and methacrylic acid, coumarin, furfural, or chloroprene. It has been reported (4) that the removal of volatile impurities, by heating a polysulfone in a current of inert gas to a temperature just below the temperature at which the polymer itself begins to decompose, will improve the molding properties of the polymer. It has been found (5) that polysulfones are more stable to heat after they have been treated with acetyl chloride or acetic anhydride. Harmon (6) has observed that the molding properties of a polysulfone are improved by washing the polymer with a mixture of solvents, one of which exhibits a swelling action on the polymer. It is of interest to note that any of these procedures might be expected to destroy residual peroxides in the polymer. This may be the reason that these treatments have practical merit.

In connection with a study of thermal stability of certain samples of 1-pentenepolysulfone it was found that the results were not concordant when different samples were used. Further investigation showed that samples of this polymer prepared from 1-pentene, obtained by the action of ethylmagnesium bromide on allyl bromide, were exceptionally stable to heat. This property was found to be due to traces of allyl bromide left in the 1-pentene. Addition of allyl bromide in extremely small amounts (1 to 2 drops to 10 cc. of olefin) to an olefin which was then converted to a polysulfone, uniformly resulted in a polysulfone of greater thermal stability than was characteristic of that polysulfone prepared in the absence of allyl bromide.

This effect seemed to be rather specific for allyl bromide as the following compounds tested similarly were ineffective: allyl chloride, ethyl bromide, allyl alcohol, crotyl bromide, camphene, 1-bromoheptene, undecylenyl bromide, β-bromostyrene, ethyl acrylate, chloromethyl ether, chloroform, heptylmercaptan, carbon tetrachloride, *p*-bromobenzyl chloride, benzyl bromide, benzyl alcohol, furfuryl alcohol, furfurylacrylic acid, and α^2-chloroisodurene.

Some improvement in the thermal stability of a preformed polysulfone could be effected by dissolving the polymer in a suitable solvent, adding some allyl bromide, and heating. However, this effect was not marked.

[1] This is the fourteenth communication on polysulfones. For the thirteenth communication see *J. Am. Chem. Soc.*, **64**, 1229 (1942).

It was also found that purification of a polysulfone by solution and reprecipitation improves its thermal stability to some extent. Likewise, a thermal treatment somewhat like that suggested by Frey and Bury (4) was effective in giving a product which had improved thermal stability. Incorporation of small

TABLE I

EFFECT OF ALLYL BROMIDE ON THE THERMAL STABILITY OF POLYSULFONE

POLYSULFONE FROM	WEIGHT LOSS AT 140° FOR TWO HOURS			WEIGHT LOSS AT 160° FOR TWO HOURS		
	SAMPLE	G.	%	SAMPLE	G.	%
1-Pentene (trace allyl bromide)	0.3898	0.0018	0.46	0.4051	0.0081	2.00
	.2758	.0009	.33	.2574	.0047	1.83
1-Pentene (control)	.1556	.0062	3.99	.3892	.0474	12.2
	.1386	.0049	3.54	.3511	.0442	12.6
2-Butene (trace allyl bromide)	.1798	.0016	0.84	.1523	.0042	2.75
	.1733	.0019	1.10	.1013	.0025	2.46
2-Butene (control)	.0758	.0007	0.92	.1308	.0045	3.44
	.1040	.0017	1.63	.1466	.0073	4.98
1-Butene (trace allyl bromide)	.2360	.0033	1.40	.2300	.0143	6.22
	.2026	.0018	0.89	.2774	.0160	5.78
1-Butene (control)	.2029	.0523	26.2	.2375	.0391	16.5
	.2311	.0560	24.2	.2602	.0388	14.9
1-Hexene (trace allyl bromide)	.2912	.0011	0.38			
	.2482	.0008	.32			
1-Hexene (control)	.2622	.0284	10.80			
	.2679	.0296	11.05			
1-Heptene (trace allyl bromide)	.3214	.0017	0.53			
	.2598	.0018	.69			
1-Heptene (control)	.2673	.0250	9.36			
	.2597	.0305	11.75			
Cyclohexene (trace allyl bromide)	.7536	.0461	6.14			
	.4523	.0284	6.28			
Cyclohexene (control)	.2082	.0375	18.00			
	.2025	.0331	16.35			

amounts of benzoyl peroxide into a polysulfone gives a product of greatly diminished stability toward heat.

EXPERIMENTAL

The heat stability tests were made by placing weighed samples of the polymers in small test tubes, which were then placed inside larger glass tubes, and these in turn were sus-

pended in an oil-bath held at the desired temperature for the specified time. The tubes containing the samples were then removed and weighed. In some cases considerable foaming occurred.

Traces of allyl bromide in the olefin. In Table I are summarized a number of experiments which show the effect of traces of allyl bromide in the olefin used for making a polysulfone on the thermal stability of the polymer. The polymers were prepared by a standard method described earlier (7), using 10 cc. of olefin, 10 cc. of liquid sulfur dioxide, 10 cc. of ethyl alcohol, and 0.1 to 0.2 g. of ascaridole in the reaction mixture. For the stability

TABLE II

EFFECT OF HEAT TREATMENT ON STABILITY OF POLYSULFONES

POLYSULFONE	WEIGHT SAMPLE	LOSS IN WEIGHT 1ST TWO HOURS AT 140°		LOSS IN WEIGHT 2ND TWO HOURS AT 140°	
		G.	%	G.	%
Propylene	0.1406	0.0032	2.28	0.0000	0
2-Butene	.1383	.0108	7.8	.0006	0.44
	.0409	.0061	14.9	.0000	0
2-Pentene	.1718	.0268	15.6	.0070	4.06
1-Pentene	.2762	.0546	19.9	.0027	1.18
	.2294	.0456	19.8	.0023	0.83

TABLE III

EFFECT OF HEAT TREATMENT FOLLOWED BY REPRECIPITATION ON STABILITY OF POLYSULFONES

POLYSULFONE	SAMPLE G.	LOSS IN WEIGHT AT 140° FOR 2 HRS.		FURTHER HEAT TREATMENT AT 140°, HRS.	WEIGHT OF REPRECIPITATED SAMPLE, G.	LOSS IN WEIGHT AT 140° FOR 2 HRS.	
		G.	%			G.	%
1-Heptene	0.2751	0.0167	6.06	2	0.2867	0.0028	0.98
	.2797	.0102	3.65				
1-Pentene	.3501	.0097	2.76	4	.4324	.0008	.19
	.3246	.0082	2.52				
1-Pentene	.7767	.0185	2.38	8	.4589	.0003	.06
	.3398	.0082	2.42	8	.4163	.0003	.07

tests the polymers were isolated by pouring the reaction mixture into water, allowing the excess sulfur dioxide to escape, heating the water to boiling to wash the polysulfone, cooling, separating the polymer cake, powdering the cake, washing it thoroughly with ethyl alcohol and ether, and drying.

Effect of allyl bromide on a preformed polysulfone. A preformed 1-pentenepolysulfone which lost about 1.5–2.0% its weight when heated to 140° for two hours was rendered more stable by boiling a 3-g. sample in 30 cc. of dioxane with 10 g. of allyl bromide for five hours. The treated sample after isolation, lost less than 0.5% its weight under the same heat treatment at 140°. Crotyl bromide and 1-bromoheptene also showed a stabilizing effect of the same order, but ethyl acrylate, camphene and cyclohexene did not.

Effect of heat treatment. Heat treatment alone was found to improve the heat stability of polysulfones. This was shown by measuring the weight loss in two consecutive two-hour heating periods, and also by heating one two-hour period, dissolving the polymer in acetone, reprecipitating, and then heating the purified polymer. In Tables II and III some of these data are collected.

Effect on heat stability of repeated purifications. A sample of 1-pentenepolysulfone was purified by taking the polymer up in acetone, then adding two to three volumes of ethyl alcohol, evaporating to one-half volume, adding alcohol to the original volume and again evaporating to half-volume to precipitate the polymer, filtering, drying, powdering in a mortar and drying under 5 mm. at 56° for four hours. When this material was heated to 140° for two hours it lost 12–14% of its weight. A sample of 1-pentenepolysulfone made by the usual procedure with ascaridole as a catalyst was taken up in chloroform, the solution boiled to remove sulfur dioxide and then ether was added to throw out the polymer. After filtering and drying at 50° at 3 mm. for four hours, the material lost 19–20% of its weight on heating two hours at 140°. A portion of this recovered polymer was boiled with water for two and a half hours, then powdered, washed with alcohol and ether, and dried at 78° and 5 mm. for five hours. It then lost 8–12% of its weight at 140° in two hours. This material was then dissolved in acetone and precipitated with alcohol as described for the first sample mentioned. This material then lost only 2–3% of its weight when heated to 140° for two hours. Another treatment of the same sort yielded a polymer which lost only 1–1.3% of its weight in the same heat treatment. Further purification by this process did not improve heat stability.

A sample of 1-hexenepolysulfone which was purified by solution in acetone and reprecipitated with alcohol as described above lost only 0.9% its weight at 140° for two hours. Repurification by the same process gave a product which lost only 0.07–0.2% its weight on the heat treatment. A sample of 2-butenepolysulfone after repeated purification showed a loss of less than 1% its weight at 140° for two hours.

Effect of added benzoyl peroxide. Addition of 2.74% benzoyl peroxide to a sample of 1-pentenepolysulfone which had been found to lose less than 0.5% its weight at 140° for two hours, gave a product which lost 12% its weight in two hours at 140°.

SUMMARY

Polysulfones made from olefins containing a trace of allyl bromide show a remarkably improved stability toward heat over that of polysulfones made from pure olefins. The preformed polysulfone can also be treated with allyl bromide to bring about some stabilizing action but the effect is less marked.

Heat treatment of polysulfones appears to remove some of the readily decom-decomposable material so that the remaining sample is more stable toward heat.

Presence of peroxides in polysulfones increases the amount of decomposition which occurs when they are heated.

URBANA, ILL.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

THEORY OF A METHOD FOR COMPARING THE STRUCTURES OF CERTAIN COMPOUND SUGARS. A PROBABLE RELATIONSHIP OF TURANOSE TO MALTOSE

C. S. HUDSON

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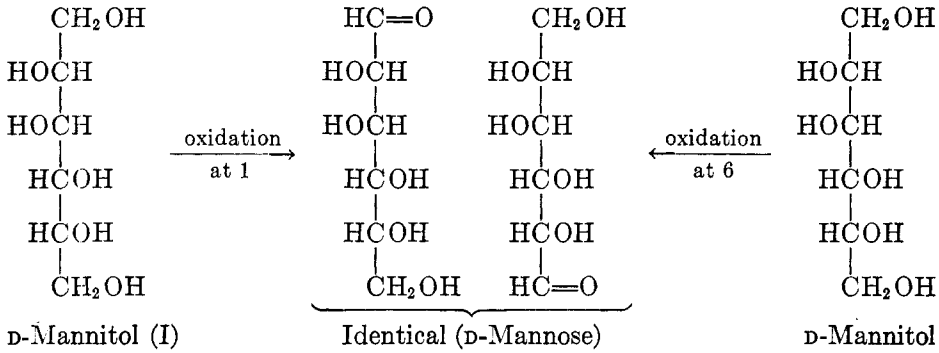
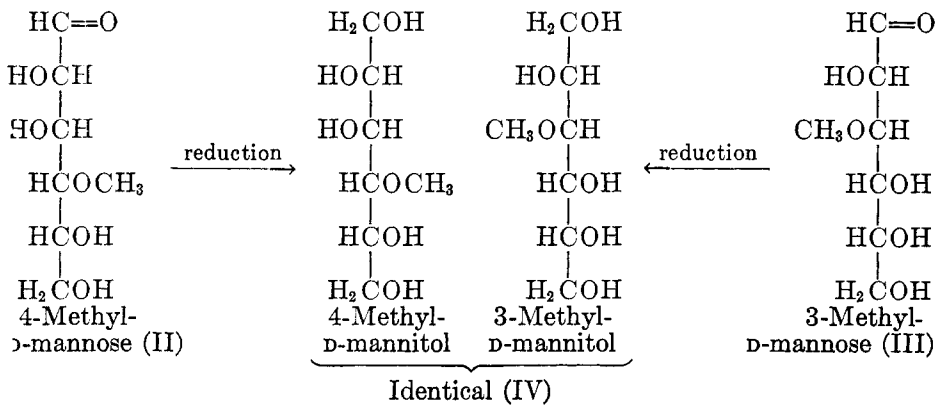
When Emil Fischer (1) discovered the configuration of mannitol (I) he called attention to its symmetry about its central point, from which it is a deduction by the mathematical principles of symmetry that oxidation at either end of the molecule of D-mannitol yields one and the same aldose, D-mannose, or that oxidation at either carbon atom 2 or 5 yields the single ketose, D-fructose. In summary, it has thus long been recognized that positions 1 and 6 in mannitol are equivalent and likewise 2 is equivalent with 5 and 3 with 4. The known 4-methyl-D-mannose (II) gives on reduction 4-methyl-D-mannitol (IV) (2);

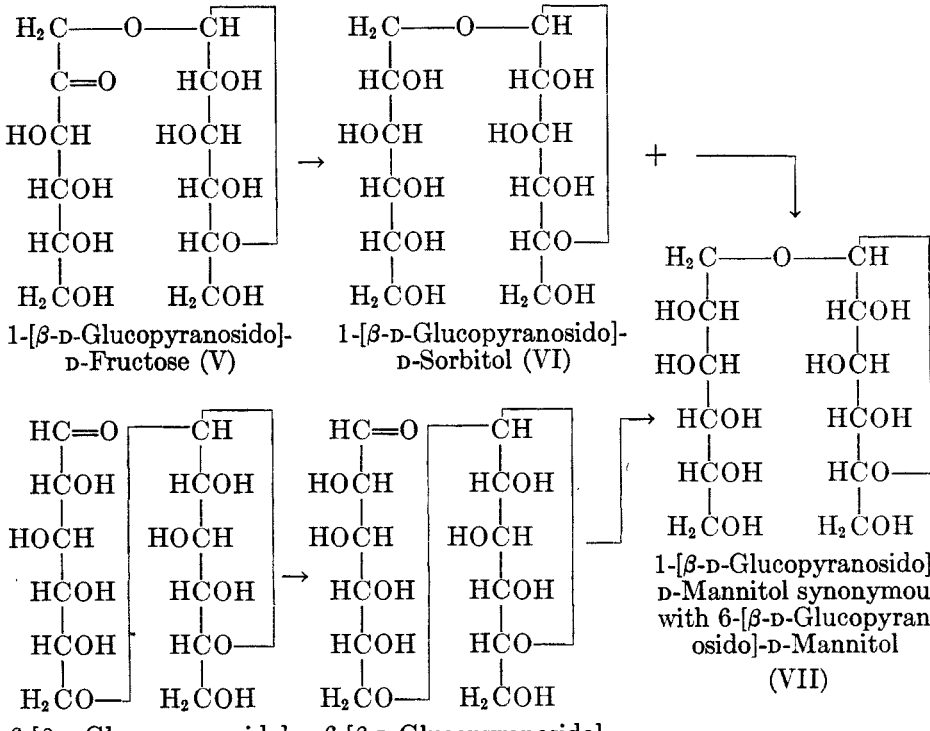


unquestionably the same reduction product would be obtained if the now unknown 3-methyl-D-mannose (III) should be reduced, because 3-methyl- and 4-methyl-D-mannitol are alternative names for a single substance. It has long been recognized that this same symmetry about the central point holds for threi-



tol, the active tartaric acids, and iditol. Applications of this specific type of symmetry for preparative results in organic chemistry have not been lacking; D-glyceraldehyde is conveniently prepared by the oxidation of 1,2;5,6-diacetone-D-mannitol with lead tetraacetate (3), and a formaldehyde acetal of D-glyceraldehyde has been prepared recently by the oxidation of 2,5-methylene-D-mannitol with per-iodic acid (4). Although the principles that underlie such applications of the center-point symmetry of mannitol, iditol etc. are known to all students of stereochemistry, it has not been recognized before that a similar application of them is possible for the purpose of comparing the structures of certain compound sugars. It is the purpose of the present communication to describe the theoretical side of this new method of comparison; since the new application can be understood very readily from the foregoing introduction, its description will be given in the form of particular examples.

Correlation of natural gentiobiose with synthetic 1-[β-D-glucopyranosido]-D-fructose. The configurational formulas for gentiobiose and its epimer are shown in (VIII) and (IX); both of these formulas have been established conclusively by syntheses. The reduction product from (IX) has never been prepared, but this unknown substance cannot conceivably have any structure other than (VII).



1-[β-D-Glucopyranosido]-D-Fructose (V)

1-[β-D-Glucopyranosido]-D-Sorbitol (VI)

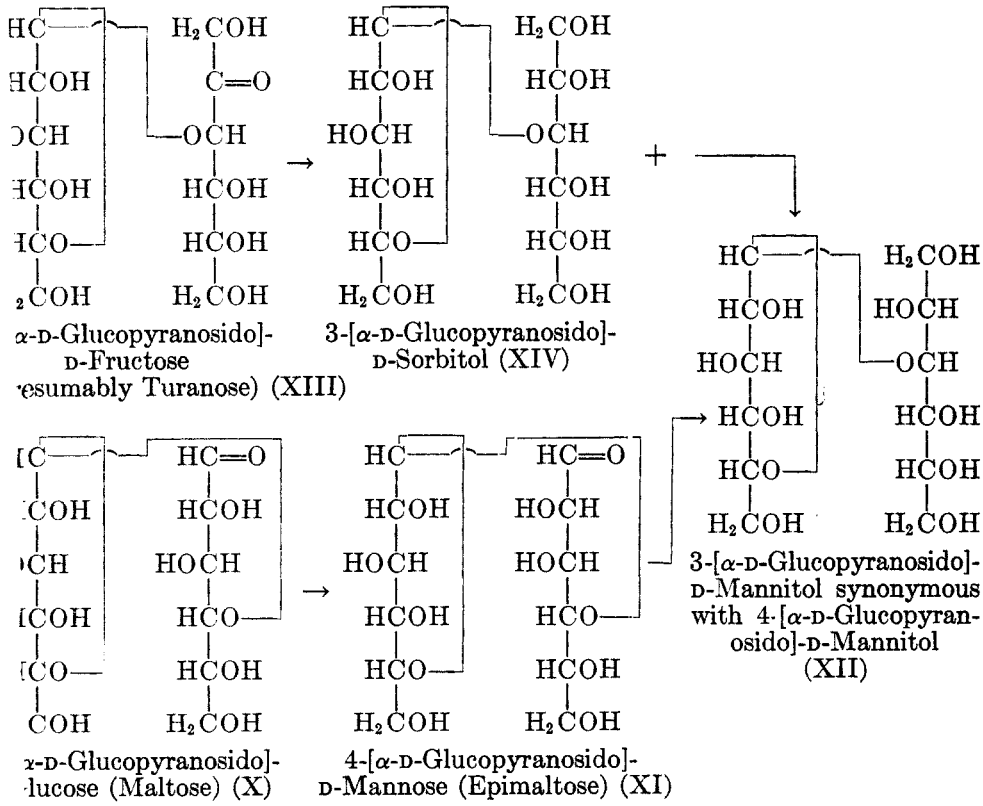
1-[β-D-Glucopyranosido]-D-Mannitol synonymous with 6-[β-D-Glucopyranosido]-D-Mannitol (VII)

6-[β-D-Glucopyranosido]-D-Glucose (Gentiobiose) (VIII)

6-[β-D-Glucopyranosido]-D-Mannose (Epigentiobiose) (IX)

Consider next the synthetic disaccharide ketose (V); in this case, also, the formula is conclusively established through synthesis (5). The reduction of this disaccharide ketose can be expected to yield a mixture of (VI) and (VII). With (VI) we are not concerned; but (VII) is the same structure that is to be expected from the reduction of epigentiobiose (IX), because of the long known equivalence of carbon atoms 1 and 6 in mannitol. In the case of this pair of disaccharides, the experimental realization of (VII) as obtainable from both (V) and (VIII) (through IX) would add nothing to present knowledge, since (V), (VIII) and (IX) are already established conclusively, and the stereochemical principles from which the conclusion is deduced are not subject to doubt. The labor of preparing (VII) from the two sources seems therefore hardly worth while. The following two examples, however, illustrate the possible usefulness of the method for obtaining conclusive proofs of structure for certain compound sugars whose formulas are not as yet finally established.

The probable relationship of turanose to maltose. The structure of maltose, beyond reasonable doubt, is 4-[α-D-glucopyranosido]-D-glucose (X); its epimer is known (6) and the structure of the latter, again beyond reasonable doubt, is (XI). The reduction of (XI) has never been made, but the formula of the



product cannot be other than (XII). There is strong, though not conclusive, evidence that the natural disaccharide turanose is 3-[α-D-glucopyranosido]-D-fructose (XIII) (5a, 7). The reduction of turanose has been shown by Pacsu and Rich (8) to yield two substances to which they ascribe the formulas (XIV) and (XII). With (XIV) we are not now concerned. These authors describe the crystalline nonaacetate of (XII) (m.p. 142°; $[\alpha]_D^{20}$ + 89.3 in chloroform), from which it is evident that (XII) is readily identifiable. Therefore, if the product from the reduction of (XI) proves to be the known (XII) from turanose, the structure of turanose will be established with the same degree of certainty as applies to that of maltose. The writer is undertaking the reduction of (XI) for the indicated test.

The possible relationship of laminaribiose to cellobiose. Barry (9) has recently reported a new disaccharide from the partial acid hydrolysis of the polysaccharide laminarin that occurs in certain seaweeds (*Laminariae*); he has adduced evidence for which the structure 3-[β-D-glucopyranosido]-D-glucose is best compatible for the disaccharide. There is evidence [Barry (9), Zechmeister and Toth (10)] that this disaccharide is also a constituent of a polysaccharide that occurs in yeast. It will be apparent from the foregoing considerations that the customary reactions 3-[β-D-glucopyranosido]-D-glucose→3-[β-D-glucopyranosido]-D-mannose→3-[β-D-glucopyranosido]-D-mannitol, and 4-[β-D-glucopyranosido]-D-glucose (cellobiose)→4-[β-D-glucopyranosido]-D-mannose (epicellobiose)→4-[β-D-glucopyranosido]-D-mannitol, should yield the same end product, because positions 3 and 4 in mannitol are equivalent.

BETHESDA, MD.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

ATTEMPTED SYNTHESIS OF HEMIPINIC ACID FROM GUAIACOL

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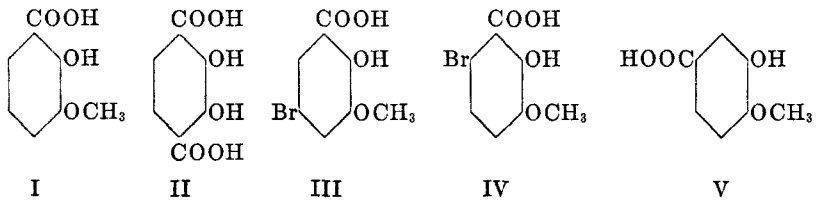
For the synthesis of hemipinic acid, which may be a valuable starting material for dye-stuffs (*e.g.* of the alizarine type), there is no easy method available; the acid is even today mostly prepared from natural products by oxidative degradation [Perkin (13)].

The experiments described were intended to connect hemipinic acid with guaiacol (2-methoxyphenol) through 2-hydroxy-3-methoxybenzoic acid (I). It is true that the introduction of substituents, *e.g.* bromine, into the guaiacol system involves in the first instance the (unfavorable) position *para* to the hydroxyl. It was hoped, however, to make use of the fact (3) that while free hydroxyl groups have a more powerful directing influence than methoxyl groups, their acetyl derivatives are less active than methoxyls. As a matter of fact, acetylguaiacol or its carbonate, on monobromination, gives 5-bromo-; free guaiacol, however, gives 4-bromo-2-methoxyphenol. Analogous observations have been made in similar cases by Adams and Baker (1), King (10), and by Raiford and coworkers (14).

The experiments substantiated the expectations in this respect. 2-Hydroxy-3-methoxybenzoic acid (I) is easily prepared under the conditions specified in the experimental part, by the Kolbe synthesis from guaiacol; at too high a temperature, partial demethylation occurs under the influence of the alkali present as in similar cases [Stoermer and Kahlert (18)] and then two-fold carboxylation takes place, leading to 2,3-dihydroxyterephthalic acid (II), which has been characterized by the preparation of a dimethyl ester, m.p. 145°, and of a diethyl ester, m.p. 90°. On bromination in glacial acetic acid or chloroform, 2-hydroxy-3-methoxybenzoic acid (I) gives a monobromo derivative, m.p. 211°, which according to the above principle is the 2-hydroxy-3-methoxy-5-bromobenzoic acid (III), the free hydroxyl group directing the substitution. The methyl ester of (I) is converted, under the same operating conditions, into the methyl ester of (III). On the other hand, when 2-acetoxy-3-methoxybenzoic acid was brominated, the acetyl derivative of a different 2-hydroxy-3-methoxybromobenzoic acid, m.p. 150°, was formed. Here, the methoxyl group exerts the directing influence, so that the new substance is the 6-bromo compound (IV).



I II III IV V

The exchange of the bromine atom in (IV) for the second carboxyl group, using sodium copper cyanide according to Rosenmund (15), was anticipated to proceed

smoothly, as the carboxyl group exerts a marked activating influence on neighboring bromine atoms [Rule and co-workers (16)]. The reaction product obtained, however, was not the desired norhemipinic acid, but isovanillic acid (V), identified with an authentic sample prepared from hemipinic acid, and characterised as methyl ester and acetyl derivative. The formation of isovanillic acid indicated that the desired reaction had occurred but that under the conditions of reaction, the original carboxyl group had been labilized and split off. Isovanillic acid was also obtained, when 5-bromoguaiacol was heated with sodium copper cyanide (9).

EXPERIMENTAL

2-Hydroxy-3-methoxybenzoic acid (*I*) was obtained in good yield and with the correct m.p. 150° when absolutely dry sodium guaiacolate was heated with carbon dioxide in an autoclave for 12 hours at 200° (2, 4, 6, 17). When the experiment was carried out at 230°, only 55% of (I) was obtained, while 35% of the reaction product consisted of 2,3-dihydroxyterephthalic acid (II); from water, fine needles, m.p. 308°. Ferric chloride gave the deep blue color reaction described in the literature.

2-Hydroxy-3-methoxy-5-bromobenzoic acid (*III*). 2-Hydroxy-3-methoxybenzoic acid (I) (8.4 g.) was dissolved in glacial acetic acid (150 cc.) and kept with bromine (2.34 cc.) at room temperature for 12 hours. The reaction product which had separated was filtered and recrystallized from 50% acetic acid; needles, m.p. 211°, giving a deep blue color reaction with alcoholic ferric chloride solution. From the original mother liquor a second crop could be obtained by concentrating and cooling; yield, 80%. Bromination in chloroform gave the same bromo derivative.

Anal. Calc'd for $C_8H_7BrO_4$: C, 38.9; H, 2.9.
Found: C, 38.6; H, 2.9.

Methyl 2-hydroxy-3-methoxy-5-bromobenzoate. Methyl 2-hydroxy-3-methoxybenzoate (9.1 g.), prepared from the acid with hydrochloric acid in methyl alcoholic solution (b.p. 105°/2 mm; from light petroleum, m.p. 73°) [Fritzsch, (5)] was brominated in chloroform solution (40 cc.) at 0° with liquid bromine (3 cc.). When the bromine had disappeared, the solution was washed with water and evaporated; from methyl alcohol, needles; from light petroleum, prisms, m.p. 122°, giving the same color reaction as the acid (III); yield, 11.4 g. Bromination in boiling methyl alcohol gave the same ester.

Anal. Calc'd for $C_9H_9BrO_4$: C, 41.3; H, 3.8.
Found: C, 41.0; H, 3.8.

Hydrolysis with alcoholic potash solution gave the above acid, from 50% acetic acid, m.p. 211°.

Methyl 2-acetoxy-3-methoxy-5-bromobenzoate. The preceding ester was boiled for 3 hours with an excess of acetic anhydride and some pyridine. From methanol, then light petroleum, clusters of crystals, m.p. 95°, which gave no color reaction with ferric chloride.

Anal. Calc'd for $C_{11}H_{11}BrO_5$: C, 43.6; H, 3.6.
Found: C, 43.7; H, 3.5.

Methyl 6-bromo-3-methoxy-2-acetoxybenzoate (*as IV*). Methyl 3-methoxy-2-acetoxybenzoate [Klemenč, (11)] (b.p. 130°/0.3 mm; m.p. 62°) (11 g.) was dissolved in glacial acetic acid (100 cc.), containing 10 g. of anhydrous sodium acetate, and a solution of bromine (5 cc.) in glacial acetic acid (10 cc.) was added. The product separated spontaneously, and was recrystallized from methyl alcohol; m.p. 124°, yield, 80%. The product gave no color reaction with ferric chloride. The same substance was obtained when the bromination was carried out in chloroform solution, or when the starting material was mixed with the theoretical amount of liquid bromine without solvent.

Anal. Calc'd for $C_{11}H_{11}BrO_5$: C, 43.6; H, 3.6.
Found: C, 43.0; H, 3.8.

6-Bromo-3-methoxy-2-hydroxybenzoic acid (IV). The foregoing substance (6 g.) was boiled for 3 hours with a solution of sodium hydroxide (3.2 g.) in aqueous alcohol (1:1). The filtered solution was acidified and the precipitate recrystallized from water; needles, m.p. 150°. Ferric chloride gave a blue color reaction.

Anal. Calc'd for C_8H_7BrO: C, 38.9; H, 2.9.
Found: C, 38.4; H, 3.1.

Isovanillic acid (V). (a) 6-Bromo-3-methoxy-2-hydroxybenzoic acid (IV) (6 g.) was heated with sodium cyanide (5. g). and cuprous cyanide (5 g.) in 50% alcohol (50 cc.) in an autoclave for 8 hours at 180°. The reaction product was diluted with water, filtered, concentrated, and acidified. The precipitate was dried and recrystallized from butyl acetate; needles, m.p. 250°, which sublime easily *in vacuo*.

(b) 5-Bromoguaiacol (10 g.), sodium cyanide (5 g.) and cuprous cyanide (5 g.) were heated in 50% alcohol (250 cc.) at 180° for 8 hours (autoclave). The brown liquid was filtered, concentrated (to 100 cc.), and acidified. The isovanillic acid was recrystallized from water containing some hydrochloric acid, or from butyl acetate; needles, m.p. 250°; yield, 7 g.

Anal. Calc'd for $C_8H_8O_4$: C, 57.7; H, 4.8.
Found: C, 57.4; H, 4.7.

Methylation with methyl alcohol and sulfuric acid gave a product which was recrystallized from light petroleum and had the correct m.p. 68° (12). Ferric chloride gave a yellow color reaction.

Anal. Calc'd for $C_9H_{10}O_4$: C, 59.3; H, 5.4.
Found: C, 59.2; H, 5.3.

SUMMARY

Like guaiacol and similar compounds, 2-hydroxy-3-methoxybenzoic acid (I) is brominated in the *para* position to the hydroxyl group (5), its acetyl derivative in the *para* position to the methoxyl group (6).

2-Hydroxy-3-methoxy-6-bromobenzoic acid (IV) reacts at 180° with sodium cuprous cyanide, replacing the 6-bromo atom. At the same time, the 1-carboxyl group is split off; instead of the desired 3-hydroxy-4-methoxyphthalic acid, isovanillic acid is obtained. Isovanillic acid is also formed from 5-bromoguaiacol under the same operating conditions.

REHOVOTH, PALESTINE.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

THE POLYMERIZATION OF ETHYLENIMINE

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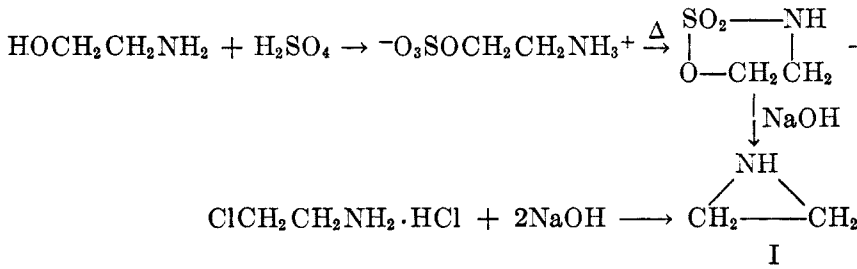
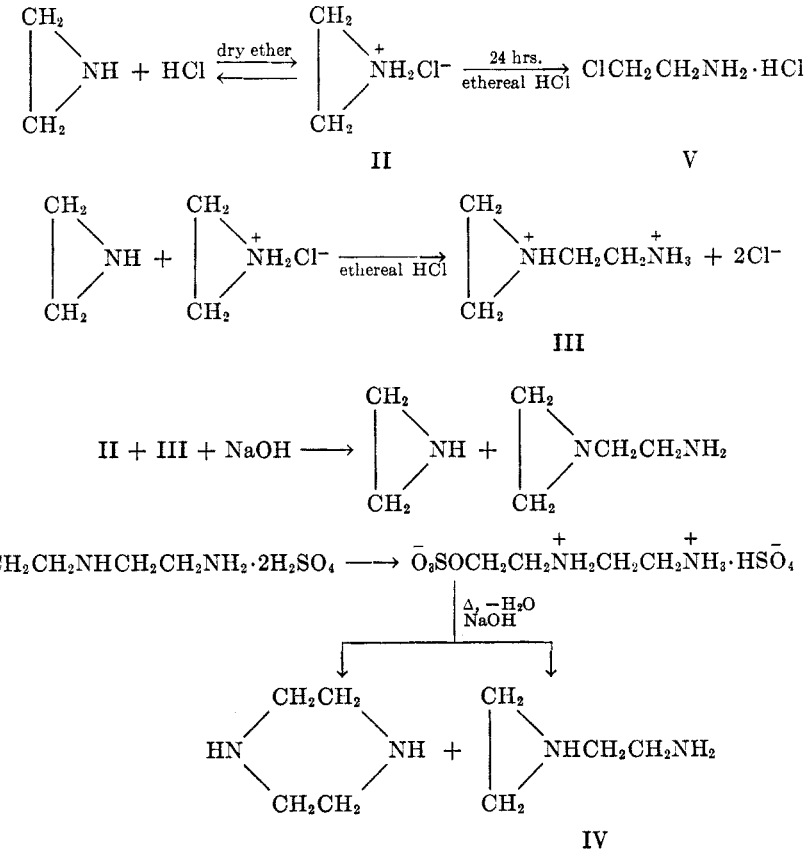
Ethylenimine (1, 2) (I) is readily made from ethanolamine by the method of Wenker (3) or from β-chloroethylamine hydrochloride by the method of Berchet (4).



Many patents exist covering the polymerization of ethylenimine by catalysts such as acids (5) [including carbon dioxide (6)], boron trifluoride (7), and ammonia under pressure (8). Since relatively little, however, was known concerning the structure of the polymer and the mechanism of polymerization, a thorough investigation was begun in the present work.

Ethylenimine stored in the absence of carbon dioxide will keep indefinitely at room temperature and polymerizes only slightly in three days at 150°. The polymerization of bulk ethylenimine by more than two mole-per cent concentrated hydrochloric acid proceeds with violence at room temperature or above; however at −78° polymerization is inhibited. Likewise large amounts of boron trifluoride cause violent polymerization at room temperature and none at −78°, at which temperature the addition complex precipitates as a gum. Polymerization proceeds more slowly in a water solution of ethylenimine to which has been added a catalytic amount of hydrochloric acid.

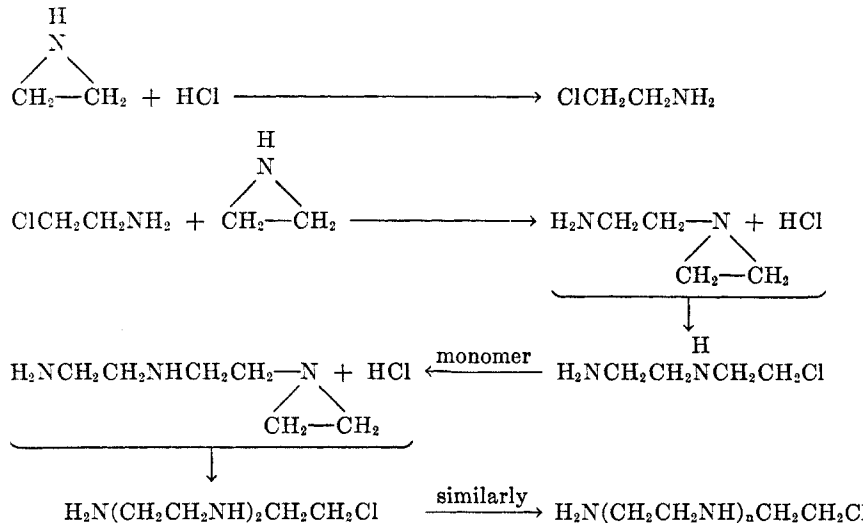
By the quick addition of a dilute solution of ethylenimine in anhydrous ether to an excess of dry ethereal hydrogen chloride, the unstable ethylenimine hydrochloride (II) has been isolated, together with the dihydrochloride of ethylenimine dimer (III). The mixed hydrochlorides were quickly filtered and placed in a desiccator at room temperature, but before ten minutes passed had polymerized suddenly with hydrogen chloride evolution. About equal proportions of ethylenimine and dimer were obtained by adding the freshly isolated hydrochlorides to aqueous alkali, extracting with ether and fractionally distilling the dried extract. N-(β-aminoethyl)ethylenimine (IV) was synthesized from aminoethylethanolamine by the Wenker method, separated from a proportionately larger yield of piperazine and shown to be identical with ethylenimine dimer.



If the mixed hydrochlorides were allowed to stand overnight in dry ethereal hydrogen chloride, conversion of the ethylenimine hydrochloride to β-chloroethylamine hydrochloride (V) occurred; however, the following test indicated that the freshly isolated mixed hydrochlorides contained no β-chloroethylamine hydrochloride. A small proportion of ethereal β-chloroethylamine was added to ethereal ethylenimine and the solution treated with aqueous alkali and dried as in the dimer isolation. When most of the ether had been distilled, sudden polymerization occurred. Therefore it is unlikely that the formation of ethylenimine dimer involved β-chloroethylamine as an intermediate, for if that were the case, at least a trace of β-chloroethylamine hydrochloride would most probably have been present in the mixed hydrochlorides and caused polymerization, preventing the isolation of the dimer. Since ethylenimine dimer is readily polymerized like ethylenimine, it is indicated that the reaction in which the dimer was isolated is really polymerization. It is indicated also that under these conditions the polymerization of ethylenimine is not a condensation polymerization requiring the formation of β-chloroethylamine as an essential intermediate.

Such a condensation polymerization mechanism might, if careful consideration were not taken, be thought particularly applicable to the aqueous polymerization

of ethylenimine by hydrochloric acid. Gabriel (1) showed ethylenimine to be converted partially to β-chloroethylamine hydrochloride on evaporation with excess hydrochloric acid; therefore β-chloroethylamine is probably present in the aqueous polymerization and the following mechanism might be suggested.



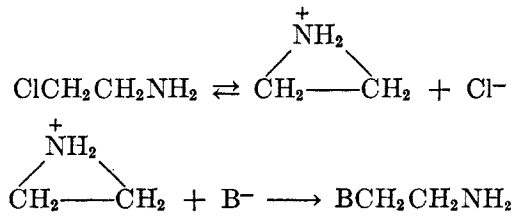
The application to this mechanism of the interpretation of the role of the neighboring group as generalized by Winstein and Buckles (9) reduces the mechanism to addition polymerization of the polar type established by Williams (10). Evidence of the validity of the Winstein and Buckles intramolecular inversion mechanism as applied to this case is the work of Freundlich and Neumann (11), who found that the rate of bromide ion production from β-bromoethylamine hydrobromide in excess alkali is first order and independent of alkali concentration. The present authors confirmed these results with β-chloroethylamine hydrochloride.

The Winstein and Buckles mechanism for the over-all replacement generalized below involves two steps, first a rate-determining, intramolecular inversion, second an anionoid cleavage.

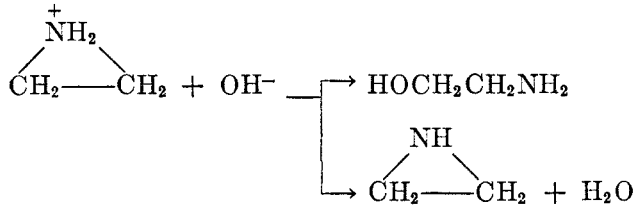
For the over-all replacement:

$$ClCH_2CH_2NH_2 + AB \longrightarrow BCH_2CH_2NH_2 + ACl$$

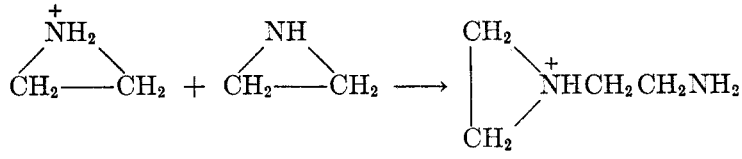
The mechanism:



With sodium hydroxide as AB, the competitive proton abstraction yielding ethylenimine occurs.



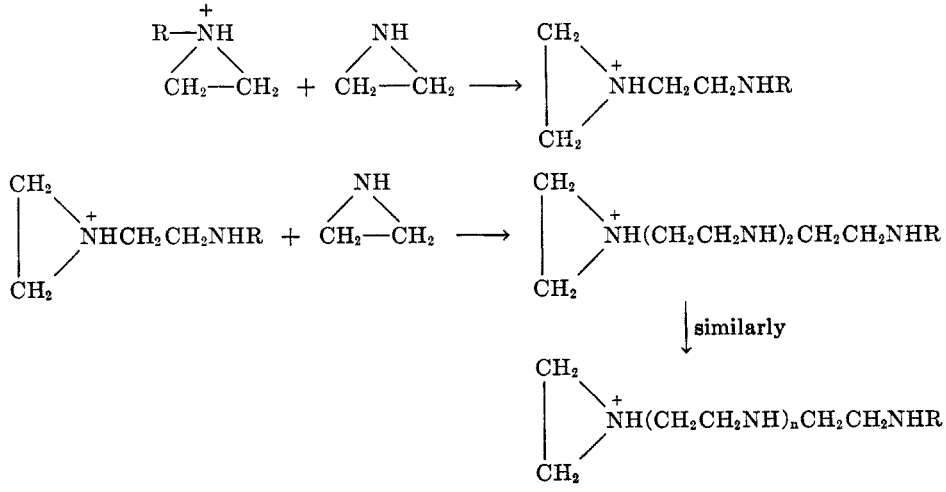
With ethylenimine as AB, the true dimeric polymerization intermediate (which differs from the stabilized isolated dimer by a proton) is obtained in a step which



has the essential characteristic of an addition polymerization mechanism, namely the reaction of a high-energy, unstable intermediate with a monomer to form a new high-energy, unstable intermediate. It seems highly unlikely that the reaction of β-chloroethylamine with the moderately anionoid reagent, ethylenimine should be a second order condensation if the reaction with the strongly anionoid sodium hydroxide is not.

In further support of the view that the formation of β-chloroethylamine is not responsible for the polymerization of ethylenimine by hydrochloric acid is the isolation by the authors of β-chloroethylamine itself, polymerizing only slowly at room temperature although rapidly at 100°.

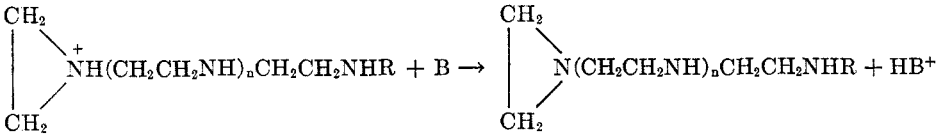
The following mechanism best explains the action of the known catalysts and these other catalysts found by the authors to be effective: allyl and benzyl chlorides and, at elevated temperatures in sealed tubes, perhydrol, potassium persulfate, cupric sulfate, ethyl nitrate, and benzoyl peroxide. The authors confirmed the reported catalysis (5) by ethanolamine sulfuric acid ester, sodium bisulfate and β-chloroethylamine.



Thus any reagent would be expected to function as a catalyst if it would produce tetravalent nitrogen, as acids, alkylating agents, oxidizing agents, and acceptors such as copper salts or boron trifluoride. Since extreme precautions for obtaining a completely anhydrous imine were not observed, those reagents which, as potassium persulfate, generate acid on heating with water might function as acid catalysts.

Termination of the polymerizing chains might occur variously with or without initiating new chains.

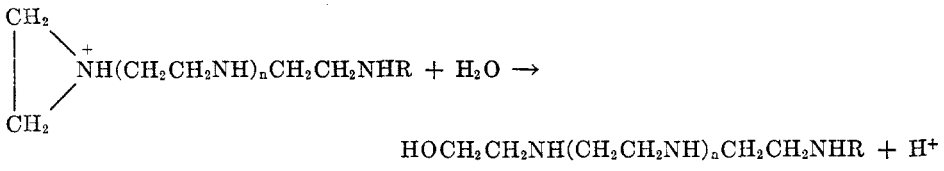
Termination A:



$$\text{NH}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR} + \text{B} \rightarrow \text{N}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR} + \text{HB}^+$$

B may be a monomer molecule, amino nitrogen in a polymer or polymerizing chain, or water; HB^+ is acidic in nature but only when B is a monomer molecule is initiation of a new chain immediate and certain.

Termination B:

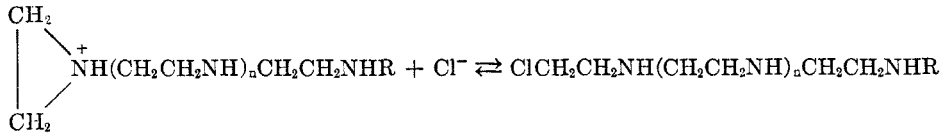


$$\text{NH}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR} + \text{H}_2\text{O} \rightarrow$$

$$\text{HOCH}_2\text{CH}_2\text{NH}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR} + \text{H}^+$$

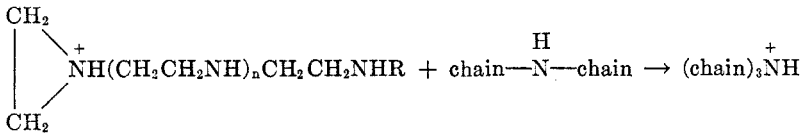
The probability of initiation of a new chain in this case depends on the relative proportion and mobility of imino and amino nitrogen in the competition for the proton.

Termination C:



$$\text{NH}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR} + \text{Cl}^- \rightleftarrows \text{ClCH}_2\text{CH}_2\text{NH}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR}$$

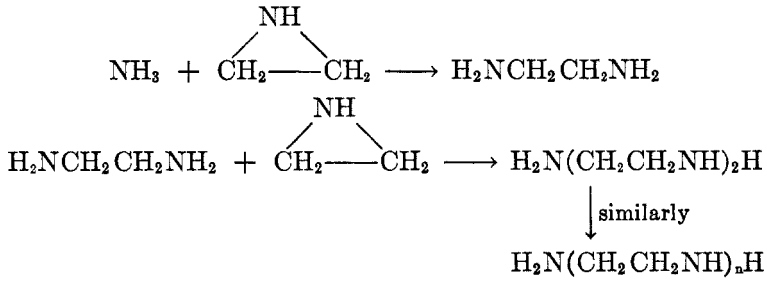
Termination D:



$$\text{NH}(\text{CH}_2\text{CH}_2\text{NH})_n\text{CH}_2\text{CH}_2\text{NHR} + \text{chain—N—chain} \rightarrow (\text{chain})_3\overset{+}{\text{N}}\text{H}$$

The last reaction would produce branching but not cross-linking. The probability of initiating a new chain by the HB^+ molecule depends on the relative proportion and mobility of imino and amino nitrogen. Since the relative proportion of imino to amino nitrogen decreases during polymerization, the rate of decrease in the concentration of active immonium ions should increase as polymerization continues.

An alternative mechanism, similar to that established by Perry and Hibbert (12) for the polymerization of ethylene oxide, is suggested by the reported (8) polymerization of ethylenimine by ammonia under pressure.



This mechanism seems contraindicated except under the conditions of the patent (8) since imino nitrogen is of the same donor ability as amino nitrogen and since ethylenimine is relatively stable in the absence of acid catalysts.

A carbonium-ion mechanism seems very improbable in view of the cleavage of 1,2-propylenimine by hydrobromic acid, shown by Gabriel and Ohle (13) to yield β-bromoisopropylamine hydrobromide rather than β-bromopropylamine hydrobromide, reaction occurring preferentially on the primary carbon.

Data on the rate of polymerization of ethylenimine in 10% aqueous solution with one-tenth the equivalent amount of hydrochloric acid are partly in accord with the bimolecular immonium ion mechanism of ethylenimine polymerization. The rate of polymerization was followed by refractive index change. The incompletely polymerized solution was driven to complete polymerization by heating until no monomer could be steam distilled. To the stock polymer solution so prepared was added a proportionate amount of acid and ethylenimine solution to give synthetic mixtures assumed to correspond to different stages of the polymerization for which the rate was measured. The relation between refractive index and percentage polymerization in the synthetic mixture was linear and this calibration curve was established for each solution employed to compensate approximately for the probable differing degree of polymerization among the solutions. The completely polymerized solutions were of approximately the same viscosity as solutions of the same concentration made by dissolving relatively pure polymer in water.

As indicated in Fig. 2 the quarter-life was proportional to the initial ethylenimine concentration at constant catalyst concentration and the half-life was inversely proportional to the initial acid concentration in solutions of the same monomer concentration.

That the kinetics are complicated is shown by the fact that the data of Fig. 1 indicate a hypothetical order of higher than four. This is readily established by plotting the usual functions of the monomer concentration (obtained by subtracting from 100 the percentage polymerization and multiplying the result by 1.85 M, the initial monomer concentration) *versus* time. These curves may be interpreted by the following rule, readily established by plotting usual functions of assumed sets of data obeying zero, first, second, third, and fourth order rate

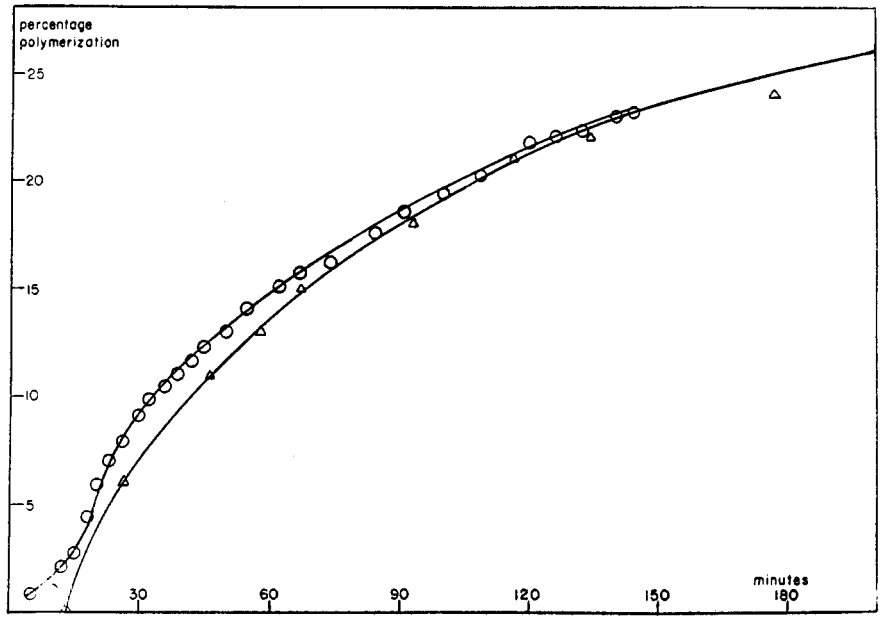


FIG. 1. RATES OF POLYMERIZATION OF 1.85 *M* ETHYLENIMINE (CIRCLES) AND 1,2-PROPYLENIMINE (TRIANGLES) IN 0.246 *N* HYDROCHLORIC ACID

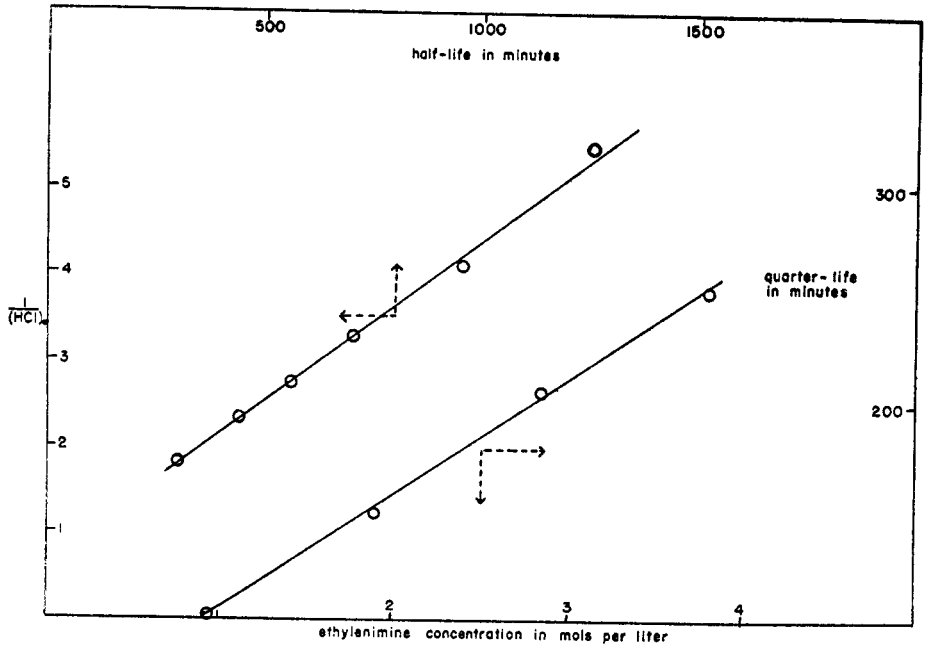


FIG. 2

equations. If data obeying higher order rate equations are plotted as zero or first order functions the curves are concave. If data obeying lower order rate equations are plotted as second or higher order functions, the curves are concave. If zero order data are plotted as second order, the curve is convex, or if data obeying higher order rate equations are plotted as lower order functions (but greater than first order), the curves are convex. All graphs are plotted with increasing ordinates and the abcissa is increasing time.

The bimolecular polymerization mechanism postulated would suggest at once that a pseudo first order rate equation should be applicable to the initial stages of the reaction, namely:

$$-\frac{d[\mathrm{M}]}{dt} = k[\mathrm{M}][\mathrm{A}]; \qquad t_{\frac{1}{2}} = \frac{ln\ 2}{k[\mathrm{HCl}]_0}$$

This equation for the rate of disappearance of ethylenimine (M) neglects differences in reaction rate with the chain length of the active center (A) and is pseudo first order because, for the initial stages of polymerization, the concentration of active centers is constant and equal to the concentration of initially added hydrochloric acid, $[\mathrm{HCl}]_0$.

The explanation for the fact that the curves of Fig. 1 fit no simple order lies apparently in a deviation from pseudo first order kinetics due to a slow decrease in [A]. The following rate equation reduces to the first equation for $t = 0$.

$$-\frac{d[\mathrm{M}]}{dt} = k\,\frac{[\mathrm{M}][\mathrm{HCl}]_0}{1 + K\dfrac{[\mathrm{M}]_0 - [\mathrm{M}]}{[\mathrm{M}]}}$$

This equation may be deduced by the assumption of reversible proton interchange as discussed under modes of termination.

$$\mathrm{A} + \text{chain—NH—chain} \rightleftharpoons \text{chain—}\overset{+}{\mathrm{N}}\mathrm{H}_2\text{—chain} + \mathrm{M}\ \text{(or substituted M)}$$

Neglecting the concentration of imine rings in polymer chains (small relative to [M]) the equilibrium constant for the equation would be represented as follows:

$$K = \frac{([\mathrm{HCl}]_0 - [\mathrm{A}])[\mathrm{M}]}{([\mathrm{M}]_0 - [\mathrm{M}])[\mathrm{A}]}$$

The quarter-life expression would be independent of monomer concentration according to either rate equation, and the direct dependence of quarter-life on monomer concentration is not explained.

Various derivatives of polyethylenimine have been prepared in the powder form and subjected to Dumas analysis. A polybenzamide and a polyphenylthiourea were obtained for which the nitrogen content agreed with that calculated for unbranched polyethylenimine derivatives. The authors were unsuccessful, however, in obtaining a hydrochloride, polynitrosamine, and polybenzyl derivative [prepared after the method of van Alphen (14) for benzylating primary amino groups only] of correct composition.

It was attempted to estimate the chain length by van Slyke amino nitrogen end-group analysis, cryoscopic measurements on the polymer, and extrapolation of viscosity data obtained with low molecular weight compounds. For this purpose ethylenediamine, triethylenetetramine, tetraethylenepentamine, heptaethylenoctamine, and nonaethylenedecamine were used, the last two being prepared by the reaction of ethylene bromide with triethylenetetramine and tetraethylenepentamine, respectively. Assuming no branching, the van Slyke results indicate a degree of polymerization of 5 units, the cryoscopic method of 42 units, and the extrapolation method of 57 units for polymer number one. Since the polymer is non-distillable, and a 1% solution has over double the specific viscosity of tetraethylenepentamine, the van Slyke result must be unreliable. The molecular weights are being re-investigated by the osmotic method.

The high temperature-coefficient of polymerization made it difficult to determine the effect of temperature on degree of polymerization; however, it is indicated to be slight.

One of the workers accidentally allowed about 1 cc. of freshly distilled ethylenimine to fall on his forearm. Although he washed his arm at once with water and dilute hydrochloric acid, considerable redness developed after five hours and blisters appeared within twelve hours. New blisters kept forming for two months and blood tests made at the time indicated some lowering of the white blood cell and platelet counts.[1] The ethylenimine vapors appeared to be irritating to the eyes as reported by Danehy and Pflaum (15).

EXPERIMENTAL PART

Preparation of alkylenimines. Ethylenimine was prepared after the method of Wenker (3) in runs of five times the size and in 30–32% yield. For polymerization tests the ethylenimine was fractionally distilled over potassium hydroxide and in a stream of dry nitrogen through a total-condensation column with a 12-inch packing of glass helices; b.p. 55–56°; n_D^{25} 1.4123.

Propylenimine was prepared from 2-amino-1-propanol (obtained from Commercial Solvents Corporation) and isopropanolamine (obtained from Carbide and Carbon Chemicals Corporation) in identical yields by the method of Cairns (16); yield 65%; b.p. 63–64°; n_D^{25} 1.4095.

Polymerization tests with ethylenimine. Ethylenimine stored in a partly filled bottle without precaution to eliminate carbon dioxide was found to undergo about 0.5% polymerization in two weeks at room temperature; this was reduced by refrigeration.

Table I summarizes results obtained with 5-cc. portions of ethylenimine, freshly distilled and carbon dioxide-free, and sealed with the catalysts in tubes of 10–15 cc. capacity. The percentage polymerization was obtained by measuring the viscosity (relative to that of pure ethylenimine) after the polymerization test. These relative viscosities were converted to percentage polymerization with the curve of Fig. 3. This calibration curve was established by measuring (in the same 2-cc. Ostwald viscosimeter used for above measurements and at 25°) the viscosity of solutions of various concentrations of polyethylenimine No. 1 in pure ethylenimine. This method of estimating the percentage polymerization neglects the effect of variation in degree of polymerization.

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[1] These tests were made under the supervision of Student Health at the State University of Iowa. *Cf.* ref. 19 for other toxicity studies.

TABLE I

EFFECT OF CATALYSTS ON POLYMERIZATION

CATALYST ADDED TO 5 CC. ETHYLENIMINE	FLUSHED	TREATMENT, TEMP., °C.	DURATION, HRS.	APPEARANCE	25°C. η rel	% POLYMERIZATION
Control	N_2	145	72	No change	1.62	6.1
Control	N_2	U.V.L., 40	75	No change	1.016	0.2
Control	Air, CO_2-free	145	72	Slightly yellow	1.479	4.85
Control	Air, CO_2-free	U.V.L., 40	75	No change	1.029	0.3
Control	Not	150	72	Yellow	1.896	8.5
Control	Not	U.V.L., 40	65	No change	1.185	2.1
Ascaridole, 0.10 cc	N_2	U.V.L., 40	75	Slightly yellow	1.061	0.7
Ascaridole, 0.20 cc	Not	150	65	Brown	1.167	1.8
Benzoyl peroxide, 0.0539 g	N_2	U.V.L., 40	75	Slightly yellow	1.261	2.5
Benzoyl peroxide, 0.149 g	Not	150	65	Yellow	Very viscous	
Old paraldehyde, 0.65 cc	Not	U.V.L., 40	65	No change	1.83	8.0
Old paraldehyde, 0.65 cc	Not	150	65	No change	1.36	4.1
Perhydrol, 0.10 cc	Not	U.V.L., 40	46	No change	1.245	2.8
Perhydrol, 0.10 cc	N_2	145	72	Slightly viscous	8.445	25
Potassium persulfate, 0.0522g	Not	U.V.L., 40	46	No change	1.136	1.6
Potassium persulfate, 0.051 g	N_2	110	0.2	Polymerized explosively		
Copper sulfate, 0.0535 g	Not	U.V.L., 40	46	No change	1.074	0.9
Copper sulfate, 0.0434 g	N_2	145	72	Very viscous polymer and free copper		
Water, 0.07 cc	N_2	145	72	No change	2.211	10.3
Ethyl acetate, 0.50 cc	N_2	145	72	Colorless and very viscous		
Ethyl nitrate, 0.50 cc	N_2	110	0.2	Polymerized explosively		
Copper bronze, 0.0502 g	Not	100	24	Brown, not apparently viscous		
Sodium hydroxide, 5 N., 1 cc	Not	25	170	No change		
Potassium persulfate, 0.5 g.; 0.5 cc. water	Not	95	24	Very viscous		

The ethyl acetate and ethyl nitrate were purified acid-free; a control in which diethylamine was substituted for ethylenimine produced no explosion with ethyl nitrate. The test solutions were homogeneous except where the catalysts were potassium persulfate, anhydrous copper sulfate, and copper-bronze. Reduction to copper was extensive in the copper sulfate test; a slight amount of copper dissolved to form a blue solution in the copper-bronze test.

A separate experiment was made to compare the effectiveness of different acids. To separate, 5-cc. (0.098-mole) portions of freshly distilled ethylenimine, chilled to 0°, were added 1-cc. portions of the following acids: nitric 2.860 *N*, hydrochloric 2.872 *N*, sulfuric

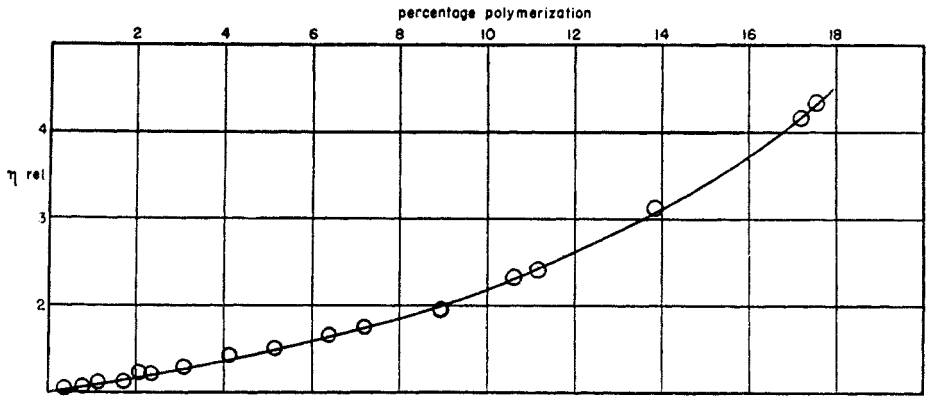

FIG. 3. PERCENTAGE POLYMERIZATION AS A FUNCTION OF VISCOSITY RELATIVE TO PURE ETHYLENIMINE

2.912 *N*, and acetic 2.866 *N*. The solutions were allowed to stand at room temperature, becoming eventually very slow-flowing, but sticky.

	VISCOSITY	
ACID	η_{rel}, ETHYLENIMINE After 20 hours	η_{rel}, 1% AQUEOUS SOLUTION After 48 days
Nitric	111.5	2.21
Hydrochloric	83.1	2.21
Sulfuric	31.3	2.10
Acetic	17.4	1.95

To 1.0-cc. portions of ethylenimine were added 0.1-g. portions of benzyl chloride, allyl chloride, *tert.*-butyl bromide, *n*-butyl chloride, and *o*-, *m*-, and *p*-nitrochlorobenzenes. The first two caused vigorous thermal polymerization within two minutes, the third produced a very viscous product in twenty-four hours, and the others caused no apparent change in a week.

Polyethylenimines studied. Polyethylenimine No. 1. To 50 cc. (0.97 mole) of freshly distilled ethylenimine chilled to −78° was added 1 cc. (0.012 mole) of concentrated hydrochloric acid. The solution slowly became honey-like after thirty-five days at 25°. From this product 10% recovered ethylenimine could be distilled at 2 mm. and 100° bath temperature. The viscous residue reduced silver nitrate and a 5% aqueous solution had *p*H 10.6. Steam distillation of a sample from a solution to which had been added sodium hydroxide yielded no alkali.

For a 1.03% solution in chloroform, η_{rel} = 1.160; for a 0.994% aqueous solution, η_{rel} = 1.157.

Polyethylenimine No. 2. To each of four tubes containing 25 cc. of freshly distilled ethylenimine chilled to −78° was added 1 cc. of concentrated hydrochloric acid. The tubes were sealed and two were allowed to warm to room temperature. One of these was placed in an iron pipe on a sand-bath at 100°, and exploded within a few minutes. The other left at room temperature and a third at 15° exploded within thirty minutes. The explosions left a low yield of gummy polymer.

The fourth tube was kept at −78° for twenty-eight days without any sign of increasing viscosity. It was then opened, corked, and allowed to warm toward room temperature. Within a few hours violent polymerization had occurred throwing out over half the contents of the tube as a viscous polymer and leaving a viscous polymeric residue, $\eta_{rel} = 1.123$ for a 1.38% aqueous solution. After steam distillation of this solution and dilution of the residue to the original volume, $\eta_{rel} = 1.143$.

Polyethylenimine No. 3. In 50 cc. of freshly distilled ethylenimine, chilled at −78°, was absorbed about 0.5 g. of boron trifluoride. During three weeks at room temperature the solution was slowly converted to a yellow, very slow-flowing polymer. The *p*H of a 5% aqueous solution was 8.7 and $\eta_{rel} = 1.309$ for a 0.96% aqueous solution. No basic material could be steam distilled; after steam distillation, $\eta_{rel} = 1.293$.

Polyethylenimine No. 4. In 25 cc. of freshly distilled ethylenimine, chilled at −78°, was absorbed 0.2 g. of boron trifluoride (determined by difference). After twenty days at −78° in a container protected with an Ascarite tube no apparent increase in viscosity had occurred and the mixture was then placed at room temperature when it polymerized slowly and incompletely. The change in viscosity relative to pure ethylenimine is indicated.

After 22 hours $\eta_{rel} = 1.167$ 2.0% polymerization
After 48 hours $\eta_{rel} = 1.695$ 8.0% polymerization
After 59 hours $\eta_{rel} = 2.405$ 11.1% polymerization

There was no further increase in viscosity for four days, and the polymer mixture was then evaporated at 30 mm. and a bath temperature of 50°; yield 50% $\eta_{rel} = 1.087$ for a 1.0% aqueous solution.

Polyethylenimine No. 5. Into 10 cc. of ethylenimine chilled at −78° was passed a large amount of boron fluoride, forming a yellow, gummy precipitate on the wall of the tube. At least 90% of the contents was still fluid without noticeable change in viscosity. There was no change in four days at −78°, the ethylenimine-boron fluoride addition product being insoluble in the cold ethylenimine. The tube was then removed from the cooling bath and after about an hour the contents polymerized quickly with spattering to a viscous mass; $\eta_{rel} = 1.085$ for a 1.0% aqueous solution.

Polyethylenimine No. 6. In 200 cc. of purified absolute butyl ether was dissolved 1.405 10^{-2} moles of boron fluoride measured at 746.8 mm. and 20°, using at 100-cc. gas burette and Hempel pipette. To 100 cc. of this solution chilled at −78° was added 5 cc. of ethylenimine, and the solution was maintained at −78° (solution A). To 100 cc. of the solution cooled to 10° was added 5 cc. of ethylenimine and the solution allowed to warm to room temperature (solution B). Both solutions became at once somewhat turbid.

After twenty-four hours a gummy precipitate had formed in both solutions. The supernatant solutions were decanted and kept at room temperature. After twenty-four hours a small amount of gummy polymer had formed in the decanted liquor of solution. About five days were required before more polymer formed in the decanted liquor of solution B.

The polymers were dissolved, the viscosities taken, and the yields determined by evaporation.

	η_{rel} FOR 1.75% AQUEOUS SOLUTION	YIELD
First crop solution A	1.365	0.0328 g.; 1%
First crop solution B	1.121	0.9533 g.; 23%
Second crop solution A	1.525	1.4856 g.; 36%
Second crop solution B	1.400	0.320 g.; 8%

SYNOPSIS OF POLYMERS DESCRIBED

NO.	ETHYLENIMINE	CATALYST	TREATMENT	FINAL APPEARANCE
1	50 cc. (0.97 mole)	1 cc. HCl conc'd (0.012 mole)	25°C. for 35 days	honey-like
2	25 cc.	1 cc. HCl conc'd	polymerized quickly on warming from −78°C.	gummy
3	50 cc.	0.5 g. BF_3	25°C. for 3 weeks	gummy, yellow
4	25 cc.	0.2 g. BF_3	25°C. for 6 days	honey-like after evaporation of unreacted monomer
5	10 cc.	large amount BF_3	polyermized quickly on warming from −78°C.	gummy
6	10 cc. in 200 cc. of purified butyl ether	$1.405\ 10^{-2}$ mole BF_3	portions treated variously	gummy

β-Chloroamine hydrochlorides. β-Chloroethylamine hydrochloride. Ethanolamine was converted to the hydrochloride by evaporating with the calculated quantity of hydrochloric acid and treated with thionyl chloride after the method of Ward (17). It was found necessary to reflux the suspension of ethanolamine hydrochloride with thionyl chloride in chloroform or benzene for about two hours; the reaction was incomplete in the cold. After several recrystallizations from dry alcoholic ether the product reached the melting point 147.5–148°; further recrystallization gave no further rise; yield 56%.

Anal. Calc'd for $C_2H_7Cl_2N$: Cl, 61.14. Found: Cl, 61.07.

*β-Chloro-*n*-propylamine hydrochloride.* In the same manner isopropanolamine was converted to β-chloro-*n*-propylamine hydrochloride, previously prepared by Gabriel and Ohle (13), in 19% yield with m.p. 180–181° after five recrystallizations from absolute alcohol.

Anal. Calc'd for $C_3H_9Cl_2N$: Cl, 54.54. Found: Cl, 54.9.

N-Phenyl-β-chloroethylamine hydrochloride. N-Phenylethanolamine (448 g., 3 moles) was treated with 250 cc. (3 moles) of concentrated hydrochloric acid. The solution was distilled from a steam-bath under reduced pressure (aspirator) until no more water distilled. The residue was a thick syrup resisting attempts to cause it to crystallize.

The residue was treated with thionyl chloride (5 moles) in 1 liter of chloroform and refluxed one hour. The excess thionyl chloride and chloroform were distilled under reduced pressure and the black thick residue dissolved in the minimum amount of hot absolute alcohol. On cooling, brown needles formed. Three recrystallizations with charcoal treatment failed to remove the color; m.p. 155–157°; yield 9.2%.

Anal. Calc'd for $C_8H_{11}Cl_2N$: Cl, 36.92. Found: Cl, 36.82.

Stability of β-chloroethylamine. To 100 cc. of cold 10% sodium hydroxide solution was added with stirring 11 g. of β-chloroethylamine hydrochloride. The solution was extracted with three 15-cc. portions of ether and the ether extracts dried with sodium sulfate at 0° for two hours. The filtered solution was distilled at 25° at 80–100 mm. until no more ether distilled. The residue (5 cc.) showed no apparent increase in viscosity after standing three hours at room temperature. Overnight the liquid changed to a turbid, fairly viscous material. A portion heated at 40° yielded in thirty minutes a thick polymer; $\eta_{rel} = 1.006$ for a 1.0% aqueous solution.

A portion of the original ether solution was evaporated on a sand-bath at 95°. When most of the ether had been removed, sudden exothermic polymerization occurred.

Isolation of ethylenimine hydrochloride. A solution of 10 cc. of ethylenimine in 2 l. of dry ether was added to 2 l. of dry ether saturated with hydrogen chloride at 0°. The addition was carried out in 0° with vigorous stirring, the stem of the separatory funnel extending

below the surface of the ethereal hydrogen chloride. The white flocculent precipitate was quickly collected on a filter and then rapidly dissolved in 150 cc. of chilled 2 *N* sodium hydroxide solution. The alkaline solution was salted out with potassium carbonate and the upper layer separated and dried with potassium hydroxide. The dried product was fractionally distilled, yielding 3 cc. of b.p. 54–57° and 10 cc. of b.p. 60–107°. Fraction 1 was recovered ethylenimine indicating that the flocculent precipitate contained ethylenimine hydrochloride.

Fraction 1: b.p. 54–57°; n_D^{20} 1.4120; d_{25}^{25} 0.8353.
Ethylenimine: b.p. 54.5–55°; n_D^{20} 1.4123; d_{25}^{25} 0.8349.

Some of the flocculent precipitate had clung to the reaction flask and had been allowed to stand overnight under filtered ethereal hydrogen chloride. The precipitate became visibly crystalline and was filtered and recrystallized from absolute alcohol; m.p. 144–145°. Melting point of β-chloroethylamine hydrochloride 146–147°. Mixed melting point 144–145°.

In another run the flocculent precipitate was filtered and transferred to a vacuum desiccator. In five minutes the originally white solid suddenly polymerized to a brown horny mass evolving a cloud of hydrogen chloride. This polymer (0.450 g.) was dissolved in water, made alkaline and salted out with potassium hydroxide. No distillate could be obtained at a bath temperature of 150° under 1 mm. pressure, the polymer being a viscous red oil. No precipitate formed when aqueous sodium nitrite was added to a solution of this polymer in aqueous hydrochloric acid; whereas with the other polyethylenimines solid, insoluble polynitrosamines were obtained.

To test the possibility that the flocculent precipitate was a mixture of β-chloroethylamine hydrochloride and ethylenimine hydrochloride the following experiment was carried out. β-Chloroethylamine hydrochloride (7 g.) was treated with 30 cc. of cold 10% sodium hydroxide solution. This solution was extracted with two 25-cc. portions of ether. The ether extracts, containing the β-chloroethylamine, were combined and dried with anhydrous sodium sulfate at 0°. To the dried ether extract was added 15 cc. of ethylenimine. After an hour no precipitate of polyethylenimine had formed and the solution was poured into 100 cc. of cold 10% sodium hydroxide. The mixture was stirred for ten minutes, the ethereal layer was then separated and dried with potassium hydroxide, and the ether distilled. When most of the ether had been distilled, polymerization suddenly occurred blowing out the cork of the distilling flask and leaving a gummy polymer.

Isolation of ethylenimine dimer. To 2.5 l. of dry ether saturated with hydrogen chloride at 0° was added a solution of 43 g. of ethylenimine in 2.5 l. of dry ether. The reaction was carried out at 0° and the addition was made rapidly in 2.5 minutes with vigorous stirring, the stem of the separatory funnel extending below the surface of the ethereal hydrogen chloride. Slight variations in this procedure resulted in violent polymerization with rapid volatilization of the ether.

The white flocculent precipitate was quickly collected on a filter and neutralized with 750 cc. of cold 2 *N* sodium hydroxide. Potassium carbonate was added to salt out the product which was then dried over potassium hydroxide. The dried product was fractionally distilled over potassium hydroxide yielding 8.5 g. or 22% of recovered ethylenimine, b.p. 54.5–60° and a fraction of boiling point range 60–126°. The latter material was redried with potassium hydroxide and redistilled, b.p. 126–127.5°; yield 10 g. or 23% of ethylenimine dimer.

Anal. Calc'd for $C_4H_{10}N_2$: C, 55.77; H, 11.70; N, 32.53.

Found: C, 56.58; H, 11.00; N, 32.71 (all N analyses Dumas). n_D^{20} 1.4547; d_{25}^{25} 0.9157. Molecular weight by freezing point depression in diphenylamine: 86.1 (calc'd); 81.7 (found).

In a test on a small sample the dimer was polymerized by a small amount of hydrochloric acid.

To a solution of 1 cc. of the dry dimer in 5 cc. of absolute alcohol was added 1 cc. of phenylisothiocyanate. The phenylthiourea crystallized on standing and was washed with absolute alcohol; yield 1.5 g.; m.p. 129–131°.

Anal. Calc'd for $C_{11}H_{15}N_3S$: N, 19.43. Found: N, 19.52.

When water was present the reaction with phenylisothiocyanate yielded a product melting with decomposition at 154–163°.

N-(β-aminoethyl)ethylenimine. To a solution of 100 g. (0.96 mole) of aminoethylethanolamine in 100 cc. of water was added a solution of 186 g. (1.8 moles) of concentrated sulfuric acid in 100 cc. of water. The resulting solution was distilled until 180 cc. of water was collected. The pressure was reduced to 11 mm. and distilling continued until charring and frothing began, with no more distillation. The contents of the flask were poured into a preheated evaporating dish and the syrupy mass vigorously stirred until it became solid. The solid was broken into small pieces and was treated with 100 cc. of 40% sodium hydroxide. The mixture was cautiously heated until the voluminous frothing subsided and the solid dissolved with the subsequent precipitation of sodium sulfate. The mixture was steam distilled until 1000 cc. of distillate was obtained. After salting out with potassium hydroxide the upper layer was chilled to −10° while piperazine hydrate crystallized. The piperazine hydrate was filtered, distilled, and converted to the dihydrochloride; yield 37%; m.p. of the hydrate 44°.

The filtrate was dried repeatedly over solid potassium hydroxide and distilled over potassium hydroxide; b.p. 126–128°; yield 14 g. or 16%; n_D^{20} 1.4553; d_{25}^{25} 0.9204. A sample of the liquid was readily polymerized by dilute hydrochloric acid. Phenylthiourea m.p. 128–130°. A mixed melting point with the phenylthiourea of the dimer of ethylenimine was 128–131°, indicating that the dimer was N-(β-aminoethyl)ethylenimine.

Derivatives of polyethylenimine. Polyethylenimine hydrochloride. A polyethylenimine prepared by rapid polymerization with concentrated hydrochloric acid was dissolved in water, suspended in benzene, and dried by distillation of the benzene at 25 mm. and 100° water-bath temperature; the process was repeated three times. The semi-solid mass remaining was dissolved in absolute alcohol and the alcoholic solution was saturated at room temperature with dry hydrogen chloride. The precipitated solid was filtered, washed with dry ether, and stored in a vacuum desiccator. It was insoluble in alcohol, very soluble in water, and very hygroscopic.

Anal. Calc'd for $(C_2H_6ClN)_n$: Cl, 44.58. Found: Cl, 25.1.

Benzamide of purified polyethylenimine No. 1. Benzoylation of 6 g. of purified polyethylenimine No. 1 by the Schotten-Baumann method at 40° yielded a white, gummy mass which was dissolved by mechanical shaking with three successive 100-cc. portions of chloroform.

The polymer was precipitated by the fairly slow addition from a separatory funnel of the chloroform solution to 2 liters of ligroin (b.p. 80–100°), the latter being used in many portions. The polymer was filtered as a white powder in 66% yield; softening point (Dennis bar) 110°.

Anal. Calc'd for $(C_9H_9NO)_n$: N, 9.52. Found: N, 9.18.

In 100 cc. of chloroform was dissolved 7.5 g. of the dry polymer benzamide. Hydrogen chloride was passed into the solution and at once a white, pulpy precipitate formed. The precipitate was filtered and placed in a desiccator. A portion became gummy at once on treatment with water. The chloroform liquor gave no precipitate on pouring into ligroin.

Anal. Calc'd for $(C_9H_{10}ClNO)_n$: N, 7.53. Found: N, 8.31.

A portion of the hydrochloride was mainly soluble in chloroform after treatment with 1 *N* sodium hydroxide. The polymer in the chloroform solution was treated with benzoyl chloride and sodium hydroxide solution and the rebenzoylated polymer isolated as before by pouring the chloroform solution into ligroin.

Anal. Calc'd for $(C_9H_9NO)_n$: N, 9.52. Found: N, 9.57.

Benzamide of polyethylenimine No. 3. The benzamide of polyethylenimine No. 3 was prepared as a tan powder as above by Schotten-Baumann benzoylation and precipitation of the chloroform solution of the product by pouring into ligroin. The color was somewhat lightened by redissolving in chloroform and reprecipitation; softening point (Dennis bar) 111°.

Anal. Calc'd for $(C_9H_9NO)_n$: N, 9.52. Found: N, 10.19.

Phenylthiourea of polyethylenimine No. 1. To 50 cc. of an aqueous solution containing 1.7 g. of the unpurified polyethylenimine No. 1 was added 5.0 cc. of phenylisothiocyanate. The solution was shaken for ten minutes; however, the phenylthiourea formed an oil which became solid after an hour of frequent stirring; yield 85%.

Anal. Calc'd for $(C_9H_{10}N_2S)_n$: N, 15.71. Found: N, 16.47.

The phenylthiourea was purified by shaking 6 g. with 100 cc. of absolute alcohol for two hours. The fine white precipitate was filtered, washed with absolute alcohol, and dried in a desiccator, m.p. (Dennis bar) 138°.

Anal. Calc'd $(C_9H_{10}N_2S)_n$: N, 15.71. Found: N, 15.27.

Benzyl derivative of polyethylenimine No. 1. Applying the method used by van Alphen (14) to prepare N,N'-di(β-benzylaminoethyl)ethylenediamine, it was attempted to benzoylate polyethylenimine on the primary nitrogen only. To 14 g. of the purified polyethylenimine No. 1 was added 35 g. of benzaldehyde. On shaking, the polymer dissolved and heat was evolved. The vessel was mechanically shaken for two hours, and a small amount of gummy polymer precipitated as the solution cooled. The mixture was dissolved in 500 cc. of absolute alcohol, giving a yellow solution smelling of benzaldehyde. To this solution was quickly added 15 g. of sodium cut in small pieces. The solution was shaken until the sodium had reacted, and turned red and finally black. After the addition of 50 cc. of water, the alcohol and water were distilled under reduced pressure. The dark, gummy residue was partly dissolved in 500 cc. of alcohol and to the mixture was added 100 cc. of concentrated hydrochloric acid. A dark upper layer formed at first; however, this disappeared and a heavy brown precipitate formed on the walls of the flask. The alcoholic solution was evaporated and the combined residues treated with 40% sodium hydroxide and dissolved in a mixture of chloroform and dioxane. The extract was dried with potassium hydroxide and hydrogen chloride passed in. The brown precipitate formed was washed with absolute ether.

Anal. Found: N, 9.905; Cl, 28.92.

The hydrochloride of the benzyl derivative was benzoylated by the Schotten-Baumann method, isolated by precipitation from chloroform solution and re-benzoylated.

Anal. Found: N, 8.34.

Nitroso derivative of polyethylenimine made in aqueous solution. A solution of 47.7 g. of freshly distilled ethylenimine in 429.1 g. of water was polymerized with 23.9 cc. of 5.545 *N* hydrochloric acid. This was actually carried out in two portions, one of which contained 2.39% added sodium chloride and the other 4.21%. Since there was no effect of the added sodium chloride on the rate of polymerization, the solutions were combined.

In 170 cc. of this solution was dissolved 50 g. of sodium nitrite and then 80 cc. of concentrated hydrochloric acid was added from a separatory funnel. A heavy white foam formed at once and became yellow as the last of the acid was added, becoming gummy after decantation of the water. After air drying for three days the product could be powdered; yield 22 g. The powder was insoluble in all the common solvents. A portion of this product was stirred with water, the water becoming strongly acid. The nitroso derivative was washed with water until acid-free and dried in a desiccator. It was still yellow and was becoming gummy at the last washing.

Anal. Calc'd for $(C_2H_4N_2O)_n$: N, 38.88. Found: N, 25.67.

A second portion was stirred with 1 *N* NaOH, becoming brown and gummy. Several times on standing overnight the alkali wash had become acid. At each fresh addition of alkali the polymer, which was now tough and spongy, effervesced. The product was removed and dried in a desiccator.

Anal. Found: N, 29.81.

Heptaethylenoctamine. After the method by which van Alphen (18) prepared N,N'-di-β-aminoethyltrimethylenediamine, heptaethylenoctamine was prepared from triethylenetetramine and ethylene bromide. A solution of 141 g. (0.75 mole) of ethylene bromide in 75 cc. of absolute ethanol was added slowly, over the period of one hour, to a mechanically stirred solution of 219 g. (1.50 moles) of triethylenetetramine in 37.5 cc. of absolute ethanol.

External cooling was used to keep the temperature from rising above 60°. The mixture was refluxed one hour after addition, and then 104 g. (1.86 moles) of solid potassium hydroxide was added. The mixture was again refluxed for one hour and then filtered.

The alcohol was distilled under reduced pressure and the residue fractionally distilled through a 6-in. electrically heated, all-glass still-head packed with single-turn glass helices. There was obtained 62 g. of recovered triethylenetetramine, b.p. 100–154° at 1.5 mm. and 45 g. of heptaethylenoctamine, b.p. 149° 1 mm. to 140° 0.45 mm.; 19% yield; n_D^{25} 1.4991. A 55-g. residue solidified on cooling.

Anal. Calc'd for $C_{14}H_{38}N_8$: N, 35.17. Found: N, 32.4.

The benzamide was prepared in the same manner as the polybenzamides; m.p. 202–220°.

Anal. Calc'd for $C_{70}H_{70}N_8O_8$: N, 9.74. Found: N, 9.61.

The heptaethylenoctamine was fractionally redistilled in a 12-in. Fenske column and a middle fraction taken; b.p. 109–110°/0.5 mm.; n_D^{25} 1.4986.

Anal. Calc'd for $C_{14}H_{38}N_8$: C, 52.91; H, 12.02; N, 35.18.
Found: C, 53.61; H, 12.84; N, 35.29.

TABLE II

PHYSICAL PROPERTIES OF AMINES

AMINE	BOILING POINT, °C.	n_D^{25}
Ethylenediamine	110[a]	1.4536
Diethylenetriamine	97–100 20 mm.[b]	1.4810
Triethylenetetramine	112–113 1 mm.[b]	1.4951
Tetraethylenepentamine	151–152 1 mm.[b]	1.5015
Heptaethylenoctamine	109–110 0.5 mm.[b]	1.4986
Nonaethylenedecamine	199–200 1 mm.[c]	1.5116

[a] Modified Claisen distilling flask;
[b] Fenske column with 12-in. packing;
[c] 6-in. packed still-head, all glass.

Nonaethylenedecamine. In the same method the reaction of ethylene bromide (0.50 mole) and tetraethylenepentamine (1.0 mole) was carried out. The product was distilled in an all-glass, unpacked still-head.

Fraction 1. 40 g. 150–200°, 1 mm., n_D^{25} 1.5091
Fraction 2. 25 g. 199–200°, 1 mm., n_D^{25} 1.5116
Fraction 3. 7.5 g. 200–230°, 1 mm., n_D^{25} 1.5145
Residue, 69.5 g.

A portion of fraction 2 was refractionated in a 12-in. Fenske column and a middle fraction taken; b.p. 205°, 2.5 mm.; n_D^{25} 1.5111.

Anal. Calc'd for $C_{18}H_{48}N_{10}$: C, 53.43; H, 11.96; N, 34.60.
Found: C, 53.39; H, 12.04; N, 34.4.

From fraction 3 the benzamide was prepared in the same manner as the polybenzamides; m.p. 75–105°; yield 50%.

Anal. Calc'd for $C_{88}H_{88}N_{10}O_{10}$: N, 9.71. Found: N, 9.44.

A second run was made in the same manner but with double the quantities. The product was distilled in a Claisen flask and the distillate redistilled through a 6-in. all-glass still-head packed with single-turn glass helices. There was obtained 108 g. of recovered tetraethylenepentamine, b.p. 100–150°, 1.5 mm., and 71 g. of nonaethylenedecamine; b.p. 128°, 0.04 mm. to 145° at 0.85 mm.; yield 17.5%; n_D^{25} 1.5072.

Determination of the Staudinger viscosity constant for polyethylenimine. The amines listed in Table II were distilled under precaution to minimize the carbonate content. The first two were distilled over solid potassium hydroxide and with purified nitrogen passing

through the system. The others were heated at 100° with nitrogen passing through the system and then distilled over solid potassium hydroxide.

With a micro Beckmann thermometer the following molecular weight measurements were made by freezing point lowering in the purified solvents indicated. The polyethylenimine was insufficiently soluble in dioxane for the use of this solvent.

These results indicate that the molecular weight found for polyethylenimine No. 1 by this method was exceedingly approximate, especially in view of the fact that a satisfactory way to free it of carbonate was not found. The low results with the octamine and decamine are attributed to the enhanced influence of a trace of carbonate; the fact that better results were obtained with the solvents of lower melting point is indicative of dissociation of the carbonate.

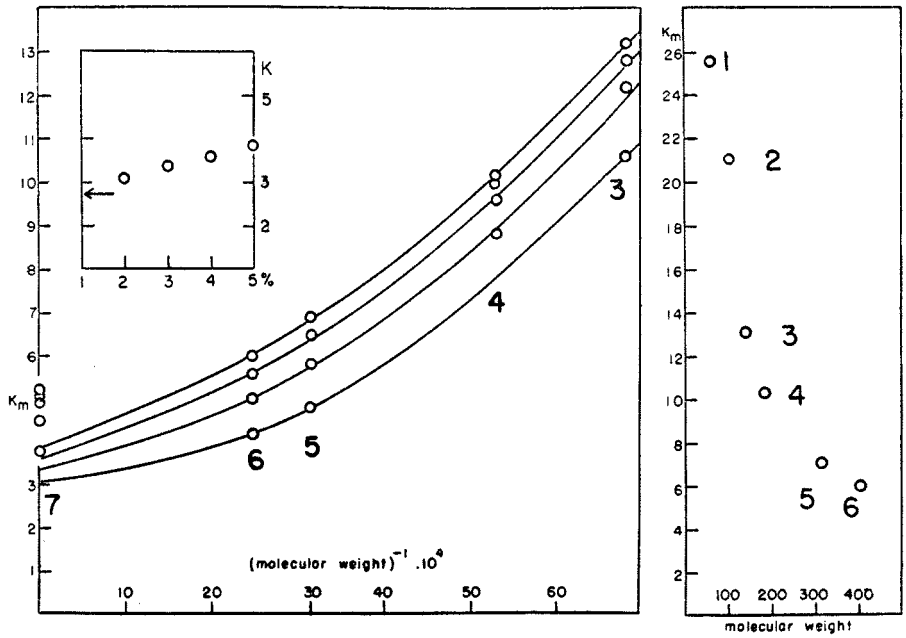

FIG. 4. ESTIMATION OF STAUDINGER CONSTANT, K_m. THE NUMBERS ON THE POINTS REFER TO THE COMPOUNDS IN TABLE II IN NUMERICAL ORDER; NUMBER 7 REFERS TO POLYETHYLENIMINE NO. 1.

Using a 5-cc. Ostwald viscosimeter the following relative viscosities were obtained at 25° for solutions of the purified amines in water which had been boiled and cooled within four hours. The values of K_m were calculated from the Staudinger equation, using $C = \frac{10 \times \text{weight per cent}}{43}$. In the case of the polyethylenimine, the cryoscopic molecular weight value 1790 was used to calculate K_m values, even though the polymer had not been purified by precipitation.

The results for the 5% solutions are shown in the right-hand graph of Fig. 4. The values of K_m for each amine at 5%, 4%, 3%, and 2% were obtained by interpolation on curves obtained by plotting the data of Table IV in a graph relating K_m to the percentage concentration of the solution for each amine. The curves were roughly extrapolated to the polymer region and the inset shows the results for the different percentages, leading to a value $K_m = 2.8 \times 10^{-4}$ for a 1% solution.

The influence of carbon dioxide as an impurity is shown in the following results with ethylene diamine.

CONCENTRATION, %	η_{rel}	K_m	
5.08	1.198	28×10^{-4}	distilled
5.18	1.186	25.8×10^{-4}	distilled with precautions to remove carbonate.

TABLE III

CRYOSCOPIC MOLECULAR WEIGHT VALUES

COMPOUND	SOLVENT	FOUND	CALC'D
Ethylenediamine	Diphenylamine	69.6	60.1
Diethylenetriamine	Diphenylamine	131	103.2
Triethylenetetramine	Diphenylamine	149.2	146.2
Tetraethylenepentamine	Diphenylamine	201	189.3
Heptaethylenoctamine	Triphenylmethane	143	318
Heptaethylenoctamine	Diphenylamine	147	318
Heptaethylenoctamine	Nitrobenzene	211	318
Nonaethylenedecamine	Diphenylamine	227	404.8
Nonaethylenedecamine	Dioxane	278	404.8
Polyethylenimine No. 1	Diphenylamine	1790	--

TABLE IV

RELATIVE VISCOSITIES OF POLYAMINES

	CONCENTRATION, %	η rel	K_m
Ethylenediamine	5.18	1.186	25.8
Diethylenetriamine	4.91	1.253	21.1
Triethylenetetramine	2.05	1.075	10.73
Triethylenetetramine	2.66	1.108	11.95
Triethylenetetramine	3.71	1.167	13.22
Tetraethylenepentamine	1.10	1.034	7.15
Tetraethylenepentamine	1.50	1.054	8.15
Tetraethylenepentamine	4.04	1.178	10.0
Heptaethylenoctamine	1.74	1.056	4.33
	2.57	1.103	5.42
	3.79	1.176	6.27
	5.11	1.268	7.12
Nonaethylenedecamine	3.04	1.136	4.76
	4.14	1.219	5.64
	5.02	1.279	5.94
Polyethylenimine No. 1	0.0994	1.157	3.80
	2.50	1.499	4.79
	5.98	2.307	5.26

The following results were obtained with solutions of purified heptaethylenoctamine in freshly boiled water:

CONCENTRATION	η_{rel}	K_m	CONCENTRATION	η_{rel}	K_m
1.74%	1.056	4.33×10^{-4}	1.67%	1.084	6.79×10^{-4}
2.57	1.103	5.42	2.09	1.097	6.30
3.79	1.176	6.27	3.13	1.153	6.66
5.11	1.268	7.12	3.91	1.196	6.78
			3.92	1.183	6.34

The same viscosity constant is indicated to be applicable to chloroform solutions. The relative viscosities of solutions of polyethylenimine No. 1 in water and chloroform were the same. For example: 0.994% in water, $\eta_{rel} = 1.157$; 1.03% in chloroform, $\eta_{rel} = 1.160$.

Van Slyke amino nitrogen determinations. Van Slyke amino nitrogen analyses were made on amines of known structure and on polyethylenimine, a micro gas burette being coupled with a macro reaction vessel for the latter.

The results are summarized in Table V (reaction time five minutes).

Polyethylenimine No. 7 was made by polymerizing at 25° a solution of 5 cc. of ethylenimine in 45 cc. of water with 2.5 cc. of 5.121 *N* hydrochloric acid, and on dilution to 1% had $\eta_{rel} = 1.135$.

To check the possibility that secondary reactions were occurring, the effect of time of reaction on triethylenetetramine was observed.

Anal. Found: N, 19.4 after 5 minute reaction time; N, 22.2 after 15 minute reaction time.

Rates of polymerization of alkylenimines. With an immersion refractometer the rate of change of refractive index in aqueous alkylenimine solutions at 25° was measured after the addition of a certain amount of hydrochloric acid. When the change had become exceedingly slow, the solutions were heated until no basic material could be steam distilled. Only traces of basic material were steam distilled, as determined by titration. Fom the stock polymer solutions so prepared were compounded mixtures with monomer solution so that

TABLE V

VAN SLYKE NITROGEN DETERMINATION

COMPOUND	% AMINO NITROGEN	
	Found	Calc'd
Ethylenediamine	49.3	46.58
Diethylenetriamine	29.4	27.1
Triethylenetetramine	19.4	19.2
Tetraethylenepentamine	16.5	14.8
Polyethylenimine No. 1	6.53	
No. 3	7.39	
No. 7	8.20	

the percentage polymerization could be established as a function of refractive index. Depending on the composition being compounded, it was necessary to add more hydrochloric acid to duplicate the hydrochloric acid concentration of the original mixture; this acid was added to the sample of polymer solution before mixing with the monomer solution.

Table VI gives the kinetic data for 1.85 *M* imine solutions 0.246 *N* in hydrochloric acid, in immersion refractometer scale readings, which were converted directly to percentage polymerization by the linear calibration curves obtained from the data of the mixtures compounded as described above. The equations for these relations are as follows. For ethylenimine: percentage polymerization = 4.52 h −195.8 and for 1,2-propylenimine: percentage polymerization = 5.62 h − 307. The immersion refractometer calibration curve in terms of refractive index is: $n_D^{25} = 0.000394\ h + 1.3405$. The data of Table VI are plotted in Fig. 1. The addition of sodium chloride (0.35 *M*) did not alter the rate.

It was necessary to establish the effect of varying acid and monomer concentration on the half-life and quarter-life scale readings, respectively, before the times required for the attainment of these readings in kinetic experiments could be measured. Table VII contains the half-life and quarter-life scale readings obtained by compounding mixtures of the composition appropriate to the half or quarter time composition of those used in the kinetic measurements. Two values of the half-life scale readings at hydrochloric acid concentrations intermediate in range were interpolated from the nearly linear relation of half-life

TABLE VI

RATES OF POLYMERIZATION

ETHYLENIMINE			1,2-PROPYLENIMINE		
Time, min.	h	Percentage polymerization	Time, min.	h	Percentage polymerization
5	43.52	0.9	6	54.60	0
12	43.79	2.1	13	54.60	0
15	43.94	2.8	26	55.60	6
18	44.29	4.4	46	56.56	11
20	44.63	5.9	58	56.93	13
23	44.86	7.0	67	57.33	15
26	45.08	7.9	93	57.79	18
29.5	45.34	9.1	116	58.38	21
32.5	45.51	9.9	134	58.59	22
36	45.63	10.5	177	58.90	24
38.5	45.77	11.1	200	59.21	26
42	45.92	11.7	220	59.56	28
45	46.05	12.3	238	59.56	28
50	46.21	13.0			
54.5	46.44	14.1			
62	46.67	15.1			
67	46.79	15.7			
74	46.91	16.2			
84	47.22	17.6			
91	47.44	18.6			
100	47.61	19.4			
109	47.81	20.3			
120	45.15	21.8			
126	48.20	22.1			
132	48.26	22.3			
140	48.41	23.0			
144	48.45	23.2			

TABLE VII

EFFECT OF CONCENTRATION ON HALF-LIFE AND QUARTER-LIFE

ETHYLENIMINE, MOLARITY	HYDROCHLORIC ACID, NORMALITY	SCALE READING OF COMPOUNDED MIXTURE	TIME, MIN.
1.85	0.173	53.0	1250 (half-life)
1.85	0.246	54.22	950 (half-life)
1.85	0.308	55.34	700 (half-life)
1.85	0.370	56.81	560 (half-life)
1.85	0.431	58.12	440 (half-life)
1.85	0.555	60.98	300 (half-life)
0.941	0.246	35.09	102 (quarter-life)
1.85	0.246	48.70	150 (quarter-life)
2.84	0.246	73.04	206 (quarter-life)
3.80	0.246	93.28	252 (quarter-life)

scale reading to hydrochloric acid concentration. The times required for the attainment of these scale readings are the times reported in the last column of Table VII and plotted in Fig. 2.

Effect of condition on the degree of polymerization of ethylenimine. To each of six tubes of 25 cc. capacity bearing ground joints and stopcocks was added 10 cc. of ethylenimine freshly distilled in a nitrogen atmosphere. To each of four of the tubes was added 2 cc. of 1.198 *N* hydrochloric acid. To the fifth tube was added 3 cc. of the same acid; and to the sixth tube, 4 cc. The tubes were chilled in a dry ice mixture during the addition of the acid. Tube 1 was placed in a bath at 50° and vigorous polymerization occurred after ten minutes, leaving a very viscous polymer and discharging part of the contents. Tubes 2, 5, and 6 were placed in a thermostat at 25° and tube 3 in a thermostat at 35°. At approximately the same rate over a period of three days tubes 3 and 6 formed a turbid viscous lower layer of polymer containing some gas bubbles and then became very viscous throughout. Tube 4 was placed in a refrigerator at 7°, becoming only slightly viscous after a month.

After 40 days the tube was placed in an ice-bath, a still-head with an ebullition tube protected with a potassium hydroxide tube was attached and the polymer solution evaporated for twenty-four hours under reduced pressure with a dry ice trap in the line. The residue was placed in a Petri dish in a vacuum desiccator for two weeks; yield 70% of a honey-like polymer.

The viscosity of this product and the viscosities of the polymers in the other tubes after a month were measured in 1% aqueous solution at 25°, the degree of polymerization (D.P.) being estimated from the Staudinger equation with the approximately determined value, $K_m = 2.8 \times 10^{-4}$.

TABLE VIII

EFFECT OF CONDITIONS ON DEGREE OF POLYMERIZATION

TUBE	MOLES HCl PER MOLE ETHYLENIMINE	POLYMERIZATION TEMPERATURE, °C.	η_{rel}	D.P.
2	0.0124	25	1.084	30
5	.0186	25	1.187	67
6	.0248	25	1.208	74
4	.0124	7	1.083	30
3	.0124	35	1.216	77
1	.0124	50	1.139	50

To one 35-cc. aliquot of a 1.0% solution of the polymer of tube 1 was added 0.09 cc. of 1.198 *N* hydrochloric acid (the amount required to increase the moles of hydrochloric acid per mole to 0.0248). To another aliquot was added 0.09 cc. of water. The relative viscosities were 1.145 and 1.154, respectively, showing that the difference in acid concentration does not greatly affect the viscosity.

To prove that in each of the tubes the ethylenimine was completely polymerized, solutions of the polymeric products were steam distilled. No appreciable amount of basic material distilled and the viscosities were unchanged. For example, 5 g. of the polymer obtained by evaporation of the contents of tube 4 was dissolved in 100 cc. of water, distilled to half this volume and re-diluted to 100 cc., yielding a yellow solution. Aliquots of 5 cc. were diluted with 20 cc. of water to make 1% solutions and the relative viscosity was 1.083 before and after the distillation. Only 0.06 milliequivalents of alkali distilled.

SUMMARY

1. The mechanism of polymerization of ethylenimine is indicated to involve a bimolecular reaction of ethylenimine and ethylenimonium or substituted ethylenimonium ions.

2. Ethylenimine dimer has been isolated, shown to be identical with N-(β-aminoethyl)ethylenimine prepared by another method, and is indicated to be an intermediate in the polymerization of ethylenimine.

3. Polyethylenimine is indicated to be a linear poly secondary amine of D.P. 25 to 100. The polybenzamide and polyphenylthiourea have been obtained in pure form and other derivatives have been prepared in powder form and studied.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

REARRANGEMENTS IN THE TERPENE SERIES. I. ISOMERIZATION AND ESTERIFICATION OF α-PINENE

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Introduction. It was first observed by Bouchardat and LaFont (1) that α-pinene reacts with certain organic acids to produce esters of borneol, in addition to isomerization products. Since that time, the direct esterification of α-pinene by organic acids has been studied by various investigators (2). Correlations between the properties of the acids and their tendency to form borneol esters are almost entirely lacking. Haller (2 f) mentions that tetrachlorophthalic acid was used "because it is exempt from Viktor Meyer's law of steric hindrance" (3). However, since the esterification of α-pinene is not analogous to the esterifications described by Meyer, and since later work (2 c, g) shows that a number of ortho substituted acids (*e.g.*, *ortho*-benzoylbenzoic acid) give good yields of ester, it is doubtful whether steric hindrance affects the course of the reaction.

Delepine, Reisman, and Suau (2 d) have observed that the reactivities of acids towards α-pinene are roughly proportional to their ionization constants. This conclusion is based upon the destruction of α-pinene by acids of varying strength; it does not correlate the quantity of borneol ester formed with the acid strength.

Present investigation. The present work is a study of the factors influencing the formation of borneol esters by the direct action of organic acids on α-pinene, with particular emphasis upon the nature of the rearrangements involved both in the main reaction and in the formation of various by-products. In all experiments *d*-α-pinene obtained by fractionation of Florida turpentine was used.

In order to determine the influence of acid strength upon the yield of borneol esters, a series of monobasic organic acids with ionization constants between 0.3×10^{-4} and 350×10^{-4} at 25° was selected. All of the acids were miscible with α-pinene in the proportions used at the reaction temperature. In all examples, 0.18 mole of acid was heated with 0.38 mole of α-pinene on an oil-bath at 135–140° for 43 hours. The terpene (largely *d*-limonene, rotation 67° in 2-decimeter tube) was removed by steam distillation, and the residual ester saponified with excess alkali. The borneol was removed from the saponification mixture by steam distillation. Yields were based upon the amount of acid used and the product obtained; this was a mixture of borneol with small quantities of isoborneol. Results are recorded in Table I.

In Figure 1 the yields are plotted against the ionization constants of the acids. The maximum lies between $K = 3.7 \times 10^{-4}$ and $K = 8 \times 10^{-4}$.

The highest possible yield of borneol under the conditions used is probably less than 80 or 85%, since, under these conditions, there is always a good deal of isomerization of the α-pinene to *d*-limonene. At higher temperatures, the

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TABLE I

FUNCTION OF ACID IN THE FORMATION OF BORNEOLS FROM α-PINENE

ACID	NO., FIG. 1.	$K \times 10^4$ (25°)	YIELD OF BORNEOLS, %
p-Methoxybenzoic	1	0.3	0.5
Cinnamic	2	0.36	4.0
Benzoic	3	0.58	2.
o-Methoxybenzoic	4	0.8	1.5
Alpha-naphthoic	5	2.	20.
Ethoxyacetic	6	2.3	27.
m-Nitrobenzoic	7	3.16	61.
o-Benzoylbenzoic	8	3.7	68.
Salicyclic	9	10.	63.
o-Chlorobenzoic	10	12.	49.
o-Bromobenzoic	11	14.2	45.
3,5-Dinitrobenzoic	12	15.5	32.
Chloroacetic	13	15.2	42.
5-Bromosalicylic	14	24.	46.
o-Nitrobenzoic	15	64.	31.
2,4-Dinitrobenzoic	16	350	27.
Trichloroacetic	17	very strong	25.

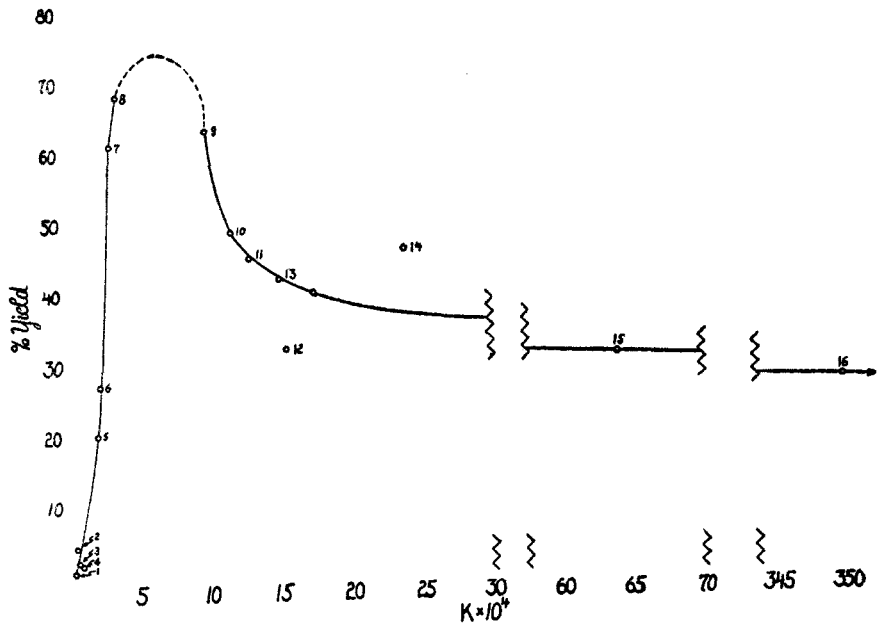


FIGURE 1. EFFECT OF ACID CONSTANT ON YIELD OF BORNEOL.

optimum acid strength required for best yields of borneol esters is somewhat lower. Thus, benzoic acid at 200° gives more than 30% of borneol as compared with 2% at 140°. Two factors probably influence the increased yield at higher

temperature. First, the α-pinene is activated, as is indicated by the rapid thermal isomerization to dipentene (*dl*-limonene). Second, an acid such as benzoic, the strength of which at 140° is less than the optimum, would be expected to be more effective at a higher temperature.

Effect of phenols. Since the strength of benzoic acid is less than the optimum at 140°, it was anticipated that the addition of polar solvents might increase the effectiveness of this acid at the temperature in question. In a series of experiments, 0.2 mole of benzoic acid plus 0.2 mole of solvent were heated with 0.38 mole of α-pinene for 43 hours at 135–140°. The reaction mixtures were worked up as previously described to recover crude borneol. The results are tabulated in Table II. Yields are based upon the amount of acid used.

It will be noted that phenols greatly increase the capacity of benzoic acid to esterify α-pinene. This effect cannot be attributed to increase in the dielectric constant of the medium.

TABLE II

FUNCTION OF DIELECTRIC OF SOLVENT IN THE FORMATION OF BORNEOLS FROM α-PINENE

SOLVENT	YIELD OF BORNEOL, %	k (DIELECTRIC OF PURE SOLVENT)
Anisole	2.	4.3 (20°)
Nitrobenzene	3.	36. (20°)
Quinoline	5.	9. (20°)
Catechol	22.	
o-Cresol	23.	8. (40°)
p-Nitrophenol	27.	
Resorcinol	26.	3.2 (22°)
Beta-naphthol	34.	
Phenol	32.	4.3 (10°)
o-Cresol	36.	13. (40°)
m-Cresol	40.	13. (40°)
Benzonitrile	9.	26. (20°)

It has been observed that certain phenols isomerize α-pinene to camphene (2 k). Since camphene esterifies readily when heated with organic acids, it at first appeared probable that the function of the phenols was to isomerize the α-pinene to camphene, which was then esterified by the acid. That this is not the mechanism, however, is proved by two considerations. First, the phenols used in the experiments here described do not isomerize α-pinene to camphene under the conditions used; second, the character of the products formed where phenols are used precludes the formation of these products by the esterification of camphene. Camphene, when treated with organic acids, yields isoborneol esters almost exclusively, whereas the direct esterification of α-pinene produces borneol esters. Haller (4) has observed that the specific rotation of isoborneol is nearly twice as great in ethanol as in toluene, whereas the rotation of borneol is approximately the same in the two solvents. Austerweil (2 e) made use of this fact to estimate the percentage content of *d*-borneol and *l*-isoborneol in samples obtained

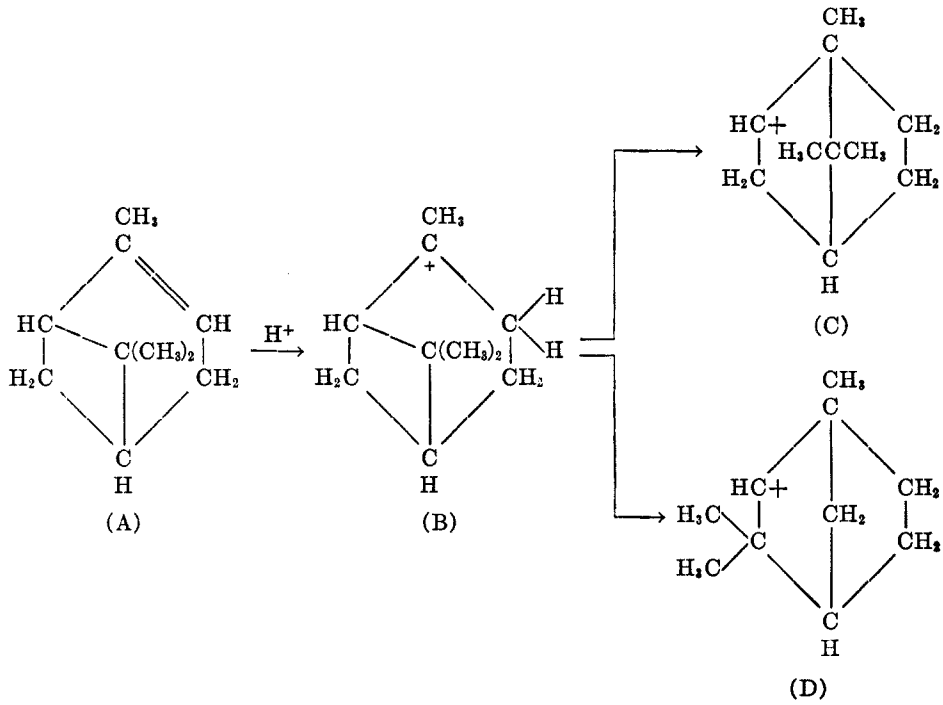
by esterifying α-pinenes. Austerweil's method would be valid if the components of the mixture were optically pure. But the alcohols obtained from α-pinene (which varies in optical purity depending upon its source) are not pure. Both *d*-borneol and *l*-isoborneol oxidize to *d*-camphor. By oxidizing a mixture of the two, their optical purity (p) can be determined from the ratio of the rotation of the camphor obtained to the rotation of pure *d*-camphor. The known optical values are:

$[\alpha]_D$ for *d*-borneol = 37.33°
$[\alpha]_D$ for *l*-isoborneol = −32.9° } in ethanol

$[\alpha]'_D$ for *d*-borneol = 37.87°
$[\alpha]'_D$ for *l*-isoborneol = −18.93° } in toluene

$[\alpha]_D$ for *d*-camphor = 43.15° in ethanol

With the aid of these values, Delepine, Reisman, and Suau (2 d) calculate the fraction (X or X') of isoborneol in a mixture by the equations: $X = \frac{(37.33)\,(p) - [\alpha]_D}{(70{:}23)\,(p)}$ or $X' = \frac{(37.87)\,(p) - [\alpha]'_D}{(56.80)\,(p)}$ where p is the optical purity as already defined and $[\alpha]_D$ and $[\alpha]'_D$ are the rotations of the borneol-isoborneol mixture in alcohol and toluene, respectively.



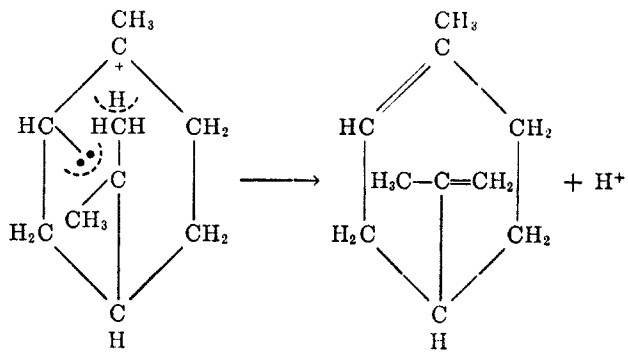
A sample of the crude borneol here obtained from α-pinene by the action of benzoic acid and cresol had the specific rotation 18.8° in ethanol (1.5 g./25 cc.) and 20.2° in toluene (1.5 g./25 cc.); this sample, when oxidized with nitric acid,

gave a camphor with $[\alpha]_D$ 25.2° (1 g./25 cc. ethanol). Accordingly $p = 0.485$, $X = 0.07$, and $X' = 0.06$. Obviously, less than 10% of the crude sample was isoborneol. This fact precludes formation of the esters from camphene. The effect of phenols upon the reaction is probably due to the increased availability of hydrogen ion in phenolic solutions of organic acids.

Mechanism of the reaction. Meerwein (5) has pointed out the analogy between rearrangements in the terpene series and the well known pinacol-pinacolin or Wagner rearrangements. *d*-Limonene is invariably formed as a principal by-product in the organic acid esterification of *d*-α-pinene. Consequently, it seems logical to regard the isomerization and esterification as parts of a single mechanism and to assume that the double bond is the point of attack. If the first step in either reaction is the capture of a hydrogen ion, a positive charge is induced on the carbon atom holding the methyl group. Since the ion thus formed is the typical unstable ion of the pinacol-pinacolin and Wagner rearrangements, it should stabilize itself by the shift of one of the bonds in the cyclobutane ring to the positive carbon holding the methyl group. These steps may be represented structurally in the formula scheme A–D on p. 151.

The addition of the acid radical to the ion (C) gives an ester of borneol or isoborneol, depending upon whether the addition occurs cis or trans to the endo ring, whereas addition to the ion (D) gives an ester of fenchyl alcohol. Small quantities of fenchyl esters are always formed in this reaction.

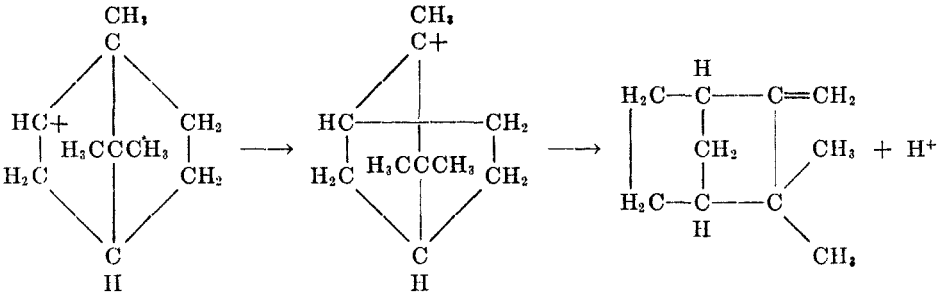
d-Limonene can be formed by the elimination of a hydrogen ion from either (B) or (C) as follows:



In the course of the present work, it was found that amides, such as formamide and acetamide, inhibit the esterification of α-pinene by organic acids, but do not inhibit the isomerization to *d*-limonene. Thus *d*-α-pinene can be successfully converted into *d*-limonene by means of organic acids in the presence of amides. The yields are very good (90 % of product, B.R. 170–180°, rotation 67° in a 2-dcm. tube). Thermal isomerization of α-pinene produces dipentene (*dl*-limonene) (6).

The isomerization of α-pinene to camphene, which can be brought about by phenols and various acid catalysts is easily understood by referring to the above schemes. The ion (C), in the absence of an anion to add to the positive carbon,

might rearrange and eliminate a proton to give camphene according to the following scheme:



The small amount of isoborneol formed in the direct esterification of α-pinene may be due to such an isomerization with subsequent esterification of the camphene formed.

It seems probable that the ion (A), rather than a tertiary ester formed by direct addition of the acid to the α-pinene double bond, is actually the first product of the esterification reaction. If a tertiary ester were the first product of the reaction, benzoylbenzoic acid should esterify ethylenic compounds such as ethyl maleate, ethyl fumarate, trimethylethylene, cyclohexene, and 1-methylcyclohexene. In spite of attempts under varying conditions, none of these compounds could be esterified with benzoylbenzoic zcid. Esterifications with organic acids of the type reported in the present investigation seem to be limited to compounds such as pinene, camphene, fenchene, etc., which undergo a simultaneous rearrangement.

SUMMARY

1. The yield of borneol esters obtained by direct esterification of α-pinene with organic acids depends upon the ionization constant of the acid used. High yields at 140° are obtained over a very narrow range of ionization constant, $K = 3.7 \times 10^{-4}$ to 8×10^{-4}. At higher temperatures, acids with lower ionization constants are fairly effective.

2. The yields of borneol esters formed by acids of lower than optimum ionization are greatly improved by the addition of phenols to the reaction mixture. This improvement is due to increased availability of hydrogen ion, not to increase in dielectric constant of the reaction medium, or to isomerization of α-pinene to camphene.

3. *d*-α-Pinene, when heated with a mixture of an organic acid and amide, is converted to *d*-limonene. The yields are good. The amide appears to inhibit esterification.

4. The principal products formed in the reaction of α-pinene with organic acids can be explained by assuming the preliminary capture of a proton by the α-pinene; the unstable ion thus formed rearranges and stabilizes itself in a variety of ways.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

SOME 9-ACYLFLUORENES AND DERIVED VINYLAMINES[1]

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The activation of the methylene hydrogen atoms of fluorene (1) is indicated by the feebly acidic character of the hydrocarbon (2, 3) and by a limited ability to enter into condensations typical of reactive methylene groups (4, 5), *e.g.*, the Knoevenagel reaction (6), the Michael condensation (4), and ester condensations of the Claisen type, the last illustrated by condensation with ethyl oxalate (7) and by the formation of formylfluorene (8, 9) and benzoylfluorene (10) by action of ethyl formate and ethyl benzoate in the presence of an alkoxide as condensing agent. In the present study this reaction was extended to preparation of 9-acetylfluorene and of 9-formyl-2,7-dibromofluorene.[2]

Enolization of 9-acylfluorenes is apparently considerable. The tautomeric character of formylfluorene is well marked (8, 9), with the enolic function more strongly developed than in the structurally similar but seemingly wholly ketonic formyldiphenylmethane (β,β-diphenylacetaldehyde) (12). The similarly related compounds 9-benzoylfluorene and benzoyldiphenylmethane afford a like contrast, the latter giving no evidence of presence of the enol form (13) while the former is considerably enolized and yields an isolable though unstable enol tautomer. These differences between acylfluorenes and acyldiphenylmethanes may be associated with the greater acidity of the parent hydrocarbon fluorene (2, 3) and with the fact that in acylfluorenes the enol double bond is cross conjugated with the extended conjugation of the fluorene ring system, tending to stabilize the enol to an extent greater than is to be expected in analogous diphenylmethane derivatives.

The nitrogen system analogs of acylfluorenes and acyldiphenylmethanes are the corresponding aminomethylene (alt. iminomethyl) compounds obtainable by action of ammonia or amines. This method of formation suggests the Schiff base (ketimine) structure, but an accumulation of evidence indicates that other compounds of this general type (regardless of how prepared) appear to exist largely or wholly in the enamine form, leading von Auwers and Süsemihl (14) to the conclusion that enamine-ketimine tautomerism is characterized by the presence of a relatively large proportion of the enamine (vinylamine) form, in contrast with the distribution of tautomers in analogous cases of enol-keto tautomerism, a fact which may be related to the relative proton-attracting and proton-fixing powers of the nitrogen and oxygen atoms. This inference is con-

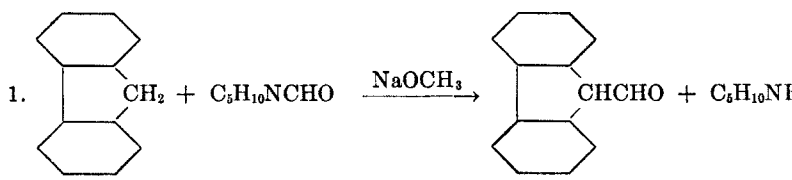
[1] This paper is a condensation of the doctoral thesis of Isaiah Von, University of Pennsylvania, October, 1943.

[2] Prior preparation of 9-formyl-2,7-dibromofluorene by Brown and Bluestein was reported in a note (11) which appeared while this paper was being written. The product obtained as described below is apparently of higher purity than Brown and Bluestein's material and is more fully characterized.

sistent with the moderate enolization of ethyl acetoacetate and the existence of its nitrogen system equivalent β-aminocrotonic ester almost wholly as such (enamine) (14, 15), and with the similar contrast between β,β-diphenylacetaldehyde, of which the enol form is unknown, and its nitrogen system equivalent β,β-diphenylvinylamine, reported by Krabbe and Schmidt (12) to exist wholly or very largely in the enamine form. It may be expected that the stabilization of the enamine structure attributable to the tendency of nitrogen to attract and immobilize the hydrogen involved in prototropy is affected by the intensity of the activation which induces prototropy (for like media). The influence of the fluorene ring upon the tautomeric state of the system $-\overset{|}{C}=CH-NH_2 \rightleftharpoons -\overset{|}{C}H-CH=NH$ has not been studied hitherto. The fact that in diphenylvinylamine the lability of the methane hydrogen atom suffices markedly to stabilize the enamine form (12) leads to the surmise that an equally or more pronounced stabilization should be observable in analogous compounds related to fluorene, *viz.*, 9-aminomethylene (alt. iminomethyl) fluorenes. Some experiments, the results of which permit a tentative affirmative conclusion, are reported below.

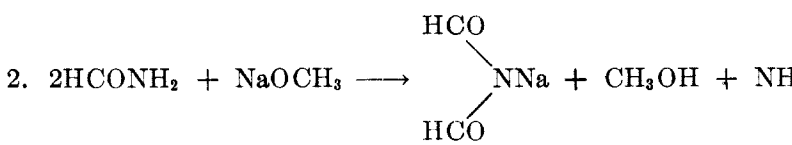
In this paper attention is centered upon (a) reactions of 9-acylfluorenes (formylfluorene, formyl-2,7-dibromofluorene, acetylfluorene) with ammonia to yield compounds presumably capable of enamine-ketimine tautomerism, or derived secondary products, and (b) the structures of these compounds and some experiments to reveal their tautomeric states. It was originally intended to extend the work into other series, by starting with the formyl derivatives of indene, cyclopentadiene, xanthene, and acridan, but these compounds could not be obtained by ester condensation or by other methods tried.

Preparation of 9-acylfluorenes. Formylfluorene (I) is obtainable in high yield from fluorene, ethyl formate, and potassium methoxide (8, 9). Formylfluorene was prepared also by a nitrogen system extension of the same method, using fluorene, formylpiperidine, and sodium methoxide:



I

In this reaction formylpiperidine appears to function as an aquo-ammono ester of formic acid. An attempted similar extension using formamide (aquo-ammono formic acid) was unsuccessful because of preferential interaction of formamide and sodium methoxide, probably as follows:



This reaction has apparently not been reported, though an analogous reaction with metallic sodium is known to occur (18). Ammonia was evolved in amount corresponding to the requirements of the equation when formamide and sodium methoxide were heated together in absence of fluorene or in its presence, and in the latter case no formylfluorene (formation of which would likewise liberate ammonia) could be detected.

The preparation of *9-formyl-2,7-dibromofluorene* (II) from 2,7-dibromofluorene, ethyl formate, and sodium methoxide proved to involve no difficulty, crude yields reaching 95%. Brown and Bluestein (11), using potassium ethoxide, obtained somewhat lower yields of a product of m.p. 171°, and supported its identification by analysis of the enol acetate. The formyldibromofluorene obtained as described below melted at 180–181° and was substantially pure, since analysis of the compound itself gave satisfactory values. Its keeping qualities are noticeably better than those of formylfluorene. The following derivatives of 9-formyl-2,7-dibromofluorene were prepared: the anil, m.p. 226–227° corr., and the benzoyl derivative, m.p. 221° corr. The derivatives obtained by action of ammonia are discussed in the next section.

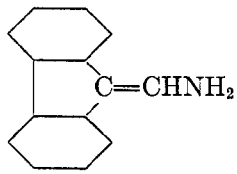
9-Acetylfluorene (III) was obtained by interaction of fluorene, ethyl acetate, and potassium methoxide,[3] yields being moderate (55 to 60%), probably because of self condensation of the ester. The product (m.p. 74.5–75.5° corr.) deteriorates rapidly on storage, with conversion to the dimer (m.p. 247–248° corr.) which, like the dimer of formylfluorene lacks the reactivity of the monomer. The following derivatives of acetylfluorene were prepared: the oxime, m.p. 137° corr., and the phenylhydrazone, m.p. (decomp.) 138–139° corr. Acetylfluorene failed to condense with either aniline or piperidine under conditions which permitted ready condensation of formylfluorene. The compound formed by action of ammonia is discussed in the next section.

Attempts to prepare formyl derivatives of indene, cyclopentadiene, xanthene, and acridan by condensation with ethyl formate were unsuccessful. Indene and cyclopentadiene reacted with ethyl formate, in the presence of potassium or sodium methoxide, more vigorously than did fluorene, but the reaction mixtures darkened rapidly and the resulting material was tarry and unworkable. Efforts to isolate formylindene as the acetyl or benzoyl derivative by acylation of the potassium salt (in the alkaline liquid, to exclude polymerization by the acid used to precipitate the condensation product) were no more successful, the products being completely tarry. Neither xanthene or acridan could be formylated by ethyl formate in the presence of any of the agents effective in the prep-

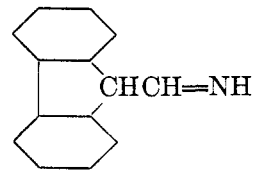
[3] It seems probable that 9-acetylfluorene is a compound not previously or not correctly reported. Its preparation from 9-fluorenyllithium or 9-fluorenylmagnesium bromide by action of acetyl chloride has been claimed (19), but the melting points reported for the compound and its oxime (107° and 167°) are much higher than those observed in the present study (74.5° and 137°) for compounds of apparent authenticity. Further, the presumably analogous reaction of 9-fluorenyllithium with benzoyl chloride yields not 9-benzoylfluorene but 9,9-dibenzoylfluorene (20, 21, 22). Prior preparation of 9-acetylfluorene by the Friedel-Crafts reaction (23) appears to have been incorrectly conceded (19), the compound referred to being 2-acetylfluorene (m.p. 132 ; m.p. of oxime 196-197°).

aration of formylfluorene, and an effort to prepare 9-formylacridan by hydrogenation of 9-formylacridine (*cf.* 24) likewise failed. It is concluded that in cyclopentadiene and indene the reactivities of the methylene hydrogen atoms, as suggested by the relative acidities of the hydrocarbons (3), suffice to permit the ester condensation, but that polymerization perhaps interferes. The failure of xanthene and of acridan to engage in ester condensation becomes explicable upon consideration of the structural differences among fluorene, xanthene, and acridan, and the effects of these differences upon the activation of methylene hydrogen.

Vinylamines and derived products from 9-acylfluorenes. The reaction of formylfluorene with dry ammonia was found by Wislicenus and Russ (9) to yield a compound $C_{14}H_{11}N$, presumably one or a mixture of the tautomers 9-(aminomethylene)fluorene or $\Delta^{9,\alpha}$—fluorenemethylamine[4] (IV a), and 9-(iminomethyl)fluorene or 9-fluorenemethylenimine[4] (IV b):

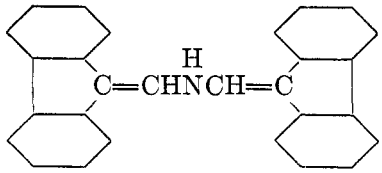


IVa

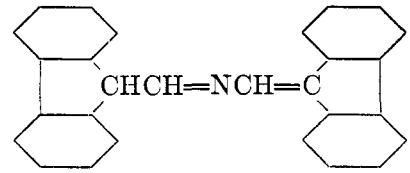


IVb

Wislicenus undertook no proof of structure nor made demonstration that the compound has a tautomeric structure. It was reported also that by inconsiderable change in procedure, formylfluorene and ammonia yielded (instead of compound IV) a compound represented, without proof of structure, as VII a, *viz.*, α,α'-imino-bis-(9-methylenefluorene) or 9,9′-(iminodimethylidyne)difluorene,[4] or VII b, *viz.*, N-(9-fluorenylmethylene)-$\Delta^{9,\alpha}$-fluorenemethylamine:[4]



VIIa

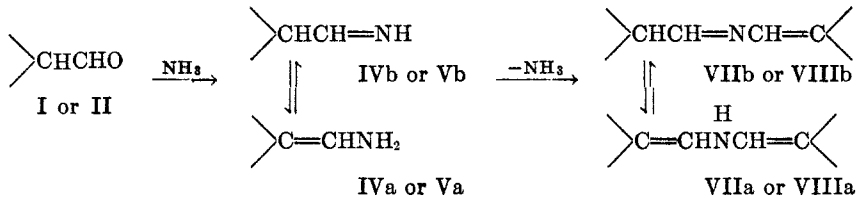


VIIb

Repetition of this work showed that by either procedure ammonia converts formylfluorene largely to compound IV, with a small proportion of compound VII formed either initially or during the isolation. The ready conversion of IV to VII is discussed below. In the present study compounds analogous to IV and VII (*viz.*, compounds V and VIII) were obtained from 9-formyl-2,7-dibromofluorene (II) and a compound analogous to IV (*viz.*, compound VI) was obtained from 9-acetylfluorene (III). The formation of compounds IV and V and their

[4] Names referred to this note were supplied by Drs. A. M. Patterson and L. T. Capell, to whom appreciative acknowledgment is made.

conversion to the corresponding secondary amines VII and VIII by partial loss of ammonia (heat; action of acid) may be represented as follows:



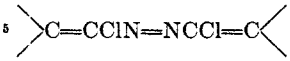
The evidence for the structures of compounds IV, V, VII, and VIII is given below. It establishes the gross structures shown, and indicates clearly the existence of the enamine forms; there is at present available no definite evidence for the ketimine forms.

The study of compound VI (formed slowly by action of ammonia upon acetylfluorene) was only partial. The gross structure is inferred from analytical data and from the facts that VI yields an acetyl derivative by action of acetic anhydride at room temperature, and that VI is hydrolyzed by aqueous acid to yield acetylfluorene, a trace of its dimer, and ammonia. Compound VI failed to yield a related secondary amine such as VII or VIII by action of acid, a behavior which contrasts with the behaviors also of β,β-diphenylvinylamine (12) and 3-aminomethylenecamphor (25). It is perhaps significant that vinylamines at present known to yield divinylamines of type VII (VIII) are all derived from formyl compounds, *i.e.*, from aldehydes.

The structure of compound IV. The essential structure (neglecting tautomerism) may be inferred somewhat uncertainly from Stolle, Munzel, and Wolf's preparation of the same compound (26) by mild reduction of bis(chloro-9-fluorenylidenemethyl)diimide.[4, 5] The (dual) structure IV was assigned by Wislicenus and Russ on the basis of analytical values and reaction analogy. The monomeric state of the compound was established by molecular weight determination as reported below. The structure is indicated with reasonable certainty to be IVa by the results of ozonolysis and brominolysis, supported by analogy with Krabbe and Schmidt's findings (12) that diphenylvinylamine is an enamine and that action of acid converts it to bis(β,β-diphenylvinyl)amine, a reaction analogous to the conversion of IV to VII.

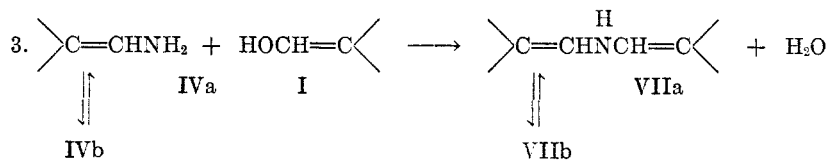
Ozonolysis of compound IV in chloroform or cyclohexane yielded fluorenone (80–85%) and formamide (32–40%), the latter identified by heating with anthranilic acid to yield 3,4-dihydroquinazolone-4, and estimated (a) by determination of the ammonia liberated by alkali hydrolysis, and (b) by determination of the hydrogen cyanide liberated by action of phosphorus pentoxide.

Bromination of compound IV (16) produced, by addition, an unstable dibromide which upon hydrolysis yielded ammonium bromide and an oily product similar to 9-bromo-9-formylfluorene, and which yielded a diethylacetal of similar

[5]  Incorrectly named "bis-(α-chloro-β-fluorenylvinyl)-diimide" in the reference cited.

appearance and melting point. An attempt to identify the brominolysis product more decisively as its phenylhydrazone was not successful, though both the hydrolysis product and an authentic specimen of 9-bromo-9-formylfluorene reacted vigorously with phenylhydrazine, in a manner not explained, with formation of phenylhydrazine hydrobromide. It is perhaps significant that Wislicenus and Russ (9) reported the two compounds to react but omitted any description of the product. Brominolysis of IV yielded also a trace of material soluble in aqueous alkali but not in water; this was not identified but may have been formylfluorene. These results, interpreted in accordance with the findings of Turcan (16) for brominolysis of Schiff bases, indicate either a great preponderance of the enamine (vinylamine) form IVa, or wide disparities in the rates of bromination of the two forms, or of their isomerization.

The structure of compound VII. Wislicenus and Russ (9) did not undertake to establish the (dual) formula proposed for this compound, though its gross structure (neglecting possible tautomerism) was inferred from the structure of compound IV and from its ready conversion to VII by heating IV above its melting point or with acid. In the present study this change was effected also cold by passing dry ammonia into a suspension of the hydrochloride of IV in dry ether; the product consisted of about two-thirds IV and one-third VII. A rational synthesis which reveals the gross structure but not the tautomeric state of VII was effected by interaction of compound IV and formylfluorene (I) in dry benzene at room temperature:



Ozonolysis of compound VII yielded fluorenone (92%). The other product, assuming structure VIIa thus suggested, should be diformamide, a compound known only as its sodium and potassium salts, and therefore not readily identified. To secure inferential proof of its presence, the water-soluble product from the ozonlysis was heated with alkali and the ammonia was collected and titrated, and the formic acid held in the residual solution was determined by the method of Scala, Auerbach, and Zeglin (27). This procedure indicated presence of more than one equivalent of formic acid with respect to ammonia, a result not readily explicable except by the assumption that diformamide was present.

Brominolysis of compound VII (16) consumed two molecular equivalents of bromine without evolution of hydrogen bromide, and yielded as cleavage products only 9-bromo-9-formylfluorene and ammonium bromide, obtainable from structure VIIa, *viz.*, α,α'-imino-bis-(9-methylenefluorene) or[4] 9,9′-(iminodimethylidyne)difluorene. The observed stability of compound VII to hydrolysis by aqueous acid or alkali is consistent with this structure.

The structures of compounds V and VIII. Brominolysis of compound V yielded 2,7,9-tribromoformylfluorene (90%), identical with a specimen prepared by

bromination of 9-formyl-2,7-dibromofluorene, and derived from structure Va *viz.*, 9-aminomethylene-2,7-dibromofluorene or[4] $\Delta^{9,\alpha}$-2,7-dibromofluorenemethylamine. Brominolysis of compound VIII yielded 2,7,9-tribromoformylfluorene in almost the theoretical amount required by structure VIIIa, *viz.*, α,α'-imino-bis-(9-methylene-2,7-dibromofluorene) or[4] 9,9′-(iminodimethylidyne)bis-2,7-dibromofluorene.

The foregoing evidence is satisfactory with respect to the structures of the compounds examined, but, as is the case with chemical evidence, cannot be regarded as decisive with respect to their tautomeric states. Its significance appears to rest upon the fact that, within the scope of the tests applied, the properly established reactions are those of the enamine forms.

EXPERIMENTAL

Materials. Fluorene (E. K. Co. "Technical") was used after crystallization from ethanol m.p. (112–113°). 2,7-Dibromofluorene was made as described by Schmidt and Bauer (28); after crystallization from ethanol it melted at 163–164°. Cyclopentadiene was prepared as needed by depolymerization of dicyclopentadiene at 180° under a short distillation column, through which the product was redistilled, the fraction of b.p. 41° being used promptly. Indene (E. K. Co. "Practical") was redistilled, the fraction of boiling range 177–183° being used. Xanthene was prepared by reduction of xanthone, using a procedure based on that of Heller and van Kostanecki (29). To a boiling solution of 5 g. of xanthone in 150 cc. of absolute ethanol there was added during two hours 15 g. of sodium in small slices. The xanthene was removed by steam distillation and the product was crystallized from ethanol. The yield was 66% and the m.p. 98°. Xanthone was made from phenyl salicylate by the method of Holleman (30). Acridan (9,10-dihydroacridine) was obtained by a modification of the method of Ullmann and Maag (31). To a boiling solution of 5 g. of acridone in 150 cc. of absolute ethanol (the use of 95% ethanol led to an inferior product) there was added, during 2.5 hours, 15 g. of sodium; 75 cc. of 50% ethanol was added to the cooled mixture, and the undissolved acridan was removed and washed with 50% ethanol. The yield was 75%, and m.p. 167–168°. Acridone was made from phenylanthranilic acid by the method of Goldberg (32). Formylacridine was prepared from 9-methylacridine and chloral by the procedure of Bernthsen and Muhlert (33); the over-all yield was 8%. 9-Methylacridine was made from diphenylamine and acetic acid as described by Bernthsen (34). Potassium methoxide was prepared immediately before use, and in the flask in which the reaction was to be run, by the following typical procedure. Potassium metal (3.5 g.) in small slices was transferred to a 200-cc. flask containing 40 cc. of dry ether and provided with a reflux condenser with attached calcium chloride tube. Absolute methanol (distilled through a 10-ball Snyder column; b.p. 64.5°) was added in small portions and finally in excess. The flask was placed in an oil-bath, the condenser was removed, and the flask was attached to a water aspirator and was heated under the lowest pressure thus obtainable, the temperature of the bath being raised gradually to 150° and held there for one-half hour after the residue in the flask was entirely dry and white. Sodium methoxide was used as received from the Mathieson Alkali Company. Triphenylmethylsodium was prepared and its quantity was estimated as directed by Renfrow and Hauser (35). Formylpiperdine was made by the method of Auwers (36); the material distilling in the range 218–226° represented a yield of 81%. Formamide was redistilled, and the fraction boiling at 126–127° at 35 mm. was used. Ethyl formate and ethyl acetate were dried over anhydrous potassium carbonate. Chloroform was shaken with conc'd sulfuric acid, washed with water, dried with calcium chloride, and distilled. Bromine was dried by shaking with conc'd sulfuric acid. Ozone was prepared in an apparatus of the type described by Smith (37) and modified by Henne (38). The oxygen was passed through three Drechsel bottles containing conc'd sul-

furic acid, and then through a U-tube packed with phosphorus pentoxide before entering the ozonizer.

Preparation of 9-acylfluorenes and some derivatives. 9-Formylfluorene (I). The procedure was based on that of Wislicenus and Waldmüller (8). Into a 200-cc. flask containing 6.30 g. (0.09 mole) of potassium methoxide (from 3.51 g. of potassium) was transferred 75 cc. of dry ether, 15 g. (0.09 mole) of fluorene, and 6.7 g. (0.09 mole) of ethyl formate, and the mixture was heated on the steam-bath at gentle reflux for 4 hours. The cooled mixture was extracted with 75 cc. of water. The water extract was shaken with several small portions of ether and was then acidified with dilute sulfuric acid. The oil which separated was extracted in ether, and the ether solution was washed with dilute sodium bicarbonate solution, then with water, and was dried using anhydrous magnesium sulfate. Evaporation of the ether left a residue of 15.8 g. (90%) of crude product, which was distilled under reduced pressure, yielding 12.5 g. (71%) of formylfluorene boiling at 169–172° at 2 mm.; values previously published are 196–197° (14 mm.) (8) and 189–192° (10 mm.) (17). Freshly distilled formylfluorene was used in all its reactions described below. The compound deteriorates, with polymerization, on storage. Formylfluorene is a skin irritant, and should be handled with suitable precautions.

When sodium methoxide was used as condensing agent under the conditions outlined above, the yield of formylfluorene was 30%. The same yield resulted by use of metallic sodium, the mixture being warmed under reflux for 2 hours and then allowed to stand for 5 hours at room temperature with mechanical stirring. A yield of 42% was obtained by use of triphenylmethylsodium. A solution of 4.15 g. (0.025 mole) of fluorene in 50 cc. of dry ether and a solution of 6.7 g. (0.025 mole) of triphenylmethylsodium in 200 cc. of dry ether were mixed and the mixture was allowed to stand for 12 hours protected from moisture, after which 1.85 g. (0.025 mole) of ethyl formate was added and the mixture was allowed to stand for 20 hours. The formylfluorene, isolated as outlined above, weighed 2.05 g.

9-Formylfluorene from fluorene and formylpiperidine (equation 1). Fluorene (4.0 g.; 0.024 mole), formylpiperidine (3.0 g.; 0.026 mole), and sodium methoxide (1.4 g.; 0.026 mole) were mixed in a 25-cc. distillation flask in an oil-bath which was heated at 130° for an hour, after which the temperature was raised gradually to 200°. The distillate (65–110°), measured 0.75 cc. The residue in the flask was extracted with water and the formylfluorene was isolated as described above. The yield was 0.95 g. (20%). The product was identified by conversion to the phenylhydrazone (m.p. 126°), shown by mixed melting point test to be identical with an authenic specimen.

Reaction of formamide and sodium methoxide (equation 2). This reaction was first observed in an attempted preparation of formylfluorene from fluorene (5.0 g.; 0.03 mole), sodium methoxide (1.65 g.; 0.03 mole), and formamide (1.5 g.; 0.033 mole); some heat was evolved on mixing. The mixture, in a test tube thrust into an oil-bath, evolved ammonia when the temperature reached 70°; gas evolution was complete after 2 hours at 130–140°. Ammonia was identified by Thatcher's test (39). In another experiment the ammonia was conveyed by aeration into boric acid solution and was titrated with standard acid (40), showing the evolved ammonia to be 0.015 mole. When the experiment was repeated with omission of the fluorene the ammonia evolved was 0.022 mole from 0.044 mole each of formamide and sodium methoxide. This is the theoretical amount as required by equation 2.

9-Formyl-2,7-dibromofluorene (II). The procedure described for the preparation of formylfluorene was used with modifications. The reactants were 12.3 g. (0.038 mole) of 2,7-dibromofluorene, 2.64 g. (0.038 mole) of potassium methoxide, and 3.0 g. (0.040 mole) of ethyl formate in 75 cc. of dry ether. The heat evolved soon after mixing caused the ether to boil, and a purple color developed. The aqueous extract, after acidification, was aerated to remove ether. The residue was oily at first but solidified. The yield of crude substance (m.p. 171–175°) was 12.7 g. (95%). After two crystallizations from benzene it melted at 180–181° corr.

Anal. Calc'd for $C_{14}H_8Br_2O$: C, 47.8; H, 2.29.
Found: C, 47.9, 47.6; H, 2.49, 2.29.

Benzoyl derivative was prepared by the Schotten-Baumann procedure: 1.0 g. (0.0028 mole) of II in 12 cc. of 1% sodium hydroxide solution was shaken cold with 0.42 g. (0.003 mole) of benzoyl chloride. The benzoate precipitated in almost theoretical yield. After crystallization from benzene it was obtained as pale yellow needles melting at 221° corr.

Anal. Calc'd for $C_{21}H_{12}Br_2O_2$: C, 55.4; H, 2.63.
Found: C, 55.6, 55.1; H, 2.93, 2.94.

The *anil* of II formed spontaneously when a solution of 1.0 g. (0.0028 mole) of II in 5 cc. of ethanol was treated with 0.30 g. (0.0032 mole) of aniline. It crystallized from ethanol in yellow needles of m.p. 226–227° corr.

Anal. Calc'd for $C_{20}H_{13}Br_2N$: N, 3.28.
Found: N, 3.20, 3.24.

9-Acetylfluorene (III). Equivalent amounts (0.09 mole) of fluorene (15.0 g.), potassium methoxide (6.3 g.), and ethyl acetate (7.9 g.) were brought together in 75 cc. of dry ether. The mixture quickly developed a green color, which later disappeared on addition of water. The procedure for the reaction was that described for the preparation of formylfluorene; the isolation procedure described for compound II was used. The yield of crude product was 60% (11.3 g.). After two crystallizations from methanol the compound was colorless and melted at 74.5–75.5° corr. It deteriorated rapidly on storage in a desiccator at room temperature, first acquiring a greenish-yellow tinge, and then after about a week liquefying to an oil, which in the course of about a month resolidified (formation of dimer; see below). The keeping qualities were much improved by refrigeration. Compound III did not condense with either aniline or piperidine when mixtures in dry benzene were heated for 30 minutes on a steam-bath.

Anal. Calc'd for $C_{15}H_{12}O$: C, 86.5; H, 5.77.
Found: C, 86.7, 86.9; H, 6.23, 6.17.

Phenylhydrazone. By condensation of 0.5 g. (0.0018 mole) of III and 0.2 g. (0.00185 mole) of phenylhydrazine in 10 cc. of ethanol for an hour at room temperature there resulted 0.48 g. (67%) of the phenylhydrazone, obtained after crystallization from alcohol as small colorless needles which melted with decomposition at 138–139° corr. The compound became discolored on storage.

Anal. Calc'd for $C_{21}H_{18}N_2$: N, 9.40.
Found: N, 9.10, 9.15.

The *oxime* was obtained in 94% yield when 0.50 g. (0.0018 mole) of III, 0.17 g. (0.0025 mole) of hydroxylamine hydrochloride and 0.35 g. (0.0043 mole) of sodium acetate were heated together in 10 cc. of ethanol for an hour on the steam-bath. After a further hour at room temperature the mixture was treated with 30 cc. of water and the precipitated product (0.51 g.) was removed. After two crystallizations from ethanol the oxime melted at 137° corr. It is a colorless crystalline compound which appears to keep well.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.7; H, 5.83; N, 6.28.
Found: C, 80.9, 80.9; H, 6.01, 6.23; N, 6.27, 6.29.

Dimeric acetylfluorene. A specimen of III which had become oily was extracted with a small amount of ether. The undissolved solid, after crystallization twice from benzene, melted at 247–248° corr. It was found to be only slightly soluble in ether and ethanol, and insoluble in aqueous alkali; it failed to react with phenylhydrazine.

Anal. Calc'd for $C_{30}H_{24}O_2$: C, 86.5; H, 5.77; mol. wt., 416.
Found: C, 86.4, 86.2; H, 5.79, 5.59; mol. wt., (cryoscopic determination in benzene), 418, 436.

Attempts to prepare formyl derivatives of cyclopentadiene, indene, xanthene, and acridan. When cyclopentadiene, ethyl formate, and sodium methoxide (0.12 mole of each) were warmed in dry ether (50 cc.) reaction was vigorous and the mixture darkened. The aqueous extract was clear at first, but soon became turbid, and acidification precipitated an oil which darkened rapidly. The usual isolation procedure yielded finally only a black mass.

Indene, ethyl formate, and potassium methoxide reacted spontaneously and vigorously on mixing in dry ether, with development of a red color. After standing for three hours the

mixture was worked up, yielding a dark and viscous oil which could not be distilled (20 mm.) Attempts to isolate derivatives by use of phenylhydrazine and of *n*-propylamine gave only tarry products. In one experiment the alkaline aqueous extract was halved, one half being treated with benzoyl chloride and the other with acetic anhydride. Only unworkable tars resulted.

Xanthene, potassium methoxide, and ethyl formate were heated together in dry benzene. The isolation procedure used for formylfluorene yielded finally only a slight turbidity, and 81% of the xanthene was recovered. Triphenylmethylsodium was equally ineffective as a condensing agent.

Attempts to condense acridan with ethyl formate in ether solution, using potassium methoxide and also triphenylmethylsodium under conditions similar to those outlined above, were wholly unsuccessful; no indication of reaction was observed. An effort to hydrogenate 9-formylacridine to 9-formylacridan in ethanol solution, using Raney nickel and hydrogen at 30 lbs./in.^{2} in a Burgess-Parr low-pressure apparatus yielded only some tarry material. When hydrogenation (of 1.1 g. of formylacridine) was checked after 8 minutes (24) some tar was formed and 52% of the starting compound was recovered.

Aminomethylenefluorenes and derived compounds. 1. *9-Aminomethylenefluorene (IV).* Into a solution of 12.5 g. (0.64 mole) of 9-formylfluorene in 35 cc. of dry benzene or 50 cc. of dry ether chilled in an ice-bath, dry ammonia gas was passed until an almost solid crystalline slurry resulted (3 to 4 hours). The mixture was transferred to a crystallizing dish and the solvent was evaporated with the aid of a current of dry air, leaving the product as a pale yellow solid and in almost theoretical yield. Extraction with a hot 3:1 mixture of benzene and ligroin (90–100°) left undissolved about 5 to 10% of material identified as compound II; the still yellowish 9-aminomethylenefluorene which crystallized from the solution melted at 143–144°. Four recrystallizations gave a colorless product which melted at 146–147° with preliminary sintering; Wislicenus and Waldmüller (8) reported the compound to sinter at 110° and to melt at 148–149°. It became discolored when kept in a desiccator, and after several weeks was dark brown. The compound reduced potassium permanganate instantly in methanol-free acetone. It was not attacked by 10% sodium hydroxide at 100°; action of acid converted it to VII (see below). Compound IV was established as monomeric by determination of its molecular weight cryoscopically in benezene. The value calculated for $C_{14}H_{11}N$ is 193; the values found were 205, 197, and 203.

The *hydrochloride* of IV, prepared by passing dry hydrogen chloride into a solution of IV in dry ether, was obtained as a white solid which near 300° charred without melting, and which darkened when exposed to the air. Conversion of IV to VII *via* the hydrochloride was observed when 0.5 g. of IV in 15 cc. of dry ether was precipitated by hydrogen chloride, excess of which was removed by passing in a slow current of dry air, after which a stream of dry ammonia was introduced, the mixture being cooled in an ice-bath. A residue of 0.14 g. insoluble in ether was removed, washed with water, and was identified as compound VII by melting point. Evaporation of the ether from the filtrate left a residue identified as compound IV.

Acetyl derivative of IV, 9-acetaminomethylenefluorene. A solution of 0.5 g. (0.00026 mole) of IV in 5 cc. of acetic anhydride was placed in a desiccator containing calcium chloride and pellets of sodium hydroxide, and the excess solvent was allowed to evaporate slowly *in vacuo*. The residue (0.56 g.; 92%) was twice crystallized from benzene; the pale yellow acetaminomethylenefluorene melted at 204.5–206° corr.

Anal. Calc'd for $C_{16}H_{15}NO$: N, 5.95.
Found: N, 5.73, 5.73.

An attempt to confirm the structure of this compound by cyclization to the corresponding isoquinoline derivative by heating with phosphorus pentoxide in toluene was unsuccessful, only an acid-insoluble tar resulting.

Ozonolysis of IV. Ozonization was effected in a wide 150-mm. test tube fitted with a paraffined two-hole cork carrying a glass tube extending to the bottom and an exit tube with a short piece of rubber tubing attached. Both chloroform and cyclohexane were used

as solvents; the former is preferable as it is the better solvent for both IV and its ozonide. One gram of IV in 35 cc. of chloroform was treated with ozone until the terminal rubber tube cracked. The contents of the tube were transferred to a beaker and the chloroform was evaporated with the aid of a current of air. The pale yellow ozonide was heated with 15 cc. of water on a steam-bath for an hour. The cooled mixture was extracted with two 15-cc. portions of ether, the ether extract was dried over magnesium sulfate, and the dissolved material (0.79 g.; 84% calc'd as fluorenone) was obtained by evaporation of the ether. It was identified as the phenylhydrazone, m.p. 148–149° after crystallization from alcohol.

To identify the formamide produced in the ozonolysis the aqueous solution was evaporated to dryness and the oily yellow residue was dissolved in 2 cc. of ethanol and was heated in a test tube with anthranilic acid (0.5 g.), first to evaporate the alcohol and then at 150° for 3 hours. The cooled fusion was extracted with ether and the undissolved quinazolone was removed, washed with 5% sodium bicarbonate solution to remove anthranilic acid, then successively with water, acetone, and ether. The product (0.06 g.) melted at 212–213°; a mixed m.p. test showed it to be 3,4-dihydroquinazolone-4. The amount of formamide was estimated by the following procedures.

(a) The water-soluble product (in 10 cc. of water) from ozonolysis of 0.50 g. (0.0026 mole) of IV was boiled with 3 cc. of conc'd hydrochloric acid for 30 minutes. The solution was transferred to a Kjeldahl flask, made alkaline, and the ammonia was distilled into boric acid solution and was titrated with standard acid (40). In two experiments the ammonia amounted to 0.00087 and 0.00105 mole indicating 34% and 40% of the theoretical formamide.

(b) The water-soluble product from ozonolysis of 1.50 g. (0.0076 mole) of IV was obtained as a dry residue in a test tube by evaporation of the water. Two grams of phosphorus pentoxide was added, and the mixture was heated in an oil-bath at 200° for 20 minutes. The liberated hydrogen cyanide was conducted, with the aid of a slow stream of air, through a trap packed with glass wool and then into a solution of silver nitrate. The silver cyanide, collected in a Gooch crucible, weighed 0.151 g. A blank determination using 0.25 g. of pure formamide showed the procedure just outlined to yield 46.5% of the theoretical hydrogen cyanide. The indicated formamide produced by ozonolysis of IV was therefore 32% of the theoretical.

Brominolysis of IV. A solution of 0.83 g. (0.0052 mole) of bromine in 10 cc. of chloroform was added in drops to a well stirred solution of 1.00 g. (0.0052 mole) of IV in 10 cc. of chloroform. The bromine was absorbed completely with no evolution of hydrogen bromide. Chloroform was removed by evaporation, using a current of dry air, and the residual solid material was treated with 15 cc. of water, which rapidly changed it to an oil, which was extracted in ether. The water layer was evaporated to dryness, leaving a colorless residue (0.44 g.; 87%) of ammonium bromide, identified by determination of ammonia. The ether solution was dried over magnesium sulfate, and the dissolved material was obtained by evaporation of the ether from the filtered solution. The oily product weighed 0.82 g. (68% calc'd as 9-bromo-9-formylfluorene). It was identified as 9-bromo-9-formylfluorene by its lachrymatory character (9) and by conversion to the acetal by stirring with ethanol. This acetal melted at 102–103°, as did the product made in the same way from an authenic specimen of 9-bromo-9-formylfluorene; a mixed melting point test showed no depression. The acetal was apparently not wholly pure, but attempts to recrystallize it led to decomposition. The m.p. reported by Wislicenus and Russ (9) is 119–120°.

Interaction of the brominolysis product, and also of 9-bromo-9-formylfluorene, with phenylhydrazine in benzene solution led to precipitation of a white solid, which after washing with ether and two crystallizations from alcohol melted at 208–210° and was identified as phenylhydrazine hydrobromide. From the benzene-ether filtrate there was obtained only an unidentified orange-red product which darkened rapidly.

The oil formed by hydrolysis of the bromination product of IV was tested for presence of formylfluorene by extraction with 5% sodium hydroxide solution. Acidification of the extract resulted in only a faint opalescence.

2. *bis-(9-Fluorenylmethylen)amine (VII). Synthesis (equation 3).* When solutions of

equivalent amounts (0.5 g. each) of formylfluorene and compound IV in 5 cc. of benzene were mixed no immediate reaction was apparent, but in the course of 48 hours at room temperature the mixture deposited a yellow precipitate of compound VII (0.81 g.; 85%), identified by melting point.

Ozonolysis of VII in chloroform solution by the procedure outlined above yielded 0.46 g. (92%) of crude fluorenone, identified as its phenylhydrazone (m.p. 148–149°). The aqueous liquid (after extraction of fluorenone in ether) was examined for presence of diformamide by making alkaline with sodium hydroxide and distilling, and titrating the ammonia, and by determining the formic acid in the residual liquid, using the method of Scala as modified by Auerbach and Zeglin (27). Three analyses, representing three ozonolyses, gave the following results.

Compound II mmol.	Ammonia mmol.	HCOOH %	HCOOH mmol.	Ratio HCOOH/NH_3
1.35	0.410	30	0.530	1.29
1.35	0.378	28	0.586	1.57
1.35	0.379	29	0.635	1.60

Brominolysis of VII. A solution (approximately 10%) of 0.87 g. (0.0054 mole) of bromine in chloroform was added to a suspension of 1.00 g. (0.0027 mole) of VII in 20 cc of dry chloroform. Following hydrolysis, there were isolated by the procedure outlined above 0.23 g. (89%) of ammonium bromide and 1.25 g. of an oily product practically insoluble in 5% sodium hydroxide solution. This material was identical with the 9-bromo-9-formylfluorene obtained from compound IV, yielding an identical acetal and showing the same behavior with phenylhydrazine. The yield (crude) was 85%.

3. *9-(Aminomethylene)-2,7-dibromofluorene (V).* Into a solution of 5.0 g. (0.0155 mole) of 9-formyl-2,7-dibromofluorene (II) in 25 cc. of dry ether, chilled in an ice-bath, dry ammonia was passed for two hours. The solid product (white at first, then yellowish) was removed by filtration and was washed with ether; the yield was 4.1 g. (82% calc'd as V). The yellow color deepened on exposure of V to the air, and was not wholly removed by several crystallizations from benzene-ligroin mixture. The compound changed into VIII on heating, which prevented a satisfactory melting point determination in a capillary tube. On the Dennis bar the melting point of 212° was observed. The compound thus obtained was apparently not pure, as is suggested by the results of analyses of three specimens (the last two prepared from dibromofluorene especially for analysis), each of which was crystallized twice from benzene-ligroin, and then was dried in an Abderhalden pistol *in vacuo* (2 mm.) at the temperature of boiling acetone for 45 to 60 minutes. In all cases the results for carbon were too high, and for the first two specimens results for nitrogen were too low. The third specimen was extracted with aqueous sodium hydroxide to remove any compound II present as impurity, which treatment yielded material for which results for hydrogen and nitrogen were acceptable.

Anal. Calc'd for $C_{14}H_9Br_2N$: C, 47.9; H, 2.56; N, 3.99.
Found: C, 48.5, 49.0; H, 2.82, 2.64; N, 3.69, 3.57.

It is pointed out that presence of compound II ($C_{14}H_8Br_2O$ = 352: C, 47.8; H, 2.29) would have no noticeable effect upon the values for carbon and hydrogen in compound V (mol. wt. 351). The presence of compound VIII (C, 49.0) is possible, since compounds II and IV may react (*cf.* equation 3) to yield VIII during recrystallization or drying, and would increase the results for carbon, but no probable contamination by VIII would cause the observed error. An effort to prepare the acetyl derivative of V (for analysis) by action of acetic anhydride yielded a mixture, of which one component was identified by melting point and mixed melting point as the enol acetate of II. The structure assigned to compound V therefore receives analytical support which is only partial, but this structure is indicated plainly by the chemical evidence: (a) formation of compound V from compound II by the same treatment that analogously converts formylfluorene (I) to compound IV, (b) formation of compound VIII (for which, as shown below, a satisfactory analysis was obtained)

from compound V by the same treatment that analogously converts IV to VII, and (c) the results of brominolysis of compound V given below.

Brominolysis of 1.0 g. (0.0028 mole) of V by the procedure described above (0.46 g. or 0.0028 mole of bromine being absorbed rapidly with no evolution of hydrogen bromide) yielded 0.22 g. (81%) of ammonium bromide and 1.16 g. (95%) of 9-formyl-2,7,9-tribromofluorene, which after crystallization from benzene melted at 228–229° and was identified by mixed melting point test using formyltribromofluorene made as described below.

9-Formyl-2,7,9-tribromofluorene. When a solution of 1.0 g. (0.0028 mole) of formyl-2,7-dibromofluorene (II) in 10 cc. of chloroform and a solution of 0.46 g. (0.0028 mole) of bromine in 10 cc. of chloroform were mixed the color of the bromine faded rapidly and a slow evolution of hydrogen bromide was observed. Evaporation of the solvent with the aid of a current of air left a light yellow crystalline residue weighing 1.20 g. (98%). After two crystallizations from benzene the formyltribromofluorene melted with decomposition at 236–237° corr.

Anal. Calc'd for $C_{14}H_7Br_3O$: C, 39.0; H, 1.63.
Found: C, 39.0, 39.2; H, 1.92, 1.84.

4. *bis-[9-(2,7-Dibromofluorenylmethylene)]amine (VIII).* Compound V (1.5 g.; 0.0043 mole) was warmed with 15 cc. of glacial acetic acid for 30 minutes on a steam-bath. The orange colored product weighed 1.46 g. (100%). It did not melt at 300°, was scarcely soluble in the common organic solvents, but was obtained as orange-yellow needles by crystallization from nitrobenzene. The same product was obtained readily by action of dilute sulfuric acid on compound V.

Anal. Calc'd for $C_{28}H_{18}Br_4N$: C, 49.0; H, 2.09; N, 2.04.
Found: C, 49.0, 49.2; H, 2.14, 2.25; N, 2.17, 2.15.

Brominolysis of VIII. A suspension of 0.5 g. (0.00073 mole) of VIII in 10 cc. of dry chloroform was treated with 0.24 g. (0.00146 mole) of bromine and the product was hydrolyzed, etc., as outlined previously. There were isolated 0.070 g. (98%) of ammonium bromide and 0.62 g. (98%) of 9-formyl-2,7,9-tribromofluorene, which after crystallization from benzene melted with decomposition at 228–229° and was identified by mixed melting point test.

5. *9-(α-Aminoethylidene)fluorene or α-methyl-$\Delta^{9,\alpha}$-fluorenemethylamine*[4] *(VI).* Dry ammonia was passed for 12 hours into a solution of 3.5 g. (0.017 mole) of acetylfluorene (III) in 25 cc. of dry ether while chilling the mixture in an ice-bath. The brown oily residue, from which most of the ether had evaporated, was treated with 5 cc. of ether, causing the separation of small colorless crystals, whch were removed and washed sparingly with ether. The product weighed 1.78 g. (51%), and after two crystallizations from methanol was obtained as colorless needles which melted (with decomposition and after preliminary sintering) at 124.5–126.5° corr. The compound darkened rapidly and became oily in a desiccator at room temperature; it deteriorated less rapidly in the refrigerator. It decolorized permanganate in acetone, and in chloroform solution absorbed bromine instantly and without disengagement of hydrogen bromide.

Anal. Calc'd for $C_{15}H_{13}N$: C, 87.0; H, 6.28, N, 6.77.
Found: C, 86.6, 86.7; H, 6.33, 6.32; N, 6.63, 6.57.

Hydrolysis of VI. When 0.5 g. of compound VI was allowed to stand at room temperature with 4% sulfuric acid the appearance of the crystals gradually changed. After 4 hours the solid was removed, washed with water, and added to 10 cc. of ether, in which it dissolved almost wholly. The small insoluble residue melted at 236–237° and was identified as dimeric acetylfluorene. Evaporation of the ether solution left a colorless residue of m.p. 71–72°, shown by mixed melting point test to be acetylfluorene.

Acetyl derivative of VI was prepared as described for the acetyl derivative of compound IV: 0.5 g. (0.024 mole) of VI yielded 0.57 g. (95%) of product, which after crystallization from benzene was colorless and melted at 180.5–181.5° corr.

Anal. Calc'd for $C_{17}H_{15}NO$: N, 5.62.
Found: N, 5.28, 5.33.

SUMMARY

The formation of 9-acylfluorenes by alkali-induced condensations of esters with the reactive methylene group of fluorene was extended to include 9-acetylfluorene. Formylfluorene was obtained by similar use of N-formylpiperidine, showing the ability of the latter to function as an aquo-ammono ester of formic acid. Ester condensation failed as a method for preparation of formyl derivatives of cyclopentadiene, indene, xanthene, and acridan. The first two reacted but yielded tarry products; the last two did not react.

The structures of the two products obtained by interaction of 9-formylfluorene and ammonia, and of the two analogous products obtained from 9-formyl-2,7-dibromofluorene and ammonia, were determined with reasonable certainty by ozonolysis and brominolysis. The simpler compound of each pair is the 9-aminomethylene compound (enamine or vinylamine), and the other compound is the secondary amine formed from two molecules of the foregoing by loss of one molecule of ammonia, and is the corresponding bis-9-fluorenylmethylenamine; a compound of the latter type was obtained by rational synthesis from formylfluorene and aminomethylenefluorene. The existence of the ketimine tautomers of these compounds cannot be excluded, as exhaustive tests for them were not made, but it is perhaps significant that the reactions observed and properly established were all those of the enamine or vinylamine forms, no reactions or degradation products of the ketimines being observed. This result parallels the results previously reported for β,β-diphenylvinylamine and some analogous compounds which appear to exist largely or wholly as enamines. The indicated stabilization of the enamine form in the tautomeric triad system $-\overset{|}{C}=\overset{|}{C}-NH- \rightleftharpoons -\overset{|}{C}H-\overset{|}{C}=N-$, of which the first carbon is carbon 9 of fluorene, may be attributed to (a) the characteristic lability (acidity) of hydrogen attached to carbon 9 of fluorene, (b) the cross conjugation of the enamine double bond with the extended conjugation of the fluorene ring system, and (c) the proton attracting and proton fixing power of nitrogen.

Acetylfluorene was found to be less reactive with ammonia or amines than are the formylfluorenes. It failed to react with aniline or piperidine, under conditions favorable to reaction of formylfluorene, but condensed slowly with ammonia to yield 9-(α-aminoethylidene)fluorene or α-methyl-$\Delta^{9,\alpha}$-fluorenemethylamine[4] (or its tautomer). Action of mineral acid upon this derivative removed ammonia completely to regenerate acetylfluorene, but did not yield a secondary amine similar to those obtained from the formylfluorenes.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

CONDENSATION OF VANILLIN SUBSTITUTION PRODUCTS WITH NITROMETHANE

L. CHAS. RAIFORD AND DONALD E. FOX

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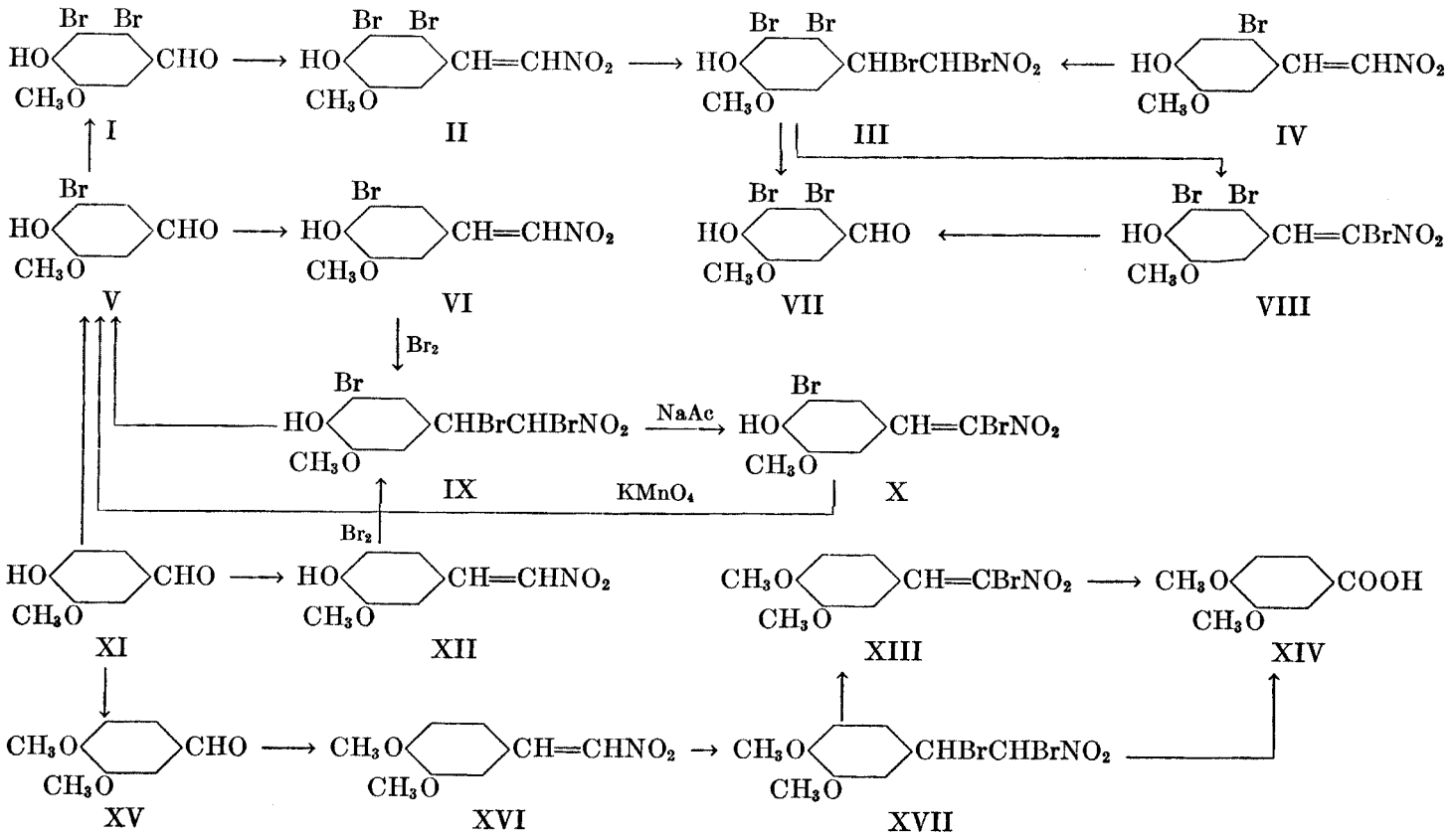
Priebs (1) obtained a 56% yield of β-nitrostyrene by condensing benzaldehyde with nitromethane in the presence of zinc chloride in a sealed tube at 160°. Posner (2) carried out this reaction with *o*- and *m*-nitrobenzaldehyde, but he reported that neither with zinc chloride nor with any other reagent could he condense other substitution products of benzaldehyde. Henry (3) found that nitromethane condenses with aliphatic aldehydes in the presence of potassium hydroxide or carbonate, while Thiele (4) showed that with aromatic aldehydes the carbonate was unsatisfactory but that alcoholic potash gave good results. Under these conditions he reported that *o*-, *m*- and *p*-nitrobenzaldehyde, respectively, condensed with equal ease, though he recorded no yields. Knoevenagel and Walter (5) found that vanillin, 3-methoxy-4-hydroxybenzaldehyde, condensed with nitromethane to give a 90% yield of product when an alcoholic solution of the reactants was allowed to stand at room temperature in the presence of methylamine. They tested none of the substitution products of vanillin. Remfry (6) studied the behavior of many monosubstituted benzaldehydes and found "that the hydroxyl group in the ortho- and meta-positions exercised no influence on the course of the reaction, but that a para-hydroxyl group, either alone or in conjunction with other groups (except in one instance), rendered condensation impossible". Rosenmund's (7) work with anisaldehyde showed in that one case, at least, that condensation occurs readily if the hydroxyl group has been methylated, and the reaction is carried out at 5° or below in the presence of alcoholic potash. Later he reported (8) that when the reaction was carried out with benzaldehyde below 8°, with sodium methoxide as condensing agent, he was able to isolate the addition product α-phenyl-β-nitroethanol which, when distilled under reduced pressure was, in part, decomposed by loss of water to give the related styrene.

In the present work several vanillin substitution products were used and a number of condensing agents were tested. Best results were obtained in most cases by gently refluxing a glacial acetic acid solution of the reactants with ammonium acetate as directed by Rao, Srikantia, and Iyengar (9). In a few instances condensation occurred when an absolute ethanol solution of the reactants was allowed to stand for several days at room temperature in the presence of the acetate.

Certain properties of these condensation products are of interest. When the compound XII, obtained from vanillin and nitromethane, was treated with slightly more than two molecular proportions of bromine, hydrogen bromide was evolved and a tribromo derivative, IX, m.p. 127°, was formed. The same substance was obtained by bromination of the condensation product, VI, ob-

FIGURE 1

STRUCTURAL RELATIONS OF CONDENSATION PRODUCTS FROM NITROMETHANE AND VANILLIN DERIVATIVES



tained from 5-bromovanillin, which shows that one of the halogen atoms in the tribromo derivative was attached to the phenyl nucleus. Proof that the other two were in the side chain was brought by oxidation with potassium permanganate, which caused loss of two bromine atoms and gave 5-bromovanillin, V. Formation of an aldehyde in this case agrees with the observations of Webster (10), made in this laboratory, to the effect that oxidation of the unsaturated side chain of a benzene derivative that contains a hydroxyl group in position 4 usually gives the aldehyde instead of the related acid. The above results stand in marked contrast to those observed in oxidation of the halogen derivative XVII obtained from the condensation product XVI, prepared in turn from veratraldehyde, which contained no exposed hydroxyl group. In this case, as reported in studies by Raiford and Perry (11), the side chain was converted into carboxyl, to give veratric acid V. They found that vanillin and its substitution products were not changed by treatment for a few minutes with boiling potassium permanganate solution while the corresponding methylated compounds, veratraldehydes, were converted into the related acids in yields of 75% or more.

In a similar way, bromination of the condensation product IV, obtained from 6-bromovanillin, gave a tetrabromo derivative III that was identical with the compound produced by bromination of substance, II, formed when the condensation was carried out with 5,6-dibromovanillin. This fixes the position of the second nuclear halogen atom in the tetrabromo derivative as 5.

The compounds containing halogen in the side chain were active toward other reagents. Repeated crystallization from ethanol of the tribromo compound IX, m.p. 127°, mentioned above, gave a dibromo product X that melted at 166–167°. This substance was also obtained when a thin ethanol paste of the tribromo compound was mixed with anhydrous sodium acetate and heated under reflux for an hour. Analysis of the product showed the presence of two bromine atoms, which indicates that in its formation the tribromo derivative had lost the elements of hydrogen bromide. The position of the remaining bromine atom in the side chain is suggested by the results of Thiele and Haeckel (12) who found that removal of hydrogen bromide from [α,β-dibromo-β-nitroethyl]benzene gave α-phenyl-β-bromo-β-nitroethene, as shown.

$$C_6H_5CHBrCHBrNO_2 \rightarrow C_6H_5CH{=}CBrNO_2 + HBr$$

Relations established in the present study are shown in Figure 1.

EXPERIMENTAL

α-[3,4-Dimethoxyphenyl]-β-nitroethene. A mixture of 5 g. of vertraldehyde, 2 g. of ammonium acetate, 2.5 cc. of nitromethane, and 20 cc. of glacial acetic acid was gently refluxed for two hours. On cooling, a crystalline mass separated. The yield was 85%. Recrystallization from 50% acetic acid gave yellow prisms that melted at 140–141°. A weighed portion was reduced by a mixture of zinc and concentrated hydrochloric acid, and the resulting material was subjected to a Kjeldahl analysis.

Anal. Calc'd for $C_{10}H_{11}NO_4$: N, 6.69. Found: N, 6.59.

Data for other products obtained by the same general procedure, modified to meet the requirements of individual cases, are given in Table I.

α-[3-Methoxy-4-hydroxy-5-bromophenyl]-α,β-dibromo-β-nitroethane. Slightly more than two molecular proportions of bromine dissolved in an equal volume of chloroform was gradually added with rapid stirring to a suspension of 10 g. of vanillal nitromethane in 250 cc. of chloroform, stirring was continued until nearly all solid was dissolved, and the mixture was

allowed to stand overnight. Some hydrogen bromide was evolved. A small portion of insoluble material was removed by filtration, the filtrate was evaporated to dryness at 50–60° in a current of air. Excessive heat decomposed the product. The yield was nearly quantitative. Crystallization from carbon disulfide gave fine, pale yellow needles that melted at 127°. The same product was obtained in 87% yield by treatment of a carbon disulfide solution of the condensation product obtained from nitromethane and 5-bromovanillin with somewhat more than one molecular proportion of bromine.

Anal. Calc'd for $C_9H_8Br_3NO_4$: Br, 55.29. Found: Br, 55.15.

α-[3-Methoxy-4-hydroxy-5,6-dibromophenyl]-α,β-dibromo-β-nitroethane. A suspension of 10 g. of 6-bromovanillalnitromethane in 100 cc. of chloroform was treated with two molecular proportions of bromine as indicated above; hydrogen bromide was evolved and the product was isolated as described. The yield was nearly theoretical. Crystallization

TABLE I

SUBSTITUTION PRODUCTS OF α-[3-METHOXY-4-HYDROXYPHENYL]-β-NITROETHENE

ADDITIONAL SUBSTITUENT IN PHENYL	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES			
						Calc'd, Br	Found, Br	Calc'd, N	Found, N
2-Bromo-	67	Ethanol 25%[a]	Yellow needles	134–135	$C_9H_8BrNO_4$	29.20	29.24		
5-Bromo-	50	Ethanol (abs.)	Red needles	190–191	$C_9H_8BrNO_4$	29.20	29.28		
6-Bromo-	64	Ethanol	Yellow needles[b]	168–169	$C_9H_8BrNO_4$	29.20	29.17		
5,6-Dibromo-	52	Ethanol	Yellow needles	166–167	$C_9H_7Br_2NO_4$	45.32	45.29		
2-Nitro-	65	Ethanol 30%	Yellow plates	188–189	$C_9H_8N_2O_6$	—	—	11.66	11.59
5-Nitro-	73	Ethanol 50%	Yellow needles	183–184	$C_9H_8N_2O_6$	—	—	11.66	11.58
2-Nitro-5-bromo	82	Ethanol 30%	Yellow needles	169–170	$C_9H_7BrN_2O_6$	25.07	25.13		

[a] Proper volume of water to give this concentration was added to a hot alcoholic solution of the compound.

[b] The same product was obtained when an absolute ethanol solution of the reactants was allowed to stand at room temperature for two days.

from ligroin (65–70°) gave pale yellow granules that melted at 126–128°, with softening a few degrees lower. This product was also obtained in 80% yield by bromination of a chloroform solution of 5,6-dibromovanillalnitromethane.

Anal. Calc'd for $C_9H_7Br_4NO_4$: Br, 62.37. Found: Br, 62.54.

α-[3,4-Dimethoxyphenyl]-α,β-dibromo-β-nitroethane. To a suspension of 5 g. of veratralnitromethane in about 350 cc. of carbon disulfide was added slowly with stirring slightly more than two molecular proportions of bromine in about ten volumes of carbon disulfide, the mixture was allowed to stand overnight, and the solvent distilled off. A yield of 90% was obtained. Crystallization from carbon disulfide gave nearly colorless granules that separated with one-half molecular proportion of solvent and melted at 113–114°.

Anal. Calc'd for $C_{10}H_{11}Br_2NO_4 \cdot 0.5\ CS_2$: Br, 39.31. Found: Br, 39.90; 40.03.

A portion of the above product was heated for an hour at about 65° to remove solvent of crystallization. The residue gave the following analysis.

Anal. Calc'd for $C_{10}H_{11}Br_2NO_4$: Br, 43.36. Found: Br, 43.25.

α-[3-Methoxy-4-hydroxy-5-bromophenyl]-β-bromo-β-nitroethene. The tribromo compound, m.p. 127°, specified above and obtained by action of bromine on vanillalnitrometh-

ane, was repeatedly crystallized from ethanol from which it finally separated in yellow needles that melted at 166–167°. In a second experiment a thin ethanolic paste of the tribromide was gently refluxed with fused sodium acetate for an hour. The solid left after cooling was collected and crystallized from ethanol which gave yellow needles that melted as indicated above.

Anal. Calc'd for $C_9H_7Br_2NO_4$: Br, 45.32. Found: Br, 45.29.

α-[3-Methoxy-4-hydroxy-5,6-dibromophenyl]-β-bromo-β-nitroethene. A portion of the tetrabromo compound, m.p. 126–128°, obtained from 6-bromovanillalnitromethane as indicated above, was boiled under reflux with a small amount of alcohol for an hour. An almost quantitative yield of a tribromo derivative, m.p. 175–176°, was obtained.

Anal. Calc'd for $C_9H_6Br_3NO_4$: Br, 55.55. Found: Br, 55.58.

α-[3,4-Dimethoxyphenyl]-β-bromo-β-nitroethene. One and one-half grams of finely powdered anhydrous sodium acetate was gradually added, with shaking, to a cool saturated ethanol solution of 1 g. of the required dibromoethane derivative, m.p. 113–114°. When nearly all the salt was in, a sudden and almost complete precipitation of the monobromide occurred. The yield was 80%. Sublimation of the product in a partial vacuum gave bright yellow needles that melted at 119–120°.

Anal. Calc'd for $C_{10}H_{10}BrNO_4$: Br, 27.77. Found: Br, 27.93.

A portion of the compound mentioned immediately above was oxidized by a calcium permanganate solution in acetone that had previously been distilled from permanganate, as directed by Reichert and Koch (13). Some degradation occurred, but there was isolated a product that melted at 177–178°, and which did not depress the melting point, 179°, of an authentic sample of veratric acid.

SUMMARY

1. Vanillin and a number of its substitution products have been condensed with nitromethane to give the related β-nitrostyrenes.

2. Treatment of these compounds with bromine saturates the side chain and introduces bromine into position 5 by substitution if position 4 is occupied by hydroxyl.

3. Oxidation of these condensation products, as well as their bromine addition compounds, with permanganate causes loss of bromine from the side chain and gives the related aldehyde.

4. When veratraldehyde is used as starting material, oxidation of the condensation product gives the related acid. This emphasizes the retarding effect of the parahydroxyl group.

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[CONTRIBUTION FROM CHEMICAL RESEARCH LABORATORY OF SCHERING CORPORATION]

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY AND AQUEOUS ALKALI. IV. THE CARBON-CARBON DOUBLE BOND

ERWIN SCHWENK, DOMENICK PAPA, BRADLEY WHITMAN, AND HELEN F. GINSBERG

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In previous work from this laboratory (1) the reduction of several compounds containing carbon-to-carbon double bonds was reported. This reaction was further studied and examples are given in Table I for the reduction not only of conjugated double bonds but of isolated and ring double bonds as well.

TABLE I

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY

COMPOUND	REDUCTION PRODUCT	YIELD, %
1. Cinnamic acid	Hydrocinnamic acid	95
2. Maleic acid	Succinic acid	90
3. Crotonic acid	Butyric acid	80
4. Oleic acid	Stearic acid	100
5. Sorbic acid	Caproic acid	80
6. *p*-Hydroxystilbene	1-(*p*-Hydroxyphenyl)-2-phenylethane	85
7. α-Phenyl-*p*-hydroxycinnamic acid	β-(*p*-Hydroxyphenyl)-α-phenylpropionic acid	95
8. α-Phenyl-*p*-methoxycinnamic acid	β-(*p*-Methoxyphenyl)-α-phenylpropionic acid	90
9. α-(*p*-Methoxyphenyl)cinnamic acid	α-(*p*-Methoxyphenyl)-β-phenylpropionic acid	90
10. α-(*p*-Hydroxyphenyl)cinnamic acid	α-(*p*-Hydroxyphenyl)-β-phenylpropionic acid	95
11. Δ^1-Cyclohexenylacetic acid	Cyclohexanacetic acid	15
12. Cyclohexylidenacetic acid	Cyclohexanacetic acid	80
13. α-(Δ^1-Cyclohexenyl)cinnamic acid	β-Phenyl-α-cyclohexylpropionic acid	90
14. α-(Δ^1-Cyclohexenyl)*p*-hydroxycinnamic acid	β-(*p*-Hydroxyphenyl)-α-cyclohexylpropionic acid	90
15. Chaulmoogric acid	Dihydrochaulmoogric acid	100
16. Stilbestrol (m.p. 170–171°)	Hexostrol, m.p. 184–185°	30
	Hexostrol, m.p. 126–128°	50
17. Phenylpropiolic acid	Hydrocinnamic acid	80
18. Δ^5-3(β)-Hydroxyetiocholenic acid	Recovered unchanged	

In all the compounds containing aliphatic chain double bonds, and a chain and alicyclic double bond in conjugation, the reduction proceeded smoothly and in good yields. An anomalous behavior was observed in the reduction of isolated ring double bonds. Δ^5-3(β)-Hydroxyetiocholenic acid[1] was recovered unchanged

[1] We have experienced no difficulty in reducing Δ^4-3-ketoetiocholenic acid. A report on the reduction of this and other steroid compounds is forthcoming.

and there was only about 15% reduction[2] of Δ^1-cyclohexenylacetic acid even though five times the normal amount of Raney nickel-aluminum alloy was used. That Δ^1-cyclohexenylacetic acid reduces at all may be due to an initial isomerization to cyclohexylidenacetic acid, which has been shown (2) to take place in an alkaline environment. In sharp contrast to the resistance to reduction of the double bond in the two aforementioned compounds, the cyclopentene ring of chaulmoogric acid underwent quantitative reduction.

With Raney nickel catalyst in alcohol, stilbestrol is hydrogenated quantitatively to the lower-melting isomer (3). However, with the nickel-aluminum alloy reduction method, both isomeric hexostrols are obtained, the higher-melting in 30% yield, the lower-melting in 50% yield. One triple bonded compound was studied and was found to undergo complete reduction.

EXPERIMENTAL

General procedure. The reductions of the compounds in Table I were carried out as previously described (1). The yields of the reduction products are based on the reduction of 10 g. of compound and represent products purified by distillation and/or recrystallization. All melting points are corrected.

β-(p-Methoxyphenyl)-α-phenylpropionic acid was obtained by the reduction of α-phenyl-*p*-methoxycinnamic acid (4) as white needles from alcohol melting at 119–120°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74. 86; H, 6.29.
Found: C, 74.66; H, 6.31.

α-(p-Methoxyphenyl)-β-phenylpropionic acid was obtained from α-(*p*-methoxyphenyl) cinnamic acid as white needles melting at 108–109° from benzene-petroleum ether.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74.86; H, 6.29.
Found: C, 74.41; H, 6.45.

The α-(*p*-methoxyphenyl)cinnamic acid was prepared by heating for 6 hours at 105–110° equimolecular proportions of potassium *p*-methoxyphenylacetate and benzaldehyde in acetic anhydride. The excess acetic anhydride was decomposed with water, the semi-solid residue extracted with ether and the ether extracts washed free of acetic acid. The α-(*p*-methoxyphenyl)cinnamic acid was then extracted from the ether with 10% sodium carbonate. Acidification of the sodium carbonate extract gave an 80% yield. On recrystallization from benzene-petroleum ether the acid melted at 152–153°.

Anal. Calc'd for $C_{16}H_{14}O_3$: C, 75.56; H, 5.55.
Found: C, 75.22; H, 5.36.

This compound has previously been prepared by another method and has been reported to melt at 132–133° (5).

α-(p-Hydroxyphenyl)-β-phenylpropionic acid was obtained from α-(*p*-hydroxyphenyl) cinnamic acid and melted at 158–159° on recrystallization from acetone and water mixture.

Anal. Calc'd for $C_{15}H_{14}O_3$: C, 74.20; H, 5.82.
Found: C, 73.99; H, 5.79.

The α-(*p*-hydroxyphenyl)cinnamic acid was prepared as described for the corresponding methoxy compound and on recrystallization from acetone and water melted at 221–222°.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.96; H, 5.06.
Found: C, 74.62; H, 5.11.

Ten grams of *Δ^1-cyclohexenylacetic acid* was reduced using 30 g. of nickel-aluminum alloy and 500 cc. of 10% sodium hydroxide. After the reaction, the product was isolated in the usual manner and was found to be unchanged. It was then treated with 100 g. of nickel-aluminum alloy and 2 liters of 10% sodium hydroxide. After isolation of the reduction product a bromine titration showed that 85% of the material was recovered unchanged.

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[2] Extent of reduction determined by bromine titration.

β-Phenyl-α-cyclohexylpropionic acid was obtained from α-(Δ¹-cyclohexenyl)cinnamic acid (6) in the form of long white needles from petroleum ether and melted at 70–71°.

Anal. Calc'd for $C_{15}H_{20}O_2$: C, 77.53; H, 8.68.
Found: C, 76.99; H, 8.63.

β-(p-Hydroxyphenyl)-α-cyclohexylpropionic acid was obtained from α-(Δ¹-cyclohexenyl)-*p*-hydroxycinnamic acid (6) and melted at 180–181° after recrystallization from a mixture of acetone and water.

Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.53; H, 8.12.
Found: C, 72.36; H, 8.08.

SUMMARY

1. Examples are given of the reduction of conjugated, isolated, and cyclic double bonds using nickel-aluminum alloy and aqueous alkali.

2. An anomalous behavior was observed in the reduction of isolated cyclic double bonds.

3. An example of the reduction of a triple bond is given.

4. The reduction of stilbestrol yielded a mixture of both low-melting and high-melting isomers of hexostrol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE REARRANGEMENT OF BETA AMINO ALCOHOLS WITH HEAT AND ALKALI[1]

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Beta-amino alcohols have been shown to undergo various rearrangements with acids (1, 2) but the effect of bases on these substances has been less thoroughly investigated. Bettzieche and Ehrlich (3) found that certain aryl-substituted amino alcohols yielded an aliphatic amine and a carbonyl compound when heated with aqueous alkali in a sealed tube:

$$(C_6H_5)_2\underset{\displaystyle OH}{\underset{|}{C}}CH_2NH_2 \xrightarrow[150^\circ]{H_2O—NaOH} (C_6H_5)_2C{=}O + CH_3NH_2$$

Stieglitz and Lenth (4) found that 1,1-diphenyl-2-aminoethanol gave methyliminobenzophenone when it was heated under anhydrous conditions with soda-lime or calcium oxide. In this rearrangement the nitrogen atom originally attached to carbon atom 2 has become attached to carbon atom 1 as well:

$$(C_6H_5)_2\overset{1}{\underset{\displaystyle OH}{\underset{|}{C}}}—\overset{2}{C}H_2—NH_2 \xrightarrow[280^\circ]{CaO} (C_6H_5)_2\overset{1}{C}{=}N—\overset{2}{C}H_3$$

In connection with our work on the formation of *beta*-amino alcohols from Grignard reagents and oximes (5, 6) it seemed of interest to study this rearrangement further, and to determine, if possible, its mechanism. With this in mind we have investigated the action of calcium oxide on 1,1-diphenyl-2-amino-1-propanol (I), 1-phenyl-1-*p*-tolyl-2-aminoethanol (II), and 1,1,2-triphenyl-2-aminoethanol (III).

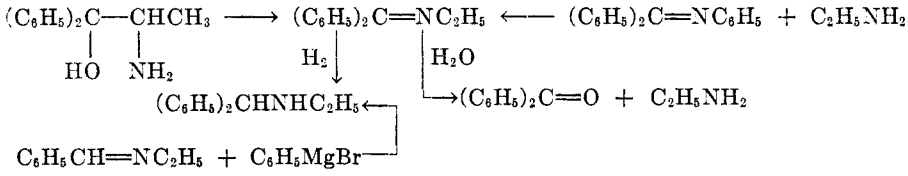
$$\underset{\displaystyle HO\ \ NH_2}{\underset{|\quad|}{(C_6H_5)_2C—CHCH_3}} \qquad \underset{\displaystyle OH}{\underset{|}{p—CH_3C_6H_4\overset{\displaystyle C_6H_5}{\overset{|}{C}}CH_2NH_2}} \qquad \underset{\displaystyle HO\ \ NH_2}{\underset{|\quad|}{(C_6H_5)_2C—CHC_6H_5}}$$

I II III

When amino alcohol I was heated with calcium oxide in an atmosphere of dry nitrogen at 265–285° it was partly rearranged to ethyliminobenzophenone. The yield of the ketimine was usually 50–75% of the theoretical amount, and some amino alcohol was always recovered. When the reaction was carried out at lower temperatures (130–230°) or in the absence of calcium oxide, no rearrangement occurred, and the alkamine was recovered almost quantitatively. The structure of the rearrangement product was established: (a) by hydrolysis to the ketone

[1] A part of this work was presented before the Organic Division at the Baltimore meeting of the American Chemical Society, April, 1939.

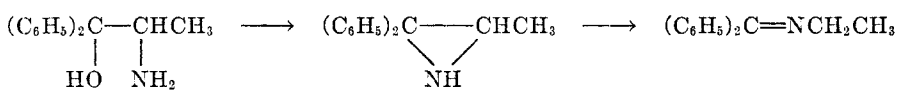
and amine; (b) by comparison of physical properties with ethyliminobenzophenone synthesized from ethylamine and benzophenone anil; (c) by reduction to the corresponding saturated amine; and (d) by comparison, through derivatives, of this amine with the amine synthesized from benzylidenethylamine and phenylmagnesium bromide. This proof was considered necessary in view of the oily nature of the ketimine and the saturated amine.



In a similar way it was established that amino alcohol II, 1-phenyl-1-*p*-tolyl-2-aminoethanol, was rearranged by calcium oxide at 260° to methylimino-*p*-methylbenzophenone. In this case rearrangement occurred more easily, and no alkamine was ever recovered. When the reaction was carried out at lower temperatures or in the absence of calcium oxide no rearrangement occurred.

Amino alcohol III, 1,1,2-triphenyl-2-aminoethanol, on heating with calcium oxide at 250° yielded an oil which was shown to be benzyliminobenzophenone.

It seemed to us that the rearrangement probably involved a dehydration of the amino alcohol to an ethylenimine, and that this substance, under the influence of the heat and alkali, undergoes a ring cleavage between the two carbon atoms.



This mechanism is supported by the fact that Coleman and Waugh (7) found that 2,3-diphenylethylenimine is rearranged to benzylidenbenzylamine by heat, while Erlenmeyer (8) had previously shown that the corresponding amino alcohol, 1,2-diphenyl-2-aminoethanol, also yields benzylidenbenzylamine on heating.

If the first step in the rearrangement is dehydration of the amino alcohol, it would help to explain the strenuous conditions found necessary in our work, for tertiary amino alcohols have been shown to be resistant to dehydration by neutral and alkaline dehydrating agents (9). The ethylenimine should, therefore, be more easily rearranged than the amino alcohol. Since the ethylenimine corresponding to amino alcohol I has recently been made readily available (10) rearrangement studies were carried out on it. The results showed that 2,2-diphenyl-3-methylethylenimine rearranged to ethyliminobenzophenone when heated, with or without calcium oxide, and that the rearrangement occurred at a much lower temperature than with the amino alcohol.

EXPERIMENTAL

A. *1,1-Diphenyl-2-amino-1-propanol and 2,2-diphenyl-3-methylethylenimine.* 1. *Rearrangement of the amino alcohol.* A mixture of 3 g. of the amino alcohol (5), m.p. 103–104°, and 1.5 g. of freshly powdered calcium oxide was heated in a small retort in a stream of dry nitrogen at 270° (oil-bath temperature) for seventy-five minutes. The cooled reaction mixture

was extracted several times with anhydrous ether. Distillation of the material remaining after evaporation of the ether yielded 1 g. of an oil, b.p. 154–159°/10 mm., n_D^{20} 1.5976, and 0.75 g. of the amino alcohol, b.p. 160–170°/10 mm., m.p. 102°. In one run the oil solidified and then melted at 58–59°. Sommelet (11) records the melting point 61–62° for ethyliminobenzophenone prepared from benzophenone dichloride.

When the amino alcohol was heated with calcium oxide at temperatures of 130–230° no rearrangement occurred, and the alkamine was recovered almost quantitatively.

2. *Hydrolysis of the rearrangement product.* One gram of the above oil was shaken for a few minutes at room temperature with 50 ml. of 6 *N* hydrochloric acid. The solution, originally clear, quickly became turbid, and a purple oil rose to the top. This oil was taken up in ether, the ether solution was dried and evaporated. The material remaining solidified after seeding with benzophenone, and then melted at 48°. The oxime prepared from this product melted at 140° and did not depress the melting point of known benzophenone oxime.

When the aqueous acid solution was made basic, a small amount of amino alcohol separated (m.p. 100°, benzamide, m.p. 188°). The filtrate was distilled into dilute hydrochloric acid. Evaporation of this distillate gave a hygroscopic hydrochloride from which a picrate was prepared. The picrate melted at 164° and did not depress the melting point of ethylamine picrate (m.p. 165°).

3. *Reduction of the rearrangement product.* One gram of the "rearrangement oil" was dissolved in 150 ml. of boiling absolute alcohol and treated with 6 g. of sodium. The cooled solution was poured into water, extracted with ether, and the dried extract distilled after removal of the ether. There was obtained 0.75 g. of an amine, b.p. 142°/8 mm., n_D^{20} 1.5680. This amine was converted into a hydrochloride, m.p. 240°, a phenylthiourea, m.p. 149–149.5°, and an *alpha*-naphthylurea, m.p. 181–182°.

4. *Ethyliminobenzophenone.* Benzophenone anil was made in 50% yield by the general method of Reddelein (12) from 10 g. of benzophenone, 5 drops of 40% hydrobromic acid, and 11 g. of aniline. Ten grams of the anil and a few crystals of aniline hydrobromide were heated at 230° for forty-five minutes while a stream of dry ethylamine was passed through the mixture. During this time 3.0 g. of aniline distilled out (calculated, 3.6 g.). The cooled residue was extracted repeatedly with dry ether, and the ether extract on distillation yielded 5 g. of a light yellow oil, b.p. 144°/7 mm., n_D^{20} 1.5895. It resisted all attempts at crystallization.

Anal. Calc'd for $C_{15}H_{15}N$: C, 86.1; H, 7.23; N, 6.70.
Found: C, 86.2; H, 7.49; N, 6.81.

One gram of the ketimine was shaken with 25 ml. of 6 *N* hydrochloric acid at room temperature. The acid-insoluble oil formed was shown to be benzophenone; the acid solution yielded ethylamine picrate.

Two grams of the ketimine was reduced with 10 g. of sodium in 100 ml. of absolute alcohol. The amine, isolated in 1 g. yield, boiled at 155–157°/12 mm., n_D^{20} 1.5698.

5. *Benzohydrylethylamine.* A solution of 13.3 g. (0.1 mole) of benzylidenethylamine (b.p. 125–126°/95 mm.) in two volumes of dry ether was added over a period of forty-five minutes to a Grignard reagent prepared from 3 g. of magnesium and 20 g. of bromobenzene. The reaction mixture was refluxed for two hours, and was then hydrolyzed with ice and ammonium chloride. There was obtained 15 g. of amine, b.p. 143–148°/8 mm., n_D^{20} 1.5656.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.24; H, 8.12; N, 6.63.
Found: C, 85.01; H, 8.43; N, 6.76.

Busch and Leefheim (13) have also prepared this amine; they report the boiling point 175°/20 mm., and obtained a hydrochloride, m.p. 248°.

6. *Rearrangement of 2,2-diphenyl-3-methylethylenimine.* A mixture of 3 g. of the ethylenimine (10) and 1.5 g. of calcium oxide was heated in a stream of nitrogen at 250–260° for one and one-half hours. The product, obtained in 2.2 g. yield, had b.p. 144–147°/10 mm., n_D^{20} 1.5868. The same compound was obtained when the ethylenimine was heated in the absence of calcium oxide, at temperatures of 175–205°.

The rearrangement product on treatment with 6 *N* hydrochloric acid yielded benzophenone and ethylamine.

Reduction of 2.1 g. of the rearrangement product with 7 g. of sodium and 100 ml. of absolute alcohol gave 1.75 g. of amine, b.p. 141–143°/9 mm., n_D^{20} 1.5683.

A comparison of the rearrangement and reduction products in this series is given in Table I.

TABLE I

REARRANGEMENT OF 1,1-DIPHENYL-2-AMINO-1-PROPANOL AND 2,2-DIPHENYL-2-METHYLETHYLENIMINE

SOURCE	COMPOUND				
	Ethyliminobenzophenone	Benzohydrylethylamine	Amine HCl M.p., °C.	Amine phenylthiourea M.p., °C.	Amine α-naphthylurea M.p., °C.
Benzylidenethylamine + C_6H_5MgBr		B.p. 143–8/8 mm. n_D^{20} 1.5656	246–247	150–151	183.5–185
Benzophenone + ethylamine	B.p. 144°/7 mm. n_D^{20} 1.5895	B.p. 155°/12 mm. n_D^{20} 1.5698	246–247	150–151	182–183
Ethylenimine	B.p. 142°/8 mm. n_D^{20} 1.5889	B.p. 143°/8 mm. n_D^{20} 1.5683	240	149	183–184
Amino alcohol	B.p. 139°/5 mm. n_D^{20} 1.5976	B.p. 142°/8 mm. n_D^{20} 1.5680	240	149–150	181–182

TABLE II

REARRANGEMENT OF 1-PHENYL-1-*p*-TOLYL-2-AMINOETHANOL

SOURCE	COMPOUND				
	Methylimino-*p*-methylbenzophenone	*p*,N-Dimethylbenzohydrylamine	Amine Hydrochloride M.p. °C.	Amine Phenylthiourea M.p. °C.	Amine α-Naphthylurea M.p.
Benzylidenmethylamine + *p*-tolylmagnesium bromide		B.p. 169–172°/16 mm. n_D^{20} 1.5700	186.5–187	140–140.5	171.5–172.5
p-Methyl benzophenone + $MeNH_2$	B.p. 165–169°/12 mm. n_D^{20} 1.5965	B.p. 144–148°/8 mm. n_D^{20} 1.5715	184–186	138–139	170–171
Amino alcohol	B.p. 169–171°/13 mm. n_D^{20} 1.5965	B.p. 148–150°/9 mm. n_D^{20} 1.5706	185–186	139.5–140	171.5–172.5

B. *1-Phenyl-1-p-tolyl-2-aminoethanol.* 1. *Rearrangement of the amino alcohol.* A mixture of 3 g. of the amino alcohol (2) and 1.5 g. of calcium oxide was heated at 260° in a stream of dry nitrogen for one hour. A viscous yellow oil was isolated in 2 g. yield, b.p. 140–143°/5 mm., n_D^{20} 1.5965. Hydrolysis of this oil with 6 *N* hydrochloric acid yielded *p*-methylbenzophenone, m.p. 58° after recrystallization from 95% ethyl alcohol, which did not depress the melting point of an authentic sample of the ketone (m.p. 58°). An amine hydrochloride,

m.p. 223°, was also isolated from the hydrolysis; this did not depress the melting point of methylamine hydrochloride, m.p. 225°. The platinichloride of the amine melted at 224–225°.

Anal. Calc'd for $C_2H_{12}Cl_6PtN_2$: Pt, 41.30. Found: Pt, 41.33.

The "rearrangement oil" (1.5 g.) was reduced with 4 g. of sodium in 100 ml. of boiling absolute alcohol. There was obtained 0.75 g. of an oil, b.p. 148–150°/9 mm., n_D^{20} 1.5706. This material was converted into a hydrochloride, m.p. 185–186°, a phenylthiourea, m.p. 139.5–140°, and an α-naphthylurea, m.p. 171.5–172.5°.

2. *Synthesis of methylimino-p-methylbenzophenone.* *p*-Methylbenzophenone anil was prepared by the general method of Reddelein (12). A mixture of 10 g. of the anil (b.p. 205°/9 mm.) and 0.5 g. of aniline hydrobromide was heated in a stream of dry methylamine at 200–210° until 3 g. of aniline distilled out. The imine was obtained in 5 g. yield as a yellow viscous oil, b.p. 165–169°/13 mm., n_D^{20} 1.5965.

Anal. Calc'd for $C_{15}H_{15}N$: N, 6.70. Found: N, 6.40.

The imine on hydrolysis with 6 *N* hydrochloric acid yielded *p*-methylbenzophenone and methylamine hydrochloride.

Reduction of 5.2 g. of the imine with 10 g. of sodium in 100 ml. of absolute alcohol yielded 4 g. of amine, b.p. 144–148°/8 mm., n_D^{20} 1.5715.

3. *Synthesis of p-N-dimethylbenzohydrylamine.* A solution of 20 g. of benzylidenmethylamine in an equal volume of dry ether was added dropwise to a Grignard reagent prepared from 38 g. of *p*-bromotoluene, 5 g. of magnesium and 150 ml. of ether. The reaction mixture was refluxed for one hour and was then worked up in the usual way. There was obtained 18 g. of amine, b.p. 169–172°/16 mm., n_D^{20} 1.5700.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.24; H, 8.12; N, 6.63.
Found: C, 85.33; H, 8.51; N, 6.69.

The hydrochloride of this amine melted at 186–187° after recrystallization from ether-alcohol mixture.

Anal. Calc'd for $C_{15}H_{18}ClN$: Cl, 14.34. Found: Cl, 14.25.

The α-naphthylurea melted at 171.5–172.5° after recrystallization from 95% alcohol.

Anal. Calc'd for $C_{26}H_{24}N_2O$: N, 7.37. Found, N, 7.36.

Semper and Lichtenstadt (14) reported this amine as a reduction product of the N-methyl ether of *p*-methylbenzophenone oxime; they did not isolate the free base, and give the melting point 199–201° for the hydrochloride.

A comparison of the derivatives from the rearrangement of 1-phenyl-1-*p*-tolyl-2-aminoethanol with the synthetic derivatives is shown in Table II.

C. *Rearrangement of 1,2,2-triphenyl-2-aminoethanol.* A mixture of 2.0 g. of the amino alcohol and 1 g. of calcium oxide was heated in a stream of nitrogen at 260° for one hour; there was obtained 1.8 g. of oil. This oil partially solidified on seeding with known benzophenone benzylimide (15). Hydrolysis of the "rearrangement oil" with dilute hydrochloric acid yielded benzophenone, identified as the oxime, m.p. 143°, and benzylamine, identified as the picrate, m.p. 197°.

SUMMARY

1. The rearrangement of three aryl-substituted *beta* amino alcohols with heat and calcium oxide has been investigated. The amino alcohols have been shown to rearrange to ketimines; in two cases the rearrangement product was identified by synthesis and by reduction to a saturated, secondary amine.

2. A mechanism has been suggested for the rearrangement, and has been partially confirmed by a study of the rearrangement of 2,2-diphenyl-3-methylethylenimine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE ACTION OF GRIGNARD REAGENTS ON OXIMES. IV. ALIPHATIC GRIGNARD REAGENTS AND MIXED KETOXIMES[1]

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In previous papers from this Laboratory (1, 2, 3) it has been shown that aryl Grignard reagents react with aryl alkyl ketoximes to yield either ethylenimines or *beta*-amino alcohols, the product obtained depending on the conditions used in the hydrolysis of the Grignard complex. This reaction constitutes a new type of synthesis of ethylenimines.

It was of interest to determine whether the reaction could be extended to aliphatic Grignard reagents. This was found to be the case; ethylenimines have been obtained from acetophenone and propiophenone oximes with ethylmagnesium and propylmagnesium bromides. With the aromatic magnesium halides the optimum temperature appears to be about 135–145°, but with the aliphatic Grignard reagents the reaction is best carried out at 95–100° in toluene solution; higher temperatures cause extensive tar formation.

The ethylenimines obtained in the present work, like those reported earlier, did not reduce an acetone solution of potassium permanganate in the cold, and they were easily hydrolyzed by dilute acid to the corresponding amino alcohols, which were also synthesized by an independent reaction for comparison. Analytical data, molecular refraction and parachor values are in accord with the ethylenimine structures.

One of the ethylenimines (2-phenyl-2-ethylethylenimine) was synthesized in poor yield from the amino alcohol by treatment with thionyl chloride, followed by alcoholic potassium hydroxide. The product so obtained agreed in properties with the material obtained from acetophenone oxime and ethylmagnesium bromide.

EXPERIMENTAL

2-Phenyl-2-ethylethylenimine. A solution of ethylmagnesium bromide prepared from 24 g. of magnesium turnings, 115 g. of ethyl bromide, and 350 ml. of dry ether was distilled until 200 ml. of ether was removed; 200 ml. of dry toluene was added, and then a solution of 34 g. (0.25 mole) of acetophenone oxime in 200 ml. of dry toluene was added dropwise over a period of two hours. The oil-bath surrounding the flask was kept at 90–95° during the addition, and for thirty minutes afterwards. The mixture was hydrolyzed at once by pouring onto ice and ammonium chloride solution; the water layer was extracted several times with ether, and the combined ether solutions were dried over magnesium sulfate. The residue remaining after removal of the ether and toluene was distilled under reduced pressure to yield 14.4 g. of material of b.p. 85–86°/7 mm., n_D^{20}: 1.5318, d_4^{20}: 0.9811, MR_D obs., 46.4, MR_D calc'd, 46.2; parachor obs., 366, calc'd, 375. This is a yield of 37%; in other runs the yields ranged from 20–60%.

[1] A part of this work was presented before the Organic Division at the St. Louis meeting of the American Chemical Society, April, 1941.

Anal. Calc'd for $C_{10}H_{13}N$: C, 81.63; H, 8.85; N, 9.52; mol. wt., 147.
Found: C, 81.52; H, 9.26; N, 9.21; mol. wt., 149.

The compound did not reduce an acetone solution of potassium permanganate at room temperature in fifteen minutes. It gave a red color with concentrated sulfuric acid.

Treatment of an anhydrous ether solution of the substance with dry hydrogen chloride in ether yielded a rather hygroscopic hydrochloride. After several recrystallizations from absolute alcohol-anhydrous ether mixture this melted at 191–191.5°.

Anal. Calc'd for $C_{10}H_{14}ClN$: Cl, 19.33. Found: Cl, 19.85.

The phenylthiourea of the amine melted at 99–100° after recrystallization from alcohol. The *alpha*-naphthylurea melted at 129–130°.

Hydrolysis. (a) The ethylenimine was refluxed with 4 *N* hydrochloric acid for five minutes or with 2 *N* sulfuric acid for ten minutes. A small amount of oil floating on the solution was removed by extraction with ether, the acid aqueous layer was made basic with ammonium hydroxide and the oil formed taken up in ether. Distillation of the residue remaining after evaporation of the ether yielded an oil, b.p. 108–112°/2 mm., n_D^{20}: 1.533. This oil gave a benzamide, m.p. 114–115.5°, and a hydrochloride, m.p. 181°. 2-Phenyl-1-amino-2-butanol was synthesized from phenacylamine hydrochloride and ethylmagnesium bromide by the method of Tiffeneau and Cahnmann (4). The product, obtained in 30% yield, had b.p. 109–111°/2 mm., n_D^{20}: 1.5331. Its hydrochloride melted at 181–182° and did not depress the melting point of the hydrochloride of the hydrolysis product. The benzamide of 2-phenyl-1-amino-2-butanol melted at 114–114.5° and did not depress the melting point of the hydrolysis product benzamide.

Anal. Calc'd for $C_{17}H_{19}NO_2$: N, 5.2. Found: N, 5.4.

(b) A 1-g. portion of the ethylenimine was refluxed with 6 *N* hydrochloric acid for thirty minutes. The acid solution was extracted with ether, and the ether extract after drying over magnesium sulfate was evaporated to dryness. The residual oil gave a semicarbazone, m.p. 152–153.5°, which did not depress the melting point of the semicarbazone (m.p. 152–152.5°) of *alpha*-phenylbutyraldehyde. The aldehyde was prepared from 2-phenyl-2-ethylethylene oxide by the method of Stoermer (5).

The acid solution remaining from the ether extraction was evaporated to dryness, and the solid so obtained was shown to be ammonium chloride.

Synthesis of 2-phenyl-2-ethylethylenimine from 2-phenyl-1-amino-2-butanol. A mixture of 5.5 g. of 2-phenyl-1-amino-2-butanol hydrochloride, 11 g. of redistilled thionyl chloride, and 100 ml. of dry chloroform was refluxed for three hours. Most of the solvent and excess thionyl chloride were removed by suction, and dry petroleum ether and diethyl ether were added to the residue. The solid so precipitated (3 g.) melted at 145–147° after recrystallization from absolute alcohol-anhydrous ether mixture. A solution of 2 g. of this compound in 60 ml. of absolute alcohol was treated with a solution of 2 g. of potassium hydroxide in 20 ml. of absolute alcohol. The mixture was allowed to stand at room temperature for eight hours, and was then poured into a large volume of water. The turbid solution was extracted several times with ether, and the ether extracts were dried over magnesium sulfate. Distillation of the oil remaining after evaporation of the ether yielded 0.5 g. of a colorless oil, b.p. 92–94°/8–9 mm., n_D^{20}: 1.5281. The hydrochloride of this oil melted at 189–191° and did not depress the melting point of the ethylenimine hydrochloride. The phenylthiourea melted at 99°.

2-Phenyl-2-propylethylenimine. This compound was prepared by the method described above for the ethyl compound, using 34 g. of acetophenone oxime and the Grignard reagent obtained from 24 g. of magnesium and 105 g. of *n*-propyl bromide. The product, isolated in 10–15 g. yield (23–35%) had b.p. 90–91°/3 mm., n_D^{20}: 1.5235, d_4^{20}: 0.9644, MR_D obs. 51.0, MR_D calc'd 50.8. Parachor, obs. 404, calc'd, 414.

Anal. Calc'd for $C_{11}H_{15}N$: C, 81.99; H, 9.32; N, 8.70; mol. wt., 161.
Found: C, 81.83; H, 9.6; N, 8.79; mol. wt., 165.

Like its lower homolog, this substance did not reduce an acetone solution of potassium permanganate in fifteen minutes at room temperature.

The hydrochloride melted at 68–69°.

Anal. Calc'd for $C_{11}H_{16}ClN$: Cl, 17.96.
Calc'd for $C_{11}H_{17}Cl_2N$: Cl, 30.04.
Found: Cl, 20.7, 20.4.

The phenylthiourea of the amine melted at 100° after recrystallization from absolute alcohol.

On hydrolysis of the amine with 2 *N* sulfuric acid a viscous oil was obtained, b.p. 119–122°/4 mm., n_D^{20}: 1.5335. The benzamide of the hydrolysis product melted at 112–113°.

1-Phenyl-1-propyl-2-aminoethanol was prepared in 7.5 g. yield from 0.5 mole of propylmagnesium bromide and 15.2 g. of phenacylamine hydrochloride. The amino alcohol boiled at 125–126°/7 mm. n_D^{20}: 1.5335.

Anal. Calc'd for $C_{11}H_{17}NO$: C, 73.74; H, 9.5; N, 7.82.
Found: C, 73.66; H, 9.66; N, 7.90.

The benzamide of this amino alcohol melted at 112–113° and did not depress the melting point of the benzamide obtained from the hydrolysis product.

Anal. Calc'd for $C_{18}H_{21}NO_2$: N, 4.94. Found: N, 5.12.

2-Phenyl-2-ethyl-3-methylethylenimine. This was obtained in 13.5 g. (50%) yield from the reaction of 26.8 g. of propiophenone oxime with 1 mole of ethylmagnesium bromide in toluene solution at 100°. The material was obtained as a clear, colorless oil, b.p. 77–79°/3 mm., n_D^{20}: 1.5205, d_4^{20}: 0.9614, MR_D obs. 50.9, MR_D calc'd 50.8. Parachor, obs. 408, calc'd, 414.

Anal. Calc'd for $C_{11}H_{15}N$: C, 81.99; H, 9.32; N, 8.70; mol. wt. 161.
Found: C, 81.84; H, 9.51; N, 8.62; mol. wt. 167.

The hydrochloride melted at 158–159°.

Anal. Calc'd for $C_{11}H_{16}ClN$: Cl, 17.96. Found: Cl, 17.72.

The phenylthiourea melted at 130–131°.

Hydrolysis of the compound with 2 *N* sulfuric acid yielded a viscous oil, b.p. 106–110°/6 mm., n_D^{20}: 1.5350. This material formed a hydrochloride, m.p. 228°, and a benzamide, m.p. 160°. At the time this work was done 1-phenyl-1-ethyl-2-aminopropanol was not described in the literature (6). It was synthesized, therefore, from *alpha*-aminopropiophenone hydrochloride and ethylmagnesium bromide. The substance so obtained had b.p. 106–108°/5 mm., n_D^{20}: 1.5347.

Anal. Calc'd for $C_{11}H_{17}NO$: C, 73.74; H, 9.5; N, 7.82.
Found: C, 73.81; H, 9.72; N, 7.78.

The hydrochloride melted at 230° and the benzamide at 160°. These derivatives did not depress the melting points of the corresponding derivatives obtained from the hydrolysis product of the ethylenimine. The benzamide was analyzed for nitrogen.

Anal. Calc'd for $C_{18}H_{21}NO_2$: N, 4.94. Found: N, 5.20.

SUMMARY

1. Ethylenimines are obtained by the action of aliphatic Grignard reagents on aryl alkyl ketoximes. Three such ethylenimines have been prepared and characterized.

2. The ethylenimines have been hydrolyzed to amino alcohols by dilute acid. The amino alcohols have been synthesized in other ways for comparison.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A SYNTHESIS OF α-MESITYLPROPIOMESITYLENE

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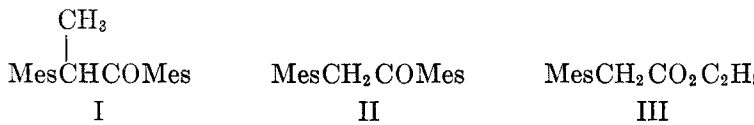
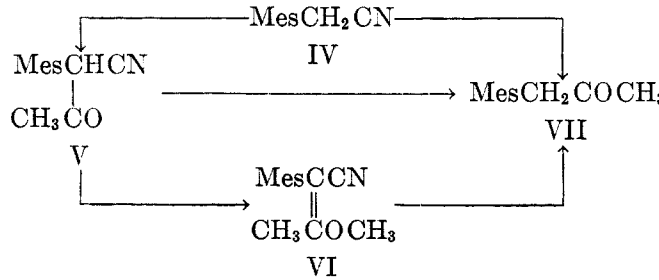
α-Mesitylpropiomesitylene (I) and a number of similar ketones (1, 2) are remarkable because their enol forms are stable. On account of the importance of these ketones, efforts have been directed to other possible synthetic routes to this type of compound. The work was planned in such a way that several of these were investigated simultaneously. Thus it came about that most of the studies were left unfinished.

An obvious approach was the methylation of the corresponding desoxybenzoins. Attempts to methylate desoxymesitoin (II), however, were unavailing. This failure made it seem probable that attachment to a mesityl radical would diminish the tendency of an active methylene group to undergo condensation reactions in general. There is evidence that this is true. It had been found earlier, for example, that the condensation of desoxymesitoin with formaldehyde took place only with difficulty (1). Ethyl mesitylacetate (III) could not be caused to react with formaldehyde or ethyl acetate. However, it did form a derivative with oxalic ester.



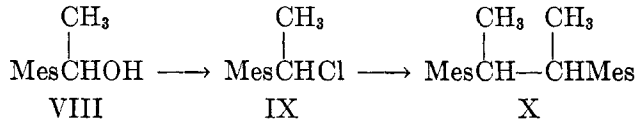
I II III

Although mesitylacetonitrile (IV) failed to condense with formaldehyde, it underwent acylation normally. The formyl and acetyl (V) derivatives were obtained in satisfactory yields. It was hoped that these could be methylated and thus serve as intermediates in the synthesis of α-mesitylpropionic acid. Methylation of α-mesitylacetoacetonitrile (V), however, yielded only the O-methyl derivative (VI). This was shown by the fact that hydrolysis converted it to mesitylacetone (VII). Mesitylacetone was formed also when the keto nitrile (V) was subjected to hydrolysis. Although Holmberg (3) isolated mesitylacetone, he did not characterize it. It was found possible to make this ketone by condensation of mesitylacetonitrile with methylmagnesium iodide.



[1] Rohm and Haas Research Assistant, 1940–1942.

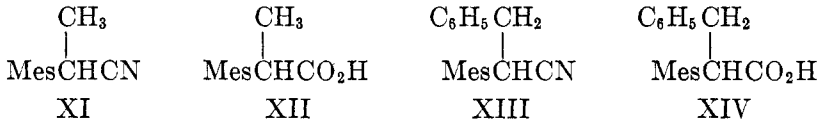
An attempt was made to prepare α-mesitylpropiomesitylene from mesitylmethylcarbinol (VIII) by way of the Grignard reagent. The carbinol was prepared by reduction of acetomesitylene by the method of Klages and Allendorff (4) and also by the condensation of mesitylmagnesium bromide with acetaldehyde. In a preliminary experiment, the crude chloride (IX) from the carbinol was treated with magnesium in ether and mesitoyl chloride was added. The only products that were isolated were mesitoic acid and a hydrocarbon which appeared to be 2,3-dimesitylbutane (X).



VIII IX X

An attempt to prepare α-mesitylpropiomesitylene by condensing α-chloropropionyl chloride with mesitylene yielded only α-chloropropiomesitylene.

The synthesis which was finally successful involved methylation of mesitylacetonitrile, hydrolysis of the resulting α-mesitylpropionitrile (XI), and condensation of the chloride of the resulting acid (XII) with mesitylene.



XI XII XIII XIV

It seems likely that this method of synthesis will prove to be general for ketones of the type MesCH(R)COMes. Alkylation of mesitylacetonitrile with benzyl chloride produced α-mesityl-β-phenylpropionitrile (XIII) from which the corresponding acid (XIV) was made by hydrolysis.

EXPERIMENTAL

Ethyl mesitylacetate. This ester was prepared from ethanol and the corresponding acid chloride, and by direct esterification of the acid in the presence of *p*-toluenesulfonic acid. The yields were, respectively, 95 and 70%. The ester boiled at 152–153° (22 mm.); n_D^{20} 1.5061.

Anal.[2] Calc'd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80.
Found: C, 75.97; H, 8.71.

Ethyl mesitylacetate was made in 67% yield from mesitylacetonitrile by treatment with a mixture of sulfuric acid and ethanol. A mixture of 50 cc. of ethanol, 15 cc. of sulfuric acid, and 32 g. of mesitylacetonitrile was heated under reflux for seventeen hours. In addition to the ester there was isolated a solid which, after recrystallization from benzene, melted at 236–237°.

Anal. Calc'd for $C_{22}H_{25}NO$: C, 82.45; H, 8.18; N, 4.37.
Found: C, 81.87; H, 8.89; N, 4.54.

This substance was not investigated further.

Condensation of ethyl mesitylacetate with ethyl oxalate. Three grams of sodium was dissolved in 50 cc. of absolute ethanol. A large part of the alcohol was removed by distillation under diminished pressure and the residue was diluted with 90 cc. of toluene. A mixture of 27 g. of ethyl mesitylacetate and 19 g. of ethyl oxalate was added and the mixture, heated

[2] The microanalyses reported in this paper were carried out by Miss Mary S. Kreger, Miss Margaret McCarthy, Miss Theta Spoor, and Miss Dorothy Schneider.

by a hot water-bath, was stirred for eight hours. It was allowed to stand overnight and poured into water. After being acidified with hydrochloric acid the solution was extracted with ether. The ether solution was dried over calcium chloride and distilled. The fraction which distilled at 123–148° (3 mm.) partially solidified. The solid was recrystallized from diluted ethanol; m.p. 49–50°.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.95.
Found: C, 68.75; H, 7.91.

From its composition this ester was thought to be ethyl mesitylmalonate. An attempt to methylate it failed.

α-Mesitylacetoacetonitrile. To a solution of 18 g. of sodium in 210 cc. of absolute ethanol was added a solution of 96 g. of mesitylacetonitrile in 80 g. of ethyl acetate. The mixture was shaken thoroughly and heated under reflux for three hours. It was allowed to stand overnight and poured into water. The aqueous mixture was extracted with ether and heated to expel the dissolved ether. It was then cooled and acidified with glacial acetic acid. The mesitylacetoacetonitrile which separated was recrystallized from high-boiling petroleum ether; m.p. 117–118°; yield 48 g.

Anal. Calc'd for $C_{13}H_{15}NO$: C, 77.57; H, 7.51.
Found: C, 77.67; H, 7.83.

Methylation of α-mesitylacetoacetonitrile. To a solution of 2.3 g. of sodium in 25 cc. of absolute ethanol was added 20.1 g. of α-mesitylacetoacetonitrile. After the mixture had been heated for an hour it was cooled, and 21.3 g. of methyl iodide added. After eighteen hours of heating under reflux the mixture was allowed to cool and poured into water. The product was extracted with ether and distilled; b.p. 152–156° (3–4 mm.).

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96.
Found: C, 78.30; H, 8.14.

That this substance was the O-methyl derivative was shown by the fact that heating for five hours in a mixture of glacial acetic and sulfuric acids converted it to mesitylacetone; m.p. 60–61°.

Mesitylacetone. An impure sample of this ketone was obtained by condensing mesitylene with chloroacetone in the presence of aluminum chloride. It yielded a semicarbazone melting at 195–197°, as indicated by Holmberg (3).

Mesitylacetone was obtained also by the condensation of mesitylacetonitrile with methylmagnesium iodide[3] by the method of Shriner and Turner (5). From 21 g. of the nitrile and a five-fold excess of the Grignard reagent was obtained 6 g. of the ketone.

A third procedure for the synthesis of mesitylacetone involved the hydrolysis of α-mesitylacetoacetonitrile. A mixture of 5 g. of the nitrile, 10 cc. of concentrated sulfuric acid, and 90 cc. of glacial acetic acid was heated under reflux for ten hours and poured into water. The crude mesitylacetone was recrystallized from high-boiling petroleum ether; m.p. 60–61°.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 82.01; H, 9.30.

β-Hydroxy-α-mesitylacrylonitrile. To a warm solution of 9 g. of sodium in 105 cc. of absolute ethanol were added in succession 40 g. of mesitylacetonitrile and 30 g. of ethyl formate. The mixture was heated under reflux for two and one-half hours and poured into 1200 cc. of water. The aqueous mixture was heated to 40° and filtered to remove unchanged mesitylacetonitrile (6 g.). The filtrate, after being washed twice with ether, was acidified with acetic acid. The yellow oil which separated was dissolved in ether. Evaporation of the solvent left the hydroxymethylene compound as a solid. After being recrystallized four times from a high-boiling petroleum ether-benzene mixture, it melted at 131.5–132.5°. After the product had stood for several hours it melted at 126.5–127.5°.

Anal. Calc'd for $C_{12}H_{13}NO$: C, 76.96; H, 7.00.
Found: C, 77.18; H, 7.24.

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[3] This preparation was carried out by Dr. Quentin F. Soper.

The *anilino* derivative, β-anilino-α-mesitylacrylonitrile, was made by boiling for fifteen minutes a mixture of 2 g. of the hydroxy nitrile, 1 cc. of aniline, and 25 cc. of absolute ethanol. The derivative was recrystallized from high-boiling petroleum ether; m.p. 151.5–153°; yield, 2 g.

Anal. Calc'd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92.
Found: C, 82.59; H, 7.12.

The *benzoate* was prepared by treating the hydroxy nitrile with benzoyl chloride in the presence of pyridine. It crystallized from ethanol in beautiful, white needles; m.p. 127–128°.

Anal. Calc'd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.81.
Found: C, 78.03; H, 6.07; N, 4.73.

The benzoate was unaffected by treatment with hydrogen in the presence of a platinum oxide catalyst.

Condensation of acetaldehyde with mesitylmagnesium bromide. The Grignard reagent was prepared from 50 g. of bromomesitylene and 6 g. of magnesium in 200 cc. of dry ether. This was cooled in an ice-bath while a solution of 15 g. of acetaldehyde in 100 cc. of dry ether was added slowly. After all of the aldehyde had been added, the mixture was allowed to stand overnight. The chief product was a solid which, when crystallized from alcohol, melted at 94–95°.

Anal. Calc'd for $C_{22}H_{30}O$: C, 85.10; H, 9.75.
Found: C, 84.94; H, 9.73.

The composition of this compound corresponds to that of the ether of the expected mesitylmethylcarbinol.

In another run the crude product of the condensation was treated in dry ether with hydrogen chloride. The impure chloride (b.p. 130–132°/22 mm.; n_D^{20} 1.5320) obtained in this way was treated with magnesium in an effort to form the corresponding Grignard reagent. The resulting mixture was treated with mesitoyl chloride. The only products that could be isolated were mesitoic acid and a hydrocarbon melting at 139–140°. Its composition corresponds to that calculated for 2,3-dimesitylbutane.

Anal. Calc'd for $C_{22}H_{30}$: C, 89.72; H, 10.28.
Found: C, 90.04; H, 10.17.

α-Chloropropiomesitylene.[4] Twenty grams of α-chloropropionyl chloride was added, with stirring, to a mixture of 40 g. of mesitylene, 33 g. of aluminum chloride, and 150 cc. of carbon disulfide at 5°. A large amount of hydrogen chloride was evolved. The reaction mixture was allowed to stand overnight at room temperature and poured into a mixture of 400 g. of ice and 50 cc. of concentrated hydrochloric acid. The solvent was evaporated and the α-chloropropiomesitylene was taken up in benzene. The benzene solution was washed and dried. Distillation yielded the chloro ketone; b.p. 99–100° (1.5 mm.); n_D^{20} 1.5273.

Anal. Calc'd for $C_{12}H_{15}ClO$: C, 68.38; H, 7.18.
Found: C, 69.09; H, 7.45.

This compound was unstable; in a short time it developed a brown color.

3,5-Dinitro-α-chloropropiomesitylene. One cubic centimeter of α-chloropropiomesitylene was nitrated according to the procedure of Fuson, Ross, and McKeever (6). The dinitro compound was obtained in good yield. It crystallized from ethanol in white needles; m.p. 127.5–128.5°.

Anal. Calc'd for $C_{12}H_{13}ClN_2O_5$: C, 47.92; H, 4.35; N, 9.32.
Found: C, 48.00; H, 4.38; N, 9.39.

3,5-Dinitro-β-chloropropiomesitylene. A comparison of the new chloropropiomesitylene with the known *beta* isomer showed the two to be different. Their dinitro derivatives were also unlike. One gram of β-chloropropiomesitylene (7) was added in small portions to 20 cc. of fuming nitric acid. The dinitro compound was isolated in the usual way (7). It crystallized from glacial acetic acid in white plates; m.p. 190–191.5°.

Anal. Calc'd for $C_{12}H_{13}ClN_2O_5$: C, 47.92; H, 4.35; N, 9.32.
Found: C, 48.41; H, 4.19; N, 8.87.

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[4] The experiments with the chloropropiomesitylenes were carried out by Dr. C. H. McKeever.

α-Mesitylpropionic acid. Twenty grams of sodium was added in small pieces to 500 cc. of liquid ammonia. A few crystals of ferric nitrate were used as a catalyst. The ammonia was allowed to evaporate, the last traces being removed on the water-pump. The sodium amide was suspended in 200 cc. of dry ether and to this suspension was added over a period of thirty minutes a solution of 100 g. of mesitylacetonitrile in 400 cc. of dry ether. The mixture was then heated under reflux for two hours. A solution of 92.6 g. of methyl iodide in 50 cc. of ether was added gradually over a period of two hours. After addition was complete the solution was heated under reflux for five and one-half hours longer. The mixture was cooled and decomposed by the addition of ice. The α-mesitylpropionitrile, b.p. 160–165° (35 mm.), was heated for five hours under reflux with a mixture of glacial acetic and concentrated sulfuric acids. The acid obtained in this way was purified by successive recrystallizations from 95% ethanol and dilute acetic acid; m.p. 102–103°. When this acid was mixed with that obtained by cleavage of α-mesitylpropiophenone (1) the melting point was not depressed.

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39.
Found: C, 74.88, 75.06; H, 8.43, 8.95.

α-Mesitylpropionamide. One gram of α-mesitylpropionitrile was heated for four hours under reflux with a solution of 1 g. of sodium hydroxide in 20 cc. of water. The mixture was poured into water and the oil which formed was allowed to crystallize. The amide was purified by recrystallization from high-boiling petroleum ether; m.p. 100–101°.

Anal. Calc'd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32.
Found: C, 75.29; H, 8.89; N, 7.33.

α-Mesitylpropiomesitylene.[5] A mixture of 10 g. of α-mesitylpropionic acid and 6.5 cc. of thionyl chloride was allowed to stand overnight. After the excess thionyl chloride had been removed under diminished pressure, 50 cc. of mesitylene was added. To this mixture was added slowly, with stirring, 6.5 g. of aluminum chloride. After the mixture had been stirred for two hours at room temperature it was heated for thirty minutes on a steam-bath. The product boiled at 160–165° (1–2 mm.) and solidified when cooled. It was recrystallized from ethanol; m.p. 74–75°.

Anal. Calc'd for $C_{21}H_{26}O$: C, 85.66; H, 8.92.
Found: C, 85.57; H, 8.98.

A mixture of this compound wth an authentic specimen of α-mesitylpropiomesitylene (1) showed no lowering of melting point.

α-Mesityl-β-phenylpropionitrile.[6] Sodium amide prepared from 8 g. of sodium in the usual way, was suspended in ether, and to the suspension was added dropwise over a period of twenty minutes a solution of 41 g. of mesitylacetonitrile in 200 cc. of absolute ether. The mixture was heated under reflux for one hour and a half. A mixture of 28.6 g. of benzyl chloride with an equal volume of absolute ether was added gradually over a period of two hours. The mixture was heated under reflux, with stirring, for an additional two hours and cooled. Ice was added and the stirring continued for twenty minutes. The ether layer was removed and washed successively with 100 cc. of 6 *N* hydrochloric acid and 50 cc. of water. When the solvent had evaporated the residual α-mesityl-β-phenylpropionitrile was purified by distillation. A fraction weighing 44 g. was collected at 173–180° (2–5 mm.). After a few days it set to a semisolid.

Anal. Calc'd for $C_{18}H_{19}N$: C, 86.70; H, 7.68.
Found: C, 86.87; H, 7.59.

α-Mesityl-β-phenylpropionic acid. A solution of 5 g. of α-mesityl-β-phenylpropionitrile in a mixture of 10 cc. of sulfuric acid and 85 cc. of acetic acid was heated under reflux for nine and one-half hours. It was allowed to cool and was then poured into 500 cc. of water. The mixture was extracted with ether. The ether solution was washed with water and extracted with dilute sodium hydroxide solution. Acidification of the latter yielded 3 g. of α-mesityl-β-phenylpropionic acid. It was recrystallized from alcohol; m.p. 136–137°.

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[5] This experiment was carried out by Mr. Sidney Melamed.

[6] This preparation was carried out by Dr. John L. Marsh.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.
Found: C, 81.22; H, 7.75.

From the ether solution was obtained a small amount of the amide. It was purified by recrystallization from low-boiling petroleum ether; m.p. 119–120°.

Anal. Calc'd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92.
Found: C, 81.08; H, 7.87

SUMMARY

α-Mesitylpropiomesitylene has been synthesized by the following sequence of transformations:

$$\mathrm{MesCH_2CN} \rightarrow \mathrm{MesCH(CH_3)CN} \rightarrow \mathrm{MesCH(CH_3)CO_2H} \rightarrow \mathrm{MesCH(CH_3)COCl} \rightarrow \mathrm{MesCH(CH_3)COMes}$$

URBANA, ILL.

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(2) FUSON AND SPERATI, *J. Am. Chem. Soc.*, **63**, 2643 (1941).
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(4) KLAGES AND ALLENDORFF, *Ber.*, **31**, 998 (1898).
(5) SHRINER AND TURNER, *J. Am. Chem. Soc.*, **52**, 1267 (1930).
(6) FUSON, ROSS, AND MCKEEVER, *J. Am. Chem. Soc.*, **61**, 414 (1939).
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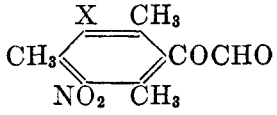
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

QUINOXALINE FORMATION AND THE ORTHO EFFECT. THE INFLUENCE OF BROMINE ATOMS AND NITRO GROUPS

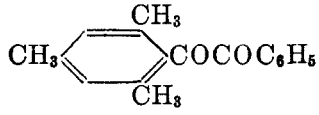
REYNOLD C. FUSON AND QUENTIN F. SOPER

Received November 26, 1943

The observation that 3,5-dinitromesitylglyoxal (I) readily formed a quinoxaline (1) whereas mesitylglyoxal itself failed to do so (2) indicated that the blocking power of the ortho methyl groups was diminished by the nitro groups. That both nitro groups were involved was shown by the observation that the mononitro compound, 3-nitromesitylglyoxal (II), did not form a quinoxaline. Results with 3-bromo-5-nitromesitylglyoxal (III) were inconclusive. It was suggested that the effect might be due to hydrogen bonding between the nitro and methyl groups (3).

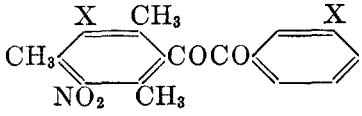


I (X = NO_2)
II (X = H)
III (X = Br)

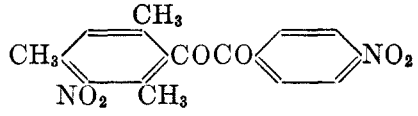


IV

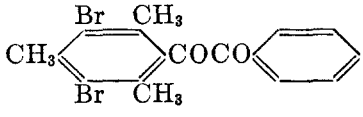
As a further test of this theory a study has been made of the tendency of certain α-diketones to form quinoxalines. Mesityl methyl diketone, like mesitylglyoxal, failed to form a quinoxaline. 3-Nitromesityl phenyl diketone (V), in accord with the hydrogen bonding theory, readily formed a quinoxaline, whereas the unsubstituted benzil, mesityl phenyl diketone (IV), failed to do so. The latter was unaffected even by long treatment with a boiling solution of *o*-phenylenediamine in glacial acetic acid or in dimethylaniline (4). Similar results were obtained with 3-nitromesityl 4-nitrophenyl diketone (VI), 3,5-dinitromesityl 3-nitrophenyl diketone (VII), and 3,5-dibromomesityl phenyl diketone (VIII). The effect of bromine atoms was not inconsistent with the explanation based on hydrogen bonding, since bromine atoms might also be bonded through hydrogen.



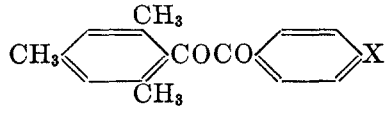
V (X = H)
VII (X = NO_2)



VI



VIII



IX (X = NO_2)
X (X = Br)

The inadequacy of the hydrogen bonding theory became apparent, however, when it was discovered that quinoxaline formation was made possible by the presence of a nitro group or a bromine atom *in the phenyl ring only*. Thus mesityl *p*-nitrophenyl diketone (IX), mesityl *m*-nitrophenyl diketone, and mesityl *p*-bromophenyl diketone (X), compounds having no substituent in the mesityl ring, were found to yield quinoxalines.

In exploratory experiments it was found that 2,4,6-triisopropylphenylglyoxal yielded only a Schiff base. Phenyl 2,4,6-triisopropylphenyl diketone as well as 3,5-dinitro-2,4,6-triisopropylphenyl 3-nitrophenyl diketone failed to react with *o*-phenylenediamine. Likewise mesitil and its tetranitro derivative could not be induced to react. As might have been expected, 4,4′-dimethoxy-2,6-xylil was no more reactive than mesitil.

Because of the report that 2,2′-dinitrobenzil failed to yield a quinoxaline (5), *o*-tolil was examined. It gave quinoxalines both with *o*-phenylenediamine and 4-nitro-*o*-phenylenediamine.

The experiments reported in this paper show that, although hydrogen bonding may be responsible for the diminution of the ortho effect in certain mesityl compounds, other factors must be involved. These results, taken together with data to be found in the literature, provide a basis for certain general observations, however.

(a) Arylglyoxals which are not sufficiently reactive to yield quinoxalines always form Schiff bases. (b) Benzils, on the other hand, always form quinoxalines if indeed they react at all. (c) Substitution of bromine atoms or nitro groups on either aromatic nucleus of a benzil enhances its tendency to undergo reaction with *o*-phenylenediamine.

EXPERIMENTAL

Selenium dioxide oxidation. Most of the 1,2-dicarbonyl compounds were prepared similarly. A solution of 0.01 to 0.09 mole of the ketone to be oxidized and a 10% excess of selenium dioxide in 100 cc. of wet dioxane was heated under reflux for approximately five hours. The reddish-yellow solution was filtered and the solvent removed by distillation at reduced pressure. Ether and Norit were added to the residue, the resulting solution was filtered and the ether removed. The residue was the crude 1,2-dicarbonyl compound. The results are listed in Table I.

Quinoxaline formation. For the transformation of the various 1,2-dicarbonyl compounds into the corresponding quinoxalines a standard procedure was adopted. Equimolecular amounts of the dicarbonyl compound and *o*-phenylenediamine were dissolved in about ten times their combined weight of glacial acetic acid, and the resulting solution was heated under reflux for thirty minutes. The quinoxalines made in this way are listed in Table II. Each of them, when added to concentrated sulfuric acid, produced the dark red coloration which is characteristic of quinoxalines.

3-Nitroacetomesitylene. The procedure was similar to that used by Powell and Johnson (10) for the preparation of nitromesitylene. An ice-cold solution of 20.8 cc. of fuming nitric acid (sp. gr. 1.51), 19 cc. of glacial acetic acid, and 18.5 cc. of acetic anhydride was added, with stirring, to a cold (below 10°) solution of 54 g. of acetomesitylene in 55.5 cc. of acetic anhydride. The temperature of the reaction mixture was kept below 20° during the mixing. The mixture was allowed to stand at room temperature for twenty-five hours, heated at 50° for ten minutes, and poured into 800 cc. of ice and water. The product was

TABLE I

Selenium Dioxide Oxidations

Glyoxal or diketone	M.p. (b.p.), °C.	Crystallizing solvents	Yield of 1,2-dicarbonyl compound %	Molecular formula	Analysis[a]			
					Calc'd		Found	
					C	H	C	H
3-Nitromesitylglyoxal	m.p. 217–218.5[b] (cor.)	Chloroform, ethyl acetate or a mixture of benzene and high-boiling petroleum ether (yellow plates)	72	$C_{17}H_{15}N_3O_7$	50.87	3.77	50.87	3.92
2,4,6-Triisopropylphenylglyoxal[c]	b.p. 129–135 (4.5 mm.)		82	$C_{17}H_{24}O_2$	78.42	9.29	77.95 77.96	9.43 9.52
Phenylhydrazone	m.p. 158.5–159.5 (cor.)	Ethanol (yellow needles)		$C_{23}H_{30}N_2O$	78.81	8.63	78.44	8.71
Semicarbazone	m.p. 179–180 (cor.)	Ethanol		$C_{18}H_{27}N_3O_2$	68.07	8.57	67.87	8.71
Hydrazone	m.p. 153–154 (decomp.)	Dilute ethanol (white cubes)		$C_{17}H_{26}N_2O$	74.41	9.55	74.38	9.65
3-Bromomesitylglyoxal[d]	m.p. 203–205[b]	Ethyl acetate (yellow prisms)	65	$C_{17}H_{15}BrN_4O_5$	46.91	3.47	47.00	3.75
3-Bromo-5-nitromesitylglyoxal[d]	m.p. 260–261[b]	Chloroform (brown-orange plates)	90	$C_{17}H_{14}BrN_5O_7$	42.52	2.94	42.58	3.13
Mesityl methyl diketone[e]	b.p. 138–139 (17 mm.)		42	$C_{12}H_{14}O_2$	75.76	7.42	75.73	7.59
Mesityl *p*-nitrophenyl diketone	m.p. 115–116 (cor.)	Ethanol; ligroin (yellow needles)	72	$C_{17}H_{15}NO_4$	68.68	5.09	68.65	5.04
Mesityl *m*-nitrophenyl diketone	m.p. 108–108.5 (cor.)	Ethanol (yellow needles) or a mixture of benzene and high-boiling petroleum ether (cubes)	81	$C_{17}H_{15}NO_4$	68.68	5.09	68.76	5.17
Mesityl *p*-bromophenyl diketone	m.p. 102–103	Ethanol or dilute acetic acid (yellow needles) or high-boiling petroleum ether (cubes)	72	$C_{17}H_{15}BrO_2$	61.64	4.57	61.64	4.68

[a] The analyses recorded in this paper are microanalyses. They were carried out by Miss Theta Spoor and Miss Dorothy Schneider.

[b] The data given in this line refer to the 2,4-dinitrophenylhydrazone.

[c] The ketone, 2,4,6-triisopropylacetophenone, from which the glyoxal was prepared, was synthesized following the procedure of Horning (6).

[d] 3-Bromoacetomesitylene and 3-bromo-5-nitroacetomesitylene were prepared by the method of Theobald (8). 3-Bromomesitylglyoxal boiled at 138–140° (5 mm.) and melted at 45–47°.

[e] The diketone was separated from unchanged propiomesitylene (7) by treatment with a saturated solution of sodium bisulfite. The solid addition product was collected on a filter and decomposed with dilute sulfuric acid. An attempt to condense the diketone with *o*-phenylenediamine was unsuccessful.

TABLE II

QUINOXALINES

DIKETONE	MELTING POINT, °C.	CRYSTALLIZING SOLVENTS	MOLECULAR FORMULA	ANALYSIS					
				Calc'd			Found		
				C	H	N	C	H	N
Mesityl *p*-nitrophenyl	211–211.5 (cor.)	Acetone; high-boiling petroleum ether	$C_{23}H_{19}N_3O_2$	74.77	5.19	11.38	75.19	4.89	11.03
Mesityl *m*-nitrophenyl	144–146	Dilute ethanol; high-boiling petroleum ether	$C_{23}H_{19}N_3O_2$	74.77	5.19		74.43	5.27	
3-Nitromesityl phenyl	151–152 (cor.)	Ethanol	$C_{23}H_{19}N_3O_2$	74.77	5.19	11.38	74.65	5.09	11.56
3-Nitromesityl 4-nitrophenyl	198–199[a] (cor.)	Acetone; mixture of benzene and high-boiling petroleum ether	$C_{23}H_{18}N_4O_4$	66.64	4.38		66.73	4.44	
3,5-Dinitromesityl 3-nitrophenyl	188–189 (cor.)	Nitromethane	$C_{23}H_{17}N_5O_6$	60.13	3.73	15.25	60.11	3.68	15.15
3,5-Dibromomesityl phenyl	187–188	Ethanol	$C_{23}H_{18}Br_2N_2$	57.28	3.76		57.50	3.97	
p-Bromophenyl mesityl	190–191	Ethanol	$C_{23}H_{19}BrN_2$	68.49	4.75		68.48	4.93	
o-Tolil	132–133	Methanol; aqueous ethanol; high-boiling petroleum ether	$C_{22}H_{18}N_2$	85.13	5.84		85.24	5.87	
o-Tolil[b]	197.5–198.5	Acetic acid; benzene-ethanol	$C_{22}H_{17}N_3O_2$	74.35	4.82		74.53	4.92	

[a] If the melting point bath was heated rapidly the quinoxaline softened at 180° and melted completely at 192.5–193.5°. If the bath was heated rapidly, partial melting occurred at 180–182° and the sample changed to a needle-like solid which melted at 198–199°.

[b] 4-Nitro-*o*-phenylenediamine prepared by the method of Heim (9) was used, the product was the corresponding nitro quinoxaline.

purified by distillation. The 3-nitroacetomesitylene was a yellow oil; b.p. 157–159° (8 mm.); m.p. 23°; n_D^{20} 1.5293; yield 84%.

Anal. Calc'd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32.
Found: C, 63.96; H, 6.45.

A mixture of 2 g. of 3-nitroacetomesitylene, 2 g. of hydroxylamine hydrochloride, 10 cc. of pyridine, and 10 cc. of absolute ethanol was heated under reflux for five hours. The ketone was recovered unchanged.

Schiff bases. Schiff bases were formed by the action of *o*-phenylenediamine with 3-nitromesityl-, 3-bromomesityl-, and 2,4,6-triisopropylphenyl-glyoxal. The product with 3-bromo-5-nitromesitylglyoxal appeared to be a quinoxaline. The properties of these compounds are shown in Table III.

3,5-Dinitro-2,4,6-triisopropylphenylglyoxylic acid. 2,4,6-Triisopropylphenylglyoxal was nitrated by a procedure similar to that of Hinkel, Ayling and Morgan (11). The glyoxal (2 g.) was added dropwise, with stirring, to a solution of 20 cc. of fuming nitric acid and 10 cc. of glacial acetic acid. The mixture was allowed to stand for five minutes and poured on ice. The product isolated was the dinitroglyoxylic acid. It was purified by recrystallization from high-boiling petroleum ether. It formed white needles; m.p. 90–92°.

Anal. Calc'd for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21.
Found: C, 63.67; H, 7.39.

A mixture of low-boiling petroleum ether and chloroform could also be used as a solvent for recrystallization. The keto acid did not yield a 2,4-dinitrophenylhydrazone by the usual procedure.

3,5-Dinitro-2,4,6-triisopropylacetophenone. 2,4,6-Triisopropylacetophenone (6) (15 g.) was added in small portions and with shaking to 150 cc. of fuming nitric acid. The mixture was cooled in an ice-bath during the addition and then poured on ice. The dinitro ketone was recrystallized from methanol and from dilute acetic acid. From the latter solvent it separated in white flakes; m.p. 144–145°.

Anal. Calc'd for $C_{17}H_{24}N_2O_5$: C, 60.69; H, 7.20; N, 8.33.
Found: C, 60.30; H, 7.33; N, 8.19.

3,5-Dinitromesityl 3-nitrophenyl diketone (VII). Ten grams of mesityl phenyl diketone (12) was added in small portions, with shaking, to an ice-cold solution of 100 cc. of fuming nitric acid. The mixture was allowed to stand for thirty minutes and poured on ice. The trinitro diketone was recrystallized from acetic acid. It formed yellow needles melting at 184–185° (cor.). The yield was nearly quantitative.

Anal. Calc'd for $C_{17}H_{13}N_3O_8$: C, 52.71; H, 3.38; N, 10.86.
Found: C, 52.77; H, 3.60; N, 10.85.

Cleavage of the diketone with hydrogen peroxide yielded a mixture of acids from which 3,5-dinitromesitoic acid (m.p. 230–231°) was isolated. The structure of the trinitro diketone was established by synthesis. It was formed by nitration of mesityl *m*-nitrophenyl diketone.

3-Nitromesityl phenyl diketone (V). To an ice-cold solution of 10 g. of mesityl phenyl diketone (12) in 17 cc. of acetic anhydride was added dropwise, with stirring and cooling, an ice-cold solution of 10 cc. of fuming nitric acid, 6 cc. of acetic acid, and 6 cc. of acetic anhydride. After the mixture had been stirred for one hour and fifteen minutes at room temperature, it was poured on ice. The nitro compound was recrystallized from ethanol and from high-boiling petroleum ether. It formed bright yellow needles melting at 89.5–90.5°.

Anal. Calc'd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09.
Found: C, 68.93; H, 5.25.

Treatment of the nitro diketone for three hours with hydrogen peroxide in boiling dioxane converted it to a mixture of benzoic and 3-nitromesitoic (13) acids.

Mesityl p-nitrobenzyl ketone. A solution of 40 g. of *p*-nitrophenylacetyl chloride (14) in 300 cc. of carbon disulfide was added, with stirring, to a mixture of 29 g. of mesitylene, 45 g. of dry aluminum chloride, and 100 cc. of carbon disulfide. During the thirty minutes required for the addition the mixture became black. After an additional five and one-half

TABLE III

REACTION PRODUCTS OF *o*-PHENYLENEDIAMINE AND CERTAIN GLYOXALS

GLYOXAL	MELTING POINT, °C.	CRYSTALLIZING SOLVENT	MOLECULAR FORMULA	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
3-Nitromesityl	258–258.5 (cor.)	High-boiling petroleum ether-benzene, dilute acetone	$C_{28}H_{26}N_4O_6$	65.36	5.09	65.56	5.30
3-Bromomesityl	165–167[a]	High-boiling petroleum ether, dilute ethanol, dilute acetic acid	$C_{28}H_{26}Br_2N_2O_2$	57.74	4.50	58.20	4.62
3-Bromo-5-nitromesityl	156–157 (decomp.)	Petroleum ether-benzene, dilute acetic acid, dilute ethanol	$C_{17}H_{14}BrN_3O_2$[b]	54.85	3.79	55.95 56.16	4.76 4.86
2,4,6-Triisopropylphenyl	173–174	Dilute ethanol	$C_{40}H_{52}N_2O_2$	81.03	8.84	81.16	8.75

[a] If the melting point bath was heated slowly the base softened at 177° and melted completely at 202°.

[b] This compound, presumably a quinoxaline, could not be obtained in pure form. Qualitative tests showed it to contain bromine and nitrogen.

hours of stirring, it was poured into a mixture of ice and hydrochloric acid. The crude mesityl *p*-nitrobenzyl ketone was distilled at reduced pressure and recrystallized from ethanol. It formed yellow needles melting at 96–97° (cor.); yield 28%.

Anal. Calc'd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05.
Found C, 72.17; H, 6.16.

3-Nitromesityl 4-nitrophenyl diketone (VI). A mixture of 5 cc. of fuming nitric acid, 3 cc. of acetic anhydride, and 10 cc. of glacial acetic acid was added dropwise, with cooling and stirring, to a solution of 4 g. of mesityl *p*-nitrophenyl diketone, 3 cc. of acetic acid, and 9 cc. of acetic anhydride. The mixture was poured on ice and the dinitro diketone (weight 4 g., m.p. 99–102°) was recrystallized from a mixture of high-boiling petroleum ether and benzene, and from ethanol; m.p. 99.5–101° (cor.).

Anal. Calc'd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12.
Found: C, 59.40; H, 4.01.

Mesityl m-nitrobenzyl ketone. A solution of 25.5 g. of *m*-nitrophenylacetyl chloride (15), 100 cc. of carbon disulfide, and 50 cc. of nitrobenzene was added dropwise, with stirring, to a mixture of 16 g. of mesitylene, 35 g. of anhydrous aluminum chloride, and 200 cc. of carbon disulfide. The reaction mixture was kept cold during the addition, then stirred at room temperature for five hours and finally allowed to stand for an additional twelve hours. The crude mesityl *m*-nitrobenzyl ketone was obtained in 94% yield after the impurities had been removed by steam distillation. It was recrystallized from ethanol and from a mixture of benzene and high-boiling petroleum ether. It formed white plates melting at 133.5–134.5° (cor.).

Anal. Calc'd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05.
Found: C, 72.13; H, 6.05.

3,5-Dibromesityl phenyl diketone (VIII). The diketone was prepared by the oxidation of 3,5-dibromo-2,4,6-trimethylbenzoin (16) by the action of copper sulfate in aqueous pyridine solution. It melted at 101–104°.

p-Bromobenzyl mesityl ketone. To a mixture of 3 g. of mesitylene, 14 g. of anhydrous aluminum chloride, and 100 cc. of carbon disulfide was added, with stirring, a solution of 5 g. of *p*-bromophenylacetyl chloride [b.p. 151.5–152° (25 mm.)] in 50 cc. of carbon disulfide. Decomposition of the mixture after two days' stirring at room temperature gave a 73% yield of the desoxybenzoin. It was recrystallized from dilute methanol, from dilute acetic acid, and from low-boiling petroleum ether. It separated from dilute acetic acid in silvery flakes melting at 82–83°.

Anal. Calc'd for $C_{17}H_{17}BrO$: C, 64.36; H, 5.40.
Found: C, 64.56; H, 5.75.

3,3',5,5'-Tetranitromesitil. Nitration of mesitil (17) with fuming nitric acid produced the tetranitro derivative. It was slightly soluble in acetic acid and dissolved readily in chloroform from which it was precipitated by the addition of ethanol. It was then recrystallized from a mixture of dioxane and ethanol; m.p. 317–319°, with decomposition.

Anal. Calc'd for $C_{20}H_{18}N_4O_{10}$: C, 50.64; H, 3.82.
Found: C, 50.83; H, 4.10.

Tetranitromesitil, like mesitil itself (18), did not react with *o*-phenylenediamine.

3,5-Dinitro-2,4,6-triisopropylphenyl 3-nitrophenyl diketone. Treatment of 4 g. of phenyl 2,4,6-triisopropylphenyl diketone (19) with fuming nitric acid produced a 72% yield of the trinitro derivative. It was recrystallized from acetic acid, from absolute ethanol, and from high-boiling petroleum ether. From ethanol it separated in small, bright yellow needles; m.p. 166–167°.

Anal. Calc'd for $C_{23}H_{25}N_3O_8$: C, 58.59; H, 5.35.
Found: C, 58.76; H, 5.49.

The diketone was recovered unchanged after treatment with *o*-phenylenediamine.

4,4'-Dimethoxy-2,6-xylil. A solution of 1.3 g. of this diketone (20), 1.1 g. of *o*-phenylenediamine, and 30 cc. of glacial acetic acid was boiled under reflux for three hours. The diketone was recovered almost quantitatively.

SUMMARY

Quinoxaline formation is made possible by the introduction of bromine atoms or nitro groups on the mesityl ring of mesitylglyoxal or mesityl phenyl diketone. In the benzil the effect persists even when the substituent is on the phenyl ring. The hydrogen bonding theory alone does not provide an adequate explanation of these observations.

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SOLUBILITIES OF HIGH MOLECULAR WEIGHT SYMMETRICAL NORMAL ALIPHATIC SECONDARY AMINES

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The physico-chemical properties of amines of the type R_2NH, where R represents an aliphatic chain containing more than six carbon atoms, have received little attention beyond measurements of the relative ionization constants of the higher homologs (1). Previous papers in this series have shown that the solubility curves of long-chain compounds, the fatty acids (2), ketones (3), nitriles (4), primary amines (5), amine salts (6), and amides, anilides, and N,N-diphenylamides (7), all conform to a characteristic pattern having a relatively steep initial slope, an abrupt change of slope at moderate dilutions, and a relatively flat slope at higher concentrations. The solubilities of the secondary amines have been investigated in order to compare them with those of other aliphatic compounds, particularly the primary amines. A study of the ketones (3) has shown that a polar group at the center of a long aliphatic chain does not change the characteristic shape of the solubility curves. In the aliphatic ketones, R—C(=O)—R, the carbon chain is continuous, while in the secondary amines, R—N(H)—R, the chain is interrupted by the presence of a nitrogen atom. The solubility behavior of the secondary amines is of unusual interest, since no solubility measurements have heretofore been made upon a series of compounds of this configuration. This paper presents the solubilities of dioctylamine, didodecylamine, ditridecylamine, ditetradecylamine, dipentadecylamine, and dioctadecylamine in fourteen organic solvents.

EXPERIMENTAL

The secondary amines were prepared by heating their respective primary amines for 5–6 hours at 200° in the presence of Raney nickel catalyst. The primary amines were of a purity comparable to that of those used in the previous solubility investigations (5). The dioctylamine was purified by fractionation *in vacuo* in a Stedman packed column. The other secondary amines were purified by repeated crystallization from ethanol-benzene mixtures in an atmosphere of nitrogen. The freezing points of these amines are listed in Table I.

The lower secondary amines, like numerous other aliphatic compounds such as oleic acid and some of the fatty acid esters, appear to be polymorphic. Two crystalline forms were observed for dioctylamine and didodecylamine. According to the usual custom, the lower-melting modification is arbitrarily designated the alpha (α) form, and the higher-melting the beta (β) form. In the case of dioctylamine, the α form precipitates as small needles and the β modification exists as characteristic long, narrow, scimitar-like blades 3 to 4 cm. or more in length. The crystalline forms of didodecylamine are not so well defined as those of the lower homolog.

The lower secondary amines react as readily with carbon dioxide as do the primary amines. A sample of dioctylamine saturated with CO_2 and titrated with standard hydrochloric acid indicated the addition of one mole of CO_2 to two moles of amine. This carbamate had the freezing point 36.6°. Hence, the reference melting points listed in Table I for dioctylamine are apparently the melting points of impure dioctylammonium dioctylcarbamate.

The solvents were those used for the previous solubility studies. They were freshly distilled and cooled without access to the atmosphere to prevent contamination with CO_2. The solubility measurements were made with the equipment and in the manner previously described (4, 6). Precautions were taken to prevent exposure of the secondary amines to CO_2.

TABLE I

FREEZING AND MELTING POINTS OF PURIFIED SECONDARY AMINES

AMINE	NO. OF C ATOMS	F.P., °C.	M.P., °C.	LIT. M.P., °C.
Dioctylamine	16	14.60	(α) 14.60 (β) 26.7	36.5 (8) 34 (9)
Didodecylamine	24	46.9	(α) 46.9 (β) 51.8	51–53 (9)
Ditridecylamine	26	56.5	56.5	—
Ditetradecylamine	28	60.6	60.6	56–58 (9)
Dipentadecylamine	30	63.3	63.3	—
Dioctadecylamine	36	72.3	72.3	71–72 (9)

RESULTS AND DISCUSSION

The solubility curves of the higher secondary aliphatic amines are similar to those of other fatty acid derivatives. The secondary amines again show the marked correlation between solubility and polarity of the solvents which is exhibited by the other aliphatic compounds of relatively low polarity, notably the ketones.

The secondary amines form simple eutectics with the non-polar solvents. These eutectic systems are illustrated graphically by the benzene (Fig. 1) and tetrachloromethane (Fig. 2) diagrams. The solubilities of the secondary amines in the non-polar solvents benzene, cyclohexane, and tetrachloromethane are listed in Tables II–IV, respectively.

In these solvents the secondary amines are most soluble in benzene and least soluble in tetrachloromethane. The compositions of the eutectics formed by the two modifications of dioctylamine with these solvents are as follows: in benzene, at 41.6% and −1.5° for the α form, and 36.7% and −0.4° for the β form; in cyclohexane, at 17.5% and −7.6°, and 12.7% and −2.8°, respectively; in tetrachloromethane, at 1.6% and −23.9°, and 0.7% and −23.4°, respectively. The eutectics of the other secondary amines with these solvents are located at much lower concentrations.

The solubilities of the secondary amines in the slightly polar solvents trichloromethane, ethyl ether, ethyl acetate, and butyl acetate are listed in Tables V–VIII, respectively. The solubility curves of the amines in ethyl acetate are shown graphically in Fig. 3.

While the secondary amines are generally more soluble in trichloromethane

than in most of the other solvents, their behavior in this solvent is not so striking as that of the primary amines. The solubilities of both crystalline forms of dioctylamine were determined in all of the above solvents. The solubilities of α-dioctylamine and of α-didodecylamine could not be determined in all of the solvents investigated since their transitions to the β modifications were either so rapid as to preclude observation, or the lower-melting form may not exist in the presence of the more polar solvents.

The solubilities of the secondary amines in acetone and in 2-butanone are listed in Tables IX and X. The solubility curves in acetone are shown in Fig. 4.

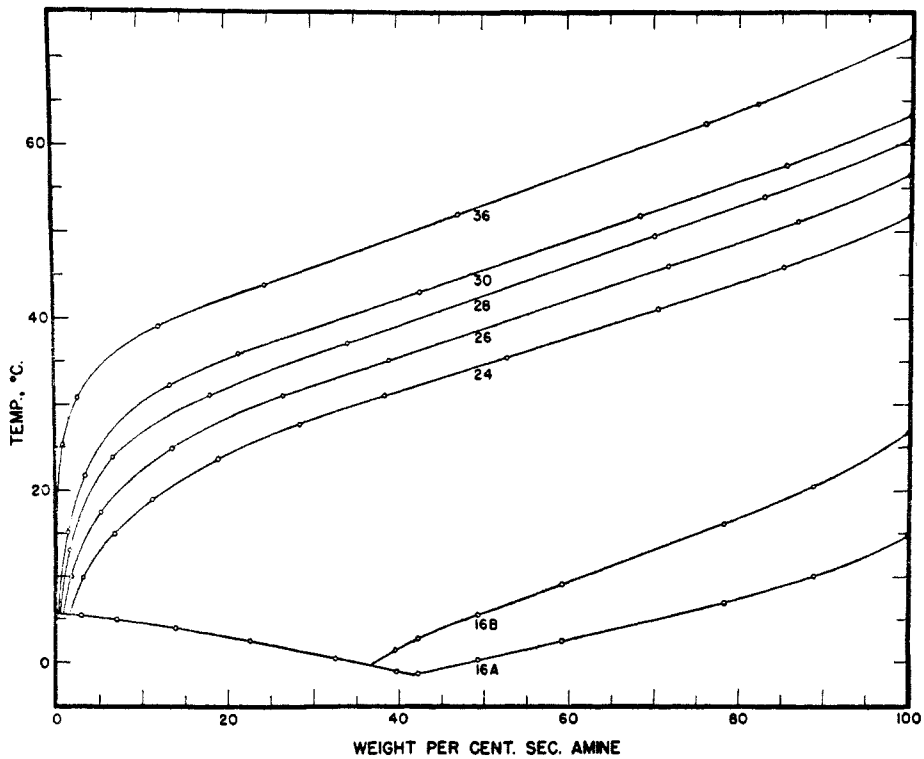

FIG. 1. SOLUBILITIES OF SECONDARY AMINES IN BENZENE
The numbers on the curves refer to the number of carbon atoms in each compound.

The secondary amines are similar to the other fatty derivatives previously investigated in that they are more soluble in 2-butanone than in acetone. They are, however, less soluble in these two solvents than in solvents of lower polarity.

The solubilities of the secondary amines in methanol, 95% ethanol, isopropanol, and *n*-butanol are listed in Tables XI–XIV, respectively. The behavior of the amines in these alcohols is illustrated by the curves in methanol (Fig. 5) and those in *n*-butanol (Fig. 6).

The secondary amines become progressively more soluble as the molecular weight of the alcohol increases, in the alcohols studied. As with a number of

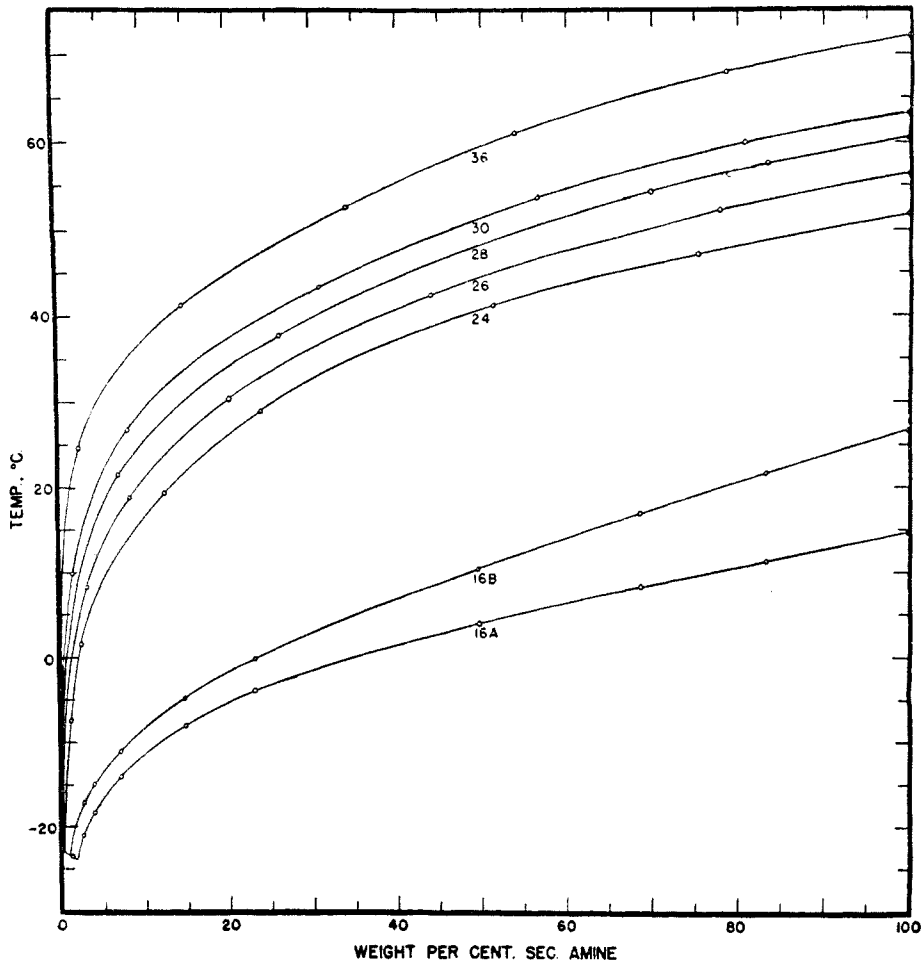

FIG. 2. SOLUBILITIES OF SECONDARY AMINES IN TETRACHLOROMETHANE

TABLE II

SOLUBILITIES OF SECONDARY AMINES IN BENZENE

NO. OF C ATOMS	G. PER 100 G. BENZENE					
	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
16 α	780	∞	∞	∞	∞	∞
16 β	160	710	∞	∞	∞	∞
24	3.3	14.6	54	205	2400	∞
26	1.7	8.0	31.4	116	505	∞
28	0.9	4.3	18.9	74	248	almost ∞
30	0.5	2.8	10.8	50	170	1130
36	<0.1	0.2	2.2	16.4	71	226

TABLE III

SOLUBILITIES OF SECONDARY AMINES IN CYCLOHEXANE

NO. OF C ATOMS	G. PER 100 G. CYCLOHEXANE					
	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
16 α	740	∞	∞	∞	∞	∞
16 β	122	650	∞	∞	∞	∞
24	2.2	12.4	46.0	182	2340	∞
26	1.0	6.3	24.5	101	500	∞
28	0.4	3.1	14.8	62	235	almost ∞
30	0.1	1.5	7.9	40.6	152	1100
36	—	<0.1	1.1	13.1	65	214

TABLE IV

Solubilities of Secondary Amines in Tetrachloromethane

No. of C atoms		G. per 100 g. tetrachloromethane					
		−10.0°	10.0°	20.0°	30.0°	40.0°	50.0°
16	α	13.2	330	∞	∞	∞	∞
	β	8.6	94	355	∞	∞	∞
24		0.7	5.9	15.0	34.0	89	845
26		0.3	3.8	10.0	24.5	61	220
28		0.1	2.3	6.3	17.1	43.2	122
30		—	1.4	4.4	12.0	32.1	84
36		—	0.2	1.2	4.6	15.1	40

TABLE V

Solubilities of Secondary Amines in Trichloromethane

No. of C atoms		G. per 100 g. Trichloromethane					
		−10.0°	10.0°	20.0°	30.0°	40.0°	50.0°
16	α	36.0	390	∞	∞	∞	∞
	β	26.0	139	435	∞	∞	∞
24		4.8	19.2	37.4	72	162	1275
26		2.5	11.5	24.4	50	106	325
28		1.1	6.5	15.7	36.2	79	195
30		0.5	4.3	11.5	26.7	59	139
36		—	0.5	2.8	9.8	25.8	62

TABLE VI

Solubilities of Secondary Amines in Ethyl Ether

No. of C atoms		G. per 100 g. ethyl ether					
		−10.0°	0.0°	10.0°	20.0°	30.0°	34.5°
16	α	17.0	58	255	∞	∞	∞
	β	9.6	30.9	89	308	∞	∞
24		—	0.2	2.1	9.1	32.5	59
26		—	—	0.1	3.9	19.6	37.5
28		—	—	—	1.2	10.5	20.4
30		—	—	—	0.1	5.7	12.5
36		—	—	—	—	0.3	1.7

TABLE VII

Solubilities of Secondary Amines in Ethyl Acetate

No. of C atoms		G. per 100 g. ethyl acetate					
		0.0°	20.0°	30.0°	40.0°	50.0°	60.0°
16	α	18.3	∞	∞	∞	∞	∞
	β	8.1	268	∞	∞	∞	∞
24		—	1.5	10.5	141	3230	∞
26		—	0.2	3.4	29.4	475	∞
28		—	—	1.1	7.9	131	almost ∞
30		—	—	<0.1	2.5	40.8	1050
36		—	—	—	<0.1	2.2	78

TABLE VIII

Solubilities of Secondary Amines in Butyl Acetate

No. of C atoms		G. per 100 g. butyl acetate					
		0.0°	20.0°	30.0°	40.0°	50.0°	60.0°
16	α	38.0	∞	∞	∞	∞	∞
	β	15.4	276	∞	∞	∞	∞
24		0.2	5.8	26.4	165	3230	∞
26		—	0.9	6.9	37.3	475	∞
28		—	—	1.7	10.5	131	almost ∞
30		—	—	0.1	2.5	40.8	1050
36		—	—	—	—	2.1	43.6

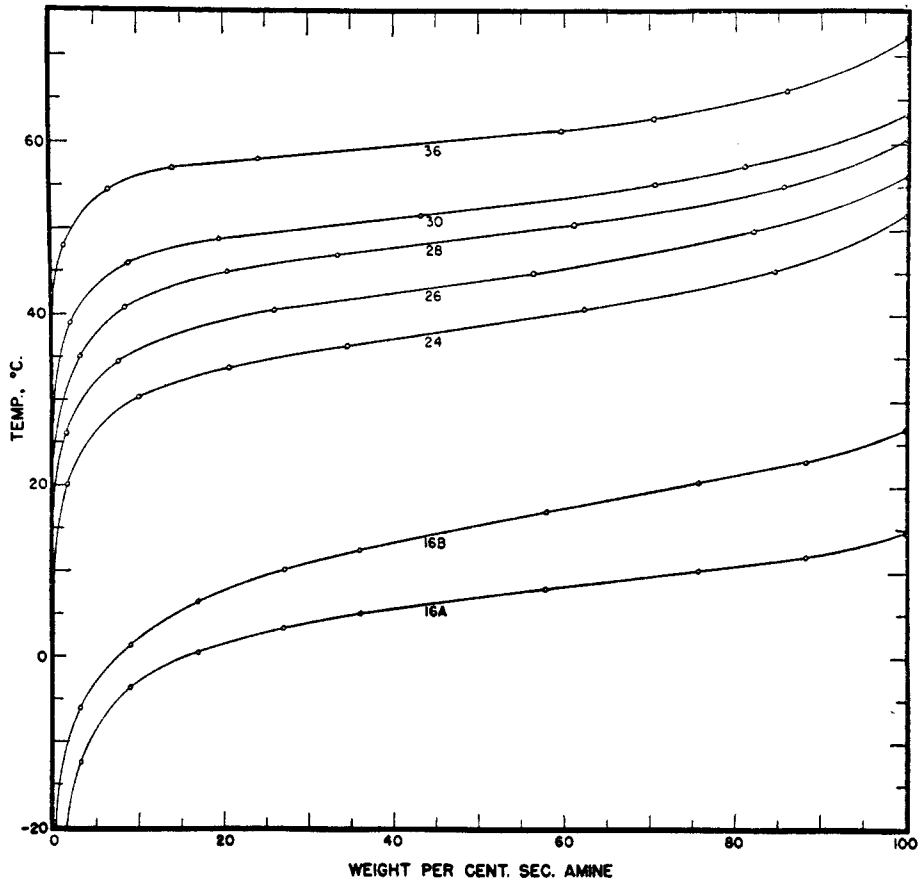

FIG. 3. SOLUBILITIES OF SECONDARY AMINES IN ETHYL ACETATE

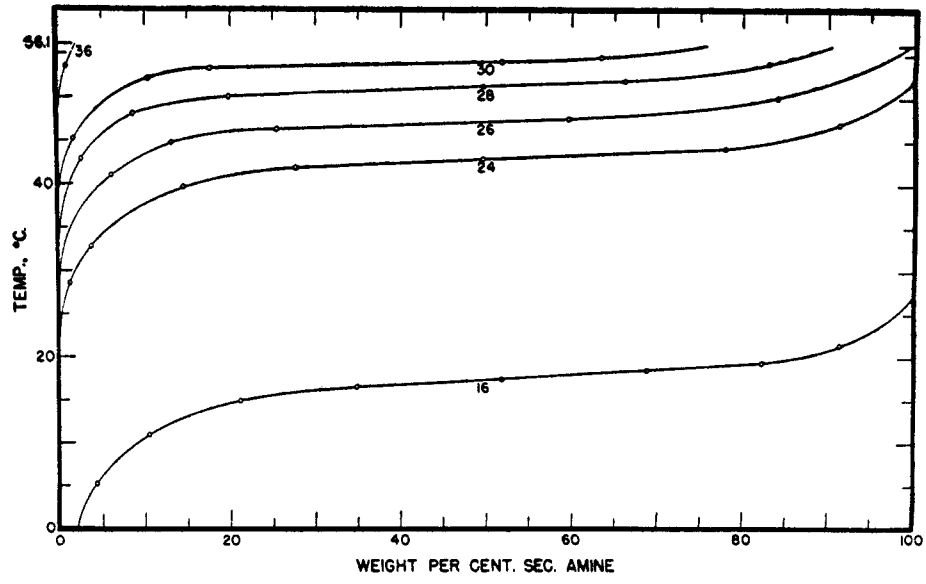

FIG. 4. SOLUBILITIES OF SECONDARY AMINES IN ACETONE

TABLE IX

Solubilities of Secondary Amines in Acetone

No. of C atoms	G. per 100 g. acetone					
	0.0°	20.0°	30.0°	40.0°	50.0°	56.1°
16	1.9	625	∞	∞	∞	∞
24	—	—	1.8	18.7	3900	∞
26	—	—	<0.1	5.2	505	almost ∞
28	—	—	—	1.1	22.5	900
30	—	—	—	<0.1	6.4	310
36	—	—	—	—	0.1	2.0

TABLE X

Solubilities of Secondary Amines in 2-Butanone

No. of C atoms	G. per 100 g. 2-butanone					
	0.0°	20.0°	30.0°	40.0°	50.0°	60.0°
16	4.9	650	∞	∞	∞	∞
24	—	1.3	13.0	178	4650	∞
26	—	<0.1	3.8	29.7	795	∞
28	—	—	0.5	9.4	222	almost ∞
30	—	—	—	3.6	55	2170
36	—	—	—	—	1.8	25.8

TABLE XI

Solubilities of Secondary Amines in Methanol

No. of C atoms	G. per 100 g. methanol					
	−10.0°	10.0°	30.0°	40.0°	50.0°	60.0°
16	58	665	∞	∞	∞	∞
24	—	—	4.3	710	5780	∞
26	—	—	—	7.2	32.1	38.5
28	—	—	—	—	14.0	17.0
30	—	—	—	—	2.5	8.0
36	—	—	—	—	—	0.6

TABLE XII

Solubilities of Secondary Amines in 95% Ethanol

No. of C atoms	G. per 100 g. 95% ethanol					
	−10.0°	10.0°	30.0°	40.0°	50.0°	60.0°
16	4.6	63	∞	∞	∞	∞
24	—	0.2	19.5	185	3350	∞
26	—	—	4.5	43.1	655	∞
28	—	—	0.4	7.8	233	almost ∞
30	—	—	—	1.8	66	1640
36	—	—	—	—	≈0.1	4.9

TABLE XIII

Solubilities of Secondary Amines in Isopropanol

No. of C atoms	G. per 100 g. isopropanol					
	−10.0°	10.0°	30.0°	40.0°	50.0°	60.0°
16	26.8	233	∞	∞	∞	∞
24	—	2.6	55	297	4080	∞
26	—	—	9.8	79	740	∞
28	—	—	0.6	13.9	269	almost ∞
30	—	—	—	2.6	71	1700
36	—	—	—	—	1.2	13.4

other aliphatic compounds, the solubilities of the amines above dioctylamine become so limited in methanol that a region of two immiscible solutions appears in the systems.

TABLE XIV

SOLUBILITIES OF SECONDARY AMINES IN *n*-BUTANOL

NO. OF C ATOMS	G. PER 100 G. *n*-BUTANOL					
	−10.0°	10.0°	30.0°	40.0°	50.0°	60.0°
16	45.9	282	∞	∞	∞	∞
24	0.4	3.4	62	312	4250	∞
26	—	1.0	18.2	103	700	∞
28	—	0.1	6.4	31.9	250	almost ∞
30	—	—	1.0	11.2	100	1330
36	—	—	—	0.2	5.4	63

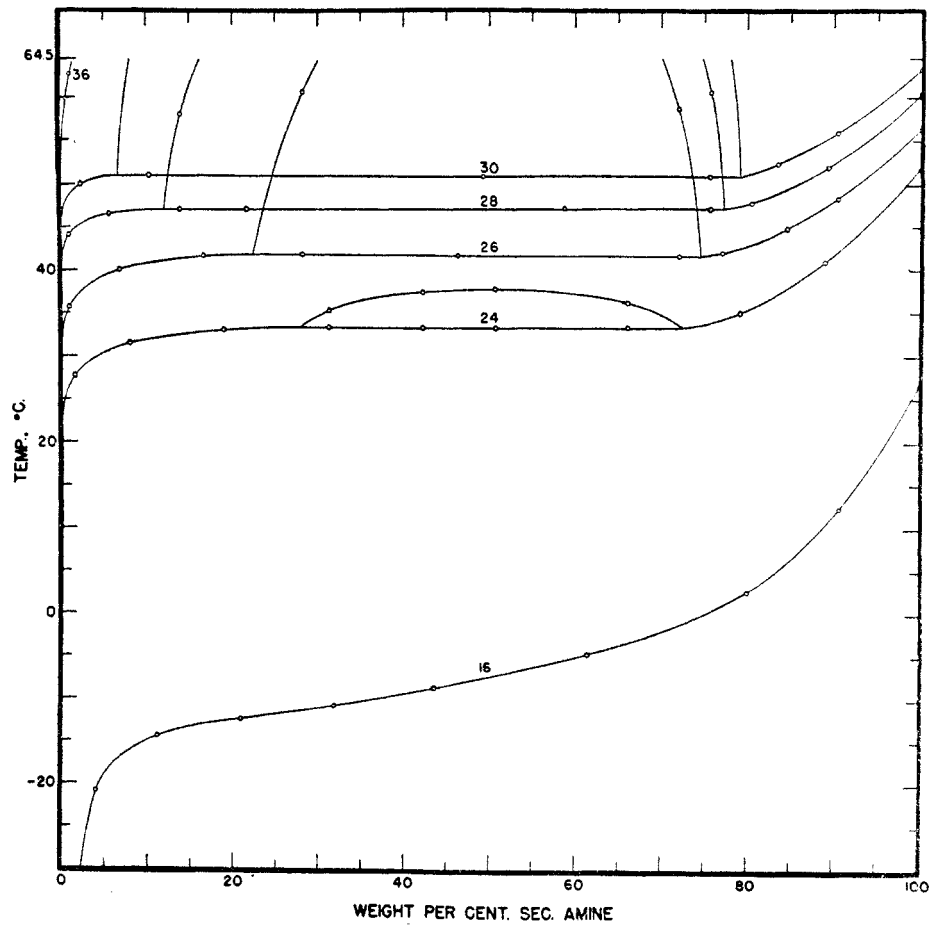

FIG. 5. SOLUBILITIES OF SECONDARY AMINES IN METHANOL

The solubilities of the secondary amines in acetonitrile are listed in Table XV The secondary amines are less soluble in this highly polar solvent than in any

other solvent investigated. All of these amines are of such limited solubility that their systems with acetonitrile over almost the entire concentration range

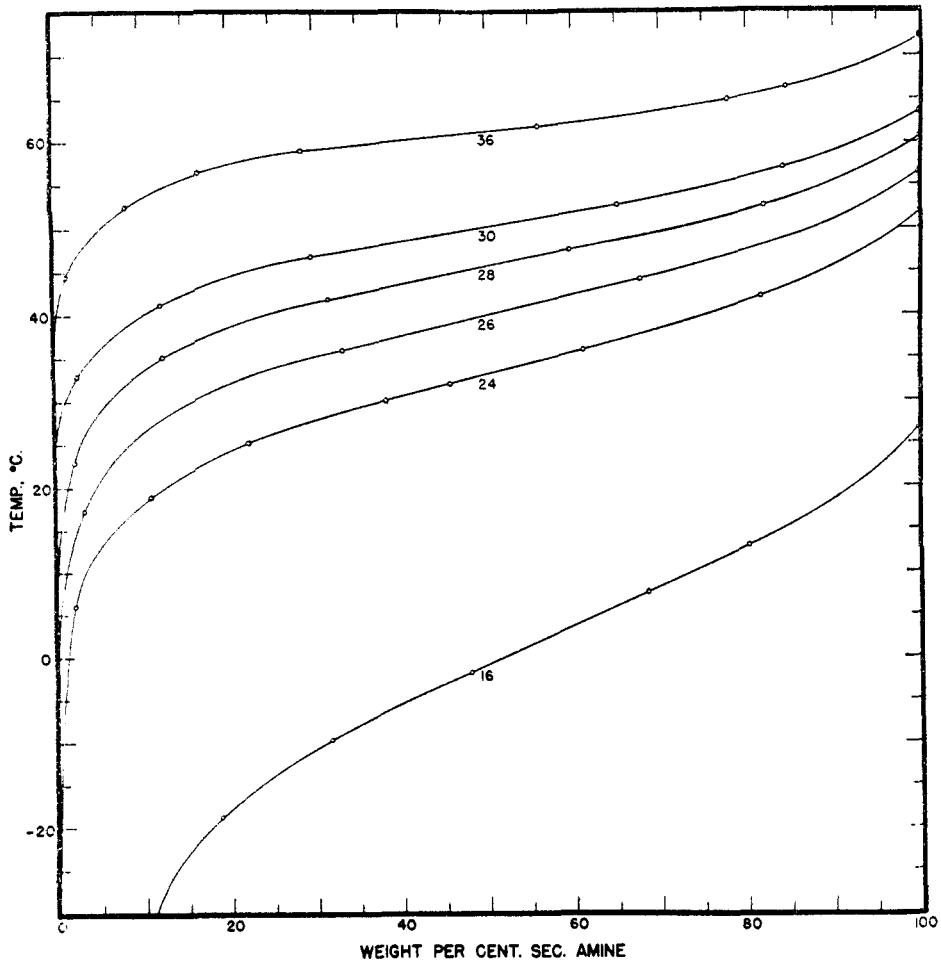

FIG. 6. SOLUBILITIES OF SECONDARY AMINES IN *n*-BUTANOL

TABLE XV

SOLUBILITIES OF SECONDARY AMINES IN ACETONITRILE

	G. PER 100 G. ACETONITRILE					
NO. OF C ATOMS	20.0°	30.0°	40.0°	50.0°	60.0°	70.0°
16	3.4	5.4	7.0	9.1	11.5	14.9
24	—	—	0.2	1.9	2.4	3.2
26	—	—	—	0.5	1.4	2.0
28	—	—	—	—	1.0	1.4
30	—	—	—	—	0.3	1.0
36	—	—	—	—	<0.1	0.7

consist of areas of two conjugate solutions, which is similar to their behavior in methanol.

In general, the secondary amines are more soluble in organic solvents than are primary amines of corresponding chain length. This behavior is apparently due to the fact that the polar group in the center of the paraffin chain causes the melting points of secondary amines to be considerably lower than those of primary amines containing the same number of carbon atoms. If a temperature correction is made for the difference in melting points, the solubility curve of any secondary amine can be practically superimposed upon that of the primary amine of equal chain length in any given solvent. Compared in this manner, the secondary amines tend to be slightly more soluble in non-polar solvents, and somewhat less soluble in the highly polar solvents, than the corresponding primary amines.

The previous papers of this series have suggested the probability that the characteristic shape of the solubility curves of aliphatic compounds may be due to some form of intermolecular association. Several attempts (10) have been made to explain this behavior on the basis of hydrogen bonding at the polar group. The solubilities of the nitriles, primary amines, and secondary amines, which have relatively weak polar groups, tend to suggest that the shapes of the solubility curves are probably due primarily to association of the paraffin chains, with the possibility that the more polar compounds such as the acids and amides may be further associated at the polar groups. Subsequent papers on the tertiary amines, alcohols, and hydrocarbons will deal further with this explanation of the behavior of high molecular weight aliphatic compounds in organic solvents.

SUMMARY

The solubilities of dioctylamine, didodecylamine, ditridecylamine, ditetradecylamine, dipentadecylamine, and dioctadecylamine have been determined in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl ether, ethyl acetate, butyl acetate, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, and acetonitrile.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

SOME LONG-CHAINED ORGANOMETALLIC COMPOUNDS

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In connection with studies on long-chained types, an examination has been made of some organometallic compounds.

Sodium, Potassium, and Calcium. The RNa, RK and RCaI types examined are insoluble in hydrocarbons including the kerosene fractions. Incidental to the preparation of these RM compounds, there are formed R(—H), RH, and R·R hydrocarbons as a consequence of disproportionation and coupling reactions. The preparation of *n*-dodecylsodium in low yields in ether is of interest because of the ready cleavage of ether by simpler alkylsodium compounds.

Lithium. The RLi compounds (where R = $C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$, and $C_{18}H_{37}$) can be prepared in several solvents, but the one of choice appears to be petroleum ether (b.p. 60–70°). The RCl compounds are most suitable for the preparation of the RLi types. 1,2,3-Trimethoxybenzene is metalated by *n*-dodecyllithium in an *ortho*-position, to give subsequent to carbonation 2,3,4-trimethoxybenzoic acid.

Mercury. The long-chained organomercury halides are not particularly suitable as derivatives for rigid differentiation of contiguous even-membered types. For example, $C_{16}H_{33}HgCl$ melts at 114–115°, $C_{18}H_{37}HgCl$ melts at 115–116°, and a mixture of equal parts of these RHgCl compounds melts at 113°. The Experimental Part contains a discussion of some regularities in melting points, and also a broad tabular comparison of mixed melting points.

Tin and Lead. The trialkytin chlorides and the trialkyllead chlorides show greater differences in melting point between homologs than do the alkylmercury chlorides. However, they are only of limited applicability as derivatives for differentiation of contiguous even-membered homologs because of the small melting point depressions of mixtures (see Table IV). It is interesting to note that $(C_{16}H_{33})_4Sn$ melts at 41.5–42.5°, $(C_{16}H_{33})_4Pb$ melts at 42°, and a mixture of equal parts of these R_4M compounds melts at 42°. Two R_4M compounds of high molecular weight were prepared: $(C_{16}H_{33})_4Pb$, 1107; and $(C_{18}H_{37})_4Sn$, 1130.

Arsenic. Tri-*n*-dodecylarsenic distils at 200°/0.009 mm., but tri-*n*-tetradecylarsenic underwent marked decomposition on an attempted distillation.

EXPERIMENTAL

Organosodium compounds. The procedures for the preparation of the long-chained organosodium compounds were essentially those described by Morton and co-workers (1). *n*-Dodecyl chloride and *n*-hexadecyl chloride were used with powdered sodium. Reaction generally started within 15 minutes; the length of the induction period depended largely

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on the temperature. The start of the reaction was marked by the darkening of the sodium, and the mixture subsequently turned brown and became a sludge. In most cases the mixture was carbonated by pouring directly into a mixture of solid carbon dioxide and ether or petroleum ether. In a few cases carbonation was effected by passing in dry gaseous carbon dioxide. Rapid carbonation converted dodecylsodium to tridecylic acid; slow carbonation gave a mixture of tridecylic acid and undecylmalonic acid. An explanation for the formation of malonic acids in slow carbonations was suggested recently (2).

In one of a number of experiments carried out with *n*-dodecyl chloride (0.0576 mole) and sodium (0.252 g. atom) in petroleum ether (b.p. 28–38°) at 14–25°, the yield of acids was 20.3%; the yield of dodecane was 27%; of dodecene, 25%; and of tetracosane, 19.5%. A similar experiment in ether at 0° gave 0.9% of acids; 71.5% of a mixture of dodecane and dodecene (20%); and 10.3% of tetracosane.

n-*Dodecylpotassium.* Clean potassium metal (8.6 g. or 0.22 g. atom) was powdered by heating under xylene to 75° and shaking. Petroleum ether (b.p. 60–70°) was added to make the metal sand sink more quickly; the solvents were decanted and replaced by petroleum ether (b.p. 28–38°).

The potassium sand was flushed into a 250-cc. three-necked flask filled with nitrogen. About 90 cc. of solvent was used. The flask was cooled in a bath of petroleum ether and dry ice to about 0°. Then 2.2 g. (0.05 mole) of *n*-dodecyl chloride was added during one hour. A color test I (3) was positive 45 minutes from the start. Color test IV (4) was also positive. The mixture was allowed to warm to room temperature. The supernatant liquid was clear and colorless, and gave a negative color test I. The suspension was poured into dry ice after a total of four hours. The mixture was decomposed with methanol, hydrolyzed, and acidified. The organic layer was dried and distilled to yield: (a) dodecane (36.8%); (b) dodecene (16.1%); (c) tridecylic acid (10.3%); (d) tetracosane (23.7%).

Organolithium compounds. The general procedures were those described in recent publications from this laboratory (5).

Diethyl ether. In general, the RCl compounds were more effective than the RBr compounds, and no examination was made of the RI compounds. The duplicability of results when RBr compounds were used varied somewhat, and freshly distilled RBr compounds are recommended. The yields, by the single acid titration analytical procedure of some comparable experiments are as follows: *n*-$C_{12}H_{25}Br$ (48%, 65%); *n*-$C_{12}H_{25}Cl$ (100%); *n*-$C_{14}H_{29}Br$ (64%); *n*-$C_{16}H_{33}Cl$ (100%); *n*-$C_{18}H_{37}Br$ (56%). Carbonation of the RLi compound prepared from *n*-$C_{16}H_{33}Cl$ gave 51% of margaric acid. In the RLi preparation from *n*-$C_{12}H_{25}Cl$, the yield calculated by the double-titration procedure of A. H. Haubein (using benzyl chloride) was 76.6%. This yield of 76.6% obtained after one hour, dropped to 41.4% at the end of 53 hours, and to 0% after 143 hours. As has been shown in other studies, the drop in yield is due to ether cleavage.

Petroleum ether (b.p. 30–35°). The RBr compounds appear to be unsatisfactory for the preparation of RLi compounds in low-boiling petroleum ether. The yields, by the single acid titration of some comparable experiments are as follows: *n*-$C_{12}H_{25}Cl$ (72%); *n*-$C_{16}H_{33}Cl$ (63%). In titration in petroleum ether and in benzene, the addition of alcohol hastens the diffusion of lithium from the organic to the aqueous layer and enables the titration to be carried out rapidly. In the *n*-$C_{12}H_{25}Cl$ experiment, undried, unpurified "Skelly A" (petroleum ether b.p. 28–38°) was used instead of the unsaturate-free solvent, and reaction was started with a little *n*-butyl bromide. After carbonation there was obtained: dodecane (5%); dodecene (4%); tetracosane (28%); and tridecylic acid (36%). Among the products obtained by carbonating the RLi compound from *n*-$C_{16}H_{33}Cl$ were: a mixture of cetane and cetene (14%); dotriacontane (about 20%); margaric acid (27%); and impure dihexadecyl ketone (23.5%). The ketone melted at 86–87°, and its oxime at 60°.

Anal. Calc'd for $C_{33}H_{67}NO$: N, 2.83. Found: N, 3.33.

Petroleum ether (b.p. 60–70°). This petroleum ether appears more satisfactory than the lower-boiling fractions, the yields being better and the time of preparation being signifi-

cantly reduced. The solvent containing the lithium was first boiled, and then the alkyl halide was added during rapid refluxing. No stirring appeared necessary. The reaction was complete in about one hour, during which time the metal gradually sank to the bottom of the flask. The yield of RLi from n-$C_{12}H_{25}Cl$ ranged from 80.3% to 86.2%. With a mixture of equal volumes of pet. ether (b.p. 30–35° and b.p. 60–70°) and a time of 3.5 hours, the yield of n-$C_{12}H_{25}Li$ was 81%; and with a mixture of pet. ether (b.p. 60–70° and b.p. 77–115°) and a time of 1.5 hours, the yield was 77.8%. The pet. ether (b.p. 60–70°) probably can be used effectively with lower RCl compounds, because the yield of n-$C_5H_{11}Li$ from n-$C_5H_{11}Cl$ in one hour was 86.8%.

Aromatic hydrocarbons.—Ziegler and Colonius (6) have shown that benzene is a good medium for the preparation of some RLi compounds. From n-$C_{12}H_{25}Cl$ in benzene and with 15-hour period of reaction, the yield of n-$C_{12}H_{25}Li$ was 83.4%. Carbonation of this preparation gave a 23% yield of tridecylic acid, and the absence of benzoic acid showed that no metalation took place. There was also isolated, as a product of the carbonation, didodecyl ketone (m.p. 73–74°), the oxime of which melted at 47–48°.

Anal. Calc'd for $C_{25}H_{51}NO$: N, 3.67. Found: N, 3.58.

The yield of n-$C_{12}H_{25}Li$ from n-$C_{12}H_{25}Cl$ in toluene (one hour) was 28.3%. From n-$C_{12}H_{25}Br$ in benzene (one hour), the yield of n-$C_{12}H_{25}Li$ was 37%.

Metalation of 1,2,3-trimethoxybenzene by n-*dodecyllithium.* A mixture of 5.4 g. (0.032 mole) of 1,2,3-trimethoxybenzene and 105 cc. of 0.3 N dodecyllithium in pet. ether (b.p. 60–70°) was allowed to stand for 15 hours at room temperature, and then poured into solid carbon dioxide and ether. The 2,3,4-trimethoxybenzoic acid isolated melted at 98–100°. The m.p. reported by Will (7) is 99°.

Anal. Calc'd for $C_{10}H_{12}O_5$: Neut. equiv., 223. Found: Neut. equiv., 228.

n-*Hexadecylcalcium iodide.* Four and eight-tenths grams of calcium was filed directly into 25 cc. of ether in a nitrogen-filled three-necked flask. To this were added a small crystal of iodine, and 0.9 g. of iodobenzene. The mixture was refluxed for an hour; color test I was then strongly positive. The ether solution of phenylcalcium iodide was decanted, and the calcium washed twice with ether to remove any phenylcalcium iodide (as shown by a negative color test I).

The calcium, activated by the above procedure, was then covered with 30 cc. of ether, and 14.1 g. (0.04 mole) of n-hexadecyl iodide in 20 cc. of ether was added slowly. Reaction set in at once; there was spontaneous refluxing, and a voluminous white precipitate formed. The mixture was allowed to stand overnight, then was warmed (since at room temperature it was nearly solid), stirred and refluxed.

The mixture was filtered through asbestos under nitrogen. The filtrate gave a positive color test, and by acid titration analysis gave a yield of 14.2% of RCaI. The residue was washed with 50 cc. of petroleum ether (b.p. 28–38°) and these washings gave no color test, indicating the essential insolubility of RCaI in the petroleum ether. The washed residue did give a color test.

The ether filtrate was carbonated by solid carbon dioxide, and the ether solution was then dried and distilled. The products isolated were: (a) a mixture of hexadecene (12%) and hexadecane (24%); (b) margaric acid (12.6%); and (c) dotriacontane (residue) (41%).

Organomercury compounds. The organomercury halides were prepared from the Grignard reagent and a mercuric halide. In essential accordance with the procedure of Gilman and Brown (8), the mercuric halide was conveniently and automatically dissolved from a Soxhlet thimble into the RMgX solution. Analyses for mercury were by the method of Tabern and Shellberg (9).

Melting points of organomercury compounds. An examination of the melting points in Table II indicates that for each group of RHgX compounds of an even number of carbon atoms, the melting points appear to be at the minimum for the dodecylmercuric salts. It was shown earlier by Vaughn, Spahr, and Nieuwland (10) that there was an alternation of melting point with even and odd members. Some of the trends indicated in Table II

TABLE I

ORGANOMERCURY COMPOUNDS

REACTANTS	PRODUCT	M.P. °C	ANAL. % Hg	
			Calc'd	Found
n-$C_{12}H_{25}MgBr$ + $HgBr_2$	$C_{12}H_{25}HgBr$[a]	108–108.7	44.60	45.37
n-$C_{12}H_{25}HgBr$ + AgOAc	$C_{12}H_{25}HgOAc$[b]	64–65	46.75	46.5
$(n$-$C_{12}H_{25})_2Hg$ + $HgCl_2$	$C_{12}H_{25}HgCl$[c]	114–114.5	49.5	49.2
$(n$-$C_{12}H_{25})_2Hg$ + HgI_2	$C_{12}H_{25}HgI$[d]	91	40.37	40.18
$(n$-$C_{12}H_{25})_2Hg$ + $Hg_3(PO_4)_2$	$(C_{12}H_{25}Hg)_3PO_4$[e]	84–86	49.97	49.49
$(n$-$C_{12}H_{25})_2Hg$ + $HgSO_4$	$(C_{12}H_{25}Hg)_2SO_4$[f]	160–161	47.99	48.10
n-$C_{14}H_{29}MgBr$ + $HgBr_2$	$C_{14}H_{29}HgBr$[g]	110–110.5	41.98	42.53, 42.69
n-$C_{16}H_{33}MgBr$ + $HgBr_2$	$C_{16}H_{33}HgBr$[h]	110.5–111.5	39.65	40.42, 40.15
$(n$-$C_{16}H_{33})_2Hg$ + $HgCl_2$	$C_{16}H_{33}HgCl$[i]	114–115	43.46	43.25
$(n$-$C_{16}H_{33})_2Hg$ + HgI_2	$C_{16}H_{33}HgI$[j]	93–93.5	36.28	35.98
n-$C_{18}H_{37}MgBr$ + $HgBr_2$	$C_{18}H_{37}HgBr$[k]	110–111	37.57	37.28
$(n$-$C_{18}H_{37})_2$ Hg + $HgCl_2$	$C_{18}H_{37}HgCl$[l]	115–116	40.97	41.20
n-$C_{18}H_{37}HgCl$ + NaCN	$C_{18}H_{37}HgCN$[m]	98.5–99	41.80	41.56, 41.46
n-$C_{12}H_{25}MgBr$ + n-$C_{12}H_{25}HgBr$	$(C_{12}H_{25})_2Hg$[n]	44–44.5	37.20	37.44
n-$C_{14}H_{29}MgBr$ + n-$C_{14}H_{29}HgBr$	$(C_{14}H_{29})_2Hg$[o]	53–54	33.70	33
n-$C_{16}H_{33}MgBr$ + n-$C_{16}H_{33}HgBr$	$(C_{16}H_{33})_2Hg$[p]	61–62	30.79	30.96
n-$C_{18}H_{37}MgBr$ + n-$C_{18}H_{37}HgBr$	$(C_{18}H_{37})_2Hg$[q]	66.5–67	28.35	28.35

[a] The crude material melted at 100–110° and weighed 10.87 g. (53.8%). Two crystallizations from ethanol gave the m.p. recorded.

[b] The reaction was carried out in 95% ethanol, and the product was crystallized from petroleum ether.

[c] Reaction was effected in refluxing 95% ethanol solution, and crytallization was from 95% ethanol.

[d] Reaction was effected by refluxing for 15 minutes in dry ether, and crystallization was from petroleum ether.

[e] Reaction was in absolute ethanol, and recrystallization first from petroleum ether and then from ethanol.

[f] Reaction was in a mixture of dry ether and absolute ethanol; and crystallization was from 95% ethanol.

[g] The product was crystallized from ethanol. Analyses for bromine by the Parr bomb procedure were low: Calc'd Br, 16.73. Found: Br, 14.3 and 14.3.

[h] The first crystallization of the 63.3% yield of RHgBr from petroleum ether (b.p. 60–70°) gave a product melting at 110–111°. Recrystallization from ethyl acetate raised the m.p. to 110.5–111.5°.

[i] Reaction was carried out in ether. Crystallization was first from petroleum ether (b.p. 77–115°) and then from ethyl acetate.

[j] Reaction was carried out by refluxing in ether for 15 minutes. Recrystallization was from petroleum ether (b.p. 60–70°).

[k] The product was twice crystallized from petroleum ether (b.p. 77–115°). This compound was prepared earlier by D. F. Pontz, but the analytical results were not confirmatory.

[l] Reaction was in ether, and recrystallization was from petroleum ether (b.p. 77–115°). This compound was prepared earlier by D. F. Pontz, but the analytical results for mercury were not confirmatory.

[m] This compound was prepared by D. F. Pontz by refluxing in 95% ethanol with two equivalents of NaCN for two hours. The yield was 85.7% and the compound was crystallized either from acetic acid or from 95% ethanol.

[n] The compound was crystallized from ethyl acetate and methanol.

[o] Recrystallization was from ethyl acetate.

[p] Recrystallization was from petroleum ether (b.p. 30–38°).

[q] The recrystallization was first from ethyl acetate and then from petroleum ether (b.p. 60–68°). D. F. Pontz prepared this compound earlier from reaction of octadecylmercuric chloride and bromide with octadecylmagnesium bromide, but his analyses for mercury were not in agreement with the expected R_2Hg compound. He also prepared the compound from n-octadecylmercuric bromide and n-octadecyllithium.

suggested a re-examination of the melting points of hexadecylmercury chloride, bromide, and iodide which were previously (11) reported as melting at 102°, 101.5°, and 82°, respectively. An article by Rumpf (13) has just been abstracted in *Chemical Abstracts* on the melting points of some of the RHgX types listed in Table II, and there is good agreement with the values reported. The one exception is the melting point of *n*-dodecylmercury chloride for which the value of 111.5° is reported.

The melting points reported in Table I for the R_2Hg compounds show a regular gradation with chain length. The relationship may be expressed as $M = 32 + 13\sqrt{n - 11}$ where M is the melting point (Centigrade) and n is the number of carbon atoms in the alkyl group. Incidentally, the dialkylmercury compounds reported are very soluble in petroleum ether and in ether, but very slightly soluble in alcohol.

Organolead compounds. The organolead compounds described in Table III were prepared as indicated. Lead analyses were in accordance with the procedure of Gilman and Robinson (14).

Tetradodecyltin. To 64 cc. of a 0.843 *N* solution of *n*-dodecylmagnesium bromide (0.054 mole), was added 4.7 g. (0.018 mole) of stannic chloride in 15 cc. of benzene. After refluxing for three and one-half hours, the mixture was hydrolyzed. Recrystallization of the 5.4 g.

TABLE II

MELTING POINTS OF ALKYLMERCURIC HALIDES

R	RHgCl	RHgBr	RHgI
Ethyl	192 (11)	198 (11)	186 (11)
n-Butyl	130 (11)	129.9–130 (10)	117 (11)
n-Hexyl	125 (11)	122.0–122.2 (10)	110 (11)
n-Octyl	115–115.5 (12)	114.8–115.0 (10)	—
n-Decyl	—	111.0–111.4 (10)	—
n-Dodecyl	114–114.5	108–108.7	91
n-Tetradecyl	—	110–110.5	—
n-Hexadecyl	114–115	110.5–111.5	93
n-Octadecyl	115–116	110–111	—

(45%) of crude material from ether and ethyl acetate removed the tetracosane. The tetradodecyltin melted at 15–16° to a turbid liquid which was clear at 21°; n_D^{30} 1.4692; n_D^{20} 1.4736.

Anal. Calc'd for $C_{48}H_{100}Sn$: Sn, 14.91. Found: Sn, 15.18.

The analysis for tin in the several organotin compounds reported here was by the method of Gilman and King (15), and it was found that the use of bromine is not necessary with these relatively non-volatile compounds.

Tetratetradecyltin. To 0.087 mole of *n*-tetradecylmagnesium bromide in ether was added 5.5 g. of stannic chloride. After refluxing for one hour and then standing overnight, the mixture was hydrolyzed, the ether was removed, and the residue was treated with ethyl acetate to dissolve out the R_4Sn compound and leave the octacosane (1.7 g.). The crude tetratetradecyltin (12.7 g. or 66%) was crystallized from ethyl acetate to give 8.6 g. of pure product melting at 33–34°.

Anal. Calc'd for $C_{56}H_{116}Sn$: Sn, 13.07. Found: Sn, 12.92.

Tetrahexadecyltin. To 102 cc. of 0.378 *N* *n*-hexadecylmagnesium bromide was added 2.5 g. of stannic chloride in benzene. After the customary procedures, the 7.5 g. (76%) of crude tetrahexadecyltin (m.p. 36–41°), was twice crystallized from ether and melted at 41.5–42.5°.

Anal. Calc'd for $C_{64}H_{132}Sn$: Sn, 11.63. Found: Sn, 11.84.

Tetraoctadecyltin. From a reaction between *n*-octadecylmagnesium bromide (0.0392 mole) and stannic chloride (0.0087 mole) was obtained 5.6 g. (56.8%) of pure tetraoctadecyltin which melted at 47° after being crystallized three times from ethyl acetate.

Anal. Calc'd for $C_{72}H_{148}Sn$: Sn, 10.48. Found: Sn, 10.36.

Tridodecyltin chloride. An ethereal solution of tetradodecyltin was saturated with dry hydrogen chloride; the tube was then stoppered and set aside overnight. Recrystallization from ethyl acetate and methanol, and then from ether-ethanol gave crystals melting at 33°.

TABLE III

ORGANOLEAD COMPOUNDS

REACTANTS	PRODUCT	M.P., °C.	ANAL. % Pb	
			Calc'd	Found
n-$C_{12}H_{25}MgBr$ + $PbCl_2$	$(C_{12}H_{25})_3PbCl$[a]	63.5	27.60	27.46
$(C_{12}H_{25})_3PbCl$ + $AgNO_3$	$(C_{12}H_{25})_3PbNO_3$[b]	44–45	26.66	26.98
$(C_{12}H_{25})_3PbCl$ + AgOAc	$(C_{12}H_{25})_3PbOAc$[c]	59	26.76	26.90
n-$C_{14}H_{29}MgBr$ + $PbCl_2$	$(C_{14}H_{29})_3PbCl$[d]	74–75	24.8	24.8
n-$C_{16}H_{33}MgCl$ + $PbCl_2$	$(C_{16}H_{33})_3PbCl$[e]	79–80	22.55	22.67
n-$C_{18}H_{37}MgBr$ + $PbCl_2$	$(C_{18}H_{37}PbCl$[f]	82–83	20.66	20.71
$(C_{14}H_{29})_3PbCl$ + $C_{14}H_{29}MgBr$	$(C_{14}H_{29})_4Pb$[g]	31	20.78	20.92
$(C_{16}H_{33})_3PbCl$ + $C_{16}H_{33}MgBr$	$(C_{16}H_{33})_4Pb$[h]	42	18.68	18.56

[a] The compound was purified by recrystallization from ethyl acetate. In order to establish more definitely that the product was tridodecyllead *chloride* and not the bromide, a synthesis was carried out using dodecylmagnesium *chloride* and lead chloride. The product of this reaction melted at 64–65°, and a mixed m.p. with the product obtained by starting with n-dodecylmagnesium bromide was 63–64°.

[b] The reaction was carried out in absolute ethanol, and crystallization was from ethyl acetate.

[c] Reaction was effected in 95% ethanol, and the product crystallized out on cooling.

[d] A first crystallization from petroleum ether left a yellow insoluble solid which may have been some R_3Pb compound. Final crystallization from ethyl acetate raised the m.p. one degree to 74–75°. A chlorine analysis by the Parr bomb procedure gave a low analysis: Calc'd, Cl, 4.25; Found, 2.48. Chlorine analyses of some organometallic compounds by this procedure are often low.

[e] The solids obtained after hydrolysis by ammonium chloride solution were first extracted (Soxhlet) with chloroform. The product obtained from the chloroform solution was first crystallized from ethyl acetate and then from petroleum ether.

[f] The Grignard reagent was filtered as usual, and this served to remove most of the coupling product (hexatriacontane). The hexatriacontane was then washed free of Grignard reagent by ether. Crystallization of the R_3PbCl product was first done with ethyl acetate and then with petroleum ether.

[g] Crystallization was from ethyl acetate and then from ether.

[h] To effect separation from R_3PbCl, the product was suspended in petroleum ether, cooled in ice, and filtered; then the filtrate was treated with methanol and ethyl acetate to obtain the R_4Pb compound which melted at this stage at 39–42°. Recrystallization from petroleum ether gave the sharp m.p. 42°. It is interesting to note that the molecular weight of this organometallic compound is 1107.

Anal. Calc'd for $C_{36}H_{75}ClSn$: Sn, 17.93. Found: Sn, 17.73.

Tritetradecyltin chloride. Attempts to cleave tetratetradecyltin in (a) petroleum ether with dry hydrogen chloride, and (b) with stannic chloride in benzene gave unchanged R_4Sn compound.

Cleavage of 3.6 g. of tetradecyltin in dry ether with dry hydrogen chloride gave, after

standing for 6 hours, 2.6 g. (85%) of tritetradecyltin chloride, melting at 46–47°. Recrystallization from ethyl acetate did not change the melting point.

Anal. Calc'd for $C_{42}H_{87}ClSn$: Sn, 15.91. Found: Sn, 15.29.

Trihexadecyltin chloride. The product obtained by saturating an ether solution of 2.1 g. (0.002 mole) of tetrahexadecyltin with hydrogen chloride at room temperature was crystallized from ethyl acetate to give 1.27 g. (74%) of trihexadecyltin chloride, melting at 55.5–56.5°.

Anal. Calc'd for $C_{48}H_{99}ClSn$: Sn, 14.30. Found: Sn, 14.75.

Trioctadecyltin chloride. From an ether solution of 2.2 g. (0.00194 mole) of tetraoctadecyltin which was saturated with hydrogen chloride and then set aside overnight was obtained 1.1 g. (62%) of trioctadecyltin chloride, melting at 61–62° after crystallizing from ethyl acetate and then from ether.

Anal. Calc'd for $C_{54}H_{111}ClSn$: Sn, 12.98. Found: Sn, 12.86.

*Tri-*n*-dodecylarsenic.* To an ether solution of *n*-dodecylmagnesium bromide (prepared from 0.082 mole of *n*-dodecyl bromide) was added slowly a solution of 7.85 g. (0.0249 mole) of arsenic tribromide in 20 cc. of ether. Two liquid layers separated, the upper brown, and the lower colorless. After hydrolysis by aqueous ammonium chloride, and drying by

TABLE IV

MIXED MELTING POINTS

A	M.P., °C	B	M.P., °C.	A + B M.P. °C.
$C_{12}H_{25}HgBr$	108–108.7	$C_{14}H_{29}HgBr$	110–110.5	102–103
$C_{16}H_{33}HgBr$	110.5–111.5	$C_{18}H_{37}HgBr$	110–111	107–109
$(C_{16}H_{33})_2Hg$	61–62	$(C_{18}H_{37})_2Hg$	66.5–67	60–67
$C_{16}H_{33}HgCl$	114–115	$C_{18}H_{37}HgCl$	115–116	113
$C_{16}H_{33}HgCl$	114–115	$C_{12}H_{25}HgCl$	114–114.5	108–109
$C_{18}H_{37}HgCl$	115–116	$C_{18}H_{37}HgBr$	110–111	109–110
$C_{12}H_{25}HgI$	91	$C_{16}H_{33}HgI$	93–93.5	83–84
$C_{16}H_{33}HgBr$	110.5–111.5	$C_{16}H_{33}HgI$	93–93.5	92–95
$(C_{12}H_{25})_3PbCl$	64–65	$(C_{14}H_{29})_3PbCl$	74–75	66–67
$(C_{16}H_{33})_4Pb$	42	$(C_{16}H_{33})_4Sn$	41.5–42.5	42
$(C_{16}H_{33})_3SnCl$	55.5–56.5	$(C_{18}H_{37})_3SnCl$	61–62	56–57
$(C_{16}H_{33})_4Sn$	41.5–42.5	$(C_{16}H_{33})_3SnCl$	55.5–56.5	52–55
$(C_{16}H_{33})_4Sn$	41.5–42.5	$(C_{18}H_{37})_4Sn$	47	42–47

sodium sulfate, the ether was removed by distillation in a stream of dry nitrogen. The dry nitrogen was passed through the heated oil overnight to remove the last traces of ether. If this is not done the material froths very much in the subsequent distillation.

Distillation was carried out in an all-glass apparatus. The tri-*n*-dodecylarsenic distilled at about 220°/0.08 mm. or 200°/0.009 mm. with the bath at 308°; the yield was 8.12 g. or 56%. Analysis for arsenic was by the method of Tabern and Shellberg (9).

Anal. Calc'd for $C_{36}H_{75}As$: As, 12.85. Found: As, 12.41.

From the values d_{20}^{35} 0.900 and n_D^{35} 1.4740, the molecular refraction is 180.6 (calculated, 181.51).

*Tri-*n*-tetradecylarsenic.* The reaction for this preparation was carried out between *n*-tetradecylmagnesium bromide and arsenic tribromide (0.024 mole), by operations like those described above.

On distillation, tetradecane was collected at 70°/0.22 mm., and octacosane at 150–160°/0.0008 mm. Then as the temperature was raised there was slight fuming followed by a sudden rapid distillation of liquid and a deposition of a black solid on the neck of the Claisen flask. After the bath had reached 310° and about half of the liquid had distilled, distillation was stopped. The distillate weighed 5.9 g., and the residue 4.6 g.

Anal. Calc'd for $(C_{14}H_{29})_3As$: As, 11.22. Found: for distillate, As, 8.6; for residue, As, 11.19.

From these constants on the residue, d_{20}^{35} 0.908 and n_D^{35} 1.4740, the molecular refraction is 206.4 (calculated, 209.26).

Mixed melting points. Approximately equal quantities of various pairs of mercury, lead, and tin compounds were mixed and the melting points were determined. The results are shown in Table IV.

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SUMMARY

A series of long-chained organometallic compounds with lithium, sodium, potassium, calcium, mercury, arsenic, tin, and lead has been prepared. Some of their properties and relationships (particularly melting points) have been noted.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE NORTH DAKOTA AGRICULTURAL COLLEGE]

MODIFIED KETENE LAMP

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Various generators for the production of ketene by the pyrolysis of acetone have been described (1, 2, 3, 4, 5, 6). The present piece of apparatus contains several novel features, not found in other ketene lamps, and is sufficiently different to justify description. Two differences in particular are worthy of note. This generator can be constructed in a short time from relatively simple materials without an advanced knowledge of glass blowing. A second advantage is the sudden cooling of the gaseous products of pyrolysis, a feature lacking in many of the other generators. This greatly increases the efficiency in terms of ketene to acetone ratio. The total capacity of the generator, moles of ketene per hour, is limited only by the size, and can be varied to meet individual needs.

DESCRIPTION OF APPARATUS

A 500-ml. three-neck flask A with standard taper interchangeable ground joints is used as a container for vaporizing the acetone by heating on a steam-bath or regulated electric heater B. The acetone vapors pass up through the tube C, constructed of a one-inch Pyrex tube, and over the filament D. This filament is made of 60 cm. of B and S No. 28 gauge Chromel-A resistance wire. This wire was previously wound on a 4 mm. glass rod, and then stretched and spiraled as shown. The two ends were securely spliced by winding to the platinum leads E, and these in turn were sealed through a standard taper interchangeable ground joint as shown at F.

The filament is heated by a Thordson 2D toy or Variac transformer. A potential from 20 to 22 volts is usually sufficient to keep the filament at a bright red heat under working conditions.

The hot gases from the filament D are immediately cooled by the "cold finger" condenser G and then further cooled by the condenser H. The condensed acetone is returned to the acetone boiler A through the trap I. The pyrolysis products, (ketene, methane, carbon monoxide, and ethylene) are then passed into the absorption flask J, as previously described (7). The entire piece of equipment is sealed together as one continuous unit except where it is attached to the three-neck flask A, also to the absorption flask J and where the heating element is introduced at F. These three connections should preferably be made of ground glass joints, although corks impregnated with water-glass may be used for A and F, and a short length of heavy walled rubber tubing to connect to the absorption flask J. The funnel K facilitates the addition of acetone. An ebulator tube L aids in keeping the acetone boiling smoothly.

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The apparatus delivered 0.068 mole of ketene per hour as determined by passing the effluent gas into a solution of aniline in acetone and weighing the acetanilide formed.

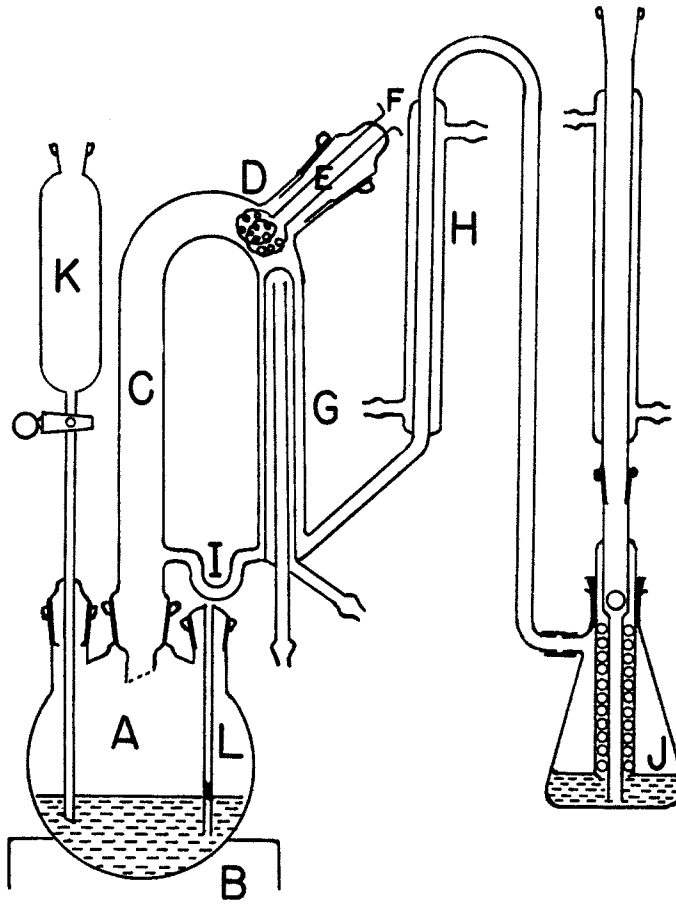

FIG. 1. MODIFIED KETENE LAMP

SUMMARY

A modified ketene lamp, that can be readily constructed from available materials, is described. The efficiency is high, and capacity may be varied with size.

FARGO, N. D.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

THE CONDENSATION OF AMINOANTIPYRINE. V. A COMPARISON OF AMINOANTIPYRINE WITH *p*-AMINODIMETHYLANILINE, *p*-PHENYLENEDIAMINE, AND *p*-AMINOPHENOL (1)[1]

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In previous articles it was reported (2) that aminoantipyrine reacted with phenols and phenolic compounds in an alkaline oxidizing medium to form colored solutions from which the colored compounds could be isolated. It was noted that this reaction was similar to that of phenolic compounds with *p*-diamines and *p*-aminophenols. The determination of the usefulness of aminoantipyrine as a reagent for phenols was made by comparison with *p*-aminodimethylaniline, *p*-phenylenediamine, and *p*-aminophenol under similar conditions.

The tests were carried out in solutions of the phenols having a concentration of 1:10000. Potassium ferricyanide was used as an oxidant[2] and each test was made in the presence of four alkalizing agents, sodium bicarbonate, sodium carbonate, ammonium hydroxide, and sodium hydroxide. The results are shown in Tables I and II.

Some of the coupling amines form colored solutions with the oxidant in the absence of phenols and, in order for one to interpret the results of the color tests, controls are necessary. Table III shows the color of the controls. In many cases, especially when the concentration of the phenol is low and the color indicative of a positive test is not transferable to the chloroform layer, a positive reaction is obscured by the colored oxidation products of the coupling amine. This situation occurs particularly with *p*-aminodimethylaniline and *p*-phenylenediamine.

DISCUSSION

A. *The coupling amines.* 1. The intensity of the color in the test solutions and the number of positive tests produced with the amines place them in the following order of decreasing sensitivity: *p*-aminodimethylaniline, aminoantipyrine, *p*-phenylenediamine, *p*-aminophenol.

2. The tests obtained with *p*-aminophenol and *p*-phenylenediamine are often

[1] Taken from part of the work submitted by K. K., H. B., and L. B. to the graduate faculty of Trinity College in partial fulfillment of the requirements for the degree of Master of Science.

[2] The following oxidizing agents were tried in some of the tests: Ammonium persulfate, ammoniacal cupric sulfate, ammoniacal silver nitrate, ammoniacal silver chloride, hydrogen peroxide, potassium chlorate, sodium hypochlorite, sodium nitrite, sodium perborate, potassium permanganate, mercuric chloride, and ceric ammonium sulfate. The persulfate is superior to the other compounds and in some respects better than potassium ferricyanide because it imparts no color of its own to the test solutions. The reaction is slow and where the colored product formed is unstable it may be destroyed almost as rapidly as it forms. Where it is known that the colored product is relatively stable it is suggested that persulfates be used in developing the reaction colorimetrically.

difficult to evaluate due to the development of turbid solutions or solutions having nondescript colors. This is especially true of *p*-phenylenediamine. Sometimes these solutions produce chloroform layers having well-defined colors, but frequently this is not the case and the results are uncertain. This disadvantage is not found with *p*-aminodimethylaniline or aminoantipyrine.

3. Solutions of the coupling amines, with the exception of aminoantipyrine, decompose to form highly colored solutions and precipitates after short standing.

4. In order to be sure of the color of the solutions the tests were made in daylight rather than in ordinary artificial light. However, the results of tests in which aminoantipyrine is used can be interpreted with equal ease in day or artificial light.

5. The compounds listed in Table II all have substituents in what is believed to be the coupling position and a positive test with them is thought to take place with expulsion of these substituents. With these compounds the reaction with the coupling amines is aminoantipyrine > *p*-aminodimethylaniline > *p*-phenylenediamine > *p*-aminophenol.

6. In a previous paper (3) it was noted that if a color reaction took place with aminoantipyrine the color would be green or blue if only two tautomeric forms are possible in the coupling ring of the phenol and red if three or more forms are possible. This great difference in the depth of color is not observed with the other coupling amines. Where it is possible for one to obtain information relating to the structure of the phenolic compound by means of color tests, aminoantipyrine has been found to be a better reagent.

B. *The alkalies.* 1. In general, sodium bicarbonate is the best alkalizing agent and sodium hydroxide the poorest for the tests. However, with *p*-aminophenol sodium hydroxide may give the best results.

2. Excess alkali is to be avoided as it tends to inhibit the reaction.

3. Where reaction takes place with compounds substituted in the coupling position the efficiency of the alkali in promoting the reaction is given by the series: sodium bicarbonate > sodium carbonate $\geqq$ ammonium hydroxide > sodium hydroxide. With aminoantipyrine it makes little difference which of the first three alkalies is used.

CONCLUSION

It has been shown that aminoantipyrine

1. Keeps well.
2. Produces clean-cut reactions with negative controls.
3. Is not too sensitive to the type of alkali.
4. Forms solutions of well-defined colors in day or artificial light.
5. Is a sensitive reagent for most phenolic compounds.

From these facts it may be concluded that it is a better reagent for phenolic compounds than the other amines tested which are deficient in one or more of the items listed above. It appears that it may also be more useful in those cases where the color reactions might give clues to the structures of the phenolic compounds.

TABLE I

THE RESULTS OF THE COLOR TESTS[a] WITH THE COUPLING AMINES AND PHENOLS WHICH HAVE THE COUPLING POSITION FREE

COUPLING AMINE[b]	AAp				*p*-ADMA				*p*-PDA				*p*-AP			
ALKALIZING AGENT[c]	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
COMPOUNDS TESTED																
Barbituric acid	3	3	3	1	4	4	4	1	3	3	2	—	1	1	1	—
	R	R	R	O	B	B	B	Bb	bV	bV	bV	—	Gb	Gb	GY	—
Catechol	2	1	1	1	4	4	3	2	3	3	3	2	2	2	2	2
	OR	OR	OR	OR	B	B	BV	BV	V	V	V	V	BR	BR	BR	BR
o-Chlorophenol	4	4	4	4	4	3	1	2	5	5	5	*	—	—	—	—
	R	R	R	R	BV	gB	YG	GB	BV	BV	BV	—	—	—	—	—
o-Cresol	3	3	3	3	4	3	3	3	3	3	3	3	—	—	2	3
	RO	RO	RO	RO	B	B	B	B	RV	RV	RV	RV	—	—	BG	B
m-Cresol	2	3	3	3	5	5	5	5	?	4	4	4	—	—	1	3
	R	R	R	R	B	B	B	B	V	V	V	BV	—	—	G	B
2,4-Diamino-6-hydroxypyrimidine	3	3	2	—	3	3	—	2	—	—	—	4	—	—	—	4
	BR	BR	R	—	P	P	—	B	—	—	—	B	—	—	—	B
2,6-Dibromophenol	5	5	5	2	4	3	2	—	4	3	3	*	—	—	—	—
	R	R	R	OR	P	BV	B	—	GB	GB	GY	—	—	—	—	—
1,3-Diethylthiobarbituric acid	4	4	2	—	5	5	5	1	3	4	1	—	2	1	1	1
	BR	BR	O	—	B	GB	G	O	V	V	O	—	Gb	Gb	GY	GY
α,γ-Diketohydrindene	3	3	2	1	5	5	5	5	?	?	?	1	?	2	?	2
	BR	BR	R	R	BR	b	b	b	b	b	b	b	b	b	b	V
1,3-Diphenylbarbituric acid	3	1	—	—	4	2	2	1	4	4	1	—	2	?	1	—
	R	O	—	—	B	O	O	O	g	g	YG	—	b	Y	GY	—

1,3-Diphenylpyrazolon-5	5	5	5	2	5	5	5	3	5	5	5	1	5	1	2	3
	R	R	R	R	R	R	R	R	V	V	V	Y	Gg	b	Rb	V
Guiacol	3	3	3	3	3	3	3	3	3	3	3	3	2	1	2	2
	R	R	R	R	B	B	B	B	V	V	V	V	Rb	Yb	Rb	B
m-Hydroxybenzoic acid	2	3	3	3	4	4	4	3	5	5	5	4	—	—	—	—
	R	R	R	R	GB	GB	GB	GB	G	G	G	B	—	—	—	—
5-Hydroxy-1,3-dimethylbenzene	3	3	3	3	4	4	4	3	?	?	2	3	*	*	*	2
	P	P	P	P	B	B	B	GB	V	V	V	RB	—	—	—	GB
4-Hydroxypyrazol	2	3	2	3	4	4	4	4	3	3	2	2	—	—	—	—
	R	BR	BR	BR	P	P	RV	P	RV	RV	RV	RV	—	—	—	—
3-Hydroxypyridine	3	3	3	2	5	3	4	2	2	5	1	—	—	—	—	—
	R	O	O	O	B	B	B	Rb	b	bR	O	—	—	—	—	—
3-Hydroxyquinaldine	1	1	1	1	2	2	2	1	—	—	—	—	—	—	—	—
	G	G	G	G	P	P	P	R	—	—	—	—	—	—	—	—
5-Hydroxyquinoline	2	2	2	2	4	4	4	4	4	4	3	3	2	2	2	2
	R	R	R	R	B	B	B	B	RV	RV	B	P	RV	RV	P	P
6-Hydroxyquinoline	3	3	3	2	3	3	3	2	—	1	—	—	—	—	—	—
	B	B	B	B	BR	BR	BR	P	—	O	—	—	—	—	—	—
7-Hydroxyquinoline	1	1	1	1	3	3	3	1	?	?	1	—	—	—	—	—
	YG	YG	YG	YG	P	P	P	O	b	b	O	—	—	—	—	—
8-Hydroxyquinoline	5	5	5	5	5	5	5	5	5	5	3	3	2	2	2	2
	R	R	R	R	P	P	BV	BV	P	BP	P	P	RO	RO	RO	RO
7-Methyl-8-hydroxyquinoline	2	2	2	1	5	4	4	3	5	5	3	3	1	1	1	3
	OR	OR	OR	O	B	B	B	B	BR	BR	BR	BR	V	V	V	B

TABLE I—*Continued*

Coupling Amine[b]	AAp				*p*-ADMA				*p*-PDA				*p*-AP			
Alkalizing Agent[c]	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Compounds Tested																
Methylisoxazolone	2	1	1	1	3	3	1	1	3	3	3	—	5	5	5	1
	RO	RO	RO	R	BR	BR	BR	O	BR	BR	BR	—	B	B	B	O
3-Methylpyrazolon-5	3	3	3	2	4	4	4	2	?	3	3	1	?	?	2	2
	R	R	R	R	P	V	V	V	b	P	R	R	b	b	Rb	Rb
α-Naphthol	5	2	2	3	5	5	5	5	5	5	5	5	5	5	5	2
	R	R	R	R	BV	BV	BV	BV	BV	V	V	RV	OR	OR	OR	OR
β-Naphthol	5	5	5	5	5	5	5	5	5	5	5	2	—	—	—	5
	G	G	G	G	V	V	V	V	gG	gG	gG	G	—	—	—	G
o-Nitrophenol[d]	3	3	3	—	—	3	3	—	—	—	—	—	—	—	—	—
	R	R	R	—	—	R	R	—	—	—	—	—	—	—	—	—
m-Nitrophenol[d]	1	*	1	—	*	2	2	—	—	—	—	—	—	—	—	—
	R	—	R	—	—	BG	G	—	—	—	—	—	—	—	—	—
Phenol	3	3	3	3	5	5	4	5	3	3	3	2	—	—	1	2
	RO	RO	RO	RO	B	B	B	B	RV	RV	RV	P	—	—	V	G
1-Phenyl-3-carboxy-4-hydroxypyrazol	2	2	1	1	2	2	2	1	—	1	1	1	2	2	—	1
	G	G	G	G	P	P	G	O	—	g	G	O	O	GY	—	O
1-Phenyl-3-carboxypyrazolon-5	3	3	3	2	4	4	3	2	5	5	3	—	2	2	2	1
	R	R	R	R	V	V	V	G	B	B	V	—	GB	G	O	GY
1-Phenyl-4-hydroxypyrazol	3	2	1	1	2	2	5	—	2	2	1	*	—	*	*	*
	G	G	G	Y	V	V	b	—	g	g	O	—	—	—	—	—
1-Phenyl-3-hydroxypyrazolon-5	2	2	1	1	5	5	3	3	—	—	3	1	3	3	1	1
	OR	OR	O	O	R	R	P	R	—	—	b	O	b	b	bO	bO

1-Phenyl-3-methylpyrazolon-5	3	3	3	2	5	5	5	5	5	5	5	5	?	?	?	1
	R	R	R	R	V	V	R	R	V	V	RV	RV	gG	gG	gG	gG
Phloroglucinol	1	1	1	1	1	1	2	2	1	1	?	1	2	1	1	1
	b	b	Yb	Rb	gb	gb	gG	gG	gb	Rb	b	Rb	b	b	b	b
Pyridoxine	*	1	2	*	3	3	3	3	2	3	3	*	—	—	—	—
	—	V	V	—	P	GB	GB	B	BG	B	B	—	—	—	—	—
Pyrogallol	—	*	—	—	—	2	*	*	—	—	—	—	3	2	1	1
	—	—	—	—	—	O	—	—	—	—	—	—	BR	BR	Ob	Ob
Resorcinol	3	2	2	2	5	3	5	3	?	?	?	?	?	?	?	?
	RO	RO	RO	RO	V	V	V	BV	b	b	b	b	b	b	b	b
Resorcinol monomethyl ether	3	3	3	3	4	4	4	3	5	4	4	4	*	*	1	3
	R	R	R	R	B	B	B	B	V	V	V	BV	—	—	G	B
Salicylic acid (1:1000)	1	1	3	3	4	5	5	4	—	—	—	—	—	1	—	2
	RO	RO	R	R	RV	RV	RV	RV	—	—	—	—	—	G	—	G
Tetronic acid	2	1	1	—	1	2	*	—	—	—	—	—	?	?	—	—
	R	R	RY	—	R	R	—	—	—	—	—	—	b	b	—	—

[a] The colors in the aqueous layer, purple, blue, green, violet, red, yellow, and orange are represented by the capital letters P, B, G, V, R, Y, and O respectively. Gray and brown are indicated by the small letters g and b respectively. The numbers are arbitrary designations of the intensity of the tests with the number 5 indicating a precipitate. The asterisk indicates apparent absence of color formation in the aqueous layer but, since the chloroform layer is colored, a slight positive test is indicated. The question mark is used in cases where it is difficult to evaluate the test.

[b] The coupling amines, aminoantipyrine, *p*-aminodimethylaniline, *p*-phenylenediamine, and *p*-aminophenol are represented by the abbreviations AAp, *p*-ADMA, *p*-PDA, and *p*-AP respectively.

[c] The alkalies, sodium bicarbonate, sodium carbonate, ammonium hydroxide, and sodium hydroxide are indicated by the letters A, B, C, and D respectively.

[d] The results of tests with *o*- and *m*-nitrophenol reported here differ from those previously reported (3). Some of the phenolic compounds are extremely sensitive to the amount and kind of alkali and a slight excess may completely inhibit the test. An excess was used in the work previously reported, a fact which undoubtedly accounts for the discrepancy. At the present time work is being done on the effect of excess alkali on this color reaction.

TABLE II

THE RESULTS OF COLOR TESTS[a] WITH THE COUPLING AMINES AND PHENOLIC COMPOUNDS WHICH HAVE THE COUPLING POSITIONS SUBSTITUTED

COUPLING AMINE	AAp				*p*-ADMA				*p*-PDA				*p*-AP			
ALKALIZING AGENT	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
COMPOUNDS TESTED																
5-Benzalbarbituric acid	3	2	1	1	4	4	1	—	1	1	—	—	—	—	—	—
	R	R	R	R	B	B	B	—	P	P	—	—	—	—	—	—
3-Carboxy-4-hydroxypyrazol	2	3	2	2	3	3	3	2	?	?	—	3	*	—	—	—
	R	R	R	R	V	V	P	V	b	b	—	V	—	—	—	—
p-Chlorophenol	3	3	3	3	3	2	3	1	?	?	?	*	—	—	—	—
	OR	OR	OR	OR	P	B	B	YG	b	b	bV	—	—	—	—	—
3,5-Dibromo-4-hydroxybenzoic acid	5	5	5	1	4	3	*	—	?	?	?	—	—	—	—	—
	R	R	R	OR	P	BV	—	—	gG	gG	gG	—	—	—	—	—
2,4-Dichlorophenol	3	3	3	1	4	3	2	—	?	?	1	*	—	—	—	—
	R	R	R	OR	B	G	YG	—	b	b	BG	—	—	—	—	—
Hydroquinone	*	*	1	*	2	1	2	*	?	?	?	?	?	1	?	1
	—	—	O	—	RV	V	R	—	g	g	g	b	Vb	Vb	b	GB
Hydroquinone monomethyl ether	2	2	3	2	4	3	3	3	4	4	4	2	*	*	*	1
	R	R	R	R	B	B	B	B	P	P	P	P	—	—	—	GB
p-Hydroxybenzoic acid	3	3	3	3	*	2	2	*	*	*	*	*	—	—	—	—
	R	R	R	R	—	V	G	—	—	—	—	—	—	—	—	—
8-Hydroxyquinoline-5-sulfonic acid	4	4	4	4	1	*	*	*	2	1	1	*	1	1	1	1
	R	R	R	R	P	—	—	—	P	P	P	—	P	G	G	G

p-Phenolsulfonic acid	1	2	1	1	*	1	1	*	?	?	*	*	—	—	—	—		
	YO	RO	RO	YO	—	bV	YG	—	b	b	—	—	—	—	—	—		
1-Phenyl-3-methyl-4-benzylidene pyrazolon-5	3	3	3	1	5	5	5	3	—	5	5	2	2	2	2	3		
	R	R	R	R	R	R	R	R	—	R	R	V	g	bR	V	V		
1-Phenyl-3-methyl-4-bromopyrazolon-5	3	3	3	1	5	5	5	2	3	5	5	1	2	1	2	2		
	R	R	R	RO	R	R	R	R	b	O	O	Y	G	bR	V	V		
1-Phenyl-3-methyl-4-isonitrosopyrazolon-5	3	2	1	1	5	5	1	1	*	*	1	1	—	—	—	—		
	R	R	R	R	R	R	O	O	—	—	O	O	—	—	—	—		
1-Phenyl-3-methyl-4-isopropylidene-pyrazolon-5	3	3	3	1	3	3	3	3	—	5	5	2	5	—	2	3		
	R	R	R	O	R	R	R	R	—	R	R	V	g	—	Rb	V		
2,4,6-Tribromophenol	5	5	5	—	4	2	*	—	5	5	5	1	—	—	—	—		
	BR	BR	OR	—	BV	GB	—	—	G	G	GB	GY	—	—	—	—		

[a] The results are recorded in the same manner as in Table I. See footnotes a, b, and c in that table.

EXPERIMENTAL

The tests were made on samples of the phenolic compounds by the second technique described in a previous article (4).

TABLE III

THE COLOR[a] OF THE SOLUTIONS OF THE CONTROLS WHEN POTASSIUM FERRICYANIDE IS THE OXIDANT

ALKALIZING AGENT	$NaHCO_3$		Na_2CO_3		NH_4OH		NaOH	
COUPLING AMINE	aq. layer	$CHCl_3$ layer	aq. layer	$CHCl_3$ layer	aq. layer	$CHCl_3$ layer	aq. layer	$CHCl_3$ layer
Aminoantipyrine	1[b] Y	—	1 Y	—	1 Y	—	1 Y	—
p-Aminodimethylaniline	3 R	R	2 RO	O	2 RO	R	1 Y	O
p-Phenylenediamine	3 b	Rb	1 Yb	O	2 Yb	Rb	1 Y	OY
p-Aminophenol	1 bY	—	1 Y	—	1 bY	—	1 YG	—

[a] The method of recording the colors of the controls is the same as that used in Table I. See footnote a of that table.

[b] A 1-Y test in the control is due to the yellow color imparted to the solution by potassium ferricyanide.

SUMMARY

Aminoantipyrine as a reagent for phenols was compared with *p*-aminodimethylaniline, *p*-phenylenediamine, and *p*-aminophenol and was found to be superior to them. For the promotion of the color test sodium hydroxide was found to be the poorest alkalizing agent and sodium bicarbonate probably the best.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

ON ESTERS OF *p*-TOLUENESULFONIC ACID

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During the past few years the esters of *p*-toluenesulfonic acid have achieved considerable practical importance as alkylating agents. They are particularly useful for the alkylation of phenolic substances containing one or more tertiary nitrogen atoms, since they react preferentially with the phenolic hydroxyl group and effect very little alkylation of the tertiary nitrogen atoms.

A satisfactory method for the preparation of these esters in high yield would therefore have great practical value. Unfortunately, however, although a number of methods for their synthesis have been evolved, most of them are unsatisfactory, for reasons to be discussed.

The various ways in which arylsulfonic esters have been synthesized fall into two main groups. The first of these consists in the action of an alkyl halide (or sulfate) on a metallic salt of the sulfonic acid (1, 2, 3).

$$(RSO_2O)_2Pb + 2EtI \rightarrow 2\ RSO_2OEt + PbI_2 \qquad (I)$$

$$2\ RSO_2ONa + Me_2SO_4 \rightarrow 2\ RSO_2OMe + Na_2SO_4 \qquad (II)$$

The applicability of this procedure is obviously limited by such factors as the reactivity, availability, and expense of the alkyl halide or sulfate.

The second method involves the action of the alcohol (or phenol) on the sulfonyl halide (4, 5), as follows.

$$RSO_2Cl + EtOH \rightarrow RSO_2OEt + HCl \qquad (III)$$

This method, in the simple form given, can only be employed successfully provided that three conditions are satisfied. The first is that excess of the alcohol (or phenol) shall be readily removable at the end of the reaction; for example, by evaporation, by extraction with a suitable solvent, or by steam-distillation.

The second requirement is that the rate of reaction between the ester produced and the hydroxylic starting material shall be so low that very little or none of the corresponding ether can be formed by the following type of reaction (6, 7).

$$RSO_2OEt + EtOH = RSO_3H + Et_2O \qquad (IV)$$

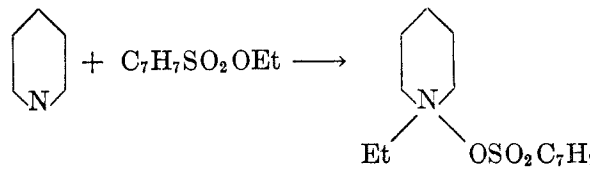
If there is a tendency for ether-formation to occur it can be reduced to the minimum by employing a large excess of the hydroxylic substance and conducting the reaction at room temperature (8). The disadvantages of this modification are the length of time required for the reaction to approach completion and the large excess of the hydroxylic substance which must be employed. The method is, therefore, not feasible for rare alcohols or phenols; nor if the sulfonyl chloride has a very low solubility in the cold hydroxylic substance (9).

The third condition to be met is that the hydrogen halide evolved in the reaction shall have little or no action on either the hydroxylic substance to be

esterified or on the desired ester. To minimize this difficulty Slotta and Franke (10) introduced the modification of aspirating dry air through the hot reaction-mixture, thereby removing hydrogen halide as fast as it is formed. Employing this procedure they were able to prepare *n*-propyl *p*-toluenesulfonate in a yield of 74% of the theoretical.

A better modification, however, consists in the introduction of a substance which will neutralize the hydrogen halide as fast as it is formed. For this purpose, inorganic and organic bases have been employed. Inorganic substances used include sodium hydroxide (11), and sodium carbonate (10, 12). A similar procedure is to allow the sulfonyl halide to react with a sodium alkoxide in the alcohol (2, 13), in dry ether (14), or dry benzene (15). The method is obviously of little or no value for such substances as partially acylated sugars, unsaturated alcohols, or halohydrins which are difficult or impossible to obtain as alcoholates.

Organic bases which have been employed include diethylaniline (12), and pyridine (16). In the preparation of esters of *p*-toluenesulfonic acid by the action of *p*-toluenesulfonyl ("tosyl") chloride upon the alcohol in the presence of pyridine, three different undesired side-reactions can take place. One of these is ether formation (17) (as in equation IV). The second is formation of the pyridinium quaternary salt (17) as in equation V.



(V)

However, Sekera and Marvel (18) stated that this by-reaction usually proceeds to only a minor extent if the reaction is performed at 0°.

The third type of side-reaction is that of chlorination; it has been encountered on attempting to tosylate phenols (19, 20), simple alcohols (21, 22), and such polyhydroxy compounds as sugars (23, 24), sugar alcohols (25), and their derivatives. A simple illustration is the chlorination of phenoxyethanol (21):

$$C_6H_5OCH_2CH_2OH \rightarrow C_6H_5OCH_2CH_2Cl \qquad \text{(VI)}$$

Although these and other examples of this chlorination reaction are to be found in the literature, it seems that it was not until 1935 that the mechanism of the reaction was revealed by Hess and Stenzel (24). However, their work was confined to sugar derivatives and, as far as is known, their theory has never been applied to other chlorinations occurring on treatment with tosyl chloride in pyridine. They discovered that the chlorination takes place *after* tosylation has occurred, according to equation VII, and that chlorination is increased by raising the temperature.

$$ROSO_2C_7H_7 + C_5H_5N \cdot HCl = RCl + C_5H_5N \cdot C_7H_7SO_3H \qquad \text{(VII)}$$

On treating β-methyl glucoside with tosyl chloride in pyridine they were able to obtain at will, by varying the temperature from one experiment to another,

tetratosyl β-methyl glucoside, monochloro-tritosyl β-methyl glucoside, or dichloro-ditosyl β-methyl glucoside.

In the present study, attention has been confined to the use of pyridine as the neutralizing agent. Of the many precautions advocated in the literature as being advisable, it is now found that only two are necessary. First, since *p*-toluenesulfonyl chloride is rapidly hydrolyzed by slightly moist pyridine, it is essential that the pyridine employed be dry and that the reaction be performed with exclusion of atmospheric moisture. Secondly, in some but not all cases to be discussed, the temperature of the reaction mixture should be kept at or somewhat below 0°. The time during which the reaction is permitted to proceed has been reduced considerably and, for convenience, the proportions of solvent and reactants have been standardized. Hence, the method now described is a simplification of the excellent one of Sekera and Marvel (18), and represents, in some respects, a return to the original method of Patterson and Frew (16).

DISCUSSION OF RESULTS

It is found that, if the substance to be esterified is first dissolved in pyridine and the resulting solution then thoroughly cooled, there is very little rise in temperature on adding all the tosyl chloride in one lot. Hence, nothing is to be gained by adding either of the reactants in portions (except in large-scale experiments).

Gentle swirling by hand, during the short period of time required for all of the tosyl chloride to dissolve, is ample to keep the temperature uniform throughout the reaction mixture. Since the mixture then becomes a homogeneous solution and remains so until the crystallization of pyridine hydrochloride (and, in some cases, of ester) commences, mechanical stirring is unnecessary.

Some hydroxylic substances are not very soluble in pyridine; if addition of a non-polar solvent helps to dissolve the material, its use is advantageous but otherwise it serves no useful purpose. Finally, the use of specially purified *p*-toluenesulfonyl chloride is unnecessary. In the following experiments, a ten per cent excess of the commercial reagent has been consistently employed.

The behavior of a number of hydroxylic substances has been studied under these conditions. Only those esters which are new, or which have been found to have properties different from those previously reported, are described in Table I. In no case was the formation of a chloro compound detected and in most instances the yield of *p*-toluenesulfonyl ester was over 75% of the theoretical, showing that the formation of ether or pyridinium salt, or both, was not large.

As examples of substances which are known to undergo chlorination in the presence of tosyl chloride and warm (or hot) pyridine or diethylaniline, we chose for study phenoxyethanol (21) and 2,4-dinitrophenol (19). Under the conditions now described, neither compound gives rise to any chloro derivative. However, the tosyl ester of 2,4-dinitrophenol, as is well known (19, 26), readily reacts with cold pyridine to give the quaternary pyridinium salt. Consequently, the yield of this ester amounted to only 26% of the theoretical.

This led us to study the formation of three tosyl esters (of ethanol, benzyl

alcohol, and 2,4-dinitrophenol, respectively) which, it is alleged, cannot be prepared in the presence of pyridine owing to the formation of their pyridinium salts. However, by the simple procedure of neutralizing the excess pyridine as soon as formation of the ester was judged to have approached the maximum, we have prepared the ethyl, benzyl, and 2,4-dinitrophenyl esters in yields of 72%, 38%, and 90%, respectively. The yield of benzyl ester is inferior to that obtained by Gilman and Beaber (27) by another method but, unlike their product, the ester obtained was quite stable (28) at room temperature, presumably (17) owing to complete elimination of traces of free benzyl alcohol.

It should be mentioned that apocupreine, which has both a phenolic and an alcoholic hydroxyl group, gives rise to a *mono*-tosyl ester only. Thus, in this respect, its alcoholic hydroxyl group seems to behave more like a tertiary than a secondary hydroxyl. As far as is known, the preparation of tosyl esters of tertiary alcohols has not yet been recorded. However, the fact that *tert.*-butyl alcohol gives (22) the chloride, on treatment with tosyl chloride in pyridine at 100°, indicates that its tosyl ester may be capable of existence, at least as a transitory intermediate.

EXPERIMENTAL

General method for preparation of p-toluenesulfonyl esters. The pyridine employed was reagent grade; it was dried over barium oxide and filtered immediately before use.

The appropriate alcohol (10 g.) was dissolved in 100 cc. of dry pyridine and the solution cooled to −5° in an ice-salt bath. *p*-Toluenesulfonyl chloride (1.1 equivalents) was now added in one portion and the flask closed by a rubber stopper through which a thermometer was inserted. The suspension was gently swirled by hand, with cooling in ice-salt, until all the tosyl chloride had dissolved. After keeping at 0° during a further 2 hours, water (10 cc.) was added in portions (1 + 1 + 1 + 2 + 5 cc.) at intervals of 5 minutes, with swirling and cooling so that the temperature did not rise above +5°. The solution was then diluted with 100 cc. of water. (In some cases, the ester crystallized out at this point; in this event, the ester was filtered off, washed with water until free from pyridine, and dried.) The aqueous pyridine solution was now extracted with three 100-cc. portions of chloroform, and the united chloroform extracts washed successively with ice-cold dilute sulfuric acid, water, and sodium bicarbonate solution. The chloroform solution was dried with anhydrous sodium sulfate, filtered, and the filtrate evaporated to dryness under diminished pressure. The resulting product was purified by distillation under high vacuum or by recrystallization. In every case, the *crude* ester was free from chloro compound.

All the compounds described in Table I were prepared by the above procedure. However, in the tosylation of many sugar derivatives, and of phenol (16), borneol (17), and apocupreine, the tendency for chlorination or pyridinium salt formation to take place is so low that external cooling is unnecessary.

Bornyl p-toluenesulfonate. On adding the tosyl chloride to the solution of borneol in pyridine at room temperature (21°) the temperature of the mixture fell to 18°. After standing overnight at room temperature, water was added as above, but without cooling; yield, 85%; m.p. 67°. The product was devoid of chlorine.

Tosyl apocupreine. Apocupreine [purified (29), and dried at 110°] was dissolved in dry pyridine and treated with tosyl chloride by the above general method but the product was isolated as follows. After portionwise addition of water to the reaction mixture, sodium bicarbonate powder was added until effervescence ceased. The solution was then evaporated under diminished pressure, with occasional addition of water, until no odor of pyridine remained. The product was dissolved in chloroform plus water, the chloroform layer separated and the tosyl ester isolated from it in the usual manner.

Treatment of apocupreine with 1.1 molar proportions of tosyl chloride gave a product containing unchanged apocupreine, as shown by analysis for sulfur and nitrogen, and by its negative specific rotation, $[\alpha]_D^{24}$ −55.5° in absolute ethanol, c = 1. Treatment with either 2.2 or 3.3 molar proportions of tosyl chloride (in the refrigerator or at room temperature) resulted in a quantitative yield of a colorless, amorphous product having $[\alpha]_D^{24}$ +14.8° (in absolute ethanol, c = 1) and the composition[1] of a *mono*-tosyl ester (30).

Anal. Calc'd for $C_{26}H_{28}N_2O_4S$: N, 6.03; S, 6.91.

Found: N, 6.09; S, 6.97.

Modified method of esterification. In those experiments in which it was desired to form an estimate of the speed of reaction from the rate of deposition of pyridine hydrochloride, the ratio of tosyl chloride to pyridine was held constant and the following standard proportions of reactants were employed: 22 g. of tosyl chloride, 88 cc. of dry pyridine, and the amount of hydroxylic substance equivalent to 20 g. of tosyl chloride. These were mixed under the conditions given above. 2,4-Dinitrophenol is not sufficiently soluble in dry pyridine to permit use of the above proportion of pyridine; its quantity was accordingly increased.

TABLE I

REFRACTIVE INDICES, MELTING POINTS AND ANALYSES OF SOME ESTERS OF *p*-TOLUENESULFONIC ACID

ESTER	YIELD, %	n_D^{25}	M.P., °C.	B.P., °C.	FORMULA	ANALYSES, %S	
						CALCULATED	FOUND
Methoxyethyl	82	1.5085	10	141/0.2 mm.	$C_{10}H_{14}O_4S$	13.93	14.07
Ethoxyethyl	92[a]	1.5026	18.5	122/0.1 mm.	$C_{11}H_{16}O_4S$	13.13	13.31
n-Propoxyethyl	93	1.5004	8	140/0.1 mm.	$C_{12}H_{18}O_4S$	12.42	12.71
n-Butoxyethyl	92[b]	1.4960		142[b]/0.1 mm.	$C_{13}H_{20}O_4S$	11.78	11.92
Phenoxyethyl	92[b]		80–81[c]		$C_{15}H_{16}O_4S$	10.97	11.08
Diethylcarbinyl	75		43–44[d]		$C_{12}H_{18}O_3S$	13.24	13.71

[a] Compare with Butler *et al.*, *J. Am. Chem. Soc.*, **57,** 575 (1935).

[b] Compare with Butler *et al.*, *J. Am. Chem. Soc.*, **59,** 227 (1937).

[c] Butler *et al.*, *J. Am. Chem. Soc.*, **59,** 227 (1937) gave m.p. 75°; Peacock and Tha, *J. Chem. Soc.*, 2303 (1928) gave m.p. 80°.

[d] Tabern and Volwiler, *J. Am. Chem. Soc.*, **56,** 1139 (1934) gave m.p. 32–35°; Green *et al.*, *J. Am. Chem. Soc.*, **61,** 1783 (1939) gave m.p. 37°.

Ethyl p-toluenesulfonate. Tosyl chloride (22 g.) was dissolved in 88 cc. of dry pyridine (the temperature rising from 22° to 24°), and the solution was cooled to −10°. Absolute ethanol (6.1 cc.) was now added, the temperature rising to −5° after 2 minutes and then falling to −10°. Crystallization commenced after a further 3 minutes, and the mixture was kept at −10° for 15 minutes more. Sulfuric acid (250 cc. of 5 *N*, cooled to 0°) was now added rapidly, with cooling. The temperature rose to 27°, the crystals dissolved and the solution became opalescent. On cooling to +4°, material crystallized out. It was filtered off, thoroughly washed with water, and dried; yield, 15 g.; m.p. 32°, in agreement with that reported in the literature (8). The whole preparation of crude ester occupied less than 30 minutes.

Benzyl p-toluenesulfonate. Benzyl alcohol (10.9 cc.) was treated exactly as described for preparation of the ethyl ester. The crystalline product was washed with heptane and water, and dried; yield, 10.5 g.; m.p. 55°. When its preparation was attempted by the

[1] Most of the analyses reported in this paper were performed microanalytically by Dr. Carl Tiedcke, New York City.

general method, all the pyridine hydrochloride deposited in the reaction mixture had redissolved after 90 minutes and no product could be isolated from the chloroform extract.

2,4-Dinitrophenyl p-toluenesulfonate. (a) A suspension of 19.3 g. of 2,4-dinitrophenol in 176 cc. of pyridine, cooled to −10°, was treated with 22 g. of tosyl chloride and then kept in the refrigerator during 3 days. The product was 2,4-dinitrophenyl pyridinium *p*-toluenesulfonate (6.5 g.). On recrystallization from boiling absolute ethanol (1 g. in 55 cc.), it was obtained as colorless platelets having m.p. 255°, in agreement with the m.p. recorded by Freudenberg and Hess (26).

Anal. Calc'd for $C_{18}H_{15}N_3O_7S$: C, 51.77; H, 3.6; N, 10.07; S, 7.69.
Found: C, 51.71; H, 3.6; N, 10.19; S, 7.56.

(b) When double this volume of pyridine (*i.e.* 352 cc.) was employed, and the solution was kept at 0° during 2 hours, the product was the desired ester (9.2 g.). On recrystallization from boiling absolute methanol (1 g. in 20 cc.) it was obtained as colorless needles having m.p. 121–122°. The literature gives (19) m.p. 121°, and (26) m.p. 124°.

Anal. Calc'd for $C_{13}H_{10}N_2O_7S$: C, 46.13; H, 3.0; N, 8.29; S, 9.5.
Found: C, 46.02; H, 3.3; N, 8.26; S, 9.0

(c) The experiment was performed as in (b) but, 15 minutes after crystallization of pyridine hydrochloride commenced, the reaction was halted by pouring the mixture into 1 liter of 5 *N* sulfuric acid (precooled to −5°). The ester crystallized immediately; it was filtered off, washed with water, and dried; yield, 32 g.; m.p. 122°.

Recrystallization of p-toluenesulfonyl esters. Each ester (10 g.) was dissolved in the stated volume of solvent, the solution cooled and kept overnight in the refrigerator.

Phenoxyethyl. 200 cc. of boiling dry ether.

Diethyl carbinyl. 20 cc. of cold, dry ether followed by addition of 250 cc. of pentane.

Bornyl. 20 cc. of warm absolute ethanol. It then had m.p. 68–69°.

SUMMARY

A simple method is described for the preparation, in high yield, of esters of *p*-toluenesulfonic acid by the familiar procedure of treatment of the alcohol or phenol with *p*-toluenesulfonyl chloride in pyridine. In the examples studied by this method, chlorination does not take place and formation of pyridinium salt is usually negligible.

If there is a pronounced tendency for the formation of the pyridinium salt, arrest of the reaction by acidification permits isolation of the desired ester.

Methoxyethyl, ethoxyethyl, and *n*-propoxyethyl *p*-toluenesulfonates have been crystallized for the first time; apocupreine gives a monotosyl ester only.

PITTSBURGH, PA.

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CONSTITUENTS OF PYRETHRUM FLOWERS. XVI. HETEROGENEOUS NATURE OF PYRETHROLONE

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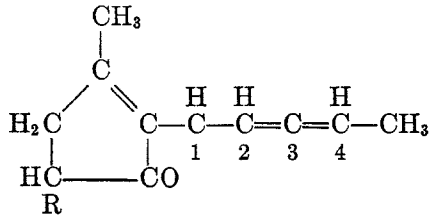
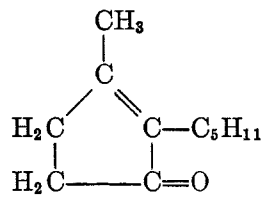
In a previous article (1) the known facts concerning the nature of the pentadienyl side chain of pyrethrolone, the substituted cyclopentenolone component of the pyrethrins, were considered in conjunction with absorption data furnished by pyrethrone (desoxypyrethrolone). It was concluded that pyrethrolone and pyrethrone should be represented by formula I, containing the cumulated system as originally proposed by Staudinger and Ruzicka (2).



Pyrethrolone (R = OH)
Pyrethrone (R = H)

I

The principal evidence for the cumulated system, and against the conjugated system suggested by Ruzicka and Pfeiffer (3), may be briefly presented as follows: Pyrethrolone and pyrethrone apparently failed to undergo the Diels-Alder reaction. On hydrogenation, pyrethrone was converted into tetrahydropyrethrone, which proved to be identical with dihydrojasomone, of known structure II (4).



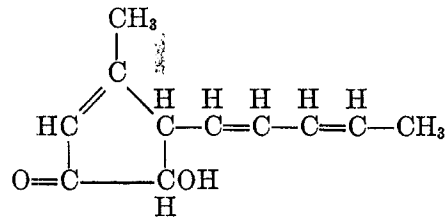
II

This compound results also on hydrogenation of pyrethrolone, its ethers, its acetyl derivative, and the pyrethrins themselves, and its formation shows the presence in all these derivatives of a double bond within the ring system.

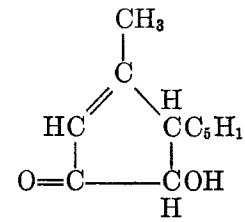
Both pyrethrolone and pyrethrone furnished acetaldehyde on ozonization, this fact locating one double bond in position 3,4 in the side chain. The choice between the cumulated and the conjugated system seemed then to depend upon the establishment of the position of the remaining double bond. Evidence in

favor of position 2,3, and hence for the cumulated system, was furnished by ultraviolet absorption data obtained on pyrethrone as compared with those observed on a reference compound with a five-membered side chain containing such a system. The reference compound, 1-cyclohexyl-2,3-pentadiene, showed no absorption in the wave-length region concerned. With the assumption of a double bond in the *alpha,beta*-position in the cyclopentenone nucleus of pyrethrone, as in formula I, the data obtained excluded the presence of a conjugated system in the side chain in conjugation with the nuclear double bond and the keto group. With position 1,2 therefore excluded, 2,3 was the only possible location for the remaining double bond.

Gillam and West (5) have recently reopened the question, not only of the nature of its side chain, but of the structure of pyrethrolone in other respects. They conclude, on the basis of absorption results, that the conjugated system is present in the pyrethrolone side chain, but that a trienone system with the *alpha,beta*-unsaturated ketonic feature of the molecule is not involved. That two separated chromophores are present apparently follows from the nature of the absorption spectrum of pyrethrolone as compared with that of tetrahydropyrethrolone, in which only the side-chain chromophore has been eliminated by hydrogenation. By subtracting the values furnished by the tetrahydro compound from those observed for pyrethrolone, the hypothetical values for the side-chain chromophore could be deduced. From these results Gillam and West conclude that pyrethrolone should be represented by formula III and tetrahydropyrethrolone by a corresponding formula IV with a saturated side chain.



III



IV

In an earlier publication Gillam and West (6) also reported results on the absorption spectra of tetrahydropyrethrolone and dihydrojasmone (tetrahydropyrethrone). The curves plotted for the two compounds were so close together that the conclusion was justified that they contained the same essential features. It is unforuntate that a spectrographic examination of pyrethrone (desoxypyrethrolone) was not made and the data compared with those furnished by tetrahydropyrethrone. Our observations on pyrethrone included only the wave-length at maximum absorption and the intensity which was regarded as adequate for the exclusion of a trienone chromophoric system. The values (λ max. 235 mμ; log. ϵ = 4.2) are not in agreement with those observed by Gillam and West for pyrethrolone.

If the pyrethrolone structure does in fact contain two separated chromophores, one in the side chain and the other consisting of the *alpha,beta*-unsaturated

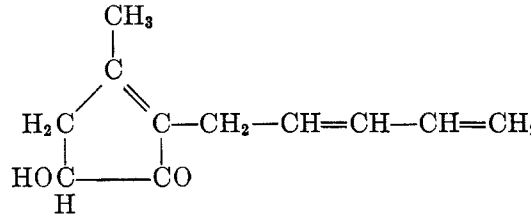
ketonic component, formula I is untenable. But the alternative formula III is also unacceptable because it is inconsistent with the following chemical facts: While it would account for the formation of acetaldehyde, it would not provide for that of malonic acid on oxidation. Since pyrethrolone is optically active, its reduction product, pyrethrone, should also be optically active, because it would still contain an asymmetric center in the nucleus at the *beta* carbon in formula III. But pyrethrone is actually optically inactive and cannot be resolved. Tetrahydropyrethrone obtained *via* the chloro compound from tetrahydropyrethrolone, which should be optically active according to formula III, is also inactive. Some of these discrepancies are explained by the assumption that reductions involving the elimination of the oxygen atom are accompanied by an isomerization whereby the nucleus as in formula III rearranges to that in formula II.

The structures of tetrahydropyrethrone and jasmone are so well established from the chemical standpoint as to be indisputable, since they are based on the nature of their oxidation products, which include levulinic acid, and especially on their syntheses (7), which definitely locate the position of the side chain relative to the ketone group in the sense of formula II.

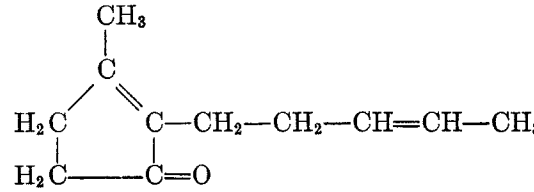
If, then, formula I for pyrethrolone is to be rejected on the grounds of absorption results, the chemical facts provide a much stronger reason against the acceptance of formula III. But if the chemical facts are to be reconciled with the absorption data, a new conception for the distribution of the double bonds in pyrethrolone and pyrethrone is required.

The results reported by Gillam and West have stimulated us to extend our own investigations on this problem.

In a recent private communication, R. B. Woodward, of Harvard University, has suggested that pyrethrolone be assigned formula V and that pyrethrone corresponds to formula VI.



V



VI

These formulas would satisfy the absorption results, but they account for the formation of acetaldehyde from pyrethrolone only in a very strained manner,—*i.e.*, with the intermediary formation of malonaldehydic acid, and formula VI is contradicted by analytical results.

At this point it may be well to mention some observations concerning pyrethrolone which have been considered unimportant. Its distillation point is not constant, and the distillate always exhibits striations which indicate lack of homogeneity. The yield of acetaldehyde on ozonization does not exceed 30% of the theory, and a considerable quantity of formaldehyde is always formed. The values obtained on analysis of pyrethrolone and its derivatives were usually slightly high for hydrogen and low for carbon, as calculated for compounds with a double unsaturated side chain. The same observations have been made in the case of pyrethrone.

We have, then, an indication that pyrethrolone may be a mixture, possibly containing a compound with a side chain similar to that in VI, an assumption that the results to be described tend to confirm.

Although the boiling range of pyrethrolone is small, upon fractional distillation of the crude product a very marked, progressive increase in the refractive index of the successive fractions was observed (8). The tetrahydropyrethrolone prepared by hydrogenation of each of the fractions, however, showed only very slight differences in refractive index.

Pyrethrone prepared from unfractionated pyrethrolone could also be separated into fractions with similar differences in refractive index, and semicarbazones prepared from the separate fractions showed different melting points. Pyrethrolone methyl ether and acetylpyrethrolone could also be fractionated with similar results.

Positive evidence that pyrethrolone is a mixture was furnished by the results obtained upon determination of the carbon-linked methyl groups in fractions of pyrethrolone and of all the derivatives mentioned. The method employed is, with slight modifications, the one described by Pregl (9). The fractions obtained from pyrethrolone gave terminal methyl values decreasing with increase in boiling range and refractive index. The same was true for the fractions of its derivatives. Although complete separation was in no case attained, the fraction with the highest refractive index and boiling range would be presumed to contain the largest proportion of the conjugated component of structure V, while the fraction with the lowest boiling range and refractive index would contain the largest proportion of the component or components differing from V in having a side chain with the grouping C=CH—CH_3, the compound of structure I not being excluded.

Pyrethrone as prepared in our earlier work, and on which our own spectrographic data were obtained, probably consisted largely of the compound with this grouping.

This demonstration of the heterogeneous nature of pyrethrolone and its derivatives reconciles the apparent contradictions that have arisen between the chemical and the physical facts.

Since analyses of samples of pyrethrolone semicarbazone from mixtures of pyrethrin semicarbazones show 1.2 to 1.3 moles of terminal methyl groups, the question arose whether one of the components is characteristic of pyrethrin I and the other of pyrethrin II. This apparently is not the case, for the analysis of pyrethrolone semicarbazone prepared from pure pyrethrin II semicarbazone (m.p. 164°) also indicated the presence of terminal methyl groups corresponding to 1.3 moles, and pyrethrolone prepared from it furnished on distillation fractions with the same characteristic differences as did pyrethrolone from mixed pyrethrin semicarbazones. It appears now that, unless in the preparation of the original pyrethrin semicarbazones a change affecting the double bonds has occurred, the pyrethrins are more complex mixtures than was previously supposed, possibly comprising at least four structurally different compounds with the possible existence of geometric variations as well.

EXPERIMENTAL

Fractionation of pyrethrolone. Pyrethrin semicarbazone was prepared in the usual manner from a purified pyrethrum concentrate (10) and recrystallized from acetone. This product, which has been shown to be a mixture of the semicarbazones of both pyrethrins but predominantly of pyrethrin I, was saponified and the pyrethrolone semicarbazone recrystallized from methanol. The product that first separated consisted of compact spherical groups of crystals. A second fraction formed flat but separated prisms. Both showed the same melting point, 210–212° (uncorr.), and the same composition.

Anal. Calc'd for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28.

Found,[1] Fraction I: C, 61.04, 60.85, 61.51; H, 7.43, 7.52, 7.57.

Fraction II: C, 61.30, 60.67; H, 7.67, 7.48.

Terminal methyl: (I) 1.20, 1.18; (II) 1.14, 1.17.

Except for an apparent difference in solubility which may later prove of importance, both these fractions will be regarded as the same compound. In the experiments to be described no fractional crystallization of pyrethrolone semicarbazone was made, the total product being employed. It was hydrolyzed in the usual manner, with aqueous potassium bisulfate. Sixteen grams of the crude pyrethrolone was distilled in an ordinary Claisen flask at an oil-bath temperature of 165–170°, and four fractions were collected. The refractive index of each fraction was determined, and each was analyzed for terminal methyl. The results are indicated in Table I.

Each of the four fractions was then separately hydrogenated, using palladium-calcium carbonate catalyst in ethanol solution; all fractions absorbed about the calculated volume of hydrogen in a few minutes. The resulting tetrahydro derivatives were distilled, and the refractive index was determined for each distillate. With a bath temperature of 170° and at 1 mm. pressure, all four hydrogenated fractions distilled almost completely between 135° and 136°. The four distillates showed only slight differences in refractive index, n_D^{26} for fraction I being 1.4907, and for fraction IV, 1.4900. It must be concluded, therefore, that the differences in physical properties among the fractions as shown in Table I are due to the distribution of the components present in pyrethrolone, which depends mainly on the nature or degree of unsaturation in the side chain.

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[1] These values, as well as those recorded in previous articles, are, with respect to hydrogen, high beyond the limit of error. A mixture of 75% of the compound $C_{12}H_{17}N_3O_2$ and 25% of one of similar formula but with two more hydrogen atoms would have a calculated value for hydrogen of 7.49% and for carbon 61.11%, while 75% of the $C_{12}H_{17}N_3O_2$ compound with 25% of the one of formula $C_{11}H_{17}N_3O_2$ would have a value for hydrogen of 7.38% and for carbon 60.74%.

Pyrethrolone was also prepared from pure pyrethrin II semicarbazone (m.p. 164°), fractionated, and the refractive index determined on three fractions obtained through a temperature range of 138–140° at 1 mm. pressure. The values n_D^{27} found for the succeeding fractions were 1.5278, 1.5343, and 1.5405.

Pyrethrolone methyl ether and acetylpyrethrolone were prepared from unfractionated samples of pyrethrolone, the derivatives fractionated, and refractive index and terminal methyl determinations made on the fractions. The results, which are given in Table II, show relations similar to those observed with pyrethrolone.

TABLE I

REFRACTIVE INDEX AND TERMINAL METHYL VALUES OF FRACTIONS OF PYRETHROLONE

FRACTION	WEIGHT, g.	B.P./0.8 MM. °C	n_D^{27}	TERMINAL METHYL[a]
1-A[b]	0.75	140	1.5221	1.64, 1.65
1	2.70	137–139	1.5297	1.46, 1.48
2	3.95	139–141	1.5329	1.35, 1.36
3	3.55	141–144	1.5367	1.22, 1.27
4	2.15	144–145	1.5416	1.15, 1.11

[a] Moles of acetic acid per mole of pyrethrolone (m.w. 178).
[b] Obtained by redistillation of fraction 1.

TABLE II

REFRACTIVE INDEX AND TERMINAL METHYL VALUES OF FRACTIONS OF METHYL ETHER, AND ACETYL DERIVATIVES OF PYRETHROLONE

FRACTION	WEIGHT, G.	DIST. RANGE, °C[a]	n_D^{27}	TERMINAL METHYL[b]
Pyrethrolone methyl ether				
1		104–105	1.5009	1.35, 1.37
2		105–106	1.5049	
3		106–107	1.5112	1.04, 1.03
Acetyl pyrethrolone[c]				
1	3.85	125–128	1.5043	2.53, 2.53
2	3.85	128–133	1.5120	2.24, 2.16
3	1.65	133–137	1.5188	2.00, 2.00

[a] At 1 mm. pressure for pyrethrolone methyl ether, and at 4 mm. for acetylpyrethrolone.
[b] Moles of acetic acid per mole of compound.
[c] Distilled with 18-cm. indented column, bath temperature 165–170°.

Pyrethrone. Another preparation of pyrethrolone was reduced with aluminum amalgam as previously described. After filtration of the ethereal solution, the solvent was removed and the crude residue was dissolved in 7 parts of ethanol and 1 of pyridine. A solution of 1 part of semicarbazide hydrochloride in 1.25 parts of water was added and the solution allowed to stand overnight. The crude semicarbazone was filtered and washed with methanol and then with water (m.p. 210–215°). The yield was about 65% of the weight of the pyrethrolone taken. The crude material was hydrolyzed with oxalic acid according to the original procedure (11), and 6 g. of crude pyrethrone was obtained from 11 g. of the

semicarbazone. This material was distilled from a flask provided with an 18-cm. indented column, with a bath temperature maintained at 110–112° and at 1 mm. pressure.

Fraction 1 (2.7 g.) was collected between 80° and 84° and showed the refractive index n_D^{25} 1.5059 and terminal methyl values of 1.56 and 1.60. It furnished a semicarbazone melting at 211–213° (uncorr.) with decomposition.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.7; H, 7.80.
$C_{12}H_{19}N_3O$: C, 65.1; H, 8.60.
Found: C, 64.78, 64.74; H, 8.77, 8.59.
Terminal methyl, 1.65, 1.69.

One and two-tenths grams of fraction 1, hydrogenated with palladium-calcium carbonate catalyst in ethanol solution, absorbed about 210 ml. of hydrogen (corr.) in 10 minutes. Pyrethrone (m.w. 162) requires 330 ml. and dihydropyrethrone (m.w. 164) 163 ml. of hydrogen per 1.2 g. for saturation of the side chain. The product of the reaction was isolated and distilled at 77–78° (2 mm. pressure). The semicarbazone melted at 176° as reported for tetrahydropyrethrone.

It may be assumed that fraction 1 consists mostly of dihydropyrethrone of structure VI, possibly formed by 1,4-addition of hydrogen to pyrethrone of structure V by the aluminum amalgam reduction. It is possible, however, that the side chain as in VI or its next lower homolog may have been originally present in one of the pyrethrolone components.

Fraction 2, which was collected in the amount of 2.7 g. between 84° and 90°, showed the refractive index n_D^{25} 1.5251 and terminal methyl values of 0.99 and 0.97. It furnished a semicarbazone melting at 214–216° with decomposition.

Anal. Found: C, 65.57, 65.50; H, 8.17, 8.14.
Terminal methyl, 1.03, 1.04.

These data indicate that in fraction 2 pyrethrone with the conjugated side chain predominates.

SUMMARY

It is shown that pyrethrolone is not a homogeneous compound, as previously assumed, but a mixture of components differing with respect to the nature of the side chain. These components can be partially separated by distillation and show marked differences in refractive index. By determination of the carbon-linked methyl groups in successive fractions, it is shown that one component possesses the conjugated system of double bonds, while the other contains a side chain terminating with the group C=CH—CH_3. Several derivatives were shown to be mixtures corresponding to the two systems of unsaturation.

With the demonstration of the heterogeneous nature of pyrethrolone, the apparent discrepancies between absorption results and chemical facts are explained, and the revisions of the formulas proposed by Gillam and West become unnecessary. The mixture of closely related compounds to which the name "pyrethrolone" has been assigned consists predominantly of the compound of structure V.

BELTSVILLE, MD.

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[U. S. DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH ADMINISTRATION, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE]

A NEW CONSTITUENT ISOLATED FROM SOUTHERN PRICKLY-ASH BARK

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The bark of southern prickly-ash, *Zanthoxylum clavaherculis* L., has previously been reported as a source of asarinin, of known structure and possessing the property of increasing the toxic effect of pyrethrum to flies in the same manner and to the same extent as does sesamin (1). The presence of an insecticidal principle in this plant has also been noted (2). That the bark contains physiologically active constituents of unknown nature has long been known, and it is available commercially as a drug.

In attempts to separate the insecticidal agent, a compound was isolated which is of unusual interest because it is closely related structurally to the sympathomimetic compounds such as ephedrine and adrenaline, and to the hormone hordenine. The compound is N-(2-*p*-anisylethyl)-N-methylcinnamamide. It does not represent the insecticidal principle of the plant, for tests show it to be without effect on flies and in combination with asarinin its toxicity is only slight.

The determination of the structure of the new compound proved to be comparatively simple. It was found to contain nitrogen, but it was not soluble in aqueous acids. It also contained methoxyl. From the analytical values a probable molecular weight of about 300 was calculated. A molecular weight determination by the Signer method as modified by Clark (3) showed the value 296. On hydrolysis with ethanolic potassium hydroxide the compound was cleaved and furnished an acid, the potassium salt of which was almost insoluble in ethanolic alkali, and a soluble base, thus characterizing the compound as an amide. The free acid was identified as cinnamic acid by its molecular weight and melting point, and by comparison with authentic material. The basic component was a liquid that formed a hydrochloride melting at 181° (uncorr.) and a picrate melting at 112°. Tests showed that the base was a secondary amine. The chlorine and methoxyl content of the hydrochloride indicated a molecular weight of about 201, corresponding to 165 for the base. Oxidation of the base with permanganate furnished anisic acid, which was identified by comparison with authentic material.

From these data three possible structures for the base might be deduced: (I) $CH_3OC_6H_4CH_2NHC_2H_5$, (II) $CH_3OC_6H_4CH(CH_3)NHCH_3$, and (III) $CH_3OC_6H_4CH_2CH_2NHCH_3$. Of these, I and II seemed improbable and I was definitely excluded by comparison of the synthetic compound with the natural amine. Compound of formula III is known, but no reference to its preparation by the more recent methods could be found in the literature. We have, however, prepared it by reaction of 1-*p*-anisyl-2-bromoethane with methylamine. Its hydrochloride and picrate, like the corresponding derivatives of the natural base, melted at 181–182° and 112°, respectively, and no depression was noted when

mixed melting points were taken with material from the natural source. The natural amine was thus identified as corresponding to formula III.

When the synthetic amine was treated with cinnamoyl chloride, the synthetic N-(2-*p*-anisylethyl)-N-methylcinnamamide proved to be identical in all respects with the natural compound obtained from prickly-ash bark.

EXPERIMENTAL

Isolation of the natural acid amide from prickly-ash bark. About 1 kg. of coarsely ground bark was exhaustively extracted with petroleum ether (b.p. 30–60°) and the extract concentrated to a thin syrup. During evaporation and on standing at room temperature the concentrate deposited crude asarinin, which was removed by filtration. The filtrate (about 80 grams) was diluted with 2 or 3 volumes of petroleum ether and extracted with 3 portions of 200 ml. of 90% acetic acid, which dissolved all the toxic material together with extraneous acid, neutral, and basic substances, among which is berberine. The acetic acid was removed in a vacuum, the acid residue dissolved in ether, and the ethereal solution washed first with water to remove the basic material as acid salts, and then with several portions of 2% potassium hydroxide, which removed a quantity of fatty acids and other alkali-soluble substances. By employing small portions of alkali solution at first, and with gentle shaking, troublesome emulsions were avoided. The residue from the ethereal solution (about 40 grams) after complete removal of the solvent was distilled in a Hickman still at 0.01–0.005 mm. pressure. The fraction obtained below about 150° was mostly liquid, from which very little crystalline material could be isolated. The fraction obtained between 150° and 180° (about 15 grams) congealed to a mass of crystalline material consisting mostly of asarinin imbedded in a viscous syrup. By filtration on silk most of the asarinin was removed, and the crystals were washed from the adhering syrup with ethanol. The washings were freed from solvent, and the residue was added to the syrupy filtrate, from which on longer standing, and especially on seeding, the amide slowly crystallized. The magma was filtered with suction on silk and most of the syrupy mother liquors removed. Further purification was effected by boiling with petroleum ether (b.p. 60–90°), in which the amide is more soluble than the syrupy by-products. On cooling and standing, the amide crystallized in rosettes of prisms, which were still contaminated with syrupy impurities and not yet free of asarinin. By repetition of the process and finally by dissolving the crystals in ether and cooling the solution to a low temperature and filtering, the pure compound was obtained in colorless prisms melting at 76°. More of the compound could be obtained by the same process from the still-residue, but more asarinin was encountered. The purification is accompanied by considerable loss and the yield does not exceed 2 or 3 grams.

The compound is very soluble in all organic solvents except petroleum ether.

Anal. Calc'd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; CH_3O, 10.51; mol. wt., 295.
Found: C, 77.09; H, 7.17; N, 4.76, 4.84; CH_3O, 10.45, 10.79; mol. wt., 296.

Alkaline hydrolysis of the amide. Five-tenths of a gram of substance in 5 ml. of 25% methanolic potassium hydroxide was heated to 100° in a closed tube for 20 hours. The amount of separated crystalline deposit increased on cooling, and was filtered off and washed with cold methanol. It was readily soluble in water, and on acidification of the aqueous solution the free acid was obtained as a voluminous precipitate. It was recrystallized from water, m.p. 133–134°, mol. wt. (titration) 152. The yield was 0.2 g. When treated with alkaline permanganate it gave a strong odor of benzaldehyde. A mixture with authentic cinnamic acid melted at 133–134°. The acid is therefore identical with cinnamic acid.

The alkaline methanol filtrate from the potassium salt was diluted with an equal volume of water and the methanol distilled off. The oily amine that separated was extracted with ether; the ethereal solution was washed with water and the base extracted with dilute hydrochloric acid. On evaporation of the acid solution and drying at 100° over potassium hy-

droxide, the crystalline hydrochloride was obtained, which after recrystallization from ethyl acetate melted at 181–182°. The yield was 0.3 g.

Anal. Calc'd for $C_{10}H_{16}ClNO$: Cl, 17.61; CH_3O, 15.33.

Found: Cl, 17.41, 17.61; CH_3O, 15.39.

The picrate was obtained by mixing equal parts of the free base and picric acid in concentrated ethanolic solution. Upon recrystallization from water it melted at 112°.

Oxidation of amine. A suspension of 0.27 g. of the base in 50 ml. of water was oxidized with potassium permanganate at 100° until the color of the reagent persisted. The excess reagent was then removed with a few drops of hydrogen peroxide and the alkaline solution concentrated to 15 ml. On acidification the acid separated as a voluminous precipitate, which was recrystallized from hot water, in which it is very difficultly soluble. It melted at 184°; yield, 0.15 g., mol. wt. (titration) 155. A mixture of the acid with authentic anisic acid (mol. wt. 152) melted also at 184°. The oxidation product of the amine is therefore anisic acid.

Synthesis of N-(2-p-anisylethyl)-N-methylamine. The first intermediate, 1-*p*-anisyl-2-ethanol, was prepared from 45 g. of *p*-bromoanisole and ethylene oxide by the method of Speer and Hill (4). The benzene solution, after being washed with dilute alkali, was dried and the solvent removed. The residue was fractionated and yielded 14.5 g. of product, b.p. 145–160° at 10 mm. pressure.

The corresponding 1-*p*-anisyl-2-bromoethane was readily obtained by bromination of the alcohol. The crude alcohol was dissolved in about 50 ml. of dry benzene, and 20 g. of phosphorus tribromide was added in small portions to the cold solution. After standing for about 30 minutes, it was heated on the steam-bath until the evolution of hydrobromic acid ceased. The solution was poured onto ice, and the aqueous layer separated. The benzene solution was washed successively with water, sodium carbonate solution, and water, and then dried over calcium chloride. The residue after removal of the benzene was fractionated at 1 mm., and yielded 9.6 g., b.p. 105–111°. In another experiment 23 g. of the alcohol yielded 16.5 g., n_D^{27} 1.5578, d_{27}^{27} 1.3872.

Anal. Calc'd for $C_9H_{11}BrO$: CH_3O, 14.41; Br, 37.21.

Found: CH_3O, 14.28; Br, 36.85.

The last mentioned quantity of 1-*p*-anisyl-2-bromoethane was heated at 100° for 24 hours in a sealed tube with 100 ml. of about 80% aqueous methanol saturated with methylamine. The contents of the tube were evaporated on the steam-bath to expel the excess amine, strong potassium hydroxide was added, the separated base extracted with ether, and the solution washed with water. The amine was extracted with a slight excess of dilute hydrochloric acid, and the solution was evaporated to dryness, first on the steam-bath, then at 100°, and finally over potassium hydroxide. It weighed 9.7 g. After recrystallization from ethyl acetate, it melted at 181–182°. A mixture of the natural and synthetic amine hydrochlorides melted also at 181–182°. The picrate melted at 112°, and the melting point was not depressed when the picrate was mixed with the picrate of the natural amine. The free amine was obtained from 4 g. of the hydrochloride by adding an excess of concentrated potassium hydroxide, extracting with ether, drying with potassium carbonate, and expelling the solvent. The base distilled at 141–142° at 19 mm. and boiled at 258–259° at 760 mm. It formed a solid carbonate on contact with the air.

Synthesis of N-(2-p-anisylethyl)-N-methylcinnamamide. Five grams of N-(2-*p*-anisylethyl)-N-methylamine hydrochloride was added to 15 ml. of water containing 3.5 g. of potassium hydroxide. An equal volume of benzene was added and the reaction mixture cooled to 0°. A solution of 4.5 g. (calc'd 4.13 g.) of cinnamoyl chloride in 15 ml. of benzene was introduced in small portions with constant agitation. After standing for about 30 minutes at room temperature, ether was added and the aqueous layer discarded. The benzene-ether solution was washed with water, dried, and concentrated to a small volume, and petroleum ether was gradually added until a turbidity was produced. It was then seeded with a little of the natural amide, and more petroleum ether was added as the crystallization proceeded. After the solution had stood for several hours in the icebox, the separated crystals were

filtered off and washed with petroleum ether. The compound without further purification melted at 75–76°, as did a mixture of it with the natural amide. The yield was 6.7 g., or 90%.

SUMMARY

A compound chemically related to adrenaline and ephedrine has been determined as N-(2-*p*-anisylethyl)-N-methylcinnamamide. Its synthesis is described.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, PURDUE UNIVERSITY]

SYNTHESIS OF IODOSULFOPHENYLAZO AND IODOCARBOXYPHENYLAZO DERIVATIVES OF NAPHTHOL AND NAPHTHYLAMINE SULFONIC ACIDS[1]

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As there is still a need for better radiographic opaques, this work on a new class of iodinated organic compounds was undertaken. Azonaphthalene sulfonic acid compounds have been found to be excreted from the liver and concentrated in the gall bladder (1); therefore, they were selected as a nucleus from which to begin. In this work, azo derivatives of naphthol and naphthylamine sulfonic acids were prepared from 3,5-diiodosulfanilic acid and 3,5-diiodo-*p*-aminobenzoic acid.

I. *Iodinated sulfophenylazonaphthalene sulfonic acids.* In this series 3,5-diiodosulfanilic acid was diazotized and coupled with the following naphthalene sulfonic acids: (A) 1-naphthol-4-sulfonic acid to give the disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthol-4-sulfonic acid; (B) 1-naphthylamine-4-sulfonic acid to give the disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4-sulfonic acid; (C) 1-naphthylamine-4,8-disulfonic acid to give the trisodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4,8-disulfonic acid.

II. *Iodinated carboxyphenylazonaphthalene sulfonic acids.* 3,5–Diiodo-4-aminobenzoic acid was diazotized and coupled with the naphthalene sulfonic acids listed under I to yield: (D) the disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthol-4-sulfonic acid; (E) the disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4-sulfonic acid; (F) the trisodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4,8-disulfonic acid.

Sodium chloride is generally a contaminating substance in these preparations since it is extremely difficult to get a complete separation of it from the dyes. Therefore, the percentages of iodine and chlorine were determined by electrometric titration with $N/10$ silver nitrate solution, using a silver electrode and a mercurous sulfate half-cell according to the method used by Klemme and Hunter (2).

EXPERIMENTAL

3,5-Diiodosulfanilic acid. This compound was prepared by a modification of the method proposed by Boyle (3). One hundred four and six-tenths grams of reagent sulfanilic acid was dissolved with heating and stirring in 3 liters of 10% hydrochloric acid. When solution was complete, 60 cc. (200 g.) of iodine monochloride was added and the mixture kept at 80° for two hours with mechanical stirring.

After standing overnight, the mixture was filtered and the moist, crude acid dissolved in boiling distilled water, activated charcoal added, and boiling continued for a few minutes.

[1]From a portion of a thesis submitted by Haakon Bang in partial fulfilment for the degree of Doctor of Philosophy, December, 1941.

Filtration yielded a reddish filtrate which was made slightly alkaline by the addition of 30 g. of potassium hydroxide dissolved in 300 cc. of distilled water. After a few minutes, a precipitate of potassium 3,5-diiodosulfanilate appeared. The solution was cooled; the crystals were filtered off and washed with water. A second crop of crystals was obtained by concentration of the mother liquor. The yield at this point was 199.2 g. of the dried salt.

The product obtained above was dissolved in 1500 cc. of boiling water containing 50 cc. of 37% hydrochloric acid. When solution was complete, activated charcoal was added and the solution filtered. The filtrate was cooled and the white crystals of 3,5-diiodosulfanilic acid filtered off and dried at 105°; yield, 149.4 g. (64.2%).

2-(2,6-Diiodo-4-sulfophenylazo)-1-naphthol-4-sulfonic acid. Forty-two and five-tenths grams of 3,5-diiodosulfanilic acid was suspended in 185 cc. of 10% hydrochloric acid and the mixture cooled to 0°. Six and nine-tenths grams of pure sodium nitrite, dissolved in about 4 cc. of ice-cold distilled water, was added gradually to the cold mixture of the 3,5-diiodosulfanilic acid, and stirred for 30 minutes, maintaining the temperature at 0°. The mixture was tested with starch iodide paper and when the test was positive, 0.1 g. of 3,5-diiodosulfanilic acid was added to decompose the excess nitrous acid.

The cold mixture containing the 3,5-diiodo-4-diazobenzene-1-sulfonic acid was poured, a small quantity at a time, into a solution containing 23.6 g. of recrystallized Eastman technical 1-naphthol-4-sulfonic acid and 40 g. of anhydrous sodium carbonate, allowing the effervescence and the foam to subside before each subsequent addition of the diazo mixture. The deep red solution was heated to boiling, cooled, and filtered. The filtrate was evaporated to about 200 cc., 50 g. of sodium chloride was dissolved in the hot solution which was then cooled, and the precipitated dye collected and dried overnight at 105°.

The dry salt cake was powdered and extracted several times with 95% methanol, using 1 liter for the first extraction and 500-cc. portions for three further extractions. The combined alcoholic extracts were evaporated to dryness on a steam-bath and the dried, powdered residue again extracted with 1500 cc. of 99.5% methanol. This alcoholic extract was evaporated, and the powdered residue dried at 105°. This powder was washed twice with a mixture of 200 cc. of ether and 100 cc. of 99.5% methanol. The insoluble dye was filtered off and again dried and powdered; yield, 29.9 g. (40.3%, corrected for sodium chloride content).

A small quantity of the dye was dissolved in distilled water, treated with a few drops of chlorine water and shaken with chloroform. The chloroform layer remained perfectly colorless, indicating the absence of free iodine or iodides.

Anal. Calc'd for $C_{16}H_8I_2N_2Na_2O_7S_2$: I, 36.05. Found: I, 35.76, 35.84.

Sodium chloride content 5.1%.

The compound when dry is a dark brownish-red powder, but on exposure to air it takes up moisture and becomes light red. It is insoluble in ether, chloroform, and acetone; soluble in ethanol and methanol. When added to water, there is an evolution of heat as the dye goes into solution. Solubility: 27.2 g. per 100 g. of water.

Disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4-sulfonic acid. The uniodinated dye was first prepared by Griess (4). Forty-two and five-tenths grams of 3,5-diiodosulfanilic acid was suspended in 185 cc. of 10% hydrochloric acid and the mixture cooled to 0°. A cold solution containing 6.9 g. of pure sodium nitrite in 5 cc. of distilled water was added in portions. After one-half hour of continuous stirring, during which the solution was kept at 0° the diazo mixture was tested for excess nitrous acid as before.

The mixture containing the yellow 3,5-diiodo-4-diazobenzene-1-sulfonic acid was poured, in small quantities, into a solution containing 25.7 g. of Eastman sodium naphthionate and 50 g. of anhydrous sodium carbonate. A slight excess of the sodium naphthionate was found to give better results since, when just the theoretical amount was used, the product obtained gave results high in per cent of iodine. It is believed that this may be due to the formation of 3,5-diiodo-4-hydroxybenzene-1-sulfonic acid. No attempt was made to isolate this substance. It was also found that the coupling reaction yielded better results

when carried out cold. Again it was necessary to use care in adding the diazo mixture to the sodium naphthionate solution to prevent excessive foaming. Constant and vigorous stirring was employed.

The deep red solution resulting from the coupling reaction was heated to boiling, cooled, and filtered. The filtrate was evaporated to complete dryness on a steam-bath, since this dye could not be salted out readily. The dried residue was extracted with 1 liter of 95% methanol and then with three 500-cc. portions. The combined extracts were evaporated to dryness and again extracted with 1 liter of 99.5% methanol. The dark red powder was then washed with an ether-methanol mixture as before; yield, 38.6 g. (54.9%, corrected for sodium chloride content.) The test for free iodine and iodides was negative.

Anal. Calc'd for $C_{16}H_9I_2N_3Na_2O_6S_2$: I, 36.10. Found: I, 35.16, 35.90.

Sodium chloride: 13.1%.

The disodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4-sulfonic acid is a fine red powder which is insoluble in chloroform, ether, and acetone. It is soluble in methanol and ethanol, the former being the better solvent. Solubility: 33.1 g. per 100 g. water.

Trisodium salt of 2-(2,6-diiodo-4-sulfophenylazo)-1-naphthylamine-4,8-disulfonic acid. Forty-two and five-tenths grams of 3,5-diiodosulfanilic acid was suspended in 185 cc. of 10% hydrochloric acid and the mixture cooled to 0° and diazotized as before.

Thirty and five-tenths grams of recrystallized Eastman technical 1-naphthylamine-4,8-disulfonic acid was dissolved with 40 g. of anhydrous sodium carbonate in 200 cc. of distilled water and the 3,5-diiodo-4-diazobenzene-1-sulfonic acid was added in small quantities with continuous and vigorous stirring, allowing the foaming to subside before each subsequent addition. The deep red solution was then heated to boiling, cooled, filtered, and the filtrate evaporated on a steam-bath to complete dryness. As in the previous experiment, it was not possible to salt out the dye with sodium chloride.

The residue was extracted with 1500 cc. of 95% methanol and a second portion of 800 cc. of methanol of the same strength. The 99.5 g. of residue obtained from the evaporation of the combined extracts was again extracted with 1500 cc. of 99.5% methanol. The filtrate from the latter extraction was evaporated to dryness on a steam-bath and the residue dried and powdered. The powder was washed twice with a mixture of 250 cc. of ether and 75 cc. of 99.5% methanol and dried at 105°; yield, 50.1 g. (62.2%, corrected for sodium chloride content.)

The dye was found to be free from iodine or inorganic iodides when tested with chloroform and fresh chlorine water.

Anal. Calc'd for $C_{16}H_8I_2N_3Na_3O_9S_3$: I, 31.52. Found: I, 31.99, 32.22.

Sodium chloride content: 15.5%.

The trisodium salt of 2-(2,6-diiodo-4-sulfonphenylazo)-1-naphthylamine-4,8-disulfonic acid is a dark red powder which is insoluble in chloroform, ether and acetone. Solubility: 48.8 g. per 100 g. of water.

4-Amino-3,5-diiodobenzoic acid. This compound was first prepared by Michael and Norton (5) and again by Wheeler and Liddle (6), who also determined the structure of the compound. The method used for the preparation of this compound was similar to that employed by Klemme and Hunter (2).

One hundred thirty-seven grams of Eastman practical *p*-aminobenzoic acid was suspended in three and a half liters of 10% hydrochloric acid and dissolved with the aid of heat. When the temperature reached 80°, 110 cc. of iodine monochloride (10% excess) was added. Stirring was continued and the mixture was kept hot for two hours then allowed to cool. After standing overnight the brown precipitate was filtered off.

The residue was suspended in boiling distilled water and dissolved by adding 25% sodium hydroxide until the mixture was slightly alkaline to litmus. The solution was boiled with activated charcoal, filtered, and while hot, precipitated with hydrochloric acid. When cool, the fine, white precipitate of 4-amino-3,5-diiodobenzoic acid was filtered off, dried at 105° and finely powdered; yield, 320.6 g. (84%).

Disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthol-4-sulfonic acid. A method for the diazotization of 4-amino-3,5-diiodobenzoic acid is described by Wheeler and Liddle (7) and used by Klemme and Hunter (8).

Thirty-eight and eight-tenths grams of 4-amino-3,5-diiodobenzoic acid was diazotized in 150 cc. of concentrated sulfuric acid at 0° by the gradual addition of 6.9 g. of pure dry sodium nitrite. Fifteen or twenty minutes after the last addition of the sodium nitrite, a drop or two of the acid solution was added to 1 cc. of distilled water and tested with starch iodide paper. Small quantities of the 3,5-diiodo-4-aminobenzoic acid were added until the test for free nitrous acid was just negative.

The acid solution was then poured into about 1 kg. of cracked ice, whereupon a yellow precipitate of 3,5-diiodo-4-diazobenzoic acid settled out. It was necessary to keep an excess of ice present to prevent decomposition of the diazo compound.

A solution was prepared by dissolving 28 g. of recrystallized Eastman technical 1-naphthol-4-sulfonic acid and 220 g. of sodium hydroxide in 500 cc. of distilled water. When this solution was cool, the diazo mixture was added slowly with stirring. The solution was allowed to stand overnight and filtered. The deep red filtrate was concentrated on a hot-plate at low heat to about 1 liter and made acid with 37% hydrochloric acid. The red precipitate which formed was filtered off and redissolved in about 300 cc. of 2% of sodium hydroxide solution. The resulting solution was filtered and the acid reprecipitated with 37% hydrochloric acid. The precipitate was filtered off, and washed with cold distilled water. The powder was dried, but upon analysis it was found necessary to repeat the purification a third time; yield, 38.5 g. (61.7%, corrected for sodium chloride content). The compound gave no test for free iodine or iodides.

Anal. Calc'd for $C_{17}H_{10}I_2N_2O_6S$: I, 40.68. Found: I, 41.36, 40.28.

Sodium chloride content: 0.6%.

To form the disodium salt of the compound, 20 g. of the acid was dissolved with 2.7 g. of anhydrous sodium carbonate, the theoretical quantity, in about 100 cc. of distilled water. The resulting solution was evaporated to dryness on a water-bath and the residue dissolved in 99.5% methanol and filtered. The methanol filtrate was evaporated and the residue dried at 105° overnight.

The disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthol-4-sulfonic acid is a fine, dark red powder. It is insoluble in chloroform, ether, and acetone, but is soluble in methanol and ethanol, the former being the better solvent. Solubility: 30.8 g. per 100 g. water.

Disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4-sulfonic acid. Thirty-eight and eight-tenths grams of 4-amino-3,5-diiodobenzoic acid was diazotized in 150 cc. of concentrated sulfuric acid at 0° as described in the previous experiment. The diazotized mixture was poured with vigorous stirring into 1 kg. of cracked ice, and this cold solution was poured slowly with stirring into 500 cc. of an aqueous solution containing 25 g. of Eastman sodium naphthionate and 220 g. of sodium hydroxide. Again it was found best to keep the reaction mixture cold.

The cool solution resulting from the coupling reaction was filtered and made acid with 37% hydrochloric acid. The precipitated acid dye was collected and redissolved in 300 cc. of distilled water containing 5 g. of sodium hydroxide (a slight excess). The deep red solution was filtered and the acid reprecipitated with 37% hydrochloric acid. The precipitate was collected, washed with distilled water, dried, and powdered; yield, 51.1 g. (81.9%, corrected for sodium chloride content.) The test for free iodine and iodides was negative.

Anal. Calc'd for $C_{17}H_{11}I_2N_3O_5S$: I, 40.49. Found: I, 40.03, 40.57.

Sodium chloride content: 5.3%.

Fifteen grams of the acid dye was mixed with the theoretical quantity of sodium carbonate and dissolved in the smallest possible quantity of water. The solution was then evaporated to dryness on a steam-bath and the residue powdered and dissolved in 99.5% methanol, filtered, and the filtrate evaporated. The residue was powdered and dried at 105°.

The disodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4-sulfonic acid is a fine red powder which when heated strongly gives off iodine vapors and finally burns to a white ash. It is insoluble in chloroform, ether, and acetone, but is soluble in methanol and ethanol. Solubility: 24 g. per 100 g. water.

Trisodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4,8-disulfonic acid. Thirty-eight and eight-tenths grams of 4-amino-3,5-diiodobenzoic acid was dissolved in 150 cc. of concentrated sulfuric acid and the solution was cooled to 0° in an ice and salt mixture. The diazotization was carried out by adding 6.9 g. of pure, dry sodium nitrite in small quantities while the mixture was stirred as prescribed before. After the reaction was complete and there was a negative test for nitrous acid, the reaction mixture was added to 1 kg. of cracked ice with vigorous stirring.

Thirty and three-tenths grams of recrystallized Eastman technical 1-naphthylamine-4,8-disulfonic acid was dissolved with 300 g. of anhydrous sodium carbonate in about 1 liter of distilled water.

The diazotized solution of the 4-amino-3,5-diiodobenzoic acid was added, in small quantities and with continuous stirring, to the solution containing the 1-naphthylamine-4,8-disulfonic acid. The coupling reaction was kept cool in an ice-bath. There was considerable effervescence and foaming. When the coupling was complete, the deep red solution was heated to the boiling point, cooled, and filtered. The filtrate was evaporated to about 700 cc. and made acid with concentrated hydrochloric acid, precipitating the acid dye. The dye was filtered off and added to a slight excess of anhydrous sodium carbonate and enough distilled water to form a solution. This solution was then filtered and evaporated to dryness. The resulting red powder was dissolved in 1700 cc. of 99.5% methanol and filtered. The filtrate was evaporated to dryness on a steam-bath, and the dark brownish-red residue was powdered and dried at 105°; yield, 28.9 g. (37.1%, corrected for sodium chloride content).

Anal. Calc'd for $C_{17}H_8I_2N_3Na_3O_8S_2$: I, 32.5. Found: I, 32.82, 33.05.

Sodium chloride content: 3.4%.

The trisodium salt of 2-(2,6-diiodo-4-carboxyphenylazo)-1-naphthylamine-4,8-disulfonic acid is a dark red powder which, when heated strongly, gives off iodine vapors and finally burns to a white ash. It is insoluble in chloroform, but slightly soluble in ether. It is very soluble in methanol and ethanol. Solubility: 37.8 g. per 100 g. water.

SUMMARY

By coupling various naphthol and naphthylamine sulfonic acids with diazotized 3,5-diiodosulfanilic and 3,5-diiodo-*p*-aminobenzoic acids, iodinated azo dyestuffs have been synthesized for testing as radiographic opaques. Several of the sodium salts of these dyestuffs are highly soluble in water.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

SOLUBILITIES OF HIGH MOLECULAR WEIGHT SYMMETRICAL NORMAL ALIPHATIC TERTIARY AMINES

A. W. RALSTON, C. W. HOERR, AND P. L. DUBROW

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Recent papers in this series have shown that the behavior of secondary aliphatic amines (1) in organic solvents resembles that of primary amines (2) containing a corresponding number of carbon atoms. For example, the solubility curve of dioctylamine in acetone is almost identical with that of primary hexadecylamine. The nitrogen atom of a secondary amine appears to behave in effect as a carbon atom. In order to investigate the influence of a third alkyl group on the nitrogen atom, the solubilities of trioctylamine, tridodecylamine, and trioctadecylamine were determined in thirteen common organic solvents.

EXPERIMENTAL

The tertiary amines were prepared by heating their corresponding secondary amines (1) with the appropriate alkyl iodides for about three hours at 160–170° at atmospheric pressure. The alkyl iodides were obtained from highly purified alcohols which had the following freezing points: 1-octanol, −13.10°; 1-dodecanol, 23.95°; and 1-octadecanol, 57.98°. The tertiary amines were crystallized several times from 95% ethanol containing a sufficient amount of benzene to prevent the separation of two liquid phases. After the final recrystallization the solvent was removed at elevated temperature under reduced pressure. The freezing points of the tertiary amines were as follows: trioctylamine, −34.6°; tridodecylamine, 15.7°; and trioctadecylamine, 54.0°. The only reference (3) to this constant in the literature gives the melting point 54–55° for trioctadecylamine. The tertiary amines used in this investigation were considered to be at least 99% pure on the basis of their cooling curves, since the freezing points of 3-g. samples held within 0.2° for more than twenty minutes.

The solvents and the procedure employed for the solubility measurements have been previously described (4, 5).

RESULTS AND DISCUSSION

The solubilities of trioctylamine, tridodecylamine, and trioctadecylamine are listed in Tables I–III, respectively. The amines form simple eutectics with the non-polar solvents benzene, cyclohexane, and tetrachloromethane. These systems are shown graphically in Figs. 1–3, respectively, and the compositions and freezing points of the eutectics are listed in Table IV.

The tertiary amines are more soluble in cyclohexane than in benzene. In this respect they differ from the primary and secondary amines. However, like the latter amines, the tertiary amines are less soluble in tetrachloromethane than in the other non-polar solvents. The solubility curves of the tertiary amines in the slightly polar solvents trichloromethane and ethyl ether resemble the tetrachloromethane curves. Trioctadecylamine differs from all of the other amines investigated in that it is less soluble in trichloromethane than in tetrachloromethane at the lower concentrations.

TABLE I

SOLUBILITIES OF TRIOCTYLAMINE[a]

SOLVENT	G. AMINE PER 100 G. SOLVENT					
	−60.0°	−50.0°	−40.0°	−30.0°	−20.0°	0.0°
Benzene[b]	—	—	—	—	—	—
Cyclohexane[c]	—	—	—	—	—	—
Tetrachloromethane[d]	—	—	—	—	∞	∞
Trichloromethane	134	287	1000	∞	∞	∞
Ethyl ether	58	147	600	∞	∞	∞
Ethyl acetate[e]	—	0.1	4.2	14.1	∞	∞
Butyl acetate	11.5	22.7	325	∞	∞	∞
Acetone[f]	—	—	0.2	1.2	1.7	3.7
2-Butanone[g]	—	0.1	5.9	14.3	37.0	∞
Methanol	—	—	<0.1	0.2	0.3	0.4
95% Ethanol	—	—	≈0.1	0.3	0.4	0.6
Isopropanol	2.3	5.0	17.0	∞	∞	∞
n-Butanol	8.1	15.5	220	∞	∞	∞

[a] ∞ with all solvents above −34.6°, except as otherwise indicated.
[b] ∞ above 5.5°. See Table IV and Fig. 1.
[c] ∞ above 6.5°. See Table IV and Fig. 2.
[d] ∞ above −23.0°. See Table IV and Fig. 3.
[e] ∞ above −22.5°. See Fig. 4.
[f] ∞ above 48.0°.
[g] ∞ above −17.5°. See Fig. 5.

TABLE II

SOLUBILITIES OF TRIDODECYLAMINE[a]

SOLVENT	G. AMINE PER 100 G. SOLVENT						
	−20.0°	−10.0°	0.0°	10.0°	20.0°	[illegible]	40.0°
Benzene	—	—	—	570	∞	∞	∞
Cyclohexane	—	—	—	570	∞	∞	∞
Tetrachloromethane	6.3	16.5	43.2	188	∞	∞	∞
Trichloromethane	7.6	26.8	106	490	∞	∞	∞
Ethyl ether	4.2	13.5	54	315	∞	∞	∞
Ethyl acetate[b]	—	0.2	1.0	≈850	∞	∞	∞
Butyl acetate	1.5	3.9	11.4	900	∞	∞	∞
Acetone[c]	—	—	—	0.1	1.4	2.2	3.4
2-Butanone	—	—	0.5	9.8	∞	∞	∞
Methanol	—	—	—	<0.1	0.3	0.5	1.2
95% Ethanol	—	—	—	—	0.2	0.7	1.5
Isopropanol[d]	—	—	<0.1	2.7	15.3	23.9	58
n-Butanol	—	<0.1	1.5	25.5	∞	∞	∞

[a] ∞ with all solvents above 17.9°, except as otherwise indicated.
[b] At 9.8° any amount from approx. 19 to 800 g./100 g. solvent is soluble.
[c] 6.7 g./100 g. solvent at 56.1° (b.p. of acetone).
[d] ∞ above 41.1°. See Fig. 6.

The solubilities of the tertiary amines decrease abruptly with increased polarity of the solvents. Their solubilities in the moderately polar solvents ethyl acetate, butyl acetate, acetone, and 2-butanone are much less than those in the solvents discussed above. Their behavior in these solvents is illustrated by the solubility curves in ethyl acetate (Fig. 4) and in 2-butanone (Fig. 5). The

TABLE III

SOLUBILITIES OF TRIOCTADECYLAMINE[a]

SOLVENT	G. AMINE PER 100 G. SOLVENT						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
Benzene	—	0.5	4.2	49.2	168	840	∞
Cyclohexane	—	2.0	18.6	77	202	950	∞
Tetrachloromethane	1.5	5.2	13.0	33.5	81	335	∞
Trichloromethane	0.9	4.1	13.5	40.6	117	650	∞
Ethyl ether[b]	<0.1	1.6	8.1	28.8	—	—	—
Ethyl acetate	—	—	<0.1	0.4	3.2	1550	∞
Butyl acetate	—	—	0.1	2.4	15.1	1550	∞
2-Butanone	—	—	—	0.1	2.4	1250	∞
Isopropanol	—	—	—	—	<0.1	2.0	5.3
n-Butanol	—	—	—	—	0.2	17.0	∞

[a] ∞ with all solvents above 54.0°, except as otherwise indicated.
[b] 50 g./100 g. solvent at 34.5° (b.p. of ethyl ether).

TABLE IV

EUTECTICS FORMED BY THE TERTIARY AMINES

SOLVENT		AMINE		
		Trioctyl	Tridodecyl	Trioctadecyl
Benzene	Wt. % amine	91.0	42.5	0.2
	Temp., °C.	−38.5	+0.3	5.5
Cyclohexane	Wt. % amine	47.0	27.6	≈0.1
	Temp., °C.	−46.5	−12.5	6.5
Tetrachloromethane	Wt. % amine	37.5	3.9	—
	Temp., °C.	−60.1	−23.7	—

solubility of the tertiary amines becomes so limited in these solvents that in several of the systems a region of two immiscible solutions appears. The most striking feature of this behavior is that the region of immiscibility becomes progressively smaller with increased molecular weight of the tertiary amines. This is opposite to the behavior of the primary and secondary amines.

The solubilities of the tertiary amines in the alcohols are illustrated by the diagrams for isopropanol and *n*-butanol in Figs. 6 and 7, respectively. The

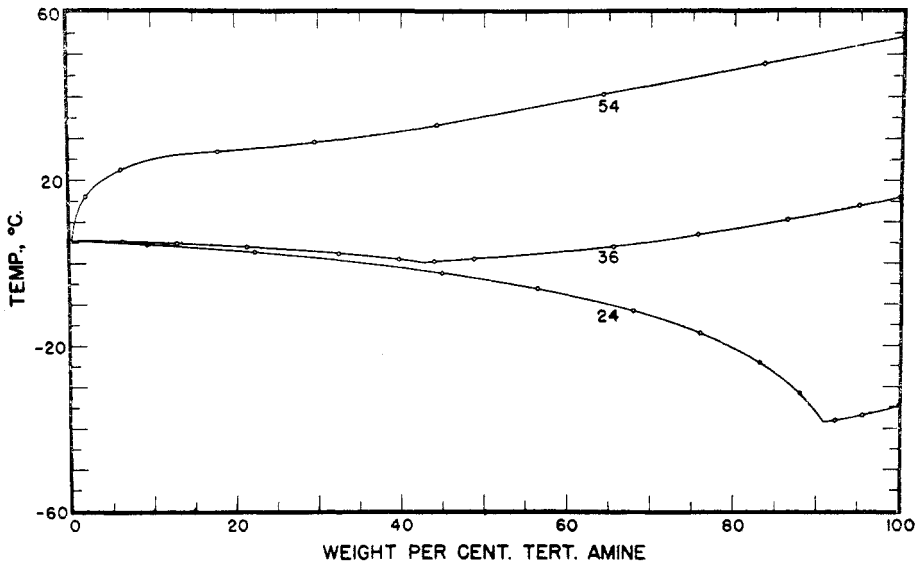

FIG. 1. SOLUBILITIES OF TERTIARY AMINES IN BENZENE. THE NUMBERS ON THE CURVES REFER TO THE NUMBER OF CARBON ATOMS IN THE AMINE MOLECULE

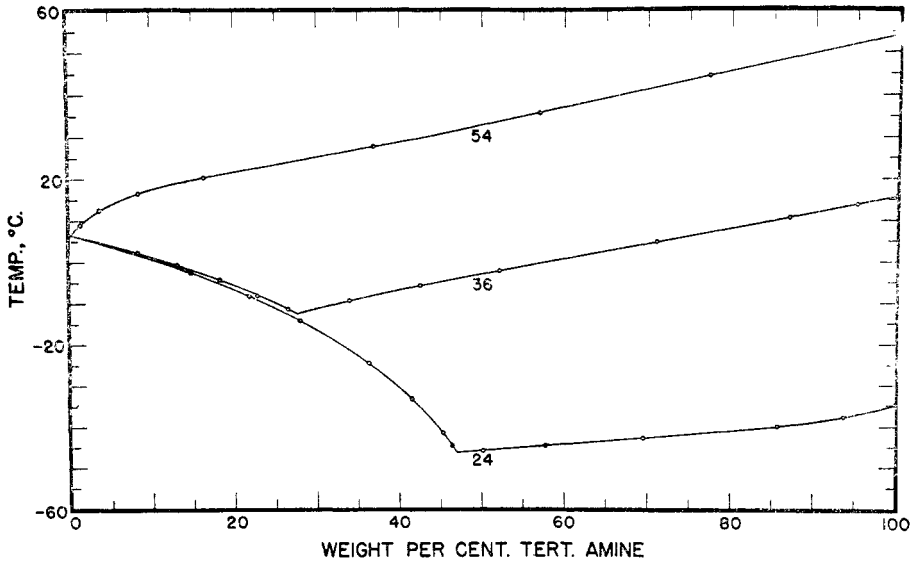

FIG. 2. SOLUBILITIES OF TERTIARY AMINES IN CYCLOHEXANE

solubility of the tertiary amines increases with increased molecular weight of the alcohols. This behavior is similar to that of the secondary amines, but opposite that of the primary amines whose solubility decreases with increased molecular

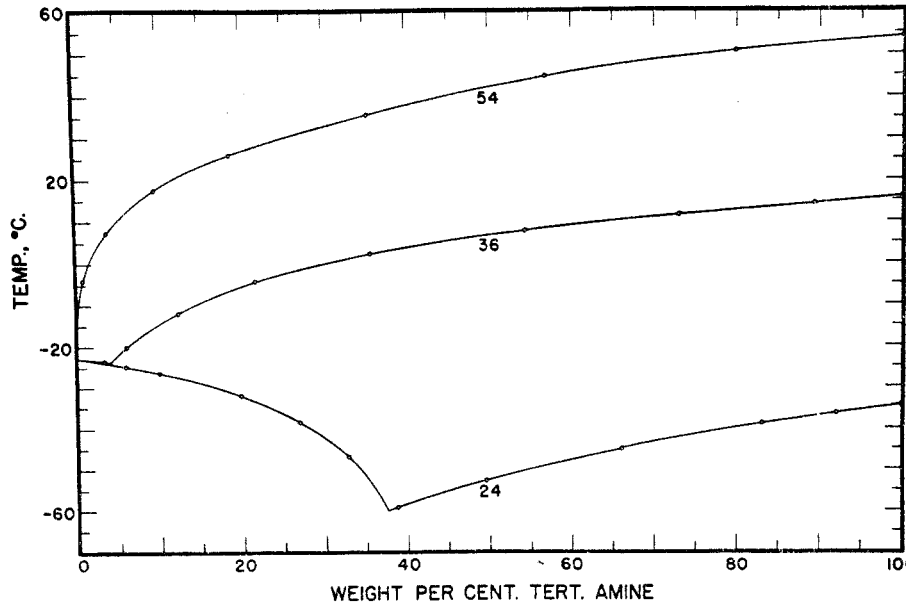

FIG. 3. SOLUBILITIES OF TERTIARY AMINES IN TETRACHLOROMETHANE

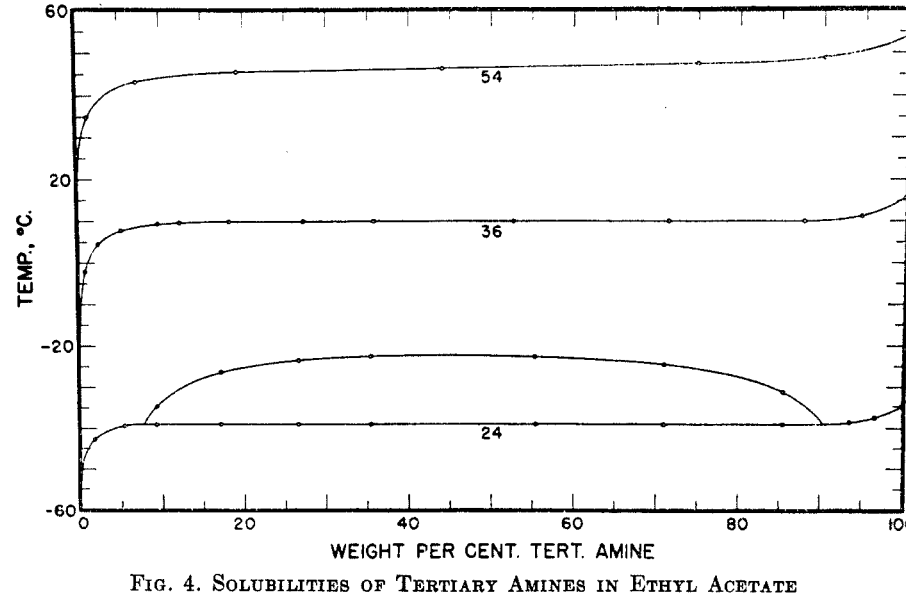

FIG. 4. SOLUBILITIES OF TERTIARY AMINES IN ETHYL ACETATE

weight of the alcohols. In methanol, 95% ethanol, and isopropanol the solubilities of the tertiary amines is so limited that over considerable ranges of concentration the systems exist as two immiscible liquids. The behavior in

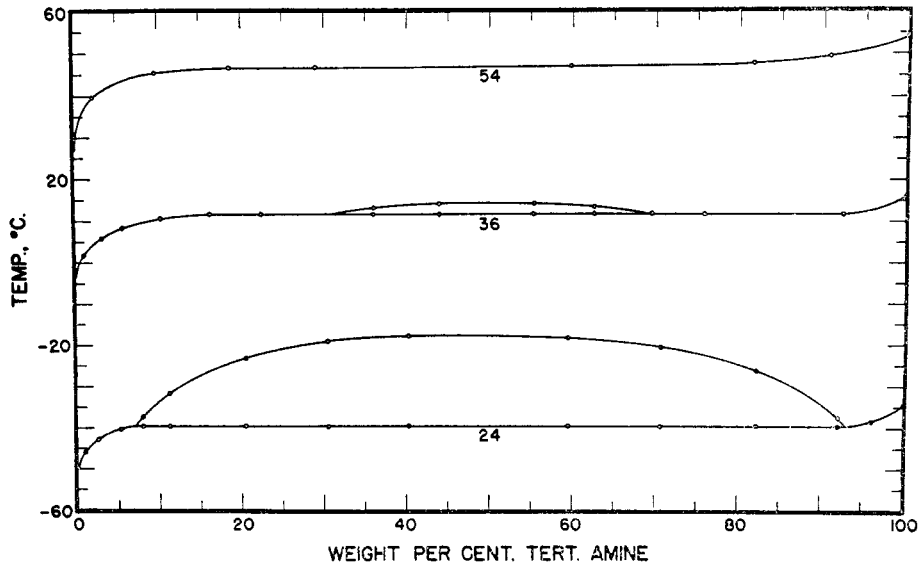

FIG. 5. SOLUBILITIES OF TERTIARY AMINES IN 2-BUTANONE

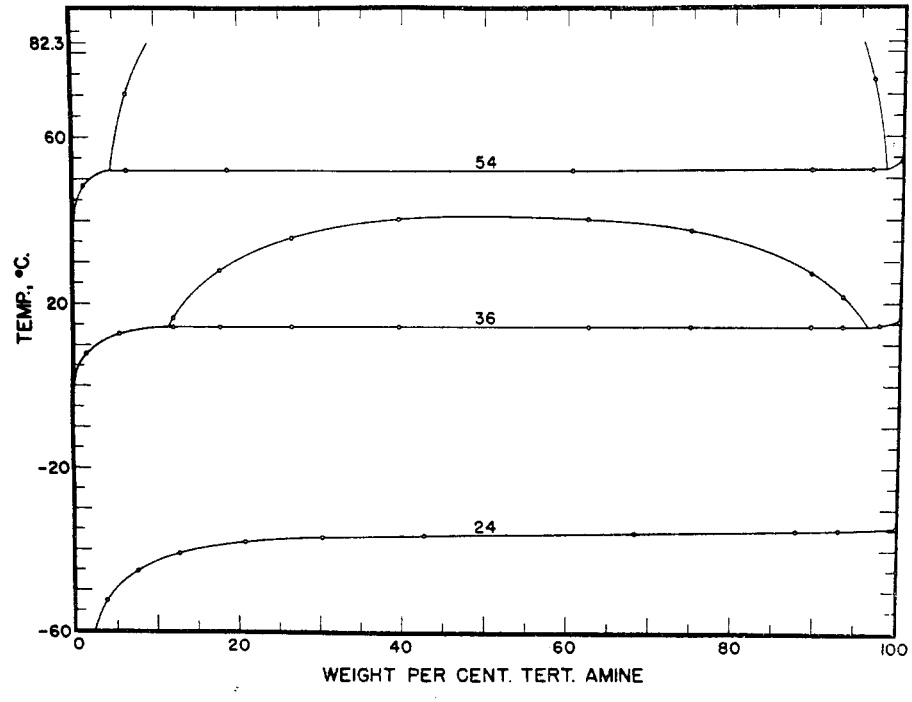

FIG. 6. SOLUBILITIES OF TERTIARY AMINES IN ISOPROPANOL

these solvents differs from that in the solvents discussed above, in that the regions of immiscibility become larger with increased molecular weight of the amine. In this respect the behavior of the tertiary amines is like that of the primary and secondary amines.

While few direct comparisons can be made, the solubility curves of the tertiary amines appear to be similar to those of primary or secondary amines containing equivalent numbers of carbon atoms. For instance, the curves for trioctylamine in the moderately polar solvents are very similar to those for didodecylamine.

The shapes of the solubility curves of the tertiary amines are characteristic of a wide variety of aliphatic compounds. Previous papers in this series (1, 2, 5, 6) have referred to several suggestions that the shapes of these curves are due to molecular association. In the case of primary amines and of nitriles, it has

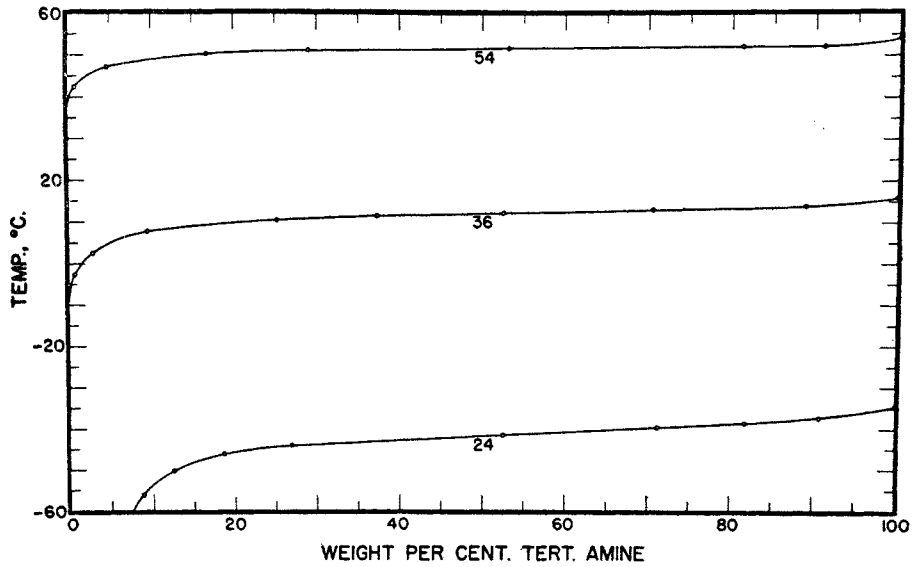

FIG. 7. SOLUBILITIES OF TERTIARY AMINES IN *n*-BUTANOL

been pointed out (2, 5) that such association could be due to hydrogen bonding at the polar group. Such a possibility is, however, precluded in the case of the tertiary amines since all of the hydrogen atoms on the nitrogen have been replaced by alkyl groups. This problem will be discussed further in connection with the solubilities of the aliphatic hydrocarbons which will be reported later in this series of investigations.

SUMMARY

The solubilities of trioctylamine, tridodecylamine, and trioctadecylamine have been determined in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl ether, ethyl acetate, butyl acetate, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, and *n*-butanol.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

SOLUBILITIES OF HIGH MOLECULAR WEIGHT NORMAL ALIPHATIC PRIMARY ALCOHOLS

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The aliphatic alcohols appear to be molecularly associated, as shown by investigations using several independent methods (1–8). The fact that the alcohols, like the fatty acids, crystallize in double molecules with their polar groups adjacent (9) is indicative of a tendency toward association in the liquid state and in solution. The relatively high dipole moment of the alcohols (10) also suggests the probability of some form of dipole-dipole coupling. Determination of the molecular weight of hexadecyl alcohol in menthol has shown (2) that in solutions as dilute as 0.001 molal the apparent molecular weight is 17.4% higher than that calculated from the empirical formula. Several investigators (6–8) have suggested that association of the alcohols occurs by hydrogen bonding at the polar groups, and that some type of interaction occurs between the solvent molecules and the alcohol (7). All of these previous investigators are generally agreed that association increases as the concentration increases, and decreases with increased temperature and increased molecular weight.

Several reports have attributed the characteristic solubility curves of long-chain compounds to molecular association (11, 12). A typical solubility curve of an aliphatic compound in an organic solvent consists of a steep initial slope, an abrupt change of slope at moderate dilution, and a relatively flat slope at higher concentrations. This type of curve is exhibited by the fatty acids (12, 13), aliphatic ketones (14), amides, anilides, and N,N-diphenylamides (15), nitriles (16), primary amines (17), secondary amines (18), tertiary amines (19), and amine salts (20).

In order to study the behavior of the alcohols, the solubilities of 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol, and 1-octadecanol have been determined in fifteen organic solvents.

EXPERIMENTAL

1-Decanol, 1-tetradecanol, and 1-octadecanol were prepared by catalytic hydrogenation of ethyl caprate, methyl myristate, and ethyl stearate, respectively, which had, in turn, been prepared from highly purified fatty acids (13). The freezing points of the α modifications and melting points of the β forms of these esters are listed in Table I.

The alcohols obtained from these esters were purified by vacuum distillation. 1-Dodecanol and 1-hexadecanol were obtained from commercial products. The former was purified by vacuum distillation in a Stedman packed column and the latter was recrystallized from acetone until a constant freezing point was obtained. The freezing points of the alcohols used in this investigation are listed in Table II.

The solubility measurements were made with the equipment and in the manner previously described (16, 20).

TABLE I

FREEZING AND MELTING POINTS OF PURIFIED ESTERS

ESTER	F.P., °C.	M.P., °C.	LITERATURE		REF.
	α form	β form	F.P., °C.	M.P., °C.	
Ethyl caprate	−19.50	−18.0	(β) −19.9	—	(21)
			−20.5	−20.3	(22)
			−19.96	—	(23)
Methyl myristate	18.39	19.0	18.35	—	(24, 25)
			18.37	18.8	(26)
Ethyl stearate	31.05	33.8	(α) 30.4	(β) 32.9	(22, 27)
			(α) 30.56	—	(23)
			(α) 31.05	(β) 33.9	(26)
			(α) 30.92	(β) 33.4	(28)
			(α) 31.05	—	(28)
			(α) 31.05	(β) 34.0	(29)
			30.5	31.7	(30)
			—	33.7–34.1	(31)

TABLE II

FREEZING POINTS OF PURIFIED ALCOHOLS

ALCOHOL	NO. OF C ATOMS	F.P., °C.	F.P., °C. (LIT.)
1-Decanol	10	6.88	6.4 (1); 5.99 (23).
1-Dodecanol	12	23.95	23.8 (1); 23.87 (23); m.p. 24 (32, 33); m.p. 21–22 (34); 23.6, m.p. 23.8 (35); m.p. 26 (36).
1-Tetradecanol	14	38.26	37.62 (23); 37.7 (24, 35); m.p. 37.5–38 (32); m.p. 38 (33); m.p. 39–39.5 (37).
1-Hexadecanol	16	49.62	49.27 (23, 28); 49.1 (27); 47.8 (30); m.p. 49–49.5 (33, 38); 49.25 (35); m.p. 48.5–49.5 (37); m.p. 49.5 (39); m.p. 49.3 (40); m.p. 48 (41); m.p. 50 (42); m.p. 49.10 (43); m.p. 48–48.2 (44); m.p. 45–46 (45); m.p. 49.1–49.2 (46); m.p. 49 (47).
1-Octadecanol	18	57.98	57.85 (23); 57.95 (28, 35); m.p. 59 (33, 48, 49); m.p. 58–59 (34); m.p. 57.60–57.75 (46); m.p. 58 (47, 50); m.p. 58.5 (51); m.p. 57–58 (52).

RESULTS AND DISCUSSION

The higher alcohols show a behavior in organic solvents similar to the other long-chain compounds investigated. Their solubility curves resemble those of the nitriles and fatty acids, whose polarity is of the same order of magnitude as that of the alcohols.

Like the other aliphatic compounds, the alcohols form simple eutectics with the non-polar solvents benzene, cyclohexane, and tetrachloromethane. These systems are shown graphically in Figs. 1–3, respectively, and the compositions and freezing points of the eutectics are listed in Table III.

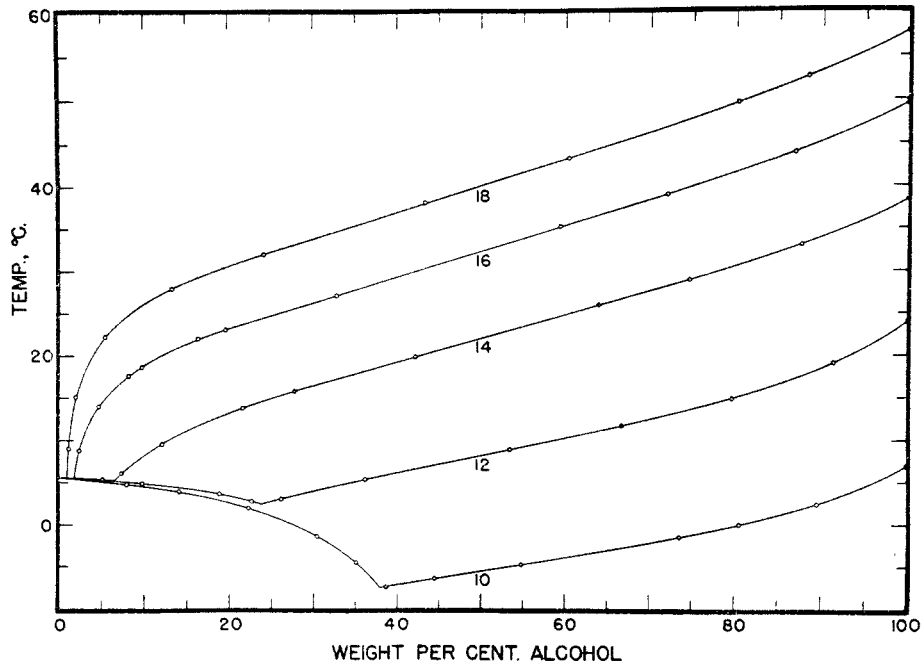

FIG. 1. SOLUBILITIES OF THE ALCOHOLS IN BENZENE. THE NUMBERS ON THE CURVES REFER TO THE NUMBER OF CARBON ATOMS

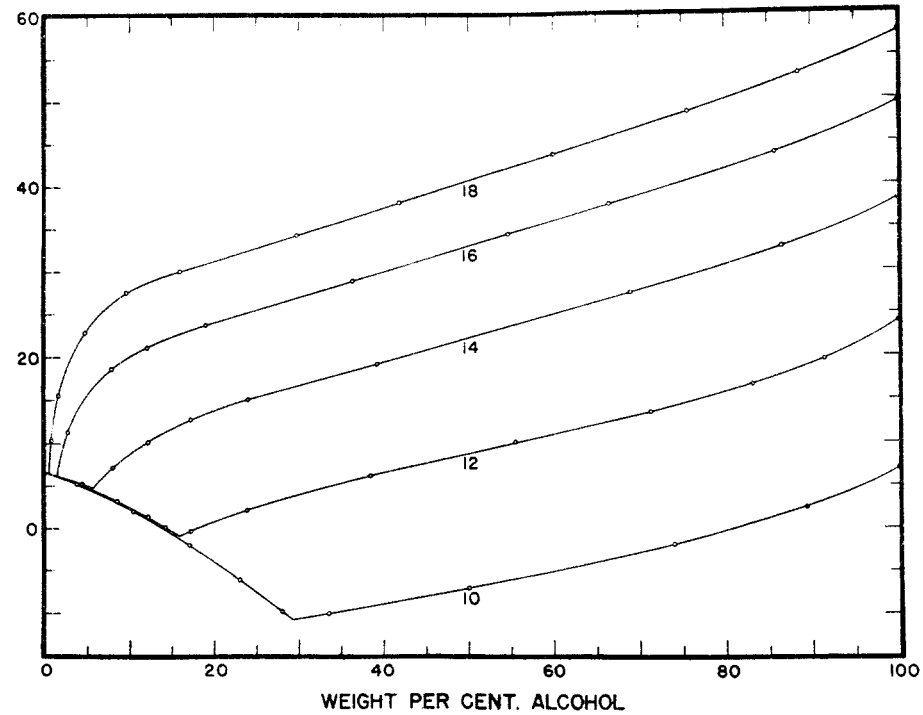

FIG. 2. SOLUBILITIES OF THE ALCOHOLS IN CYCLOHEXANE

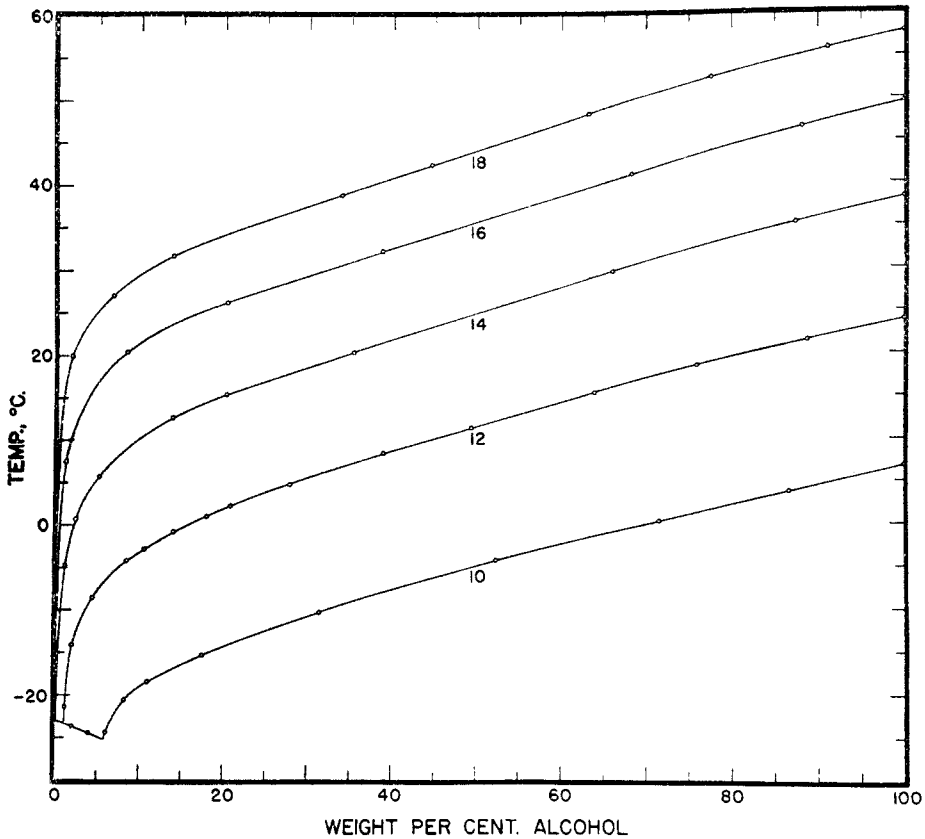

FIG. 3. SOLUBILITIES OF THE ALCOHOLS IN TETRACHLOROMETHANE

TABLE III

EUTECTICS FORMED BY THE ALCOHOLS

SOLVENT		NO. OF C ATOMS				
		10	12	14	16	18
Benzene	Wt. % alcohol	38.0	23.9	6.5	1.7	0.8
	Temp., °C.	−7.5	2.5	5.2	≈5.5	≈5.5
Cyclohexane	Wt. % alcohol	29.3	15.8	5.6	1.4	0.4
	Temp., °C.	−10.8	−0.9	4.8	6.0	6.5
Tetrachloromethane	Wt. % alcohol	5.7	1.1	0.1	—	—
	Temp., °C.	−25.2	−23.3	−23.0	—	—

The solubilities of the alcohols above the melting points of these solvents are listed in Tables IV–VI respectively. The alcohols are most soluble in benzene and least soluble in tetrachloromethane.

TABLE IV

SOLUBILITIES OF ALCOHOLS IN BENZENE

NO. OF C ATOMS	G. PER 100 G. BENZENE				
	10.0°	20.0°	30.0°	40.0°	50.0°
10	∞	∞	∞	∞	∞
12	139	1390	∞	∞	∞
14	14.2	74	355	∞	∞
16	2.8	13.5	73	302	∞
18	1.2	4.2	22.3	98	430

TABLE V

SOLUBILITIES OF ALCOHOLS IN CYCLOHEXANE

NO. OF C ATOMS	G. PER 100 G. CYCLOHEXANE				
	10.0°	20.0°	30.0°	40.0°	50.0°
10	∞	∞	∞	∞	∞
12	125	1290	∞	∞	∞
14	13.4	72	350	∞	∞
16	2.2	11.0	66	285	∞
18	0.6	3.2	18.1	92	400

TABLE VI

SOLUBILITIES OF ALCOHOLS IN TETRACHLOROMETHANE

NO. OF C ATOMS	G. PER 100 G. TETRACHLOROMETHANE					
	−20.0°	0.0°	10.0°	20.0°	30.0°	40.0°
10	9.7	240	∞	∞	∞	∞
12	1.3	18.9	83	450	∞	∞
14	0.2	2.0	10.5	54	210	∞
16	—	0.4	1.5	8.6	47.7	185
18	—	<0.1	0.3	1.7	12.0	60

TABLE VII

SOLUBILITIES OF ALCOHOLS IN TRICHLOROMETHANE

NO. OF C ATOMS	G. PER 100 G. TRICHLOROMETHANE					
	− 40.°	−20.0°	0.0°	20.0°	30.0°	40.0°
10	6.8	33.3	390	∞	∞	∞
12	1.3	4.1	47.5	820	∞	∞
14	—	0.6	8.2	85	305	∞
16	—	—	1.6	24.0	76	262
18	—	—	0.2	6.7	28.3	95

The solubilities of the alcohols in the slightly polar solvents trichloromethane, ethyl ether, ethyl acetate, and butyl acetate are listed in Tables VII–X, respectively. The solubility curves in trichloromethane are shown in Fig. 4, and those in ethyl acetate in Fig. 5.

TABLE VIII

SOLUBILITIES OF ALCOHOLS IN ETHYL ETHER

NO. OF C ATOMS	G. PER 100 G. ETHYL ETHER					
	−40.0°	−20.0°	0.0°	20.0°	30.0°	34.5°
10	8.0	38.9	520	∞	∞	∞
12	1.4	5.3	44.2	960	∞	∞
14	0.1	1.2	9.3	100	380	1180
16	—	0.1	3.0	26.1	76	123
18	—	—	0.5	7.7	26.4	46

TABLE IX

SOLUBILITIES OF ALCOHOLS IN ETHYL ACETATE

NO. OF C ATOMS	G. PER 100 G. ETHYL ACETATE					
	−20.0°	0.0°	10.0°	20.0°	30.0°	40.0°
10	14.7	320	∞	∞	∞	∞
12	2.7	16.1	76	980	∞	∞
14	0.1	3.4	10.2	41.5	272	∞
16	—	0.8	3.1	9.1	34.2	220
18	—	0.1	0.6	2.8	10.4	49.5

TABLE X

SOLUBILITIES OF ALCOHOLS IN BUTYL ACETATE

NO. OF C ATOMS	G. PER 100 G. BUTYL ACETATE					
	−20.0°	0.0°	10.0°	20.0°	30.0°	40.0°
10	17.9	320	∞	∞	∞	∞
12	5.5	21.8	84	980	∞	∞
14	1.1	6.2	17.0	58	276	∞
16	0.3	2.1	5.3	13.8	46.0	225
18	—	0.3	1.7	5.4	17.0	59

While the alcohols are more soluble in trichloromethane than they are in tetrachloromethane, they differ from the other aliphatic compounds in that they are, in general, more soluble in ethyl ether than in any of the solvents investigated. With the increased polarity of ethyl acetate and butyl acetate, the solubilities of the alcohols decrease appreciably.

The solubilities of the alcohols in acetone and in 2-butanone are listed in Tables XI and XII, respectively, and the solubility curves in acetone are shown in Fig. 6.

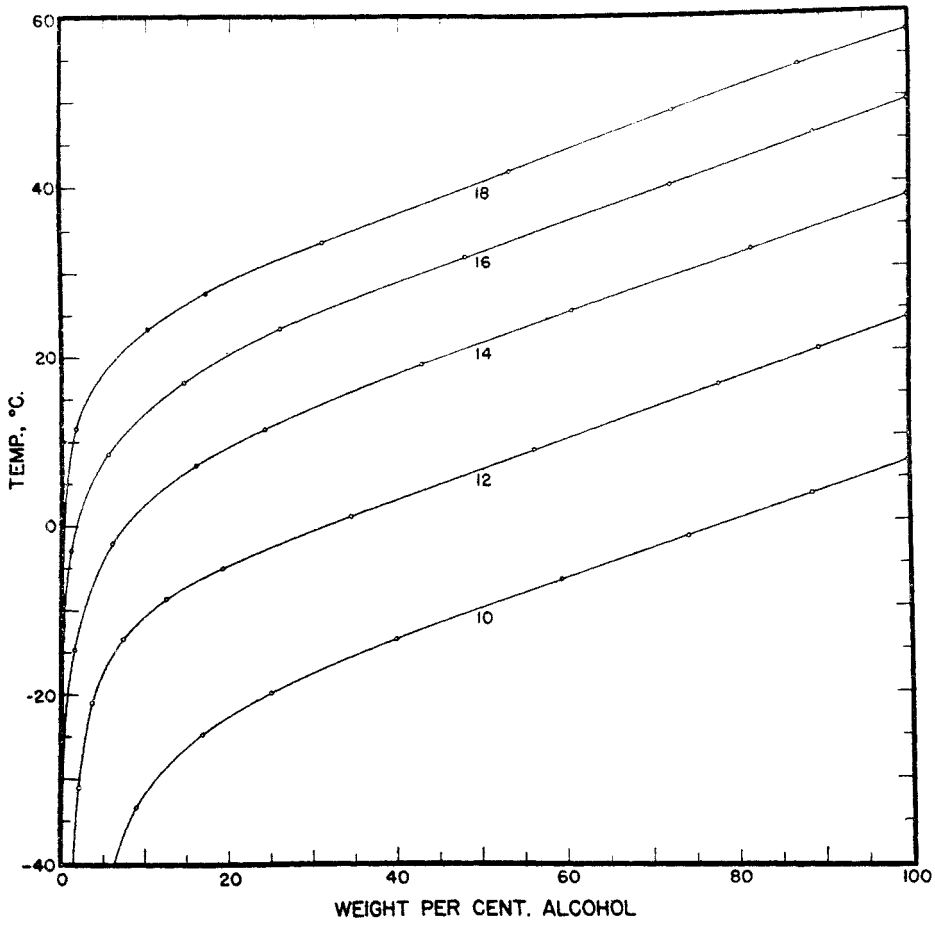

FIG. 4. SOLUBILITIES OF THE ALCOHOLS IN TRICHLOROMETHANE

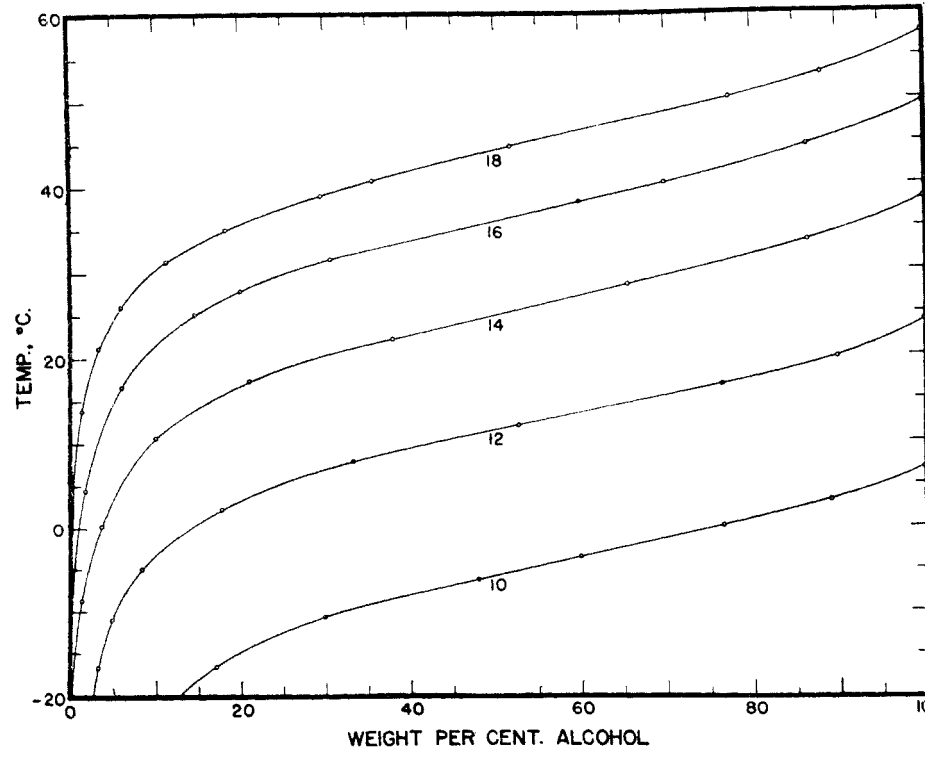

FIG. 5. SOLUBILITIES OF THE ALCOHOLS IN ETHYL ACETATE

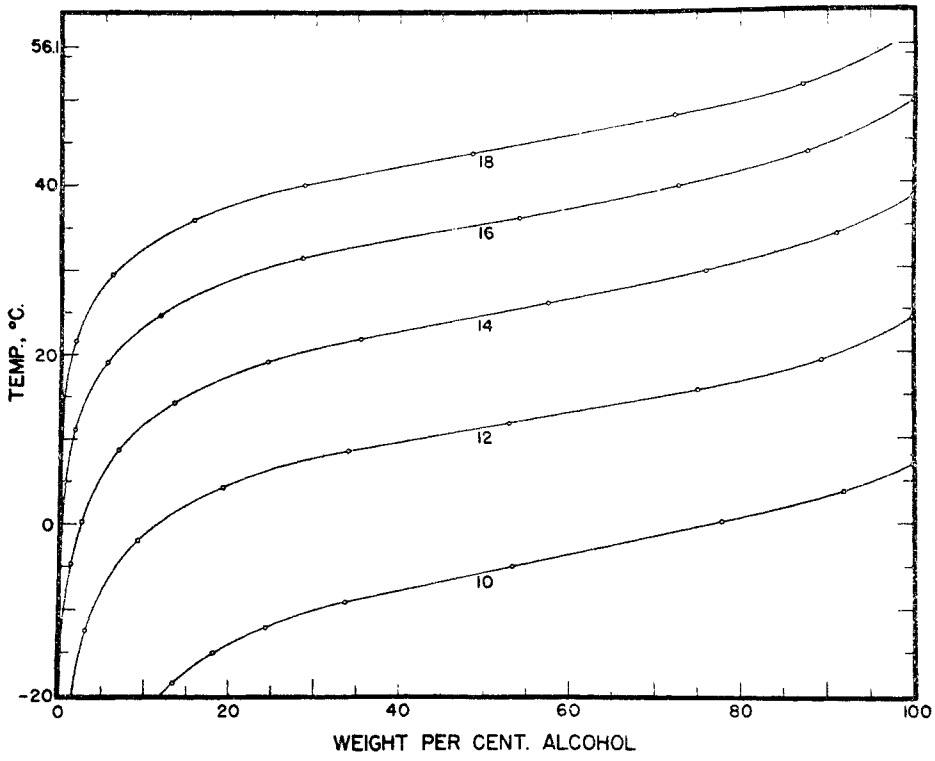

FIG. 6. SOLUBILITIES OF THE ALCOHOLS IN ACETONE

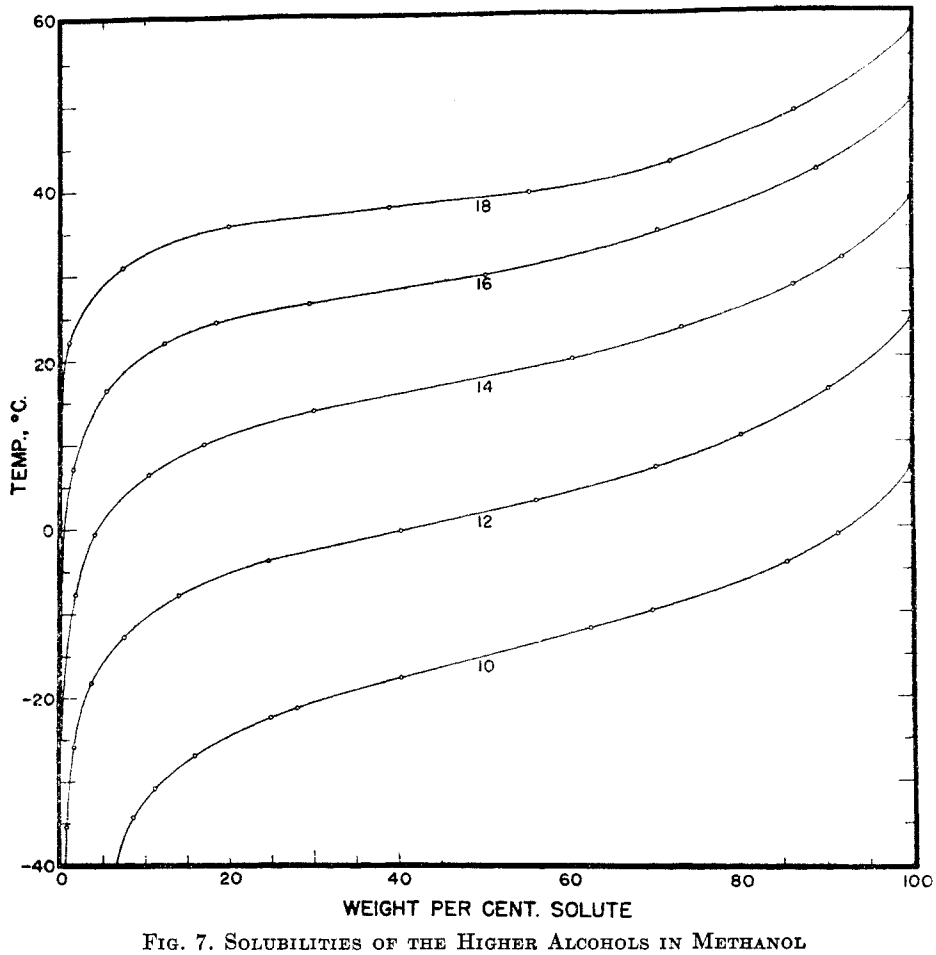

FIG. 7. SOLUBILITIES OF THE HIGHER ALCOHOLS IN METHANOL

With the higher polarities of these solvents, the solubilities of the alcohols decrease at lower temperatures, but increase at higher temperatures. For example, the alcohols are less soluble in acetone than in ethyl acetate at $-20°$, but the opposite is true at 10°.

The solubilities of the higher alcohols in methanol, 95% ethanol, isopropanol, and *n*-butanol are listed in Tables XIII–XVI, respectively. The solubility curves in methanol are shown in Fig. 7, and those in *n*-butanol in Fig. 8.

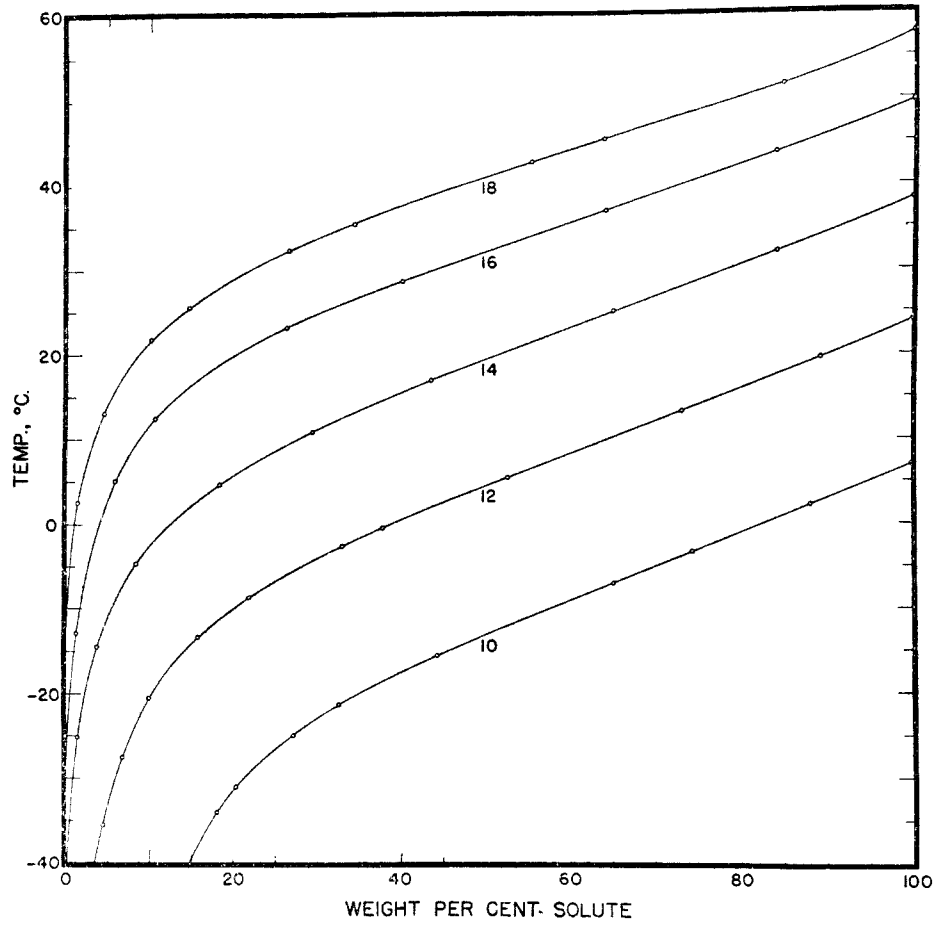

FIG. 8. SOLUBILITIES OF THE HIGHER ALCOHOLS IN *n*-BUTANOL

In these solvents, the higher alcohols are more soluble in *n*-butanol than in methanol at the lower temperatures. At higher temperatures, however, the solubilities are reversed, and the higher alcohols are almost as soluble in methanol as they are in the non-polar and slightly polar solvents.

The solubilities of the alcohols in nitroethane and acetonitrile are listed in Tables XVII and XVIII, respectively, and are shown graphically in Figs. 9 and 10, respectively.

TABLE XI

SOLUBILITY OF ALCOHOLS IN ACETONE

NO. OF C ATOMS	G. PER 100 G. ACETONE					
	−20.0°	0.0°	10.0°	20.0°	30.0°	40.0°
10	13.6	335	∞	∞	∞	∞
12	1.6	12.9	75	1150	∞	∞
14	<0.1	2.4	8.7	38.6	340	∞
16	—	0.1	1.3	6.7	30.9	290
18	—	—	0.1	1.1	7.0	41.4

TABLE XII

SOLUBILITIES OF ALCOHOLS IN 2-BUTANONE

NO. OF C ATOMS	G. PER 100 G. 2-BUTANONE					
	−20.0°	0.0°	10.0°	20.0°	30.0°	40.0°
10	16.3	355	∞	∞	∞	∞
12	3.7	19.6	88	1150	∞	∞
14	0.6	4.7	16.5	60	340	∞
16	—	1.6	4.9	14.2	50	290
18	—	0.1	1.0	3.8	12.7	62

TABLE XIII

SOLUBILITIES OF ALCOHOLS IN METHANOL

NO. OF C ATOMS	G. PER 100 G. METHANOL					
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°
10	7.1	48.5	1310	∞	∞	∞
12	0.5	3.0	73	2340	∞	∞
14	—	0.2	4.6	158	870	∞
16[a]	—	—	0.3	10.0	105	590
18	—	—	—	0.4	6.6	146

[a] 96.9 g./100 g. methanol at 23.9° (53).

TABLE XIV

SOLUBILITIES OF ALCOHOLS IN 95% ETHANOL

NO. OF C ATOMS	G. PER 100 G. 95% ETHANOL					
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°
10	7.1	43.6	1150	∞	∞	∞
12	0.6	4.2	52	2120	∞	∞
14	—	0.4	6.4	105	630	∞
16[a]	—	—	1.8	15.9	89	430
18	—	—	0.2	5.0	22.2	120

[a] 102.2 g./100 g. ethanol at 23.9°; 410 g. at 39° (53).

TABLE XV

SOLUBILITIES OF ALCOHOLS IN ISOPROPANOL

NO. OF C ATOMS	G. PER 100 G. ISOPROPANOL					
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°
10	14.8	55	635	∞	∞	∞
12	1.5	10.0	72	1330	∞	∞
14	—	1.2	12.8	123	545	∞
16	—	<0.1	3.1	23.7	95	410
18	—	—	<0.1	7.7	29.0	119

TABLE XVI

SOLUBILITIES OF ALCOHOLS IN *n*-BUTANOL

NO. OF C ATOMS	G. PER 100 G. *n*-BUTANOL					
	−40.0°	−20.0°	0.0°	20.0°	30.0°	40.0°
10	17.4	53	475	∞	∞	∞
12	3.6	11.3	63	950	∞	∞
14	0.2	2.3	14.0	105	365	∞
16	—	0.5	4.0	24.8	78	275
18	—	—	1.0	9.2	27.7	89

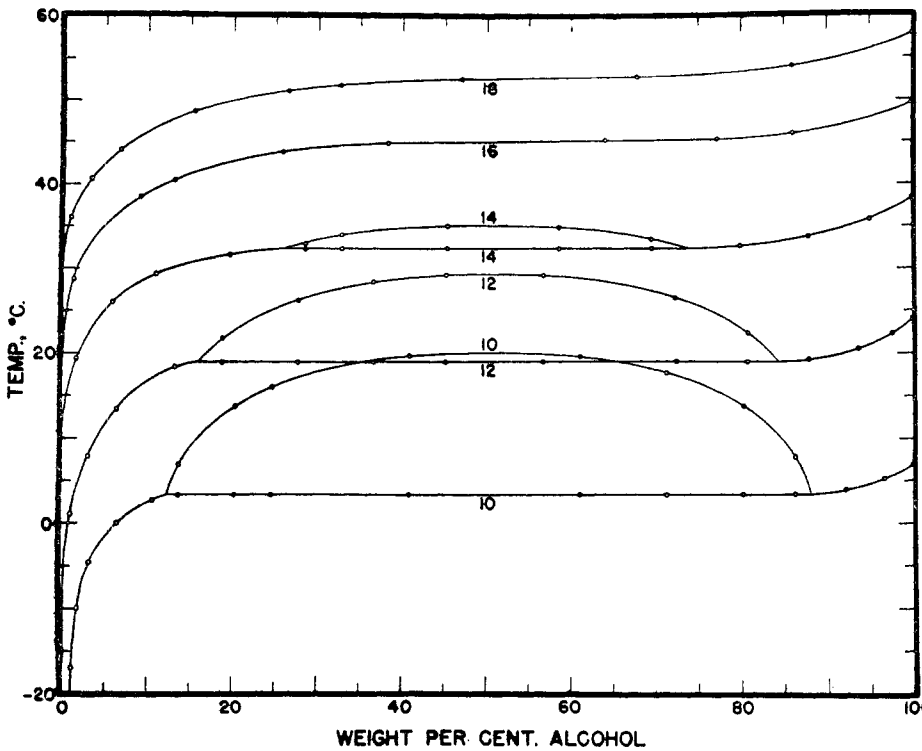

FIG. 9. SOLUBILITIES OF THE ALCOHOLS IN NITROETHANE

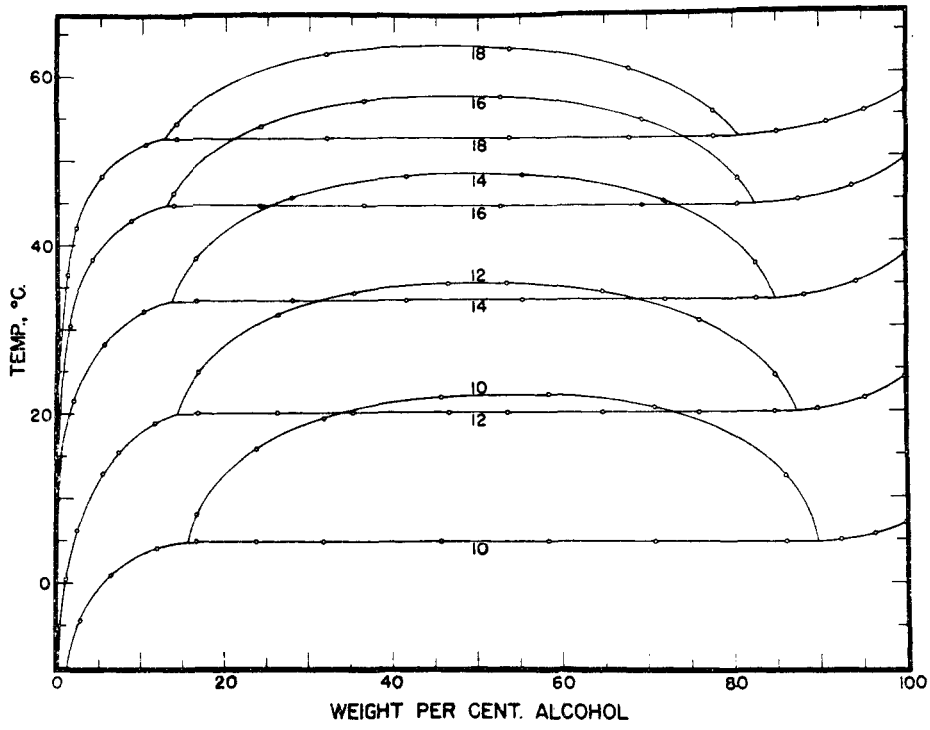

FIG. 10. SOLUBILITIES OF THE ALCOHOLS IN ACETONITRILE

TABLE XVII

SOLUBILITIES OF ALCOHOLS IN NITROETHANE

NO. OF C ATOMS	G. PER 100 G. NITROETHANE					
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°
10	7.1	16.9	∞	∞	∞	∞
12	0.9	4.2	20.2	∞	∞	∞
14	—	<0.1	1.9	14.5	∞	∞
16	—	—	<0.1	1.6	13.4	∞
18	—	—	—	<0.1	2.7	25.4

TABLE XVIII

SOLUBILITIES OF ALCOHOLS IN ACETONITRILE

NO. OF C ATOMS	G. PER 100 G. ACETONITRILE					
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°
10	5.8	21.6	52	∞	∞	∞
12	1.0	3.9	16.7	29.9	∞	∞
14	—	<0.1	1.3	7.7	22.1	∞
16	—	—	≈0.1	1.1	5.6	20.9
18	—	—	—	0.3	1.6	7.6

The solubilities of the alcohols in these highly polar sovents become so limited that the systems exist as two immiscible solutions over considerable ranges of concentration. In both of these solvents the regions of immiscibility become markedly smaller with increased molecular weight of the alcohols. In the nitroethane systems with 1-hexadecanol and with 1-octadecanol this region is not present. Of the wide variety of aliphatic compounds studied in this series, the tertiary amines are the only ones which exhibit a similar behavior.

As the molecular weight of the alcohols increases, the initial slopes of the solubility curves become more steep, the change in slope is more abrupt, and the curves become flatter at higher concentrations. If it is assumed that molecular association is responsible for this behavior, then apparently association increases with increased temperature and with increased molecular weight of the alcohols. Since it has been shown, however, that the opposite effect occurs, at least in the case of the lower alcohols (1–8), it appears that molecular association alone does not explain the behavior of the higher alcohols.

SUMMARY

The solubilities of 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol, and 1-octadecanol have been determined in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl ether, ethyl acetate, butyl acetate, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XV. THE STEROLS OF STARFISH. II[1]

WERNER BERGMANN AND HARRY A. STANSBURY, JR.

Received March 3, 1944

The name stellasterol was assigned in 1915 by Kossel and Edlbacher (1) to a di-unsaturated sterol of the probable formula $C_{27}H_{44}O$, which occurs together with astrol in the unsaponifiable matter of the starfish *Asterias rubens*. The suggestion has been made in a previous communication of this series (2), that asteriasterol (3), the sterol of *Asterias forbesi*, is a mixture of astrol, stellasterol, and other ill-identified sterols. Since then it has been shown by the present authors (4) that astrol is identical with batyl alcohol. A resumption of the investigation of starfish sterols was made possible through the generous cooperation of Mr. Charles F. Lee, Wildlife Service, U. S. Department of Interior, who supplied a large quantity of acetone-soluble material from *Asterias forbesi*. A preliminary study of this material led to results similar to those described previously (2). The sterol fraction proved to be a complex mixture of at least two sterols, the complete separation of which has not yet been accomplished. In the course of twelve recrystallizations the melting point of the sterol mixture rose from 120–133° to 149–150°, which is the melting point of stellasterol. The substance, however, was not yet pure, for upon further recrystallizations the melting point went up to 156–158°. After twenty recrystallizations of a mixture of steryl acetates a fraction was obtained which like stellasteryl acetate melted at 177°, and which upon further recrystallization gave a product melting at 180°.

These preliminary observations suggest the identity of stellasterol with the least soluble sterol of the present sterol mixture. The probable identity between the two sterols, however, appears to be discounted by the marked difference in the melting points of the respective sterols. Thus stellasteryl benzoate has been reported to melt at 100° to a turbid liquid which turns clear at 125°. In contrast, the various fractions of steryl benzoates obtained during the present investigation melted considerably higher, the lowest at 129–134°, and the highest at 194–197°. A rational explanation for this discrepancy of results was eventually found in the observation, to be described below, that starfish sterols possess a cyclic double bond which readily isomerizes under the influence of hydrochloric acid. The method used by Kossel for the preparation of stellasteryl benzoate consisted in the heating to 160° of a mixture of stellasterol and benzoyl chloride. It is certain that the hydrochloric acid formed during the reaction led to a rearrangement of the double bond, and that the benzoate obtained was not the benzoate of stellasterol, but the derivative of one or more of its isomers. In contrast, the present benzoates were prepared in the absence of free hydrochloric

[1] This communication describes work done by Harry A. Stansbury, Jr. in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, Yale University, 1944.

acid, by treating the sterols with benzoyl chloride in the presence of pyridine. When the benzoates thus obtained were exposed to the action of anhydrous hydrochloric acid, a mixture of compounds was obtained which melted at 100° or below.

It soon became apparent that the available starting material was insufficient for the isolation of pure compounds by fractional crystallization of the sterols, their acetates or benzoates. Attempts to separate the acetate mixture by adsorption on alumina were abandoned because of inconclusive results. In one experiment the principal fraction of the eluate, which represented about seventy per cent of the starting material, melted forty degrees below the melting point of the original mixture. This observation suggested that adsorption was accompanied by some chemical reaction, such as isomerization. Titration of various fraction of sterols and their acetates with perbenzoic acid gave values which suggested the presence of a mixture of mono- and di-unsaturated sterols. In previous instances (5) the separation of such mixtures was effected by means of bromine addition products. The application of this method to the separation of the starfish sterols, however, did not appear promising, because it had been shown previously (2) that these sterols and their derivatives react with bromine with the formation of green-colored decomposition products. Nevertheless a sample of acetate was brominated, principally in order to test for the presence of cholesteryl acetate, which would form a difficultly soluble dibromide of melting point 117°. The only crystalline product obtained in this reaction was a very small amount of an unknown dibromide melting at 184–185°. Because of its small yield, and the extensive destruction of the bulk of the material, this method of separation was abandoned.

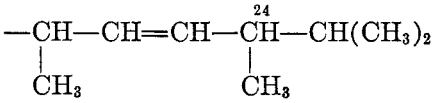
After the failure of the methods listed above to bring about the isolation of pure compounds, it was decided to obtain evidence concerning the structure of the starfish sterols by an investigation of the chemical behavior of their mixture. The selection of suitable methods was guided by a working hypothesis formulated on the basis of certain properties of the mixture which seemed to be of particular significance. As has been mentioned before, the degree of unsaturation of the sterol mixture suggests the presence of mono- and di-unsaturated sterols. According to Kossel, stellasterol is a di-unsaturated compound, and in agreement with this formulation the present sterol fractions most closely resembling stellasterol show the presence of two double bonds (2). It was now assumed as part of the working hypothesis that like the co-occurring sponge sterols, poriferasterol and clionasterol (5), the starfish sterols are closely related compounds differing from each other only in the presence of a double bond in the side chain. For the simplification of the discussion the name stellasterol shall be retained to designate the di-unsaturated sterol, and the mono-unsaturated sterol shall be referred to as stellastenol.

All fractions of the starfish sterols and their derivatives were found to be slightly dextro-rotatory. These observations at once suggested that unlike all other known unsaturated animal sterols, the starfish sterols were devoid of a 5,6-ethenoid linkage which is known to confer a strong negative contribution to

the rotation of steroids. All fractions of the starfish sterols and their derivatives give a green color reaction with bromine, which had already been observed by Kossel (1). This coloration which is now known under the name of Tortelli-Jaffé reaction (6) is generally believed to be typical for steroids possessing a double bond joined to the C-8 atom of the ring system. It was therefore assumed as a further part of the working hypothesis that both stellasterol and stellastenol possessed a double bond in the γ-(7,8), δ-(8,9) or α-(8,14)- position.

The presence of an ethenoid linkage in the side chain of one of the sterols, provisionally named stellasterol, was readily shown by the ozonization of the sterol mixture. An oily, water-insoluble, steam-distillable aldehyde was isolated in the form of its 2,4-dinitrophenylhydrazone, m.p. 119–120°, $[\alpha]_D^{26}$ +14.5°, which gave analytical values for the derivative of an aldehyde of the formula $C_5H_{11}CHO$. When mixed with a sample of the corresponding derivative of methylisopropylacetaldehyde, m.p. 124–124.5°, $[\alpha]_D^{26}$ −37.7°, which had been prepared from ergosterol, the melting point was 119–122.5°. Bearing in mind that partial recemization of the aldehydes is difficult to prevent, these data at once suggest that the aldehydes from stellasterol and ergosterol are optical antipodes. Methyl-*n*-propylacetaldehyde is the only other asymmetric aldehyde of the formula $C_5H_{11}CHO$. Since this aldehyde lacks the usual isopropyl group of the sterol side chain, its identity with the aldehyde from stellasterol seems highly improbable. It is therefore reasonable to assume that stellasterol carries a side chain of the structure I in which the optical configuration at C-24 is the opposite of that of ergosterol. The occurrence of this type of isomerism among

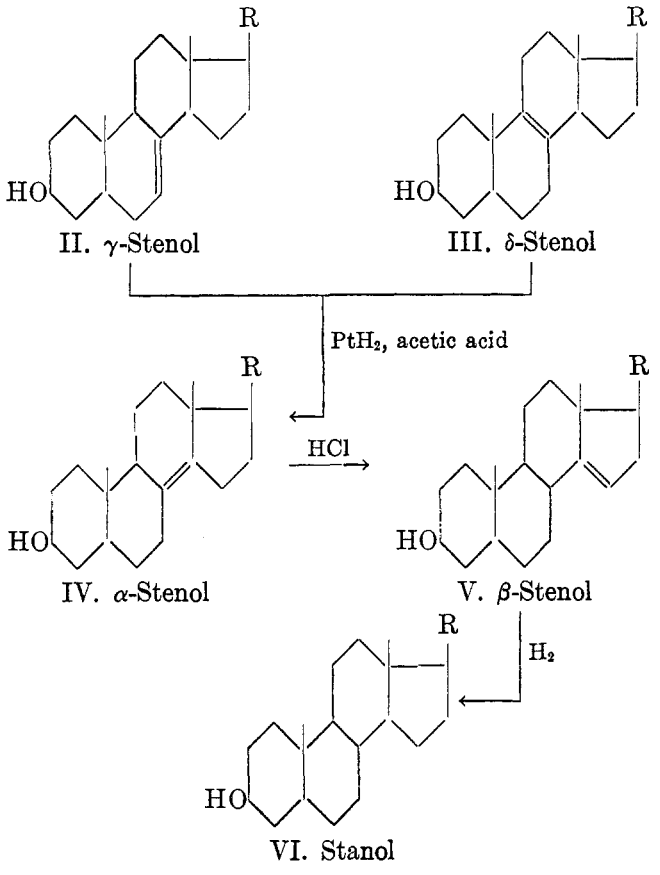
(I)



natural sterols was first described by Fernholz and Ruigh (7) who proved convincingly that campesterol and 22,23-dihydrobrassicasterol differ only in the optical configuration on C-24. The present case represents the second example of this type of isomerism, and the first of its kind to be found among animal sterols.

It had been assumed for reasons discussed above that stellasterol and stellastenol possess double bonds at C-8 in the positions shown in formulas II–IV. Such double bonds are known to be resistant to hydrogenation. When treated with platinum and hydrogen in acetic acid, γ- (II) and δ- (III) unsaturated steroids rearrange to the α-isomers (IV). The latter are very resistant to catalytic hydrogenation under ordinary conditions but can be isomerized by anhydrous hydrochloric acid to the β-isomers (V), which absorb hydrogen readily to give the corresponding saturated compounds (VI). Preliminary studies on the hydrogenation of starfish sterols indicated the presence of inert double bonds, in support of the assumptions made above. If then both stellasterol and stellastenol were to possess double bonds in the γ-, δ-, or α-position, and if an additional double bond were present in the 22,23-position of the side chain of stellasterol, the catalytic hydrogenation of a mixture of such sterols should give a uniform

product, α-stellastenol. Accordingly a mixture of acetates, which titrated for 1.4 double bonds, was hydrogenated with a platinum black catalyst in acetic acid at room temperature and atmospheric pressure. The reaction stopped after about one-half mole of hydrogen had been consumed. The reaction product, which will be named α-stellastenyl acetate, proved to be a uniform compound of constant melting point 105–106°, $[\alpha]_D^{26}$ + 12.5°; it showed the presence of one double bond on titration with perbenzoic acid. Hydrolysis of the acetate



gave α-stellastenol, m.p. 123–125°, $[\alpha]_D^{26}$ + 19.8°, the *m*-dinitrobenzoate of which gave analysis for a sterol of the molecular formula $C_{28}H_{47}OH$. As expected, α-stellastenyl acetate isomerized in a chloroform solution with dry hydrogen chloride at 0°. A β-stellasteryl acetate, m.p. 94–96°, $[\alpha]_D^{26}$ + 19.8°, was thus obtained, which on hydrolysis gave β-stellastenol, m.p. 122–124°, $[\alpha]_D^{22}$ +29.4°. On hydrogenation at room temperature the β-acetate gave the completely saturated stellastanyl acetate, m.p. 138–139°, $[\alpha]_D^{24}$ +13.5°. Stellastanol, m.p. 143°, $[\alpha]_D^{22}$ +23° gave a *m*-dinitrobenzoate which gave values for the derivative of a sterol of the molecular formula $C_{28}H_{49}OH$. The optical activities of

the two stellastenols and stellastanol agree with the general rule (8) that α-unsaturated steroids have a less positive, and β-unsaturated steroids a more positive rotation than the corresponding saturated sterols. Stellastanol is isomeric with ergostanol and campestanol (7), and like the latter it differs from ergostanol in the configuration at C-24. A comparison of the data shown in Table I also shows that stellastanol is different from campestanol.

The results of the analyses of the *m*-dinitrobenzoates mentioned above, and the isolation of methylisopropylacetaldehyde from the products of ozonization, prove that the starfish sterols are C_{28}-sterols. They are the first principal sterols of this order to be found to occur in animal tissue. Up to the present the only C_{28}-sterol known to occur in animals has been ergosterol, which constitutes the provitamin-D of certain snails and the earthworm, *Lumbricus terrestris* (9). The fact that the starfish sterols are of the order C_{28} is difficult if not impossible to reconcile with the hypothesis of the exogenous origin of the sterols of marine invertebrates, which has been tentatively advanced by one of the present authors (10). The starfish *Asterias forbesi* feeds principally on bivalves, crustaceans,

TABLE I

COMPARISON OF SATURATED STEROLS OF THE FORMULA $C_{28}H_{50}O$

NAME	STEROL		ACETATE		*m*-DINITROBENZOATE	
	m.p. °C	α_D	m.p. °C	α_D	m.p. °C	α_D
Stellastanol	143	+22	139	+13	204	
Ergostanol	144	+15	145	+6	203	+13
Campestanol (7)	147	+31	147	+18	198	+22

and fish, animals which contain sterols of the order C_{29} like ostreasterol (11) or of the order C_{27} like cholesterol. On the basis of the hypothesis one should expect sterols of these orders to occur in starfish, but no evidence for their presence has as yet been discovered.

The structures of all natural, unsaturated sterols which were known before 1940 included a double bond in the 5,6-position, and it appeared at that time that the presence of this double bond was indeed typical for allunsaturated, naturally occurring sterols. That this is by no means true was first shown in the cases of zymosterol from yeast (12) and α-spinasterol from higher plants (13) which are both unsaturated sterols devoid of the 5,6-double bond. The starfish sterols represent the first example of this type of unsaturated sterols to be found to occur in animal tissues.

As far as the cyclic double bond of the starfish sterols is concerned, the available evidence only shows its attachment to C-8, but does not establish it as a γ-, δ-, or α-double bond. The possibility may well be envisaged that the original sterol mixture consists of mono- and di-unsaturated with double bonds in any one of these three positions. A mixture of such complexity might well account for the unusual difficulties encountered in the attempts to bring about a separa-

tion, and also for the ease with which it is converted into the uniform α-stellastenol on catalytic hydrogenation.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3 cc. of chloroform.

Isolation of the starfish sterols. The unsaponifiable matter from the oil of the starfish *Asterias forbesi* was dissolved in the minimum amount of hot methanol, and the brownish crystalline material which separated upon cooling was removed by filtration. After two recrystallizations of this material from low-boiling petroleum ether, there was obtained a colorless mixture of compounds of m.p. 129–135°, $[\alpha]_D^{23}$ +9.4°. Sixteen recrystallizations of this mixture from acetone in a Skau-tube brought about a slow but steady rise of the melting point to 155–158°, $[\alpha]_D^{23}$ +5.9°.

Anal. Calc'd for $C_{28}H_{46}O + 0.5\ H_2O$: C, 82.90; H, 11.28.
$C_{28}H_{48}O + 0.5\ H_2O$: C, 82.50; H, 11.62.
Found: C, 82.12; H, 11.77.

The sample m.p. 155–158° gave an acetate of m.p. 162–166°, which showed the presence of 1.6 double bonds upon titration with perbenzoic acid.

Preparaton of the steryl acetates. Refluxing the crude sterol mixture with acetic anhydride gave a mixture of steryl acetates of m.p. 137–146°, $[\alpha]_D^{24}$ +3.8°. It was recrystallized sixteen times from absolute ethanol in a Skau-tube. During the last three recrystallizations the melting point seemingly remained constant at 170–173°. Subsequent recrystallizations from acetone, however, brought about a further rise of the melting point, and eventually a very small amount of a product was obtained which melted at 178–181°, $[\alpha]_D^{23}$ 0°.

Anal. Calc'd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.97.
$C_{30}H_{50}O_2$: C, 81.39; H, 11.38.
Found: C, 81.12; H, 11.50.

Attempted separation by chromatography. A solution of 1.25 g. of an acetate of m.p. 130–133° in 45 cc. of hexane was passed through a column (19 by 1.5 cm.) of activated alumina. It was followed by 40 cc. of hexane. The percolates were collected in ten fractions of 5 cc. each and evaporated to dryness. No weighable residues were obtained. The column was then eluted with a saturated solution of dry methanol in hexane. Five fractions of 10 cc. each gave a total of less than 10 mg. residue of m.p. 118–131°. The column was then eluted with a saturated solution of hexane in dry methanol. The first fraction, 10 cc., gave 0.23 g. of residue which melted at 101–115° after one recrystallization from methanol. The second fraction, 5 cc., contained the bulk of the material, 0.84 g., which melted at 89–94° after one recrystallization. Three of the following fractions, 20 cc., gave a total of 0.14 g. of a product of m.p. 94–100°. The wide difference between the melting points of the original acetate and of the bulk of the recovered material indicated that some chemical reaction had accompanied the adsorption.

Bromination of the steryl acetates. A solution of 122 mg. of acetates of m.p. 135–137° in 1.2 cc. of ether was treated dropwise with a 5% solution of bromine in glacial acetic acid. During the addition, the solution was cooled in an icebath. Some crystalline precipitate formed in the solution, which rapidly turned green and then black. After standing in the refrigerator overnight, the precipitate was filtered and washed with glacial acetic acid. There was obtained 8 mg. of a bromide of m.p. 184–185°.

Anal. Calc'd for $C_{31}H_{50}Br_2O_2$: Br, 26.0. Found: Br, 23.24.

Preparation of the steryl benzoates. A solution of 4.7 g. of sterols of m.p. 127–130° in 50 cc. of dry pyridine was treated with 15 cc. of benzoyl chloride. The mixture was left standing at room temperature for twenty-four hours and then poured slowly with stirring into 300 cc. of ice-cold 3 *N* sulfuric acid. The precipitated material was filtered, washed with water, and recrystallized twice from absolute ethanol. A total of 4.4 g. of colorless needles was thus obtained, which melted at 159–166°. During fourteen recrystallizations of this

material from acetone the melting point rose continually and eventually a very small amount of a product of m.p. 194–197° was obtained.

Anal. of a fraction of m.p. 176–179°, $[\alpha]_D^{24}$ +9.0°. Calc'd for $C_{35}H_{50}O_2$: C, 83.61; H, 10.02.
$C_{35}H_{52}O_2$: C, 83.28; H, 10.38.
Found: C, 82.98; H, 10.12.

Anal. of fraction of m.p. 194–197°. Calc'd for $C_{35}H_{50}O_2$: C, 83.61; H, 10.02.
$C_{35}H_{52}O_2$: C, 83.28; H, 10.38.
Found: C, 83.15; H, 10.30.

Action of hydrochloric acid on the steryl benzoates. A stream of dry hydrochloric acid was passed at 0° for three and one-half hours through a solution of 1 g. of benzoate, m.p. 162–164°, in 50 cc. of chloroform. The solvent was then removed *in vacuo*, and the residue recrystallized from ethyl acetate and absolute ethanol. The product (140 mg.) appeared to be unchanged starting material. Concentration of the mother liquor gave 580 mg. of a crystalline product melting at about 60°. After numerous recrystallizations from ethyl acetate and ethanol it melted at 91–92°.

Ozonization of the steryl acetate mixture. One gram of acetate, m.p. 137–146°, was suspended in 12 cc. of glacial acetic acid, and an excess of ozone was passed through the vigorously stirred suspension at 20°. The ozonization was discontinued fifteen minutes after all suspended material had gone into solution. Zinc dust was added to the solution, which was stirred vigorously for twenty minutes. A few drops of silver nitrate solution were then added, and the stirring continued until the mixture no longer gave a positive test for peroxides. The liquid filtered from the zinc dust was poured into water, and the resulting milky suspension was distilled until oily droplets no longer passed over with the distillate. The distillate, about 80 cc., was mixed with 30 cc. of a warm solution of 2,4-dinitrophenylhydrazine (Brady's reagent) (14). The crystalline precipitate, 121 mg. was dissolved in dry benzene, and the solution was passed through a 1 cm. by 11 cm. column of activated alumina. By washing the column with dry benzene a yellow percolate was obtained, which was evaporated to dryness *in vacuo*. The residue, after several recrystallizations from ethanol, melted at 119–120°, $[\alpha]_D^{24}$ +14.1° (25.5 mg., α + 0.12°). When mixed with the 2,4-dinitrophenylhydrazone of *l*-methylisopropylacetaldehyde, m.p. 124–124.5°, prepared from ergosterol, it melted at 119.5–122.5°, and when mixed with the 2,4-dinitrophenylhydrazone of *l*-ethylisopropylacetaldehyde from stigmasterol, it melted at 107–122°.

Anal. Calc'd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.76.
$C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16.
Found: C, 51.66; H, 5.97.

2,4-Dinitrophenylhydrazone of l-methylisopropylacetaldehyde. Ergosteryl acetate was ozonized, and the aldehyde isolated as the 2,4-dinitrophenylhydrazone in the manner described above. After several recrystallizations from ethanol the compound melted at 124–124.5°, $[\alpha]_D^{24}$ −37.7° (20.7 mg., α −0.26°).

Anal. Calc'd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.76.
Found: C, 51.83; H, 5.90.

α-Stellastenyl acetate. A solution of 1 g. of steryl acetates m.p. 149–154°, 1.4 double bonds, in 100 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure with a platinum black catalyst. The reaction stopped completely after about 0.5 moles of hydrogen had been absorbed. The solution was filtered from the catalyst and concentrated to a small volume. Methanol was then added until a copious precipitate appeared, which was then filtered and recrystallized several times from ethanol. The acetate gave a strong Liebermann test, and showed the presence of one double bond upon titration with perbenzoic acid. It melted at 105–106°, $[\alpha]_D^{23}$ +12.5° (24.0 mg., α + 0.10°).

Anal. Calc'd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38.
Found: C, 81.13; H, 11.48.

α-Stellastenol. The saponification of α-stellastenyl acetate with a hot 5% solution of potassium hydroxide in 90% ethanol yielded α-stellastenol, which after several recrystallizations from methanol melted at 123–125°, $[\alpha]_D^{21}$ +19.8° (31.9 mg., α + 0.21°).

Anal. Calc'd for $C_{28}H_{48}O$: C, 83.92; H, 12.08.
Found: C, 84.05; H, 12.08.

α-Stellastenyl 3,5-dinitrobenzoate. A solution of 300 mg. of α-stellastenol and 1.2 g. of 3,5-dinitrobenzoyl chloride in 4 cc. of anhydrous pyridine was heated for three hours at 80–90°. It was then poured into 20 cc. of ice-cold, 6 *N* sulfuric acid. The precipitate was filtered, washed with water and acetone, and recrystallized several times from a mixture of equal parts of ethyl acetate and absolute ethanol. The compound crystallized in plates and melted at 196.5–197.5°.

Anal. Calc'd for $C_{34}H_{48}N_2O_6$: C, 70.31; H, 8.33.
$C_{35}H_{50}N_2O_6$: C, 70.67; H, 8.40.
$C_{36}H_{52}N_2O_6$: C, 71.02; H, 8.61.
Found: C, 70.70; H, 8.49.

β-Stellastenyl acetate. A rapid stream of anhydrous hydrogen chloride was passed through an ice-cold solution of 1.7 g. of α-stellastenyl acetate in 100 cc. of chloroform. After eight hours the solution was washed thoroughly with a solution of sodium bicarbonate and water, dried over potassium carbonate and evaporated to dryness *in vacuo* at room temperature. The residual oil solidified upon rubbing with methanol. After several recrystallizations from absolute ethanol, the acetate melted at 94–96°, $[\alpha]_D^{28}$ +19° (40 mg., α + 0.25°).

Anal. Calc'd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38.
Found: C, 80.95; H, 11.43.

β-Stellastenol. The saponification of the β-acetate in the usual manner gave β-stellastenol, which crystallized from absolute ethanol in the form of short needles, m.p. 122–124°, $[\alpha]_D^{28}$ +29.4° (48.8 mg., α +0.48°).

Stellastanyl acetate. A solution of β-stellastenyl acetate in glacial acetic acid was hydrogenated with a platinum black catalyst at room temperature and atmospheric pressure until hydrogen was no longer absorbed. The reaction product which was isolated in the usual manner, melted at 132–134°, and gave a faint Liebermann test. A solution of 200 mg. of this material in 3 cc. of chloroform was treated with a mixture of 0.3 cc. of chloroform containing one drop of concentrated sulfuric acid and 0.3 cc. of acetic anhydride. After thirty minutes the solution had turned green. It was then washed successively with water, sodium bicarbonate solution, and water, decolorized with Norit and dried with sodium carbonate. The residue remaining after evaporation of the solvent was recrystallized several times from methanol. The acetate no longer gave a Liebermann reaction. It crystallized in the form of small needles and melted at 138–139°, $[\alpha]_D^{24}$ +13.5° (42.3 mg., α +0.19°).

Anal. Calc'd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79.
Found: C, 81.26; H, 11.96.

Stellastanol. The saponification of the acetate described above gave a sterol which after several recrystallizations from methanol melted at 143°, $[\alpha]_D^{28}$ +22.0° (39.6 mg., α +0.29°).

Anal. Calc'd for $C_{28}H_{50}O$: C, 83.51; H, 12.53.
Found: C, 82.21; H, 12.48.

Like most other saturated sterols, stellastanol contains solvent of crystallization which is difficult to remove.

Stellastanyl 3,5-dinitrobenzoate. This derivative was prepared in the usual manner. After three recrystallizations from a mixture of equal parts of ethyl acetate and absolute ethanol it melted at 204–205°.

Anal. Calc'd for $C_{35}H_{52}N_2O_6$: C, 70.44; H, 8.78.
Found: C, 70.61; H, 8.88.

SUMMARY

The mixture of sterols which is obtained from the starfish, *Asterias forbesi*, has been reinvestigated. It was found in accordance with the results of a pre-

vious investigation that the least soluble, highest-melting sterol shows close resemblance to the di-unsaturated stellasterol. It has been proposed to retain the name stellasterol for the di-unsaturated sterol present in the mixture, and to assign the name stellastenol to the mono-unsaturated sterol. A complete separation of the sterols has not yet been effected.

An explanation has been given for the discrepancies between the reported melting points of stellasteryl benzoate.

It has been shown that the starfish sterols, unlike all other unsaturated principal sterols of animal origin which so far have been discovered, are of the order C_{28}, possess a slight positive rotation and are devoid of the usual 5,6-double bond.

It has been shown that the side chain of stellasterol from C-22 on is identical with that of ergosterol but for an opposite configuration at C-24.

It has been shown by indirect evidence that the starfish sterols possess a cyclic double bond at C-8. Catalytic hydrogenation of a mixture of the steryl acetates gave the uniform α-stellastenyl acetate, which has a double bond in the 8,14-position.

Treatment of α-stellastenyl acetate with hydrochloric acid gave β-stellastenyl acetate, which upon catalytic hydrogenation gave stellastanyl acetate. Stellastenol is isomeric with ergostanol and campestanol.

The significance of these observations has been discussed.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XVI. 7-DEHYDROCLIONASTEROL

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Heilbron (1), and Bock and Wetter (2) have shown by spectrographic and chemical means that sterols of invertebrates are as a rule considerably richer in 7-dehydrosterols than the sterols which have so far been isolated from vertebrates. In a few instances (2) the 7-dehydrosterols of invertebrates have been isolated and identified as 7-dehydrocholesterol or ergosterol. As yet very little is known about the 7-dehydrosterols of sponges. In the case of the marine sponge, *Spheciospongia vesparia*, the presence of a small amount of 7-dehydrosterol was indicated by spectrographic evidence (3). Of greater significance is the work of Mazur (4) who by chromatography isolated a sterol fraction from the fresh-water sponge *Spongilla* which contained 56% of 7-dehydrosterol.

In connection with certain studies on the sterols of sponges it became desirable to have available a sample of a 7-dehydrosterol which might conceivably be present in sponges. Since clionasterol is one of the more common sterols found in sponges (5) it appeared reasonable to assume that 7-dehydroclionasterol might be present in the same source material, and for this reason a preparation of this substance was carried out by the conventional procedure.

Clionasteryl acetate was oxidized to 7-ketoclionasteryl acetate (6), which was then reduced by aluminum isopropoxide to the mixture of 7-hydroxyclionasterols. In one series of experiments, benzoic acid was split out of the dibenzoates of the diols by heating with dimethylaniline according to the method of Haslewood (6). The monobenzoate thus obtained was then hydrolyzed to give 7-dehydroclionasterol.

Better results were obtained in the second series of experiments where the dibenzoates were first hydrolyzed according to Wintersteiner and Ruigh (7) to give the isomeric 7-benzoxyclionasterols, from which benzoic acid was then removed with boiling dimethylaniline. The 7-dehydroclionasterol thus formed was isolated as its digitonide, and the latter converted directly into 7-dehydroclionasteryl acetate with acetic anhydride. The absorption spectrum of the acetate was identical with that of ergosteryl acetate, $\log \epsilon_{232} = 4.04$.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3.0 cc. of chloroform.

7-Ketoclionasteryl acetate. A solution of 17.2 g. of chromic anhydride in 160 cc. of glacial acetic acid and 5 cc. of water was added dropwise over a period of 150 minutes to a well stirred solution of 20 g. of clionasteryl acetate in 200 cc. of acetic acid. During the addition and for four hours afterwards the solution was kept at 60–65°. The excess chromic anhydride was then reduced by alcohol, and the solution concentrated *in vacuo* to a small volume. Water was then added and the mixture extracted with ether. The ether extract was washed with alkali and water, dried over anhydrous sodium sulfate and evaporated to

dryness. The residue after four recrystallizations from ethanol gave 4.0 g. of 7-ketoclionasteryl acetate of m.p. 172–173°, $[\alpha]_D^{27}$ −99.44° (6.10 mg., α −1.92°).

Anal. Calc'd for $C_{31}H_{50}O_3$: C, 79.10; H, 10.70.
Found: C, 79.10; H, 10.98.

7-Hydroxyclionasteryl dibenzoate. A solution of 4 g. of 7-ketoclionasteryl acetate in 60 cc. of anhydrous isopropanol was treated with 3.5 g. of aluminum isopropoxide. The solution was then heated under a fractionating column until the distillate no longer gave a nitroprusside test for acetone. One hundred cc. of a 7% aqueous solution of potassium hydroxide was then added to the solution in the distilling flask, and the solid material which precipitated was filtered, washed, and dissolved in ether. The washed and dried ether solution was then concentrated to a small volume and diluted with 200 cc. of low-boiling petroleum ether. Upon cooling, 1.2 g. of a crystalline diol, m.p. 153–158°, was obtained. Concentration of the mother liquor gave the lower-melting epimer.

One gram of the diol of m.p. 153–158° was benzoylated in pyridine in the usual manner. There was obtained 1.2 g. of a dibenzoate, which after four recrystallizations from acetone-methanol formed nice needles and melted at 159–160°, $[\alpha]_D^{24}$ +93.4° (46.4 mg., α +1.45°).

Anal. Calc'd for $C_{43}H_{58}O_4$: C, 80.83; H, 9.15.
Found: C, 80.70; H, 8.91.

The lower-melting diol gave 1.2 g. of a benzoate of m.p. 135–145°.

7-Dehydroclionasteryl benzoate. A solution of 0.5 g. of the dibenzoate of m.p. 159–160° in 5 cc. of freshly distilled dimethylaniline was refluxed for eight hours. The solution was then poured into dilute hydrochloric acid, and the precipitated material was extracted with ether. The ether extract was washed with water, dried, and evaporated to dryness. Recrystallization of the residue from absolute ethanol gave 0.21 g. of 7-dehydroclionasteryl benzoate which melted to a turbid liquid at 133–135° and turned clear at 138°.

Anal. Calc'd for $C_{36}H_{52}O_2$: C, 83.67; H, 10.14.
Found: C, 83.32; H, 10.04.

When treated in the same manner, 1.2 g. of the lower-melting benzoate gave 0.2 g. of 7-dehydroclionasteryl benzoate.

7-Dehydroclionasterol. A solution of 0.4 g. of 7-dehydroclionasteryl benzoate in 50 cc. of ether was added dropwise to 25 cc. of a boiling 2% solution of potassium hydroxide in methanol. The ether was distilled off slowly while a stream of nitrogen was passed through the solution. The solution was then cooled, and the crystalline material which settled out was filtered, washed with water and methanol, and recrystallized from absolute ethanol. It formed glistening plates and melted at 138°, $[\alpha]_D^{25}$ −98.2° (18.6 mg., α −0.61°). The 7-dehydroclionasterol was rather unstable and turned yellow on standing.

Anal. Calc'd for $C_{29}H_{48}O \cdot 0.5\ H_2O$: C, 82.59; H, 11.71.
Found: C, 82.47; H, 11.54.

7-Dehydroclionasteryl acetate. To 0.4 g. of 7-hydroxyclionasteryl dibenzoate dissolved in 8 cc. of benzene, a solution of 0.26 g. of sodium methoxide in 13.5 cc. of anhydrous methanol was added, and the mixture was allowed to stand at room temperature for one day. It was then poured on cracked ice, and the benzene layer was washed several times with cold water. Evaporation of the benzene solution gave an oil, which was at once refluxed with 10 cc. of freshly distilled dimethylaniline in an atmosphere of carbon dioxide for three hours. The solution was then cooled, diluted with ether, and freed from dimethylaniline by thorough extraction with hydrochloric acid. A spectrographic assay of the ether solution indicated a yield of 67% of 7-dehydroclionasterol.

The ether solution was then evaporated to dryness in an atmosphere of carbon dioxide, and the residue was dissolved in 90% ethanol and precipitated with a 1% solution of digitonine. The digitonide, 0.68 g., was refluxed for thirty minutes with 10 cc. of acetic anhydride, and the 7-dehydroclionasteryl acetate which separated on cooling was recrystallized several times from ether-methanol. It melted at 139–140°, $[\alpha]_D^{24}$ −71.6° (15.5 mg., α −0.37°). Log ϵ_{282} = 4.04.

Anal. Calc'd for $C_{31}H_{50}O_2$: C, 81.88; H, 11.10.
Found: C, 81.68; H, 11.14.

SUMMARY

A preparation of 7-dehydroclionasterol and some of its derivatives has been described.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

VOLEMITOL HEPTAACETATE

W. DAYTON MACLAY, RAYMOND M. HANN, AND C. S. HUDSON

Received March 16, 1944

The literature concerning this substance is very confusing. Since we had occasion some years ago to prepare it, the following description of its properties is published, with a historical preface that will elucidate, we believe, the curious mistakes of identity that are now known with certainty to be present in some of the records concerning it.

Bourquelot (1) discovered volemitol in a somewhat rare species of mushroom, *Lactarius volemus* Fr., which also contains D-mannitol, the hexitol that has been found in most mushrooms. At that time the m.p. 166° had been established for mannitol, and for mannitol hexaacetate the existing data were near those now accepted, which are m.p. 123° and $[\alpha]_D$ +25° in chloroform and +18.8° in glacial acetic acid. The m.p. which Bourquelot found for volemitol was 140–142°, which showed it to be a different substance from mannitol; its crystals were also different in appearance, and it was much more soluble than mannitol. These characteristics, together with others that may be passed over for brevity, convinced Bourquelot that he had in hand a new polyhydroxy alcohol, a relative of mannitol, and he named it volemitol. He acetylated a sample of volemitol (which became known later to have been impure because subsequent researches established the m.p. of pure volemitol as 153–154°) and obtained *in low yield* a crystalline acetate, m.p. 119° and $[\alpha]_D$ +19.1° in "acide acetique". He remarked that its properties closely resemble those of mannitol hexaacetate.

The number of carbon atoms in the molecule of volemitol was not known at that time. Mannitol had long been recognized as a hexitol, through its reduction by hydriodic acid and phosphorus to a hexyl iodide (2). Perseitol, a polyhydroxy alcohol which had been discovered (3) in *Persea gratissima* Gaert. and long thought to be a hexitol, had been shown by Maquenne (4) through the analysis of several of its derivatives (especially dibenzylideneperseitol), to be a heptitol. Fischer's phenylosazone researches had disclosed a simple way to determine the length of the carbon chain in such polyhydroxy alcohols and his method could be used with moderately small amounts of substance. Bourquelot applied to him for a decision regarding the molecular formula of volemitol, sending him 10 g. of the rare substance. Fischer (5) found the m.p. after four recrystallizations of the sample from hot alcohol to be 151–153° (corr.) with sintering at 147°. [We remark at this point that Fischer's data furnish an early indication of the fact, which became well established later, that it is very difficult to obtain volemitol free from other alcohols (in this case mannitol) simply by repeated recrystallizations.] Fischer oxidized the sample with hypobromite and prepared from the product through reaction with phenylhydrazine a crystalline substance, named by him phenylvolemosazone, the analysis of which for carbon, hydrogen, and nitrogen proved beyond question that it was a phenylheptosazone and that volemitol was accordingly a heptitol. This decision not only confirmed Bour-

quelot's recognition of volemitol as a different alcohol from mannitol, it also brought into clearer recognition the fact that at least five classes of non-cyclic polyhydroxy alcohols exist in wide distribution in nature, namely, the three-carbon glycerol, the four-carbon erythritol (a constituent of lichens), the five-carbon adonitol (from *Adonis vernalis* L.), the six-carbon mannitol, sorbitol, and dulcitol, and the seven-carbon perseitol and volemitol.

Seven years later Bougault and Allard (6) isolated volemitol from three species of primrose (*Primula grandiflora* L., *elatior* Jacq., and *officinalis* Jacq.), identifying it by comparison with a sample of volemitol from Bourquelot, prepared from *Lactarius volemus*. They recrystallized volemitol to full purity (m.p. 154°) and prepared several derivatives, among which was its heptaacetate, for which they found the m.p. 63° but did not record its rotation. They expressed the opinion that the acetate of m.p. 119° which Bourquelot had believed to be volemitol acetate was really mannitol hexaacetate, resulting from the presence of some mannitol in Bourquelot's early samples of volemitol (m.p. 140–142°). As Bourquelot aided the work of Bougault and Allard, it appears that he agreed with their conclusion regarding the acetate since no dissent is recorded. Bougault and Allard's work showed that it is very difficult to free volemitol from mannitol even when one knows the identifying characteristics of the pure substances; it became obvious that Bourquelot's original discovery of volemitol was remarkable. Remarkable not because so excellent an experimentalist as Bourquelot had failed to obtain it in full purity, but because he had shown such great skill in recognizing it at all. It seemed now definitely settled that volemitol heptaacetate is a crystalline substance of m.p. 63°; and thus the matters stood for twenty-seven years. Then Ettel (7) began a study of volemitol, which he prepared from *Lactarius volemus*, a research which led him in three years to his establishment of the configuration of sedoheptulose through precise theoretical interpretation of his patient experimental studies (7b). As a minor part of these, which has no bearing on his real and permanent contribution, he prepared what he believed to be volemitol heptaacetate (7a), and he found m.p. 120–121° and $[\alpha]_D$ +20.7° in chloroform, values which confirmed Bourquelot's early data and indicated that Bourquelot's acetate was not mannitol hexaacetate after all. To some of us who were following the ramifications of this recondite subject it seemed that Ettel's result settled the question again. Apparently either Bougault and Allard had made an error, or their volemitol acetate of reported m.p. 63° was a dimorphic form of Bourquelot's acetate. Accordingly, the reader can imagine our interest six years ago when we acetylated 2.0 g. of carefully purified synthetic volemitol (D-manno-D-*talo*-heptitol) with 8 cc. of acetic anhydride and 0.5 g. of sodium acetate and obtained in nearly quantitative yield and high purity Bougault and Allard's volemitol hexaacetate of m.p. 63°. Its rotation, now published for the first time, is $[\alpha]_D^{20}$ +36.1° (*c*, 2.0) in chloroform, and +30.8° (*c*, 0.8) in glacial acetic acid. This proves that the substance is not a dimorphic form of the acetate that Bourquelot and Ettel described, which rotated eleven degrees lower. Our initial interest now changed to surprise and we studied the

material with special attention. Recrystallization of our product from 150 parts of hot water did not change its properties. Its deacetylation produced in nearly quantitative yield pure volemitol (m.p. 153°). Its analysis agrees with the formula of a heptitol heptaacetate (theory, C, 49.79; H, 5.97; CH_3CO, 59.49; found, C, 49.66; H, 6.18, CH_3CO, 59.54). It was also obtained from a sample of natural volemitol which was kindly supplied by Dr. C. Jelleff Carr, who had isolated it from *Primula* roots. Volemitol heptaacetate crystallizes from either hot water, in which it is sparingly soluble, or from 20 parts of 85% alcohol, as clear well-built crystals with six faces prominent, approximately rectangular prisms somewhat elongated. It is unquestionably the acetate which Bougalt and Allard discovered, and we agree with them that in all probability Bourquelot's data apply to mannitol hexaacetate. Ettel's article (7a) shows that he had pure volemitol in hand (m.p. 153°) during his studies; the present evidence leads us to believe that an impure sample of the natural product, one containing some mannitol, was used for his acetylation experiment, and that his data agree with those of Bourquelot because both observers measured mannitol hexaacetate believing it to be the fully acetylated derivative of volemitol. As an aid to future investigations, crystals of D-volemitol heptaacetate and D-mannitol hexaacetate are illustrated in Plates I and II.

The description of the unusual history of volemitol and its heptaacetate leads to the surmise that this alcohol may be of far wider distribution in nature than has been reported. So far mannitol has always been found associated with it, and mannitol is of very wide distribution. Can it be that volemitol and mannitol are frequently associated where only mannitol has been reported? The historical record leads one to believe that small amounts of volemitol in association with mannitol, perseitol, or sorbitol would have escaped detection in past researches on plant constituents. It seems reasonable to assume that the discovery of volemitol in *Lactarius volemus* and in *Primula* species was facilitated by a favorable proportion of it or some other factor which aided its initial crystallization. It forms mixed crystals with mannitol and also with perseitol; possibly the careful study of crude crystalline mannitol from various natural sources, by the methods that have been disclosed in the researches on volemitol, will lead to its recognition in many other natural products. Any wholly crystalline sample of natural mannitol which shows a depressed melting point should be suspected of containing volemitol, especially if it proves difficult to raise the m.p. to 166° by recrystallization. The known seven-carbon alcohols and sugars of nature (D-perseitol, D-volemitol, D-mannoheptulose, D-sedoheptulose, and L-perseulose) constitute a biological group, a discussion of which will be included in review papers from this laboratory by Dr. N. K. Richtmyer and by one of the writers (C. S. H.).

There will now be described the procedure which was devised to obtain pure volemitol from the mixture of it with D-perseitol that results from the reduction of D-mannoheptulose; the directions may prove helpful in the detection of volemitol in plants.

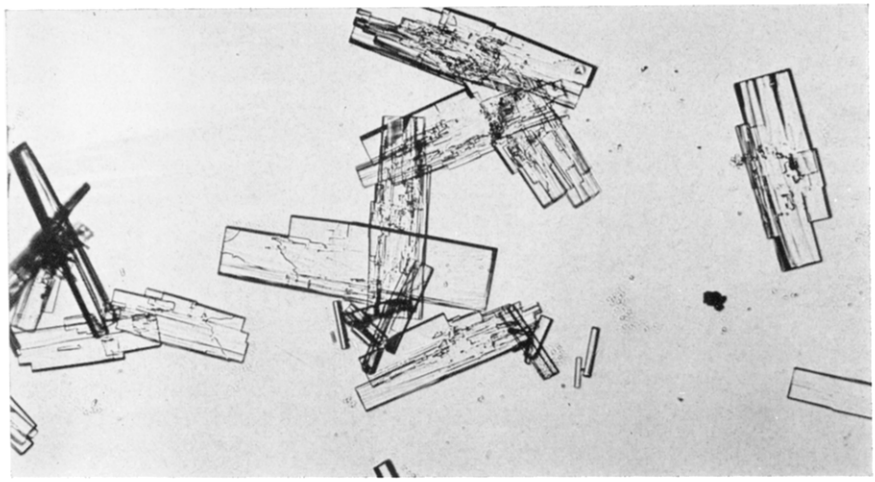

PLATE I. D-VOLEMITOL HEPTAACETATE (× 96). CRYSTALS FROM WATER

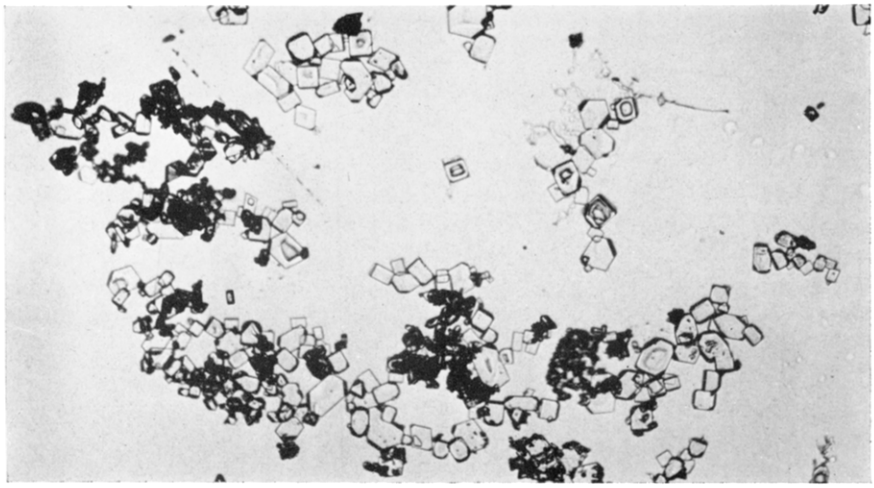

PLATE II. D-MANNITOL HEXAACETATE (× 96). CRYSTALS FROM WATER

The reduction of D-mannoheptulose. A solution of the ketose (25 g.) in water (70 cc.) was agitated in the bomb with 3 g. of Raney nickel and hydrogen (130 atmos.) for six hours at 98°. The Fehling test was negative. Removal of the catalyst, treatment of the solution with hydrogen sulfide to precipitate a small amount of heavy metals, filtration, and concentration to dryness gave a crystalline residue. It was dissolved in 80 cc. of water, 100 cc. of 95% alcohol was added, and a crop of perseitol was filtered off, wt. 11.25 g. The filtrate was concentrated to dryness, the residue was dissolved in 16 cc. of water and hot 95% alcohol (64 cc.) was added; crystallization in the refrigerator yielded 9.5 g. of material which melted at 140–142° (white, indicating presence of some perseitol). The filtrate from these crystals was concentrated to dryness and dissolved in 10 cc. of boiling 85% alcohol, yielding a small crop of crystals of m.p. 143–145° (white). Previous attempts to separate the low-melting material by further recrystallizations had failed. The combined material of m.p. 140–145° was shaken with 2 parts of benzaldehyde and 2 parts of 50% sulfuric acid, the crystalline tribenzylidenevolemitol (80% yield) was filtered off, washed with water and bicarbonate solution, and recrystallized from 100 parts of 95% alcohol, yield 60%, m.p. 155–162°. A second recrystallization of this product from 200 parts of absolute alcohol gave a yield of 75%, m.p. 190–192°. Ettel (7) has shown that this benzylidenevolemitol material is a mixture of at least two acetals; the separation of it into components is not necessary for the present objective, and the two recrystallizations suffice for removing perseitol. The benzylidenevolemitol was next hydrolyzed by refluxing for three hours with 18 parts of 4% hydrochloric acid;[1] the benzaldehyde was removed by extraction with ether, the hydrochloric acid by silver carbonate, and traces of remaining silver in solution by hydrogen sulfide. The solution was concentrated to a dry crystalline solid; its crystallization from 20 parts of 85% alcohol gave a 60% yield of pure volemitol, m.p. 153–154°. The over-all yield of pure volemitol from the crude material of m.p. 140–145° was thus about 24%; this could doubtless be increased considerably by further experience.

BETHESDA, MD.

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[1]While preparing this article we noticed a remark by J. Meunier (8) which had escaped our attention during our experimental work; it is possible that the benzylidenevolemitol can be hydrolyzed under much milder conditions than we used, *provided some excess benzaldehyde is present as a second liquid phase.*

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

PREPARATION OF SOME GLYCOL BENZOATES

HAROLD C. HEIM AND CHARLES F. POE

Received December 6, 1943

The examination of a number of food products recently has revealed that propylene glycol and certain esters of the hydroxy benzoic acids have been used as preservatives. The present research was undertaken for the purpose of preparing a series of glycol benzoates, which might be used as food preservatives.

Only a few of the glycol benzoates have been described in chemical literature. Wurtz (1) by whom ethylene glycol was discovered, prepared and described ethylene glycol dibenzoate before 1860. Propylene glycol dibenzoate was first prepared in 1871 by Friedel and Silva (2), by treating silver benzoate with propylene bromide dissolved in anhydrous ether. Trimethylene glycol dibenzoate was prepared in 1878 by Reboul (3), by treating 1,3-dibromopropane with silver benzoate. Gilmer (4) prepared ethylene glycol disalicylate. The monobenzoate of ethylene glycol was first prepared by Taub and Hahl in 1911. (5)

Ethylene, diethylene, propylene, and trimethylene glycols were used to prepare the dibenzoates, disalicylates, and the diortho-, dimeta-, and dipara-chlorobenzoates. In addition to these compounds the monobenzoates, monosalicylates, and mono-*p*-hydroxybenzoates were each prepared from ethylene glycol; and the mono-*p*-hydroxybenzoate was prepared from trimethylene glycol.

Whenever the acid chlorides of the different benzoic acids were available, the dibenzoates of the glycols were prepared by means of the acid chloride condensation. One molecular proportion of the glycol was dissolved in two molecular proportions of pyridine, after which the solution was cooled to approximately 10°. Two molecular proportions of the acid chloride were then gradually added, accompanied by constant stirring with a mechanical agitator. After the reaction was complete, the mixture was poured into cold water, and the ester separated. The solid esters were purified by crystallization, and the liquid esters were purified by distillation under reduced pressure.

The remaining substituted dibenzoates of the glycols were prepared by direct esterification. One molecular proportion of the glycol and 0.2 cc. of 60° Baumé sulfuric acid as catalyst, was treated with an excess of the benzoic acid. The flask was then placed in an electrically heated oven adjusted to 100°. By this arrangement the water formed in the reaction could escape from the reactants as vapor, but the high-boiling glycols were not volatilized to an appreciable extent. The flask was allowed to remain at this temperature for 6 to 8 hours, after which the mixture was poured into a solution of sodium bicarbonate to neutralize the excess acid. The ester was then separated and purified. Yields ranging from 60 to 80% were obtained by this method.

The monobenzoate and the monosalicylate of ethylene glycol were prepared by refluxing one molecular proportion of the sodium salt of the acid with an excess of ethylene chlorohydrin for 6 to 8 hours. The mixture was then poured into water and the ester separated and purified.

In general, all the solid esters which were prepared were found to be soluble in ethyl alcohol but insoluble in hot or cold water. Consequently they were purified by recrystallization from ethyl alcohol-water mixtures. The *p*-chlorobenzoic acid esters of ethylene glycol, trimethylene glycol, and diethylene glycol were found to be most readily soluble in chloroform, and were purified by crystalliza-

TABLE I

GLYCOL BENZOATES

COMPOUND	B.P./12 MM., °C.	M.P., °C.	CHLORINE, %		SAPONIFICATION NO.	
			Found	Calc'd	Found	Calc'd
Ethylene glycol dibenzoate	—	73			413.8, 415.7	415.5
Trimethylene glycol dibenzoate	—	53			394.0, 393.2	395.0
Propylene glycol dibenzoate	232	—			389.6, 394.2	395.0
Diethylene glycol dibenzoate	247	—			353.0, 353.4	357.3
Ethylene glycol disalicylate	—	84			371.1, 369.4	371.5
Trimethylene glycol disalicylate	—	75			348.4, 350.9	354.4
Propylene glycol disalicylate	186	—			347.2, 351.0	354.4
Diethylene glycol disalicylate	—	68			319.2, 326.9	323.8
Ethylene glycol di-*o*-chlorobenzoate	223	—	20.83, 20.92	20.92		
Trimethylene glycol di-*o*-chlorobenzoate	234	—	20.00, 19.87	19.80		
Propylene glycol di-*o*-chlorobenzoate	269	—	19.94, 19.66	19.80		
Diethylene glycol di-*o*-chlorobenzoate	260	—	18.73, 18.60	18.51		
Ethylene glycol di-*m*-chlorobenzoate	—	91	20.88, 21.00	20.92		
Trimethylene glycol di-*m*-chlorobenzoate	—	67	19.77, 19.62	19.80		
Propylene glycol di-*m*-chlorobenzoate	198	—	19.98, 19.70	19.80		
Diethylene glycol di-*m*-chlorobenzoate	208	—	18.74, 18.63	18.51		
Ethylene glycol di-*p*-chlorobenzoate	—	140	21.02, 21.07	20.92		
Trimethylene glycol di-*p*-chlorobenzoate	—	101	19.92, 19.85	19.80		
Propylene glycol di-*p*-chlorobenzoate	—	104	19.99, 19.83	19.80		
Diethylene glycol di-*p*-chlorobenzoate	—	139	18.72, 18.68	18.51		
Ethylene glycol monobenzoate	—	45			334.6, 336.7	337.7
Ethylene glycol monosalicylate	—	37			306.5, 309.1	308.1
Ethylene glycol mono-*p*-hydroxybenzoate	—	135			303.6, 304.2	308.1

tion from this solvent. Melting points were determined in a Thiele apparatus, and in every instance recrystallization was continued until no change in the melting point was observed.

Liquid esters which decomposed upon boiling at atmospheric pressures were purified by distillation under reduced pressure (10–15 mm.). The ester was

placed in a 50-cc. Claisen flask which was half filled with glass wool to prevent bumping. A water jacket was fitted around the exit tube of the flask and a receiver was used whereby fractions distilling at different temperatures could be reserved.

The esters of the chlorobenzoic acids were analyzed by the method proposed by Stepanow as outlined by Kamm (6). Other esters were analyzed by determining the saponification number. In both instances duplicate determinations were made.

Table I lists the glycol benzoates with analyses.

In all, 24 benzoates were prepared and analyzed. Of this number 18 compounds previously had not been reported in the literature.

The esters reported in this publication, together with others, are being used to study the antiseptic power of esters of the benzoic acids. The results of this study will be reported in a later communication.

BOULDER, COLO.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

QUINOLINE DERIVATIVES FROM 2- AND 4-CHLOROQUINOLINES[1]

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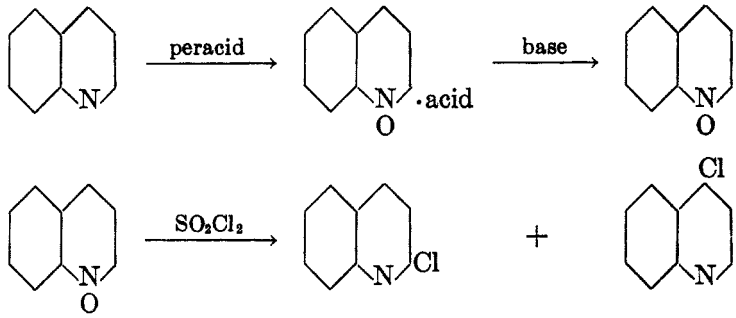
PREPARATION OF CHLOROQUINOLINES

Quinoline and related N-heterocycles react readily with peracids to give N-oxides, and these in turn react with various chlorinating agents to give a mixture of *alpha*- and *gamma*-chloro derivatives



These reactions, first studied by Meisenheimer (4) and later by Bobranski (1), give ready access to the 4-position of quinolines in which the pyridine ring is otherwise unsubstituted.

The ratio of 2-chloro to 4-chloro derivatives formed is about 1:1.7 for quinoline itself and 1:0.6 for 6-methoxyquinoline. In applying this reaction to various quinolines, we have found that the nature of a substituent already present on the benzenoid nucleus is the primary factor influencing the ratio of *alpha*- to *gamma*-chloro derivative obtained. Thus with 6-nitroquinoline the 4-chloro derivative predominates and the ratio is about 1:3.5. On the other hand, changes in the reaction conditions appear to have very little influence on the ratio. Thus, with 6-methoxyquinoline N-oxide, the use of an inert solvent, such as carbon tetrachloride, does not appreciably affect the course of the reaction. Other solvents and possible catalysts such as sulfuric acid, acetic acid, or phosphorus pentoxide cause undesirable side reactions. Also, whether the oxide, oxide dihydrate, or oxide hydrochloride is used, the amounts of *alpha* and *gamma* derivatives formed are about the same. It should be noted, however, that it is possible to reduce 2-chloro-6-methoxyquinoline catalytically to 6-methoxyquinoline and to recycle this material and obtain more of the 4-chloro derivative.

In Table I will be seen the results of applying the Meisenheimer reactions to 6-methoxy-, 6-chloro-, 6-nitro-, and benzo-(*f*)-quinolines. In all of these syntheses the Meisenheimer procedure was greatly simplified by the preparation of the N-oxide phthalate by the method of Bobranski(1), but converting this salt to the

[1] Presented at the Cleveland meeting of the American Chemical Society, April, 1944.

free base instead of the hydrochloride. The latter is more difficult to obtain. It is surprising to note that a third isomer, possibly the 3-chloro compound, was

TABLE I

QUINOLINE DERIVATIVES

FORMULA	M.P. (COR.) °C.	YIELD %	RATIO ISOMERS	ANALYSIS, %	
				Calc'd	Found
N-OXIDES					
6-MeO-quinoline N-oxide[b]	108–109				
6-Cl-quinoline N-oxide[a]	126.5			N, 7.8	7.8, 7.7
6-NO_2-quinoline N-oxide[a]	220–222			N, 14.8	15.1, 15.0
Benzo-(*f*)-quinoline N-oxide[a]	132			C, 80.0	80.2, 80.0
				H, 4.7	4.7, 4.7
CHLOROQUINOLINES[c]					
2-Cl-6-MeO-quinoline[b]	106–107	55	1.00		
4-Cl-6-MeO-quinoline[b]	79	35	.63		
2,6-dichloroquinoline[d]	161.5	49	1.00	C, 54.6	55.0, 55.3
				H, 2.6	2.7, 2.6
4,6-dichloroquinoline[a]	104	35	1.38	C, 54.6	54.8, 54.7
				H, 2.6	2.6, 2.8
2-Cl-6-NO_2-quinoline[e]	230	16	1.00		
3(?)Cl-6-NO_2-quinoline[a]	145	3.5	.22	Cl, 17.0	16.8, 17.0
4-Cl-6-NO_2-quinoline[a]	142.5	56.5	3.53	N, 13.4	13.2, 13.3
3-Cl-benzo-(*f*)-quinoline[f]	112.5	32	1.54		
1-Cl-benzo-(*f*)-quinoline[g]	66–67	21[h]	1.00		
HYDROXYQUINOLINES					
2-OH-6-Cl-quinoline[i]	267.5				
4-OH-6-Cl-quinoline[a]	269			C, 60.2	60.7, 60.9
				H, 3.4	3.4, 3.5
2-OH-6-NO_2-quinoline[j]	280				
4-OH-6-NO_2-quinoline[a]	325			N, 14.7	14.7, 14.8

[a] New compound. All were white in color except the hydroxyl and N-oxide derivatives of 6-nitroquinoline which were yellow.

[b] Magidson, *J. Gen. Chem.* (USSR), **7,** 1896 (1937).

[c] In each group the isomers are listed in the order of their precipitation from acidic solution by alkali.

[d] Fischer, *Ber.*, **35,** 3683 (1902); m.p. 156°.

[e] Fischer and Guthmann, *J. prakt. Chem.*, (2), **93,** 381 (1916); m.p. 235°.

[f] Hamer and Kelly, *J. Chem. Soc.*, 777 (1931); m.p. 114°.

[g] Brit. Patent 481,874 (March 14, 1943): m.p. 66–67°. Mueller and Hamilton, *J. Am. Chem. Soc.*, **65,** 1017 (1943); m.p. 62–63°.

[h] Higher yields should be possible; only one trial was made.

[i] Einhorn and Lauch, *Ann.*, **243,** 345; m.p. 262–263°.

[j] Fischer and Guthmann, *loc. cit.*; m.p. 280°.

isolated in the case of 6-nitroquinoline. The hydroxy compounds listed were obtained by acid hydrolysis of the *alpha-* and *gamma*-chloro derivatives.

TABLE II

DERIVATIVES FROM CHLOROQUINOLINES

FORMULA	TEMP. °C	REACTION TIME, HOURS	YIELD, %	B.P. °C. (MM.)	M.P. (COR.) °C	ANALYSIS %	
						Calc'd	Found
A. *R=6-methoxyquinolyl*							
R-4-NHCH(C_2H_5)CH_2N(C_2H_5)$_2$	175	50	32[a]	195 (0.5)	117		
Dipicrate					198	C, 47.4	47.3, 47.5
						H, 4.4	4.3, 4.4
R-4-NHCH(C_2H_5)CH_2N(CH_2CH_2)$_2$O	175	24	22[b]		170	N, 13.3	13.5, 13.5
R-4-NH(CH_2)$_6N$(C_2H_5)$_2$	175	4	60[b]		oil	N, 12.8	12.9
Monohydrate					83	C, 69.1	68.6, 68.6
						H, 9.6	9.7, 9.7
R-4-NHCH$_2$C(CH_3)$_2CH_2N$(CH_3)$_2$	145–170[e]	14	16[a]	200 (0.1)		C, 71.0	70.6, 70.9
						H, 8.8	8.4, 8.4
Dihydrochloride					222	C, 56.4	56.4, 56.3
						H, 7.6	7.6, 7.5
R-2-NHCH[CH_2N(CH_3)$_2$]$_2$	173	12	41[a]	185–190 (0.3)			
Picrate					182–183	N, 18.4	17.8, 18.2
Dihydrochloride					245–246	C, 54.4	53.8, 54.1
						H, 7.5	7.1, 7.3
R-4-NHCH[CH_2N(CH_3)$_2$]$_2$	150	20	72[c]		140	C, 67.5	66.5, 66.8
						H, 8.7	8.5, 8.8
Trihydrochloride					255	N, 12.0	12.2, 11.9
Trihydrochloride hydrate					245 (dec.)	N, 11.5	11.3
R-4-NHCH[CH_2N(C_2H_5)$_2$]$_2$	175	8	50[a]	205 (0.3)	85		
Trihydrochloride					255	N, 12.0	12.17, 11.94
R-4-NHCH[CH_2N(C_3H_7)$_2$]$_2$	155	17	56[a]	222 (0.15)	56	C, 73.0	72.13, 72.08
						H, 9.8	10.20, 10.27
R-4-NHCH[CH_2N(C_4H_9)$_2$]$_2$	175	13	62[a]	240 (0.04)		C, 74.0	73.2, 73.4
						H, 10.7	10.2, 10.3

Trihydrochloride					103	C, 60.1 H, 9.2	59.0, 58.9 9.2, 9.4
Dihydrochloride					145	C, 64.1 H, 9.6	63.6, 63.2 9.7, 9.6
R-4-NHCH{$CH_2N[CH_2CH(CH_3)_2]_2$}$_2$	175	15	44[b]		116	C, 74.0 H, 10.7	73.84, 73.78 10.76, 10.80
R-4-$OCH_2CH_2N(C_2H_5)_2$·2HCl	140	5	89[d]		188	C, 55.4 H, 7.0	54.9, 54.9 7.0, 6.8
R-4-OCH[$CH_2N(C_2H_5)_2$]$_2$	135	3	55[a]	190 (0.1)		C, 70.2 H, 9.0	71.4, 71.5 9.6, 9.4
Trihydrochloride					191	C, 53.8 H, 7.7	53.7, 53.0 7.8, 7.7
R-4-(6′-methoxy-8′-quinolylamino)-H_2O	140	7	62[c]		178.5	C, 68.8 H, 5.5	68.5, 69.0 5.6, 5.6
R-4-(8′-quinoxy)·2HCl	172	3	58[d]		268	C, 60.8 H, 4.3	61.2, 61.3 4.6, 4.3
B. *Q=6-hydroxyquinolyl*							
Q-4-$NHCH_2C(CH_3)_2CH_2N(CH_3)_2$	120	2.5	56	240 (0.03)	225	C, 70.3 H, 8.5 N, 15.4	70.6, 70.9 8.6, 8.6 15.2, 15.4
Dihydrobromide					226–227	C, 44.2 H, 5.8	43.9, 43.8 6.2, 6.1
Q-4-NHCH[$CH_2N(CH_3)_2$]$_2$·3HBr	120	2			270	C, 36.2 H, 5.1	36.5, 36.7 5.3, 5.4
Q-4-NHCH[$CH_2N(C_2H_5)_2$]$_2$·3HBr	120	2			242	C, 40.8 H, 6.2	40.8, 41.2 6.3, 5.8
C. U=6-chloroquinolyl							
U-2-$NH(CH_2)_3N(C_2H_5)_2$	152	6	60[a]	202 (0.3)		N, 14.4	14.3, 14.1
Dihydrochloride					229–230	N, 11.5	11.8, 11.5
Dihydrochloride hydrate					75 (dec.)	N, 10.5	10.8, 10.6

TABE II—*Concluded*

FORMULA	TEMP. °C	REACTION TIME, HOURS	YIELD, %	B.P. °C (MM.)	M.P. (COR.) °C	ANALYSIS, %	
						Calc'd	Found
U-2-NHCH[$CH_2N(CH_3)_2$]$_2$	175	6	45[a]	188 (0.3)		C, 62.6	62.4, 62.4
						H, 7.6	7.7, 7.2
Trihydrochloride					257	C, 46.2	46.1, 45.8
						H, 6.3	6.3, 6.4
U-2-$OCH_2CH_2N(C_2H_5)_2$	132	4	55[a]	164 (0.3)		C, 64.6	64.2, 65.3
						H, 6.9	6.9, 6.8
Monohydrochloride					164.5	C, 57.1	57.4, 57.1
						H, 6.4	6.4, 6.4
D. W=6-Nitroquinolyl							
W-4-$NH(CH_2)_3N(C_2H_5)_2$	100	8	45[a]	220 (0.15)	67	N, 18.5	18.5, 18.8
Monohydrate					68		
W-4-NHCH[$CH_2N(CH_3)_2$]$_2$	100	21	65[c]		140.5	C, 60.5	60.5, 60.5
						H, 7.3	7.3, 7.4
						N, 22.1	21.6, 21.6

[a] By distillation.
[b] By concentration of ether extract.
[c] By precipitating from acidic solution by alkali.
[d] By addition of alcoholic HCl to ether extract.
[e] Solution refluxed; temperature range due to rising boiling point.

DERIVATIVES FROM CHLOROQUINOLINES

The 2- and 4-chloroquinolines are readily converted into the corresponding quinoline amines and ethers through reaction with amines and the sodium derivatives of alcohols. A series of such compounds was prepared for the purpose of studying their pharmacological activity, especially towards the plasmodia of malaria.

In general, the compounds prepared were characterized by the difficulty with which they were obtained crystalline. The free bases were usually difficultly crystallizable oils and the hydrochlorides tended to be hygroscopic. Those derivatives containing several basic nitrogen atoms formed more than one hydrochloride and more than one picrate and it was often difficult to obtain a suitable material for analysis. Distillation of the free base under high vacuum was almost essential to obtain crystalline products.

TABLE III

TRIAMINES

FORMULA	B.P. °C (MM.)	d_4^{30}	n_D^{30}
$[(C_3H_7)_2NCH_2]_2CHNH_2$	115(0.2)	0.8473	1.4458
$[(C_4H_7)_2NCH_2]_2CHNH_2$	135(0.2)	.8505	1.4488
$\{[(CH_3)_2CHCH_2]_2NCH_2\}_2CHNH_2$	165(13)	.8377	1.4439

SYNTHESIS OF TRIAMINES

Some of the side chains employed were derived from new triamines obtained by reducing the Mannich condensatiom products between various secondary amines, formaldehyde, and nitromethane.

$$2R_2NH + 2H_2CO + CH_3NO_2 \longrightarrow (R_2NCH_2)_2CHNO_2$$

$$(R_2NCH_2)_2CHNO_2 \xrightarrow[\text{Raney nickel}]{H_2} (R_2NCH_2)_2CHNH_2$$

These reactions have been studied by Henry (3) and Cerf de Mauny (2) who used dimethylamine and diethylamine in the synthesis. We found that the higher secondary amines give equally good results, although the initial condensation may be somewhat more sluggish. The physical properties of the new members of this series are given in Table III.

EXPERIMENTAL

Perphthalic acid. This was prepared according to the procedure given in Organic Syntheses (5). It was found advantageous to use very concentrated alkali (40%) and add finely crushed ice directly to the mixture. A single extraction with 100 ml. of ether for each 17 g. of phthalic anhydride taken was found to extract most (86%) of the perphthalic acid formed, resulting in an economy of ether and giving a more concentrated solution.

N-oxide phthalates. The quinoline base was added in a suitable form to a quantity of the ether solution of perphthalic acid corresponding to a 50% excess. Liquid bases, as 6-methoxyquinoline, were added directly, using stirring and slow addition. 6-Chloro-

quinoline was melted, supercooled to room temperature, then added in a like manner. For benzo-(*f*)-quinoline, a saturated ether solution of the solid was prepared. Since 6-nitroquinoline is insoluble in ether, a saturated solution in dioxane was used.

Such additions usually resulted in a turbidity, marking the precipitation of an oil, probably a complex (perphthalate salt) of the acid and the base. It was found best not to permit this oil to settle as a separate layer, because its subsequent transformation to the solid N-oxide phthalate is an exothermic reaction, and the heat evolved may cause decomposition if not dissipated. Stirring in a bath of tap water (15°) until the transformation was complete gave good results. 6-Nitroquinoline did not give such an oily precipitate. Its N-oxide phthalate separated directly as a solid when the clear solution was allowed to stand in the ice-box for 2 to 4 days.

The resulting crystalline N-oxide phthalates were filtered and washed with ether, and were then pure enough to be converted directly to the free oxides.

N-oxides. The oxide phthalate, finely ground in a mortar, was covered with a liberal excess of 5% aqueous ammonia and stirred mechanically for fifteen minutes. The insoluble free oxide, in most cases a hydrate, was collected on a filter, washed with water, and dried in the air. Continued drying of the hydrate results in a slow conversion to the anhydrous form. It is usually difficult to determine exactly when a water content corresponding to the hydrate has been reached in the drying process. 6-Nitroquinoline N-oxide apparently does not form a stable hydrate. The oxide hydrates which were isolated are listed below (see Table I for anhydrous forms).

6-Methoxyquinoline N-oxide·$2H_2O$, white, m.p. 88–89° (cor.).

6-Chloroquinoline N-oxide·$2(?)H_2O$, white, m.p. 55–59° (cor.).

Benzo-(*f*)-quinoline N-oxide·$2(?)H_2O$, white m.p. 75–79° (cor.).

Chloroquinolines. Oxides, oxide hydrates, and oxide hydrochlorides all gave essentially the same results in their conversions to chloroquinolines. In all cases the material was added in portions to a volume of phosphorus oxychloride, chilled in ice, corresponding to 5 ml. for each 1 gram of the base. After addition was complete, the mixture was warmed gently under a condenser until refluxing began. An ice-bath was kept at hand in case the reaction became suddenly violent. Refluxing was continued for thirty minutes. The cooled reaction mixture was poured with stirring on crushed ice (500 g. for each 100 ml. of $POCl_3$), the solution diluted if necessary to dissolve any sparingly soluble chloroquinoline hydrochloride, and then filtered from any weakly basic chloroquinoline (6-nitro-2-chloroquinoline and 2,6-dichloroquinoline) which was present. Successive partial neutralizations of the filtrate with concentrated aqueous ammonia gave a series of precipitates of chloroquinoline derivatives in the order of increasing basicity. Usually only two products were formed: the 2- and 4-chloro isomers, and usually the 2-chloro was least basic and separated first. The isomers are listed in the order of their precipitation by alkali in Table I.

Aliphatic triamines. The diaminonitro compounds were prepared by the procedure of Cerf de Mauny (2) except that the longer reaction times indicated were used: di-*n*-propylamine 3 hrs; di-*n*-butylamine 48 hrs; di-isobutylamine 24 hrs. The products were yellow oils in all cases and were obtained uniformly in crude yields of 85%. All attempts at purification by distillation, even at very low pressures, resulted in decomposition. However, the products were pure enough for reduction.

For this step the nitro compound, dissolved in an equal volume of absolute ethanol, was reduced in a Parr hydrogenator at 60 lbs. pressure, using a Raney nickel catalyst. Reduction proceeded at once and the highly exothermic reaction was controlled by passing a rapid air blast through a copper jacket surrounding the reduction bottle. Reduction usually required from 45 to 60 minutes. Absorption of hydrogen was 80–90% of the theoretical amount.

The filtered mixture was dried over Drierite and distilled. The triamines obtained were colorless liquids with a characteristic amine odor. Their properties are given in Table III.

Derivatives from chloroquinolines. The derivatives of 6-methoxy-, 6-chloro-, and 6-nitroquinolines were prepared in all cases by heating, without a solvent, the corresponding active

chloro derivative with an excess (100%) of an amine, the sodium derivative of an amino alcohol, or, in one case, with 8-hydroxyquinoline. The temperatures and reaction times (listed in Table II) had to be varied according to the activity of the chloroquinoline and the nature of the side chain. Where the required reaction temperature was higher than the boiling point of the mixture, the reaction was conducted in a sealed tube. Heating was best achieved by surrounding the reaction tube with the vapor of a refluxing liquid of suitable boiling point. Chlorobenzene, *o*-dichlorobenzene, and *o*-xylene were among the compounds found useful for this purpose.

The cooled reaction mixture, often very viscous, was dissolved in three volumes of concentrated hydrochloric acid, and the free base was precipitated in a separatory funnel with aqueous alkali. It was then extracted with ether and dried. Such extracts were usually distilled under a high vacuum, but in certain cases (noted in Table II) it was advantageous to crystallize out the free base by concentrating the extract, or to precipitate a hydrochloride of the base by the addition of alcoholic hydrogen chloride. In a few cases the base as precipitated by alkali was a solid. One or two recrystallizations from pentane, heptane, or other solvent then usually gave the pure compound.

The distilled free bases sometimes solidified upon standing, in which case they were recrystallized from a suitable solvent. More often the oils were dissolved in ether and treated with alcoholic hydrogen chloride to form the hydrochlorides. Frequently these separated as oils which could be obtained crystalline only by chilling and scratching, washing with another solvent, reprecipitation from a good solvent by addition of a poor one, or by long standing. Once a solid salt was obtained, alcohol, sometimes mixed with dioxane or dibutyl ether, was usually the best recrystallizing solvent for the hydrochlorides.

The derivatives of 6-hydroxyquinoline were obtained from the corresponding 6-methoxy compounds by refluxing a solution of the derivative in concentrated hydrobromic acid (Baker's C.P., 5 ml. for each 1 g. of base) for two hours. The solution was then diluted with four volumes of water. In most cases cooling and scratching induced the separation of a nicely crystalline hydrobromide hydrate which was removed and recrystallized from ethanol. When this procedure was not effective, the reaction mixture was evaporated to dryness under a vacuum on a steam cone, and the solid residue recrystallized from ethanol.

SUMMARY

1. A number of *alpha*- and *gamma*-chloroquinolines have been prepared by treatment of their N-oxides with phosphorus oxychloride. Several of these are new.

2. A number of aminoalkylamino, diaminoalkylamino, and aminoalkoxy derivatives have been prepared from these chloroquinolines and characterized.

3. Three new aliphatic triamines have been prepared and characterized.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

THE REACTION OF β-HALOGEN ETHERS WITH METALS. MECHANISM OF THE REACTION AND RELATED PROCESSES

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It is a well established fact that when β-halogen ethers are acted upon by the more electropositive metals such as sodium, magnesium or zinc they suffer fission of the ether linkage and produce a molecule of metal alkoxide and a molecule of olefin. The present communication reviews briefly a representative number of these reactions which are already in the literature. In view of the lack of a comprehensive mechanism applicable to all of them such a mechanism and the experimental evidence supporting it are here presented.

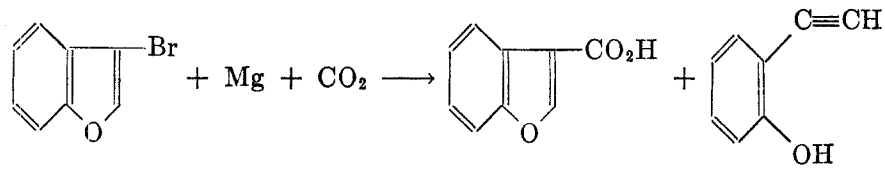
The literature affords as examples of β-halogen ether behavior the reaction of β-bromoethyl phenyl ether with magnesium to yield ethylene and bromomagnesium phenoxide (1). [Wohl and Berthold (2) have achieved the same result by the use of sodium.] Also the bromides derived from a number of cellosolves have been found to react in the same manner with magnesium in the presence of dry ether (3).[1] In the synthesis of olefinic hydrocarbons which bears his name, Boord (5) has used zinc to achieve the same result.

It is commonly noticed in these cases where the more active metals are employed, that some Wurtz coupling has occurred, and that the amount of such product obtained is greater the more electropositive the metal. It is usual also where magnesium is employed, that the actively reacting mixtures give a negative Gilman test for Grignard reagent. In an effort to prove the presence or absence of a Grignard reagent as intermediate in this type of reaction Robinson and Smith (6)[2] investigated rather fully the behavior of magnesium and tetrahydrofurfuryl bromide. Even when the reaction was carried out in the presence of moist or alcoholic ether, no tetrahydrosylvan was produced. Penten-4-ol-1 was the only product. This may be taken to indicate that the Grignard reagent or its constituent ions, if, indeed, either are present at all, must be extremely fugitive. In the present work it was found that β-bromotetrahydrofuran underwent the same type of ring opening to produce allyl carbinol. It appeared to differ from tetrahydrofurfuryl bromide only in that it possessed a lower degree of halogen reactivity. It failed to react with magnesium but was attacked by lithium. The Gilman test was negative at all times.

At this point, however, it is important to note that Reichstein (8) was able to prepare an organomagnesium compound from β-bromocoumarone.

[1] That the ether oxygen may also be of the acetal type is shown by the work of Wislicenus (4) who found that diethylchloroacetal on treatment with sodium at 130–140° produced vinyl ethyl ether, sodium ethoxide, and sodium chloride.

[2] Paul (7) had earlier reported a Grignard reagent which rearranged on heating to the bromomagnesium salt of penten-4-ol-1.



That the β-halogen ether structure is important here also is shown by the fact that some *o*-ethynylphenol was simultaneously produced.

It is thus apparent that any mechanism purporting to explain[3] the metal induced fission of β-halogen ethers must likewise take into account the formation of the Grignard reagent and the products of Wurtz coupling since all three reactions are exhibited by the members of the β-halogen ether class. The relationship between the modes of formation of the various products is clear from the following series of reactions:

$$\mathrm{R{-}O{-}CH_2{-}CH_2{-}Br + \cdot Mg\cdot \rightarrow R{-}O{-}CH_2{-}\underset{\downarrow}{CH_2}{-}Br{\leftarrow}\cdot Mg\cdot}$$

$$\mathrm{(A)\ RO{-}CH_2{-}CH_2\cdot + \cdot MgBr\ (B)} \qquad \text{(I)}$$

Process I is envisioned as a free radical attack of the metal atom upon the halogen in which the metal functions as an electron donor (typical metal action). The products are two different free radicals which attempt to stabilize themselves in one or more of the usual ways. If species (A) reacts with species (A) the reaction II leads to the usual Wurtz coupling product.[4]

$$\mathrm{R{-}O{-}CH_2{-}CH_2\cdot + R{-}O{-}CH_2{-}CH_2\cdot \rightarrow R{-}O{-}(CH_2)_4{-}O{-}R} \qquad \text{(II)}$$

Reaction of species (A) with species (B) leads to the familiar form of the Grignard reagent.

$$\mathrm{R{-}O{-}CH_2{-}CH_2\cdot + \cdot MgBr \rightarrow R{-}O{-}CH_2{-}CH_2{-}MgBr} \qquad \text{(III)}$$

However, it is not at all certain that Process III may not be just as accurately written as a simple disproportionation:

$$\mathrm{R{-}O{-}CH_2{-}CH_2\cdot + \cdot MgBr \rightarrow R{-}O{-}CH_2{-}CH_2^- + MgBr^+} \qquad \text{(IV)}$$

Indeed it has been suggested (10) that Process IV may even be with certain structures an equilibrium reaction. Splitting of the ether linkage is believed now to occur as a process by which the anion in IV stabilizes itself by transferring the negative charge from carbon to oxygen:

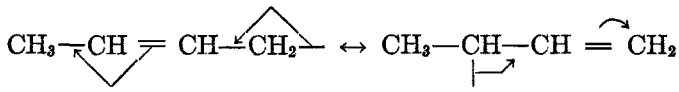
$$\mathrm{R{-}O \longleftarrow CH_2{-}\overset{\curvearrowleft}{CH_2}{-} \longrightarrow R{-}O^- + CH_2 = CH_2} \qquad \text{(V)}$$

Jacobs (11) has suggested that the metal induced fission of β-halogen ethers may be compared to the resonance of butenyl anions from crotyl halide and

[3] No attempt is made in this paper to deal with the non-reactivity of certain metal-halide combinations mentioned later.

[4] Processes (I), (II), and (III) are essentially those proposed by Gobmerg and Bachmann (9).

methylvinylcarbinyl halide. If the relationship between the butenyl anion and the ether anion systems is as close as is suspected then it is not surprising



that tests for the Grignard reagent in the latter case should be negative. Process V would be entirely too rapid (the rate approaching that of the resonance change) and would probably allow the fission to occur even before a neighboring water molecule could enter the reaction (6). The aforementioned work of Reichstein is not considered to invalidate the above considerations. Indeed, it rather strengthens them since in this case the anionic charge is developed on a carbon atom which is part of an aromatic system, capable, to some extent, of absorbing the charge by resonance.

The mechanism of splitting given above may now be summarized in general terms:

$$R - X - A - B - Y \rightarrow$$

$$R - X \leftarrow A \overset{\curvearrowleft}{-} B \overset{\curvearrowright}{-} \rightarrow R - X^- + A = B \quad \text{(VI)}$$

It is to be expected that splitting of the X—A bond will occur provided three conditions are satisfied:

(a) Group Y must be removed without its pair of bonding electrons,

(b) Atom X must have a higher effective nuclear charge than atom B,

(c) The covalence between atoms A and B must be capable of being increased by *one unit*.[5]

An example will be cited later on in which atoms A and B are not both carbon.

The validity of the mechanism has been examined in several ways. First it was to be expected that atom X (VI) could vary so long as the conditions of requirement (b) are met. Accordingly it was of interest to examine the behavior of such a substance as β-bromoethyl phenyl sulfide with magnesium. These substances were found to react vigorously together to produce thiophenol, a substance thought to be the coupling product, 1,4-dithiophenoxybutane, and a gas which decolorized a chloroform solution of bromine. The thiophenol was identified by oxidation to the disulfide which was compared with an authentic specimen.[6] The presence of thiophenol among the products proves that splitting of the X—A bond had occurred. That atom X may also be nitrogen was shown

[5] Cases have already been cited in which double and triple bonds are produced in the reaction. Jacobs (11) has reported the interesting case of the decomposition of phenoxyethynylmagnesium iodide on heating in a neutral solvent. This constitutes the only case in which the A to B covalence is three in the starting compound. The splitting has been correctly attributed by these authors to an electron displacement toward oxygen in the free or unfree phenoxyethynyl anion. Phenol is produced.

[6] What appears to be a reaction of this sort, although it was not recognized as such, was reported by Kretov (12) who identified ethylene as one of the products of reaction of mustard gas with zinc metal.

by the reaction of N-β-chloroethylmorpholine and sodium. Mason and Block (13) have reported this halide to be nonreactive toward magnesium and the present work confirms this. Lithium likewise has been found to be without very appreciable reaction even after a week's standing, and after the familiar accelerating devices had been tried. On heating with sodium, however, the halide rapidly decomposed, evolving a gas which decolorized bromine in chloroform. The residue contained considerable morpholine, which was identified by conversion to the *p*-toluenesulfonamide. Comparison with an authentic specimen completed the identification. Some Wurtz coupling was noted in this reaction also.

In order to prove the necessity for condition (a) in the general mechanism it was considered essential to determine whether fission could occur during the course of a reaction which could be assumed not to produce an anionic charge on atom (B)[7]. For this purpose we have examined the reactions of nitrous acid on certain ethylamines substituted on the β-carbon by other "negative" groups. Ethanolamine, β-bromoethylamine, ethylenediamine, and N-β-aminoethylmorpholine all react with nitrous acid but fail to evolve ethylene. This is taken to be indicative of failure to split the X—A bond (VI).

That condition (c) is necessary is obvious from a consideration of the reaction of such compounds as *o*-bromophenetole with magnesium. Here the A—B covalency is incapable of being increased.

It would be of interest in this connection to investigate the behavior of compounds in which atom X has a lower effective nuclear charge than B in reactions which produce a cationic charge on B (VI). Such a structure should undergo fission but by a different process than that just discussed.

$$R - M - CH_2 - CH_2 - NH_2 + HONO \rightarrow R - M - \overset{\curvearrowright}{CH_2} - CH_2^+$$

$$R - M^+ + CH_2 = CH_2$$

It is now appropriate to review several well known reactions which appear to proceed by way of the mechanism outlined above. The familiar debromination of 1,2-dibromides by means of active metals (15) is an example of the behavior of the structure in which atom X is monovalent. According to Process VI the reaction is[8]

$$R-\underset{Br}{CH}-\underset{Br}{CH}-R + Zn \longrightarrow R-\underset{Br}{CH}-CH-R + ZnBr^+$$

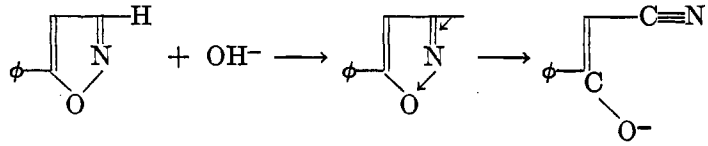
$$\downarrow$$

$$R-CH=CH-R + Br^-$$

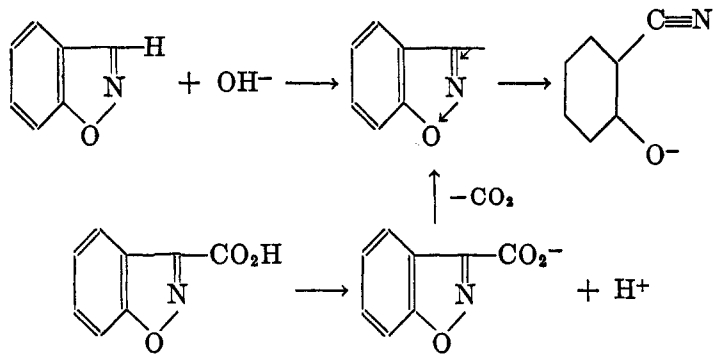
[7] It is considered that Whitmore's work (14) constitutes strong proof of the formation of a carbonium carbon upon the decomposition of alkyl diazonium compounds. The assumption is also made here that negative substituents at the β-position do not alter this situation.

[8] It is believed to be highly probable that the Wurtz reaction, of which this reaction may be considered to be an intramolecular variety, can proceed in more than one way, depending

It has long been known that isoxazoles unsubstituted on position 3 are isomerized to substituted acetonitriles by the action of alkalies (16).



Benzoisoxazoles (17) undergo a similar rupture of the N—O bond. When benzoisoxazole-3-carboxylic acid is heated somewhat above its melting point it loses carbon dioxide and undergoes the above rearrangement. The initial step is considered to be ionization followed by loss of CO_2 and production of the anion.



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EXPERIMENTAL

β-Bromotetrahydrofuran had been prepared earlier by Pariselle (18). His method was used except for the first step, which is the synthesis of allyl carbinol from allyl bromide. Here the Grignard reagent was first prepared (observing the necessary precautions for this active halide) and then treated with gaseous formaldehyde. Allyl carbinol b.p. 108–113°

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upon the type of reactants involved. It is most likely that in the reaction of chlorobenzene and sodium metal, the formation of the various polynuclear products may best be explained on the basis of free radical action. [See Bachmann and Clarke, *J. Am. Chem. Soc.*, **49**, 2089 (1927).] The coupling of the Grignard reagent with such active halides as allylbromide, however, may well be explained on the basis of carbon-anion attack on the carbon holding the halogen.

$$X{-}Mg^{+}\ R^{-} \rightarrow \underset{\displaystyle Br}{\overset{\displaystyle |}{CH_2}} - CH = CH_2 \rightarrow X{-}Mg^{+} + Br^{-} + R{-}\underset{\displaystyle CH_2}{\overset{\displaystyle \|}{CH_2}}{-}CH$$

[For purposes of the argument here presented it is not necessary to consider the isomers produced in Grignard reagent attack on substituted allyl halides. This question has already been treated by Young and collaborators, *J. Am. Chem. Soc.*, **59**, 2441 (1937).] The mechanism here given for dehalogenation of 1,2-dihalides properly belongs in the second category.

(nearly all at 113°), n_D^{25} 1.4189 yield, 64%; b.p.[9] of phenylurethan, 169° at 16 mm. Pariselle reported b.p. 113–114°, n_D^{17} 1.421, yield 18–25%. Allyl carbinol (23.8 g.) was dissolved in about 75 cc. of dry freshly distilled carbon tetrachloride in a 200-cc. 3-necked flask fitted with a mechanical stirrer, dropping-funnel, and thermometer. To this solution, cooled to +2°, was added dropwise a solution of the calculated quantity (51.2 g.) of bromine in an equal volume of carbon tetrachloride. The temperature was maintained throughout the addition below +5°. On removal of the solvent under diminished pressure and distillation of the residue there was obtained 51.5 g. (67% yield) of 1,2-dibromobutanol-4, b.p. 110° at 3 mm., b.p. 124–127° at 12 mm., n_D^{25} 1.5417. Pariselle records b.p. 112–114° at 11 mm., n_D^{18} 1.548. The 1,2-dibromobutanol-4 was converted to β-bromotetrahydrofuran by treatment with powdered potassium hydroxide in dry ether. Twenty grams of the dibromide was dissolved in about 100 cc. of dry ether in a 3-necked flask fitted with a mechanical stirrer. Dry powdered potassium hydroxide was added in portions of about two grams until a ten- to fifteen-fold excess had been added. Stirring was continued for about one hour, the ether solution was filtered, dried over anhydrous magnesium sulfate, and distilled under diminished pressure. The residue remaining after removal of the desired compound was added to fresh dibromide and treated again with potassium hydroxide in ether. In this way there was obtained from 61 g. of dibromide a total of 30.6 g. (77% yield) of β-bromotetrahydrofuran, b.p. 49° at 11 mm., 61° at 29 mm., 83° at 79 mm., 144° at 755 mm., n_D^{25} 1.4912, d_4^{25} 1.5766, MR_D (calc'd) 27.88, MR_D (obs.) 27.71. Pariselle found b.p. 150–151°, n_D^{12} 1.496, d^{12} 1.59.

The reaction of β-bromotetrahydrofuran. Although the usual devices such as vigorous stirring (a monel stirrer with sharp edges was used in all metal reactions), addition of iodine, and refluxing were tried, the halide underwent no visible reaction with magnesium over a period of several days. Of the 7.5 g. of halide used, 6.4 g. of redistilled compound was recovered.

To a suspension of 1 g. (0.143 g. atom) of lithium metal in 50 cc. of dry ether in a 200-cc. 3-necked flask equipped as for Grignard preparation was added about 2 g. of β-bromotetrahydrofuran. The ether was heated to refluxing and the stirrer started. After one-half hour a slight turbidity became apparent so the rest of the halide (total 7.5 g., 0.05 mole) in about 25 cc. of dry ether was added dropwise. Gradually the solution acquired a light brown color and after three days standing with occasional stirring considerable brown solid had formed. Gilman's test during this time was negative. Although it was apparent the reaction was still progressing slowly the mixture was filtered and worked up as usual. Distillation through a 6″ Widmer column gave a first fraction of ether (b.p. up to 41°). The temperature of the vapors then rose abruptly to 114° where 1 g. of substance n_D^{33} 1.4179 was obtained. It instantly decolorized bromine in carbon tetrachloride and gave a very weak Beilstein test. Its phenylurethan boiled at 169° at 16 mm. which established the identity of the reaction product as allyl carbinol. The residue left from the distillation amounted to 3.5 g. of dark red liquid which gave a strong Beilstein test and undoubtedly contained unreacted β-bromotetrahydrofuran, (b.p. 144° at 755 mm.), possibly mixed with the coupling product.

Reaction of β-haloethyl phenyl sulfides. The starting material, β-hydroxyethyl phenyl sulfide was prepared in excellent yield from thiophenol and ethylene chlorohydrin by the method of Meyer (19) as modified by Steinkopf (20); b.p. 134–135° at 7 mm. (bath 170–178°), n_D^{25} 1.5897. The corresponding chloride was synthesized from the alcohol by the action of thionyl chloride adapting the procedure of Kirner and Windus (21). The chloride boiled at 121–122° at 15 mm. (bath 160°), n_D^{25} 1.5828, yield 81 %. The β-bromo compound was obtained in almost quantitative yield from the alcohol and a 50% excess of phosphorus tribromide in the usual manner, b.p. 135° at 11 mm. (bath 165°), n_D^{25} 1.6046.

β-Chloroethyl phenyl sulfide in ether failed to react with magnesium over the course of one week's time. The ether was refluxed, iodine added and the magnesium crushed under the solution.

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[9] Pariselle (18) reported that the phenylurethan could not be made to crystallize. In this work we have been similarly unsuccessful with the 3,5-dinitrobenzoate.

In contrast to the chloride the bromide underwent immediate and smooth reaction. Into a round-bottom flask were placed 5.3 g. (0.025 mole) of β-bromoethyl phenyl sulfide, 0.6 g. (0.025 g. atom) of magnesium turnings, and about 10 cc. of anhydrous ether. The gas which immediately began to be evolved was passed through two absorbers containing a chloroform solution of the calculated quantity (4.0 g.) of Br_2. The first absorber contained only a small quantity of Br_2 so that decolorization could be observed in case less than the calculated quantity of ethylene was evolved. Several tests with Michler's ketone made during the period of vigorous reaction were negative. At the end of 24 hours, when reaction was complete, a heavy white precipitate remained in the flask. Water and a small amount of acid were then added and the whole extracted with several portions of ether. The combined ether extracts were well shaken out with 5% NaOH solution to remove acidic constituents.

The NaOH solutions were combined, acidified with HCl and extracted with ether. The ether extracts, which smelled strongly of thiophenol, were combined and evaporated on a hot-plate. The heavy oil remaining was mixed with about 10 cc. of very dilute ammonia. The precipitate formed at the end of 24 hours was filtered and recrystallized from 95% alcohol. The white crystalline product melted at 60–61° as did also a sample mixed with authentic diphenyl disulfide.

The neutral ethereal solution from the alkaline extraction was dried over $MgSO_4$ and evaporated to remove ether. The liquid residue remaining completely crystallized on cooling. It melted at 45–61°. After 4 recrystallizations from 95% alcohol it melted at 68.4–69.6°.

Anal. Calc'd for $C_{16}H_{18}S_2$ ($C_6H_5S(CH_2)_4SC_6H_5$): S, 23.36.
Found: S, 25.79, 25.83.

The impurity in the product was believed to be diphenyl disulfide which was formed by atmospheric oxidation of the magnesium thiophenoxide in the original reaction.

Preparation of 1,4-dithiophenoxybutane. The authentic specimen was prepared from tetramethylene bromide and sodium thiophenoxide in alcohol (20). The material twice recryst. from alcohol and once from benzene melted at 87.6–89.1°.

Anal. Calc'd for $C_{16}H_{18}S_2$: S, 23.36. Found: S, 23.03, 23.51.

Reaction of N-β-chloroethylmorpholine. N-β-chloroethylmorpholine was prepared from the alcohol and thionyl chloride according to Mason and Block (13). It boiled at 109° at 30 mm. (bath 150°).

The reactions of the chloride with magnesium, lithium, and sodium were carried out according to the procedure usually employed in the preparation of a Grignard reagent. In spite of the application of the customary accelerating devices magnesium showed no reaction at the end of a week. The lithium had become slightly coated with a white adherent surface which was not effectively removed even with the sharp blade monel stirrer. The sodium very slowly evolved a gas and likewise acquired an adherent coating. Portions of the surface became black. At the end of a week all action had ceased so the ether was removed by evaporation. The oil and metal were removed to a ground glass 30-cc. flask surmounted by a water cooled condenser. Slightly above the melting point of the sodium reaction set in. The gas which was evolved was passed through the absorber system already described. The color of the chloroform in the first absorber rapidly faded. The brown solid residue remaining after reaction had ceased was treated with water and filtered with infusorial earth. The clear yellow filtrate was saturated with K_2CO_3 and extracted twice with 25-cc. portions of ether. The ether was dried over $MgSO_4$ and evaporated leaving 0.7 g. of clear, light brown oil having a strong odor of morpholine. The oil was shaken for twelve hours with 2.5 g. of *p*-toluenesulfonyl chloride and 10 cc. of 10% NaOH. The solid formed (0.34 g.) was filtered off and recrystallized from 95% ethanol; m.p. 148–148.5°, mixed with authentic *p*-toluenesulfonmorpholide, m.p. 147–148°. The aqueous liquor from which the sulfonamide was removed was saturated with potassium carbonate and extracted with ether. The dried ether extract upon evaporation gave 0.4 g. of light yellow oil of strong ammoniacal odor. During the course of an hour it solidified, after which it was taken up in ligroin and the solution allowed to evaporate. The transparent platelets de-

posited weighed approximately 0.05 g. and melted at 69–72°. They were dissolved in dry ether and precipitated as the hydrochloride salt with dry HCl gas.

Anal. Calc'd for $C_{12}H_{24}Cl_2N_2O_2$: Cl, 23.7. Found Cl, 23.1.

The tertiary amine was therefore probably N,N′-1,4-dimorpholinobutane, the product of Wurtz coupling.

N-β-Bromoethylmorpholine was prepared by reaction of the ethanol (13.1 g., 0.1 mole) with PBr_3 (18 g., 0.066 mole) in 40 cc. of $CHCl_3$. Pouring the reaction mixture into water, extraction with ether, drying, and evaporation of the solvents gave about three grams of material of which about one-half was solid. The solid, which was removed by filtration, proved to be insoluble in ether and very soluble in water. It gave an instantaneous test for halogen. Heated in a microgenerator with 50% KOH it produced acetylene (black explosive powder on absorption in $AgNO_3$ solution). The solid was therefore, in all probability, N,N′-dispiromorpholinopiperazonium dibromide which was produced from the expected product during the evaporation of the ether. In view of the obvious rapidity with which this dimerization took place the liquid obtained above was treated immediately in ether solution with an estimated slight excess of clean lithium metal. At the end of two weeks' time it was apparent that the bromide was very little more reactive toward lithium than the chloride and the experiment was therefore discontinued.

Reaction of nitrous acid with certain β-negatively substituted ethylamines: N-β-Aminoethylmorpholine (22), β-bromoethylamine (23), ethanolamine, ethylenediamine. Since the procedure used in all cases was identical, description of one typical case will suffice. The amino compound (0.05 mole) was treated with a calculated excess of dilute HCl. β-Bromoethylamine was isolated and used as the hydrobromide. To the amine hydrochloride solution cooled to +10° was added the calculated quantity of cooled sodium nitrite solution. The mixed solutions were then allowed to warm up slowly to room temperature and then gradually heated to about 40°. The evolved gases were passed through a semi-micro spiral (Friedrich's) absorber filled with 10% NaOH soln., through a small $CaCl_2$ drying train and finally through a semi-micro spiral absorber filled with a dilute solution of Br_2 in $CHCl_3$. In no case was the color of the absorber indicator diminished and the absence of ethylene among the reaction products was thereby proved. No attempt was made to ascertain the identity of the other products of the reactions.

SUMMARY

The reactions of β-bromotetrahydrofuran, β-bromoethyl phenyl sulfide, and N-β-chloroethylmorpholine with active metals have been described. A mechanism has been suggested to account for the splitting observed in such reactions. Examples of the application of the mechanism to other reactions reported in the literature are given.

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SOLUBILITIES OF SOME NORMAL SATURATED ALIPHATIC HYDROCARBONS

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In view of the extensive experimentation upon the aliphatic hydrocarbons, it is noteworthy that the literature contains few references to their behavior in organic solvents. Hildebrand (1) has recorded some solubilities of several hydrocarbons containing 4 to 8 carbon atoms, but in this case the hydrocarbons have been considered primarily as solvents and not as solutes. Except for a few investigations of ebullioscopic behavior (2) and viscosities of solutions (3), physical measurements of the higher hydrocarbons have dealt predominantly with the differences between the normal aliphatic homologs and their isomers.

Solubility determinations of a wide variety of paraffin-chain compounds (4) have indicated that their polar groups do not exert as great an influence upon their behavior in solution as had previously been thought. Many of the physical properties of the aliphatic compounds, such as the melting points and refractive indices, are markedly dependent upon the nature of the polar groups, and their dipole moments appear to be a specific function of the polar groups. The slopes of the solubility curves of these compounds, however, are so consistently similar, irrespective of the polar groups, that the nature of the solubility curve appears to be a specific function of the length of the alkyl chain. The solubilities of several representative hydrocarbons have been determined in order to compare their behavior with that of the polar compounds. The slopes of the solubility curves of polar aliphatic compounds have been attributed to molecular association (4). It is evident, however, that the zero dipole moments of the aliphatic hydrocarbons (5) preclude any possibility of dipole-dipole coupling.

This paper presents the solubilities of octane, dodecane, hexadecane, heptadecane, and dotriacontane in 11 organic solvents.

EXPERIMENTAL

The highly purified normal aliphatic hydrocarbons used in this investigation were prepared by the following methods. Octane was obtained by the reaction on *n*-butyl bromide with sodium, and was subsequently distilled through a Stedman packed column. Dodecane was prepared by catalytic hydrogenation of dodecene and purified by vacuum distillation in a Stedman packed column. Hexadecane and dotriacontane were obtained simultaneously by reaction of hexadecyl iodide with sodium. Hexadecane was separated by vacuum distillation, crystallized from acetone, and then subjected to two further vacuum distillations. Dotriacontane was recrystallized three times from trichloromethane at −30°. Heptadecane was prepared by Dr. W. O. Pool by heating stearic acid (f.p. 69.3°) to 350° in the presence of Raney nickel catalyst. Pure heptadecane was separated from a small amount of lower unsaturated hydrocarbons by two vacuum distillations in a Stedman packed column.

The freezing points of these hydrocarbons are listed in Table I.

The solubility measurements were made with the equipment and in the manner previously described (40).

RESULTS AND DISCUSSION

In the non-polar and slightly polar solvents, the solubility curves of the normal aliphatic hydrocarbons are qualitatively similar to the curves of the polar aliphatic compounds of corresponding chain lengths. As the polarity of the solvents increases above that of acetone, the solubility of the hydrocarbons decreases abruptly. The hydrocarbons are practically immiscible with the strongly polar solvents such as methanol, ethanol, nitroethane, and acetonitrile. The polar aliphatic compounds, on the other hand, are generally miscible with these strongly polar solvents. Even such long-chain compounds as laurone and myristone are appreciably soluble in acetonitrile, although they resemble the hydrocarbons in other behavior. Thus, a polar group imparts a definite solubilizing effect upon a paraffin-chain compound, particularly in a polar solvent.

TABLE I

FREEZING POINTS OF PURIFIED HYDROCARBONS

HYDROCARBON	NO. OF C ATOMS	F.P., °C.	F.P., °C. (LIT.)
Octane	8	−56.84	−57.3(6); −56.90(7); −56.82(8); −56.5(9); −56.8(10, 11, 12); −57(13); m.p. −56.84(14); m.p. −57.0(15).
Dodecane	12	−9.64	−9.73(7); −9.61(8); −12.0(9); −9.604 ± .003(12); m.p. −12(16).
Hexadecane	16	18.18	17.9(11); 18.145 ± .003(12); 17.6(17); 18.10(18); m.p. 18.2(19); m.p. 18(20); m.p. 17.8(21).
Heptadecane	17	21.72	22.0(12); m.p. 21.2(15); 21.92(22); m.p. 22.5(23, 24); m.p. 21(25); m.p. 21.8(26).
Dotriacontane	32	70.16	69.6(27); m.p. 70(28, 29, 30); m.p. 70.0(31); m.p. 68–70(32); m.p. 69.8(33); m.p. 71(34); m.p. 70.5(35); m.p. 74–75(36); m.p. 70.2(37); m.p. 69.9(38); m.p. 69.6(39).

The hydrocarbons form eutectics with benzene, cyclohexane, tetrachloromethane, and trichloromethane. The compositions and freezing points of the respective eutectics are listed in Table II. The solubilities of the hydrocarbons above the freezing points of the solvents are listed in Tables III–VII, and these solubilities are illustrated by the diagrams of several representative systems shown in Figs. 1–8.

These hydrocarbons exhibit a pronounced correlation between their solubility and the polarity of the solvents. Thus, the solubilities of any of the hydrocarbons investigated decrease progressively as the dielectric constants, ϵ, of the solvents (5) increase in the following order: benzene 2.3, trichloromethane 4.9, butyl acetate 5.0, ethyl acetate 6.2, 2-butanone 18, acetone 21, methanol 33. The hydrocarbons are, however, somewhat more soluble in isopropanol and in *n*-butanol than would be anticipated on the basis of the dielectric constants of these solvents.

TABLE II

EUTECTICS FORMED BY THE HYDROCARBONS

SOLVENT		NO. OF C ATOMS				
		8	12	16	17	32
Benzene	Wt. % solute	91.8	65.1	32.4	37.2	—
	Temp., °C.	−58.4	−17.9	−1.3	−1.9	—
Cyclohexane	Wt. % solute	39.1	28.5	17.6	17.5	0.5
	Temp., °C.	−71.6	−32.9	−12.5	−10.8	6.5
Tetrachloromethane	Wt. % solute	39.1	9.9	3.5	3.3	—
	Temp., °C.	−66.3	−34.2	−26.2	−25.6	—
Trichloromethane	Wt. % solute	25.3	0.3	—	—	—
	Temp., °C.	−67.8	−63.6	—	—	—

TABLE III

SOLUBILITIES OF *n*-OCTANE[a]

SOLVENT	G. PER 100 G. SOLVENT				
	−75.0°	−70.0°	−65.0°	−60.0°	−55.0°
Trichloromethane	—	—	—	275	∞
Ethyl ether	37.5	68	147	550	∞
Ethyl acetate	1.1	3.2	7.9	25.0	∞
Butyl acetate	8.8	13.3	26.4	120	∞
Acetone[b]	≈1.0	1.7	2.8	5.3	8.0
2-Butanone	3.0	4.4	8.0	31.2	∞
Isopropanol	7.1	9.9	15.9	36.0	∞
n-Butanol	12.2	15.4	22.1	45.1	∞

[a] ∞ above −56.8° with solvents listed, except acetone.
[b] ∞ above −5.5°.

TABLE IV

SOLUBILITIES OF *n*-DODECANE[a]

SOLVENT	G. PER 100 G. SOLVENT					
	−60.0°	−50.0°	−40.0°	−30.0°	−20.0°	−15.0°
Tetrachloromethane	—	—	—	—	114	260
Trichloromethane	0.5	1.3	4.9	19.8	117	317
Ethyl ether	0.9	3.4	10.0	39.1	186	490
Ethyl acetate	—	—	0.3	2.8	13.6	106
Butyl acetate	0.3	0.9	2.6	7.4	34.6	178
Acetone[b]	—	—	0.5	1.2	3.3	6.2
2-Butanone	0.4	0.7	1.3	3.2	12.0	41.8
Isopropanol	—	0.1	0.7	2.7	9.0	21.1
n-Butanol	0.5	1.0	2.0	4.6	13.6	31.4

[a] ∞ above −9.6° with solvents listed, except acetone.
[b] ∞ above 16.5°.

TABLE V

SOLUBILITIES OF *n*-HEXADECANE[a]

SOLVENT	G. PER 100 G. SOLVENT					
	−30.0°	−20.0°	−10.0°	0.0°	10.0°	15.0°
Benzene	—	—	—	—	360	1440
Cyclohexane	—	—	—	—	430	1440
Tetrachloromethane	—	5.5	15.1	56	245	790
Trichloromethane	0.4	2.2	8.1	32.4	214	1020
Ethyl ether	1.4	5.4	16.3	64	302	1200
Ethyl acetate	—	—	≈0.1	3.0	50	840
Butyl acetate	—	≈0.2	1.6	9.9	138	1090
Acetone[b]	—	—	<0.1	1.2	5.3	13.0
2-Butanone	—	—	0.3	2.6	17.6	830
Isopropanol	—	<0.1	0.4	1.7	7.5	21.2
n-Butanol	—	0.3	1.2	4.1	16.7	≈50

[a] ∞ above 18.2° with solvents listed, except acetone.
[b] ∞ above 35.8°.

TABLE VI

SOLUBILITIES OF *n*-HEPTADECANE[a]

SOLVENT	G. PER 100 G. SOLVENT					
	−30.0°	−20.0°	−10.0°	0.0°	10.0°	15.0°
Benzene	—	—	—	—	260	640
Cyclohexane	—	—	—	—	274	640
Tetrachloromethane	—	4.7	12.5	47.0	174	380
Trichloromethane	0.9	3.1	10.2	42.2	174	420
Ethyl ether	1.0	4.6	13.2	49.5	196	480
Ethyl acetate	—	0.1	0.9	4.1	24.2	420
Butyl acetate	0.5	1.3	3.2	9.5	97	530
Acetone[b]	—	—	—	0.3	3.2	8.5
2-Butanone	—	0.3	0.8	3.8	16.7	≈220
Isopropanol	—	—	<0.1	0.8	5.0	11.7
n-Butanol	—	—	0.4	2.7	13.0	35.6

[a] ∞ with all solvents above 21.8°, except acetone.
[b] ∞ above 38.0°.

TABLE VII

SOLUBILITIES OF *n*-DOTRIACONTANE

SOLVENT	G. PER 100 G. SOLVENT					
	20.0°	30.0°	40.0°	50.0°	60.0°	70.1°
Benzene	0.6	4.2	19.7	97	400	∞
Cyclohexane	3.6	11.0	36.8	115	400	∞
Tetrachloromethane	1.4	5.8	20.0	64	224	∞
Trichloromethane[a]	0.3	3.1	14.8	71	250	—
Ethyl ether[b]	1.7	6.0	—	—	—	—
Ethyl acetate	—	—	0.2	2.3	≈115	∞
Butyl acetate	—	<0.1	1.0	8.0	180	∞
Acetone[c]	—	—	—	<0.1	—	—
2-Butanone	—	—	0.2	2.5	≈75	∞
Isopropanol[d]	—	—	—	0.2	2.2	12.2
n-Butanol	—	—	—	0.9	9.2	∞

[a] 298 g. per 100 g. trichloromethane at 61.2° (b.p. of solvent).
[b] 10.0 g. per 100 g. ethyl ether at 34.5°.
[c] About 0.6 g. per 100 g. acetone at 56.1°.
[d] 24.4 g. per 100 g. isopropanol at 82.3°.

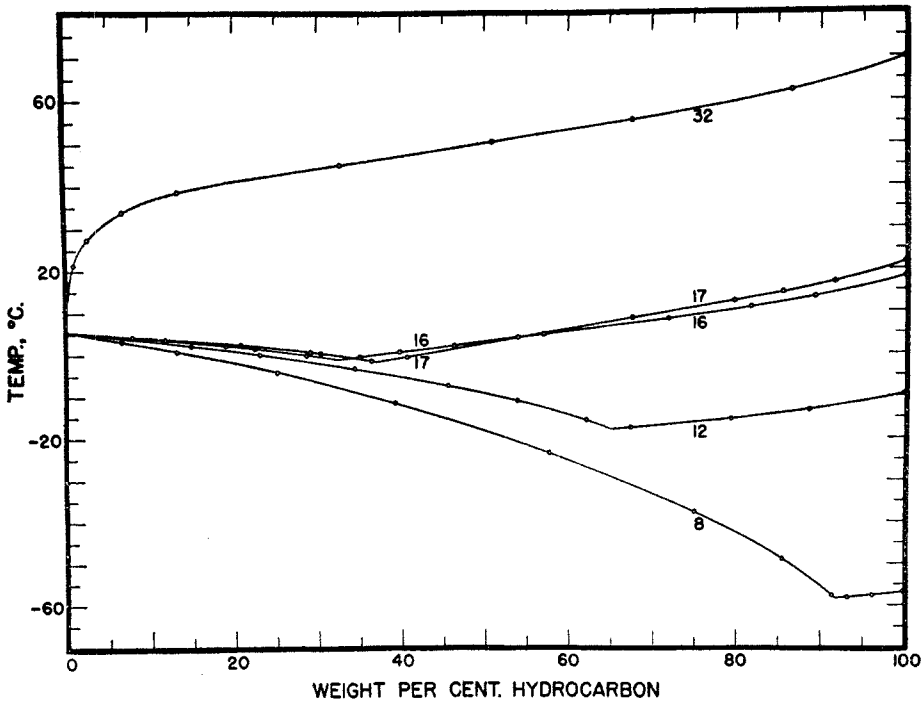

FIG. 1. SOLUBILITIES OF THE HYDROCARBONS IN BENZENE
The numbers refer to the number of carbon atoms

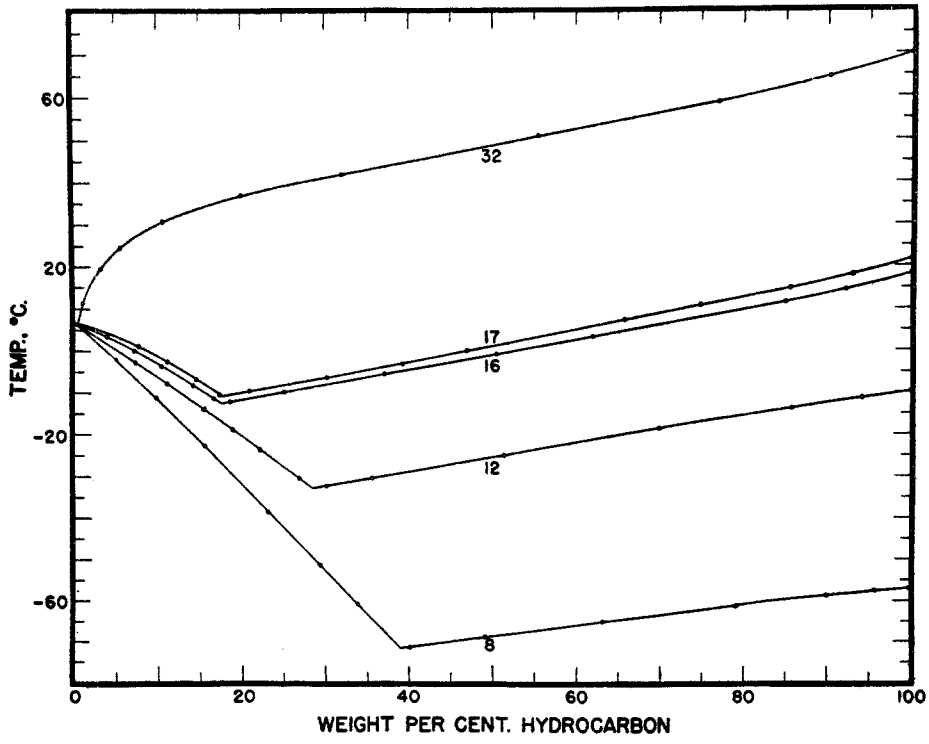

FIG. 2. SOLUBILITIES OF THE HYDROCARBONS IN CYCLOHEXANE

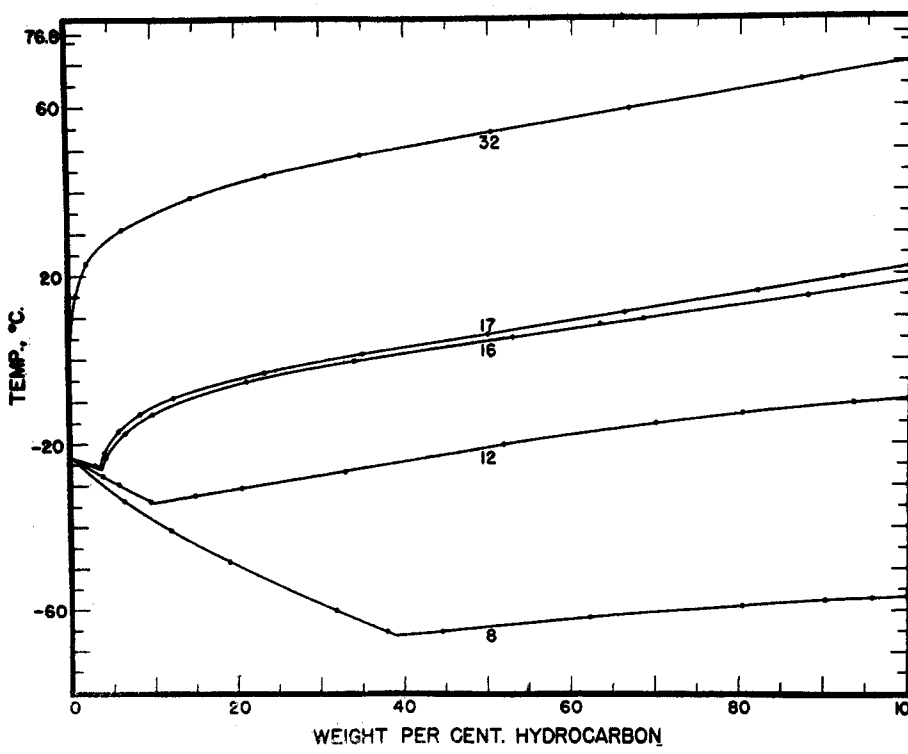

FIG. 3. SOLUBILITIES OF THE HYDROCARBONS IN TETRACHLOROMETHANE

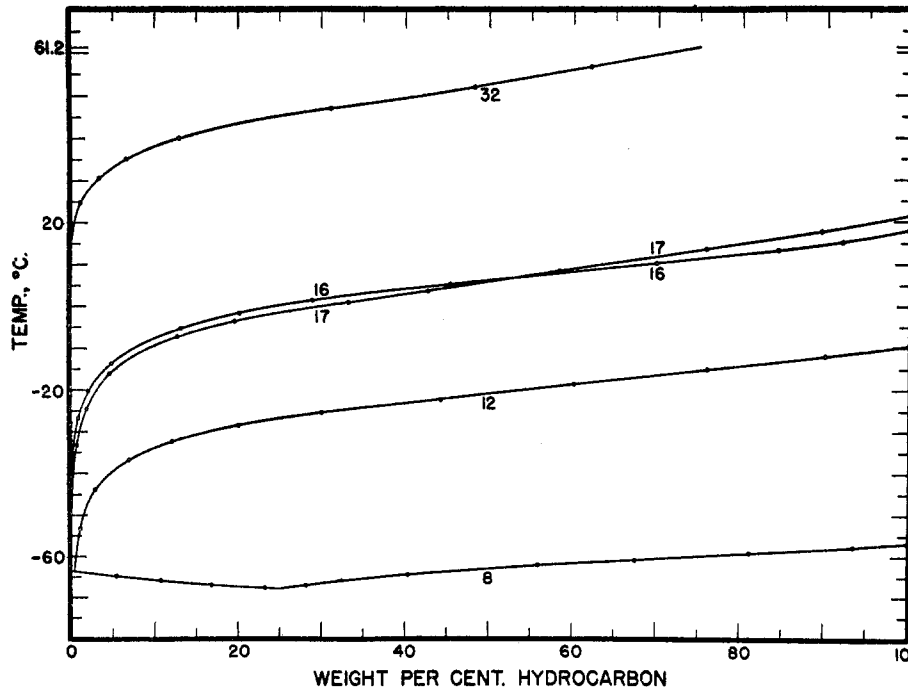

FIG. 4. SOLUBILITIES OF THE HYDROCARBONS IN TRICHLOROMETHANE

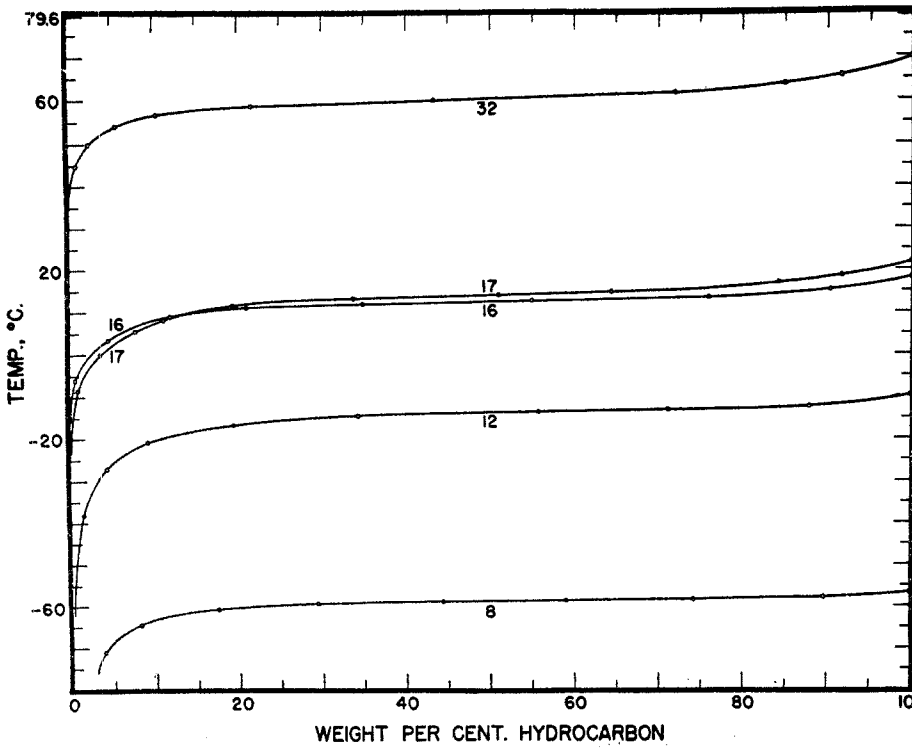

FIG. 5. SOLUBILITIES OF THE HYDROCARBONS IN ETHYL ACETATE

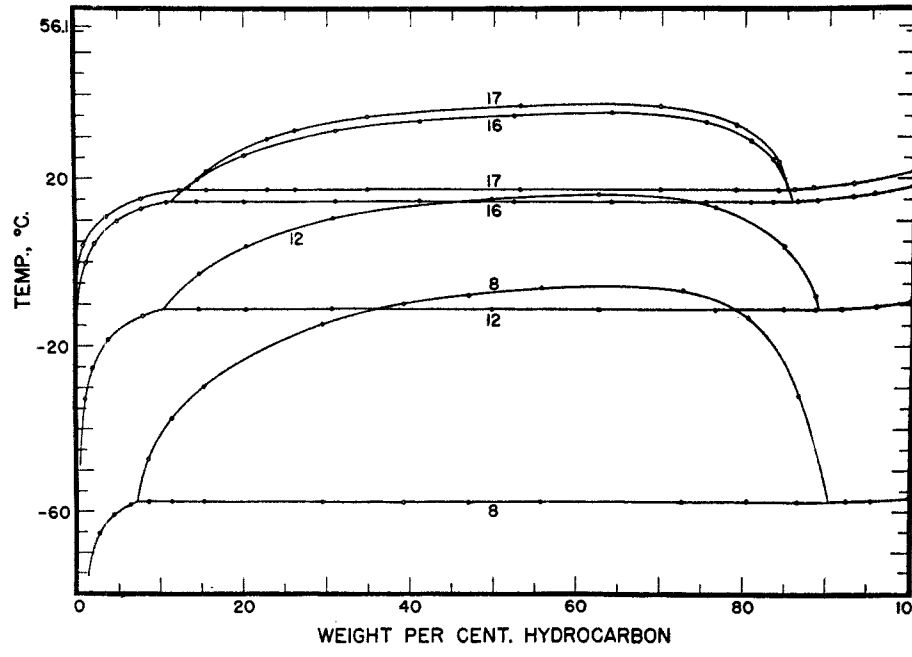

FIG. 6. SOLUBILITIES OF THE HYDROCARBONS IN ACETONE

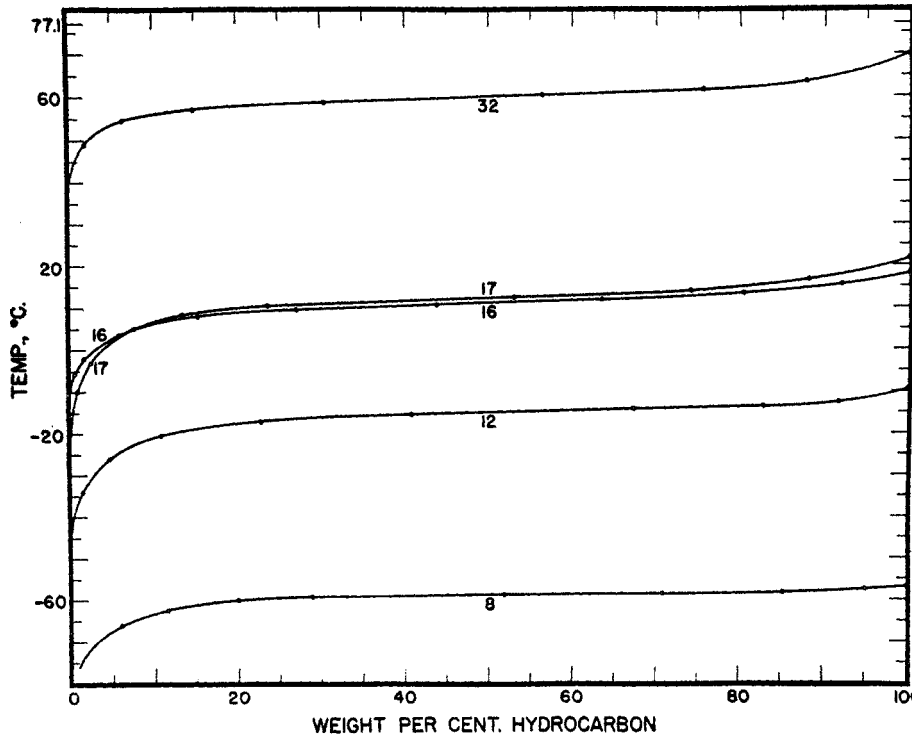

FIG. 7. SOLUBILITIES OF THE HYDROCARBONS IN 2-BUTANONE

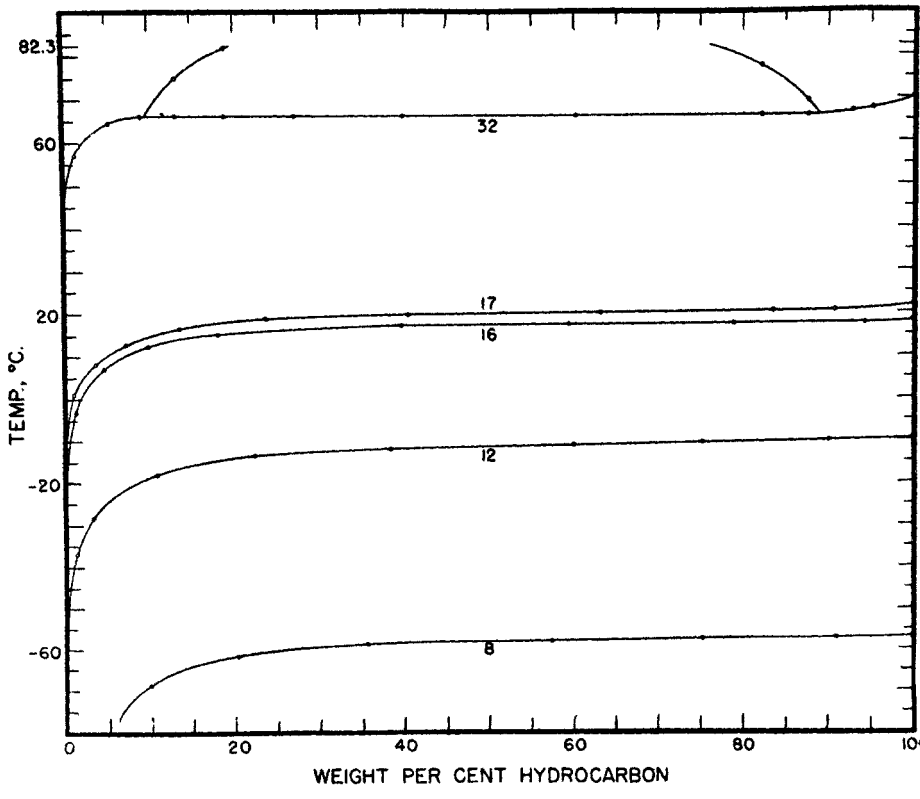

FIG. 8. SOLUBILITIES OF THE HYDROCARBONS IN ISOPROPANOL

Previous papers in this series (4) have referred to several suggestions that the slopes of the solubility curves of long-chain compounds are due to molecular association. In view of the marked similarity of the hydrocarbon solubility curves to those of the polar aliphatic compounds, the simple explanation on the basis of molecular association becomes paradoxical. If association results in the formation of dimers in solution, then the solubility curves of palmitic acid, for example, should theoretically resemble that of dotriacontane in the less polar solvents. Actually, the solubilities of dotriacontane generally resemble those of an acid containing more carbon atoms than palmitic acid.

A number of investigators (1, 2, 41) have warned against arbitrarily assuming that calculations of apparent molecular weights from cryoscopic or ebullioscopic measurements necessarily indicate molecular association. The apparently abnormal values which have been reported for a number of long-chain compounds may, to some extent, be due to failure to consider the effect of the van der Waals forces acting upon the paraffin-chains. Hence, the deviations of the solubilities of the aliphatic hydrocarbons from a linear relationship with temperature appear to be due entirely to intermolecular forces between the paraffin-chains and to the disparity between the polarities of the solvents and those of the hydrocarbons. Since the polar groups possess negative heats of fusion, they should easily enter the liquid state, and it is probable that the deviations from lineality observed in the solubility curves of long-chain aliphatic compounds, including the hydrocarbons, can be attributed to a mutual attraction of the alkyl chains. The limited solubilities of the higher aliphatic compounds in highly polar solvents may be due to the difficulty of such solvents to overcome these forces.

SUMMARY

The solubilities of octane, dodecane, hexadecane, heptadecane, and dotriacontane have been determined in benzene, cyclohexane, tetrachloromethane, trichloromethane, ethyl ether, ethyl acetate, butyl acetate, acetone, 2-butanone, isopropanol, and *n*-butanol.

The relationship which exists between the slopes of the curves of the hydrocarbons and of polar compounds has been discussed.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

THE SOLUBILITIES OF THE NORMAL SATURATED FATTY ACIDS. II.

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An earlier report from this laboratory (1) presented the solubilities of the normal saturated fatty acids from caprylic to stearic acid, inclusive, in water, ethanol, acetone, 2-butanone, benzene, and glacial acetic acid. This paper reports the further investigation of the behavior of these acids in cyclohexane, tetrachloromethane, trichloromethane, ethyl acetate, butyl acetate, methanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

Several of the acids employed in this investigation possessed slightly higher freezing points than those of the acids used in the previous study (1). The freezing points of the present acids are listed in Table I.

The solubilities of these acids were determined in highly purified solvents by the method previously described (1, 2).

RESULTS AND DISCUSSION

The solubilities of the fatty acids in cyclohexane are similar to their behavior in benzene (1) in that they form eutectics with both solvents. The compositions and freezing points of these eutectics are listed in Table II. The solubilities of the acids above the freezing point of cyclohexane are listed in Table III, and the systems are shown graphically in Fig. 1.

The solubilities of the acids in tetrachloromethane and in trichloromethane are listed in Tables IV and V, respectively, and the solubility curves in trichloromethane are shown in Fig. 2.

The acids are generally more soluble in trichloromethane than in any other solvent investigated. In the above three solvents, as with benzene, the fatty acids are paired, with the next higher odd-numbered homolog being the more soluble of the pair.

In each of the following solvents, all of which are more polar than trichloromethane, the adjacent homologs are also paired. In these instances, however, the paired solubility curves intersect at moderate dilutions. Thus, the next higher odd-numbered homolog is the less soluble of each pair at temperatures below the intersection, and the solubilities of the acids decrease without alternation as the series is ascended. In the less polar solvents, this intersection of the paired solubility curves occurs above lauric acid at ordinary temperatures, while in the more polar solvents it occurs also in the lower acids.

The solubilities of the acids in ethyl and in butyl acetates are listed in Tables VI and VII, respectively, and the curves in ethyl acetate are shown in Fig. 3. The solubilities in these solvents correspond qualitatively to those in acetone and in 2-butanone (1) whose polarities approximate those of the acetates.

The solubilities of the acids in methanol, isopropanol, and *n*-butanol are listed

TABLE I

FREEZING POINTS OF PURIFIED FATTY ACIDS

ACID	NO. OF C ATOMS	F.P., °C.	ACID	NO. OF C ATOMS	F.P., °C.
Caprylic	8	16.30	Myristic	14	54.15
Nonylic	9	12.25	Pentadecylic	15	52.54
Capric	10	31.24	Palmitic	16	62.82
Undecylic	11	28.13	Heptadecylic	17	60.94
Lauric	12	43.92	Stearic	18	69.32
Tridecylic	13	41.76			

TABLE II

EUTECTICS FORMED BY ACIDS WITH CYCLOHEXANE

NO. OF C ATOMS	WT. % ACID	TEMP., °C.
8	22.0	−14.0
9	23.9	−17.5
10	14.1	−3.2
11	16.2	−5.9
12	6.8	+3.2
13	8.6	1.9
14	2.4	5.6
15	2.9	5.4
16	0.4	6.4
17	0.7	6.3
18	<0.1	≈6.6

TABLE III

SOLUBILITIES OF FATTY ACIDS IN CYCLOHEXANE

NO. OF C ATOMS	G. PER 100 G. CYCLOHEXANE					
	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	670	∞	∞	∞	∞	∞
9	2340	∞	∞	∞	∞	∞
10	103	342	7600	∞	∞	∞
11	150	525	∞	∞	∞	∞
12	19.8	68	215	1310	∞	∞
13	31.0	100	330	8200	∞	∞
14	5.3	21.5	72	217	1310	∞
15	6.8	27.1	88	277	2460	∞
16	0.9	6.5	27.4	92	285	2530
17	1.5	8.4	34.0	108	365	7600
18	0.2	2.4	10.5	43.8	133	450

in Tables VIII–X, respectively. The curves in methanol are shown in Fig. 4, and those in *n*-butanol in Fig. 5. These solubilities form a regular series with

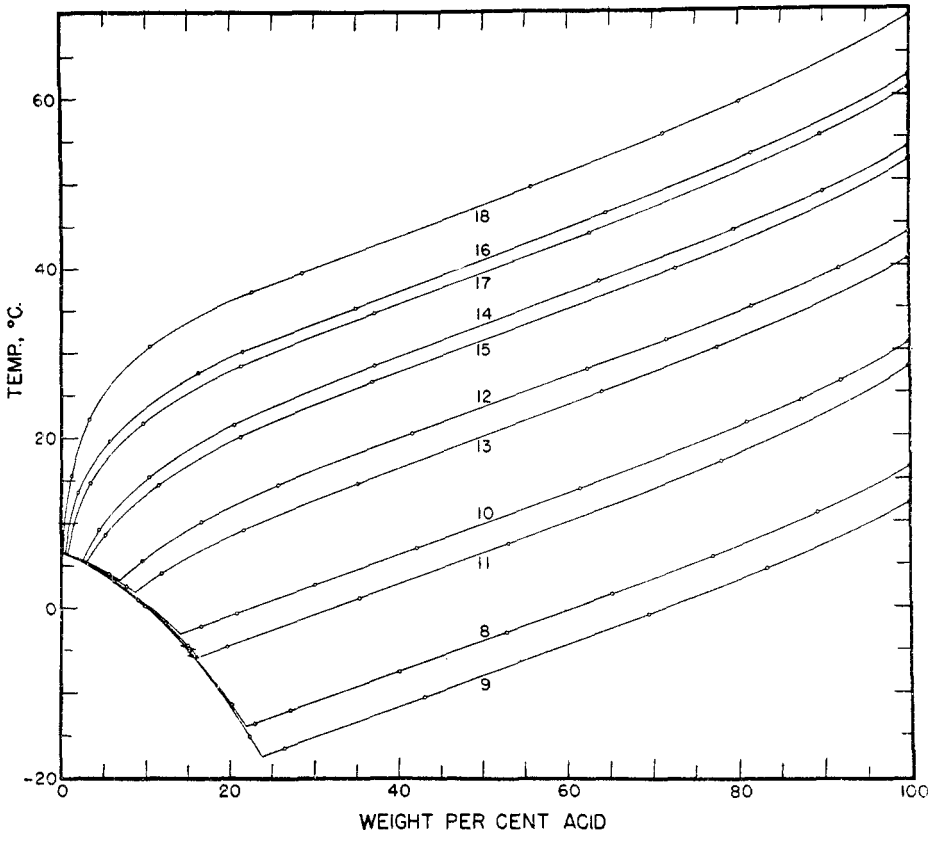

FIG. 1. SOLUBILITIES OF THE FATTY ACIDS IN CYCLOHEXANE

The numbers on the curves refer to the number of carbon atoms in the acid molecule.

TABLE IV

SOLUBILITIES OF FATTY ACIDS IN TETRACHLOROMETHANE

NO. OF C ATOMS	G. PER 100 G. TETRACHLOROMETHANE						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	115	370	∞	∞	∞	∞	∞
9	158	1150	∞	∞	∞	∞	∞ ∞
10	27.0	64	210	4650	∞	∞	∞ ∞
11	35.1	88	318	∞	∞	∞	∞ ∞
12	9.2	20.5	53	160	835	∞	∞ ∞
13	11.3	26.9	75	240	5450	∞	∞ ∞
14	3.2	6.8	17.6	55	166	870	∞
15	3.8	8.4	22.2	69	208	1560	∞
16[a]	0.6	1.8	5.8	21.5	72	212	1590
17	0.7	2.0	6.8	25.1	83	250	4650
18[b]	—	0.2	2.4	10.7	36.4	108	325

[a] Both 0.477 and 0.5486 g./100 g. solvent are reported at 0° (3).

[b] 11.42 g./100 g. solvent at 25° (4).

TABLE V

Solubilities of Fatty Acids in Trichloromethane

No. of C atoms	G. per 100 g. trichloromethane						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	213	720	∞	∞	∞	∞	∞
9	336	2340	∞	∞	∞	∞	∞
10	61	122	326	6550	∞	∞	∞
11	74	161	485	∞	∞	∞	∞
12	22.4	39.1	83	207	2120	∞	∞
13	28.4	53	116	315	6550	∞	∞
14	8.1	15.1	32.5	78	205	1000	∞
15	9.5	17.7	38.1	91	246	1750	∞
16	2.9	6.0	15.1	36.4	91	250	1820
17	3.6	7.5	17.8	42.6	106	297	5000
18[a]	0.4	2.0	6.0	17.5	48.7	124	365

[a] 18.40 g./100 g. solvent at 25° (4).

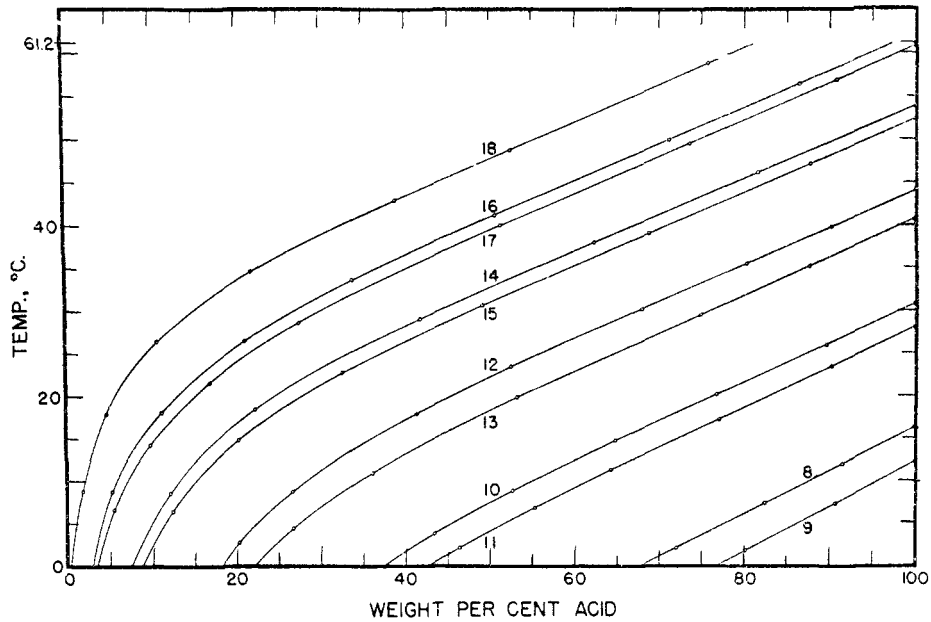

Fig. 2. Solubilities of the Fatty Acids in Trichloromethane

TABLE VI

Solubilities of Fatty Acids in Ethyl Acetate

No. of C atoms	G. per 100 g. ethyl acetate						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	161	610	∞	∞	∞	∞	∞
9	250	2020	∞	∞	∞	∞	∞
10	34.2	90	289	7850	∞	∞	∞
11	38.7	114	425	∞	∞	∞	∞
12	9.4	18.5	52	250	1250	∞	∞
13	10.1	22.5	70	281	8200	∞	∞
14	3.4	6.6	15.3	44.7	164	1350	∞
15	2.8	6.2	15.4	51	208	2370	∞
16[a]	0.8	2.2	6.1	17.6	53	203	2340
17	0.4	1.6	5.3	16.8	59	242	6000
18[b]	—	—	0.5	5.2	21.6	78	348

[a] 12.0 at 25° (5).
[b] 7.94 at 25° (4).

TABLE VII

Solubilities of Fatty Acids in Butyl Acetate

No. of C atoms	G. per 100 g. butyl acetate						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	206	700	∞	∞	∞	∞	∞
9	316	2340	∞	∞	∞	∞	∞
10	44.6	111	330	8230	∞	∞	∞
11	55	145	515	∞	∞	∞	∞
12	13.0	26.8	68	212	1350	∞	∞
13	14.5	33.0	95	322	9000	∞	∞
14	4.8	9.9	21.6	61	208	1370	∞
15	4.5	9.7	22.3	66	253	2460	∞
16	1.5	3.8	8.9	23.4	69	226	2330
17	1.2	3.5	8.7	24.0	75	269	6350
18	<0.1	0.2	1.6	8.1	28.7	97	350

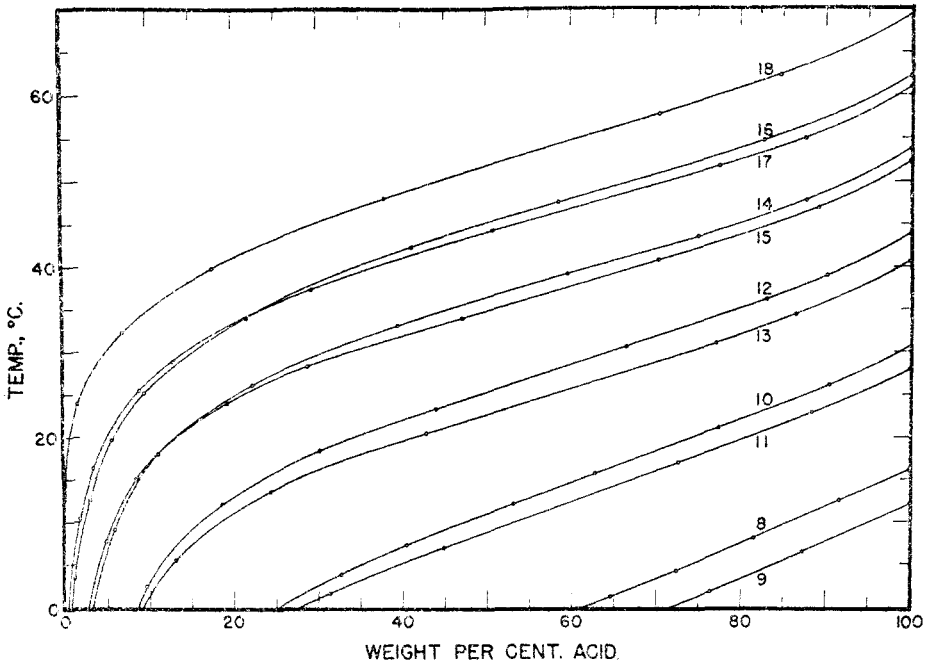

Fig. 3. Solubilities of the Fatty Acids in Ethyl Acetate

TABLE VIII

Solubilities of Fatty Acids in Methanol

No. of C atoms	G. per 100 g. methanol						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	330	1300	∞	∞	∞	∞	∞
9	510	4650	∞	∞	∞	∞	∞
10	80	180	510	9900	∞	∞	∞
11	105	235	740	∞	∞	∞	∞
12	12.7	41.1	120	383	2250	∞	∞
13	12.6	48.5	148	515	14,000	∞	∞
14	2.8	5.8	17.3	75	350	2670	∞
15	2.2	5.0	16.4	75	400	4400	∞
16[a]	0.8	1.3	3.7	13.4	77	420	4650
17	0.1	0.7	2.5	9.9	62	500	12,000
18	—	—	0.1	1.8	11.7	78	520

[a] 0.73 at 0°, 5.4 at 21°, 41.8 at 36° (6).

TABLE IX

Solubilities of Fatty Acids in Isopropanol

No. of C atoms	G. per 100 g. isopropanol						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	280	900	∞	∞	∞	∞	∞
9	422	2920	∞	∞	∞	∞	∞
10	67	140	360	5750	∞	∞	∞
11	82	182	540	∞	∞	∞	∞
12	21.5	44.1	100	253	1270	∞	∞
13	22.1	52	125	340	6550	∞	∞
14	7.2	13.6	31.6	82	230	1210	∞
15	6.2	13.3	34.4	95	272	2070	∞
16	2.4	4.6	10.9	32.3	94	270	2460
17	1.2	3.0	10.8	37.9	108	345	6550
18	≈0.1	0.4	2.0	10.0	38.1	118	422

TABLE X

Solubilities of Fatty Acids in *n*-Butanol

No. of C atoms	G. per 100 g. *n*-butanol						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	225	750	∞	∞	∞	∞	∞
9	355	2530	∞	∞	∞	∞	∞
10	59	103	280	4650	∞	∞	∞
11	64	131	415	∞	∞	∞	∞
12	21.4	37.2	83	217	1070	∞	∞
13	21.5	39.8	100	295	5750	∞	∞
14	7.3	13.1	28.7	71	194	980	∞
15	7.1	12.5	28.4	74	220	1680	∞
16	1.9	4.2	10.5	30.0	84	243	1960
17	1.6	3.6	9.5	27.4	85	274	4900
18	—	0.2	1.6	9.0	36.2	111	370

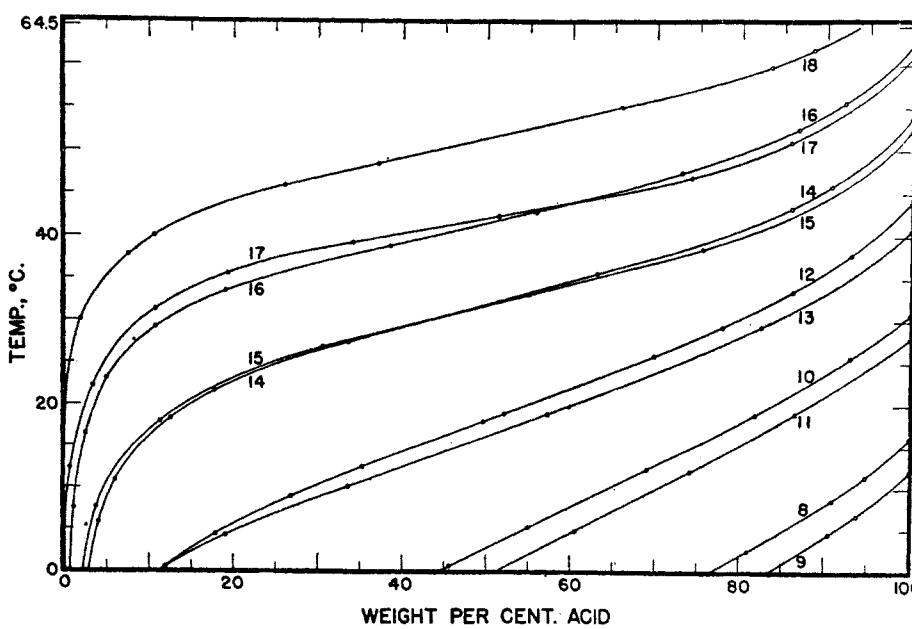

Fig. 4. Solubilities of the Fatty Acids in Methanol

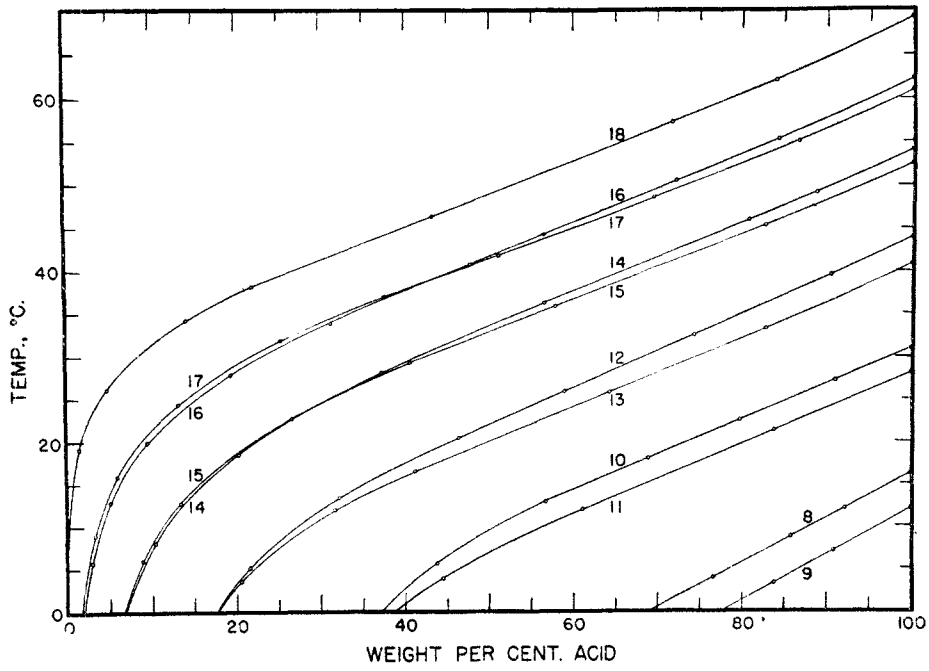

FIG. 5. SOLUBILITIES OF THE FATTY ACIDS IN *n*-BUTANOL

TABLE XI

SOLUBILITIES OF FATTY ACIDS IN NITROETHANE

NO. OF C ATOMS	G. PER 100 G. NITROETHANE						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	25.2	790	∞	∞	∞	∞	∞
9	45.0	2340	∞	∞	∞	∞	∞
10	9.2	12.5	55	7000	∞	∞	∞
11	8.1	13.2	131	∞	∞	∞	∞
12	1.9	2.8	5.4	16.3	1460	∞	∞
13	1.4	2.1	4.5	17.3	9000	∞	∞
14	0.3	0.5	1.2	3.3	10.7	1180	∞
15	0.1	0.2	0.7	2.4	10.2	2460	∞
16	—	—	<0.1	0.7	2.6	10.0	1650
17	—	—	—	0.2	1.9	9.6	4250
18	—	—	—	—	0.3	2.7	14.0

TABLE XII

SOLUBILITIES OF FATTY ACIDS IN ACETONITRILE

NO. OF C ATOMS	G. PER 100 G. ACETONITRILE						
	0.0°	10.0°	20.0°	30.0°	40.0°	50.0°	60.0°
8	44.5	1020	∞	∞	∞	∞	∞
9	51	3470	∞	∞	∞	∞	∞
10	11.8	21.0	66	7600	∞	∞	∞
11	8.7	17.3	185	∞	∞	∞	∞
12	2.1	2.8	7.6	24.4	1540	∞	∞
13	1.4	2.0	5.8	21.4	8600	∞	∞
14	0.7	0.9	1.8	4.1	13.0	1210	∞
15	0.4	0.5	1.1	2.9	10.5	2460	∞
16	<0.1	0.2	0.4	1.0	2.8	9.9	1200
17	—	<0.1	0.2	0.6	1.9	8.3	3600
18	—	—	<0.1	0.3	0.8	2.0	10.3

those in ethanol (1). The acids are, in general, more soluble in methanol than in *n*-butanol at higher temperatures, while at lower temperatures the order is reversed.

The fatty acids are somewhat more soluble in the lower alcohols than in the other solvents investigated, with the exception of trichloromethane. This behavior has been observed in the solubilities of the aliphatic alcohols (7), primary amines (8), and amides (9). On the other hand, the aliphatic hydrocarbons (10) and tertiary amines (11) are soluble to only a very limited extent in the lower alcohols. This behavior suggests the occurrence of hydrogen bonding (12). Thus, the hydrocarbons and tertiary amines, possessing no active hydrogen atoms, lack affinity for active molecules such as the alcohols, while the compounds

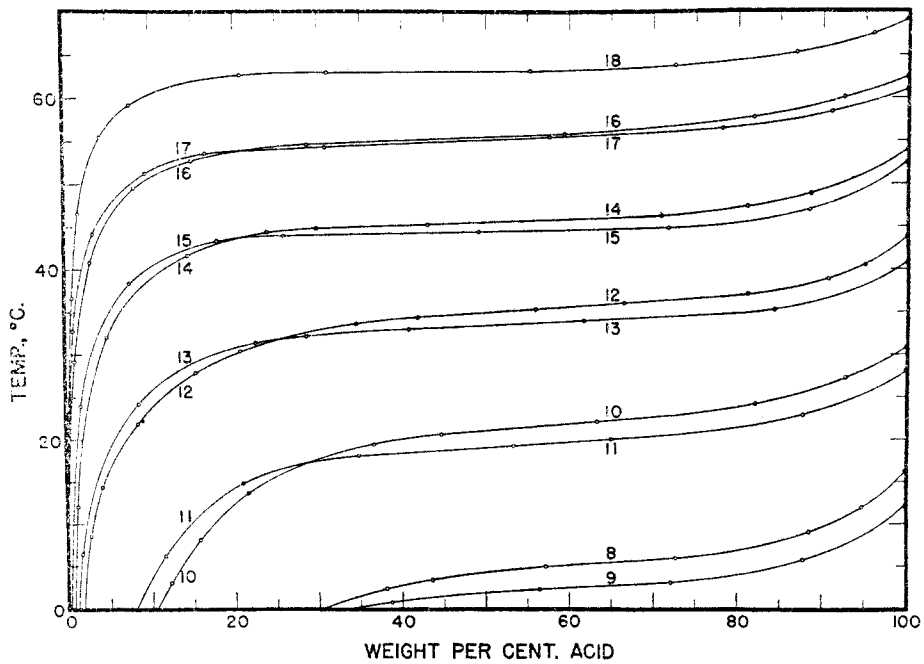

FIG. 6. SOLUBILITIES OF THE FATTY ACIDS IN ACETONITRILE

containing carboxyl, hydroxyl, and amino groups can readily form hydrogen bonds with solvents containing similar groups.

The solubilities of the fatty acids in nitroethane and in acetonitrile are listed in Tables XI and XII, respectively, and the curves in acetonitrile are shown in Fig. 6. The acids are less soluble in these highly polar solvents than in any of the other solvents investigated.

Except for their behavior in the alcohols, the fatty acids show a marked correlation between their solubilities and the polarities of the solvents. In the nonpolar solvents, the solubilities of the acids are almost linearly dependent upon temperature, but as the polarity of the solvent increases, the relation between concentration and temperature deviates considerably from linearity.

SUMMARY

The solubilities of the fatty acids from caprylic to stearic acids, inclusive, have been determined in cyclohexane, tetrachloromethane, trichloromethane, ethyl acetate, butyl acetate, methanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

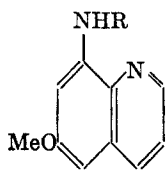
THE SEARCH FOR SUPERIOR ANTIMALARIALS. II. THE SYNTHESIS OF 6,7-DIMETHOXYQUINOLINE DERIVATIVES AND OF SOME INCIDENTAL COMPOUNDS

KURT C. FRISCH[1] AND MARSTON TAYLOR BOGERT

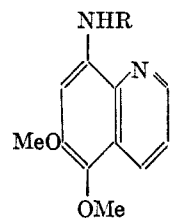
Received April 1, 1944

A recent German patent (1), covering the preparation of N-substituted 5,6-dialkoxy-8-aminoquinolines, in one of its opening paragraphs, contains the following: "On further study of this class of compounds, it has been found that the hitherto undescribed 5,6-dialkoxy-8-aminoquinolines, with a basic substituent on the amino group, are prominently distinguished from the already known nuclear substitution products of N-substituted aminoquinolines, by their especially favorable ratio between therapeutic and toxic action."

In a later publication (2), Schönhöfer expressed the opinion that the high plasmodicidal activity of Plasmochin (I) was due in part to the 6-methoxyl group, and claimed that an additional methoxyl at 5 enhanced still further the specific gametocidal action of the compound. Plasmochin subjected to the Roehl test with canaries, showed a therapeutic index of 1:30, whereas the index for 5-methoxy-Plasmochin (II) was 1:125. Surprisingly, when a third methoxyl group was present at 7 (III), the compound was entirely inactive. Hence he blamed this inactivity upon the methoxyl at 7, and cited as further proof of the dystherapeutic effect of a 7-methoxyl the inactivity of compounds IV and V.



I



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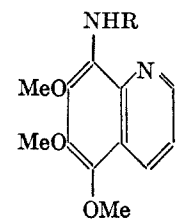

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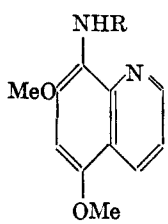
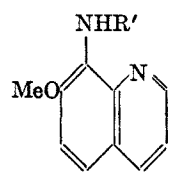
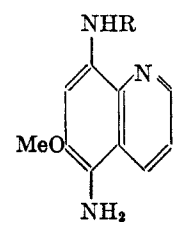


IV



V



Va

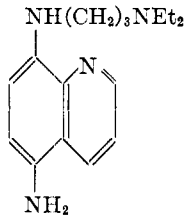
R = —CHMe$(CH_2)_3NEt_2$

R′ = —$CH_2CMe_2CH_2NMe_2$

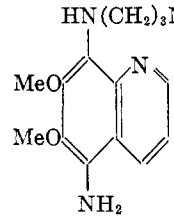
[1] Hopkinson Research Fellow at Columbia University.

This article by Schönhöfer did not come to our attention until it appeared in the September 10, 1943 issue of *Chemical Abstracts* (p. 5064), by which time practically all of the work described in the following pages had been completed.

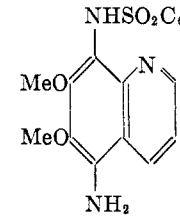
It is of interest, therefore, that two of our products which have been tested for antimalarial properties, *viz.* VII and VIII, on white Pekin ducks (*P. lophurae*) also proved to be inactive.



VI



VII



VIII

6,7-Dihydroxyquinoline and its ethers have been studied but little (3, 4, 5, 6, 7, 8, 9). The purpose of this and of the antecedent communication (10) has been to explore further the possibilities of discovering useful antimalarials in this group, and the compounds described were built up with this in mind. In comparison with Plasmochin, the likelihood that an additional methoxyl group at 7 would prove dystherapeutic seemed at the time to be offset by the favorable effect of a similar addition at 5, as recorded in the excerpt from the German patent (1) noted above. Further, since Fourneau and his co-workers (11) found such compounds as VI decidedly active against *P. relictum* in canaries, and Va is one of the products cited as an example in the aforementioned German patent (1), it seems unlikely that the inactivity of VII and VIII is due to the amino group at 5.

In the previous paper (10), the preparation of 5,8-diamino-6,7-dimethoxyquinoline and certain of its condensation products with bibasic acid anhydrides, was described. In all cases, both amino groups reacted, and the yields of the corresponding amidic acids were excellent. On the other hand, when experiments were conducted for the replacement of the amino hydrogens by acetyl, sulfanilamido, or dialkylaminoalkyl groups, involving condensations in which acid molecules were split out, but one of the two amino groups reacted, with formation of monosubstitution products only. The fact that one amino group seemed to be more basic than the other was confirmed by diazotization. Under normal diazotization cold, the uptake of sodium nitrite corresponded to only one amino group instead of two, and again only monosubstitution products were obtained. The phenomenon that diazotization occasionally occurs instead of the expected tetrazotization in diamines has been reported in the literature (12, 13, 14), and has been proved to be due to a decreased basicity of one amino group.

In the 5,8-diamino-6,7-dimethoxyquinoline (IX) there are three centers of basicity, namely the two amino groups and the heterocyclic nitrogen. *A priori*, each nitrogen atom carries an unshared pair of electrons, is basic, and can participate in the displacement reaction: $N: + RX \rightarrow \overset{+}{N} - R + X^-$.

Reaction on the quinoline nitrogen would give an N-substituted quinolone imine (A) (15, 16). Inasmuch as the monosubstitution products obtained in this work could not be diazotized, and in the case of the diamine itself (IX), only one amino group reacted, it is believed that in the acylation and alkylation leading to monosubstitution products, one of the two amino groups has reacted, and not the quinoline nitrogen. For this reason, such a structure as (A) for the monosubstitution product is considered improbable.

A choice between the structure shown in VII or VIII, involving a reaction upon the 8-amino group, and (B) representing a similar reaction on the 5-amino group, may be made by consideration of the following facts: (a) The two amino groups are each ortho to a methoxyl group, and in view of this equivalence one can assume a correlation between the tendency of an amino group to share its unshared pair of electrons with a proton, and the ease with which it takes part in the displacement reaction by sharing its pair of electrons in a C—N covalent bond and displacing a halide ion.

(b) A consideration of the electronic and resonance structures of the molecule will show that the 8-amino is more basic than the 5-amino group, and hence structures VII and VIII for the monosubstitution products are probably correct as given.

The well-known behavior of the quinoline ring on attack by electrophilic reagents can be explained from the resonance picture of quinoline, where there is an increased electron density at the nitrogen at the expense of that about carbon atoms 2, 4, 5, 7, and 9, this unbalancing of the electron density being accomplished by regular shifting of the electrons. Amino groups may become part of this resonating picture by carrying some of the electron deficiency imposed on the ring by the heterocyclic nitrogen. Since the amino group has an octet of electrons, its participation can only involve the formation of a C—N double bond accompanied by assumption of a positive charge, as shown in (H) and (J).

The result of the resonance is simply a further increase in the electron density of the heterocyclic nitrogen and a decrease in the availability of the amino groups in unshared pairs of electrons below that observed in aniline. Therefore the amino groups in the positions mentioned are extremely weak bases or, stated in a different manner, addition of the proton to the 5-amino group in (J), for example, leads to a fixed position of the positive charge (I), whereas addition of the proton to the quinoline nitrogen, leads to a monobasic resonating system in which both nitrogen atoms may bear a positive charge (L and M). Accordingly, in dilute acid, quinolines carrying an amino group in the "critical positions" form only monohydrochlorides. Theory and experimental results are in agreement with respect to the formation of a dihydrochloride by 5,8-diaminoquinoline and IX, which salts can therefore be represented by (N) and (O).

These conclusions bear upon the results of the diazotization experiments, since the salt of an aromatic amine is required for such a reaction. It is therefore probable that the amino group diazotized was the one in position 8 (N and O). Other examples of this apparently anomalous behavior appear in the litera-

ture (12, 13, 14), and are likewise explainable by the decreased basicity of one of the amino groups.

In further support of the greater basicity of the 8-amino group may be mentioned the fact that in 8-aminoquinoline chelation occurs in which one hydrogen atom of the amino group is bonded to the heterocyclic nitrogen. This causes a weakening in the covalent bond between the amino nitrogen and the hydrogen atom and the 8-amino nitrogen is therefore able to attract more readily a proton.

It is believed, therefore, that of the two amino groups present in (IX), that in position 8 is the more strongly basic, and therefore participates more readily in the displacement reactions described, and the monosubstitution products formed are hence believed to be the 8-N-substituted derivatives.

The greater reactivity of the group in the 8-position is utilized in German Pat. 536,447 (1) for the synthesis of antimalarials from 5,8-dinitro-6-methoxyquinoline.

6,7-Dimethoxyquinoline was readily prepared from 4-aminoveratrole by the Skraup reaction (10), and the corresponding quinaldine (XVIII) was obtained in good yield from the same initial compound, by the Doebner-von Miller reaction. XVIII was synthesized some time ago, by Rilliet (18), by condensing 6-aminoveratraldehyde with acetone.

Condensation of 4-aminoveratrole (XVII) with acetoacetic ester, followed by cyclization (Knorr-Conrad-Limpach reactions), gave 4-methyl-6,7-dimethoxycarbostyril (XX).

Application of the same reaction to 3-nitro-4-aminoveratrole (XXI), depending upon the conditions, produced either the corresponding acetoacetamino derivative (XXII), or the *beta*-aminocrotonic ester (XXIV), the former being cyclized by sulfuric acid to the 4-methyl-6,7-dimethoxy-8-nitrocarbostyril (XXIII), the latter to the 4,6(?)-dihydroxy-7(?)-methoxy-8-nitroquinaldine (XXV). The crotonic ester was obtained in two allotropic forms, m.p. 76–78° and 91–92°, which were interconvertible under conditions described in the experimental part.

An attempt to synthesize the 8-bromo-6,7-dimethoxyquinoline from 3-bromo-4-aminoveratrole failed because it was found impossible to degrade the 2-bromoveratramide to the corresponding amine by the Hofmann reaction. Recourse must therefore be had to different processes, such as those of Curtius (8), Lossen, and others.

As reported in the previous paper (10), direct nitration of 6,7-dimethoxyquinoline, yielded the 5,8-dinitro derivative. All attempts to obtain the mononitro compound by varying the conditions of nitration proved futile. Either the quinoline remained un-nitrated, or the dinitro derivative was the sole product isolated.

Acknowledgments. Without the generous support of Mr. Russell Hopkinson, of New York, N. Y., in maintaining at Columbia University a Hopkinson Research Fellowship, this investigation could not have been carried out. We are also deeply grateful to the following corporations, through the courtesy of the individuals mentioned, who kindly helped us by contributing various much-

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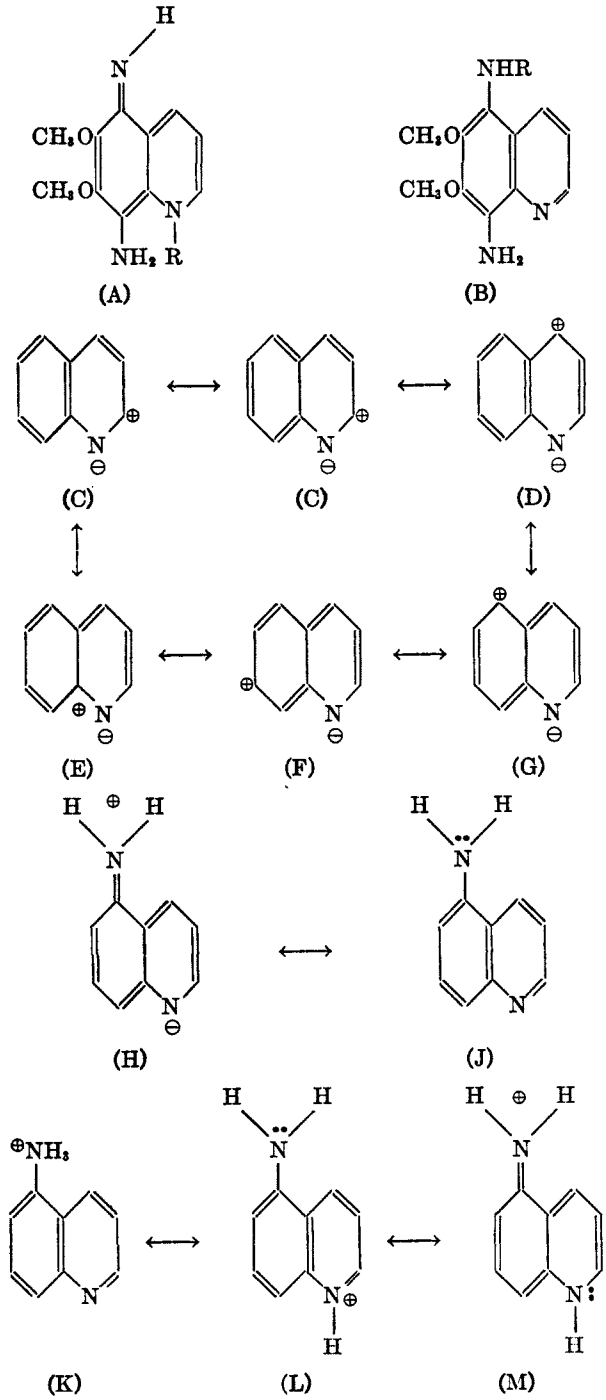

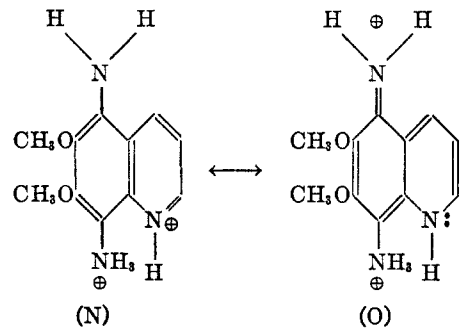

(N) (O)

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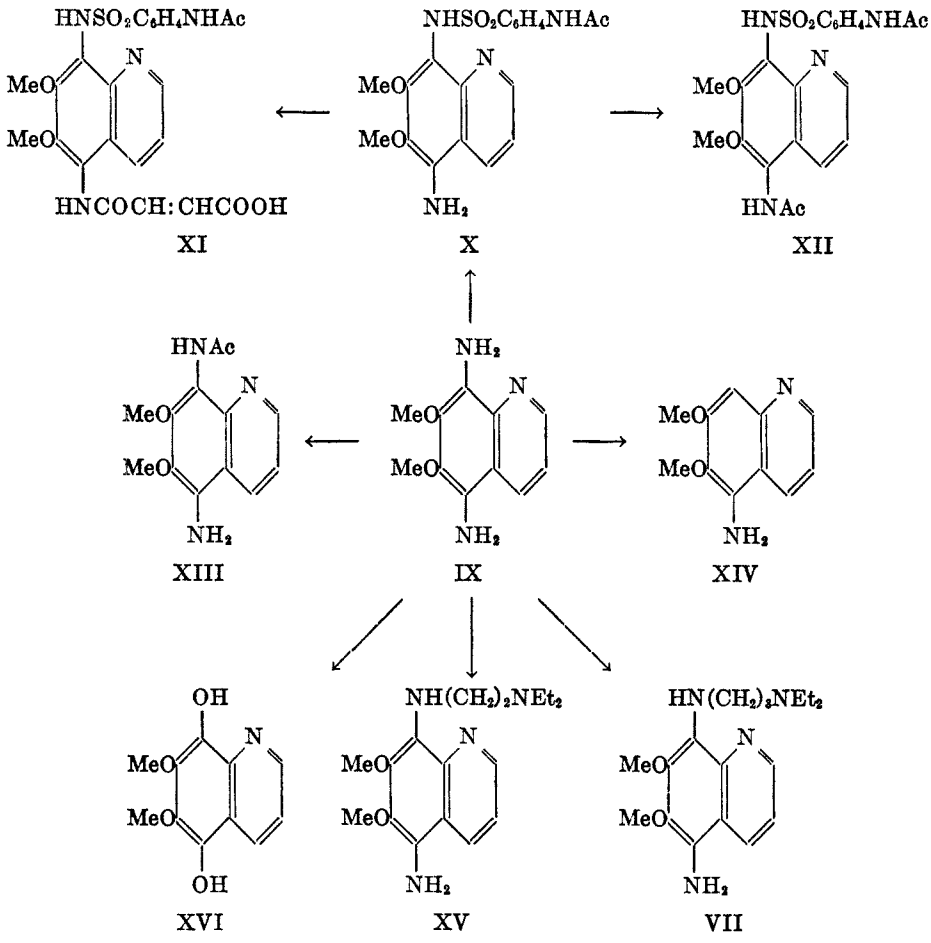

needed chemicals: American Cyanamid Co., through Dr. Richard O. Roblin, Jr., and P. S. Winnek, Stamford, Conn.; Armour Chemical Division, through H. M. Corley, Chicago, Ill.; Carbide & Carbon Chemicals Corp., through C. A.

Setterstrom and H. G. Goodman, Jr., New York; Commercial Solvents Corp., through Edward F. Arnold and W. E. Scheer, New York; Fritzsche Bros., Inc., through John H. Montgomery, Secretary, New York; Merck & Co., Inc., through Dr. Randolph T. Major, Rahway, N. J.; and Winthrop Chemical Co., Inc.,

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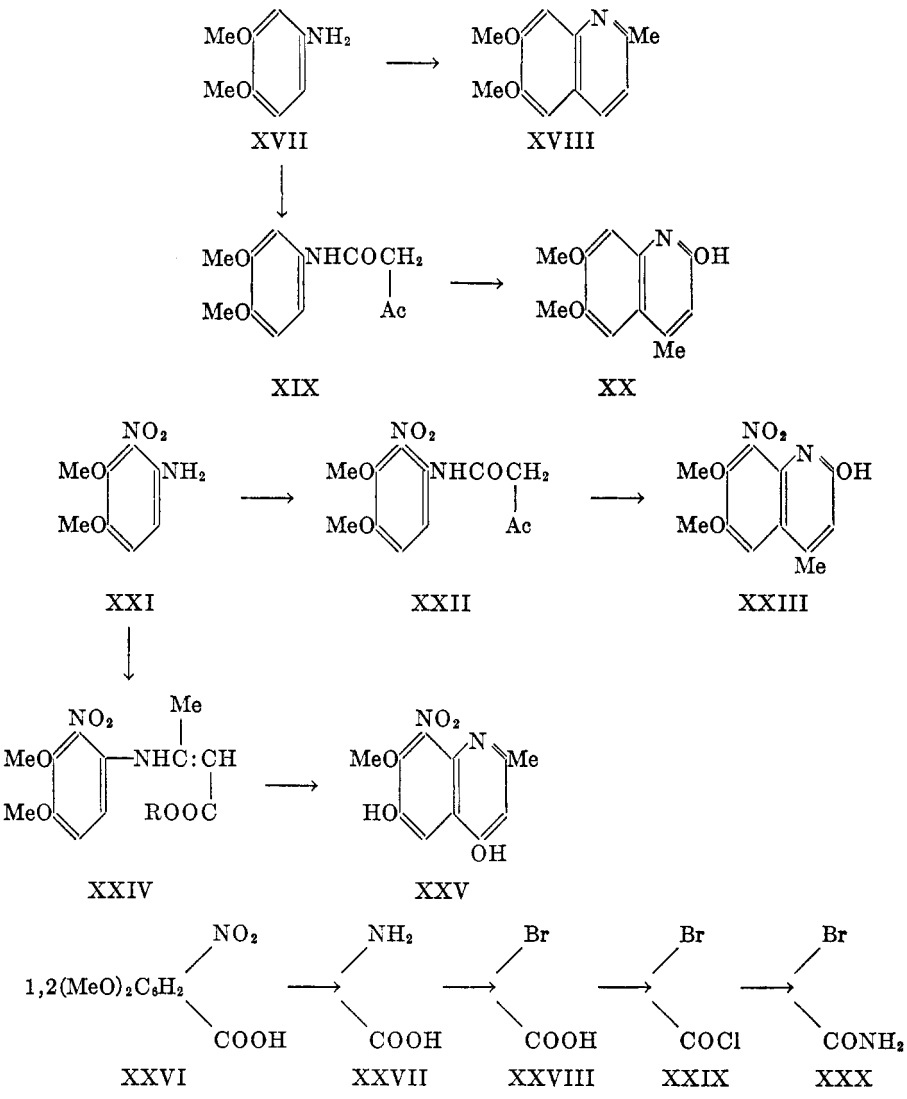

through J. B. Rice and Charles B. McDermott, New York. The fine cooperation of Dr. Wiselogle and the central office of the Survey of Antimalarial Drugs has been invaluable in arranging for screening tests of our products and, through their clearing-house function, in keeping us posted on current progress in this

extensive field. To Miss Frances Marx, we owe the microanalyses recorded in the experimental part of this communication.

EXPERIMENTAL

Unless otherwise stated, all temperatures recorded have been corrected for thermometer stem exposure.

DMQ. To economise space, this abbreviation is used for *dimethoxyquinoline* in naming compounds in the following pages.

5-Amino-8-acetylsulfanilamido-6,7-DMQ (X). The condensation of 5,8-diamino-6,7-DMQ with *p*-acetylsulfanilyl chloride was carried out in two different ways:

(a) According to the procedure of Juneja, Narang, and Rây (19), 1.2 g. of the diamine was dissolved in 75 cc. of dry chloroform and 2 g. of *p*-acetylsulfanilyl chloride was added. The mixture was refluxed for 30 minutes on the steam-bath. On cooling, bright red crystals separated, which were filtered out and recrystallized several times from alcohol. The melting point of the pure product was 204–205°. It was found that this red compound was not the free base but the hydrochloride of X, since it gave a positive chlorine test and was easily converted into the free amine by ammonium hydroxide.

Anal. Calc'd for $C_{19}H_{21}ClN_4O_5S$: C, 50.3; H, 4.6.
Found: C, 50.3; H, 4.8.

The formation of the hydrochloride can be explained by the fact that the hydrochloric acid split off in the course of the condensation then combined with the quinoline nitrogen.

The *free base* was obtained in pale yellow needles which, when recrystallized from alcohol, melted at 209.5°.

Anal. Calc'd for $C_{19}H_{20}N_4O_5S$: C, 54.8; H, 4.8.
Found: C, 55.1; H, 4.9.

(b) The second procedure led directly to the free base. A solution of 1.2 g. of the diamine was prepared in 20 cc. of acetone, and to this solution was added 1 g. of potassium carbonate dissolved in the minimum amount of water, followed by a solution of 3 g. of *p*-acetylsulfanilyl chloride in 40 cc. of acetone. A small amount of potassium carbonate which separated was dissolved by the addition of a few cc. of water. The mixture was refluxed for 30 minutes on the steam-bath, and the acetone was then removed by distillation. The resulting greenish solution was poured into water and a pale greenish precipitate soon separated. This was collected, washed with a small amount of water, and crystallized thrice from alcohol and water, giving pale yellow needles, m.p. 209.2°; yield, about 80%. This product was identical with that obtained by the first procedure, as determined by melting point and analysis.

Anal. Calc'd for $C_{19}H_{20}N_4O_5S$: C, 54.8; H, 4.8; N, 13.45.
Found: C, 54.95; H, 5.2; N, 13.3.

In this reaction it was observed that, in spite of the presence of potassium carbonate to absorb the by-product hydrochloric acid and an excess of *p*-acetylsulfanilyl chloride, only the monosubstitution product was formed.

Experiments were carried out, to introduce an acetylsulfanilamido side chain also into the unchanged amino group at 5, by condensing the above compound (X) with *p*-acetylsulfanilyl chloride, according to procedure (b), but only the original monosubstitution product was recovered from the reaction mixture.

5-Amino-8-sulfanilamido-6,7-DMQ (VIII). The deacetylation of X was effected as follows: 1 g. of X was dissolved in 20 cc. of hydrochloric acid (sp. gr. = 1.15) and refluxed for 10 minutes on the steam-bath. On making the cooled solution alkaline with ammonium hydroxide, there first resulted a greenish-grey sludge which became entirely crystalline when scratched. This product was removed, washed with water, and dried at 100°; yield of crude product, 90%. Recrystallized from alcohol, in the presence of charcoal, it formed pale brown crystals, m.p. 213.5–214.5° (dec.).

Anal. Calc'd for $C_{17}H_{18}N_4O_4S$: C, 54.5; H, 4.8.
Found: C, 54.8; H, 5.05.

8-Acetylsulfanilamido-6,7-dimethoxyquinolyl-5-maleamic acid (XI). The presence of a free primary amino group in X was demonstrated by condensation with maleic anhydride. To a solution of 1.5 g. of X in 25 cc. of acetone, one equivalent of maleic anhydride was added and the mixture refluxed for 3 minutes. As the solution cooled, a precipitate separated, which was removed and crystallized from alcohol, giving pink crystals, m.p. 212° (dec.).

Anal. Calc'd for $C_{23}H_{22}N_4O_8S+0.5H_2O$: C, 52.8; H, 4.4; N, 10.7.
Found: C, 53.1; H, 4.7; N, 11.0.

It is interesting to note that the di-maleamic acid described in the earlier paper (10) contained one molecule of water of crystallization.

5-Acetylamino-8-acetylsulfanilamido-6,7-DMQ (XII). The monoacetyl derivative (X) was heated with an excess of acetic anhydride on the steam-bath for 15 minutes. As the solution cooled, a copious white precipitate formed, which was repeatedly recrystallized from alcohol, and gave white needles, m.p. 248–248.5° (dec.); yield, about 90%.

Anal. Calc'd for $C_{21}H_{22}N_4O_6S$: C, 55.0; H, 4.8; N, 12.2.
Found: C, 55.1; H, 4.6; N, 11.9.

5-Amino-8-acetylamino-6,7-DMQ (XIII). The preparation of this acetyl derivative was carried out by adding an excess of acetic anhydride to the diamine and heating the reaction mixture for 30 minutes at 100°. Even while hot, a pale yellowish precipitate formed. This was removed, washed with petroleum ether (Skellysolve B), and then with a small amount of alcohol. The white product, recrystallized from alcohol, formed white needles, m.p. 270.5° (dec.).

Anal. Calc'd for $C_{13}H_{15}N_3O_3$: C, 59.8; H, 5.7.
Found: C, 59.7; H, 5.6.

As the above analysis indicates, acetylation of the diamine also led only to the monosubstitution product, in spite of the presence of an excess of acetic anhydride.

5-Amino-8-(β-diethylaminoethylamino)-6,7-DMQ (XV). The condensation of the diamine (IX) with dialkylaminoalkylamines was carried out essentially according to the procedure of Magidson and his co-workers (20, 21, 22).

A mixture of 9 g. of the diamine with 12.5 g. of β-diethylaminoethyl chloride hydrochloride in a wide test tube, protected from moisture by a calcium chloride guard tube, was heated for 8 hours at 120–130°, with occasional stirring.

After the heating was completed, the dark oily residue was dissolved in hot water, the solution saturated with potassium carbonate, and extracted repeatedly with ether. The ether extracts were dried over anhydrous potassium carbonate, the solvent driven off, and the resulting dark oil distilled at low pressure in an atmosphere of nitrogen. The pure product came over at 168°/0.03 mm., as a viscous red oil. On prolonged standing in the air, it darkened considerably.

Anal. Calc'd for $C_{17}H_{26}N_4O_2$: C, 64.1; H, 8.2.
Found: (sample 1) C, 63.8; H, 8.2. (sample 2) C, 64.1; H, 8.4.

The above analytical figures show that again only monosubstitution occurred.

5-Amino-8-(γ-diethylaminopropylamino)-6,7-DMQ (VII). A mixture of 14 g. of the diamine (IX) with 19 g. of γ-diethylaminopropyl chloride hydrochloride was heated for 8 hours at 125–130° (oil-bath temperature). The residue was worked up as described above for the preparation of (XV). The product from the ether extraction was a dark oil, which was subjected to further purification by high-vacuum distillation in an atmosphere of nitrogen. The yield of crude product was about 12 g. The pure product distilled over at 170–180°/0.03–0.04 mm., as a dark red viscous oil.

Anal. Calc'd for $C_{18}H_{28}N_4O_2$: C, 65.0; H, 8.4.
Found: C, 64.9; H, 8.3.

Analogous condensations of the diamine (IX) with 1-methyl-4-diethylaminobutyl chloride hydrochloride and 1-methyl-4-dimethylaminobutyl chloride hydrochloride were

carried out. The yields in these reactions were much smaller than in the two reactions described above, and the amounts of the resulting viscous dark red oils too small to subject them to a final purification by high vacuum distillation.

The dialkylaminoalkyl chloride hydrochlorides which were used in these condensations were prepared according to the following general procedure:

A solution of 2 moles of thionyl chloride in 1 liter of benzene was placed in a three-necked flask, equipped with thermometer, dropping-funnel, mechanical stirrer, and gas outlet tube. The solution was kept in an ice-bath and 1 mole of the corresponding dialkylaminoalkanol (commercially available) was added slowly with stirring, keeping the rate of addition such that the temperature did not rise above 25°. After all of the alcohol had been added, the temperature was raised to 60° and kept there for 3–4 hours. The solvent was then removed under reduced pressure and the residue purified by several distillations with small amounts of alcohol and benzene, leaving a crystalline product in the flask. Most of these dialkylaminoalkyl chloride hydrochlorides were hygroscopic and were best kept in a vacuum desiccator. The yields were 80–90%.

The same observation, that generally only one amino group of the diamine (IX) was attacked, was made in the diazotization of this substance. At 0° the uptake of sodium nitrite corresponded to the diazotization of a single amino group.

Furthermore, monosubstitution products of the diamino-DMQ (IX), such as the 5-amino-8-acetylamino-(XIII), and 5-amino-8-acetylsulfanilamido-(X) derivatives, possessing a free amino group in the 5 position, do not undergo diazotization under ordinary conditions.

5-Amino-6,7-DMQ (XIV). The replacement of the 8-amino group by hydrogen in the diamine (IX), was accomplished as follows: 1.8 g. of the diamine was dissolved in a mixture of 2.5 cc. of sulfuric acid and 6 cc. of water and the mixture cooled to 0°. A 20% sodium nitrite solution was added dropwise with constant stirring until the end of the reaction was indicated by starch-potassium iodide paper.

The diazonium solution was poured into a mixture of concentrated sodium hydroxide solution and ice, and a solution of sodium stannite (3 g. of stannous chloride dissolved in just sufficient excess of sodium hydroxide to dissolve all of the stannous hydroxide formed) was added with stirring. The reaction mixture was then kept on a steam-bath until no more evolution of nitrogen took place. The alkaline mixture, possessing a distinct ammoniacal odor, was extracted with ether or ethyl acetate, the extracts dried over anhydrous sodium sulfate and the solvent evaporated. The amine remained as a reddish oil, which was not analyzed but was identified by its derivatives. The procedure used in the above reaction is that of Friedländer (23).

5-Acetylamino-6,7-DMQ. The acetylation of the above amine (XIV) was carried out with acetic anhydride. The crude product, several times recrystallized from alcohol, gave white needles, m.p. 141.5°.

Anal. Calc'd for $C_{13}H_{14}N_2O_3$: C, 63.5; H, 5.7.
Found: C, 63.4; H, 5.6.

Picrate. Recrystallized from alcohol, it formed orange needles, m.p. 229–230°.

Anal. Calc'd for $C_{17}H_{15}N_5O_9$: C, 47.2; H, 3.5.
Found: C, 47.3; H, 3.6.

That tetrazotization of the diamine (IX) may occur under more drastic conditions, was shown by the preparation of the dihydroxy compound.

5,8-Dihydroxy-6,7-DMQ (XVI). Four grams of the diamine was dissolved in a mixture of 5 cc. of concentrated sulfuric acid and 15 cc. of water. The solution was heated to 80°, and a solution of 2 g. of sodium nitrite in 16 cc. of water slowly added through a dropping-funnel, whose end reached almost to the bottom of the flask, in order to prevent decomposition of the sodium nitrite by falling upon the hot surface. The addition of the nitrite took about 10–15 minutes, keeping the temperature of the solution at 80–90°. When the addition was complete, the heating was continued at the same temperature for 30 minutes, by which time no more evolution of nitrogen was observed. After cooling, the acid solution was

extracted with ether, the yellow ether extracts dried over anhydrous sodium sulfate and the solvent evaporated. The orange-red oil which remained was taken up in alcohol and, on scratching the sides of the container, changed over to an orange-yellow crystalline solid, m.p. 77–79°, which darkened on standing in the light. Since the analytical figures for carbon and hydrogen in the dihydroxy compound and in the aminohydroxy compound are about the same, a nitrogen analysis was run.

Anal. Calc'd for $C_{11}H_{11}NO_4$: N, 6.4.

Found: N, 6.8. For the aminohydroxy compound, N = 12.7.

This dihydroxyquinoline gave a characteristic chelate metallic complex with copper salts, and it has been shown by various investigators (17) that only those hydroxyquinolines which carry their OH in position 8 are able to form such internal metallic complexes and lakes between the quinoline nitrogen and the OH group.

6,7-Dimethoxyquinaldine (XVIII). This has been previously prepared by Rilliet (18) by treatment of 6-aminoveratraldehyde with acetone. A more convenient synthesis, however, was found in the application of the Doebner-von Miller reaction to 4-aminoveratrole (XVII), which latter is easily available in excellent yields (10).

To a mixture of 31 g. of 4-aminoveratrole and 60 cc. of concentrated hydrochloric acid, was added 45 cc. of paraldehyde, and the mixture was refluxed for 3.5 hours. The reaction set in only after warming and proceeded without violence. After cooling, the reaction mixture was made alkaline with concentrated sodium hydroxide solution and steam-distilled.

The residue was transferred to a continuous extractor and extracted with ether overnight. The ether extracts were dried with anhydrous sodium sulfate and the solvent evaporated. The dark oil which remained was subjected to a vacuum distillation. Rejecting the forerun, a pale yellow, viscous oil was obtained, distilling at 135°/0.45 mm. The yields were good.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.4.

Found: C, 70.6; H, 6.6.

The identity of this compound (XVIII) was established by comparing the m.p. of its *picrate* (from an alcoholic solution) with that obtained by Rilliet (18). Rilliet gave the m.p. of his picrate as 217°, which is the figure found for the picrate of the above product.

4-Methyl-6,7-dimethoxycarbostyril (*6,7-dimethoxy-α-lepidone*) (XX). Ten grams of ethyl acetoacetate was heated in an open flask to 160°, and 3 g. of 4-aminoveratrole (XVII) slowly added, so that the internal temperature did not fall below 160°, which took about 25 minutes. The contents of the flask were stirred occasionally, to facilitate removal of the alcohol formed and heating was continued for 30 minutes after all of the aminoveratrole had been added. On cooling, the mixture formed a dark liquid which was concentrated under reduced pressure, to remove the excess of acetoacetic ester. The residual oil, representing the *4-acetoacetaminoveratrole* (XIX) was not crystallized, but used directly for the ring closure.

To this oil was added an equal volume of concentrated sulfuric acid, and the mixture was carefully heated to 90–95°. Fumes developed at this temperature, indicating that the reaction had set in. After this reaction had subsided (the temperature of the reaction mixture must not exceed 95°), the mixture was heated at 95° for 10 minutes, then cooled to 60° and poured into water. A grey precipitate formed, which was removed and recrystallized from alcohol and water, giving white needles, m.p. 236–237° (dec.).

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.9.

Found: C, 65.7; H, 6.1.

The yield of this substance was about 70%, calculated to the 4-aminoveratrole.

3-Nitro-4-acetoacetaminoveratrole (XXII). Ten grams of acetoacetic ester was heated to 160° (inside temperature) and 3 g. of 3-nitro-4-aminoveratrole (24) (XXI) was slowly added, maintaining the temperature at 160°. This took about 10–15 minutes. After 30 minutes longer at 160°, with occasional shaking, to facilitate removal of the alcohol formed, the clear orange liquid was allowed to cool; yellow crystals separated on short standing.

These crystals were filtered out, washed with a small amount of cold alcohol, and recrystallized thrice from alcohol. Light yellow needles were obtained, m.p. 118.5–119.5°; yield (first crop), 2.5 g.

Anal. Calc'd for $C_{12}H_{14}N_2O_6$: C, 51.0; H, 5.0.
Found: C, 51.3; H, 5.2.

4-Methyl-6,7-dimethoxy-8-nitrocarbostyril (6,7-dimethoxy-8-nitro-α-lepidone) (XXIII). A mixture of 9.5 g. of the above XXII with 10 cc. of concentrated sulfuric acid was heated to 95°, forming a dark red solution. The heating was continued for 10 minutes at the same temperature and the mixture was then cooled and poured into water. A yellowish-brown precipitate resulted, which was filtered out and dried at 100°; yield of crude product, 2.5 g. This crude product was crystallized several times from alcohol, giving light yellow needles m.p. 210° (dec.).

Anal. Calc'd for $C_{12}H_{12}N_2O_5$: C, 54.6; H, 4.6; N, 10.6.
Found: C, 55.0; H, 4.9; N, 10.6.

This procedure for the ring closure is that of Michailov (25).

The filtrate from the ring closure product was made alkaline, whereby 3-nitro-4-aminoveratrole came down (4 g.), indicating hydrolysis of some of the XXII.

Ethyl 2-nitro-3,4-dimethoxy-β-anilinocrotonate (XXIV). The condensation of 3-nitro-4-aminoveratrole (XXI) with acetoacetic ester was carried out exactly as described above for the preparation of XXII, except that the temperature was allowed to go up to 173°. When the crude mixture was cooled, poured into water, and chilled with ice, deep yellow cubical crystals separated, which were filtered out and washed with alcohol; m.p. 76–78°.

On standing in the sunlight, these deep yellow crystals faded to a pale yellow, a transformation which took place also when the deep yellow form was recrystallized from alcohol. The pale yellow crystals melted at 91–92° and, on prolonged standing, reverted partially to the deep yellow form.

Anal. Calc'd for $C_{14}H_{18}N_2O_6$: C, 54.2; H, 5.8.
Found: C, 54.1; H, 5.8.

4,6(?)-Dihydroxy-7(?)-methoxy-8-nitroquinaldine (XXV). The ring closure of XXIV was carried out with concentrated sulfuric acid as described for the preparation of XXIII. Under the conditions of the experiment, this took place with simultaneous hydrolysis of one methoxyl group, presumably that at 6. The yield of this product was very small. It formed bright yellow needles, m.p. around 300°.

Anal. Calc'd for $C_{11}H_{10}N_2O_5$: C, 52.8; H, 4.0; N, 11.2.
Found: C, 52.7; H, 4.2; N, 10.9.

2-Aminoveratric acid (XXVII). The reduction of 2-nitroveratric acid (XXVI) to the corresponding aminoveratric acid by tin and hydrochloric acid in alcoholic solution, is not a satisfactory method, as Tiemann and Matsmoto (26) have reported. Catalytic reduction of the nitro acid with palladium black in alcoholic solution was tried, but no hydrogen uptake could be observed, even during a period of many hours.

The reduction was successfully carried out, however, with ferrous sulfate and ammonium hydroxide, following the procedure of Pschorr and Sumuleanu (27); m.p. 186°; (lit., 184°); yield, 83%.

2-Bromoveratric acid (XXVIII). The diazotization of 2-aminoveratric acid and the replacement of the amino group by bromine were accomplished as described by Zincke and Francke (28). The bromo acid was obtained in white needles, m.p. 206–208° (lit. 201–202°); yield, 62%.

2-Bromoveratroyl chloride (XXIX). This compound was prepared by dissolving 1.2 g. of 2-bromoveratric acid in 8 cc. of thionyl chloride, refluxing the solution for 30 minutes, and distilling off excess thionyl chloride under diminished pressure. The acid chloride was not isolated from the residue, which was used directly for the preparation of the amide.

2-Bromoveratramide (XXX). The crude acid chloride was added slowly to a concentrated ammonium hydroxide solution with constant stirring, keeping the reaction mixture ice-cold. The white precipitate which formed was filtered out, washed with water, and

dried at 100°; yield, 1.2 g., which is nearly that calculated. Recrystallized from alcohol, it gave colorless prisms, m.p. 197–198°. Another sample, recrystallized from benzene, showed the same melting point, indicating that no esterification had taken place in the recrystallization from alcohol.

Anal. Calc'd for $C_9H_{10}BrNO_4$: C, 41.4; H, 3.8.
Found: C, 41.1; H, 3.7.

2-Bromoveratramide was subjected to the Hofmann degradation, under various conditions of temperature, amounts of reagents, etc., but in no case could the corresponding amine be isolated from the reaction mixture. Other methods therefore, such as the Curtius and Lossen rearrangements, must be tried for the preparation of the amine.

SUMMARY

1. From 5,8-diamino-6,7-dimethoxyquinoline, derivatives have been prepared in which hydrogens of the amino groups have been replaced by —Ac, $—SO_2NHC_6H_4NHAc$, $—(CH_2)_nNR_2$, —COCH:CHCOOH. In all cases where such substitutions involved elimination of molecules of an acid, only one of the two amino groups participated in the reaction. An explanation of this, along electronic lines, is suggested. The antimalarial inactivity of the few compounds tested so far, supports Schönhöfer's (2) conclusion that a methoxyl group at 7 in such quinoline derivatives is definitely dystherapeutic.

2. Under ordinary conditions, only one of the two amino groups could be diazotized. One amino group thus has been removed, without affecting the other one. Using concentrated acids and higher temperature, both amino groups have been diazotized.

3. In the above reactions, it is believed that the 8-amino group is the more reactive one and hence is the one primarily attacked.

4. 4-Aminoveratrole has been converted into 6,7-dimethoxyquinaldine, by the Döbner-von Miller reaction; and into the 6,7-dimethoxy-α-lepidone by the Knorr-Conrad-Limpach procedure.

5. 3-Nitro-4-aminoveratrole, likewise by the Knorr-Conrad-Limpach reactions, has been converted into 6,7-dimethoxy-8-nitro-α-lepidone, or 4,6(?)-dihydroxy-7(?)-methoxy-8-nitroquinaldine, the course of the reaction depending upon the temperature used in the condensation.

6. An attempt to synthesize 3-bromo-4-aminoveratrole from 2-nitro-3,4-dimethoxybenzoic acid proved unsuccessful, because it was found impossible to degrade the 2-bromo-3,4-dimethoxy-benzamide by the Hofmann reaction.

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[CONTRIBUTIONS FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

CYCLOÖLEFINS AS PHILODIENIC COMPONENTS IN THE DIELS-ALDER REACTION

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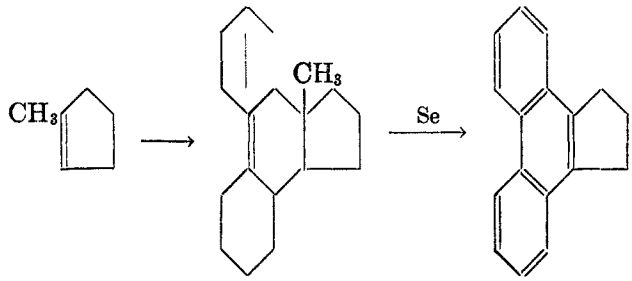
The philodienic component in the Diels-Alder reaction is usually represented by an ethylenic or acetylenic group, which is activated by a substituent. The latter acts in most cases by its electromeric effect as resonance promoting group (C=O, C≡N, C_6H_5, etc.), but sometimes by its inductive effect (CH_2OH, CH_2Br, etc.). Simple olefinic hydrocarbons were only recently found by Joshel and Butz (1) to condense with dienes under rather drastic conditions, *e.g.*, ethylene reacted with butadiene or 2,3-dimethylbutadiene to give the corresponding cyclohexenes.

The fact that the cyclohexenes were obtained as final reaction products indicated that cycloölefins would be unable to undergo the Diels-Alder condensation. Nevertheless, the idea of trying such a type of diene reaction seemed attractive in view of the difficulties which are usually encountered in converting, *e.g.*, quinone adducts into the corresponding hydrocarbons. Therefore, in the present study, we investigated the general applicability of the Diels-Alder reaction to cyclic olefins.

Our first series of experiments was concerned with bicyclohexenyl, because this diene had already proved to be exceedingly reactive towards a great variety of philodienes (2, 3). Condensation with cyclohexene, 1-methylcyclohexene, 1,2-dihydronaphthalene, and 4-methyl-1,2-dihydronaphthalene was unsuccessful under various conditions. 1-Methylcyclopentene, however, gave a positive result. It yielded the adduct I, which was dehydrogenated to the known 9,10-cyclopentenophenanthrene (II) (4, 5). 1,3-Dimethylindene yielded III, which was aromatized to 9-methyl-1,2,3,4-dibenzfluorene (IV). The same series of reactions with indene has previously been described (6a) and indene has been added to other dienes (6b).

In a second series of reactions, 2-isopropenylnaphthalene (V) and 2-(1,2-dimethylvinyl)naphthalene (VI) were used as dienes, the latter in the hope of obtaining the still unknown hydrocarbon 1,2-dimethyl-3,4-benzphenanthrene. The compound V has been described by Ruzicka and Capato (7) as an oil, b.p. 126° (12 mm.). We found it to crystallize readily (m.p. 56°). The general ability of both dienes to undergo Diels-Alder reactions will be reported later. As with bicyclohexenyl, no reaction occurred with cyclohexenes, and therefore this line of research was abandoned.

As the main result of our experiments, the conspicuous difference in behavior between cyclohexenes and cyclopentenes appears to be established. It forms a counterpart to the differences observed when either cycle belongs to butadienic systems in which one double bond forms part of an aromatic nucleus. Thus, 1-(1-cyclopenten-1-yl)naphthalene (VII) gave very satisfactory results in the



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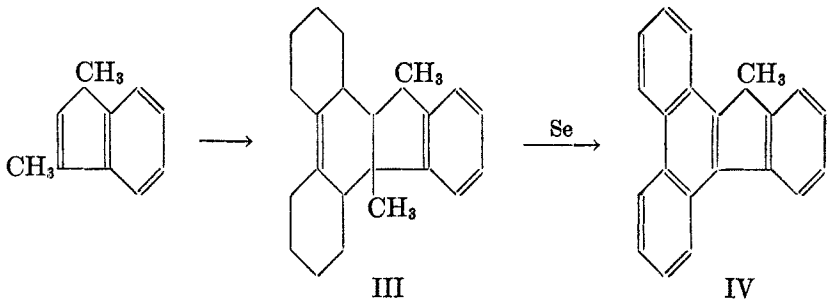

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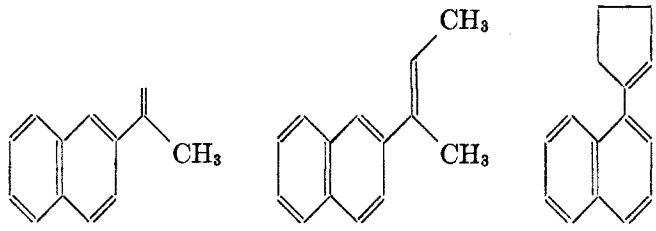
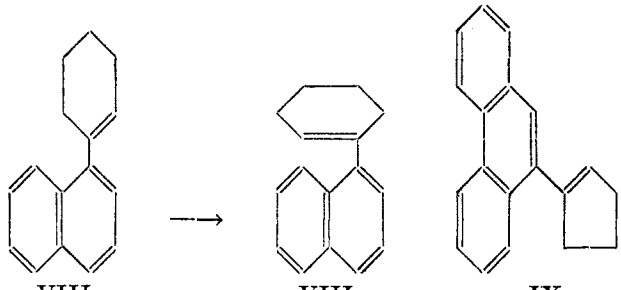
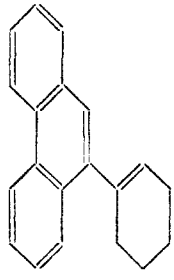


V VI VII



VIII VIIIa IX



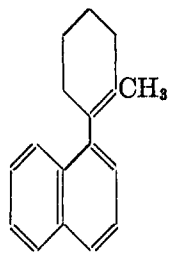
X

Diels-Alder reaction (8), whereas the corresponding cyclohexenyl compound (VIII) was entirely refractory (5). A similar distinction was found among the 9-cycloalkenylphenanthrenes (IX and X) (9).

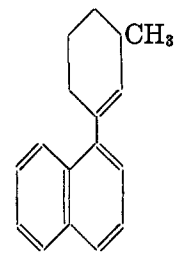
Non-reactivity in such dienic systems was sometimes explained by a special kind of linking. Cook and Lawrence, *e.g.*, pictured the diene VIII in the modified form VIIIa, in order to explain the inertness of the ethylenic bond (10). Such an explanation should, however, be valid likewise for the homologous cyclopentenyl compound (VII). Furthermore, 1-(2-methyl-1-cyclohexen-1-yl) naphthalene (XI) is unable to assume a coplanar structure corresponding to VIIIa. XI proved, however, to be entirely unreactive towards maleic anhydride. That this inability to function as diene component is inherent in cyclohexenyl derivatives of aromatic compounds is further suggested by the examples of the 3- (XII) and 4-methyl (XIII) isomers of XI. On the other hand, 1-vinylcyclohexene and 1-methyl-2-vinylcyclohexene react normally with philodienes (20).

A search for the reason for these surprising differences reveals that a number of other reactions also show typical deviations with either the cyclohexenyl or cyclopentenyl derivatives. Dieckmann (11) observed that ethyl cyclopentanone-2-carboxylate is in equilibrium with only 4.5% of its enol form, whereas ethyl cyclohexanone-2-carboxylate contains about 76% of enol. Kon and Speight (12) found that condensation of malonic ester with cyclopentanone yields the α,β-unsaturated cyclopentylidene derivative, whereas in the corresponding reaction with cyclohexanone the double bond shifts into the ring (to the β,γ-position).

The difference between the two series of conjugated compounds, containing either a cyclopentene or a cyclohexene ring, was confirmed by spectrographic



XI



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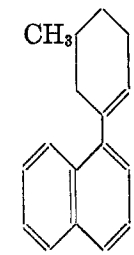
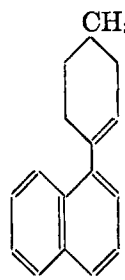


XII



XIII

XIV

examination (13): IX, but not X, shows the diffuse absorption bands characteristic for conjugated systems.

Inspection of Fisher-Hirschfelder models also leaves no doubt that essential differences exist between the cyclopentene-cyclopentane pair on one hand, and the cyclohexene-cyclohexane pair on the other. The cyclopentane ring is nearly coplanar and built up with but little strain,[1] whereas closing the cyclopentene ring requires considerable strain and distortion. A different situation prevails in the six-membered rings: The same form of oscillation which is possible in the cyclohexane ring and confers on it such a high degree of stability, is permitted also to the four non-ethylenic carbon atoms of cyclohexene. In the simplest model either carbon atoms 3 and 5, or 4 and 6 are placed alternatively outside the plane determined by the other four ring-atoms. Thereby the cyclohexene ring is built up without strain and appears to be not less stable than the cyclohexane system. The general result is that cyclopentene derivatives will show a considerable readiness to pass into cyclopentane or cyclopentylidene compounds respectively, whereas the opposite trend is recognizable in six-membered rings. We therefore conclude, that the quantitative differences in the relative stability of the pairs cyclopentene-cyclopentane and cyclohexene-cyclohexane cause the qualitative difference observed in the Diels-Alder reaction. This explanation is supported by the fact that introduction of strain into the cyclohexene ring by a carbon bridge, as in the bicycloheptene (XIV), reintroduces the ability to function as philodienic component (15). It will be of interest to examine the behavior of polymembered cycloölefins in connection with the above reflections. We feel, however, that the steric factors involved may be of much more complex nature than stated above, because physical constants, *e.g.* the heat of hydrogenation (16, 17), show differences with a trend opposite to the expected one.

EXPERIMENTAL

All melting points are uncorrected.

Preparation of dienes. (a) *2-Isopropenylnaphthalene (V).* 2-Acetylnaphthalene (17 g., 0.1 mole) was added to a Grignard solution from methyl iodide (28.5 g.) and magnesium (4.8 g.). The reaction was vigorous and was completed by refluxing for one hour. The product was directly dehydrated by either potassium bisulfate at 160° or by boiling acetic anhydride, or by distillation at normal pressure. The isopropenyl compound was purified by distillation, b.p. 155° (11 mm.), and crystallized on standing in naphthalene-like scales. After trituration with a small amount of ice-cold methanol, it showed the m.p. 56°; yield 85%. No crystalline picrate could be obtained.

Anal. Calc'd for $C_{13}H_{12}$: C, 92.9; H, 7.1.
Found: C, 92.8; H, 7.0.

Catalytic reduction with Raney nickel in ethyl acetate proceeded rapidly and the reaction was strongly exothermic. Twelve grams of the isopropenyl compound absorbed during one hour 1720 cc. of H_2 (p = 763 mm.; t = 28°); calc'd, 1780 cc. Distillation yielded 2-isopropylnaphthalene as a water-white oil, b.p. 99–100° (0.2 mm.), which formed in ethanolic solution the picrate of m.p. 90–93° described by Ruzicka (7).

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[1] Ashton (14) concludes from spectroscopical data that cyclopentane can best be represented by a non-planar model with one atom out of the plane. In the models used, however, the deviation from a planar form is not appreciable.

Anal. Calc'd for $C_{13}H_{14}$: C, 91.8; H, 8.2.
Found: C, 91.6; H, 8.2.

(b) *2-(1,2-Dimethylvinyl)naphthalene (VI).* The Grignard reaction between 2-acetylnaphthalene (0.1 mole) and ethylmagnesium bromide (0.2 mole) proceeded vigorously as above. Distillation gave a yellow oil, b.p. 128–129°/0.2 mm., which was shown by analysis to be a mixture of carbinol and dehydrated product.

Anal. Calc'd for $C_{14}H_{16}O$: C, 84.0; H, 8.0.
for $C_{14}H_{14}$: C, 92.3; H, 7.7.
Found: C, 89.9; H, 8.2.

Dehydration with potassium bisulfate at 160° for twenty minutes gave 14 g. (77%) of a liquid, b.p. 108–112° (0.15 mm.); n_D^{20} 1.6202.

Anal. Calc'd for $C_{14}H_{14}$: C, 92.3; H, 7.7.
Found: C, 91.9; H, 7.7.

Again the picrate was unstable. It crystallized from a hot saturated solution of picric acid as orange needles, mixed with picric acid, but it could not be isolated in a pure state. Three and three-tenths grams of the unsaturated hydrocarbon was reduced in acetic acid over palladium-barium sulfate (p = 760 mm., t = 14°). Within one hour 440 cc. of H_2 was absorbed (calc'd 430 cc.). Distillation yielded 2-*sec.*-butylnaphthalene as a colorless oil, b.p. 147–148° (33 mm.); n_D^{20} 1.5814.

Anal. Calc'd for $C_{14}H_{16}$: C, 91.3; H, 8.7.
Found: C, 91.0; H, 8.7.

(c) *1-(2-Methyl-1-cyclohexen-1-yl)naphthalene (XI)* was prepared according to Cook (10). We found that it gives a well-defined picrate of orange-yellow prisms, m.p. 105–106° (from methanol).

Anal. Calc'd for $C_{23}H_{21}N_3O_7$: C, 61.2; H, 4.7.
Found: C, 61.0; H, 4.5.

Dehydrogenation with sulfur at 170–190° gave a 70% yield of 1-*o*-tolylnaphthalene. This hydrocarbon did not form a crystalline picrate. Compound XI was unreactive towards maleic anhydride or benzoquinone under a variety of conditions.

(d) *1-(3- or 5-Methyl-1-cyclohexen-1-yl)naphthalene (XII)* was prepared from 3-methylcyclohexanone by the same method as XI. It forms a yellowish oil, b.p. 131° (0.2 mm.), n_D^{14} 1.6054; yield 40%. It gave no diene reaction with maleic anhydride or benzoquinone.

Anal. Calc'd for $C_{17}H_{18}$: C, 91.8; H, 8.2.
Found: C, 91.4; H, 8.0.

The picrate crystallized from isopropanol in beautiful orange-yellow, long prismatic rods, m.p. 105–106°. A mixed m.p. determination with the picrate of the 2-methylcyclohexenyl isomer gave 104–105°. The properties of the picrate of XII make it probable that XII is homogeneous and not a mixture of the two possible isomers.

Anal. Calc'd for $C_{23}H_{21}N_3O_7$: C, 61.2; H, 4.7.
Found: C, 60.9; H. 4.7.

Dehydrogenation with sulfur at 170–190° for four hours gave an oil, b.p. 140–145° (0.15 mm.), 1-*m*-tolylnaphthalene.

Anal. Calc'd for $C_{17}H_{14}$: C, 93.6; H, 6.4.
Found: C, 93.4; H, 6.2.

It yielded a crystalline picrate. From methanol, dark yellow, short needles with unsharp m.p. 89–94°.

Anal. Calc'd for $C_{23}H_{17}N_3O_7$: N, 9.4. Found: N, 9.6.

(e) *1-(4-Methyl-1-cyclohexen-1-yl)naphthalene (XIII)* was obtained from 4-methylcyclohexanone as described above; b.p. 142° (0.15 mm.), n_D^{14} 1.6040. It did not undergo Diels-Alder reactions.

Anal. Calc'd for $C_{17}H_{18}$: C, 91.8; H, 8.2
Found: C, 91.3; H, 8.2.

With picric acid in ethanol a crystalline picrate was formed. Recrystallization from isopropanol yielded short, canary yellow rods, m.p. 111°.

Anal. Calc'd for $C_{23}H_{21}N_3O_7$: C, 61.2; H, 4.7; N, 9.3.
Found: C, 60.9; H, 4.5; N, 9.6.

Dehydrogenation with sulfur at 180–190° for four hours yielded 1-*p*-tolylnaphthalene as an oil, b.p. 148–150° (0.15 mm.), but in this case no crystalline picrate was obtained.

Anal. Calc'd for $C_{17}H_{14}$: C, 93.6; H, 6.4.
Found: C, 93.2; H, 6.4.

It is noteworthy that all three methylcyclohexenylnaphthalenes readily form stable picrates, whereas among the 1-tolylnaphthalenes only the *m*-derivative gives a crystalline compound.

II. *Condensation reactions.* (Only positive experiments or experiments of general interest are reported here.)

(a) *With 2-isopropenylnaphthalene (V).* When this hydrocarbon (5 g.) was heated with cyclohexene (5 g.) in a sealed tube at 175–180° for 17 hours, the starting materials were recovered quantitatively. The same experiment at 240–250° gave a complicated mixture. Besides the starting materials, three fractions were separated: 1, b.p. 130–138° (0.1 mm.), 0.75 g.; 2, b.p. 140–155° (0.1 mm.), 0.5 g.; 3, b.p. 190–200° (0.3 mm.), 1.5 g., very thick oil with blue fluorescence. The third fraction, according to its analysis, was a polymerization product of 2-isopropenylnaphthalene.

Anal. Calc'd for $(C_{13}H_{12})_x$: C, 92.9; H, 7.1.
Found: C, 92.5; H, 7.2.

Fractions 1 and 2 were not identified. After dehydrogenation of both fractions with selenium, no trace of 1-methyl-3,4-benzphenanthrene (18) was detectable.

(b) *With bicyclohexenyl. Condensation with 1-methylcyclopentene.* Bicyclohexenyl (8 g.) and 1-methylcyclopentene (8 g.) were heated in a sealed tube to 250° for 18 hours. Fractionation of the reaction mixture yielded 3 g. of the olefin, 4.5 g. of the diene, and 2.5 g. (20%) of a yellow oil, b.p. 150–160° (0.2 mm.). This last fraction was heated with selenium (4.5 g.) to 250–280° for 10 hours, then to 300–310° for 5 hours. Distillation over sodium gave 0.75 g. of a green-yellow, viscous oil, b.p. 180–190° (0.1 mm.). This oil was gently heated with a saturated solution of picric acid in acetic acid. Acetone was added dropwise until the smeary precipitate became crystalline. The crude m.p. 160° rose to 164–165° upon recrystallization from alcohol. The substance was identified as the picrate of II by mixed m.p.'s with an authentic sample (5) of m.p. 164°, and by analysis.

Anal. Calc'd for $C_{23}H_{17}N_3O_7$: C, 61.7; H, 3.8; N, 9.4.
Found: C, 62.1; H, 4.0; N, 9.2.

Condensation with 1,3-dimethylindene. Bicyclohexenyl (12 g.) and 1,3-dimethylindene (7 g.) (19) were heated in an open flask to 230–240° for 13 hours. Distillation of the product gave 12.5 g. of starting materials and 3 g. (20%) of a high-boiling oil, b.p. 200–205° (4 mm.). It was heated with selenium (6 g.) to 260–280° for 8 hours, then to 300–310° for five hours and to 320° for 10 minutes. The viscous mass obtained by extraction with benzene was distilled *in vacuo*, b.p. 215–220° (0.5 mm.); yield 0.7 g. This product and picric acid (2 g.) were dissolved in a mixture of benzene (5 cc.), acetic acid (2 cc.), and ethyl acetate (2 cc.) by gently warming. The red picrate of IV crystallized slowly, and showed the m.p. 180–185°. Two crystallizations from butanol gave brick-red clusters, m.p. 202–203°.

Anal. Calc'd for $C_{28}H_{29}N_3O_7$: C, 66.0; H, 3.7.
Found: C, 65.7; H, 4.1.

The hydrocarbon IV was recovered from the picrate (300 mg.) as a thick yellow syrup, b.p. 230–240° (0.6 mm.). So far, all attempts at crystallization were unsuccessful.

SUMMARY

Cyclohexene and derived hydrocarbons do not undergo the Diels-Alder reaction. On the contrary, 1-methylcyclopentene and indenes yield the corresponding adducts with bicyclohexenyl. Like 1-(cyclohexen-1-yl)naphthalene, three

homologs with a methyl group in the cyclohexenyl ring did not function as dienes towards maleic anhydride, in contrast to the corresponding cyclopentenylnaphthalene. These differences, which are reflected in other known reactions of compounds containing either cycloölefin, are discussed on the basis of molecular models of the pair cyclopentane-cyclopentene on one hand and cyclohexane-cyclohexene on the other.

REHOVOTH, PALESTINE

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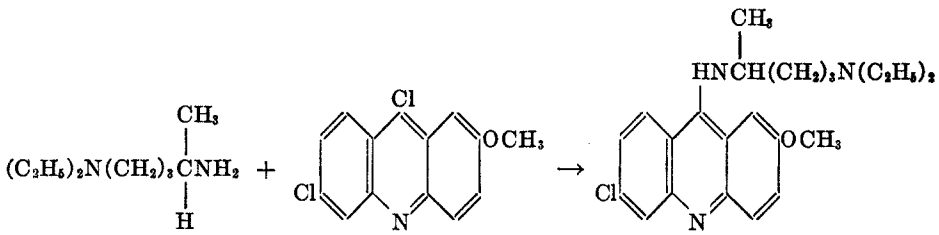
[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

THE CONVERSION OF QUATERNARY PYRROLIDINIUM SALTS TO OPEN-CHAIN DIAMINES

M. S. KHARASCH AND CHARLES F. FUCHS

Received April 3, 1944

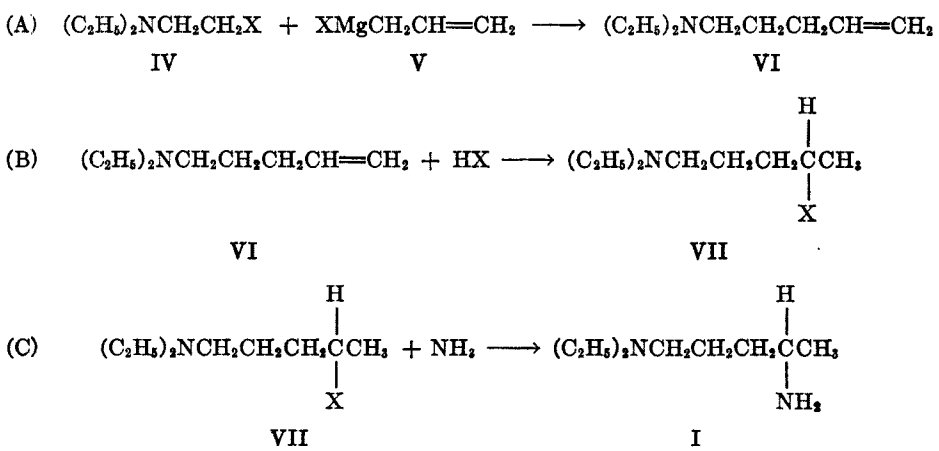
Atabrine (III), the most useful synthetic antimalarial now known, is formed by the reaction of 1-diethylamino-4-aminopentane (I) on 2-methoxy-6,9-dichloroacridine (II).



I II III

The reaction is a general one and many different primary-tertiary diamines may be used in place of (I). These, when coupled with (II), form compounds (hereafter referred to as atabro derivatives) analogous to (III) in structure but of varying antimalarial potency. The preparation of (II) and its condensation with a diamine analogous to (I) offer no great difficulties. The present methods for preparing diamines like (I) are, however, by no means satisfactory.

The work here described was, therefore, undertaken in the hope of improving the synthesis of (I) and related compounds. The reactions planned (A, B, and C) were the following, where X is any halogen atom.

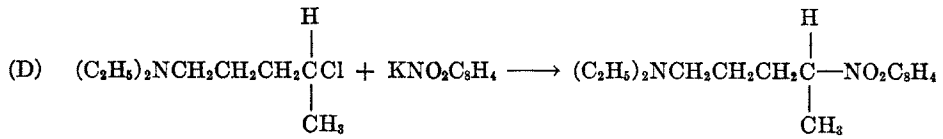


Since various halogenated tertiary amines might be used in place of (IV) and various substituted allyl Grignard reagents in place of (V), there was reason to

hope that the synthesis outlined might be developed into a fairly general method for preparing primary-tertiary diamines.

Reaction (A) proved easy to carry out. Contrary to literature reports, no difficulty was experienced in condensing β-chloroethyldiethylamine (IV) with allylmagnesium chloride (V), in spite of the low solubility of the latter compound in organic solvents. Reaction (B) also runs very smoothly. If a solution of (VI) in concentrated hydrochloric acid is saturated with hydrogen chloride, the addition reaction at room temperature is complete within 36 hours.

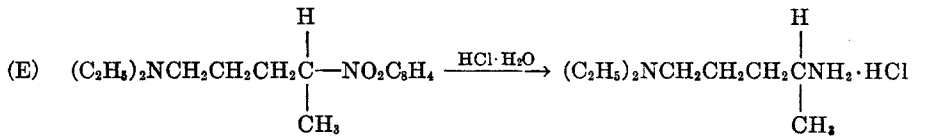
Reaction (C), on the other hand, proved quite difficult to handle. Liquid ammonia failed to give the desired result. Sodamide, acetamide, hexamethylenetetramine, and urea were equally ineffective. Success in replacing the chlorine atom by an amino group was finally obtained by taking recourse to the Gabriel synthesis. The chlorinated amine (VII) was treated with potassium phthalimide, the intention being to carry out the following reaction:



(D) $(C_2H_5)_2NCH_2CH_2CH_2\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C}}Cl + KNO_2C_8H_4 \longrightarrow (C_2H_5)_2NCH_2CH_2CH_2\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C}}—NO_2C_8H_4$

VII VIII

The anticipated product (VIII) should be the phthalimido derivative of (I). It was expected that when this compound was treated with concentrated hydrochloric acid, phthalic acid and the hydrochloride of (I) would be obtained.



(E) $(C_2H_5)_2NCH_2CH_2CH_2\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C}}—NO_2C_8H_4 \xrightarrow{HCl\cdot H_2O} (C_2H_5)_2NCH_2CH_2CH_2\overset{\overset{H}{|}}{\underset{\underset{CH_3}{|}}{C}}NH_2\cdot HCl$

VIII Hydrochloride of I

As a matter of fact, the phthalic acid residue was easily split off from the product of reaction (D). But when the free base was recovered from the amine hydrochloride thus obtained, it proved to be not a single compound, but a mixture of two components.

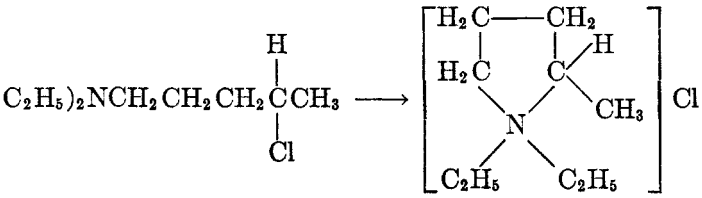
These two components (IX) and (X) were separated by distillation through a one hundred-plate column. Compound (IX), which formed about 10% of the mixture, was quickly identified (by its index of refraction and by the melting points of its picrate and atabro derivative) as (I). The analysis and titration value of (X) proved it to be a diamine isomeric with (I). But its index of refraction and the melting points of its picrate and atabro derivative showed conclusively that it was a distinct chemical compound.

It was, therefore, evident that at least one of the reactions (A, B, and D) had not proceeded in the manner indicated; reaction (E) seemed scarcely open to question. Various possibilities suggested themselves:

(a) In reaction (A), the coupling of (IV) and (V) might have been accompanied by a shift in the position of the double bond.
(b) In reaction (B), the addition of the halogen acid might not have proceeded as indicated; instead it might have taken place in the reverse direction.

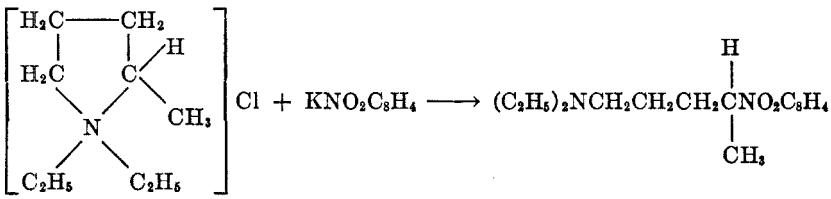
Careful investigation (see Experimental Part), however, showed that neither of these suppositions was correct. Both reaction (A) and reaction (B) were proved to have taken place in the manner indicated. The difficulty must, therefore, lie in reaction (D).

The following considerations support this latter hypothesis. Halogenated tertiary amines like (VII) are rather unstable compounds; they show a strong tendency to form cyclic quaternary ammonium salts. When (VII) undergoes such quaternization, the product is 1,1-diethyl-2-methylpyrrolidinium chloride

(F) 

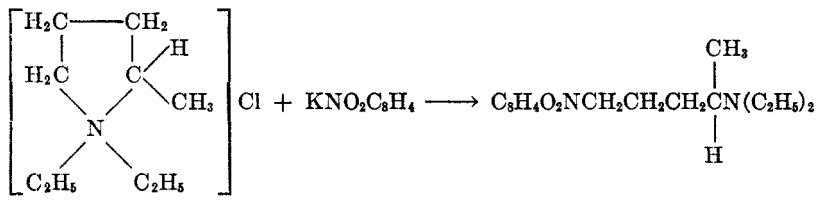
VII XI

(XI). Potassium phtnalimide might react in two distinct ways with (XI) to give an open-chain diamine. The splitting of the ring might take place either between the nitrogen atom and carbon atom 2 of the ring:

(G) 

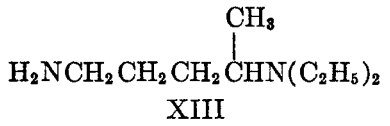
XI VIII

or between the nitrogen atom and carbon atom 5 of the ring:

(H) 

XI XII

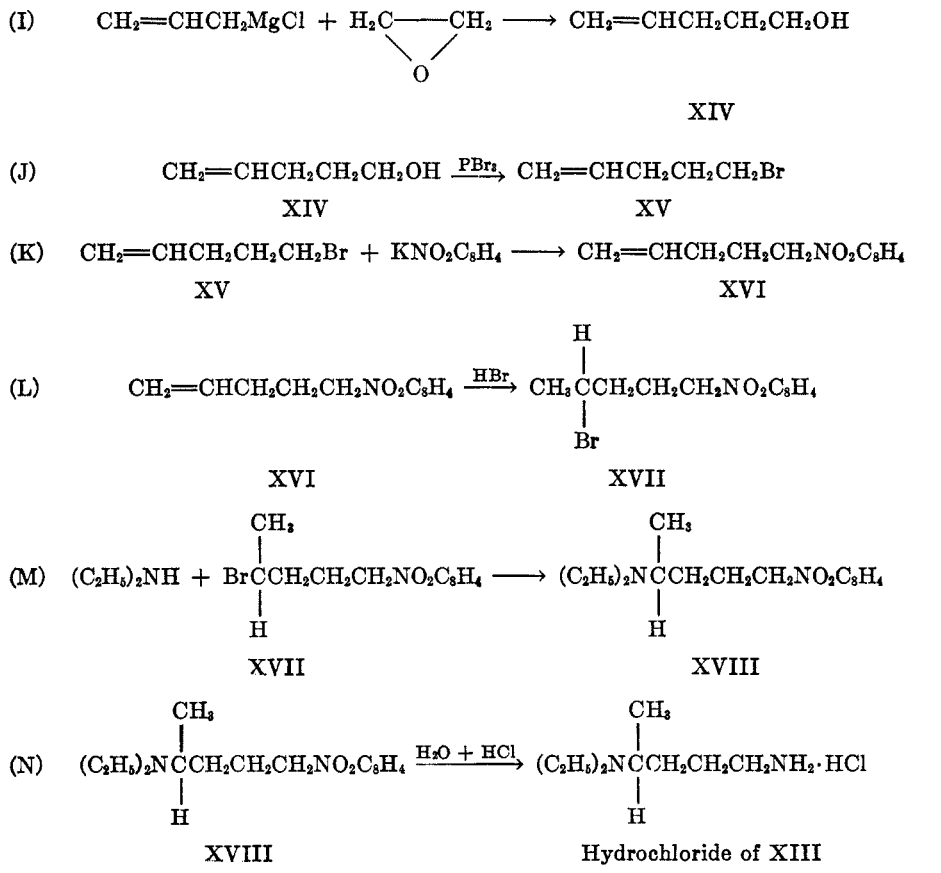
Compounds of the type (VIII) and (XII) are hereafter referred to as "phthalimido compounds." Hydrolysis of (VIII) would give (I). Hydrolysis of (XII), on the other hand, would give 1-amino-4-diethylaminopentane (XIII), isomeric with (I).



XIII

If the potassium phthalimide reacted on (XI) in both of the ways indicated, hydrolysis of the reaction product should give a mixture of (I) and (XIII). Since (VII) was treated with potassium phthalimide at a rather elevated temperature, it might well have been converted (at least to a considerable extent) into (XI) before the reaction with the phthalimide took place. Under these circumstances the product (X) [obtained along with the small amount of (I)] would in all probability have the structure given for (XIII). And such, indeed, proved to be the fact.

In order to establish the structure (XIII) for the product (X), it was necessary to synthesize (XIII) independently. This was done by the following series of reactions:



Of the intermediate compounds prepared in the above synthesis, (XIV) and (XV) were already known. The properties of the compounds obtained in re-

actions (I) and (J) agreed with those given in the literature. The analysis and unsaturation value of the product obtained in reaction (K) agreed accurately with those demanded by the formula (XVI). Compounds (XVII) and (XVIII) were identified by analysis only. The picrate of (XVIII) had the same melting point as one of the picrates isolated from the mixture obtained by treating with picric acid the mixture of "phthalimido compounds" obtained in the original synthesis. The final product (XIII) had the same boiling point and index of refraction as the product (X). Moreover, the picrates of compounds (X) and (XIII), as well as a mixture of the two all melted at 139–140°. Compounds (X) and (XIII) are, therefore, identical; and since the structure of (XIII) is established by its synthesis (reactions I–N), the structure of (X) is likewise determined. This structure lends strong support to the mechanism indicated in reactions (F), (G), and (H).

In order to check the conclusion thus reached, small amounts of (VII) were converted into quaternary salts. Both the quaternary chloride and the quaternary bromide were isolated in pure form and treated with potassium phthalimide. From the "phthalimido products," the free bases were isolated. The picrates of these clearly indicated that the free bases were mixtures. But the amount of material was too small to permit the isolation of any pure picrate save that of the major component. This proved to be (X) = (XIII) in both instances; but there is no reason to doubt that the minor component was (I), the same minor component isolated when large quantities of (VII) were treated with potassium phthalimide without preliminary isolation of the intermediate quaternary salt.

Chemically, the most interesting aspect of the work just recounted is the fact that it involves a novel method of preparing primary-tertiary diamines by the reaction of potassium phthalimide on quaternary pyrrolidinium salts. In order to determine the scope of the reaction, 1,1-diethylpyrrolidinium chloride, 2-methyl- and 2-phenyl-1,1-diethylpyrrolidinium halides and spiro(piperidine)-1,1-(2-methylpyrrolidinium) chloride, as well as quaternary halides derived from piperidine and pyridine, were treated with potassium phthalimide, sodium succinimide, sodium phenylacetylene and sodamide. The results obtained can be briefly summarized. Only quaternary pyrrolidinium compounds undergo ring-opening in the manner indicated in (G) and (H); the quaternary salts derived from pyridine or piperidine, when heated with potassium phthalimide, yield *N*-alkylphthalimide and (respectively) pyridine or *N*-alkylpiperidine. Only the alkali salts of phthalimide and succinimide open the pyrrolidine ring in such a way as to produce derivatives of diamines. Sodium phenylacetylene and sodamide open the ring to give unsaturated tertiary amines, a reaction similar to the Hofmann degradation. The low temperature (135°) at which these latter reactions occur may be of considerable importance for purposes of synthesis.

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EXPERIMENTAL

Preparation of allylmagnesium chloride. The preparation is carried out in an all-glass apparatus consisting of a three-liter, round-bottom, three-neck flask, an efficient stirrer, a reflux condenser and a dropping-funnel. The reflux condenser is connected through a drying tube to a water bubbler which permits the rate of formation of gaseous products to be observed. Magnesium turnings (80 g.) and dry ether (400 cc.) are placed in the flask, which is cooled in an ice-bath. The contents of the flask are vigorously stirred. Allyl chloride (230 g.) mixed with dry ether (400 cc.) is added through the dropping-funnel at a rate such that very little gas is evolved. Formation of the Grignard reagent begins soon, and is usually complete within 10 hours. The allyl Grignard reagent thus prepared is a white crystalline solid which forms a smooth suspension in the ether.

It has hitherto been generally believed (1) that a large excess of magnesium must be used to prepare allyl Grignard reagents, and that only allyl bromide yields a soluble reagent suitable for further reactions. Where allylmagnesium chloride has been employed (2), only a filtered and, therefore, very dilute solution of the compound has been used. Results here obtained indicate that Grignard compounds prepared from allyl and substituted allyl chlorides are indeed very slightly soluble in ethers or other solvents used in the preparation of Grignard reagents. But when such insoluble Grignard compounds react in suspension, the yields are better than when clear Grignard solutions of the corresponding bromides are used. Furthermore, these allyl and substituted allylmagnesium chlorides can be successfully prepared without the use of a large excess of magnesium.

Preparation of Unsaturated Amines (Reaction A)

Preparation of 1-diethylaminopentene-4. To the allylmagnesium chloride, formed as described, 1-diethylamino-2-chloroethane (330 g., 2.44 moles) is added at room temperature with continuous stirring. The addition through the dropping-funnel is conducted at such a rate that the heat of reaction keeps the ether gently boiling. (In case the reaction mixture becomes too thick to permit good stirring, dry ether may be added.) After the addition of the amine is complete, refluxing is continued for four hours. The flask is then cooled with ice, and, while the stirring is continued, carbon dioxide is blown over the surface of the reaction mixture to destroy most of the excess Grignard reagent. The pasty reaction product is then poured slowly onto ice (1 kg.) contained in a 5-liter flask. An excess of sodium hydroxide solution is then added, and the reaction product is removed from the alkaline mass by steam distillation. The 1-diethylaminopentene-4 is extracted with ether from the steam distillate. The ether extract is dried with anhydrous sodium sulfate or pellets of sodium hydroxide. After removal of the ether, the residue is distilled at reduced pressure. The yield is 85% of the amount calculated on the basis of the amine used. The same yield may be obtained if an ether solution of the allyl chloride and 1-diethylamino-2-chloroethane are mixed and introduced slowly into the flask containing magnesium covered with ether. If allylmagnesium bromide is used instead of allylmagnesium chloride, the yield of amine is considerably lower.

1-Diethylaminopentene-4 $(C_2H_5)_2N(CH_2)_3CH{=}CH_2$, is a colorless liquid, slightly soluble in water. Its boiling point is 156.4°/746 mm.; 81.6°/68 mm.; n_D^{20} 1.4310; d_{20}^{20} 0.8285. This unsaturated compound and the others that follow were analyzed for unsaturation by the bromate-bromide method. A 20% sulfuric acid solution was used as a solvent.

Anal. Calc'd for 0.2418 g. of $C_9H_{19}N$: Br, 0.2674 g. Found: Br, 0.2680 g.

The substance forms with ethyl iodide a quaternary salt which, after crystallization from acetone, melts at 147–148°.

The following tertiary amines have been prepared by the method described.

1-Diethylamino-4-methylpentene-4, $(C_2H_5)_2N(CH_2)_2C(CH_3){=}CH_2$, obtained in 75–80% yield from methylallylmagnesium chloride and 1-diethylamino-2-chloroethane; b.p. 83°/32 mm.; n_D^{20} 1.4377.

Anal. Calc'd for 0.2549 g. of $C_{10}H_{21}N$: Br, 0.2685 g. Found: Br, 0.2672 g.

1-Diethylaminohexene-5, $(C_2H_5)_2N(CH_2)_4CH{=}CH_2$, obtained in 75–80% yield from crotylmagnesium chloride and 1-diethylamino-2-chloroethane; b.p. 67–68°/31 mm.; n_D^{20} 1.4322.

Anal. Calc'd for 0.2695 g. of $C_{10}H_{21}N$: Br, 0.2774 g. Found: Br, 0.2753 g.

Tris(5-pentenyl) amine, $(CH_2{=}CHCH_2CH_2CH_2)_3N$, obtained in 90% yield from one mole of tris(2-chloroethyl)amine and three moles of allylmagnesium chloride; b.p. 90–91°/4 mm.; n_D^{20} 1.4618.

Anal. Calc'd for 0.1625 g. of $C_{15}H_{27}N$: Br, 0.3436 g. Found: Br, 0.3356 g.

1-Dimethylaminopentene-4, $(CH_3)_2N(CH_2)_3CH{=}CH_2$, obtained in 80% yield from allylmagnesium chloride and 1-dimethylamino-2-chloroethane (b.p. 118°/750 mm.; $n_D^{17.5}$ 1.4202). This base forms a methiodide which melts at 227–229°. Both the base and the methiodide had been previously prepared (3) by a process involving the Hofmann degradation of N-dimethylpiperidinium hydroxide.

1-Piperidinopentene-4, $C_5H_{10}N(CH_2)_3CH{=}CH_2$, obtained in 80% yield from 1-piperidino-2-chloroethane and allylmagnesium chloride; b.p. 94–95°/30 mm; n_D^{20} 1.4617. The hydrochloride and picrate of this unsaturated amine melt at 196° and 93–94°, respectively. v. Braun (4) prepared this compound by the Hofmann degradation of N-spirobispiperidinium hydroxide.

Addition of Halogen Acids to Unsaturated Amines (Reaction B)

Preparation of 1-diethylamino-4-chloropentane, $(C_2H_5)_2N(CH_2)_3\underset{\displaystyle Cl}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}CH_3$. 1-Diethylaminopentene-4 (152 g.) is slowly added to 250 cc. of cooled concentrated aqueous hydrochloric acid. The mixture is cooled with ice, saturated with hydrogen chloride, and allowed to stand for 12 hours. Then it is again cooled, resaturated with hydrogen chloride, and allowed to stand at least 12 hours longer. At this point, a sample is withdrawn in order to test the completeness of the saturation by bromate-bromide titration. If practically no bromine is absorbed, the reaction is regarded as complete. Otherwise, the mixture is again saturated with hydrogen chloride and allowed to stand for another twelve hours. When saturation is complete, the excess acid is neutralized with sodium carbonate, and the base liberated with concentrated sodium hydroxide. During these steps, the reaction mixture is kept cool by immersing the reaction vessel in ice water. The free base is purified by vacuum distillation; b.p. 64–67°/5 mm. The yield of this substance is 90% of the amount calculated.

The following compounds were prepared by the method just outlined:

1-Diethylamino-4-methyl-4-chloropentane, $(C_2H_5)_2N(CH_2)_3\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_3$, obtained in 75% yield from 1-diethylamino-4-methylpentene-4; b.p. 64–65°/3 mm.; n_D^{20} 1.4459.

1-Piperidino-4-chloropentane, $C_5H_{10}N(CH_2)_3\underset{\displaystyle Cl}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}CH_3$, obtained in 90% yield from 1-piperidinopentene-4; b.p. 88–92°/4 mm.

Preparation of Quaternary Pyrrolidinium Salts (Reaction F)

Preparation of the 1,1-diethyl-2-methylpyrrolidinium chloride. 1,1-Diethyl-2-methylpyrrolidinium chloride is easily prepared by heating a xylene solution of 1-diethylamino-

4-chloropentane to 140–150°. The quaternary salt precipitates as a white crystalline solid. The reaction is complete in 2–4 hours. The salt can be purified by collecting it on a filter, and washing it with dry ether. Such purification is unnecessary if the substance is to be used for the preparation of the phthalimido derivatives of primary-tertiary diamines.

The bromide of this base has also been prepared by addition of gaseous hydrogen bromide to 1-diethylaminopentene-5 and quaternization of the bromo derivative in ether solution.

The following compounds have also been prepared by the method just described:

Spiro(piperidine)-1,1-(2-methylpyrrolidinium) chloride. The bromide corresponding to this compound was prepared by v. Braun (5).

1,1-Diethyl-2-phenylpyrrolidinium chloride is prepared from 1-diethylamino-4-chloro-4-phenylbutane, which is obtained as follows. 1-Diethylamino-4-hydroxy-4-phenylbutane is prepared by the method of Marxer (6). A chlorine atom is introduced in the place of the hydroxyl group by heating the hydroxy compound with concentrated hydrochloric acid. The free base derived from the chloro compound thus formed is not purified but is merely dried *in vacuo* and quaternized by heating in xylene solution. It can be crystallized from acetone (m.p. 139–140°).

1,1-Diethylpyrrolidinium chloride was prepared from pyrrolidine by standard methods.

Reaction of Quaternary Pyrrolidinium Halides with Potassium Phthalimide (Reactions G and H)

1,1-Diethylpyrrolidinium chloride. 1,1-Diethylpyrrolidinium chloride (8 g.) is mixed with potassium phthalimide (10 g.) and 35 cc. of dry xylene. The mixture is stirred and heated to 155° (bath temp.) for 10 hours. The "phthalimido compound" (9 g., 64% yield) is obtained as a light yellow oil; b.p. 162–163°/0.3 mm.; n_D^{20} 1.5339.

Anal. Calc'd for $C_{16}H_{22}N_2O_2$: N, 10.46. Found: N, 10.35.

Its picrate melts at 121–122.5°.

Upon hydrolysis of this "phthalimido compound", a diamine hydrochloride is obtained. The picrate of this compound melts at 158–159°. The same melting point is reported (7) for the picrate of 1-diethylamino-4-aminobutane.

1,1-Diethyl-2-phenylpyrrolidinium chloride. 1,1-Diethyl-2-phenylpyrrolidinium chloride (4.2 g.) is mixed with potassium phthalimide (5 g.) and dry xylene (20 cc.). The reaction is carried out as previously described. The crude "phthalimido compound" is a clear, orange-yellow oil (yield 90%). This "phthalimido compound" when hydrolyzed with hydrochloric acid, gives phthalic acid and a diamine. The melting point of the picrate of this diamine is 185–186°.

1,1-Diethyl-2-methylpyrrolidinium chloride. In the following experiment the pyrrolidinium halide is formed *in situ*. 1-Diethylamino-4-chloropentane (171 g.) is mixed with 250 cc. of dry xylene in an all-glass, three-neck, one-liter flask provided with a stirrer and a reflux condenser. Dry potassium phthalimide (190 g.) is added, and the mixture is continuously stirred and gradually heated in an oil-bath to 130–140°. After a short time, a fairly violent reaction takes place which is merely the quaternization whereby 1,1-diethyl-2-methylpyrrolidinium chloride is formed from the free base. The bath temperature is then raised to 150–160° and the stirring is continued for 10–12 hours. At the end of this time, the reaction mixture consists of an orange-yellow liquid and a small amountof crystalline solid (potassium chloride). To the cooled mixture, water (200 cc.) and 2 *N* sodium hydroxide solution (50 cc.) are added to dissolve the potassium chloride and any phthalimide or phthalic acid which may be present; the whole mixture is then extracted three times with ether. The combined ether extracts are dried over anhydrous sodium sulfate. After the ether has been distilled from the extract, the xylene is distilled from the residue under reduced pressure. The xylene distillate contains a mixture of unsaturated tertiary amines which can be extracted from the xylene with dilute hydrochloric acid. This mixture of amines is mostly 1-diethylaminopentene-4 (identified by its ethiodide). The total amount of unsaturated amines recovered is about 10–15% of the 1-diethylamino-4-chloropentane used. A mixture of two "phthalimido compounds" remains after the xylene fraction is

removed. This mixture is a yellow oil which can be distilled below 1 mm. without decomposition. The yield of the two compounds is 80–85%.

The "phthalimido compounds" are soluble in dilute mineral acids, and can be recovered by treating the cold acid solution with alkali. If they are dissolved in dry ether and treated with dry hydrogen chloride, a mixture of crystalline hydrochlorides precipitates (m.p. 170–172°). Titration of these hydrochlorides with silver nitrate solution gives the correct value for $C_{17}H_{25}ClN_2O_2$.

Hydrolysis of the "Phthalimido Compounds" (Reaction E)

The "phthalimido compounds" (414 g.) prepared according to the method just described (Reaction D), are dissolved in 800 cc. of cooled concentrated hydrochloric acid. The clear solution is refluxed for 8 hours and cooled. The phthalic acid which precipitates is removed by filtration, and the filtrate is again refluxed for 8 hours. The additional phthalic acid which precipitates when the mixture is cooled is removed by filtration. The filtrate is concentrated *in vacuo* to remove the excess of hydrochloric acid and water. The viscous, semi-liquid residue is cooled, and the free bases are liberated by adding 40% sodium hydroxide solution and enough sodium hydroxide pellets to form a semi-solid mass. The diamines are extracted by stirring this mass with ether and decanting the supernatant ether extract. This procedure is repeated about 8 times. The combined ether extracts are dried over sodium hydroxide pellets, and the ether is removed by distillation. The remaining diamines are fractionated through a 100-plate column. Two fractions (a) and (b) are obtained. *Fraction (a)*: b.p. 101°/37 mm.; n_D^{20} 1.4435; 10% of the distillate.

Anal. Calc'd for $C_9H_{22}N_2$: N, 17.72. Found: N, 17.70.

The picrate of this substance melts at 134–136°. The melting point of a mixture of this picrate, with a picrate prepared from known 1-diethylamino-4-aminopentane showed no depression. Condensation of this diamine fraction with 2-methoxy-6,9-dichloroacridine gives a compound, the dihydrochloride of which melts at 244–245°‖ (decomp.); the melting point of a mixture of this substance with atabrine dihydrochloride (m.p. 244–245°) shows no depression.

Fraction (b): b.p. 104°/37 mm.; n_D^{20} 1.4475; 90% of the distillate.

Anal. Calc'd for $C_9H_{22}N_2$: N, 17.72. Found: N, 17.83.

The picrate of this compound melts at 139–140°. A mixture of the picrates of fractions (a) and (b) melts at 105–115°. The picrate of fraction (b) (m.p. 139–140°) and the picrate of 1-amino-4-diethylaminopentane (139–140°) (the synthesis of which is described later) give no melting point depression. Condensation of the fraction (b) with 2-methoxy-6,9-dichloroacridine gives a compound, the dihydrochloride of which crystallizes in fine yellow needles (m.p. 229° dec.) from a mixture of three parts acetone and one part alcohol. The sample analyzed was dried *in vacuo* at 60°. For the determination of the water the sample was dried *in vacuo* to constant weight at 105°.

Anal. Calc'd for $C_{23}H_{33}ClO \cdot 2HCl \cdot H_2O$: N, 8.56; H_2O, 3.67.
Found: N, 8.46; H_2O, 3.62.

Spiro(piperidine)-1,1-(2-methylpyrrolidinium) chloride. In the following experiment, the quaternary halide is formed *in situ*. 1-Piperidino-4-chloropentane (145 g.) is treated in the manner just described in dry xylene (200 cc.) and potassium phthalimide (140 g.). The crude "phthalimido compounds" (80% yield) are a clear, light orange oil. These "phthalimido compounds" are hydrolyzed with concentrated hydrochloric acid, and the free diamines isolated in the manner described. The diamines are distilled through a 20 cm. Vigreux column.

Fraction (a) b.p. 55–85°/6 mm.; about 10% of the total distillate.

Fraction (b) b.p. 87–89°/6 mm.; n_D^{20} 1.4763; about 85% of the total distillate. The picrate prepared from fraction (b), when crystallized from methanol, melts at 146.5–148°. The melting point of a mixture of this picrate with a picrate prepared from 1-amino-4-piperidinopentane (the synthesis of which is described later) shows no depression. Condensation of

the 1-amino-4-piperidinopentane thus obtained with 2-methoxy-6,9-dichloroacridine gives an "atabro" compound the dihydrochloride of which, upon crystallization from a mixture of acetone and alcohol, melts at 245° (dec.).

The syntheses hitherto described were carried out with 1-dialkylamino-4-chloropentanes as starting materials. Parallel reactions in which the starting materials were the pure quaternary pyrrolidinium chlorides or bromides (prepared by heating the 1-dialkylamino-4-halopentanes) have also been carried out. Every "phthalimido compound" or diamine thus obtained was identical with its analog obtained as already described (identity of physical constants and the melting points of the picrates and the atabro derivatives). The yields of the reaction products were at least as good as those already reported.

Reaction between 1,1-Diethyl-3-Methylpyrrolidinium Chloride and Sodium Succinimide

1,1-Diethyl-2-methylpyrrolidinium chloride (10 g.) was mixed with freshly prepared sodium succinimide (8.2 g.) and dry xylene (30 cc.). The mixture was heated to 150° (bath temp.) for 12 hours, continuously stirred, and then worked up in the manner previously described. The 5.5 g. of basic substances obtained were distilled below 70° at 100 mm. The distillate (2.5 g.) was identified by its index of refraction and the melting point of its ethiodide; it was mainly 1-diethylaminopentene-4. The non-volatile residue (2.5 g.) proved to be mainly 1-diethylamino-5 succinimidopentane. Hydrolysis of this "succinimido compound" gave succinic acid (1.1 g.; m.p. 185°) and the hydrochloride of the diamine. The melting point of the crude picrate prepared from the diamine was 132–135°. The compound, when recrystallized from alcohol, melted at 138–139°. The melting point of a mixture of this picrate with the picrate of 2-diethylamino-5-aminopentane showed no depression. There was no evidence to indicate the presence of a cyclic tertiary amine among the reaction products. Although the yield of "succinimido compounds" obtained in the above experiment is smaller than those obtained where potassium phthalimide was used, the courses of the two reactions are probably similar.

Reaction between 1,1-Diethyl-2-Methylpyrrolidinium Chloride and Sodamide

Freshly prepared sodamide (3 g.) was mixed with dry xylene (25 cc.) and 1,1-diethyl-2-methylpyrrolidinium chloride (25 cc.). The mixture was stirred, gradually heated to 150–155°, and kept at that temperature for 12 hours. The formation of a volatile base (probably methylamine) was observed during this period. Dry ether was added to the cooled mixture. The solid material (4.3 g.) was removed by filtration, and washed with dry ether. The basic substances were extracted from the clear, colorless filtrate with cold dilute hydrochloric acid. The bases were liberated from the acid solution with concentrated sodium hydroxide, and then extracted with ether. The ether extract was dried and the ether distilled off. The liquid residue was fractionated through a small Vigreux column.

Fraction (a) b.p. 63°/32 mm.; n_D^{20} 1.4307; (1.5 g.).

Fraction (b) b.p. 65–66°/32 mm.; n_D^{20} 1.4311; (3.7 g.).

Fraction (b) was identified as 1-diethylaminopentene-4; fraction (a) was identified as an unsaturated tertiary amine. It is probably 2-diethylaminopentene-4. No primary amines could be detected. The total yield of unsaturated tertiary amines was 82%.

Reaction between 1,1-Diethylpiperidinium Chloride and Sodamide

1,1-Diethylpiperidinium chloride (4.6 g.) was mixed with freshly prepared sodamide (2.6 g.) and dry xylene (20 cc.). The mixture was placed in a bath and heated first to 130° for 12 hours and then to 155° for 7 hours. During all this time it was continuously stirred. A volatile base was formed. The reaction mixture was worked up in a manner similar to that previously described. The extract contained only one detectable basic compound, 1-ethylpiperidine (2 g.). This compound was identified by its boiling point and the melting point of its picrate (168–168.5°). The melting point of a mixture of this picrate with pure 1-ethylpiperidine picrate showed no depression. No unsaturated tertiary amine and no primary amine could be detected.

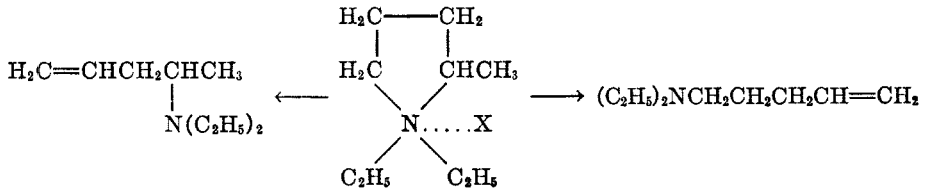
Reaction between 1,1-Diethyl-2-methylpyrrolidinium Chloride and Sodium Phenylacetylene

1,1-Diethyl-2-methylpyrrolidinium chloride (7.8 g.) was mixed with sodium phenylacetylene (6 g.) and dry xylene (25 cc.). The mixture was stirred and heated for 12 hours to 135° (bath temp.). The free bases were isolated in the manner previously described. Yield 90%.

Fraction (a) b.p. 143–151°/745 mm.; n_D^{20} 1.4313; (1.2 g.).

Fraction (b) b.p. 155–156°/745 mm.; n_D^{20} 1.4312; (4.2 g.).

The ethiodide prepared from fraction (b) melted at 146–147°. The melting point of a mixture of this ethiodide with the ethiodide prepared from 1-diethylaminopentene-4 showed no depression. The ethiodide prepared from fraction (a) melted at 160–162°. The structure of the unsaturated tertiary amine comprising fraction (a) was not established. This amine is probably an isomer of the one in fraction (b) since the pyrrolidine ring may be opened up in two ways.



Fraction (a) Fraction (b)

Reaction between 1,1-Dimethylpiperidinium Chloride and Sodium Phenylacetylene

1,1-Dimethylpiperidinium chloride (11.5 g.) was added to a mixture of freshly prepared sodium phenylacetylene (8.5 g.) and dry xylene (25 cc.). The mixture was stirred and heated to 150–160° (bath temperature) for 36 hours. The free bases were isolated in the usual manner. 1-Methylpiperidine (2 g., 25% yield) was identified by its picrate (m.p. 148–150°). The melting point of a mixture of this picrate with the picrate of pure 1-methylpiperidine (149–151°) showed no depression. No unsaturated base could be detected.

Reaction between 1,1-Dimethylpiperidinium Chloride and Potassium Phthalimide

1,1-Dimethylpiperidinium chloride (10 g.) was mixed with potassium phthalimide (14 g.) and dry xylene (35 cc.). The mixture was stirred and heated for 40 hours to 145° (bath temp.). The cooled reaction product was mixed with water (150 cc.) and 2 *N* sodium hydroxide solution (20 cc.); it was then extracted three times with benzene. The alkaline aqueous residue was acidified with 10% hydrochloric acid. The acidified mixture was at first clear; after being heated to 50–60° for two hours, it deposited phthalic acid (7 g.). This behavior indicated that, in the reaction, the phthalimide was probably converted to a phthalamic acid. No higher-boiling basic substance could be found in the aqueous mother liquor. The benzene-xylene extract was extracted with dilute hydrochloric acid. From this acid extract, the basic substances were liberated with cold 40% sodium hydroxide solution. 1-Methylpiperidine, the base thus obtained (yield 2.0 g.), was identified by its index of refraction (n_D^{20} 1.4378) and the melting point of its picrate (149–151°). The melting point of a mixture of this picrate with the picrate of 1-methylpiperidine (149–151°) showed no depression. N-Methylphthalimide (4 g.) was isolated from the benzene-xylene solution. It was identified by its melting point (136–137°); the melting point of a mixture with pure N-methylphthalimide showed no depression.

Reaction between Spiro-N-dipiperidyl Bromide and Potassium Phthalimide

Spirodipiperidyl bromide (16.5 g.) and potassium phthalimide (7.5 g.) were mixed with dry xylene (40 cc.). The mixture was stirred and heated to 155–165° (bath temp.) for 20 hours. A test made at this point on a small portion of the reaction mixture showed that no unsaturated compound had been formed. Consequently, the solvent was distilled off

and the residue was heated for 6 hours at 210°. Xylene (35 cc.) was again added, and the mixture heated 24 hours longer at 160–170°. After the mixture had been cooled, the solid crystalline material was removed by filtration and washed with dry ether. The yield of solid material was 15.5 g. It was identified as spiro-N-dipiperidyl bromide. This experiment indicates that quaternary nitrogen spirans with two six-membered rings, do not react with potassium phthalimide under the conditions used.

Reaction between 1-Methylpyridinium Chloride and Potassium Phthalimide

Dry 1-methylpyridinium chloride (12.5 g.) was mixed with 19 g. of potassium phthalimide and 30 cc. of dry xylene. The mixture was stirred and heated to 80–90° (bath temp.) for 8 hours. It turned brownish, even in the absence of air. For this reason, the reaction temperature was not raised above the point indicated. The mixture was worked up by a procedure similar to the one previously described. The only products identified were: N-methylphthalimide (3 g.) and pyridine (2 g.). The former was identified by its melting point, the latter by the melting point of its picrate.

Syntheses of Substances Mentioned in Reactions (I, J, K, L, M, and N)

Preparation of Pentene-1-ol-5 (XIV). The preparation is carried out in an all-glass apparatus, consisting of a three-liter, round-bottom, three-neck flask, an efficient stirrer, and a reflux condenser adapted for the use of dry ice and alcohol as a cooling agent. Two moles of allyl chloride are used to prepare allylmagnesium chloride in the manner previously described. An excess of dry ethylene oxide is then added at room temperature to the Grignard reagent. This addition, which is carried out with continuous stirring, is conducted at such a rate that almost no condensation of ethylene oxide in the reflux condenser is noticeable. After the addition is complete, the mixture is stirred at room temperature for 4 hours and then left to stand for 12 hours. It is then refluxed and stirred for two hours, cooled, and the reaction product decomposed by pouring it slowly onto ice (1 kg.). Acetic acid (20% sol.) is added until all the magnesium salts are dissolved. The mixture is then extracted four times with ether; the combined ether extracts are dried over anhydrous sodium sulfate. After removal of the ether by distillation, the residue is fractionated through a 100-plate column; b.p. 76.4°/60 mm.; n_D^{20} 1.4299. The yield is 60%, calculated on the basis of the allyl chloride used.

Pentene-1-ol-5 had been previously prepared in poor yield (14–22%) by other methods (8, 9). The method here described is not restricted to the preparation of pentene-1-ol-5, but is useful in the preparation of homologous unsaturated alcohols from substituted allyl halides and various epoxides.

Preparation of 5-Bromopentene-1 (XV). 5-Bromopentene-1 (9) is prepared by treating pentene-1-ol-5 with phosphorus tribromide in the presence of pyridine (b.p. 125–126°/760 mm.; n_D^{20} 1.4632).

Preparation of 5-phthalimidopentene-1 (XVI). The preparation is carried out in an all-glass, three-neck, round-bottom, 500-cc. flask provided with a stirrer and a reflux condenser. Potassium phthalimide (106 g.) is mixed with dry xylene (150 cc.) and 5-bromopentene-1 (82 g.). The mixture is stirred and gradually heated in an oil-bath to 150° (bath temp.). Heating and stirring are continued for 6 hours, during which period the bath temperature is raised to 160°. The reaction product is cooled and mixed with water (250 cc.) and 2 *N* sodium hydroxide solution (50 cc.). The mixture is extracted three times with ether, and the ether extract dried over anhydrous sodium sulfate. The solvents (ether and xylene) are removed by distillation, first under atmospheric and then under partly reduced pressure. The residue is an orange colored oil which distills at 155–157°/2 mm. The distilled phthalimido-5-pentene-1 forms colorless crystals. After being recrystallized from cold, low-boiling ligroin, it melts at 40°; the yield is 90%.

Anal. Calc'd for $C_{13}H_{13}NO_2$: N, 6.51. Found: N, 6.20.

Preparation of 2-bromo-5-phthalimidopentane (XVII). 5-Phthalimidopentene-1 (20 g.)

is placed in a bomb tube with dry hydrogen bromide (20 g.). The sealed tube is heated for 2 hours to 40° and allowed to stand at room temperature for 40 hours. The reaction product is extracted with ether. The ether extract is washed with cold sodium bicarbonate solution and with water; it is then dried with anhydrous sodium sulfate. The solvent is removed by distillation, and the reaction product is heated to 60–70° at 2 mm. for 4 hours to remove any volatile material. The 2-bromo-5-phthalimidopentane thus obtained is a light yellow oil. The yield is 98%. The compound crystallizes when cooled in a dry ice-alcohol mixture. It was analyzed by hydrolysis with 8% alcoholic sodium ethoxide and titration of the bromide ion thus formed.

Anal. Calc'd for $C_{13}H_{14}BrNO_2$: Br, 27.0. Found: Br, 26.80.

Preparation of 2-diethylamino-5-phthalimidopentane (XVIII). 2-Bromo-5-phthalimidopentane (10 g.) and dry diethylamine (20 g.) are heated to 90–100° in a bomb tube for 12 hours. The excess of free diethylamine is removed by evacuating the bomb tube at room temperature. The residue is taken up with ice cold water and dilute hydrochloric acid. The mixture is then extracted with ether to remove neutral impurities. The aqueous solution is then made alkaline with sodium hydroxide solution, and basic substances are extracted with ether. The ether is removed from the dried extract by distillation, and the remaining light yellow oil is distilled *in vacuo*; b.p. 165–167°/0.2 mm.; n_D^{20} 1.5308.

Anal. Calc'd for $C_{17}H_{24}N_2O_2$: N, 9.72. Found: N, 9.51.

The yield of the 2-diethylamino-5-phthalimidopentane is 60%. It forms a crystalline picrate which melts at 137–138°.

Preparation of 2-diethylamino-5-aminopentane (XIII). 2-Diethylamino-5-phthalimidopentane (4 g.) is dissolved in concentrated hydrochloric acid (12 cc.). The clear solution is boiled under a reflux condenser for 10 hours. It is then cooled, and the phthalic acid (2.4 g.) which separates is removed. The filtrate is concentrated to dryness under reduced pressure. The residue is the crude dihydrochloride of 2-diethylamino-5-aminopentane. From this dihydrochloride, the free base is recovered by treatment with 50% sodium hydroxide solution and extraction with ether. The ether is removed from the extract by distillation, and the residue is distilled under reduced pressure; b.p. 103–104°/37 mm.; n_D^{20} 1.4478 (1.6 g.). The picrate of this base, when crystallized from alcohol, melts at 138–140°.

Preparation of 2-piperidino-5-phthalimidopentane. 2-Piperidino-5-phthalimidopentane (*cf.* the preparation of 2-diethylamino-5-phthalimidopentane) is prepared by treating 2-bromo-5-phthalimidopentane with piperidine. The "phthalimido compound" is sufficiently purified if it is heated at 100° and 2 mm. for four hours to remove all volatile impurities. It is a light orange colored oil. The yield is 65%.

2-Piperidino-5-aminopentane is prepared by hydrolysis of the "phthalimido compound" just described; b.p. 90–92°/7 mm.; n_D^{20} 1.4765. The picrate, when recrystallized from methanol, melts at 147–148.5°.

Preparation of 1-diethylamino-3-aminopentane. In the course of establishing the structure of the compound (XIII), obtained by the reaction between 1-diethylamino-4-chloropentane and potassium phthalimide, the possible formation of the diamine $(C_2H_5)_2NCH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CH_3$ was taken into account. This compound was prepared by the following series of reactions. Condensation of β-chloropropionyl chloride with zinc diethyl to give β-chlorodiethyl ketone; treatment of this latter compound with diethylamine to give the β-diethylaminodiethyl ketone; hydrogenation of the oxime of this ketone in the presence of platinum oxide to give 1-diethylamino-3-aminopentane (b.p. 104°/37 mm.; n_D^{20} 1.4430). The picrate of this diamine melts at 155.5–156.5°.

Fourneau (10) mentions a compound of the plasmoquine type which contains the above diamine as a side chain; but he gives no data for the preparation of the diamine. The plasmoquine compound was probably prepared in the usual way from an aminoquinoline and 1-diethylamino-3-chloropentane.

SUMMARY

1. A method for the conversion of quaternary pyrrolidinium compounds to primary-tertiary open-chain diamines has been developed.

2. Alkali phthalimides, when heated with quaternary pyrrolidinium compounds in xylene at 150–160°, rupture the ring and yield the corresponding N-dialkylamine-4-phthalimidopentanes.

3. Alkali succinimides react like the alkali phthalimides.

4. Sodium phenylacetylene and sodium amide with quaternary pyrrolidinium compounds, when heated at 135° in xylene, yield products usually formed in the Hofmann degradation.

5. Quaternary salts derived from pyridine and piperidine, when heated with potassium phthalimide at 150–165° in xylene, yield pyridine, or N-alkyl piperidine, respectively, and an alkylated phthalimide.

6. The Grignard reagents formed from allyl chloride, or substituted allyl chlorides, are more useful synthetic reagents than the Grignard reagents formed from the corresponding allyl bromides, the reagents recommended by other investigators.

7. The preparation and properties of a large number of new unsaturated tertiary amines and unsaturated alcohols are described.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ANTIMALARIAL STUDIES IN THE QUINOLINE SERIES

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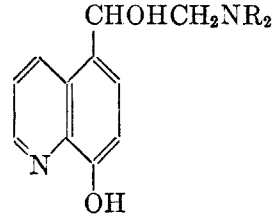
Quinine has often been regarded as a complex quinoline amino alcohol, and simpler compounds retaining these structural features have been synthesized in the search for new antimalarials. Amino alcohol groups —$CHOHCH_2NR_2$ were placed in positions 3 and 4 but not in the benzenoid ring of the quinoline system. Fränkel and Grauer (1) prepared an aminoacetyl-8-methoxyquinoline but did not reduce the carbonyl group.

We have now attempted to synthesize 1-(8-hydroxy-5-quinolyl)-2-dialkylaminoethanol derivatives (I) starting from 5-chloroacetyl-8-hydroxyquinoline.



I

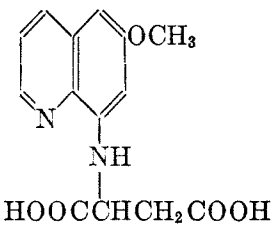
Matsumura (2), who first prepared this chloro ketone by chloroacetylation of 8-hydroxyquinoline, did not mention any difficulty in separating it from aluminum salts in acid solution, while Rosenmund and Karst (3) had to break up the insoluble aluminum complex salts of several 8-hydroxy-5-acyl quinolines by acetylation, separation of the aluminum acetate, and hydrolysis of the 8-acetoxy group. Our product from the Friedel and Crafts reaction consisted largely of aluminum complex salts of the desired chloro ketone, and had to be decomposed by digestion with hot concentrated hydrochloric acid.

5-Chloroacetyl-8-hydroxyquinoline reacted with secondary amines to yield the respective tertiary-amino ketones. Aluminum isopropoxide reduction of these compounds was not feasible because, again, insoluble complex salts precipitated out and were thus withheld from the reaction. Therefore, hydrogenation in the presence of Adams' catalyst was tried. Not all the amino ketones could be reduced under the conditions employed, but the morpholino ketone hydrochloride absorbed slowly 1.3 moles of hydrogen. The analytical values of the reduction product agreed closely with those calculated for 1-(8-hydroxy-5-quinolyl)-2-(4-morpholino)ethanol hydrochloride, but the figures for a Py-tetrahydroquinolyl morpholino ketone of corresponding structure lie within the limits of the experimental error of those found for our product, and a decision between these two structures has not been reached.

Another approach to antimalarials was based on the observation of Oesterlin (4) that succinic and fumaric acids and similar cell respiration factors increase

the activity of plasmoquine. Frisch and Bogert (5) prepared several succinamides, succinimides, and related substances substituted by methoxyquinoline groups in order to test the effect of connecting the two types of compounds.

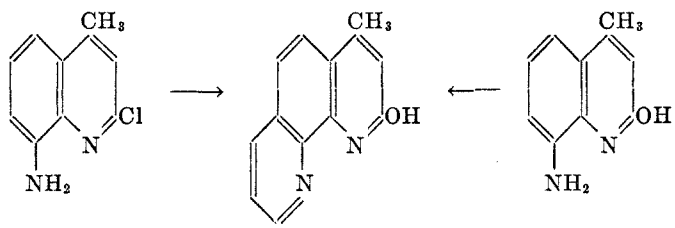
It appeared possible that the biological interaction of 8-aminoquinoline derivatives and succinic or fumaric acid could be due to the formation of an α-amino acid having the aminoquinoline system directly attached to the linkage participating in biological oxidations. We have therefore synthesized *dl*-N-(6-methoxy-8-quinolyl)aspartic acid (II). Diethyl bromosuccinate and 6-methoxy-



II

8-aminoquinoline were condensed under mild conditions, the resulting ester was hydrolyzed, and the dicarboxylic acid isolated as its hydrochloride in 32% yield.

Basic derivatives of various tricyclic systems containing the quinoline nucleus as part of their ring structure have been tested successfully as antimalarials. We had available 2-chloro- (III) and 2-hydroxy-4-methyl-8-aminoquinoline (IV) (6) and have used these materials now in the synthesis of suitably substituted 1,10-phenanthrolines. The Skraup reaction with IV yielded 2-hydroxy-4-methyl-1,10-phenanthroline (V) which was also formed from III by the same



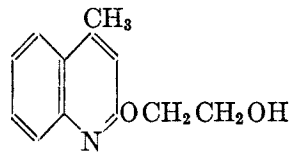
III V IV

reaction accompanied by hydrolysis of the reactive halogen atom. 2-Chloro-4-methyl-1,10-phenanthroline, obtained by treating V with phosphorus chlorides, reacted with 4-(2-aminoethyl)morpholine to give 2-[4-(2-aminoethyl)morpholino]-4-methyl-1,10-phenanthroline.

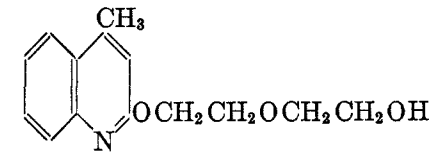
In order to study the effect of further nuclear substitution on the antimalarial activity of such dialkylaminoalkylamino phenanthrolines, the nitration of V was investigated. Under conditions comparable to those used with 2-hydroxylepidine (7) a dinitro derivative was formed. A comparison with the orientation in the analogous 2-hydroxylepidine series (8), and the non-availability of the favored 8- position of the lepidone portion of the molecule, indicate that one nitro group must have entered position 3, and the other one position 6 of the 1,10-phenanthroline system.

Since direct nitration did not stop at a mononitro-2-hydroxy-4-methyl-1,10-phenanthroline, we attempted to synthesize such a compound by another route. 5-Nitro-8-aminoquinoline, prepared from 5-nitro-8-hydroxyquinoline (9) with ammonia under pressure, was converted to 5-nitro-8-acetoacetaminoquinoline. Ring closure of this compound to 2-hydroxy-4-methyl-6-nitro-1,10-phenanthroline could not be effected under a variety of conditions, including heating with sulfuric acid at 60° and 100°, in paraffin oil at 220°, with phosphorus pentoxide in paraffin oil at the same temperature, or in syrupy phosphoric acid, or with phosphorus pentoxide or pentachloride in boiling xylene. Analogous difficulties had been encountered by Balaban (10) in the ring closure with *p*-nitroacetoacetanilide, and by Utermohlen and Hamilton (11) in the Skraup synthesis with nitronaphthylamines.

Aside from dialkylaminoalkylamino derivatives, certain aromatic amidine ethers (12) and quinoline dialkylamino ethers (13) have shown protozoicidal action. As part of an investigation of such compounds we have synthesized the mono-2-lepidyl ethers of ethylene glycol (VI), and diethylene glycol (VII), with the hope of converting the terminal alcohol groups through the halides to amino groups.



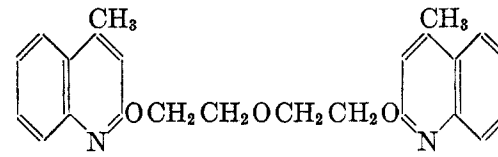
VI



VII

The ethers were prepared from 2-chlorolepidine and the respective monosodium glycolates. Numerous attempts to replace the primary alcohol group with halogen by the action of thionyl chloride or phosphorus halides under mild conditions, failed. These reagents only caused a scission of the heterocyclic ether linkage, splitting the compounds practically quantitatively to 2-hydroxylepidine.

Disodium diethylene glycolate and 2-chlorolepidine furnished the dilepidyl ether of diethylene glycol VIII, which could be nitrated to 2,2′-di-(4-methyl-6-



VIII

nitro-2-quinolinoxy)ethyl ether. Reduction with tin and hydrochloric acid produced the corresponding diamine.

Several of the compounds described have been found inactive in antimalarial tests carried out in the Lilly Research Laboratories. Details of these tests will be communicated elsewhere.

EXPERIMENTAL

5-Chloroacetyl-8-hydroxyquinoline. To a mixture of 87 g. of 8-hydroxyquinoline,[1] 600 cc. of *sym.*-tetrachloroethane and 150 cc. of nitrobenzene was added 72.4 g. of chloroacetyl chloride at 0°. Aluminum chloride (234.2 g.) was added in five to ten portions with good cooling and agitation. The mixture was then placed on a steam-bath and heated for about thirty hours until no more hydrogen chloride was evolved. After cooling to room temperature it was poured onto 300 g. of crushed ice and 200 cc. of 10% hydrochloric acid. The precipitated aluminum complex salts were filtered from the ice-cold solution, washed with 500 cc. of ether, and digested with 100 cc. of concentrated hydrochloric acid on a steam-bath for one-half hour. The crude chloro ketone hydrochloride was filtered with some difficulty, and recrystallized from 10 l. of boiling water. The insoluble black tar was re-digested with hot hydrochloric acid, yielding additional amounts of the hydrochloride, which were recrystallized from the aqueous mother liquors of the first batch. The total yield was 51%.

The free phenolic chloro ketone was obtained by stirring the hydrochloride with 800 cc. of 6% sodium acetate solution for thirty minutes. The yield was 60.6 g. (45.6% based on 8-hydroxyquinoline). Recrystallization from 2 l. of ethanol rendered 52 g. of colorless crystals, m.p. 157–158°.

Borsche and Groth (14) reported the melting point 159° for 8-methoxy-5-chloroacetylquinoline. We found that the methyl ether group of 8-methoxyquinoline is readily cleaved in Friedel and Crafts reactions, and it is not unlikely that these authors actually isolated the hydroxy ketone.

8-Hydroxy-5-piperidinoacetylquinoline. A solution of 11.9 g. of 8-hydroxy-5-chloroacetylquinoline in 800 cc. of ether was treated with 4.9 g. of piperidine, and the mixture allowed to stand for three weeks. The separated piperidine hydrochloride was filtered, and the filtrate neutralized with alcoholic hydrogen chloride. The salt mixture was recrystallized repeatedly from large amounts of ethanol, and the mono- and di-hydrochlorides of the piperidino ketone were isolated.

The *monohydrochloride* melted at 262° (decomp.).

Anal. Calc'd for $C_{16}H_{18}N_2O_2 \cdot HCl$: C, 62.63; H, 6.24.
Found: C, 62.36; H, 6.58.

The colorless crystals of the *dihydrochloride* melted at 246–249° (decomp.).

Anal. Calc'd for $C_{16}H_{18}N_2O_2 \cdot 2HCl$: N, 8.16. Found: N, 7.98.

8-Hydroxy-5-morpholinoacetylquinoline. Twelve and one-half grams of the chloro ketone was suspended in a solution of 10.3 g. of morpholine in 1200 cc. of ether and allowed to stand for four days with occasional shaking. The mixture was extracted with dilute hydrochloric acid, the acid solution made alkaline with sodium bicarbonate, and the deep red solution extracted exhaustively with ether. The residual yellow semi-solid from the ether extract was heated at 70° under reduced pressure in order to remove any unchanged morpholine, and converted to the hydrochloride in acetone-methanol solution. Four recrystallizations from methanol-acetone gave 2.5 g. of colorless crystals, m.p. 250° (decomp.).

Anal. Calc'd for $C_{15}H_{16}N_2O_3 \cdot HCl$: N, 9.07. Found: N, 9.11.

1-(8-Hydroxy-5-quinolyl)-2-(4-morpholino)ethanol. One-tenth gram of platinum oxide was added to a solution of 2.5 g. of 8-hydroxy-5-morpholinoacetylquinoline hydrochloride in 75 cc. of methanol, and hydrogenation carried to completion over a period of thirty-six hours. The morpholino alcohol hydrochloride was isolated in the customary manner and recrystallized from ethanol-ether. The colorless crystals melted at 274° (decomp.). The salt was readily soluble in water; the yield was 1 g.

Anal. Calc'd for $C_{15}H_{18}N_2O_3 \cdot HCl$: C, 57.96; H, 6.16.
Found: C, 57.89; H, 6.06.

dl-N-(6-Methoxy-8-quinolyl)aspartic acid (II). A solution of 5.2 g. of 6-methoxy-8-

[1]Kindly furnished by Mr. H. A. Shonle, The Lilly Research Laboratories, Indianapolis, Ind.

aminoquinoline and 9.0 g. of diethyl bromosuccinate in 20 cc. of absolute ether was allowed to stand at room temperature. A crystalline precipitate of 6-methoxy-8-aminoquinoline hydrobromide began to appear after one day and increased slowly on further standing. After three months, it was filtered and washed with ether. The filtrate was evaporated, and the oily residue refluxed with 100 cc. of a 3% ethanolic potassium hydroxide solution for thirty minutes. The mixture, which now contained a yellow precipitate, was evaporated under reduced pressure, the yellow solid digested with 150 cc. of boiling water, cooled, and unchanged 6-methoxy-8-aminoquinoline (2.5 g.) extracted into ether. The alkaline solution was acidified with concentrated hydrochloric acid and deposited slowly yellow crystals of *dl*-N-(6-methoxy-8-quinolyl)aspartic acid dihydrochloride. The yield was 3.5 g. (32%). The salt was recrystallized from ethanol-ether, m.p. 214–216° (decomp.).

Anal. Calc'd for $C_{14}H_{14}N_2O_5 \cdot 2HCl$: C, 46.29; H, 4.44; N, 7.71.
Found: C, 46.46; H, 4.18; N, 8.01.

2-Hydroxy-4-methyl-1,10-phenanthroline (V). A mixture of 4.2 g. of 2-hydroxy-4-methyl-8-aminoquinoline, 3.48 g. of arsenic acid, 6.6 g. of sulfuric acid, and 7.2 g. of glycerol was refluxed for three hours in a bath at 155–160°. After cooling, the liquid was poured into ice-water, neutralized with sodium hydroxide solution, and allowed to stand overnight. The resulting precipitate was filtered, dissolved in hot toluene, and the solution concentrated. The colorless crystalline product from this solution was purified by sublimation at 120° and 1 mm. It was soluble in hot sodium hydroxide solution and melted at 177–179°. The yield in several runs averaged 20 to 30%.

Anal. Calc'd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.80.
Found: C, 73.84; H, 5.01.

The same hydroxyphenanthroline was obtained by an analogous Skraup reaction with 2-chloro-4-methyl-8-aminoquinoline using the same relative amounts of reagents as above.

2-Chloro-4-methyl-1,10-phenanthroline. A mixture of 7 g. of 2-hydroxy-4-methyl-1,10-phenanthroline, 7 g. of phosphorus pentachloride and 56 cc. of phosphorus oxychloride was heated at 130° for five hours, decomposed with ice, the solution filtered, and made ammoniacal. The precipitate thus obtained was recrystallized from ethanol; the yellow needles melted at 210–212°. The yield was 5.3 g. (69%).

Anal. Calc'd for $C_{13}H_9ClN_2$: C, 68.27; H, 3.97; N, 12.25.
Found: C, 67.87; H, 4.29; N, 12.98.

2-[4-(2-Aminoethyl)morpholino]-4-methyl-1,10-phenanthroline. Ten grams of 2-chloro-4-methyl-1,10-phenanthroline and 20 cc. of 4-(2-aminoethyl)morpholine[2] was heated at 150° for four hours. After cooling, the liquid was extracted with dilute hydrochloric acid, the acid solution made ammoniacal, and the precipitated oil extracted into ether. Neutralization of the dried ether solution with alcoholic hydrogen chloride gave fine yellow needles of the dihydrochloride, m.p. 261–263°, yield 6.0 g. (35%).

Anal. Calc'd for $C_{19}H_{22}N_4O \cdot 2HCl$: C, 57.72; H, 6.12; N, 14.18.
Found: C, 56.91; H, 6.35; N, 14.20.

2-Hydroxy-4-methyl-(3,6 ?)-dinitro-1,10-phenanthroline. Six grams of 2-hydroxy-4-methyl-1,10-phenanthroline was stirred slowly into a mixture of 18 cc. of concentrated sulfuric acid and 18 cc. of nitric acid (d = 1.5) at 0°. After heating on a steam-bath for fifteen minutes, the solution was poured into cold water; the yellow dinitro product precipitated in quantitative yield. Sublimation of the dried material at 2 mm. and 150° furnished bright yellow needles, m.p. 255–260° (decomp.).

Anal. Calc'd for $C_{13}H_8N_4O_5$: C, 52.00; H, 2.67.
Found: C, 51.78; H, 3.13.

5-Nitro-8-aminoquinoline. A sealed tube containing 1 g. of 5-nitro-8-hydroxyquinoline (9), 1 cc. of ethanol, and 10 cc. of 20% ammonium hydroxide was heated at 180–190° for six hours. A quantitative yield of a red amorphous solid was obtained by filtration of the cooled reaction mixture. Recrystallization from benzene gave orange-red needles, m.p.

[2] Kindly supplied by Carbide and Carbon Chemicals Corporation.

195–196°. A mixture melting point with an authentic sample of 5-nitro-8-aminoquinoline showed no depression.

5-Nitro-8-acetoacetaminoquinoline. A mixture of 1 g. of 5-nitro-8-aminoquinoline and 1.0 g. of ethyl acetoacetate was boiled for ninety seconds. On cooling, an orange solid crystallized in a yield of 0.8 g. (55%). It was recrystallized from ethyl acetate and appeared as orange needles, m.p. 156–158°.

Anal. Calc'd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.02.
Found: C, 57.46; H, 4.38.

2,2'-Di-(4-methyl-2-quinolinoxy) ethyl ether (VIII). Seven grams of sodium was dissolved in 45 cc. of diethylene glycol with reflux, toluene being added as solution progressed in order to prevent oxidation of the sodium derivative. When all the sodium had gone into solution, 38 g. of 2-chlorolepidine in 50 cc. of toluene was added, the mixture refluxed for seven hours, and washed with water. The toluene was removed under reduced pressure, the solidified residue dissolved in alcoholic hydrogen chloride, and the salt precipitated with ether. It melted at 140–142°. It was dissolved in water, and the colorless solid base precipitated with sodium bicarbonate solution. Recrystallization from acetone yielded 30 g. (72%) of colorless crystals, m.p. 121°.

Anal. Calc'd for $C_{24}H_{24}N_2O_3$: C, 74.19; H, 6.23; N, 7.22.
Found: C, 74.02; H, 6.64; N, 7.11.

2,2'-Di-(4-methyl-6-nitro-2-quinolinoxy) ethyl ether. To an ice-cold solution prepared by dissolving 3.0 g. of 2,2'-di-(4-methyl-2-quinolinoxy) ethyl ether in 24 cc. of concentrated sulfuric acid, a mixture of 6 cc. of nitric acid ($d = 1.43$) and 6 cc. of concentrated sulfuric acid was added slowly. After standing at room temperature for two hours the mixture was poured into water. The dinitro ether precipitated out partly, the rest appeared when sodium carbonate was added to the solution. Recrystallization from β,β'-dichloroethyl ether furnished the pure product, m.p. 210.5°. The yield was 1.3 g. (37%).

Anal. Calc'd for $C_{24}H_{22}N_4O_7$: N, 11.72. Found: N, 11.30.

2,2'-Di-(4-methyl-6-amino-2-quinolinoxy)ethyl ether. A solution of 8 g. of the dinitro ether just described and 80 g. of stannous chloride in 25 cc. of 18% hydrochloric acid was refluxed for two hours, poured into ice-water, and made alkaline with strong potassium hydroxide solution. The resulting precipitate was filtered, dissolved in dilute hydrochloric acid, and the tin ions were removed with hydrogen sulfide. The diamino ether, purified through the hydrochloride, and finally by recrystallization from dioxane-ether, melted at 214°.

Anal. Calc'd for $C_{24}H_{26}N_4O_3$: C, 68.87; H, 6.27.
Found: C, 68.67; H, 6.77.

2-(4-Methyl-2-quinolinoxy)-2'-hydroxyethyl ether (VII). To a solution of 10.5 g. of sodium in 75 cc. of boiling diethylene glycol a solution of 100 g. of 2-chlorolepidine in 100 cc. of toluene was added. The mixture immediately turned deep red. It was boiled under reflux for five hours, the separated sodium chloride dissolved in water, and the toluene removed by steam distillation. The residual oil was dissolved in alcohol, and this solution deposited 7.5 g. of the diether VIII on standing. The filtrate was concentrated, the oily residue extracted into ether, the ether solution dried over sodium sulfate, and the solvent distilled. The residue was fractionated under 5 mm. pressure. A clear viscous oil distilled at 202–205°. It was converted to the hydrochloride in alcohol solution, and the colorless salt recrystallized from alcohol-ether; m.p. 151.5–153.5°, yield, 73 g. (45%).

Anal. Calc'd for $C_{14}H_{17}NO_3 \cdot HCl$: C, 59.24; H, 6.40.
Found: C, 58.88; H, 6.49.

2-(2-Hydroxyethoxy)-4-methylquinoline (VI). One gram of sodium was dissolved in 8 cc. of hot ethylene glycol, and a solution of 5 g. of 2-chlorolepidine in 10 cc. of benzene was added. After refluxing for six hours, the precipitated sodium chloride was dissolved in water, and the benzene distilled. The residual clear mobile oil was converted to the hydrochloride in alcohol-ether solution. The colorless salt melted at 167°.

Anal. Calc'd for $C_{12}H_{13}NO_2 \cdot HCl$: N, 5.85. Found: N, 5.71.

SUMMARY

1. The preparation of two 8-hydroxyquinoline-5-α-tertiary-amino ketones, and the reduction of one of them to the corresponding amino alcohol has been described.

2. *dl*-N-(6-Methoxy-8-quinolyl)aspartic acid has been synthesized.

3. 2-Hydroxy-4-methyl-1,10-phenanthroline has been prepared, and converted to a dinitro derivative, as well as to 2-[4-(2-aminoethyl)morpholino]-4-methyl-1,10-phenanthroline.

4. Some mono- and di-2-lepidyl ethers of ethylene glycol and diethylene glycol, and some derivatives of the latter have been studied.

CHARLOTTESVILLE, VA.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

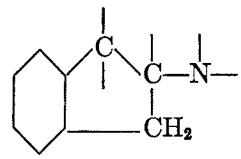
PHYSIOLOGICALLY ACTIVE INDANAMINES[1]

NATHAN LEVIN*, BOYD E. GRAHAM, AND H. G. KOLLOFF

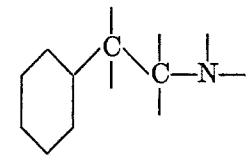
Received April 17, 1944

INTRODUCTION

In connection with the studies in these Laboratories on physiologically active amines chemically related to ephedrine, it appeared of interest to include an investigation of a series of indanamines of the general formula (I):

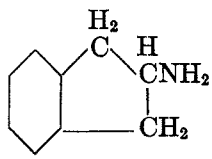


I

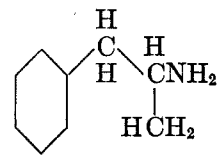


II

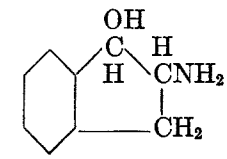
Structurally, these indanamines form an interesting group of compounds; they are characterized by the presence of the phenethylamine skeleton (II) and, further, they may be looked upon as indane analogs of the well-known phenylisopropylamines. Thus, 2-aminoindane (III) is the indane analog corresponding to amphetamine (IV); an analogous structural relationship is found with 2-amino-1-indanol ("indanolamine") (V) and propadrine (phenylpropanolamine) (VI):



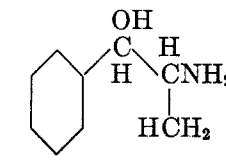
III



IV



V



VI

The effect of N-alkylation on pressor activity of primary amines structurally related to phenethylamine is well known (1); however, studies of the effects produced by such structural modifications on other physiological functions, such as bronchodilator activity, are incomplete. In view of the number of N-substituted phenylalkylamine derivatives which have been described as active bronchodilators in recent patents (2, 3), and the structural analogy of the phenylisopropylamines and the corresponding indane analogs, it was desirable to prepare a group of N-alkyl and N-aralkyl-2-aminoindanes and 2-amino-1-indanols for pharmacological study.

2-Aminoindane has been previously prepared (4–7) and studied pharmacologically (4, 8) but there is no mention in the literature of N-substituted derivatives. In order to make available for pharamacological study a group of N-substituted

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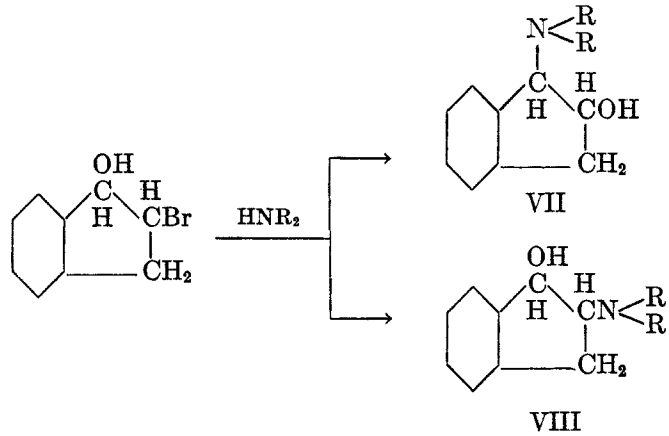
2-aminoindanes, a search was first made for a satisfactory method of making the primary amine. The chief objection to the use of 2-indanone oxime as an intermediate is the lack of a suitable method of reduction. Thus, Benedickt (6) reduced the oxime with sodium amalgam in acetic acid but reported only traces of 2-aminoindane. Hückel and his associates (7) carried out the reduction using sodium and alcohol and obtained a mixture of isomeric amines. Catalytic reduction, using platinum black catalyst, gave the secondary amine, diindanylamine, only (7). Using platinum oxide catalyst, the primary amine was formed, but from 45 g. of oxime only 20 g. (about 30%) of 2-aminoindane hydrochloride was obtained; the reaction proceeded very slowly, two days being required to reduce 5 g. of oxime (7). In the present investigation, a study was made of the Hartung method of catalytic reduction with the anticipation that 2-aminoindane might be obtained pure and in good yields. Using palladinized Norit catalyst in absolute ethanol containing anhydrous hydrogen chloride according to the general procedure (9–11), reduction failed to take place. However, when *active* palladium catalysts were used, hydrogen uptake occurred smoothly and reduction proceeded to completion; it was possible to reduce several portions of 0.03 mole of oxime within 8 to 10 hours at room temperature with the formation of 2-aminoindane hydrochloride in practically quantitative yields. *Active* palladium catalysts were prepared by shaking palladium chloride with Norit in 0.5 *N* or 1.0 *N* aqueous sodium acetate solutions instead of distilled water as previously employed (9). These catalysts are extremely active, sensitive, and pyrophoric and care must be used in working with them.[2]

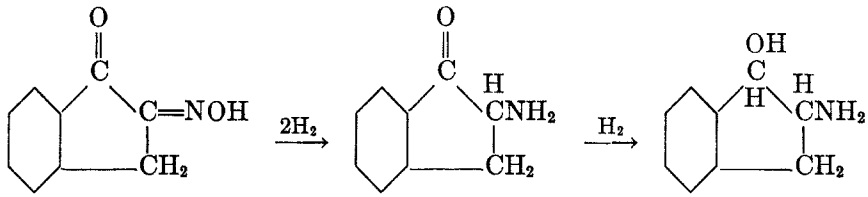
The reaction of ammonia with 2-bromo-1-indanol for the preparation of "indanolamine" (V) has been reported by various workers (12–14). However, subsequent studies by Braun and Weissbach (15) showed that ammonia and amines react with 2-bromo-1-indanol to form 1-amino-2-indanol derivatives (VII) and not 2-amino-1-indanols (VIII),



[2] One of the authors (N. L.) became acquainted with these catalysts in the course of his doctorate studies under Dr. Walter H. Hartung at the University of Maryland. A paper describing the properties and uses of *active* palladium catalysts will be published when sufficient information is obtained. (Hartung, personal communication).

and, as to be expected, the data recorded by previous workers (12–14, 16–18) are misleading.[3] In view of the above findings, it was decided to include the preparation of a group of N-substituted 1-amino-2-indanols for pharmacological study and comparison with the isomeric 2-amino-1-indanols.

2-Amino-1-indanol (V) has been obtained by the catalytic hydrogenation of 2-isonitroso-1-indanone:



According to the patent literature (19), reduction directly to the amino alcohol occurred in the presence of colloidal palladium, but with palladinized charcoal catalyst, reaction stopped at the amino ketone stage. When this point was reached, nickel catalyst was added and the reduction completed at 80° and 10 atmospheres pressure. In the present study, the general method of Hartung (10, 11) was applied. The first two equivalents of hydrogen were taken up with ease; when this point was reached there was a sharp break in hydrogen absorption, and, if reaction was allowed to continue, reduction to the amino alcohol proceeded very slowly and generally not to completion. The addition of fresh palladinized Norit facilitated reaction and reduction to the amino alcohol occurred readily at room temperature. By this procedure, formation of the amino ketone and subsequent reduction to the 2-amino-1-indanol were practically quantitative.

N-Benzal derivatives of 2-aminoindane and 2-amino-1-indanol were prepared from the amine hydrochlorides and these were catalytically reduced to the corresponding benzyl derivatives. A study was made of the possible application of several benzal derivatives in the preparation of N-methylindanamines according to the Decker and Becker alkylation method (20). When methyl iodide was employed as the alkylating agent, reaction failed completely. 2-Methylaminoindane, the analog corresponding to N-methylamphetamine, was finally obtained in low yields by the reaction of methyl sulfate with 2-piperonilidenaminoindane and hydrolyzing the quaternary salt formed. Attempts to prepare 2-methylamino-1-indanol, the indane analog of ephedrine, by the same method have thus far failed.

The pharmacological data for ten indanamines are of particular interest and a summarized report follows. The 2-aminoindane hydrochlorides (IX, XIII, XVI), given intravenously in white rats, are less toxic than amphetamine hydrochloride. Compared to *l*-ephedrine, they are more effective bronchodilators as shown by the bronchial perfusion of isolated rabbit lung method of Sollmann and von Oettingen (21). 2-Benzylaminoindane (XIII) shows a regular and rather

[3] Swanson [*J. Am. Pharm. Assoc.*, **11**, 1125, (1932)] studied the pharmacological properties of an "indanolamine" described as 2-amino-1-indanol. However, no mention was made of the method by which it was prepared.

efficient bronchial action and, on the basis of the experimental data obtained, is rated as a "good" bronchodilator.

The 1-amino-2-indanols (XXVII, XXX, XXXI, XXXIII), though lacking the phenethylamine structure, and the 2-amino-1-indanols (XIX, XXVI) are active bronchodilators; in general, members of both series show a regular bronchial action. Both primary amines, 2-amino-1-indanol (XIX) and 1-amino-2-indanol (XXVII) have low acute toxicities. N-Alkylation serves to increase toxicity, the increase being in proportion to the degree of substitution; with this, however, there is no significant change in bronchodilator activity. For all practical purposes, members of all three series, given intravenously in dogs, have little or no effect on blood pressure.

2-Amino-1-indanone (XVII) is an active bronchodilator and shows regularity.

TABLE I

N-SUBSTITUTED 2-AMINOINDANES

NO.	NR_2	M.P.°C.	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
IX	$-NH_2 \cdot HCl$	220[b] (uncorr.)	$C_9H_{12}ClN$	8.27	8.27	20.93	20.89
X	$-N{=}CHC_6H_5$	56–67[a]	$C_{16}H_{15}N$	6.34	6.20		
XI	$-N{=}CHC_6H_3(-O-O-)CH_2$	93.5–95.5	$C_{17}H_{15}NO_2$	5.28	5.07		
XII	$-N{=}CHC_6H_4OCH_3$	100–101	$C_{17}H_{17}NO$	5.56	5.70		
XIII	$-NHCH_2C_6H_5 \cdot HCl$	205[b]	$C_{16}H_{18}ClN$	5.4	5.66	13.66	13.72
XIV	$-NHCH_2C_6H_3(-O-O-)CH_2 \cdot HCl$	234[c] (uncorr.)	$C_{17}H_{18}ClNO_2$	4.61	4.74	11.7	11.8
XV	$-NHCH_2C_6H_4OCH_3 \cdot HCl$	233[c] (uncorr.)	$C_{17}H_{20}ClNO$	4.84	5.07	12.26	12.31
XVI	$-NHCH_3 \cdot HCl$	210[c]	$C_{10}H_{14}ClN$	7.63	7.72	19.35	19.30

[a] Dimorphic mixture.

[b] Darkens with slow rise in temperature.

[c] Decomposes.

Its acute toxicity is rather low, and on blood pressure it is slightly depressant. This amino ketone gives a characteristic red coloration on epidermis and paper.

EXPERIMENTAL

All melting points reported (unless otherwise indicated) were taken with an Anschütz thermometer entire stem immersed in bath. The microanalyses were carried out by C. H. Emerson and Wm. A. Struck of our Analytical Laboratories.

Amine hydrochlorides. The hydrochloride salts of the amines, except those isolated as such from the reaction mixtures were obtained by treating an absolute ethanolic solution of the amine with absolute ethanolic hydrogen chloride and precipitating the salt by the addition of excess anhydrous ether. All of the amine hydrochlorides were obtained as colorless crystals.

Catalytic hydrogenations. Catalytic hydrogenations using palladium catalysts were carried out by shaking an alcoholic solution of the substance to be reduced in an atmosphere

of hydrogen delivered from a graduated cylinder under a pressure of approximately 30 inches of water. The reaction flask was connected a hydrogen delivery train by means of neoprene tubing; no rubber connections were employed. Palladinized Norit catalysts were prepared by shaking an aqueous solution of palladium chloride (Bishop) with Norit in an atmosphere of hydrogen until saturated (9). The palladinized Norit was filtered with suction, washed well with water, then ethanol and finally with absolute ethanol and dried with suction. The *active* palladium catalysts were prepared in 0.5 or 1.0 *N* aqueous sodium acetate and were employed while alcohol-moist to prevent ignition.

The Schiff bases were reduced at room temperature in a Parr catalytic hydrogenator (22) in the presence of platinum oxide catalyst (American Platinum Works); 0.02 g. of catalyst was used per 0.01 mole of Schiff base.

TABLE II

N-SUBSTITUTED 2-AMINO-1-INDANOLS

NO.	NR_2	M.P.°C.	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
XIX	$-NH_2 \cdot HCl$	171–172[a]	$C_9H_{12}ClNO$	7.55	7.37	19.14	19.29
XX	$-N{=}CHC_6H_5$	163–164[b]	$C_{16}H_{15}NO$	5.91	5.96		
XXI	$-N{=}CHC_6H_3(-O-O-)CH_2$	174.8–175.8[b]	$C_{17}H_{15}NO_3$	4.98	4.95		
XXII	$-N{=}CHC_6H_4OCH_3$	171.8–173.0	$C_{17}H_{17}NO_2$	5.24	5.30		
XXIII	$-NHCH_2C_6H_3(-O-O-)CH_2 \cdot HCl$	216–217[c] (uncorr.)	$C_{17}H_{18}ClNO_3$	4.38	4.48	11.11	11.12
XXIV	$-NHCH_2C_6H_4OCH_3 \cdot HCl$	212–213	$C_{17}H_{20}ClNO_2$	4.55	4.75	11.60	11.49
XXV	$-NHCH_2CH_2C_6H_5 \cdot HCl$	182[d]	$C_{17}H_{20}ClNO$	4.84	4.99	12.24	12.28
XXVI	$-NHCH_2C_6H_5$	144.5–145.0	$C_{16}H_{17}NO$	5.86	5.94		
	$-NHCH_2C_6H_5 \cdot HCl$	(225[c] uncorr.)	$C_{16}H_{18}ClNO$	5.08	5.10	12.89	13.11

[a] Calc'd for C, 58.22; H, 6.47.
Found C, 58.40; H, 6.26.
[b] Forms red melt.
[c] Decomposes.
[d] Darkens with slow rise in temperature.
[e] Decomposes with effervescence.

SYNTHESIS OF INTERMEDIATES

2-Bromo-1-indanol. 2-Bromo-1-indanol was prepared in 85% yields according to the method recently described by Suter and Milne (23). The procedures of Pope and Read (13, 14) and Read and Hurst (24) gave much lower yields.

1-Indanone. Decomposition of 2-bromo-1-indanol in 7% aqueous sulfuric acid according to the procedure of Porter and Suter (25) gave 72–82% yields of crude 1-indanone. The Friedel-Craft cyclization of phenylpropionyl chloride (26, 27), according to the following modified procedure gave good results: To 84.3 g. (0.5 mole) of phenylpropionyl chloride (b.p. 122–123°/20 mm.), dissolved in 250 cc. of anhydrous carbon disulfide, is added, in divided portions, 80.0 g. (0.6 mole) of anhydrous aluminum chloride. After gentle refluxing, the aluminum chloride complex is decomposed and the product separated by steam distillation. The yield of pure 1-indanone distilling at 118–120°/13 mm. is 55.6 g. (84.3%).

2-Isonitroso-1-indanone. The general nitrosation procedure recently described by Levin and Hartung (28) was applied. Twelve and three-tenths grams (0.105 mole) of freshly

distilled butyl nitrite is added to a solution of 13.2 g. (0.1 mole) of 1-indanone in 200 cc. of ether (U.S.P.) with stirring and simultaneous introduction of anhydrous hydrogen chloride. The isonitroso ketone precipitates out during the course of the reaction; after all of the nitrite is in, 200 cc. of benzene is added and the mixture cooled. The product is removed by filtration, washed well with ether and dried; yield, 14.0 g. (87%). Recrystallization from dilute ethanol gives colorless crystals darkening at 200°.

2-Indanone. 2-Indanone was prepared by several procedures. The method of Porter and Suter (25), involving the acid decomposition of 1,2-indene glycol (from the alkaline hydrolysis of the 2-bromo-1-indanol) gave an over-all yield of only 28%. The acid hydrolysis of 2-methoxy-1-indanol according to the method of Read and Hurst (24) gave 60% yields

TABLE III

N-SUBSTITUTED 1-AMINO-2-INDANOLS

NO.	NR_2	M.P.°C.	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
				Calc'd	Found	Calc'd	Found
XXVII	$-NH_2 \cdot HCl$[a]	232[e] (uncorr.)	$C_9H_{12}ClNO$	7.55	7.66		
XXVIII	$-N{=}CHC_6H_5$[a]	164.2–165.2	$C_{16}H_{15}NO$	5.91	6.07		
XXIX	$-N{=}CHC_6H_4OCH_3$	193–194[d]	$C_{17}H_{17}NO_2$	5.24	5.22		
XXX	$-NHCH_3 \cdot HCl$[b]	174–175	$C_{10}H_{14}ClNO$	7.02	7.20	17.8	17.65
XXXI	$-N(CH_3)_2 \cdot HCl$[c]	183–184	$C_{11}H_{16}ClNO$	6.56	6.62		
XXXII	$-NHCH(CH_3)_2 \cdot HCl$	222–223[d] (uncorr.)	$C_{12}H_{18}ClNO$	6.15	6.16	15.60	15.73
XXXIII	$-NHCH_2C_6H_5$	102–103	$C_{16}H_{17}NO$	5.86	5.66		
	$-NHCH_2C_6H_5 \cdot HCl$	203[c]	$C_{16}H_{18}ClNO$	5.08	5.15		
XXXIV	$-NHCH_2C_6H_4OCH_3 \cdot HCl$	202–203	$C_{17}H_{20}ClNO_2$	4.55	4.56	11.60	11.51
XXXV	$-NC_5H_{10} \cdot HCl$	211[d]	$C_{14}H_{20}ClNO$	5.52	5.66	14.00	14.25
XXXVI	$-NHCH_2CH_2C_6H_5$	125–126	$C_{17}H_{19}NO$	5.57	5.79		
	$-NHCH_2CH_2C_6H_5 \cdot HCl$	205–206[d]	$C_{17}H_{20}ClNO$	4.84	4.79	12.24	12.16
XXXVII	$-N(CH_3)CH_2C_6H_5 \cdot HCl$	172.0–173.3	$C_{17}H_{20}ClNO$	4.84	5.02	12.24	12.33
XXXVIII	$-NC_4H_8O$	175.8–177.0	$C_{13}H_{17}NO_2$	6.39	6.52		
	$-NC_4H_8O \cdot HCl$	225[f] (uncorr.)	$C_{13}H_{18}ClNO_2$			13.9	14.01

[a] Previously described by Pope and Read (13, 14).

[b] Previously described by Braun (15).

[c] Previously described by Braun (16).

[d] Decomposes.

[e] Darkens with slow rise in temperature.

[f] Decomposes with effervescence.

of crude 2-indanone. The procedure described by Heusler and Schieffer (29) in which the intermediary 2-methoxy-1-indanol was first isolated and purified before acid hydrolysis appeared to be the most satisfactory; this method gave 1-indanone in over-all yields of 63% according to the following procedure: 2-Methoxy-1-indanol is first prepared by refluxing for one hour a mixture of 127.8 g. (0.6 mole) of 2-bromo-1-indanol and a solution of 30.0 g. (1.3 moles) of sodium in 300 cc. of methanol. Approximately one-half of the solvent is recovered and the reaction mixture is diluted with 1 liter of water; after cooling, the dark oil which separates is extracted with ether. The ether extracts are dried over anhydrous potassium carbonate, the solvent is recovered and the product distilled. The yield of colorless 2-methoxy-1-indanol distilling at 149–152°/11–12 mm. is 79.4 g. (82.4%).

Hydrolysis of 2-methoxy-1-indanol is carried out by refluxing for one hour a mixture of 49.2 g. (0.3 mole) of the methoxy alcohol with a solution of 66.0 cc. of concentrated sulfuric acid in 360 cc. of water. Steam distillation gives 2-indanone which, on cooling, forms colorless crystals, m.p. 56–57°; yield, 29.5 g. (74.5%). 2-Indanone resinifies slowly even at low temperatures; accordingly, its immediate conversion to the oxime is desirable.

2-Indanone oxime. The use of heat in the oximation of 2-indanone, particularly in the presence of alkali, results in decomposition. The following procedure gives excellent results: Twenty-nine and seven-tenths grams (0.225 mole) of 2-indanone is dissolved in 150 cc. of pyridine and a solution of 18.8 g. (0.270 mole) of hydroxylamine hydrochloride in 60 cc. of dilute ethanol is added with cooling and agitation. After standing at room temperature for 48 hours, the reaction mixture is stirred into 500 cc. of ice water; the precipitated oxime is filtered with suction and washed well with cold water. Recrystallization from hot 60% ethanol gives colorless crystals of 2-indanone oxime, decomposing at 152–153°; yield, 31.5 g. (95.2%).

SYNTHESIS OF AMINES

IX. *2-Aminoindane hydrochloride.* Using *active* palladium catalysts, 2-indanone oxime was reduced to the primary amine in good yields according to the following procedure: To a suspension of 4.4 g. (0.03 mole) of 2-indanone oxime in 100 cc. of absolute ethanol containing 3.3 g. (0.09 mole) of hydrogen chloride is added 3.0 g. of *active* palladinized Norit (10%) and 0.3 g. of crystalline palladium chloride. Hydrogen uptake proceeds smoothly and, after shaking for approximately eight hours, reduction is complete. The reaction mixture is then warmed on a steam-bath to keep the amine hydrochloride in solution; the catalyst is removed and the filtrate concentrated under slightly reduced pressure in a current of dry air and finally dried *in vacuo*. The crystals of 2-aminoindane hydrochloride, after recrystallization from absolute ethanol-ether, darken at 220° (uncorr.) (slow rise in temperature); yield, 4.9 g. (96.3%).

X. *2-Benzalaminoindane.* A mixture of 8.5 g. (0.05 mole) of 2-aminoindane hydrochloride, 5.0 cc. (0.05 mole) of benzaldehyde, and 4.6 g. (0.055 mole) of sodium bicarbonate in 75 cc. of alcohol is refluxed on a steam-bath for two hours. The reaction mixture is then allowed to cool to room temperature and diluted with 200 cc. of water. After thorough chilling, the crystals are removed by filtration and dried with suction. Recrystallization from dilute alcohol with the addition of Norit gives 10.6 g. (95.5%) of colorless crystals, melting at 58–67°. The product is recrystallized from ligroin for analysis. No significant change in melting point occurs after several recrystallizations from ligroin, and, in view of the fact that indane derivatives exhibit dimorphism, it may be presumed that this product is a mixture of dimorphic forms. No attempt was made to separate the crystalline forms; purity of the product was indicated by its reduction to 2-benzylaminoindane (XIII).

XI. *2-Piperonylidenaminoindane.* Using the above procedure, from 5.1 g. (0.03 mole) of 2-aminoindane hydrochloride, 4.8 g. (0.032 mole) of piperonal and 2.6 g. (0.031 mole) of sodium bicarbonate in 50 cc. of ethanol, there is obtained 2-piperonylidenaminoindane which forms small, colorless needles from ethanol (60%); m.p. 93.5–95.5°; yield, 5.9–6.3 g. (73.7–79.2%).

XII. *2-Anisalaminoindane.* From 5.1 g. (0.03 mole) of 2-aminoindane hydrochloride, 3.6 g. (0.03 mole) of anisaldehyde and 3.4 g. (0.04 mole) of sodium bicarbonate in 50 cc. of ethanol, there is obtained, after recrystallization from dilute ethanol, 6.9 g. (90.8%) of colorless crystals, m.p. 100–101°.

XIII. *2-Benzylaminoindane hydrochloride.* Using platinum oxide catalyst, 4.4 g. (0.02 mole) of 2-benzalaminoindane (m.p. 58–67°) dissolved in 25 cc. of absolute ethanol gives 4.6 g. (90%) of benzylaminoindane hydrochloride, which begins to darken at 205°.

XIV. *2-Piperonylaminoindane hydrochloride.* 2-Piperonylidenaminoindane (5.3 g., 0.02 mole) dissolved in 100 cc. of absolute ethanol gives on catalytic reduction 5.9 g. (96.7%) of colorless flakes decomposing at 234° (uncorr.).

XV. *2-(p-Methoxybenzyl)aminoindane.* Using 50 cc. of glacial acetic acid as the solvent, 5.0 g. (0.02 mole) of 2-anisalaminoindane is catalytically reduced to the corresponding benzylamine derivative. The hydrochloride salt of 2-(*p*-methoxybenzyl)aminoindane forms small, colorless flakes, which, after recrystallization from methanol-acetone, decompose at 233° (uncorr.); yield, 5.4 g. (93.1%).

XVI. *2-Methylaminoindane hydrochloride.* The following modification of the Decker-Becker method (20, 30) was adapted for the preparation of 2-methylaminoindane hydrochloride: In a 500 cc. round-bottom flask are placed 5.6 g. (0.02 mole) of 2-piperonylideneaminoindane, 2.9 cc. (0.03 mole) of freshly-distilled methyl sulfate, and 125 cc. of anhydrous ethylbenzene. The reaction flask is thoroughly flushed with nitrogen, securely stoppered and heated on a steam-bath. A heavy, dark oil separates and, after heating for 50 hours, the flask is cooled to room temperature; 100 cc. of diluted methanol (8:1) is added and the mixture refluxed for one-half hour. Following the addition of 5 cc. of concentrated hydrochloric acid, the condenser is arranged for downward distillation and the methanol recovered, after which the ethylbenzene is removed in a current of steam. The aqueous solution remaining is then cooled, extracted with ether, and made strongly alkaline with concentrated ammonia (28%). The dark purple amine is extracted with ether and the ether extracts are treated with dilute hydrochloric acid. The acid extracts are evaporated to dryness on a steam-bath and dried *in vacuo*. Recrystallization of the residue from absolute ethanol-ether, with the addition of a little Norit, gives colorless crystals decomposing at 210°; yield, 0.8 g. (21.6%).

XVII. *2-Amino-1-indanone hydrochloride.* To 8.1 g. (0.05 mole) of 2-isonitroso-1-indanone suspended in 100 cc. of absolute alcohol containing 5.5 g. (0.15 mole) of hydrogen chloride is added 3.0 g. of 10% palladinized Norit; the mixture is shaken in an atmosphere of hydrogen as described under *Catalytic hydrogenations*. Two equivalents of hydrogen are taken up in 20 to 25 minutes and the reduction comes to a standstill; the reaction flask is then warmed on a steam-bath to dissolve the amino ketone hydrochloride and the catalyst is removed. The filtrate is concentrated to one-half its original volume and treated with excess anhydrous ether. After chilling, the precipitated 2-amino-1-indanone hydrochloride is filtered, washed well with ether and recrystallized from anhydrous methanol-ether. By this procedure, 9.0 g. (97.8%) of colorless crystals, darkening at 200°, is obtained. The same catalyst can be employed in the reduction of subsequent batches of the isonitroso ketone.

Anal. Calc'd for $C_9H_{10}ClNO$: N, 7.63. Found: N, 7.67.

Diindeno[1,2-b,1′,2′-e]pyrazine is obtained by treating 1.9 g. (0.01 mole) of 2-amino-1-indanone hydrochloride dissolved in 25 cc. of warm methanol with 100 cc. of diluted ammonia (5%). After standing at room temperature for 72 hours, the red precipitate obtained is separated by filtration and dried with suction; yield, 1.0 g. Recrystallization from acetone-ligroin with the addition of a little Norit gives pale yellow crystals. The sample for analysis, after recrystallization from benzene-ligroin, forms small, pale yellow flakes which become red at 265° (uncorr.). Winans and Adkins (31) obtained this pyrazine (which was reported to melt at 270–271°) by reducing 2-isonitroso-1-indanone in the presence of Raney nickel at elevated temperature and pressure.

Anal. Calc'd for $C_{18}H_{12}N_2$: C, 84.4; H, 4.71; N, 10.9.
Found: C, 84.43; H, 5.02; N, 10.83.

XVIII. *2-Benzal-1-indanone.* To a suspension of 3.7 g. (0.02 mole) of 2-amino-1-indanone in 100 cc. of alcohol are added 2.0 cc. (0.02 mole) of benzaldehyde and 1.7 g. (0.02 mole) of sodium bicarbonate. The flask is thoroughly flushed with nitrogen and shaken for 10 hours at room temperature. After standing overnight, 150 cc. of water is added, the mixture cooled and filtered, and the red precipitate obtained is then dried *in vacuo*. Recrystallization from benzene-ligroin gives 1.0 g. (21.3%) of pale yellow crystals. On heating, 2-benzal-1-indanone becomes pink at about 200° and decomposes at 215°.

Anal. Calc'd for $C_{16}H_{13}NO$: N, 5.96; Found: N, 5.89.

XIX. *2-Amino-1-indanol.* With a catalyst consisting of 3.0 g. of 10% palladinized Norit and 3.0 cc. of palladium chloride solution (10%), it is possible to reduce several batches of 18.4 g. (0.1 mole) of 2-amino-1-indanone hydrochloride, suspended in 135 cc. of ethanol, to 2-amino-1-indanol in about 40 minutes. The product is isolated as described under 2-amino-1-indanone hydrochloride; recrystallization from absolute alcohol-ether gives colorless crystals melting at 171–172°; yield, 18.0 g. (96.8%). The stereoisomeric forms of 2-amino-1-indanol hydrochloride melting at 206° and 176° are reported in the patent literature (19). The crude product obtained in this investigation melts at 164–165° and after several recrystallizations melts at 171–172°; no attempt was made to separate the two forms.

XX. *2-Benzalamino-1-indanol.* A mixture of 6.5 g. (0.035 mole) of 2-amino-1-indanol hydrochloride, 3.5 cc. (0.035 mole) of benzaldehyde, and 2.8 cc. (0.035 mole) of pyridine in 100 cc. of ethanol is refluxed on a steam-bath for one hour, after which an excess of 10% sodium carbonate is added. The mixture is further refluxed for an additional 15 minutes and then concentrated to about one-half its original volume, whereupon crystals precipitate. An equal volume of water is added and, after chilling, the Schiff base is filtered off and dried with suction. Recrystallization from dilute ethanol gives 6.2 g. (74.7%) of 2-benzalamino-1-indanol forming a red melt at 163–164°.

XXI. *2-Piperonylidenamino-1-indanol.* From 4.3 g. (0.051 mole) of sodium bicarbonate, 9.3 g. (0.05 mole) of 2-amino-1-indanol, and 7.7 g. (0.051 mole) of piperonal in 150 cc. of ethanol colorless crystals of 2-piperonylidenamino-1-indanol are obtained; recrystallization from ethylene chloride-ligroin gives a product forming a red melt at 174.8–175.8°; yield, 11.0 g. (80%).

XXII. *2-Anisalamino-1-indanol.* From 11.1 g. (0.06 mole) of 2-amino-1-indanol hydrochloride, 7.9 cc. (0.065 mole) of anisaldehyde and 13.6 cc. (0.20 mole) of 28% ammonia in 100 cc. of ethanol, there is obtained, after recrystallization from benzene-ligroin, colorless crystals of 2-anisalamino-1-indanol, melting at 171.8–173.0°; yield, 14.0 g. (87%).

XXIII. *2-Piperonylamino-1-indanol hydrochloride.* 2-Piperonylidenamino-1-indanol (4.2 g., 0.015 mole) is dissolved in a mixture of 100 cc. of absolute ethanol and 50 cc. of glacial acetic acid and catalytically reduced to 2-piperonylamino-1-indanol. The yield of the colorless hydrochloride is 4.6 g. (98%); recrystallization from absolute ethanol-ether gives crystals decomposing with effervescence at 216–217° (uncorr.).

XXIV. *2-(p-Methoxybenzylamino)-1-indanol hydrochloride.* Reduction of 4.0 g. (0.015 mole) of 2-anisalamino-1-indanol dissolved in 50 cc. of glacial acetic acid gives 4.1 g. (90%) of 2-(*p*-methoxybenzylamino)-1-indanol isolated as the hydrochloride. The product consists of colorless crystals melting with effervescence at 212–213°.

XXV. *2-Phenethylamino-1-indanol hydrochloride.* A mixture of 3.7 g. (0.02 mole) of 2-amino-1-indanol hydrochloride, 3.7 g. (0.02 mole) of phenethyl bromide and 2.3 g. (0.022 mole) of anhydrous sodium carbonate in 100 cc. of absolute alcohol is heated for 48 hours in an autoclave immersed in an oil-bath maintained at 130–135°. The reaction product is then diluted with water and treated with hydrochloric acid until strongly acid. After warming with Norit, the mixture is filtered and the filtrate made alkaline with concentrated ammonia. The purple precipitate obtained is separated by filtration, dried with suction, and then dissolved in absolute alcoholic hydrogen chloride. On the addition of absolute ether, colorless crystals darkening at 175° are obtained. After several recrystallizations, the product begins to darken at 182° (slow rise in temperature); the yield is poor.

XXVI. *2-Benzylamino-1-indanol.* (*a*) *Catalytic reduction of 2-benzalamino-1-indanol.* 2-Benzalamino-1-indanol (11.4 g., 0.05 mole) in 100 cc. of glacial acetic acid is catalytically reduced to 2-benzylamino-1-indanol. Recrystallization of the free base from benzene-ligroin gives 11.5 g. (97.1%) of colorless crystals forming a red melt at 144.4–145.0°.

(*b*) *Reductive benzylation.* A mixture of 9.3 g. (0.05 mole) of 2-amino-1-indanol hydrochloride, 4.2 g. (0.05 mole) of sodium bicarbonate, 5.5 cc. (0.055 mole) of benzaldehyde, and 100 cc. of ethanol, contained in a hydrogenation bottle, is warmed on a steam-bath until the evolution of carbon dioxide ceases; 4.1 g. (0.05 mole) of anhydrous sodium acetate and

0.1 g. of platinum oxide catalyst are then added and the reaction bottle shaken at room temperature (initial hydrogen pressure 60 pounds). The theoretical amount of hydrogen is taken up in about five hours, after which the amino alcohol is isolated as in procedure (a). There is obtained 10.9 g. of crude product which, after several recrystallizations, gives colorless crystals forming a red melt at 144–145°; a mixed melting point determination with pure 2-benzylamino-1-indanol shows no lowering.

The hydrochloride salt of 2-benzylamino-1-indanol forms colorless crystals decomposing at 225° (uncorr.).

XXVII. *1-Amino-2-indanol hydrochloride.* This was prepared according to the procedure of Pope and Read (13, 14). From 21.3 g. (0.1 mole) of 2-bromo-1-indanol and 205 cc. of ammonia (28%), there is obtained 8.5 g. (56%) of 1-amino-2-indanol melting at 126–127°; the hydrochloride salt begins to darken at 232° (uncorr.).

XXVIII. *1-Benzalamino-2-indanol.* The procedure of Pope and Read (13) was used; from 4.5 g. (0.03 mole) of 1-amino-2-indanol and 3.0 cc. (0.03 mole) of benzaldehyde dissolved in 50 cc. of alcohol, there is obtained 6.7 g. (94.4%) of practically colorless crystals melting at 162°. Recrystallization from benzene gives colorless crystals, melting at 164.2–165.2°; a mixed melting point determination with 2-benzalamino-1-indanol (m.p. 163–164°) produces a lowering to 140–142°.

XXIX. *1-Anisalamino-2-indanol.* From 6.0 g. (0.04 mole) of 1-amino-2-indanol and 4.8 cc. (0.04 mole) of anisaldehyde in 100 cc. of ethanol, there is obtained 1-anisalamino-2-indanol, which, after recrystallization from toluene, forms colorless flakes decomposing at 193–194°; yield, 10.2 g. (95.3%).

XXX. *1-Methylamino-2-indanol hydrochloride.* Using the method of Braun and Weissbach (15), from 21.3 g. (0.1 mole) of 2-bromo-1-indanol and 150 cc. of 35% aqueous methylamine there is obtained 13.0 g. (65.2%) of 1-methylamino-2-indanol isolated as the hydrochloride salt; m.p. 174–175°.

XXXI. *1-Dimethylamino-2-indanol hydrochloride.* Braun (16) obtained this amine by refluxing 2-bromo-1-indanol with excess dimethylamine in benzene. In these studies 1-dimethylamino-2-indanol was prepared by shaking 10.7 g. (0.05 mole) of 2-bromo-1-indanol with 50 cc. of aqueous dimethylamine (33%) at room temperature for 40 hours; the yield of product isolated as the hydrochloride salt is 6.0 g. (56%); m.p. 183–184°.

XXXII. *1-Isopropylamino-2-indanol hydrochloride.* A mixture of 10.7 g. (0.05 mole) of 2-bromo-1-indanol and 42.7 cc. (0.5 mole) of isopropylamine is shaken at room temperature for 40 hours. The insoluble material is removed by filtration and the filtrate concentrated to a small volume. After treatment with dilute hydrochloric acid and Norit, the mixture is filtered while hot. To the cooled filtrate is added an excess of 20% aqueous sodium hydroxide; the colorless crystals of the base are filtered and dried *in vacuo*. Conversion of the free base to the hydrochloride salt gives colorless crystals decomposing at 222–223° (uncorr.); yield, 7.2 g. (63%).

XXXIII. *1-Benzylamino-2-indanol hydrochloride.* (*a*) *From 2-bromo-1-indanol and benzylamine.* A mixture of 42.6 g. (0.2 mole) of 2-bromo-1-indanol and 45.7 cc. (0.42 mole) of benzylamine dissolved in 150 cc. of anhydrous benzene is refluxed on a steam-bath for 48 hours. The precipitated benzylamine hydrochloride is removed by filtration and the filtrate treated with absolute hydrogen chloride. The crude hydrochloride salt of 1-benzylamino-2-indanol thus obtained is dissolved in warm water and treated with excess 30% aqueous sodium hydroxide. The yield of colorless crystals, after recrystallization from dilute ethanol is 20 g. (41.8%); m.p. 102–103°. The hydrochloride salt decomposes at 203°.

(*b*) *By the catalytic reduction of 1-benzalamino-2-indanol.* By the general procedure, 5.9 g. (0.025 mole) of 1-benzalamino-2-indanol is catalytically reduced to 1-benzylamino-2-indanol in practically quantitative yields; the product is identical with that prepared from the bromohydrin and benzylamine.

XXXIV. *1-(p-Methoxybenzyl)amino-2-indanol.* From 5.3 g. (0.02 mole) of 1-anisalamino-2-indanol dissolved in 50 cc. of glacial acetic acid, there is obtained by catalytic

reduction practically quantitative yields of 1-(*p*-methoxybenzyl)amino-2-indanol isolated as the hydrochloride salt; m.p. 202–203°.

XXXV. *1-Piperidyl-2-indanol hydrochloride.* A mixture of 21.3 g. (0.1 mole) of 2-bromo-1-indanol and 39.8 g. (0.4 mole) of piperidine, dissolved in 100 cc. of anhydrous ethylbenzene, is heated on a steam-bath for 40 hours. The precipitated piperidine hydrobromide is separated and the filtrate distilled under reduced pressure to remove unreacted piperidine. After cooling, the undistilled portion is treated with excess absolute ethanolic hydrogen chloride and on the addition of absolute ether the hydrochloride of 1-piperidyl-2-indanol precipitates out. Recrystallization from absolute ethanol-ether gives colorless crystals decomposing at 211°; yield, 15.6 g. (61.5%).

The *p*-nitrobenzoate ester of 1-piperidyl-2-indanol hydrochloride is prepared by heating a mixture of 5.1 g. (0.02 mole) of 1-piperidyl-2-indanol hydrochloride and 18.6 g. (0.10 mole) of *p*-nitrobenzoyl chloride on a steam-bath for three hours and then at 120° for two hours. On the addition of ether, pale yellow crystals are obtained, which decompose at 225° (uncorr.); yield, 7.0 g. (84.3%). The free base is obtained by dissolving the hydrochloride in hot water and neutralizing with dilute sodium hydroxide solution. Recrystallization from acetone-water gives small flakes of 1-piperidyl-2-indanol *p*-nitrobenzoate melting at 155.8–156.5°.

Anal. Calc'd for $C_{21}H_{22}N_2O_4 \cdot HCl$: Cl, 8.8. Found: Cl, 8.8.
Calc'd for $C_{21}H_{22}N_2O_4$: N, 7.63. Found: N, 7.62.

XXXVI. *1-Phenethylamino-2-indanol hydrochloride.* This amine is prepared by the procedure given for 1-benzylamino-2-indanol hydrochloride. From 12.8 g. (0.06 mole) of 2-bromo-1-indanol and 14.5 g. (0.12 mole) of phenethylamine (Eastman Kodak) in 100 cc. of benzene, there is obtained 4.0 g. (26.3%) of 1-phenethylamino-2-indanol melting at 125–126° after recrystallization from dilute ethanol. Conversion to the hydrochloride gives 4.1 g. of colorless crystals, decomposing at 205–206°.

XXXVII. *1-Methylbenzylamino-2-indanol hydrochloride.* Fourteen and nine-tenths grams (0.07 mole) of 2-bromo-1-indanol and 19.4 g. (0.16 mole) of methylbenzylamine are dissolved in 100 cc. of decalin and the solution is heated on a steam-bath for 50 hours. The precipitated methylbenzylamine hydrobromide is separated and the unreacted methylbenzylamine is recovered by distilling at 2–3 mm. until the distillate gives no precipitate with alcoholic hydrogen chloride. The product is then isolated as the hydrochloride; yield, 9.5 g. (46.8%). After several recrystallizations from ethanol-ethyl acetate, the 1-methylbenzylamino-2-indanol hydrochloride melts at 172.0–173.3°.

XXXVIII. *1-Morpholinyl-2-indanol hydrochloride.* Fourteen and seven-tenths grams (0.07 mole) of 2-bromo-1-indanol and 26.4 g. (0.30 mole) of morpholine dissolved in 100 cc. of anhydrous benzene, contained in a securely stoppered flask, are heated on a steam-bath for 80 hours; the precipitated morpholine hydrochloride is filtered off and the filtrate treated with alcoholic hydrogen chloride. The crystals obtained are filtered off and dissolved in warm water; on the addition of 30% aqueous sodium hydroxide, 1-morpholinyl-2-indanol precipitates out; yield, 9.2 g. (60.1%). Recrystallization from benzene-ligroin gives colorless crystals melting at 175.8–177.0°. The hydrochloride, recrystallized from absolute ethanol-ether, decomposes with effervescence at 225° (uncorr.).

SUMMARY

1. The preparation of a group of *N*-substituted derivatives of 2-aminoindane, 2-amino-1-indanol, and 1-amino-2-indanol is described.

2. A summarized pharmacological report for ten derivatives indicates that several are active bronchodilators, although they have little or no effect on blood pressure.

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THE DETERMINATION OF COMPOSITION OF MIXTURES OF α-BROMO-α-METHYL- AND α-BROMO-β-METHYL-SUCCINIC ACIDS

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In the course of a study of the addition of hydrogen bromide to substituted α,β-unsaturated acids, a method for the determination of composition of α-bromo-α-methyl- and α-bromo-β-methyl-succinic acids was required. While it was found possible to effect qualitative separation of these isomeric compounds by differential adsorption upon activated charcoal, and by systematic crystallization, the quantitative analysis of their mixtures proved more difficult. The ultraviolet absorption spectra of these substances provided no basis for differentiation (Figure 1) nor did the behavior of their salts in neutral solutions or in buffered solutions of low alkalinity under many conditions. However, the rates of hydrolysis of the secondary and tertiary bromo acids in unbuffered alkali were sufficiently different so that under rigidly controlled conditions significant and constant differences in *p*H at the end of a fixed period could be observed potentiometrically. Composition-*p*H curves constructed from these data (Figure 2) were found accurate to about ±2.5%.

EXPERIMENTAL

Melting points and boiling points are corrected values.

α-Bromo-α-methylsuccinic acid. Citraconic acid was prepared by the method of Shriner, Ford, and Roll (1). The product melted at 92°, comparing favorably with the reported melting point 92–93°. By the addition of hydrogen bromide to this substance according to the directions of Autenrieth and Pretzell (2) α-bromo-α-methylsuccinic acid was obtained; it melted at 148.5–149.2° with decomposition. Lutz (3) reports the value 149°.

α-Bromo-β-methylsuccinic acid was synthesized from propane-1,1,2-tricarboxylic acid and aqueous bromine according to the directions of Bischoff and Gutzeit (4). The steps leading to the tricarboxylic acid started with propionic acid and proceeded by a series of standard techniques for bromination, esterification, malonation, and hydrolysis. The product melted at 203–204°, comparing favorably with the melting point 203.5° reported by Bischoff and Gutzeit. Repeated attempts to isolate the unknown diastereomer from the products of this synthesis were unsuccessful, as were those attempts with the hydrogen bromide adducts of citraconic acid.

The determination of the composition of mixtures of α-bromo-α-methylsuccinic and α-bromo-β-methylsuccinic acids depended upon the difference in the rates of reaction of the isomers with alkali. In order to obtain optimal accuracy, the following procedure was used. Exactly 0.100 gram of the bromo acids was weighed out (in duplicate) and dissolved in 10 cc. of distilled water, previously boiled. Into this was run 9.79 cc. of 0.1060 *N* sodium hydroxide from a microburette supplied from an alkali-stable stock bottle suitably pro-

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[2] This research was initiated by the late Professor Arthur Michael. The statements contained in this report, and the responsibility for them, are those of the junior author.

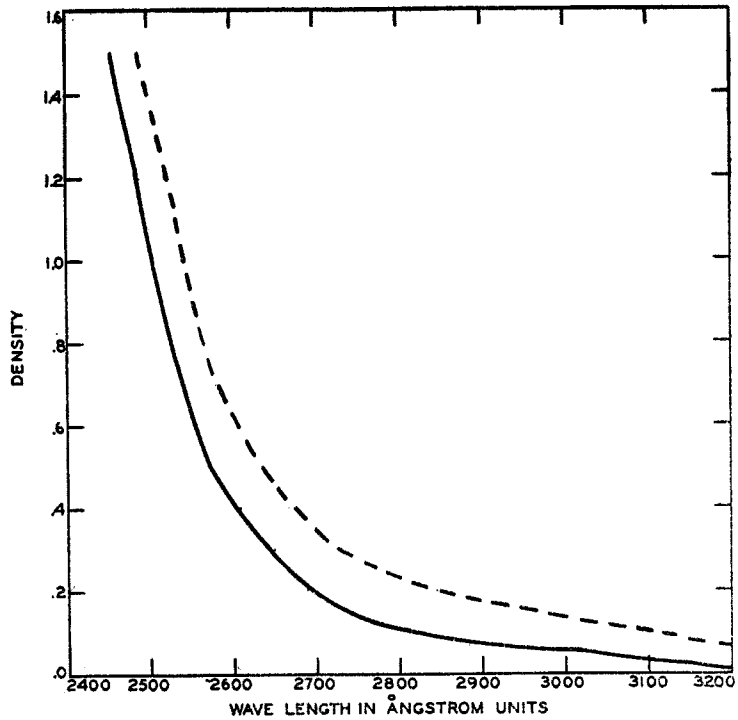

FIGURE 1. ABSORPTION SPECTRA OF α-BROMO-α-METHYLSUCCINIC ACID (DOTTED LINE) AND α-BROMO-β-METHYLSUCCINIC ACID (SOLID LINE), 0.01 *N* SOLUTION IN 0.01 *N* AQUEOUS HYDROCHLORIC ACID

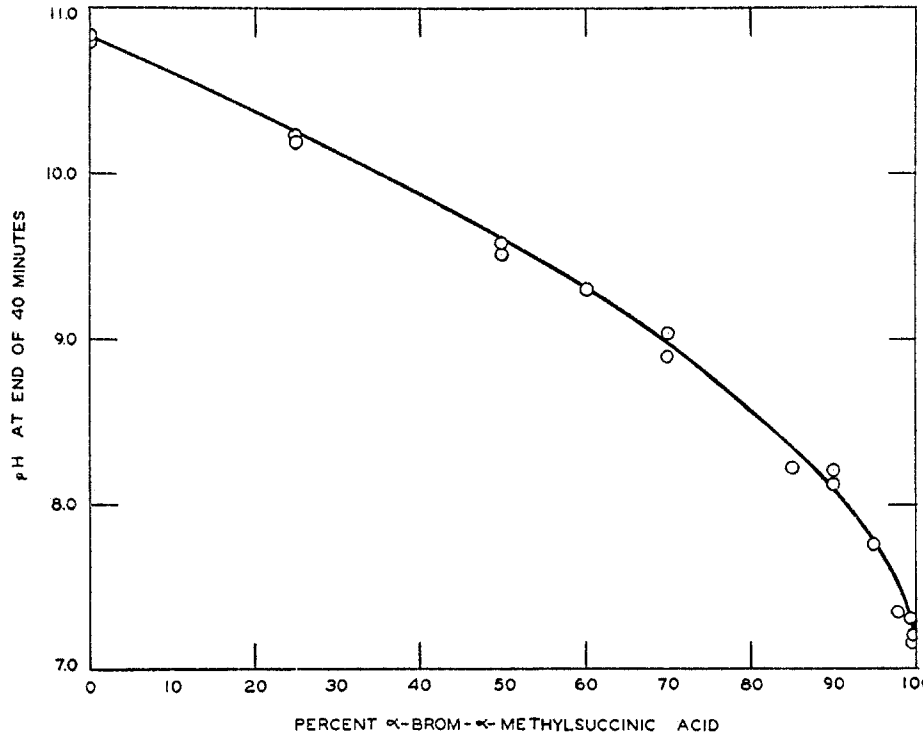

FIGURE 2. THE RELATIONSHIP BETWEEN THE COMPOSITION OF MIXTURES OF α-BROMO-α-METHYL- AND α-BROMO-β-METHYL-SUCCINIC ACIDS AND THE *p*H OF THEIR ALKALINE SOLUTIONS AT THE END OF FORTY MINUTES

tected. The rate of decrease of *p*H of the resulting solution at 27° was measured; timing commenced when 8.94 cc. of alkali had been added, and the final reading taken at 40 minutes. All solutions were kept in the thermostat previous to use. The *p*H was followed by a glass electrode (Coleman Electric Co., model 3D); the calomel half-cell was also thermostatted at 27°, connected to the reaction vessel through a sintered-glass potassium chloride bridge which was flushed from a stock bottle after each determination.

SUMMARY

A method for the determination of composition of α-bromo-α-methyl- and α-bromo-β-methyl-succinic acids has been developed and found accurate to about ±2.5%.

CAMBRIDGE, MASS.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

BENZOYLATION OF AMINO ACIDS

ROBERT E. STEIGER

Received April 19, 1944

N-Benzoylamino acids are most conveniently prepared by the action of benzoyl chloride upon amino acids in aqueous solution in the presence of some alkali. Enough alkali, generally sodium hydroxide, is used to neutralize the hydrochloric acid liberated in the reaction, to maintain the benzoyl compound in solution until the end of the operation, and to destroy any excess of benzoyl chloride. For smoothness and rapidity the method leaves nothing to be desired. The material isolated upon the addition of hydrochloric acid to the alkaline solution contains no secondary product save benzoic acid.

This method was introduced by Baum (1) and was commonly employed in about its original form (2–10) until six years after Fischer (11) had strongly recommended the use of sodium bicarbonate as a substitute for alkali.[1] Carter and Stevens (13) abandoned Fischer's bicarbonate procedure after they found it to be conducive to the formation of mixed anhydrides of N-benzoyl-α-amino acids and benzoic acid. As these compounds, when originating from optically active α-amino acids, are racemized under the experimental conditions prior to their hydrolysis in the sodium bicarbonate solution, Carter and Stevens (13) benzoylate optically active amino acids by Baum's method, in the following way: One mole of amino acid is dissolved in 750 cc. of 2 *N* sodium hydroxide and 250 cc. of water. The solution, maintained below 30°, is treated with 2 moles (230 cc.) of benzoyl chloride and 2300 cc. of 2 *N* sodium hydroxide. It is then cooled in an ice-bath and acidified with 340 cc. of concentrated hydrochloric acid. The mixture of solids obtained is extracted with hot high-boiling petroleum ether to remove the benzoic acid (1 mole or more). The benzoyl derivative is purified in the appropriate manner.

In the course of the last ten years the writer has prepared large quantities of N-benzoylamino acids by Baum's method, using a technique somewhat different from that adopted by Carter and Stevens. Ice-cold aqueous solutions of one mole of amino acid in one mole of sodium hydroxide were treated with one mole of benzoyl chloride and one mole of sodium hydroxide:

$$\text{(I)} \qquad NH_2\text{—}\mathbf{R}\text{—}COOH + NaOH = NH_2\text{—}\mathbf{R}\text{—}COONa + H_2O$$

$$\text{(II)} \quad NH_2\text{—}\mathbf{R}\text{—}COONa + C_6H_5COCl + NaOH = C_6H_5CONH\text{—}\mathbf{R}\text{—}COONa + NaCl + H_2O$$

The reaction mixtures were then treated with one mole of hydrochloric acid to precipitate the N-benzoylamino acid:

$$\text{(III)} \quad C_6H_5CONH\text{—}\mathbf{R}\text{—}COONa + HCl = C_6H_5CONH\text{—}\mathbf{R}\text{—}COOH + NaCl$$

[1] However, Fischer (12) invariably used the sodium hydroxide procedure when benzoylating diamino-monocarboxylic acids. No explanation was given.

It should be understood that, simultaneously, benzoic acid was liberated from the little sodium benzoate formed as a by-product in the reaction. To convert all unreacted amino acid into the hydrochloride a further quantity of hydrochloric acid was added. The yields of purified benzoyl derivatives were high, 89-98%. The benzoyl compounds prepared in this manner had been obtained by various workers in other ways, but in lower yields and apparently not always in the pure state.

EXPERIMENTAL

General procedure for benzoylating amino acids. One mole of amino acid is placed in a three-necked round-bottomed flask, fitted with an efficient stirrer, and dissolved in 1000 cc. of 1 *N* sodium hydroxide (1 mole). The flask is then almost completely immersed in a large-sized bath of ice and water (temperature about +1°) and the stirrer is now set in very rapid motion. To the solution is added, dropwise, 116 cc. (1 mole) of pure benzoyl chloride and, at a rate 4.3 times faster, 500 cc. of 2 *N* sodium hydroxide (1 mole), also in a continuous flow. The operation may be interrupted at any time to refill the graduated analytical burettes through which the two reagents are best delivered. The two burettes are adapted to the side necks of the flask by means of one-hole rubber stoppers. The middle neck of the flask is covered with a round piece of glazed cardboard, thinly coated with vaseline, through which passes the stirring rod. A ⌐——— shaped stirrer (glass rod bent at a 45° angle or less), nearly touching the bottom of the flask, will most effectively disperse the benzoyl chloride in the alkaline solution. Stirring should be effected at a speed such that the liquid is forcibly projected against the walls of the vessel. The time for the introduction of the reagents is about one hour for runs on 0.2 mole of amino acid and three hours for runs on 1.5 moles of amino acid. The final volume of the solution should not exceed one-half of the capacity of the reaction flask. In runs on more than one mole of amino acid, alkali of a higher concentration than 1 *N* sodium hydroxide may be used to dissolve the amino acid (*e.g.*, 2 *N* sodium hydroxide for α-aminoisobutyric acid), provided the sodium salt of the benzoyl compound is sufficiently soluble at 0° to remain in solution. When crystallization of the sodium salt of the benzoylamino acid occurs before all the benzoyl chloride has been added, the benzoyl compound is obtained in a lower yield than usual. To prevent this crystallization the amino acid is dissolved in alkali of a suitably lower concentration than 1 *N* sodium hydroxide (*e.g.*, 0.2 *N* sodium hydroxide for anthranilic acid). When the reagents have been added, the solution is stirred for an additional fifteen minutes, and, if necessary, is treated with Norit at room temperature and filtered with suction. The clear solution is made strongly acid to Congo red by the addition of 5 *N* hydrochloric acid (200 cc. of this is theoretically required). The hydrochloric acid used in excess will dissolve the unreacted portion of those amino acids which are only sparingly soluble in water. The hydrochloric acid is added very slowly with continuous stirring and outside cooling in ice and water. The well cooled suspension is filtered and the crystals are washed with ice-cold water, in small portions. The filtrate should be concentrated under reduced pressure, if containing a quantity of benzoyl compound sufficient to warrant its isolation. When precipitated at low temperature, certain benzoyl compounds are of a crystalline texture such that filtration of the suspension is extremely slow and thorough washing of the material is well-nigh impossible. Precipitation, then, may be effected as follows: To the solution is added 5 *N* hydrochloric acid, at room temperature, until the appearance of the first crystals. The mixture is then heated on a steam-bath and the remainder of the theoretical amount of 5 *N* hydrochloric acid is added with continuous stirring. The suspension is immediately cooled in an ice and water mixture and made strongly acid to Congo red by the addition of a further quantity of 5 *N* hydrochloric acid.

Drying of substances. The crude products, as obtained by precipitation with 5 *N* hydrochloric acid, were dried in a vacuum desiccator over phosphorus pentoxide and sodium hydroxide, the latter being used to remove any hydrochloric acid that may have been

retained by the wet crystals. The precaution is all the more necessary if the product is to be recrystallized from an alcohol. All substances were eventually dried to constant weight in a vacuum desiccator over phosphorus pentoxide alone. The weights given refer to materials dried in this way. The final substances were preserved over phosphorus pentoxide.

Melting points. These were taken in the melting point apparatus described by Steiger (14) with total immersion precision thermometers. Unless otherwise stated, the bath was brought to a temperature about 5° lower than the melting point, before the capillary tube was introduced into the apparatus; the temperature of the bath was then raised very slowly.

N-Benzoyl-dl-α-aminophenylacetic acid (*N-benzoyl-dl-phenylglycine*). A solution of 30.22 g. (0.2 mole) of *dl*-α-aminophenylacetic acid (15) in 200 cc. of 1 *N* sodium hydroxide (0.2 mole) was treated with 23.2 cc. (0.2 mole) of benzoyl chloride and 100 cc. of 2 *N* sodium hydroxide (0.2 mole) in the way described. The solid benzoylation product was washed with 1 liter of ice-cold water in small portions, then freely with benzene, which dissolves only the contaminating benzoic acid. The yield was 49.50 g. (97.0%). The product was suspended in benzene, the mixture was boiled under a reflux condenser and filtered while hot; the residue was washed on the funnel with hot benzene and dried. Very little substance was lost in this operation, designed to remove any benzoic acid not previously eliminated. The benzoyl compound was dissolved in boiling acetone and the solution filtered while hot, after addition of Norit. The hot filtrate was treated with warm water until turbidity was just produced. The mixture was stirred while allowed to cool very slowly to room temperature. The crystals were washed first with water containing a little acetone, later with water, and dried. The substance melted sharply at 178.0–178.5° (corr.) with decomposition. It melted at the same temperature after recrystallization from acetone and water. Prepared previously by: Kossel (16), m.p. 174°; Bayer and Co. (3), m.p. 175.5°; Baum (17), m.p. not given; Shemin and Herbst (18), m.p. 175° (corr.).

N-Benzoyl-dl-α-amino-β-phenylpropionic acid (*N-benzoyl-dl-β-phenylalanine*). A solution of 33.02 g. (0.2 mole) of *dl*-α-amino-β-phenylpropionic acid in 200 cc. of 1 *N* sodium hydroxide (0.2 mole) was treated with 23.2 cc. (0.2 mole) of benzoyl chloride and 100 cc. of 2 *N* sodium hydroxide (0.2 mole) in the way described. The solid benzoylation product was washed with 1 liter of ice-cold water, in small portions, and dried. To this was added the material isolated from the filtrate upon its concentration to a small volume under strongly reduced pressure. The crude product weighed 51.10 g. (94.9% yield, assuming no contaminating benzoic acid present). It was suspended in 6 times its weight of heptane, the mixture was boiled under reflux, and filtered while hot; the residue was freely washed on the funnel with hot heptane and dried. The yield was 47.90 g. (89.0%). This material was dissolved in 13 times its weight of boiling 50% (by weight) ethanol. The solution was treated with Norit and filtered with suction, as hot as possible. Crystallization set in immediately. The suspension was eventually cooled in ice and water and filtered. The crystals were washed first with ice-cold 50% ethanol, later with water, and dried. They melted at 186° (corr.). After recrystallization from acetone (a very suitable solvent), the substance melted at 187.0° (corr.). Other authors: Erlenmeyer (19), m.p. 182–183°; Fischer and Mouneyrat (20), m.p. 187–188° (corr.); Mohr and Stroschein (21), m.p. 182–183°; Waser (22), m.p. 184°; Lamb and Robson (23), m.p. 184–185°.

N-Benzoyl-dl-β-amino-β-phenylpropionic acid. A solution of 33.02 g. (0.2 mole) of *dl*-β-amino-β-phenylpropionic acid (24) in 200 cc. of 1 *N* sodium hydroxide (0.2 mole) was treated with 23.2 cc. (0.2 mole) of benzoyl chloride and 100 cc. of 2 *N* sodium hydroxide (0.2 mole) in the way described. The solid benzoylation product precipitating upon the addition of an excess of 5 *N* hydrochloric acid to the ice-cold reaction mixture was so voluminous that the suspension had to be diluted several times with water to facilitate stirring. The product was washed with 1 liter of ice-cold water, in small portions, and then with alcohol-free ethyl ether to remove benzoic acid. The filtrate was concentrated under strongly reduced pressure; it yielded only a small quantity of benzoyl compound. The yield was 52.71 g. (97.9%). The entire material was dissolved in 8 times its weight of

boiling 95% ethanol. The clear solution obtained was cooled to room temperature and continuously stirred. The crystals deposited were washed first with some ice-cold 95% ethanol, later with water, and dried. They weighed 44.0 g. Most of the benzoyl compound contained in the mother liquor of crystallization may be recovered by heating and adding a large volume of water; it crystallizes on cooling. The substance was crystallized once more from 8 times its weight of boiling 95% ethanol. It then melted sharply at 199.5° (corr.). Posner (10) reported the melting point 194–196°.

N-Benzoyl-α-aminoisobutyric acid. A solution of 154.6 g. (1.5 moles) of α-aminoisobutyric acid in 750 cc. of 2 *N* sodium hydroxide (1.5 moles) was treated with 174 cc. (1.5 moles) of benzoyl chloride and 750 cc. of 2 *N* sodium hydroxide (1.5 moles) in the way described. The solid benzoylation product was washed with ice-cold water, in small portions, and then with ether to remove benzoic acid. Upon concentration under strongly reduced pressure, the filtrate yielded a further quantity of benzoyl compound. The crude product weighed 284.0 g. (91.4% yield, assuming no contaminating benzoic acid present). It was suspended in 500 g. of ether, the mixture was boiled under a reflux condenser, and filtered after cooling; the residue was washed on the funnel with ether and dried. The yield was 274.7 g. (88.4%). After two crystallizations from 8 times its weight of boiling acetone. the substance melted and decomposed at 202° (corr.). Previously prepared by: Mohr and Geis (25), m.p. 198° (softening at 195°); Gabriel (26), m.p. not given; Heller and Lauth (27), m.p. 199°.

N-Benzoyl-2-aminobenzoic acid (*N-benzoylanthranilic acid*). A solution of 27.41 g. (0.2 mole) of anthranilic acid in 1 liter of 0.2 *N* sodium hydroxide (0.2 mole) is treated with 23.2 cc. (0.2 mole) of benzoyl chloride and 100 cc. of 2 *N* sodium hydroxide (0.2 mole) in the way described. A little of the sodium salt of N-benzoylanthranilic acid separates in the course of the benzoylation. When afterwards the reaction mixture is stirred for some time at room temperature a clear solution is obtained. This, if colored, should be decolorized with Norit at room temperature and filtered with suction. The solution is placed in a two-liter beaker and treated with a little 5 *N* hydrochloric acid until crystallization sets in. The mixture is heated in a steam-bath as high as possible, kept hot, and vigorously stirred while there is added, drop by drop, the remainder of the 40 cc. of 5 *N* hydrochloric acid theoretically required to set free the benzoylamino acid. Immediately thereafter the suspension is cooled in an ice- and water-bath and treated with 10 cc. of 5 *N* hydrochloric acid with stirring. After thorough cooling, the suspension is filtered and the crystals are washed with 1 liter of ice-cold water in small portions, then sucked as dry as possible, and dried. The yield is 46.24 g. (95.9%). This material melts at 181–182° (corr.) with decomposition.

For purification, there is added to this material somewhat less 0.1 *N* sodium hydroxide than theoretically required to form the sodium salt. The mixture, which then contains a little undissolved benzoyl compound, is treated with Norit at room temperature and filtered with suction. To the colorless solution, which is continuously heated in a steam-bath and vigorously stirred, is added in a thin stream just enough 0.5 *N* hydrochloric acid to liberate the benzoyl compound. The suspension is immediately cooled in ice and water and now made strongly acid to Congo red with 0.5 *N* hydrochloric acid. The crystals are exhaustively washed on the funnel with water at room temperature. The purification is repeated in exactly the same manner. N-Benzoylanthranilic acid melts and decomposes at 182° (corr.), the melting point tube being introduced into the bath at 176° (corr.).

This compound has been prepared twice previously by benzoylation of anthranilic acid: Brückner (28), using a procedure which was not described, gave the melting point 182°. Bamberger and Sternitzki (4), using Baum's method, but giving no details, found the melting point 177°. N-Benzoylanthranilic acid has been obtained very often in other ways, but only exceptionally has it been found to melt at a temperature higher than 177°. Confirmation of the high melting point, 182°, reported by Brückner, has hitherto been lacking. It would appear that the compound exists in two modifications having different melting points, or that it obstinately retains traces of organic solvents, causing a lowering of the melting point. The issue is very much obscured by the fact that in the molten state the

substance undergoes dehydration to its azlactone. At any event, N-benzoylanthranilic acid should not be purified by crystallization from organic solvents. Unlike the material precipitated from solutions of its sodium salt with hydrochloric acid, the products obtained on crystallization from organic solvents will melt almost instantaneously if the capillary tube is introduced in the bath at 176° (corr.); they then solidify more or less completely to melt again at a higher temperature, always below 182° (corr.), because at the first fusion a certain amount of azlactone is formed.

Acknowledgment. The author wishes to thank Professor H. T. Clarke for his interest in the work and the facilities accorded.

SUMMARY

1. N-Benzoylamino acids may be obtained, in high yields, by the action at about +1° of only one mole of benzoyl chloride upon the amino acids, in the presence of the required amount of aqueous sodium hydroxide. Little benzoic acid is formed as a by-product under the conditions of the procedure used.

2. Five N-benzoylamino acids were prepared and purified in the appropriate manner. The highest melting points recorded in the literature for these compounds have either been confirmed or found to be definitely too low.

NEW YORK, N. Y.

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[From The Kedzie Chemical Laboratory, Michigan State College]

FRAGMENTATION OF ALCOHOLS IN THE PRESENCE OF ALUMINUM CHLORIDE. I. 2,3,4-TRIMETHYLPENTANOL-3 AND 2,4-DIMETHYL-3-ETHYLPENTANOL-3

RALPH C. HUSTON AND JORGE AWUAPARA

Received April 22, 1944

Earlier work in this laboratory (1, 2) has shown that the accumulation of methyl groups on the carbon atom adjacent to the carbinol carbon of tertiary alcohols causes a marked reduction in the yield of the expected tertiary alkylbenzene when these alcohols are condensed with benzene in the presence of aluminum chloride.

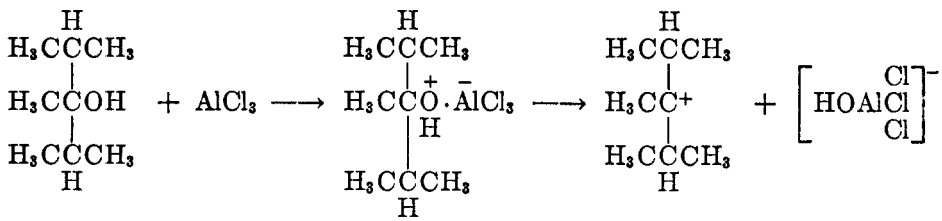
Isolation of tertiary butylbenzene as a reaction product in a number of cases led us to suspect that the low yields resulted from fragmentation of the carbon chain rather than from a depressive influence on the condensing capability of the alcohol. This suspicion was strengthened by the observation that 2,4,4-trimethylpentanol-2, in which there is no branching on the carbon adjacent to the carbinol carbon, gave large yields of tertiary butylbenzene and very low yields of 2,4,4-trimethyl-2-phenylpentane.

This is the first of a series of reports on the fragmentation of tertiary alcohols, in which we hope to establish relationships between types of chain branching and tendency to rearrange and split.

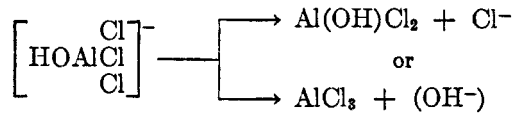
The addition of 2,3,4-trimethylpentanol-3 to a suspension of aluminum chloride in benzene gave the following products:

An octylbenzene, 2,3,4-trimethyl-3-phenylpentane (9%); a butylbenzene, 3-methyl-3-phenylpropane (48%); alkyl halides, $C_8H_{17}Cl$, probably 2,3,4-trimethyl-3-chloropentane, with some 2,3,4-trimethyl-2-chloropentane; unsaturated hydrocarbons, C_8H_{16}, which were formed by elimination of hydrochloric acid from the alkyl halides, mostly 2,3,4-trimethylpentene-2.

It is proposed that the initial step in the reaction is the combination of alcohol and aluminum chloride by a dative bond and that this is followed by the formation of an alkyl cation.



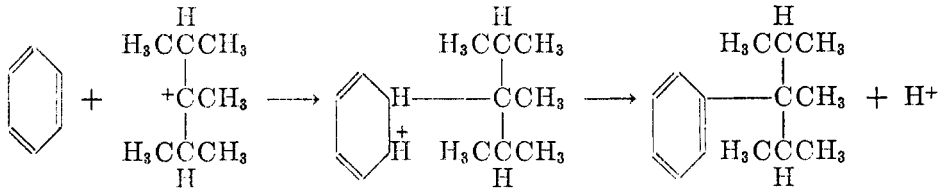
The complex anion may lose either a chlorine ion or a hydroxyl ion.



The presence of protons, formed either by the condensation of the cation with benzene or by the formation of an alkene, will form as end products aluminum chloride and water. The formation of $\left[\begin{matrix}HO\\HO\end{matrix}\ Al\ \begin{matrix}Cl\\Cl\end{matrix}\right]^-$ and $\left[\begin{matrix}HO\\HO\end{matrix}\ Al\ \begin{matrix}Cl\\OH\end{matrix}\right]^-$ as intermediates is also possible. In any case, the reaction will terminate when the aluminum chloride is hydrated to such an extent that it no longer forms a dative bond with the alcoholic oxygen.

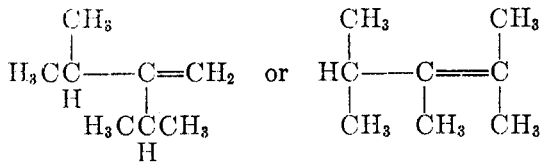
When one mole of alcohol is added to one-third of a mole of aluminum chloride in benzene, the addition of the first one-third mole must be drop-wise. The second third may be added more rapidly while the last third may be added at one time, without causing the temperature to rise. During the addition of this last third there is definite evidence of the development of *back* pressure in the system.

The further reactions of the cation will depend upon its stability and its environment. In normal alkylation, it will unite with the benzene which has been activated by aluminum chloride and a proton will be eliminated (3).

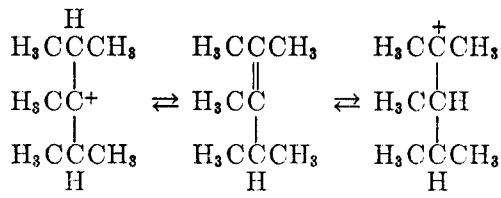


The significance of the relative ability of the benzene ring to react with the cation is shown by comparing the ease of alkylation of benzene and phenol. The highly reactive phenolic ring condenses with 2,3,4-trimethylpentanol-3 to give a sixty per cent yield of the alkylphenol (4) with no evidence of rearrangement or fragmentation. Under similar conditions, benzene yields about ten per cent of *t*-octylbenzene, while the yield of products resulting from rearrangement and fragmentation is high.

The fraction of the cation which fails to condense with benzene may unite with ionic chlorine from the complex aluminum anion to form the alkyl chloride, or it may lose a proton to form either or both of the alkenes:

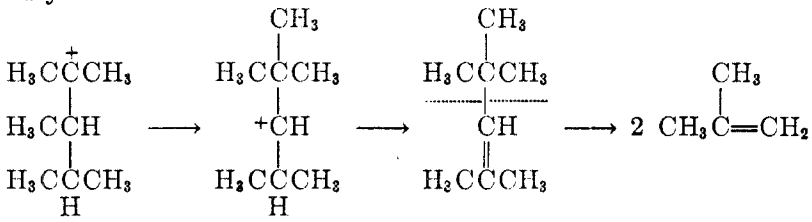


The first of these, 3-methyl-2-isopropylbutene-1 could add a proton, or hydrocloric acid, and the resulting cation or alkyl chloride could condense with benzene, or the unsaturated hydrocarbon could condense directly (5). In any case the product would be 2,3,4-trimethyl-3-phenylpentane. On the other hand, the addition of proton to 2,3,4-trimethylpentene-2 would give a mixture of two cations which may be considered in equilibrium.



Of these, the first would condense to give 2,3,4-trimethyl-3-phenylpentane, while the second would give 2,3,4-trimethyl-2-phenylpentane. It has been found that 2,3,4-trimethylpentanol-2 rapidly undergoes fragmentation (2). The experiments now under consideration gave no evidence of the formation of 2,3,4-trimethyl-2-phenylpentane.

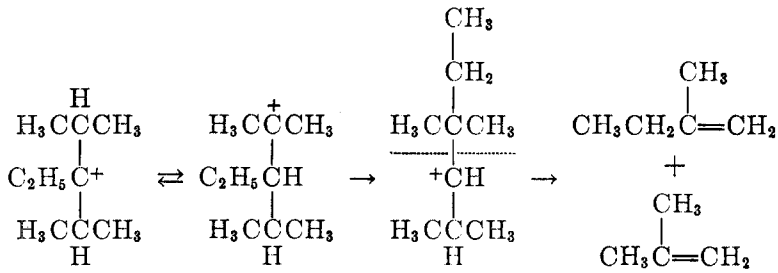
The transient existence of the second cation (above) may be attributed to its tendency to rearrange (6) to a cation which by loss of a proton would yield di-isobutylene.



The formation of a tertiary alkyl (butyl) group, with its low energy level, adjacent to a positive (unsaturated) carbon, sets up a condition highly favorable to chain rupture. One of the fragments could well be in the form of a cation, while the other could form a cation by proton addition.

It may be significant that the yield of tertiary butyl benzene from 2,3,4-trimethylpentanol-3 is about the same as from 2,4,4-trimethylpentanol-2. In neither case was there evidence of an appreciable amount of tertiary butyl chloride in the reaction mixture, but in both cases there was evidence of the formation of gaseous hydrocarbon.

The condensation of 2,4-dimethyl-3-ethylpentanol-3 with benzene was undertaken for the purpose of observing the effect of the size of the migrating group. Nonylbenzene was isolated in a yield of twenty-six per cent. By analogy, this was tentatively assigned the structure of 2,4-dimethyl-3-phenylpentane. Both 2-methyl-2-phenylpropane and 2-methyl-2-phenylbutane were isolated as split products in practically equal amounts, 3%.



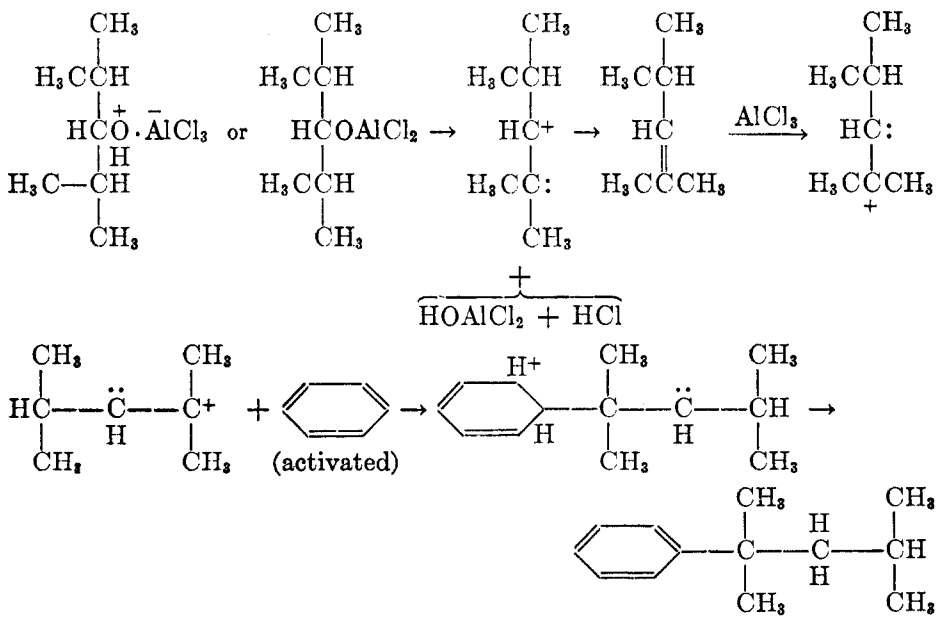
The nonyl chloride fraction (12%) which by analogy contained mostly 3,4-dimethyl-3-ethyl-3-chloropentane was decomposed, partly by boiling and completely by dilute sodium hydroxide, to a constant-boiling alkene fraction, probably 2,3-dimethyl-3-ethylpentene-2.

The formation of tertiary butylbenzene and tertiary amylbenzene gives definite information as to the mechanism of fragmentation.

The small yields of split products result because the ethyl group has less tendency to migrate than does the methyl group. The formation of two alkyl benzenes proves that both fragments are capable of uniting with the benzene ring.

If the theory is correct, 2,3,4-trimethylpentanol-3 condenses with benzene to form 2,3,4-trimethyl-3-phenylpentane, because *a cation is formed which is sufficiently stable to allow condensation to occur before unsaturation.* It was, therefore, of interest to determine the behavior of 2,4-dimethylpentanol-3 in which the hydroxyl is part of a secondary alcoholic group, adjacent to a carbon atom on which there is branching. Distillation of the reaction products gave two fractions and a high-boiling residue. The first fraction consisted of an unstable alkyl chloride (or chlorides), 15%, which was decomposed by boiling with dilute sodium hydroxide to 2,4-dimethylpentene-2. The second fraction proved to be 2,4-dimethyl-2-phenylpentane as shown by the melting points of the α-naphthylurethan and the benzoyl ester of its p-hydroxyl derivative (7). There was no evidence of fragmentation and it is apparent that the critical intermediate in this reaction is the unsaturated compound.

The hydroxyl of the secondary alcohol is less readily released as a part of the complex anion than that of a tertiary alcohol. An unsaturated compound may be formed either by direct decomposition of the intermediate addition complex or through the aluminate.



As in the formation of cations from tertiary alcohols, it is essential to the theory that the $Al(OH)Cl_2$ react with hydrochloric acid to form $AlCl_3$ and water, or that $Al(OH)Cl_2$ and $Al(OH)_2Cl$ form complexes by means of the dative bond with a second and third molecule of alcohol.

It has been shown that the condensation of secondary alcohols with benzene must take place through the unsaturated hydrocarbon as an intermediate (8), also that aluminates may be formed (9) when aluminum chloride reacts with primary or secondary alcohols. Tertiary alcohols react with aluminum chloride at room temperature, or below, to give excellent yields of alkyl chloride.

EXPERIMENTAL

Condensation. The same technique was used in all condensations. High temperatures were avoided because the advantages of increased fragmentation by heating were more than offset by irregularities in the course of the reaction and yields of products. On the other hand, low temperatures are not desirable because they decrease the amount of fragmentation and increase the yield of alkyl chlorides.

One-half mole of the alcohol, dissolved in 50 ml. of benzene, was added drop by drop to a vigorously stirred suspension of 50 g. of anhydrous aluminum chloride in 400 ml. of anhydrous thiophene-free benzene. During this addition, the temperature was maintained at 20–30°. The reaction mixture was stirred for one hour, allowed to stand overnight and then poured on ice. The benzene layer was separated, washed with water, then with a dilute solution of sodium carbonate and again with water. After drying over anhydrous sodium sulfate, the benzene was removed and the residual liquid was fractionated.

2,3,4-Trimethylpentanol-3. This was prepared from di-isopropyl ketone and methyl magnesium bromide (10), b.p. 156–157°/750.

Fractionation of the condensation product gave:

Fraction	B.P (10 mm.)	Yield (grams)
1	46–50°	8
2	52–54°	30
3	102–105°	9
4	residue	18

The first fraction proved to be a mixture. When nitrated it gave a small amount of *p*-nitro-*t*-butylbenzene. Determination of chlorine (Carius) indicated about 80% of $C_8H_{17}Cl$. Treatment of 2,3,4-trimethylpentanol-3 in ether solution with dry hydrochloric acid gave an alkyl chloride which boiled at 47–49° (10 mm.). Fractions of this range from several condensations were combined and refluxed with dilute sodium hydroxide. Extraction with ether and repeated distillation of the extract gave an unsaturated hydrocarbon boiling at 112–116°; d_4^{20} 0.733; n_D^{20} 1.4204 (11).

The fraction boiling at 52–54° (10 mm.) consisted of *tert.*-butylbenzene. It was identified by the melting point (168–170°) and mixed melting point of its acetamino derivative which was prepared by a modification of the method of Ipatieff and Schmerling (12).

After several fractionations the third fraction came over at 104–105° (11 mm.). It was nitrated, reduced, and diazotized to 2,3,4-trimethyl-3-*p*-hydroxyphenylpentane and this was identified by the melting points of the 3,5-dinitrobenzoyl derivative and the α-naphthylurethan (4).

2,4-Dimethyl-3-ethylpentanol-3. This was prepared from di-isopropyl ketone and ethylmagnesium bromide (10), b.p., 176–177°/750, d_4^{20} 0.8485; n_D^{20} 1.4388.

Four fractions were obtained from the condensation:

Fraction	B.P. (750 mm.)	Yield (grams)
1	146–160°	10
2	165–172°	2.5
3	188–193°	3
4	106–114° (10 mm.)	25
5	Residue	10

The first fraction consisted of an alkyl chloride (or alkyl chlorides) which liberated hydrochloric acid at the boiling point (2,4-dimethyl-3-ethyl-3-chloropentane prepared from the alcohol and hydrochloric acid boiled with decomposition at 156–160° under atmospheric pressure). The fractions from these condensations were combined and decomposed by refluxing with dilute sodium hydroxide. The unsaturated compound came over after three distillations at 126–128°. The density (d_4^{20} 0.7332) and refractive index (n_D^{20} 1.4148) gave the molecular refraction 43.02 as compared with 43.14 calculated for 2,4-dimethyl-3-ethylpentene-2. There is no record in the literature of the constants of this hydrocarbon.

The second fraction was identified as tertiary butylbenzene by means of its acetamino derivative (12). The third fractions from three condensations were combined and refractionated several times. Most of the product came over at 188–190°. It was identified by the melting point of its acetamino derivative (12) as tertiary amylbenzene.

The fourth fraction had, after several refractionations, a constant boiling point, 251–253° (750 mm.) and 112–114° (10 mm.). Its analysis and physical constants proved it to be a nonylbenzene; d_4^{25} 0.8706, n_D^{25} 1.4920. MR, 68.01 (Calc'd 67.88).

Anal. Calc'd for $C_{15}H_{24}$: C, 88.16; H, 11.84.

Found C, 87.83; H, 12.05.

2,4-Dimethylpentanol-3. This was prepared by reducing di-isopropyl ketone by means of di-isopropylmagnesium bromide (13); b.p. 136–137°/745; d_4^{20} 0.8157, n_D^{20} 1.4159.

Fractionation of the condensation products gave:

Fraction	B.P.	Yield (grams)
1	112–118° (745 mm.)	10
2	101–104° (20 mm.)	30
3	Residue	10

The alkyl halide (or halides) of the first fraction was decomposed by boiling with dilute sodium hydroxide. The unsaturated compound came over at 83–85°. Oxidation with acid potassium dichromate gave a small yield of isobutyric acid. Physical constants checked closely with those given (14) for 2,4-dimethylpentene-2; d_4^{20} 0.6961, n_D^{20} 1.4016.

The second fraction proved to be 2,4-dimethyl-2-phenylpentane (1), b.p. 216–217° (745 mm.), d_4^{20} 0.8724, n_D^{20} 1.4928.

When nitrated, reduced, and diazotized it gave 2,4-dimethyl-2-*p*-hydroxylphenylpentane as proved by the melting points of the benzoyl ester (70–71°) and the α-naphthylurethan (7) (114–115°).

SUMMARY

1. As a part of an investigation of the fragmentation of tertiary alcohols, 2,3,4-trimethylpentanol-3 was added to a suspension of aluminum chloride in benzene. The yield of 2,3,4-trimethyl-3-phenylpentane was about ten per cent.

2. The principal product of fragmentation, *tert*-butylbenzene, was obtained in a yield of approximately fifty per cent (calculated on the 1:1 basis). A mechanism is suggested. Alkyl halides, $C_8H_{17}Cl$, and alkenes, C_8H_{16}, were by-products.

3. Similar treatment of 2,4-dimethyl-3-ethylpentanol-3 gave a fair yield of nonylbenzene (30%) and, as fragmentation products, small yields of *tert*-butylbenzene and *tert*-amylbenzene. Nonyl chloride and nonene fractions were isolated.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

SUBSTITUTED STILBENES AND 1,4-DIPHENYLBUTADIENES. PART II. SYNTHESIS AND PROPERTIES OF MONOHALOGENO DERIVATIVES

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The Perkin reaction is the method most commonly used for the synthesis of substituted stilbenes. However, its applicability is frequently restricted by the inaccessibility of the reactants. The Meerwein reaction, on the other hand, is based on the coupling of cinnamic acids with diazotized amines which are, in general, readily available. Despite this obvious advantage, the latter method has been applied in but a few cases since the original publication of Meerwein in 1939 (1). Fuson and Cooke (2) used the reaction for the preparation of 4-carbalkoxystilbenes from alkyl *p*-aminobenzoates, and in this laboratory it has been used with substituted naphthylamines (3). Furthermore, the vinylog of cinnamic acid, cinnamalacetic acid, has been used as the second reactant. This extension of the Meerwein method permits the synthesis of unilaterally substituted 1,4-diphenylbutadienes and has since been used by Bachman and Hoaglin (4) for the preparation of 1-(*o*-nitrophenyl)-4-phenyl-1,3-butadiene. Koelsch (5) found that, in contrast to all other α,β-unsaturated acid derivatives, which add the aryl residue at the α-carbon atom, acrylonitrile or acrylic esters combine with the diazotized component through the β-carbon atom. The theoretical significance of this observation will be discussed below.

In recent years we have applied the Meerwein reaction in a large number of cases with the purpose of determining the limits of its applicability and of elucidating its mechanism. In the present paper we describe three isomeric monochloro- and monobromo-stilbenes and the chlorodiphenylbutadienes.

Meerwein originally used only *o*- or *p*-substituted anilines in the reaction. We have found that *meta*-derivatives also react, the same observation having been made in the meantime by Koelsch (5). Usually the yield decreases in the order *para* > *meta* > *ortho*, and the *ortho*-substituted products as a rule are so impure that the usual means of isolation, *e.g.*, distillation or crystallization, are unsatisfactory. In these cases the easy conversion of the products into the di- or tetra-bromides, respectively, has been used to advantage. Two standard methods for the regeneration of the unsaturated compounds from the bromides were used: (a) boiling in quinoline solution [the original method of Pfeiffer (6), who used pyridine for the same purpose, did not succeed in a number of cases] and (b) treatment of the bromides with potassium iodide in acetone solution. With either method the tetrabromides lose all four bromine atoms at once Debromination with potassium iodide proceeded in all cases at room temperature. Although no direct comparison of stereoisomeric pairs as to rate of reaction was possible, it is indicated by the work of Young, Pressmann, and Coryell (7), that the bromides of *trans*-stilbenes react over a hundred times as rapidly as those of

the *cis*-derivatives. The easy and complete removal of bromine, therefore, makes it probable that the stilbenes and diphenylbutadienes which are formed in the Meerwein reaction possess the *trans* and *trans,trans* configuration, respectively. This conclusion is in accord with other chemical evidence which has been brought forward previously (3, 4).

TABLE I

MONOHALOGENO STILBENES AND DERIVATIVES

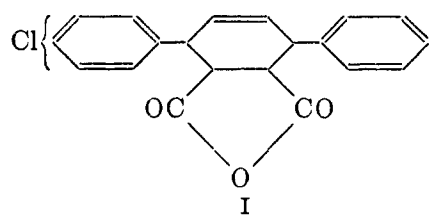
SUBSTITUENT	M.P., °C	M.P. OF DIBROMIDE °C	M.P. OF DIBENZYL °C
None	124	237	52
o-Chloro	40[a]	182[a]	liquid
m-Chloro	74	166	liquid
p-Chloro	129[b, c]	190[b]	49
o-Bromo	34	181	?
m-Bromo	89	166	?
p-Bromo	139	202[b]	32[d]

[a] Klages and Terzner, *Ber.*, **35**, 3965 (1902) report the m.p. 176° for the dibromide.
[b] Anschutz, *Ber.*, **60**, 1320 (1927).
[c] v. Walther and Wetzlich, *J. prakt. Chem.*, **61**, 196 (1900).
[d] Speer and Hill, *J. Org. Chem.*, **2**, 139 (1937).

TABLE II

MONOCHLORO-1,4-DIPHENYLBUTADIENES

SUBSTITUENT	M.P., °C	FLUORESCENCE	COLOR WITH H_2SO_4	M.P. OF TETRA-BROMIDE, °C	M.P. OF ADDUCT (I), °C	M.P. OF DIPHENYL-BUTANE, °C
None	152	blue	none	236	207	52
o-Chloro	110	blue	brown	220	179	liquid
m-Chloro	112	blue	violet	202	188	liquid
p-Chloro	161	blue-violet	red-violet	221	218	35



I

In Tables I and II, which summarize our results, several general features are recognizable. The melting points show a regular trend in nearly all cases. Since only one factor, the position of the substituent, is varied in all series, the substances are suitable for comparison. First may be noted the enormous differences between the saturated dibenzyls or diphenylbutanes and the corresponding di- or tetra-bromides. It is known that these bromides assume a more or less rigid structure due to the repulsive forces between the bromine atoms

themselves and between bromine atoms and the benzene ring (8).[1] Similarly, in the adducts of the various diphenylbutadienes with maleic anhydride (I) two kinds of intramolecular movements are theoretically possible, free rotation of the benzene rings about the C-aryl bonds, and oscillative puckering of the central cyclohexene ring. Both are overcome by electronic interaction between the phenyl groups and the carbonyl groups in the anhydride ring. We may therefore conclude that the rigid structure of such molecules is associated with a comparatively high melting point, *i.e.*, with high intermolecular attractive forces, resulting in high lattice energy. On the other hand, the free intramolecular rotations or oscillations in the saturated hydrocarbons diminish the lattice energy.

In the unsaturated compounds, in which conjugation of the olefinic links with the aromatic rings occurs, the free rotation of the phenyl ring is restricted by resonance, which imparts some double-bond character to the C-aryl bonds. The substituents then modify the degree of resonance. Halogen in the *para* position enhances resonance, as should also an *ortho* substituent. Here, however, the inverse effect is observed, partly due to steric hindrance—bromine has a more pronounced effect than chlorine—and partly due to direct electronic interaction with the adjacent double bond. A *meta* substituent can exert only an inductive effect, which in this case enhances free rotation.

A striking difference between the chloro- and bromo-stilbenes is observed during catalytic hydrogenation. All three isomeric chlorostilbenes are reduced quantitatively to the chlorodibenzyls. On the other hand, the bromo compounds split off hydrogen bromide simultaneously with saturation of the olefinic bond, although the reaction stops after the absorption of about one mole of hydrogen. The product consists of a mixture of dibenzyl and bromodibenzyl which can not be separated satisfactorily. It is known that in catalytic hydrogenations halogen can be removed from aromatic rings in the order I > Br > Cl (10). However, in all these cases, the halogen has to be activated by further substituents, *e.g.*, nitro groups. No such activating influence has so far been recognized for a vinyl group as an additional substituent. The nature of this influence is not yet clear. In this connection it is of great interest that in the reaction of halogenated stilbenes with alkali metals, even chlorine is quantitatively removed from the benzene ring. This peculiar reaction will be described in a forthcoming paper.

EXPERIMENTAL

All melting points are uncorrected.

1. o-Chlorostilbene. (*a*) *Meerwein reaction.* A solution of *o*-chloroaniline in water (100 cc.) and hydrochloric acid (80 cc.) was diazotized at 0° with a solution of sodium nitrite (15 g.) in water (30 cc.). The clear diazo solution[2] was added to a cooled solution of cin-

[1] That not merely the mass or the size of the substituent is responsible for the high melting point, is indicated by comparison of *trans*-stilbene dibromide (227°) with hexahydrostilbene dibromide (153°), in which one phenyl ring has been completely reduced (9).

[2] For the successful accomplishment of Meerwein reactions the preparation of completely clear diazo solutions is the fundamental condition. A simple method, which permits quantitative diazotization in dilute acid of even the weakest aniline bases, will be published later.

namic acid (30 g.) in acetone (250 cc.). After addition and solution of sodium acetate (44 g.) a solution of cupric chloride (8.5 g.) in water (20 cc.) was added. The temperature was allowed to rise slowly to 20°, when gas evolution began. Stirring was continued at 23–24° for 3 hrs. At the end of the coupling reaction two layers had formed in the mixture. The upper layer consisted of a dark green oil, and the lower layer of a bright green water-acetone mixture. After steam distillation the oil was dissolved in benzene, washed several times with 3 *N* ammonium hydroxide, and then with water. Distillation yielded 7 g. of a red oil boiling at 150° at 0.1 mm. The red color could not be removed by repeated distillation and the oil did not crystallize. For purification it was converted into the dibromide by treatment with excess bromine in carbon tetrachloride. The dibromide crystallized in long rods from petroleum ether (130°) and melted at 181–182°.

The dibromide was dissolved in acetone and treated with 4 moles of potassium iodide. Reaction proceeded quickly at room temperature and was completed by heating on the water-bath for an hour. Distillation gave a nearly colorless oil boiling at 145° at 0.03 mm.; yield 4 g. or 9%. The substance crystallized on standing, and melted at 39–40°.

(*b*) *Grignard reaction.* The reaction between benzylmagnesium chloride (0.15 mole) and *o*-chlorobenzaldehyde (0.1 mole) yielded an oil, from which by distillation a fraction boiling at 145° at 0.05 mm. was isolated. It crystallized on trituration with methanol, and was recrystallized from the same solvent, melting at 75°. The substance is the expected carbinol, benzyl-*o*-chlorophenylcarbinol; yield 30%. The same carbinol resulted in about 70% yield from the interaction of *o*-chloroiodobenzene and phenylacetaldehyde.

Anal. Calc'd for $C_{14}H_{13}ClO$: C, 72.4; H, 5.6.
Found: C, 72.2; H, 5.3.

T e carbinol is remarkably resistant to dehydration. Potassium bisulfate at 180° was ineffective. When the carbinol was acetylated with acetic anhydride and the acetate heated to 300° for one hour, deacylation occurred. The *o*-chlorostilbene distilled at 208–210° at 30 mm.; yield 80%.

Reduction of *o*-chlorostilbene with palladium-barium sulfate in ethanol gave an oil boiling at 138–139° at 3.5 mm., $n_D^{16.5}$ 1.5850.

Anal. Calc'd for $C_{14}H_{13}Cl$: C, 77.8; H, 6.0.
Found: C, 77.4; H, 6.2.

2. m-Chlorostilbene. The Meerwein reaction was carried out as described above with the same quantities of material. Evolution of gas took place at 16–20°. The oily product was distilled *in vacuo*, and boiled at 175–180° at 0.2 mm. The yellow-red distillate crystallized immediately. It was triturated with ligroin and recrystallized from ethanol, m.p. 73–74°; yield 7 g. or 16%.

Anal. Calc'd for $C_{14}H_{11}Cl$: C, 78.5; H, 5.1.
Found: C, 78.3; H, 5.2.

The dibromide crystallized from petroleum ether (130°) in branched leaflets, m.p. 166°.

Anal. Calc'd for $C_{14}H_{11}Br_2Cl$: C, 44.9; H, 2.9.
Found: C, 45.0; H, 2.6.

m-Chlorostilbene (1.3 g.) in ethanol (20 cc.), when reduced with Raney nickel absorbed 130 cc. of hydrogen in 5 minutes (*t*, 13°; *p*, 762 mm.); calc'd 142 cc. Distillation of the product gave a yellow oil boiling at 148° at 3 mm. which did not crystallize, n_D^{18} 1.5790.

Anal. Calc'd for $C_{14}H_{13}Cl$: C, 77.8; H, 6.0.
Found: C, 78.1; H, 5.8.

3. p-Chlorostilbene. Reaction occurred at 14–16°. The residue which remained after steam distillation was dissolved in benzene and washed as above. After removal of the solvent a crystalline residue was obtained directly, which crystallized as shiny leaflets from isopropyl alcohol, m.p. 129°; yield 40%.

The dibromides formed prismatic plates from petroleum ether (130°) and melted at 189–190°.

p-Chlorostilbene (5 g.) in ethanol (75 cc.), when reduced in the presence of Raney nickel absorbed in one hour 525 cc. of hydrogen (*t*, 16°; *p*, 762 mm.); calc'd 550 cc. The residue crystallized on trituration with a little methanol, and melted at 49°.

Anal. Calc'd for $C_{14}H_{13}Cl$: C, 77.8; H, 6.0.
Found: C, 77.6; H, 5.8.

4. o-Bromostilbene. The Meerwein reaction was carried out as before. The reaction temperature was 23–27°. Distillation *in vacuo* yielded a red-brown oil which was purified *via* the dibromide. The dibromide was recrystallized twice from petroleum ether (130°) and melted at 181°.

Anal. Calc'd for $C_{14}H_{11}Br_3$: C, 40.1; H, 2.6.
Found: C, 40.4; H, 2.9.

Decomposition of the dibromide with potassium iodide in acetone yielded a yellowish oil which boiled at 143–145° at 0.15 mm.; yield 4 g. or 8%. After several days the oil crystallized in big plates melting at 34°.

Anal. Calc'd for $C_{14}H_{11}Br$: C, 64.9; H, 4.2.
Found: C, 64.9; H, 4.0.

o-Bromodibenzyl. (a) Catalytic reduction of *o*-bromostilbene in ethanol over Raney nickel gave an oily product boiling at 135–140° at 3 mm., which according to analysis consisted of a mixture of hydrocarbon and brominated compounds.

Anal. Calc'd for $C_{14}H_{13}Br$: C, 64.4; H, 5.0.
Found: C, 75.0; H, 5.8.

(b) *Sandmeyer reaction with o-aminodibenzyl* (*11*). *o*-Aminodibenzyl (11 g.) was converted into its sulfate with 12 g. of sulfuric acid and 135 cc. of water. The sulfate was diazotized with 5 g. of sodium nitrite in 15 cc. of water at 0–5°. The filtered diazo solution was added dropwise to a warm (40°) solution of cuprous bromide (5 g.) and the reaction mixture was stirred for half an hour at 45°.

The semi-solid precipitate was dissolved in ether, the solution filtered and washed with sodium hydroxide solution and dilute hydrochloric acid. Rectification gave 7.5 g. of an oil which boiled at 115° at 0.3 mm.

Further distillation gave a fraction boiling at 160° at 22 mm. which crystallized immediately, and melted at 51°. It was halogen-free and gave no melting point depression in mixture with dibenzyl. Another fraction boiling at 180° at 22 mm., showed on analysis about 79% carbon. This fraction, therefore, again consisted of a mixture of dibenzyl and *o*-bromodibenzyl.

Anal. Found: C, 79.4; H, 6.2.

5. m-Bromostilbene. The diazo compound reacted in this case at 25°. The reaction mixture, after standing overnight, deposited a dark oil which was taken up in benzene. On washing with ammonia a heavy emulsion was formed. Separation of the benzene and water layer was facilitated by addition of concentrated sodium chloride solution. The benzene solution, after evaporation of the solvent, left a resinous residue which was extracted several times with boiling ethanol. The ethanol solution was boiled with charcoal and the solvent partly distilled off. The residue crystallized on trituration with ethanol and acetone. Recrystallization from ethanol gave clusters of needles, and from petroleum ether (80°), twinned plates melting at 89–90°; yield 17%.

Anal. Calc'd for $C_{14}H_{11}Br$: C, 64.9; H, 4.2.
Found: C, 64.7; H, 4.3.

The dibromide, which was prepared in chloroform solution, formed long lancets from petroleum ether (130°) and melted at 166°.

Anal. Calc'd for $C_{14}H_{11}Br_3$: C, 40.1; H, 2.6.
Found: C, 39.9; H, 2.9.

m-Bromostilbene (0.8 g.) in ethanol (25 cc.) absorbed 75 cc. of hydrogen during about one hour in the presence of Raney nickel (*p*, 760 mm.; *t*, 16°). Then absorption came to a standstill. Calc'd (for 1 mole of hydrogen) 73 cc. The oily product was distilled *in vacuo*, b.p. 140–145° at 0.5 mm.

Anal. Calc'd for $C_{14}H_{13}Br$; C, 64.4; H, 5.0.
$C_{14}H_{13}Br + C_{14}H_{14}$: C, 75.8; H, 6.1.
Found: C, 77.3; 77.4; H, 6.5; 6.3.

Analysis shows that the mixture is composed of about 50% bromodibenzyl and 50% dibenzyl.

6. p-Bromostilbene. Reaction occurred at 24°. The benzene residue crystallized immediately from isopropanol, and melted at 139°. Seventeen grams of *p*-bromoaniline yielded 6 g. of *p*-bromostilbene, or 23%. The dibromide crystallizes from xylene-petroleum ether (130°) in prismatic plates melting at 201–202°. *p*-Bromostilbene (1.7 g.) in ethanol (30 cc.) absorbed 145 cc. of hydrogen in the presence of Raney nickel (*t*, 16°; *p*, 760 mm.); calc'd 155 cc. The oily residue was distilled, boiling at 155–160° at 0.5 mm. Analysis shows that it consists almost exactly of an equimolecular mixture of dibenzyl with bromodibenzyl.

Anal. Calc'd for $C_{14}H_{13}Br + C_{14}H_{14}$: C, 75.8; H, 6.1.
Found: C, 75.2; H, 6.0.

7. o-Chlorodiphenylbutadiene. A solution of *o*-chloroaniline (6.4 g.) in concentrated hydrochloric acid (6 cc.) and water (20 cc.) was diazotized with a solution of sodium nitrite (4.2 g.) in water (8 cc.). The clear diazo solution was added to a solution of cinnamalacetic acid[3] (8.8 g.), in acetone (250 cc.). A cloudy precipitate was formed. After addition of sodium acetate (10 g.) and cupric chloride (2 g.) the temperature was raised slowly. Reaction started at 20° and the solution gradually became clear. After steam distillation, the residual oil was dissolved in chloroform and washed with sodium hydroxide. Distillation in a high vacuum gave about 2 g. of a main fraction boiling at 220° at 0.04 mm. This oil crystallized on trituration with methanol-acetone. Recrystallized twice from ethanol, the 1-(*o*-chlorophenyl)-4-phenyl-1,3-butadiene formed clusters of leaflets melting at 110°; yield 1.2 g. or 10%.

Anal. Calc'd for $C_{16}H_{13}Cl$: C, 80.0; H, 5.4.
Found: C, 79.9; H, 5.6.

Bromination was carried out in chloroform solution. The oily residue was triturated with ethanol and recrystallized from butyl acetate, forming plates which melted at 220°.

Anal. Calc'd for $C_{16}H_{13}Br_4Cl$: C, 34.3; H, 2.3.
Found: C, 33.8; H, 2.2.

Catalytic reduction in ethyl acetate over palladium-barium sulfate gave a greenish oil boiling at 180° at 0.05 mm.

Anal. Calc'd for $C_{16}H_{17}Cl$: C, 78.7; H, 7.0.
Found: C, 78.3; H, 6.6.

1-(*o*-chlorophenyl)-4-phenyl-1,3-butadiene (0.15 g.) and maleic anhydride (0.6 g.) were melted together at 110° and the liquid mixture heated on a water-bath for one hour. The mass was dissolved in acetic acid and the reaction product (0.1 g.) precipitated by water. It was recrystallized twice from butanol-acetic acid, forming twinned plates which melted at 178–179°.

Anal. Calc'd for $C_{20}H_{15}ClO_3$: C, 71.0; H, 4.4.
Found: C, 71.3; H, 4.1.

8. 1-(m-Chlorophenyl)-4-phenyl-1,3-butadiene. Reaction occurred at 35°. After steam distillation, a semi-solid brown mass deposited on the bottom of the flask. The water was decanted and the residue kneaded with acetic acid. From ethanol, 3.5 g. or 29% of twinned leaflets were obtained melting at 114°.

Anal. Calc'd for $C_{16}H_{13}Cl$: C, 80.0; H, 5.4.
Found: C, 80.0; H, 4.9.

The tetrabromide crystallized from petroleum ether (130°) in plates melting at 202°.

Anal. Calc'd for $C_{16}H_{13}Br_4Cl$: C, 34.3; H, 2.3.
Found: C, 34.7; H, 2.4.

Catalytic reduction: 1 g. of 1-(*m*-chlorophenyl)-4-phenyl-1,3-butadiene in glacial acetic acid (25 cc.) absorbed the required amount of hydrogen in 20 minutes. Distillation gave a nearly colorless oil which boiled at 190° at 0.06 mm.

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[3] The method of Plati, Strain, and Warren (12) proved much superior to previous syntheses. In our experience, it is essential to recrystallize the cinnamalacetone from ligroin before oxidation with sodium hypochlorite, in order to secure an acid of good quality and in satisfactory yield.

Anal. Calc'd for $C_{16}H_{17}Cl$: C, 78.7; H, 7.0.
Found: C, 79.1; H, 7.1.

The maleic anhydride adduct was formed by heating on a water-bath 1-(*m*-chlorophenyl)-4-phenyl-1,3-butadiene (0.35 g.) and maleic anhydride (1 g.) for 12 hours. The product was isolated by treatment with dilute acetic acid. Recrystallization from butyl acetate-petroleum ether (130°) gave clusters of plates melting at 188°; yield 0.3 g.

Anal. Calc'd for $C_{20}H_{15}ClO_3$: C, 71.0; H, 4.4.
Found: C, 70.9; H, 4.3.

9. 1-(p-Chlorophenyl)-4-phenyl-1,3-butadiene. Reaction occurred at 23°. The residue from the steam distillation crystallized directly on trituration with acetic acid. The substance (11 g.) was first recrystallized from acetic acid, then from petroleum ether (130°), forming flat plates which melted at 161°; yield of the pure product 4 g. or 33%.

Anal. Calc'd for $C_{16}H_{13}Cl$: C, 80.0; H, 5.4.
Found: C, 80.3; H, 5.4.

The tetrabromide crystallized in clusters of plates from petroleum ether (130°) with addition of a few drops of xylene. It melted at 224°.

Anal. Calc'd for $C_{16}H_{13}Br_4Cl$: C, 34.3; H, 2.3.
Found: C, 34.1; H, 2.0.

Catalytic reduction of 1-(*p*-chlorophenyl)-4-phenyl-1,3-butadiene (1 g.) over Raney nickel in warm acetic acid (25 cc.) proceeded during 10 minutes; 200 cc. of hydrogen was absorbed (*p*, 759 mm.; *t*, 22°); calc'd 190 cc. The product was distilled *in vacuo*, boiling at 175–180° at 0.6 mm., and crystallized spontaneously, melting at 35°.

Anal. Calc'd for $C_{16}H_{17}Cl$: C, 78.7; H, 7.0.
Found: C, 78.5; H, 7.4.

The maleic anhydride adduct of 1-(*p*-chlorophenyl)-4-phenyl-1,3-butadiene (0.4 g.) with maleic anhydride (1 g.) was formed on heating the mixture on a water-bath for five hours. The mass was dissolved in hot acetic acid. On cooling, the adduct precipitated. From glacial acetic acid, clusters of plates were formed melting at 212°; yield 0.4 g.

Anal. Calc'd for $C_{20}H_{15}ClO_3$: C, 71.0; H, 4.4.
Found: C, 71.4; H, 4.2.

SUMMARY

By means of the Meerwein reaction, the three series of monochloro-, monobromo-stilbenes, and monochloro-1,4-diphenylbutadienes and certain derivatives were prepared. The regular variations in melting points, observed in all three series, are related to the different factors which influence the rigidity of molecular structure. On catalytic hydrogenation, all the chloro derivatives give the saturated chloro compounds, whereas the bromine is removed from the aromatic ring to about 50%.

REHOVOTH, PALESTINE.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

SUBSTITUTED STILBENES AND 1,4-DIPHENYLBUTADIENES. PART III. MEERWEIN REACTION WITH *p*-AMINOBIPHENYL A NEW SYNTHESIS OF *lin.*-QUATERPHENYL

FELIX BERGMANN AND JAEL WEIZMAN

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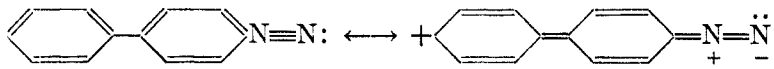
Among the factors which influence the successful achievement of the Meerwein reaction, an important role is played by the nature and the position of substituents in the diazo component. The mechanism by which substituents influence the course of the coupling reaction has not yet been cleared up. The most obvious feature, which varies from one substituent to another, is the stability of the diazo compounds. Snow (1), in a comprehensive study, has shown that certain groups, preferably halogens, alkoxyl, or nitro groups, stabilize the diazo compound appreciably. As coupling with the olefinic component in the Meerwein reaction usually proceeds at about 20° or higher, the stability of the diazotized amine up to this temperature is one fundamental condition. This is clearly pointed out by experiments with aniline itself, which in the stability scale of Snow stands near to the end. Coupling with cinnamic acid gives a very low yield of stilbene (1–2%), and with cinnamalacetic acid only traces of 1,4-diphenylbutadiene. A phenyl group in the para position stabilizes the diazonium ion enormously by resonance (*e.g.*, I ↔ Ia).



I Ia

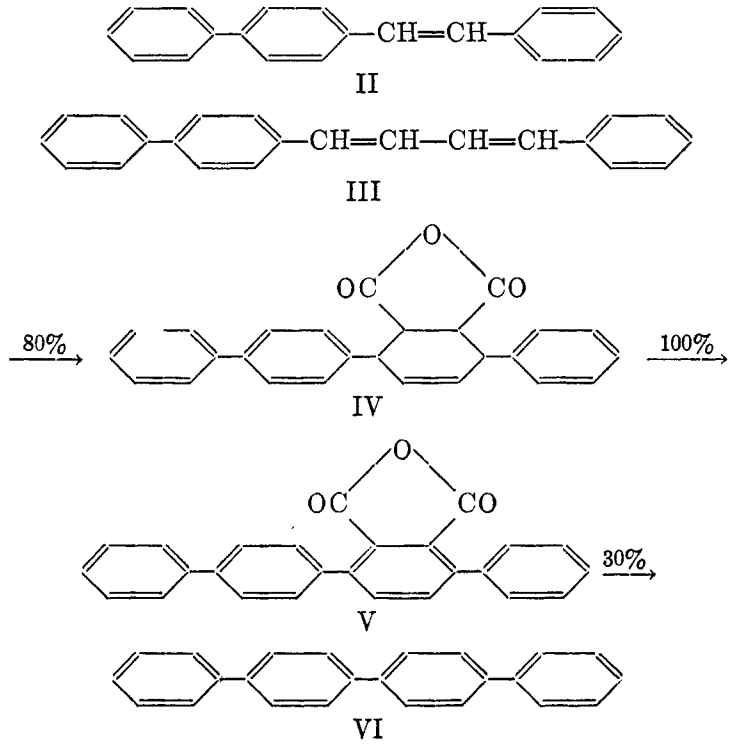
Therefore, *p*-aminobiphenyl gives a 12% yield of *p*-phenylstilbene (II) (2) and 20% of 1-phenyl-4(*p*-phenylphenyl)-1,3-butadiene (III), respectively. On the other hand, a phenyl group in the ortho position completely prevents coupling, presumably because of its large size.

The enhanced resonance in the conjugated systems II and III is reflected in their physical properties (Table I). Light absorption is shifted to longer wavelengths, and the melting points are raised considerably.

When the diene (III) was heated to 140° with 10 moles of maleic anhydride, the adduct (IV) resulted in 80% yield. The melting point of IV is lowered during recrystallization from 260° to 250°, a phenomenon which may be explained by the shift of the double bond in the cyclohexene ring (2). In contrast to similar cases (3), nitrobenzene effected aromatization of the adduct with great difficulty. After boiling the reactants 2 hours in this solvent, only IV was obtained. After 10 hours, a mixture of IV and V was obtained, but an appreciable part of the product was decomposed. The method of Kuhn (2),[1] who achieved dehydrogenation of the disodium salt with ferricyanide, also gave negative results. On the other hand, dehydrogenation with sulfur yielded V

[1] Lohaus (4) prepared terphenyl in quantitative yield from 3,6-diphenyldihydrophthalic acid with potassium ferricyanide in one step.

quantitatively. Decarboxylation by basic copper carbonate in boiling quinoline then produced quaterphenyl (VI) in 30% yield. Although the last step gave only a moderate yield, the present method provides a convenient route to VI, as regards availability of starting materials and purity of end product (5).



EXPERIMENTAL

All melting points are uncorrected.

Stilbene. Coupling of diazotized aniline (0.1 mole) with cinnamic acid[2] gave a resinous product which, after distillation in a high vacuum, yielded 200 mg. (1.2%) of stilbene, the melting point and mixed melting point of which was 123°.

1,4-Diphenylbutadiene. The same reaction with cinnamalacetic acid (8.5 g. or 0.05 mole) yielded a sirupy product which was dissolved in methanol-acetone. After several days it deposited a few mg. of crystals melting at 143°. After the compound had been recrystallized from glacial acetic acid the melting point and mixed melting point was 151–152°.

p-Phenylstilbene (II) (2). *p*-Aminobiphenyl (8.6 g. or 0.05 mole) was dissolved in ethanol (400 cc.), and concentrated hydrochloric acid (6 cc.) added dropwise to the boiling solution. On cooling, the hydrochloride crystallized in shiny yellowish plates melting at 285°.

The hydrochloride (10.5 g.) was suspended in 10 cc. of concentrated hydrochloric acid and 20 cc. of ice-water, and diazotized with sodium nitrite (4 g.). The clear diazo solution was added at 5° to a solution of cinnamic acid (7.4 g.) in acetone (150 cc.). After addition of sodium acetate (10 g.) and cupric chloride (2 g.), the temperature was allowed to rise slowly. Evolution of gas started at 16°, but for completion of the reaction it was necessary

[2] This reaction is already mentioned by Meerwein (6).

to heat at 40° for 4 hours. After steam distillation of the crude substance a granular product remained, which was distilled in a vacuum (boiling point *ca.* 300° at 1 mm.), and which crystallized on trituration with ethanol. From petroleum ether (130°) ill-defined crystals (needles?) formed, melting at 209°; yield 1.2 g. or 12%. Kuhn (2) reports the melting point 221° (corr.).

Anal. Calc'd for $C_{20}H_{16}$: C, 93.75; H, 6.25.
Found: C, 93.9; H, 6.5.

The dibromide, which was prepared in chloroform, crystallized on trituration with ethanol. From petroleum ether (130°) it crystallized in colorless long rods melting at 229°.

Anal. Calc'd for $C_{20}H_{16}Br_2$: C, 57.7; H, 3.9.
Found: C, 57.6; H, 3.9.

Catalytic reduction of 300 mg. of II over palladium-barium sulfate in ethyl acetate proceeded smoothly. After distillation of the solvent, the residue was recrystallized from ethanol, giving branched plates melting at 109°.

Anal. Calc'd for $C_{20}H_{18}$: C, 93.0; H, 7.0.
Found: C, 92.9; H, 7.0.

1-Phenyl-4-(p-phenylphenyl)-1,3-butadiene (III). Coupling with cinnamalacetic acid (8.8 g.) in acetone (150 cc.) was carried out as described above. Evolution of gas became rapid at about 30° and was completed by heating to 37° for 3 hours. After steam distillation, the residue was heated with acetic acid. Recrystallization from butyl acetate, then from xylene (brown solution with intense violet-red fluorescence) gave thin yellow plates melting at 214–215°; yield 2.8 g. or 20%. With concentrated sulfuric acid, a deep violet color is obtained, which changes on heating to violet red, then to brown.

TABLE I

PHYSICAL PROPERTIES

COMPOUND	M.P., °C	COLOR	REACTION WITH CONC'D H_2SO_4	FLUORESCENCE	BROMIDE M.P., °C	ADDUCT WITH MALEIC ANHYDR., M.P., °C	HYDROGENATION PRODUCT M.P., °C
Stilbene	124	none	none	blue	237		52
II	209	yellowish	blue	violet	229		109
1,4-Diphenylbutadiene	152	yellowish	none	blue-violet	236	207	52
III	215	deep yellow	deep violet	bright blue	238	250	77

Anal. Calc'd for $C_{22}H_{18}$: C, 93.6; H, 6.4.
Found: C, 93.8; H, 6.5.

The tetrabromide was triturated with ligroin and recrystallized from petroleum ether (130°) and xylene. Clusters of plates appeared, melting at 238°. Although the substance was recrystallized four times, analysis showed a deficit of 2% in carbon. It is possible that a small amount of a nuclear brominated product was present.

Anal. Calc'd for $C_{22}H_{18}Br_4$: C, 43.9; H, 3.0.
Found: C, 42.0, 42.0; H, 3.1, 3.0.

Catalytic reduction of III (0.4 g.) in ethyl acetate (20 cc.) over palladium-barium sulfate was accomplished during one hour. Absorbed hydrogen: 60 cc.; calc'd: 62 cc. The 1-phenyl-4-(*p*-phenylphenyl)butane crystallized from ethanol in coarse blocks melting at 77°.

Anal. Calc'd for $C_{22}H_{22}$: C, 92.3; H, 7.7.
Found: C, 92.3; H, 7.6.

III (1.4 g.) and maleic anhydride (5 g. or 10 equivalents) were heated together at 140–150° for one hour. The mass was dissolved in boiling acetic acid, and deposited on cooling 1.5 g. or 80% of the adduct, IV. The crude product showed the melting point 260°, which

after one recrystallization from butyl acetate decreased to 255°, and after a second one from xylene, to 250°. The colorless solution showed a weak blue fluorescence and deposited stars of long slender needles.

Anal. Calc'd for $C_{26}H_{20}O_3$: C, 82.1; H, 5.3.
Found: C, 81.8; H, 5.3.

When the adduct (1 g.) was suspended in ethanol (20 cc.) and 10% sodium hydroxide (10 cc.), it dissolved on gentle heating. On dropping the solution upon ice and hydrochloric acid, a snow-white precipitate was obtained. Recrystallization from ethanol gave colorless lancets. The dicarboxylic acid derived from IV sinters at 190°, and gives a clear yellow melt at 206°. It can be heated up to 230°, above which temperature decomposition occurs (dehydration?).

Anal. Calc'd for $C_{26}H_{22}O_4$: C, 78.4; H, 5.5.
Found: C, 78.3; H, 5.8.

Dehydrogenation of the dicarboxylic acid with potassium ferricyanide (2, 4) gave an amorphous product. The diene reaction in boiling nitrobenzene for 2 hours gave the tetrahydro product, IV, in 20% yield, the melting point and mixed melting point of which is 250°. When the reaction time was extended to 10 hours, the product, on recrystallization from xylene, presented a mixture of needles (IV) and boats (V). The yield was, however, so small that this method was abandoned.

The adduct, IV, (1.5 g.) and sulfur (0.3 g.) were intimately mixed and heated to 240°, whereupon evolution of hydrogen sulfide started. The violent reaction ceased after 10 minutes and was completed by heating to 300° for 2 minutes. The product was triturated with hot acetic acid and recrystallized from xylene with addition of charcoal. Yellow boatlike crystals (V) were formed, melting at 218° (with previous sintering); yield 1.5 g. (quantitative).

Anal. Calc'd for $C_{26}H_{16}O_3$: C, 83.0; H, 4.3.
Found: C, 82.8; H, 3.7.

3-Phenyl-6-(*p*-phenylphenyl)phthalic anhydride (V) (1 g.) and basic copper carbonate (2 g.) were heated in quinoline (30 cc.) to 140°. At this temperature reaction started. The water which formed was slowly distilled off with quinoline during one hour; then the mixture was boiled for 30 minutes. The quinoline was removed by steam, the water decanted, and the residue extracted with boiling xylene. After two recrystallizations from xylene, 250 mg. (31%) of quaterphenyl (VI) were obtained as plates melting at 312°.

Anal. Calc'd for $C_{24}H_{18}$: C, 94.1; H, 5.9.
Found: C, 94.1; H, 6.2.

SUMMARY

p-Aminobiphenyl easily undergoes the Meerwein reaction, yielding *p*-phenylstilbene and 1-phenyl-4-(*p*-phenylphenyl)-1,3-butadiene. The latter, through diene reaction with maleic anhydride, opens up a new route to quaterphenyl.

REHOVOTH, PALESTINE.

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THE REDUCTION OF CERTAIN HALOGENATED NITROPARAFFINS BY LIQUID AMMONIA

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Only one reducing agent, titanous chloride, has been found to react with both tetranitromethane and the dihalogendinitromethanes in a similar manner, namely, by the reduction of nitro groups, to amino groups. One reducing agent in particular, anhydrous liquid ammonia, has been used with tetranitromethane and not with the dihalogendinitromethanes. This investigation was undertaken to see if halogen or nitro group would be removed when dihalogendinitromethanes were treated with anhydrous liquid ammonia. If one group only is removed, the reactivity of the group and the molecule might be studied.

Tetranitromethane reacts with a variety of reducing agents in alkaline solution, losing a nitro group with formation of a salt of nitroform. Reducing agents which give this reaction are liquid ammonia (1), potassium ferrocyanide (2), sodium arsenite, sodium phosphite, and sodium potassium tartrate (3), hydrazine (4), potassium hydroxide (5), and sodium sulfite (6). However, titanous chloride (5) and zinc plus hydrochloric acid (7) give guanidine as the final product, while phenylhydrazine in alkali (8) gives the salt of mononitromethane. Equations illustrating these three types of reaction are:

$$6C(NO_2)_4 + 14NH_3 \rightarrow 6C(CO_2)_3NH_4 + 3NH_4NO_3 + 3H_2O + 4N_2$$

$$C(NO_2)_4 + 9H_2 \xrightarrow{(TiCl_2)} (NH_2)_2C = NH + HNO_2 + 6H_2O$$

$$C(NO_2)_4 + 3C_6H_5NHNH_2 + 4KOH \rightarrow CH_2NO_2K + 3C_6H_6 + 3N_2 + 3KNO_2 + 4H_2O$$

Dihalogendinitromethanes also react with reducing agents in alkaline solution, but with loss of a halogen rather than a nitro group. Dichlorodinitromethane and dibromodinitromethane react with potassium hydroxide and potassium iodide (9) and hydrazine plus alkali (10), with loss of one halogen, *e.g.*:

$$2\ Br_2C(NO_2)_2 + N_2H_4 + 4KOH \rightarrow 2BrC(NO_2)_2K + 2KBr + N_2 + 4H_2O$$

With potassium cyanide (9) dibromodinitromethane gives finally the potassium salt of dinitromethane:

$$Br_2C(NO_2)_2 + KCN \rightarrow BrC(NO_2)_2K + CNBr$$

$$2BrC(NO_2)_2K + 2KCN + H_2O \rightarrow 2CH(NO_2)_2K + KBr + CNBr + KCNO$$

Postassium chlorodinitromethane does not react according to the last equation. With potassium nitrite (9) dichlorodinitromethane gives potassium chlorodini-

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tromethane only, while dibromodinitromethane gives a 12–15% yield of potassium nitroformate. Titanous chloride (5) reacts with dibromodinitromethane to give the diamine, the halogens not being attacked. Phenylhydrazine plus alkali (8) reacts with dibromodinitromethane, taking off both bromines.

The mixed halogen dinitromethanes react in similar fashion. Usually the more active halogen (I > Br > Cl) is removed, but sometimes the less active halogen is also removed. The ratio of potassium chlorodinitromethane to potassium bromodinitromethane formed in the reaction of chlorobromodinitromethane with potassium hydroxide is about four to one (9).

In general, therefore, tetranitromethane reacts with reducing agents to lose a nitro group, but dihalogendinitromethanes react to lose halogen. Titanous chloride reduces nitro groups to amino groups in each type of compound, and does not remove halogen from the dihalogendinitromethanes. This investigation shows that anhydrous liquid ammonia removes halogen from dihalogendinitromethanes and does not affect the nitro groups except insofar as the nitro group functions in forming salts of pseudo acids.

EXPERIMENTAL

Preparation of materials. Dibromodinitromethane. The method of Losanitsch (11) was used except in purification of the material for determination of physical constants. Dry 2,4,6-tribromoaniline (12) was treated with concentrated nitric acid (10 ml. per g. of tribromoaniline) and the mixture heated until the reaction proceeded with rapid evolution of bromine and oxides of nitrogen. At this stage the flask was cooled to maintain control. After one hour the mixture was steam distilled, the dibromodinitromethane coming over as a greenish-black, heavy, insoluble oil. The oil was separated, washed with 1% sodium hydroxide until excess acid had been neutralized, and then with distilled water. It was then dried over anhydrous calcium chloride and vacuum distilled, dibromodinitromethane (60 g.) being collected at 72.4° under 16 mm. The dibromodinitromethane was further purified by treating it with anhydrous liquid ammonia (as described below), dissolving the ammonium bromonitroformate in distilled water, and reforming the dibromodinitromethane by the addition of bromine. A more extensive study was made of this particular compound than any of the others described in this paper. The physical constants of dibromodinitromethane are: b.p. 72.4–73° (16 mm.); m.p. 5.5°; d_4^{20} 2.4400; n_D 1.5280; surface tension 47.7 dyne/cm.; parachor, calc'd 286.8, found 284.3; viscosity (20°) 46.84 millipoises; molecular refraction, calc'd 33.39, found 33.30.

Dichlorodinitromethane. Two methods were used in the preparation of dichlorodinitromethane. The method of Downing and Orr (10) starting with 2,4,6-trichloroaniline is similar to that of Losanitsch for dibromodinitromethane. After reaction between the trichloroaniline and concentrated nitric acid, steam distillation, and separation, the oil was washed with 1% sodium hydroxide. When the aqueous layer became alkaline, a brilliant purple color appeared. This might have been due to some aromatic dinitro compound, indicating that the initial reaction of nitric acid with the trichloroaniline is nitration. This color change was not observed in the preparation of dibromodinitromethane.

After drying over anhydrous calcium chloride, the light yellow oil was vacuum distilled, b.p. 34.5–37° (13 mm.); d_4^{20} 1.6124; n_D 1.4575.

The dichlorodinitromethane was also prepared from ammonium chlorodinitromethane by passing chlorine into an ice-cold aqueous solution of the salt. The ammonium chlorodinitromethane was obtained readily from reaction of chlorobromodinitromethane with liquid ammonia (described below), and showed the physical constants: b.p. 34.5–36.5° (13 mm.); d_4^{20} 1.6123; n_D 1.4575; molecular refraction, calc'd 28.59, found 29.55.

Chlorobromodinitromethane. Chlorine was passed into an ice-cold aqueous solution of ammonium bromodinitromethane. The latter was obtained along with ammonium bromide from the reaction of dibromodinitromethane with liquid ammonia. A heavy oil separated which was washed with 1% sodium hydroxide, distilled water, dried over anhydrous alumina for several months, and vacuum distilled. The following physical constants of chlorobromodinitromethane were determined: b.p. 75–76° (15 mm.); d_4^{20} 2.0394; n_D 1.4739; m.p. 9.2–9.3°; molecular refraction, calc'd 30.22, found, 30.61; parachor, calc'd 272.6, found 275.9.

Reaction of dibromodinitromethane with anhydrous liquid ammonia. A fragile glass bulb filled with a weighed amount of dibromodinitromethane was placed in the reaction chamber which was kept at −33° by a Dewar flask filled with liquid ammonia. The chamber was evacuated and then liquid ammonia (about 50 ml.) was distilled into it. The bulb was broken by means of a plunger. A violent reaction occurred between the slightly yellow solidified dibromodinitromethane and the liquid ammonia, accompanied by rapid evolution of a colorless gas. Ammonia was removed from the evolved gases by bubbling the gas through water which was continually kept fresh.

On completion of the run, residual gases in the reaction chamber were forced over into the eudiometer by replacing the bath of liquid ammonia with a hot water-bath. The gas collected in the eudiometer was then drawn into a previously evacuated drying chamber which contained phosphorus pentoxide in order to remove water vapor and traces of ammonia. After drying for two days the gas was drawn into the evacuated flask of known volume

TABLE I

QUANTITATIVE REDUCTIONS OF SOME DIHALODINITROMETHANES

FORMULA	QUANTITY		N_2 LIBERATED MOLES	$\frac{X_2C(NO_2)_2}{N_2}$
	GRAMS	MOLES		
$Br_2C(NO_2)_2$	3.7565	0.01424	0.00443	3.2:1
$Br_2C(NO_2)_2$	2.7118	.01028	.00366	2.8:1
$Cl_2C(NO_2)_2$	1.8025	.01030	.00355	2.9:1
$Cl_2C(NO_2)_2$	2.3665	.01352	.00450	3.0:1

and the density determined. The molecular weight of the contained gas was calculated to be 29. Molecular weight, insolubility in water, and inertness to combustion indicated that the gas was nitrogen. The ratio of moles of dibromodinitromethane to moles of nitrogen formed is given in Table I.

The bright yellow solid left in the reaction chamber was dissolved in distilled water and treated with chlorine at 0°. The heavy oil which separated was washed with 1% sodium hydroxide, then with distilled water, dried over calcium chloride, and vacuum distilled; b.p. 75–76°; d_4^{20} 2.0392; n_D 1.4738.

On other samples the bright yellow reaction product decomposed readily on heating, leaving a white solid residue of ammonium bromide. The percentage of ammonium bromide found in the reaction product by precipitation of silver bromide and titration with standard ammonium thiocyanate ranged from 36% to 43%.

Addition of strong acid to an aqueous solution of the reaction product changed it from a yellow to a colorless solution. Neutralization of this colorless solution brought back the yellow color. The mixture of ammonium bromide and yellow salt was analyzed for total ammonia and found to contain 12.0%.

Reaction of dichlorodinitromethane with anhydrous liquid ammonia. Runs were made with samples of dichlorodinitromethane in the same manner as with dibromodinitromethane. The dichlorodinitromethane remained liquid even at −33°. When the glass bulb was first broken, two layers were observed in the reaction chamber, an upper yellow layer and a red layer at the bottom in which crystals were seen to form. After four minutes,

the red layer had disappeared. The ratio of moles of dichlorodinitromethane to moles of nitrogen formed is given in Table I.

The yellow reaction product was dissolved in distilled water and treated with bromine water. The heavy oil which separated was washed with 1% sodium hydroxide, distilled water, dried over calcium chloride, and vacuum distilled; b.p. 75–76° (15 mm.); d_4^{20} 2.0393; n_D 1.4739. These physical constants indicate that the compound is chlorobromodinitromethane.

Reaction of chlorobromodinitromethane with anhydrous liquid ammonia. This reaction was carried out by breaking a glass bulb of chlorobromodinitromethane in a Dewar flask containing liquid ammonia as previously described. A vigorous reaction occurred, similar in every respect to the reactions of dibromodinitromethane and dichlorodinitromethane. Excess ammonia was evaporated and the yellow reaction product taken up in distilled water. The solution was just acidified with nitric acid and then steam distilled to remove chlorodinitromethane. The solution was then tested for chloride ion using Miller's reagent. No chloride was found, but ammonium bromide was identified, indicating that bromine only had been removed in the reaction with liquid ammonia. This is in accordance with thermochemical data. The single bond energies in kilogram calories per mole, for the two types of bonds are (13): C-Br, 54.0 Kcal.; C-Cl, 66.5 Kcal.

Discussion of Results

The evidence shown in Table I indicates that the reaction of dibromodinitromethane and dichlorodinitromethane with anhydrous liquid ammonia proceeds according to the general equation (X = halogen):

$$3X_2C(NO_2)_2 + 8NH_3 \rightarrow 3XC(NO_2)_2NH_4 + 3NH_4X + N_2$$

According to this equation, 3 moles of dihalogendinitromethane reacts with liquid ammonia to yield 1 mole of nitrogen. This agrees well with the experimental values given in Table I. An equimolar mixture of ammonium bromodinitromethane and ammonium bromide would contain 40% ammonium bromide and 12% total ammonia. This checks with the observed values of 36–43% ammonium bromide and 12% total ammonia. The preparation of chlorobromodinitromethane from the yellow product of each reaction is additional proof that the reaction proceeds as indicated.

The reaction of chlorobromodinitromethane proceeds, with elimination of bromine to give ammonium chlorodinitromethane, ammonium bromide, and nitrogen. There was no evidence that chlorine was split off in this reaction.

The induction period in the dichlorodinitromethane reaction has been noted and will be studied further. The general rate curves agree with the order of reactivity of the halogens (Br > Cl).

Summary

(1) An equation is given for the reaction between dihalogendinitromethanes and anhydrous liquid ammonia.

(2) The reaction between chlorobromodinitromethane and anhydrous liquid ammonia proceeds with elimination of bromine only.

(3) New methods of preparing dichlorodinitromethane and chlorobromodinitromethane are reported, and additional physical constants for these compounds are given.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

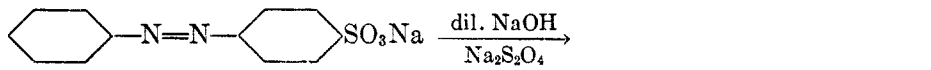
SODIUM *p*-AZOBENZENESULFONATE FROM NITROBENZENE AND SULFITE WASTE LIQUOR[1]

IRWIN A. PEARL

Received May 13, 1944

In a recent paper (1) it was reported that sodium *p*-azobenzenesulfonate was obtained as a reduction product from the action of sulfite waste liquor and alkali on nitrobenzene. This communication describes the identification of this salt and some of its reactions and, in addition, indicates that lignin is the active reducing agent involved in this unusual reaction.

Sodium *p*-azobenzenesulfonate (I) separated from the mixture when reduction was carried out at atmospheric pressure, as bright orange-colored crystals which gave irridescent orange plates on recrystallization from ethanol. Analysis indicated its composition and the color suggested the azo linkage. Reduction of the salt with tin or stannous chloride and acid gave benzidine as the main product, together with small amounts of aniline and sulfanilic acid. Alkaline reductions gave colorless solutions which, on acidification, gave benzidine sulfate (III) indicating that sodium hydrazobenzenesulfonate (II) must have been formed first and then rearranged on acidification.



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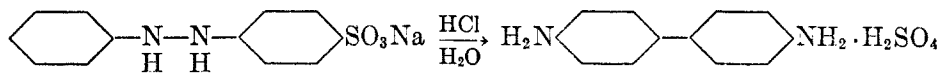

II III

Authentic sodium *p*-azobenzenesulfonate was prepared from *p*-azobenzenesulfonic acid which was made from azobenzene and oleum according to Chrzaszczewska and Dobrowolski (2). The properties of the two materials were identical. The reduction and rearrangement of the ammonium salt of *p*-azobenzenesulfonic acid was noted by Griess (3) and Noelting and Werner (4).

Having established the identity of the sodium *p*-azobenzenesulfonate, which is formed in approximately 25% yields by the reaction of sulfite waste liquor, sodium hydroxide, and nitrobenzene, a study was undertaken to determine what constituents in the alkaline waste liquor mixture were responsible for this unusual reaction. The principal components of sulfite waste liquor are sulfur dioxide, calcium sulfite and bisulfite, calcium lignosulfonates, and sugars. When nitrobenzene was refluxed for 8 hours with concentrated solutions of sodium sulfite and sodium hydroxide, the reactants were recovered unchanged

[1] This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Committee on Waste Disposal and conducted for the Committee by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the Committee to publish these results.

except for a small amount of azobenzene which was probably formed by the action of the sodium hydroxide on nitrobenzene (5). In an identical experiment using azoxybenzene (the most abundant reduction product of atmospheric pressure sulfite waste liquor reductions of nitrobenzene) in place of nitrobenzene, all the starting materials were recovered. Sodium *p*-azobenzenesulfonate was formed in small amounts by the reduction of nitrobenzene with purified calcium lignosulfonate containing no inorganic sulfites. Dextrose and alkali reduced nitrobenzene to azoxybenzene (6), and dextrose and alkali in the presence of inorganic sulfites reduced nitrobenzene only to azoxybenzene. Isolated alkali lignin together with sodium sulfite and sodium hydroxide reduced nitrobenzene to sodium *p*-azobenzenesulfonate in good yield. Conditions and results of the experiments are contained in Table I.

Expts. 1 and 2 prove that the sodium *p*-azobenzenesulfonate formed in the alkaline reductions of nitrobenzene with sulfite waste liquor could not have been formed by the reaction of alkaline sodium sulfite alone upon nitrobenzene or its reduction product (azoxybenzene) which was always obtained as the chief product. Expts. 5 and 6 indicate that isolated lignin in the presence of inorganic sulfite will reduce nitrobenzene to sodium *p*-azobenzenesulfonate, whereas dextrose under the same conditions does not. The fact that the yield of sodium *p*-azobenzenesulfonate, obtained by reduction with basic calcium lignosulfonate containing no inorganic sulfites (Expt. 3), is not increased by the addition of dextrose (Expt. 4) indicates that only lignin acts as a reducing agent in its production. In these two experiments the inorganic sulfite was obtained by the reaction of calcium lignosulfonate and alkali. The small yield of the azobenzenesulfonate, obtained by reduction with partially desulfonated lignin containing only a small amount of sulfur, was substantially increased by the addition of inorganic sulfite. These experimental results lead to the conclusion that, in the alkaline sulfite waste liquor reductions of nitrobenzene, the formation of sodium *p*-azobenzenesulfonate must result from the reduction of nitrobenzene by lignin in alkaline solution and the sulfonation of the reduced product in an active state by inorganic sulfites, which may be present in the original waste liquor or may be formed by desulfonation of the calcium lignosulfonate by the alkaline treatment. The fact that alkaline sulfite solution will not sulfonate nitrobenzene reduced by alkaline dextrose treatment implies that, in the case of sulfite waste liquor reductions of nitrobenzene, the sulfonation reaction occurs with a nitrobenzene reduction product which is liberated at a reduction potential characteristic of lignin alone. Only a large number of experiments could determine just what other organic compounds, if any, would reduce nitrobenzene at the right potential for sulfonation by inorganic sulfites to form sodium *p*-azobenzenesulfonate or other salts of azobenzenesulfonic acid.

The preparation of benzidine from sodium *p*-azobenzenesulfonate was studied in some detail. As noted above, reduction with tin and hydrochloric acid yielded benzidine and reduction with sodium hydrosulfite or hydrogen sulfide in alkaline solution (with subsequent acidification) yielded benzidine sulfate. In this connection, it is interesting to note that the conditions generally used for

splitting the azo linkage to two primary amines (namely, boiling with tin or stannous chloride in dilute hydrochloric acid) resulted in rearrangement of the intermediate hydrazo compound before reduction was complete. Sodium sulfide reduction with subsequent acidification yielded interesting results. Benzidine sulfate was obtained when the exact amount of sodium sulfide was used in the reduction, whereas the presence of an excess of the alkali sulfide resulted in the production of benzidine (in solution as the hydrochloride). Evidently the excess sodium sulfide reduced the labile sodium sulfonate radical so that sulfate ions were not formed upon acidification. Ferrous sulfate reacted similarly to sodium hydrosulfite.

EXPERIMENTAL

Starting materials. The sulfite waste liquor used was a concentrate prepared from a spruce Mitscherlich liquor. The digester-strength liquor was concentrated under reduced pressure below 50° to exactly 50% solids. The solids contained 7.05% methoxyl and 11.2% ash.

The basic calcium lignosulfonate was a commercial product prepared by the fractional precipitation of sulfite waste liquor with lime; it contained 20.58% ash, 9.06% methoxyl, 4.91% total sulfur (as sulfur) and 0.18% sulfite sulfur (as sulfur).

The alkali lignin was a sample of commercial Meadol; it contained 21.62% methoxyl and 1.2% ash.

The partially desulfonated lignin was material obtained by acidifying the extracted reaction mixtures of nitrobenzene, sulfite waste liquor, and alkali. It contained 11.26% methoxyl, 6.43% ash, and 1.63% total sulfur.

Reduction of nitrobenzene with sulfite waste liquor and alkali. To a solution of 90 g. of sodium hydroxide in 200 g. of water contained in a 1-liter, 3-neck flask fitted with a reflux condenser and a mercury-sealed stirrer was added with stirring 350 g. of sulfite waste liquor and 72 g. of nitrobenzene. The flask was sealed with a rubber stopper carrying a thermometer reaching below the surface of the reaction mixture. The warm solution was heated to boiling with vigorous agitation, refluxed for 8 hours, and allowed to cool with stirring. The mixture was then distilled with steam. The steam distillate was acidified and extracted with ether which, upon drying and distilling, yielded a small amount of azoxybenzene. The acid aqueous distillate was made alkaline with sodium hydroxide, saturated with sodium chloride, and extracted with ether, which yielded 13.0 g. (23.9%) of aniline. The alkaline residual solution from the steam distillation was centrifuged. It was found that sodium *p*-azobenzenesulfonate was very soluble in acetone in the presence of a small quantity of water. Therefore, the wet centrifuge residue (consisting of inorganic material, some lignin material, sodium *p*-azobenzenesulfonate, and azoxybenzene) was extracted with warm acetone. The azobenzenesulfonate and azoxybenzene dissolved in the acetone. The acetone was evaporated almost to dryness, the residue was taken up in ether, and the mixture was filtered. Pure sodium *p*-azobenzenesulfonate, which is insoluble in ether, was obtained as bright orange platelets in a yield of 25.0 g. (29.9%). The azoxybenzene obtained from the ether extract, together with that obtained from the steam distillate, amounted to 25.6 g. (46.0%).

The experiments listed in Table I were performed in essentially the same manner.

Identification of sodium p-*azobenzenesulfonate.* The material upon recrystallization from alcohol was obtained as irridescent orange platelets.

Anal. Calc'd for $C_{12}H_9N_2NaO_3S$: N, 9.86; S, 11.27; Na, 8.10.
Found: N, 10.0; S, 11.2; Na, 8.10.

Chlorination with phosphorus pentachloride and crystallization from ether yielded *p*-azobenzenesulfonyl chloride melting at 124–125°; a mixed m.p. with authentic *p*-azobenzenesulfonyl chloride (2) showed no depression. The amide was prepared by treatment

TABLE I

REACTIONS AT ATMOSPHERIC PRESSURE FOR 8 HOURS

EXPT.	REACTION MIXTURE		ANILINE, %	AZOXY-BENZENE, %	SPABS,[a] %	NITRO-BENZENE RECOVERED, %	NITRO-BENZENE ACCOUNTED FOR, %
		g.					
1	Nitrobenzene	72	0	2.1	0	97.1	99.2
	NaOH	90					
	Na_2SO_3	75					
	H_2O	250					
2	Azoxybenzene	58	0	98.9	0		98.9[b]
	NaOH	90					
	Na_2SO_3	75					
	H_2O	250					
3	Nitrobenzene	72	9.2	44.9	4.3	33.8	91.2
	NaOH	90					
	BCLS[c]	105					
	H_2O	250					
4	Nitrobenzene	72	25.1	55.0	3.5	18.1	101.7
	NaOH	90					
	Dextrose	40					
	BCLS	105					
	H_2O	250					
5	Nitrobenzene	72	11.0	35.9	12.9	40.5	100.3
	NaOH	90					
	$NaHSO_3$	35					
	Alkali lignin	75					
	H_2O	250					
6	Nitrobenzene	72	10.0	21.2	0	62.1	93.3
	NaOH	90					
	$NaHSO_3$	46					
	Dextrose	50					
	H_2O	250					
7	Nitrobenzene	72	10.5	11.7	2.8	75.5	100.5
	NaOH	90					
	PDL[d]	75					
	H_2O	175					
8	Nitrobenzene	72	13.4	5.3	5.3	72.3	96.3
	NaOH	90					
	Na_2SO_3	75					
	PDL	75					
	H_2O	200					

[a] SPABS represents sodium *p*-azobenzenesulfonate.

[b] Azoxybenzene accounted for.

[c] BCLS represents basic calcium lignosulfonate.

[d] PDL represents partially desulfonated lignin obtained as a by-product in nitrobenzene reductions (1).

with ammonium hydroxide; crystallized from ethanol, it melted at 220–221°; a mixed m.p. with authentic *p*-azobenzenesulfonamide (2) showed no depression.

Reduction of 5.0 g. with tin in boiling dilute hydrochloric acid, alkalization with sodium hydroxide, extraction with ether, and removal of the ether resulted in a basic mixture which was separated by distillation under reduced pressure. The distillate consisted of 0.2 g. of aniline, which was identified as its benzoyl derivative (m.p. 160–161°). The residue (weighing 2.7 g.), when crystallized from alcohol, melted at 127–128°. The m.p. of a mixture with authentic benzidine was not depressed. A few crystals of sulfanilic acid (m.p. of its amide, 165–166°) were obtained from the acidified solution.

Reduction with sodium hydrosulfite. A suspension of 28.4 g. of sodium *p*-azobenzenesulfonate in 250 cc. of boiling 2% sodium hydroxide solution was gradually treated with 25 g. of sodium hydrosulfite. Shortly after addition was complete, the mixture became colorless and clear. The solution was allowed to cool somewhat and was then acidified with 3 *N* hydrochloric acid. Benzidine sulfate separated immediately in quantitative yield. Treatment with alkali, followed by extraction with ether and isolation of the base, yielded pure benzidine, m.p. 127–128°. A mixed m.p. with authentic benzidine showed no depression.

Reduction with hydrogen sulfide in alkaline solution. Ten grams of sodium *p*-azobenzenesulfonate was dissolved in 250 cc. of boiling 2% sodium hydroxide solution. Hydrogen sulfide was introduced until the solution became colorless. Exact neutralization of the cooked solution with 3 *N* hydrochloric acid caused the separation of a little sulfur. The mixture was filtered and the filtrate was acidified with 3 *N* hydrochloric acid. A quantitative yield of benzidine sulfate was obtained.

Reduction with sodium sulfide in alkaline solution. A 30% solution of sodium sulfide crystals, added drop by drop in place of hydrogen sulfide gas in the above reduction, gave identical results.

When an excess of sodium sulfide crystals was added at one time to the boiling alkaline solution, subsequent acidification did not produce benzidine sulfate. A clear solution was obtained after filtration of precipitated sulfur. Addition of sulfuric acid or sodium sulfate solution caused the quantitative separation of benzidine sulfate.

Reduction with ferrous sulfate. A solution of 10 g. of sodium *p*-azobenzenesulfonate in 250 cc. of boiling 2% sodium hydroxide solution was treated with an excess of ferrous sulfate solution. Boiling was continued until the orange color disappeared. The black precipitate of iron oxide was removed by filtration and the clear filtrate was acidified; benzidine sulfate was obtained in a yield of 8.2 g. (82.5%).

SUMMARY

Sodium *p*-azobenzenesulfonate has been identified as a product of the reduction of nitrobenzene with sulfite waste liquor at atmospheric pressure.

The constituents in the alkaline sulfite waste liquor mixture responsible for its formation have been determined.

A number of its reduction reactions have been studied.

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REDUCTION OF AROMATIC NITRO COMPOUNDS WITH SULFITE WASTE LIQUOR[1]

IRWIN A. PEARL

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In a recent paper (1) a comprehensive study of the reduction of nitrobenzene with sulfite waste liquor was reported. The results obtained, and the possibility of using sulfite waste liquor as a substitute for metals in commercial organic reductions led to other studies of sulfite waste liquor as a reducing agent. This paper recites a number of experiments on the reduction of aromatic nitro compounds which, at the present time, are reduced commercially by other means to give valuable intermediates for use in the dyestuff, pharmaceutical, and organic chemical industries. The compounds selected were 2- and 4-nitrophenol, 2- and 4-nitrotoluene, 2-nitroanisole, 2-nitrocymene, 2-nitrobiphenyl, and 2-nitrochlorobenzene.

These compounds were treated with sulfite waste liquor and alkali at both atmospheric and superatmospheric pressures, employing reactant ratios and reaction conditions which were found to give total reduction of nitrobenzene (1). Table I[2] gives the data and results of those reductions using reaction mixtures of 0.6 mole of the nitro compound, 300 g. of sulfite waste liquor containing 50% solids, 90 g. of sodium hydroxide, and 100 g. of water. All experiments were performed in the same general manner as outlined in the experimental part.

Schulz (2) claimed that nitrophenols and alkali oxidized sulfite waste liquor to vanillin at elevated temperatures. From this, one would assume simultaneous reduction of the nitro compounds. Experiments at atmospheric pressure indicated that neither 2- nor 4-nitrophenol yielded increased quantities of vanillin with sulfite waste liquor. Furthermore neither compound was reduced by the alkaline liquor. Condensation with the lignin or some other component of the waste liquor must have taken place because only a fraction of the nitrophenol could be recovered. Raising the temperature of the reaction mixture resulted in reduction to aminophenols. No other reduction product was obtained.

The facts that *p*-cymene is formed, together with sulfite waste liquor, as a by-product of the sulfite pulp industry, and that reduction products of nitrocymene have recently attained commercial importance, led to the selection of 2-nitrocymene for reduction studies. The crude 2-nitrocymene used in the

[1] This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Committee on Waste Disposal and conducted for the Committee by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the Committee to publish these results.

[2] Whereas this paper is concerned chiefly with the reduction products of the nitro compounds, the simultaneous vanillin yields from the oxidation of the lignin have been included in Table I. Under the conditions of these experiments, vanillin is the principal and substantially the total recovered oxidation product of the lignin, the remainder being mostly degraded lignin material (1).

atmospheric reductions contained 5% of 4-nitrotoluene. Only a small amount of 2-aminocymene was obtained from the nitrocymene in the reductions, but the 4-nitrotoluene was quantitatively reduced to *p*-toluidine. Reduction of pure

TABLE I

REDUCTIONS OF AROMATIC NITRO COMPOUNDS WITH SULFITE WASTE LIQUOR

EXPT.	NITRO COMPOUND	TEMP., °C.	TIME, HOURS	RECOVERED NITRO COMPOUND, %	AMINO COMPOUND, %	AZOXY COMPOUND %	AZO COMPOUND, %	TOTAL REDUCTION OBSERVED, %	TOTAL NITRO COMPOUND ACCOUNTED FOR, %	VANILLIN,[a] %
1	4-Nitrophenol[b]	108	8	49.6	0	0	0	0	49.6	1.2
2	4-Nitrophenol	120	4	38.1	22.0	0	0	22.0	60.1	Not det'd.
3	2-Nitrophenol	140	4	2.5	56.0	0	0	56.0	58.5	2.2
4	2-Nitrocymene (crude)	108	8	88	10.2	0	0	10.2	98.2[c]	8.8
5	2-Nitrocymene (pure)	130	6	39.5	32.9	22.6	0	55.5	95.0	17.5
6	4-Nitrotoluene	108	8	34.7	13.0	32.1	4.2	64.9[d]	99.6	12.7
7	4-Nitrotoluene	130	5	0	26.3	0	73.1	99.4	99.4	19.8
8	2-Nitrotoluene	108	8	53.4	13.0	22.7	0	41.0[e]	95.4	11.5
9	2-Nitrotoluene	130	5	0	50.3	0	52.4	102.7	102.7	18.7
10	2-Nitrotoluene	130	2	37.5	20.0	0	40.0	61.1[f]	98.6	14.0
11	2-Nitrobiphenyl	108	8	80.8	6.7	3.9	0	10.6	91.4	10.9
12	2-Nitrobiphenyl	130	6	0	40.9	52.2	0	93.1	93.1	22.3
13	2-Nitroanisole	108	8	53.2	12.9	26.4	0	38.3	91.5	Not det'd.
14	2-Nitroanisole	140	2	0	91.5	0	0	91.5	91.5	Not det'd.
15	2-Nitrochlorobenzene	108	7	24.7	12.2	21.0	0	33.2	99.0[g]	10.2

[a] Vanillin is reported as percentage of initial lignin present in the sulfite waste liquor.

[b] In Experiments 1, 2, and 3 an additional amount of sodium hydroxide was added equivalent to the phenolic hydroxyl of the nitrophenol.

[c] In addition to the products listed, *p*-toluidine was recovered in an amount corresponding to 5% of the 4-nitrotoluene in the original crude 2-nitrocymene. Therefore, the yields of recovered 2-nitrocymene and 2-aminocymene are based on 95% of the crude nitrocymene used.

[d] This value includes 15.7% of sodium 4,4′-dimethylazobenzene-3-sulfonate obtained in this experiment.

[e] Includes 6.3% of sodium 2,2′-dimethylazobenzene-4-sulfonate.

[f] Includes 1.1% of sodium 2,2′-dimethylazobenzene-4-sulfonate.

[g] Includes 41.1% of 2-nitrophenol which was formed by hydrolysis of the nitrochlorobenzene.

nitrocymene at 130° resulted in the formation of 2-aminocymene and a new compound, 2,2′-azoxy-*p*-cymene (2,2′-dimethyl-5,5′-diisopropylazoxybenzene).

Because all the 4-nitrotoluene present as an impurity in the crude 2-nitrocymene was reduced to *p*-toluidine in the atmospheric reduction of 2-nitrocy-

mene, it was assumed that sulfite waste liquor would quantitatively reduce 4-nitrotoluene to *p*-toluidine at atmospheric pressure. The data of Experiment 6 indicate that this assumption was far from correct. In the nitrocymene experiment the large excess of reducing agent must have caused the quantitative reduction of the small amount of 4-nitrotoluene, the 2-nitrocymene being inert. The chief reduction product of this experiment was 4,4′-azoxytoluene. In addition to the known products obtained in this experiment a yellow, crystalline, sodium-containing compound was obtained. Reduction of this compound with tin and hydrochloric acid yielded *p*-toluidine and 4-amino-2-toluenesulfonic acid, indicating that the unknown compound was sodium 4,4′-dimethylazobenzene-3-sulfonate, which was also prepared according to Janovsky (3). The formation of this compound is analogous to the formation of sodium *p*-azobenzenesulfonate in nitrobenzene-sulfite waste liquor reaction mixtures (4).

Sulfite waste liquor reductions of 2-nitrotoluene at atmospheric pressure gave 2,2′-azoxytoluene as the chief reduction product, together with a smaller amount of *o*-toluidine. Reduction for 5 hours at 130° resulted in approximately equal amounts of *o*-toluidine and 2,2′-azotoluene and lower ratios of toluidine for shorter reaction times. Complete reduction took place in 5 hours. The presence of sodium 2,2′-dimethylazobenzene-4-sulfonate was definitely established in reaction mixtures of 2-nitrotoluene and alkaline sulfite waste liquor. The golden crystals obtained were dissolved in boiling dilute alkali and treated with sodium hydrosulfite. The colorless solution, upon acidification and re-alkalization yielded *o*-tolidine (3,3′-dimethylbenzidine). The formation of *o*-tolidine indicates that 2,2′-dimethylhydrazobenzene or 2,2′-dimethylhydrazobenzene-4-sulfonic acid must have been formed during the reaction. Since these compounds could be formed only by reduction of the corresponding azo or azoxy compounds and since analytical data agreed with the azo structure, the unknown golden crystals must have been sodium 2,2′-dimethylazobenzene-4-sulfonate. The method of proof of structure is analogous to that used for sodium *p*-azobenzenesulfonate (4).

Substantial reduction of 2-nitrobiphenyl took place only at elevated pressures. Under those conditions 2,2′-azoxybiphenyl and 2-aminobiphenyl were the reduction products. In addition to the known 2,2′-azoxybiphenyl melting at 157–158° (5), a product melting sharply at 149–150° was obtained in substantial yield. This compound gave analysis for azoxybiphenyl and upon reduction with tin and hydrochloric acid, it yielded only 2-aminobiphenyl. Therefore, this compound must be a geometric isomer of Friebel and Rassow's (5) compound and, for convenience, has been called iso-2,2′-azoxybiphenyl.

Of all the nitro compounds studied, 2-nitroanisole was the only one that yielded the amino compound as the sole reduction product in practically quantitative yield. The facts that a fair yield of 2,2′-azoxyanisole was obtained at atmospheric pressure and that at 140° the yield of 2-anisidine was practically quantitative indicate that at some temperature between 108° and 140°, all of the intermediate reduction products of 2-nitroanisole are further reduced to the ultimate reduction product, 2-anisidine.

Reduction studies on a halogen-substituted nitro compound (2-nitrochlorobenzene) indicated that the halogen was more susceptible to hydrolysis by the alkaline solution than the nitro group was to reduction by the sulfite waste liquor. It is interesting to note that the 4-nitrophenol obtained in Experiment 15 was recovered quantitatively, whereas only 50% was recovered in the atmospheric reduction of 4-nitrophenol (Experiment 1). Because of the large degree of hydrolysis taking place at atmospheric pressure, no high-temperature experiments were made on 2-nitrochlorobenzene. The reduced chlorobenzenes were stable toward hydrolysis—no amino or azoxy-phenol was found.

The experiments in this study demonstrate that these high-boiling nitro compounds, which contain no strongly active group, can be totally reduced by sulfite waste liquor and alkali at temperatures higher than reflux temperatures. Except in the reduction of 2-nitroanisole under pressure, the largest part of these compounds is reduced to bimolecular products instead of to monomolecular compounds. Lower temperatures favor azoxy compound formation and higher temperatures favor the production of azo and amino compounds. The yields of vanillin obtained in these experiments from the simultaneous oxidation of the sulfite waste liquor were a function of the total reduction observed. The vanillin yields agreed remarkably with those obtained in the nitrobenzene study (1).

EXPERIMENTAL

All melting points given are uncorrected.

Starting materials. The sulfite waste liquor used was a concentrate prepared from a spruce Mitscherlich liquor. The digester-strength liquor was concentrated at atmospheric pressure to 50% solids (7.16% methoxyl). Assuming that 90% of the methoxyl belonged to lignin and that lignin has a methoxyl content of 14.5%, the lignin content of the sulfite waste liquor was 22.2%.

2-Nitrocymene was prepared from *p*-cymene by the method of Doumani and Kobe (6). The product obtained boiled at 128–132° at 13 mm.; n_D^{20} 1.5299. Under the conditions of nitration some 4-nitrotoluene was formed and, because it could not be separated by distillation, the resulting 2-nitrocymene contained 4-nitrotoluene. From the refractive index-composition diagram of Doumani and Kobe (6) the amount of 4-nitrotoluene was found to be approximately 5%. The pure 2-nitrocymene used in several experiments was that recovered from atmospheric sulfite waste liquor reductions in which all the 4-nitrotoluene was reduced. Upon distillation pure 2-nitrocymene was obtained, n_D^{20} 1.5287.

2-Nitrobiphenyl was a commercial product kindly furnished by Monsanto Chemical Company. All the other nitro compounds were Eastman Kodak Company products and were used without further purification.

The method for atmospheric pressure reductions may be illustrated by that used in reducing 4-nitrotoluene.

Reduction of 4-nitrotoluene with sulfite waste liquor at atmospheric pressure. Into a 1-liter, 3-neck flask fitted with a reflux condenser and a mercury-sealed stirrer were placed in order (with stirring) 300 g. of sulfite waste liquor, 90 g. of sodium hydroxide dissolved in 100 g. of water, and 82.5 g. of 4-nitrotoluene. The flask was closed with a rubber stopper carrying a thermometer reaching below the surface of the reaction mixture, and the mixture was heated to boiling. Refluxing and stirring were continued for 8 hours, after which the mixture was allowed to cool with stirring. After diluting with water the alkaline solution was distilled with steam. The steam distillate was acidified with hydrochloric acid to dissolve organic bases and extracted with ether. The ether solution, after drying, evaporating, and distill-

ing the residue under reduced pressure, yielded 28.7 g. (34.7%) of 4-nitrotoluene as light yellow needles, m.p. 51–52°. The acid steam distillate was alkalized with sodium hydroxide, saturated with sodium chloride, and extracted with ether. The ether solution was dried, the solvent removed, and the residue distilled under reduced pressure. A yield of 8.4 g. (12.9%) of *p*-toluidine, m.p. 42–43°, was obtained. The alkaline residue from steam distillation was centrifuged, and the clear centrifugate reserved for vanillin determination. The residue from the centrifuging operation was extracted with wet acetone, and the acetone removed by distillation. The residual wet brown oil was extracted with ether. An aqueous layer formed and between the ether and aqueous layers a golden precipitate separated. The aqueous layer was drawn off, the precipitate was filtered, and the ether layer was distilled, leaving a residue which was separated by fractional distillation *in vacuo*. The residue consisted of 21.9 g. (32.1%) of 4,4′-azoxytoluene as microscopic yellow needles, m.p. 68–69° and 2.7 g. (4.2%) of 4,4′-azotoluene as microscopic orange crystals, m.p. 143–144°. Mixed melting points with authentic samples showed no depression. The golden precipitate (14.9 g.) was recrystallized from ethanol. Reduction with tin and hydrochloric acid yielded equivalent weights of *p*-toluidine and 4-amino-2-toluenesulfonic acid (identified as its amide, m.p. 164°), indicating it to be sodium 4,4′-dimethylazobenzene-3-sulfonate.

Anal. Calc'd for $C_{14}H_{13}N_2NaO_3S$: C, 53.8; H, 4.17; N, 8.97; S, 10.3; Na, 7.37.
Found: C, 53.7; H, 4.27; N, 9.06; S, 10.3; Na, 7.27.

An aliquot of the centrifugate was acidified with dilute sulfuric acid, and thoroughly extracted with ether. The ether solution was extracted with 21% sodium bisulfite solution. The bisulfite extract was acidified with dilute sulfuric acid, aspirated under reduced pressure to remove sulfur dioxide, and precipitated with 2,4-dinitrophenylhydrazine according to Pearl (7). The vanillin yield amounted to 8.45 g. or 12.7% on the basis of the lignin present in the sulfite waste liquor.

In experiments where steam distillation was not complete, an ether extraction of the alkaline solution was employed. Under these conditions all the basic and neutral substances were obtained in the ether extract.

Reductions at superatmospheric pressure. These experiments were made in a stainless steel autoclave which was shaken in a heated rocker at the desired temperature for the required length of time. Upon cooling, the tube was opened and the contents were transferred to a flask for steam distillation. After this, the mixture was worked up as described for the experiment at atmospheric pressure.

Variations in the physical and chemical properties of the different nitro compounds and their reduction products necessitated minor deviations from the standard procedure. However, these deviations were of little consequence.

*2,2′-Azoxy-*p*-cymene.* The alkaline residue from steam distillation in Experiment 5 was extracted with ether. After removing basic substances with dilute hydrochloric acid, the ether was dried with calcium chloride, and distilled. The residue was fractionated under a high vacuum. A yellow crystalline product (10.7 g.), which boiled at 180–190°/1 mm. and which, when recrystallized from methanol, melted at 50–51°, was obtained. Reduction with tin and hydrochloric acid resulted in the recovery of only 2-aminocymene, b.p. 116–118°/12 mm., n_D^{20} 1.543.

Anal. Calc'd for $C_{20}H_{18}N_2O$: C, 77.5; H, 8.40; N, 9.04.
Found: C, 77.88; H, 8.55; N, 9.04.

Sodium 2,2′-dimethylazobenzene-4-sulfonate. This compound was isolated from 2-nitrotoluene and sulfite waste liquor reaction mixtures in a manner identical with that described for sodium 4,4′-dimethylazobenzene-3-sulfonate from 4-nitrotoluene reductions. The orange crystals were recrystallized from ethanol.

Anal. Calc'd for $C_{14}H_{13}N_2NaO_3S$: C, 53.8; H, 4.17; N, 8.97; Na, 7.37.
Found: C, 53.6; H, 4.52; N, 8.89; Na, 7.35.

One gram was dissolved in 100 g. of hot water, made alkaline with sodium hydroxide, and treated with sodium hydrosulfite. The colorless solution was acidified with hydrochloric acid, treated with decolorizing carbon, filtered, and the filtrate made alkaline with sodium

hydroxide. Ether extraction, followed by drying and removal of the ether, yielded 0.5 g. of *o*-tolidine, m.p. 128–129° (ethanol-water); a mixed m.p. was not lowered. The yield of *o*-tolidine, recrystallized from dilute ethanol, was 74%.

Iso-2,2'-azoxybiphenyl. The neutral fraction of the ether extract of Experiment 12 yielded 17.4 g. (32.8%) of 2,2'-azoxybiphenyl, m.p. 157–158° (alcohol) [mixed m.p. with authentic 2,2'-azoxybiphenyl (5), 157–158°] and 10.3 g. (19.4%) of iso-2,2'-azoxybiphenyl, m.p. 149–150° (light tan crystals from methanol).

Anal. Calc'd for $C_{24}H_{18}N_2O$: C, 82.28; H, 5.14; N, 8.00.

Found: C, 82.28; H, 5.32; N, 7.98.

Reduction with tin and hydrochloric acid yielded only 2-aminobiphenyl, m.p. 44–45°. The m.p. of a mixture with authentic 2-aminobiphenyl was not depressed.

SUMMARY

A number of aromatic nitro compounds has been reduced with sulfite waste liquor and alkali at both atmospheric and superatmospheric pressures.

For total reduction of these high-boiling nitro compounds by sulfite waste liquor and alkali, temperatures higher than reflux temperatures are necessary.

Except in the reduction of 2-nitroanisole under pressure, the largest part of these compounds is reduced to bimolecular products instead of to monomolecular compounds.

The reaction between 2-nitrochlorobenzene and alkaline sulfite waste liquor results in the hydrolysis of a large part of the nitrochlorobenzene to 2-nitrophenol.

A number of new compounds has been isolated and identified.

APPLETON, WIS.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. VIII. LOWER HOMOLOGS OF HORMONES OF THE PREGNANE SERIES: 10-NOR-11-DESOXY-CORTICOSTERONE ACETATE AND 10-NORPROGESTERONE[1]

MAXIMILIAN EHRENSTEIN

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It is known that estrogenic activity does not depend to a great extent on specific chemical structures and configurations. Syntheses have yielded a number of therapeutically valuable estrogens which are structurally only slightly, if at all, related to the naturally occurring hormones. No comparable synthetic compounds exist in the field of androgenic, progestational, and adrenal-cortical hormones. It appears that progestational and adrenal-cortical activities depend particularly on very specific chemical structures and configurations. Information regarding those structures which are essential for biological activity would be of use in developing total syntheses in this field. In particular, the question arises whether simplifications in the structures of the naturally occurring hormones are associated with an appreciable loss of physiological activity.

With this problem in mind we considered the question of lower homologs of progestational and adrenal-cortical hormones. A lower homolog of progesterone, the 20-norprogesterone (17-formyl-4-androstene-3-one) (1) possesses only slight progestational activity even when high doses (10 or 20 milligrams) are given.[2] The question arises as to the activity of compounds in which either one or both angular methyl groups are replaced by hydrogen. Such structures resemble closely those of the natural hormones in that the characteristic side chain is left unchanged.

Strophanthidin (I) appeared to present a proper starting material for the preparation of compounds in which the methyl group at carbon atom 10 is replaced by a hydrogen atom. It has been found to be the aglycon of a number of cardiac glycosides,[3] namely k-strophanthin (from *Strophanthus Kombé*), cymarin (from *Apocynum cannabium* or *A. androsaemifolium*) and, more recently, also convallatoxin (from *Convallaria majalis* L.) (7).[4] From a practical point

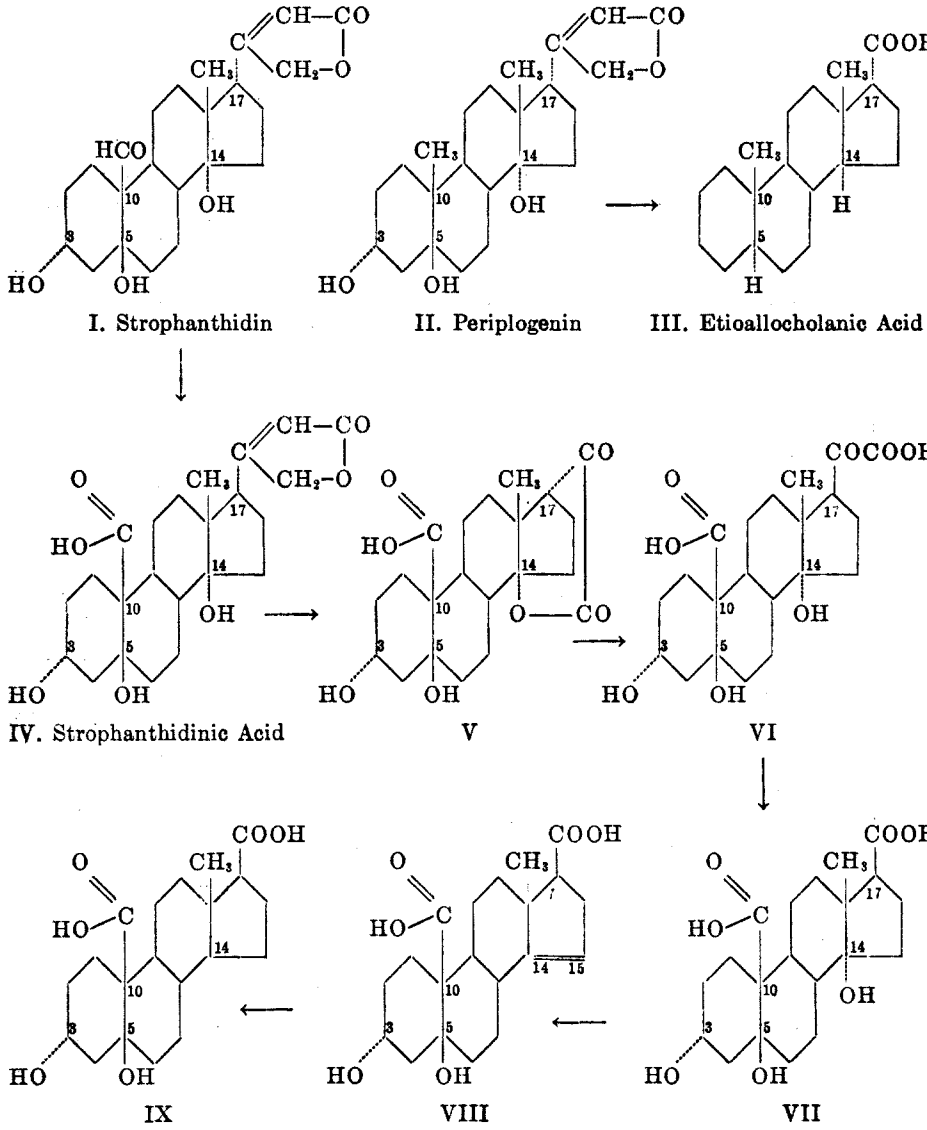
[1] Aided by a grant from the Smith, Kline, and French Laboratories in Philadelphia. The chemical findings were presented before the Division of Organic Chemistry at the Cleveland meeting of the American Chemical Society, April 6, 1944.

[2] It appears that, in the progesterone and desoxycorticosterone series, any C_{17}-side chain homolog is physiologically inferior to the parent hormone. Among the higher homologs of both series, compounds in which the additional carbon atoms appear introduced between carbon atom 17 and the keto group of the side chain, *e.g.* nor-4-cholene-3,22-dione (2), 17-[17²-oxopropyl]-4-androstene-3-one (3), 23-acetoxynor-4-cholene-3,22-dione (2), are inactive even when high doses are given. In the progesterone series, lengthening of the side chain by introducing aliphatic substituents at carbon atom 21 is accompanied by a loss of physiological activity, the degree of loss apparently increasing with the length of the aliphatic radical (4).

[3] For older literature *cf.* (5, p. 259), (6, p. 130).

[4] Convallatoxin was subjected to a new cleavage method which had first been employed in the isolation of g-strophanthidin from g-strophanthin (ouabain) (8).

of view k-strophanthin presents the most suitable starting material for the preparation of larger quantities of strophanthidin (9). Regarding chemical structure and configuration strophanthidin (I) is completely analogous to periplogenin (II).[5] Since the latter has been transformed into etioallocholanic



acid (III),[6] the correlation with the steroid hormones is evident. In particular, the configuration at carbon atom 17 can be considered established, as the methods during the course of this transformation precluded an inversion at this point.

[5] For literature *cf.* (5, pp. 275–276, 413).
[6] For literature *cf.* (5, pp. 284–285, 288–289).

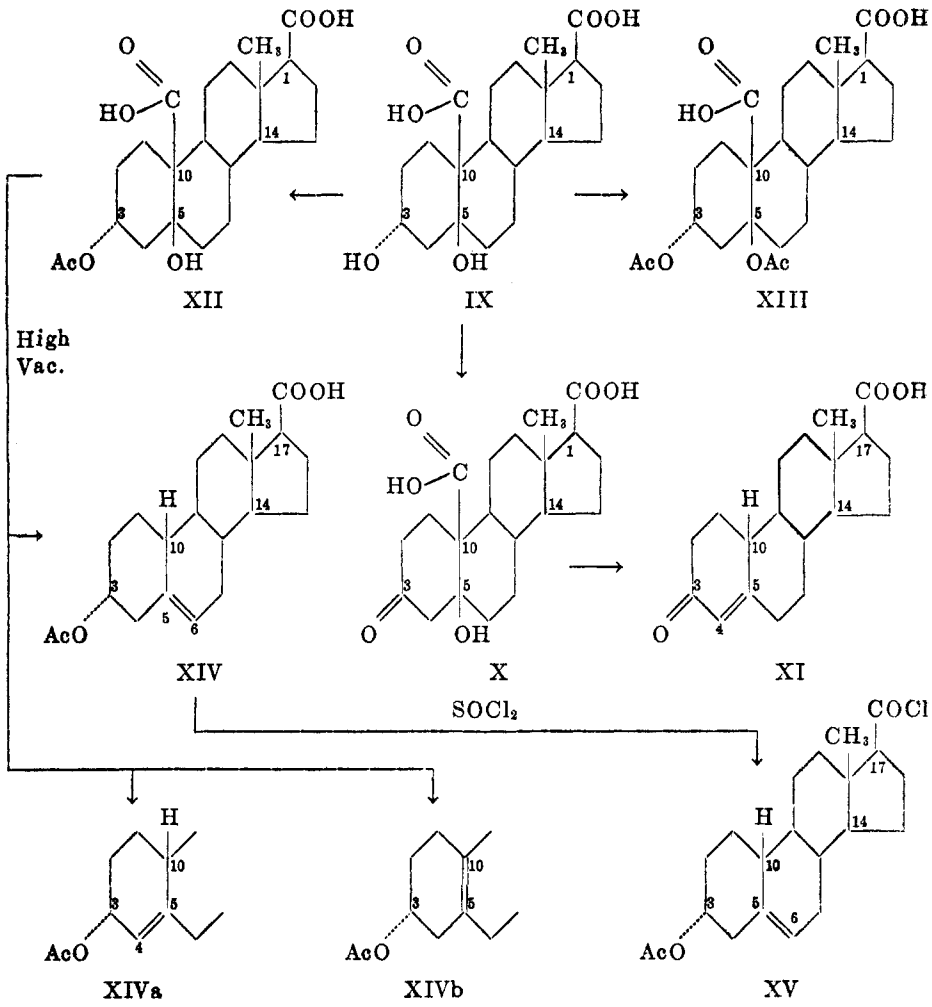
Jacobs (10) oxidized strophanthidin (I) with permanganate in a neutral solution and obtained the monobasic strophanthidinic acid (IV). When this acid was oxidized with permanganate after the lactone ring had been opened by treatment with alkali, a new acid was obtained. It possesses structure V and is therefore an α-ketolactone acid. On boiling with alkali, the lactone opens, the resulting acid being represented by formula VI. Under the influence of the alkali treatment, rearrangement has also taken place at carbon atom 17, obviously by way of enolization of the carbonyl group. Through this rearrangement the side chain at carbon atom 17 is placed in *trans* position to the hydroxyl group at carbon atom 14, a configuration which prevents relactonization. These reactions, though published by Jacobs (10) as early as 1923 were given their final interpretation by Elderfield (11) in 1936. Elderfield also subjected the dicarboxylic acid VI to further degradation by treatment with hydrogen peroxide. This furnished the new dicarboxylic acid VII [3,5,14-trihydroxyestrane-10,17-dicarboxylic acid]. As, according to available evidence, the oxidation of an α-keto carboxylic acid eliminates the carboxyl group adjacent to the carbonyl group, it may be assumed that the configuration at carbon atom 17 remains unchanged in the dicarboxylic acid VII.

The dicarboxylic acid VII was dehydrated by treating it under mild conditions with alcoholic hydrochloric acid. From the reaction mixture a crystalline anhydrodicarboxylic acid was isolated, in which the double bond must center at carbon atom 14. Since catalytic hydrogenation of this acid proceeded very smoothly, the double bond was assumed to extend from carbon atom 14 to carbon atom 15 as shown in formula VIII [14-estrene-3,5-diol-10,17-dicarboxylic acid].[7] The saturated dicarboxylic acid possesses structure IX [estrane-3,5-diol-10,17-dicarboxylic acid]. This work was interrupted by us at this point early in 1939 and was not taken up again until early in 1943. In the meanwhile a paper was published by Butenandt and Gallagher (12) in which the dicarboxylic acids VIII and IX were described. Our compound VIII is completely identical with that described in the German publication. There was one difference, however, regarding compound IX in that Butenandt and Gallagher (12, p. 1869) report the specific rotation $[\alpha]_D^{16}$ +35° (ethanol) whereas we found $[\alpha]_D^{20.5}$ +60.0° (ethanol). In the hydrogenation of the anhydrodicarboxylic acid VIII one would expect (*cf.*, *e.g.*, 13) a hydrogenation product in which the hydrogen atom at carbon atom 14 is in *trans* position to the methyl group at carbon atom 13 (as in etiocholanic acid). The presence of a certain amount of stereoisomeric material in either of the two preparations may account for the difference in the optical rotations.

By oxidation with chromic acid, Butenandt and Gallagher transformed the saturated dicarboxylic acid IX into the ketodicarboxylic acid X [estrane-3-one-5-ol-10,17-dicarboxylic acid]. When the latter was treated with weak alcoholic hydrogen chloride, not only dehydration but also decarboxylation took place, thus furnishing the ketomonocarboxylic acid XI [4-estrene-3-one-17-carboxylic acid].

[7] Under somewhat different conditions of dehydration an anhydrodicarboxylic acid was obtained which is probably isomeric with VIII (*cf.* experimental part).

Although compound XI might be considered as an intermediate in the preparation of the lower homologs of desoxycorticosterone and progesterone, its use was not attempted because the last two steps (IX → X → XI) apparently give only small yields.[8] It was decided, therefore, to proceed from compound IX in a different fashion.



As is known from the bile acid series, one of the most effective means of dehydration consists in distillation in a vacuum or high vacuum (*cf.*, *e.g.*, 5, pp. 124, 365–366; 14, p. 20; 15, pp. 1416–1417). Certain hydroxyl groups may be protected from joining in such a dehydration by means of acetylation. Based on this experience it was planned to acetylate the hydroxyl group at carbon atom

[8] The average yield of X, as obtained from IX, is 14%. No yield of XI is stated (12, p. 1869).

3 in the dicarboxylic acid IX and to distill the resulting monoacetate XII in a high vacuum. It was hoped that the expected dehydration, *i.e.* the elimination of the tertiary hydroxyl group at carbon atom 5, might be accompanied by simultaneous decarboxylation at carbon atom 10.

By treating the dicarboxylic acid IX with acetic anhydride and pyridine at room temperature, a crystalline compound was obtained which apparently represents the 3,5-diacetate XIII. Acetylation of the tertiary hydroxyl group at carbon atom 5 under these experimental conditions is unexpected and hence this should be reported with a certain amount of reservation. On the other hand, the behavior of this compound, when subjected to distillation in a high vacuum (*cf.* experimental part), is in agreement with the structure of a 3,5-diacetate. Formation of compound XIV (or its isomers) apparently does take place, though the reaction proceeds much more slowly than with the 3-monoacetate.

By boiling the dicarboxylic acid IX with acetic anhydride, a glassy substance was obtained which consists essentially of the 3-monoacetate XII. It could not be crystallized and was subjected directly to distillation in a high vacuum. The reaction is practically terminated after one such treatment but to assure completeness the distillation was carried out once more. The resulting material was also a glass which gave a strong reaction with tetranitromethane, indicating the presence of a double bond. On titrating, the presence of exactly one equivalent of acid was found. Also the carbon-hydrogen determination was in agreement with structure XIV. It is possible that the double bond is in the 5,6-position as in formula XIV or in positions 4,5 or 5,10 as in formulas XIVa and XIVb respectively. It is probably a mixture of such isomers. As it was hoped that the double bond in positions 5,6 (XIV) and perhaps also 5,10 (XIVb)[9] might become rearranged to the 4,5 position once a keto group was established at carbon atom 3, no attempt was made to separate these isomers. The material was directly transformed into the corresponding acid chloride (XV and/or isomers) by means of thionyl chloride. The crude acid chloride was used for the preparation of 10-nor-11-desoxycorticosterone acetate (XIX)[10] and of 10-norprogesterone (XXII) respectively.

The method of preparing 10-nor-11-desoxycorticosterone acetate (XIX) from the acid chloride was similar to the procedure which was originally utilized by Reichstein (17) in the preparation of desoxycorticosterone and which has subsequently been used by a number of authors in analogous cases. By treating the acid chloride (XV and/or isomers) with diazomethane, the corresponding acetoxydiazo ketone (XVI and/or isomers) was obtained which, on saponification with alkali, yielded the hydroxydiazo ketone (XVII and/or isomers). The latter was dehydrogenated according to Oppenauer's method (18). After the treatment of the resulting diketodiazo compound (XVIII) with

[9] An analogous case where such a shift of the double bond apparently does not take place is the transformation of scillirosid into dehydroscillirosid (16).

[10] The prefix "10-nor-" implies that the methyl group at carbon atom 10 is replaced by hydrogen.

glacial acetic acid the desired 10-nor-11-desoxycorticosterone acetate (XIX) could be isolated. Neither of the intermediates XVI, XVII, and XVIII was isolated in a pure form, but the final product (XIX) was subjected to a thorough purification by repeated chromatographic adsorptions and eventual distillation in a high vacuum.

The substance thus obtained was an almost colorless resin ($[\alpha]_D^{21}$ +56.6°) which could not be crystallized. The ultraviolet absorption spectrum[11] shows the characteristics of an α,β-unsaturated ketone (λ_{max} = 238 mμ; ϵ = 14720).

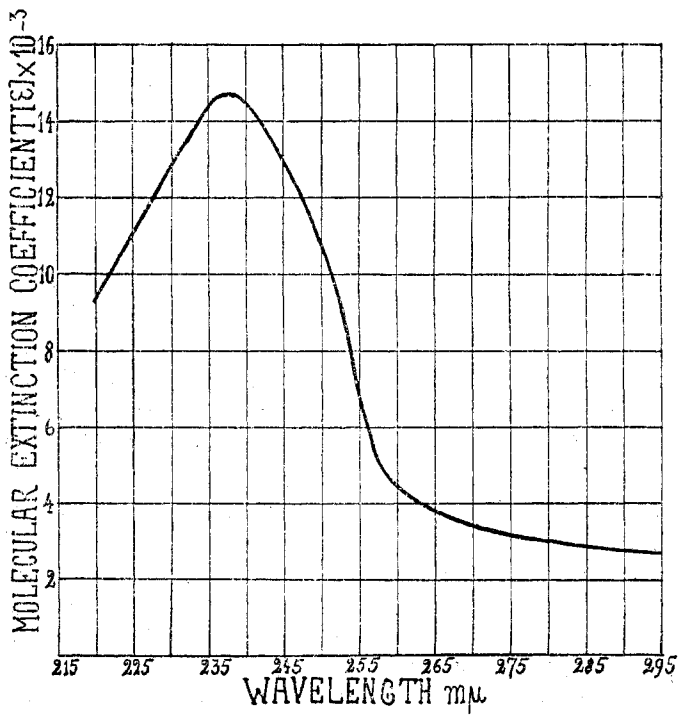


FIG. 1. ABSORPTION CURVE OF 10-NOR-11-DESOXYCORTICOSTERONE ACETATE (IN ABSOLUTE ALCOHOL)[11]

As expected, the substance reduced complex silver-ammonium salts at room temperature.

There are some questions regarding the stereochemical configuration at some of the asymmetric carbon atoms. It is uncertain whether the configuration at carbon atom 10 is analogous to that in the common sterols or to that in the lumisterol series. As has been discussed, it is likely that, regarding the configuration at carbon atom 14, that form predominates in which the methyl group at carbon atom 13 and the hydrogen atom at carbon atom 14 are in *trans*

[11] We are indebted to Professor George R. Harrison and Mr. Rockwell Kent, 3rd., of the Spectroscopy Laboratory of the Massachusetts Institute of Technology for the determination of the ultraviolet absorption spectra.

position, as is the case in the natural steroid hormones. As was mentioned, treatment with alkali of the acid V changed the "normal" configuration at carbon atom 17 to the "iso" arrangement. If conditions in the 10-norpregnane series are analogous to those in the pregnane series (19, 20; *cf.* espec. 19, p. 1848) there is a good chance that the configuration at carbon atom 17 shifted back to the "normal" arrangement in the major part of the material when the acetate XVI was saponified by means of alkali. In brief, regarding the stereochemical configuration the 10-nor-11-desoxycorticosterone acetate may only be

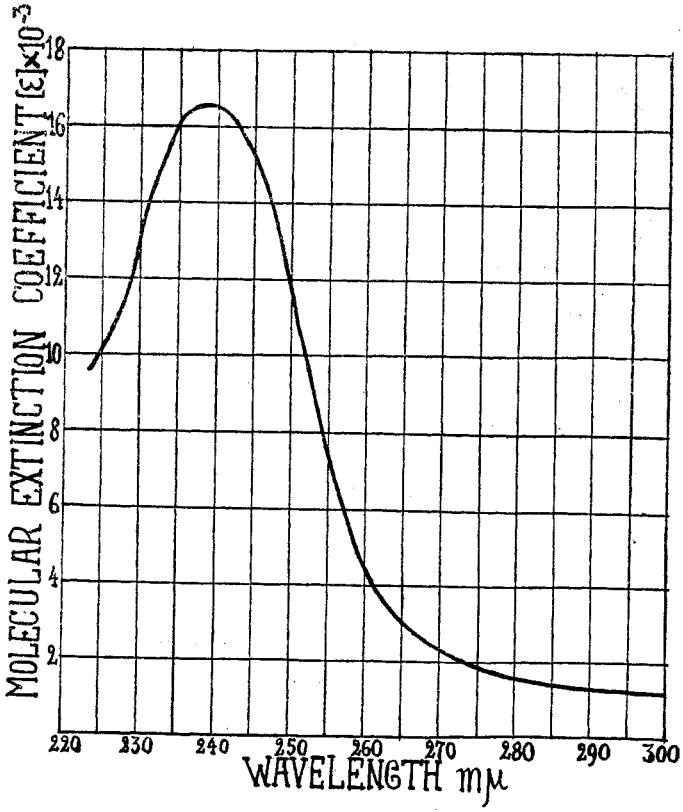


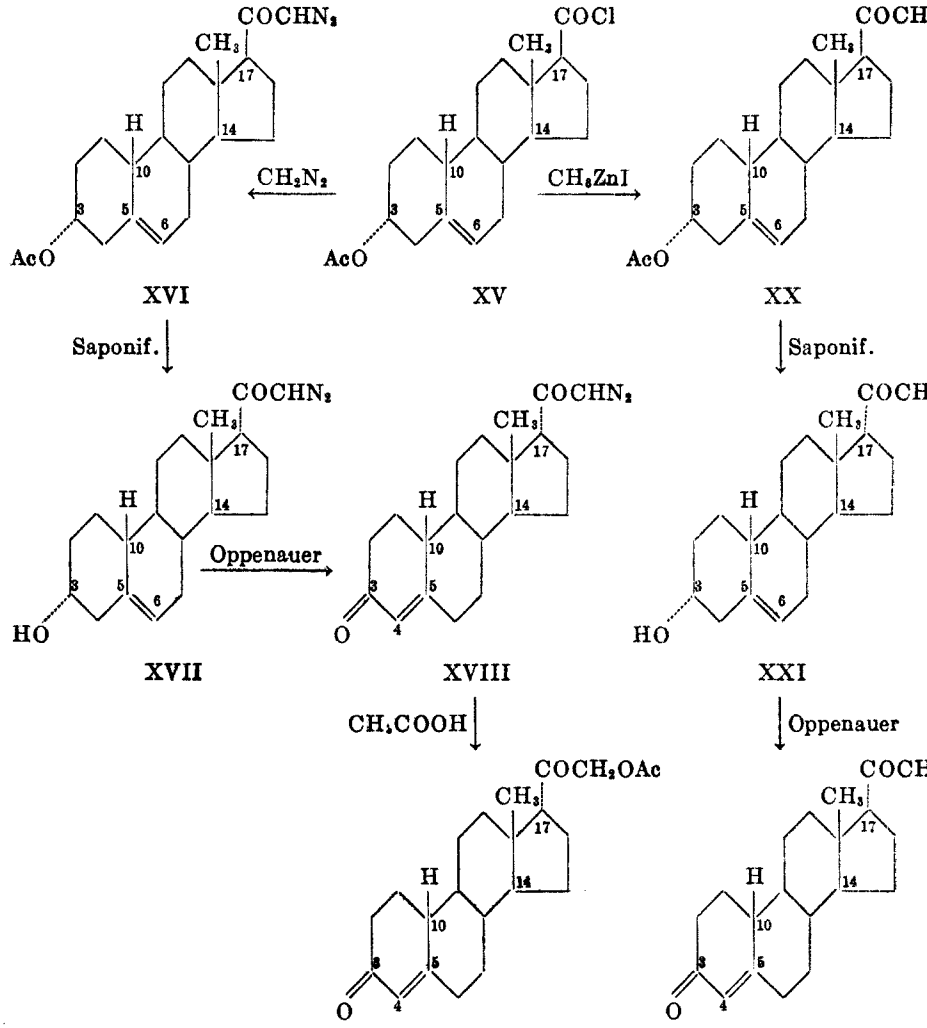
FIG. 2. ABSORPTION CURVE OF 10-NORPROGESTERONE (IN ABSOLUTE ALCOHOL)[11]

partly analogous to the naturally occurring 11-desoxycorticosterone. It is probable that the new compound is not uniform in a stereochemical sense and this may explain the lack of tendency to crystallize.[12]

The 10-nor-11-desoxycorticosterone acetate (XIX) was kindly examined for adrenal-cortical activity by Dr. Dwight J. Ingle of the Research Laboratories of the Upjohn Company (Kalamazoo, Mich.). Five male, adrenalec-

[12] There are numerous examples of non-crystalline mixtures of stereoisomers in the field of steroids. *Cf. e.g.* Robinson's (21) recent total synthesis of a mixture of stereoisomeric androstenediones.

tomized rats weighing 180 grams were treated daily for seven successive days with a solution of 0.2 milligram of material in 0.2 cc. of sesame oil.[13] Two additional animals were placed on a daily dosage of 0.25 milligram. All animals lost weight, whereas all five adrenalectomized control animals treated



XVI XV XX

XVII XVIII XXI

XIX. 10-Nor-11-Desoxycorticosterone acetate

XXII. 10-Norprogesterone

with 0.1 milligram of desoxycorticosterone acetate daily gained weight. The work performance (for method *cf.* 22) of the animals treated with the new substance was within the range of that of untreated adrenalectomized animals. It

[13] Injections in divided doses twice daily.

follows, therefore, that the new substance is at any rate considerably less active than desoxycorticosterone acetate.

As was pointed out, the new substance is possibly not uniform regarding its configuration at carbon atom 17. It is known that 17-isodesoxycorticosterone acetate (23) and 17-isoprogesterone (24) are physiologically less active than the compounds with the "normal" configurations at carbon atom 17. Rearrangement can be performed by boiling with hydrochloric acid and thus the hormones with the "normal" configurations can easily be isolated. After subjecting 10-nordesoxycorticosterone acetate to this treatment, the resulting resinous product showed practically the same optical rotation as the untreated material. In the pregnane series, an inversion from the "iso" to the "normal" configuration at carbon atom 17 is connected with a remarkable change of the optical rotation in a positive direction. Our finding may mean, therefore, that, provided no simultaneous inversions have occurred at other carbon atoms, treatment with hydrochloric acid has produced no change at carbon atom 17. Hence the material may have initially represented in its entirety a normal configuration at carbon atom 17.

The substance, after treatment with hydrochloric acid, was again subjected to physiological tests in adrenalectomized rats (2 animals) at a dosage level of 0.3 milligram per day. These animals lost weight and the work performance was within the range of that of untreated adrenalectomized rats.

Attempts to obtain 10-norprogesterone (XXII) have also been successful. When the crude acid chloride XV was treated with methylzinc iodide according to the method of E. E. Blaise (25)[14] a methyl ketone (XX) was formed which was purified by chromatographic adsorption as well as by separation with Girard's reagent. The purified substance, after distillation in a high vacuum, was resinous. It was saponified and the crude saponified product (XXI) subjected to dehydrogenation according to the method of Oppenauer (18). The resulting material was purified by chromatographic adsorption and subsequent distillation in a high vacuum. The final substance, 10-norprogesterone (XXII), was a soft resin ($[\alpha]_D^{20} + 89.3°$). The ultraviolet absorption spectrum[11] possesses the characteristics of an α,β-unsaturated ketone ($\lambda_{max} = 238.5 m\mu$; $\epsilon = 16560$). Regarding the stereochemical purity, involving carbon atoms 10, 14, and 17, the same considerations have to be applied as in the foregoing instance of the 10-nor-11-desoxycorticosterone acetate. The substance may have predominantly "normal" steroid configurations at carbon atoms 14 and 17. No opinion is ventured regarding the configuration at carbon atom 10. It is believed that, at any rate, the 10-norprogesterone (XXII) represents a mixture of stereoisomers and probably for this reason does not crystallize.[12]

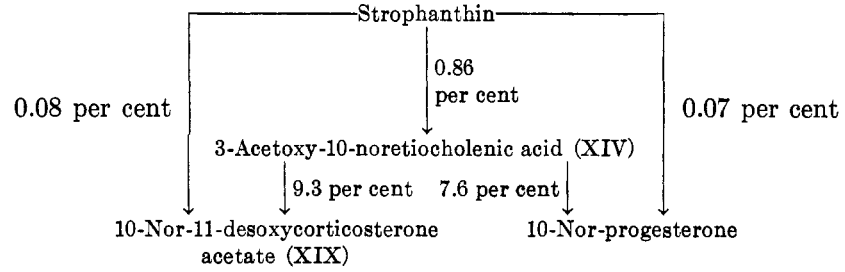
The 10-norprogesterone (XXII) appears to be fully as active as progesterone, perhaps even more so[14a]. All other compounds related to progesterone which have progestational activity are considerably less active than progesterone.

[14] This reaction has been successfully applied in the syntheses of higher homologs of progesterone (26).

[14a] For physiological data, *cf.* ref. 31

This indicates that the angular methyl group at carbon atom 10 can be replaced with hydrogen without impairing the physiological activity.

The *over-all yields* in the discussed chemical reactions are presented in the following scheme.



EXPERIMENTAL

Unless marked as uncorrected, the melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company (Pittsburgh, Pa.). The readings are sufficiently near the true melting points so that no corrections have been made. Unless stated otherwise, the microanalyses were carried out by Mr. William Saschek, Columbia University, New York. The limited value of the optical rotations of mixtures of isomers must be kept in mind.

A. *Preparation of the trihydroxydicarboxylic acid* $C_{20}H_{30}O_7$ [*3,5,14-trihydroxyestrane-10,17-dicarboxylic acid*] (*VII*). The procedures used were essentially those of Jacobs (10) and Elderfield (11). Butenandt and Gallagher (12) had utilized these methods with minor modifications without stating any yields. As the intermediate products were prepared by us a number of times, new observations on the procedures will be recorded and the yields be compared with those reported by Jacobs (10) and Elderfield (11).

Strophanthidin (*I*). Strophanthin Merck U.S.P. X served as starting material. Hydrolysis with 0.5% hydrochloric acid (9) furnished the crude crystalline strophanthidin. Six experiments; yields ($C_{36}H_{54}O_{14} \rightarrow C_{23}H_{32}O_6 + 2H_2O$): 75.1–79.5%; average 76.6%. On recrystallizing (5 parts hot methanol + 15 parts hot water) more than four-fifths of the material was recovered in the first crop; m.p.'s between 164° and 171° decomp. (uncorr.).

Strophanthidinic acid (*IV*). Preparation according to the procedure of Jacobs (10, p. 556), by oxidizing recrystallized strophanthidin (I) with potassium permanganate in a neutral solution of acetone. The crude reaction product was purified *via* the ammonium salt. Three experiments; yields ($C_{23}H_{32}O_6 + 2H_2O \rightarrow C_{23}H_{32}O_7$): 17.9 (prelim. expt.); 27.3; 29.8%. Yield obtained by Jacobs (10, p. 556): 27.2%. This material was used for the next step without recrystallization.

Ketolactonecarboxylic acid $C_{21}H_{28}O_7$ (*V*).[15] Strophanthidinic acid (IV) was oxidized in an alkaline aqueous solution with potassium permanganate according to Jacobs (10, p. 559). Three experiments; yields of the crude reaction products: 66.1; 63.5; 58.2%. By recrystallization from 95% ethanol a number of crystalline fractions were obtained; m.p.'s: between 245° and 256° decomp. (uncorr.); yields after recrystallization: 38.8; 38.2; 28.1%. Yield of the recrystallized acid as obtained by Jacobs (10, p. 559): 53.6%.

Ketodicarboxylic acid $C_{21}H_{30}O_8$ (*VI*).[15] A solution of the recrystallized ketolactonecarboxylic acid (V) in 2% sodium hydroxide was heated on the water-bath for 30 minutes,

[15] Mrs. Marguerite Twaddell Decker rendered valuable assistance in the purification of this acid.

cooled to room temperature, and then acidified by slowly adding 25% sulfuric acid (10, p. 562). The ketodicarboxylic acid (VI) is rather easily soluble in water. The precipitate obtained in our first experiment proved to be completely soluble in water; yield: 63.9%. Yield of the crude reaction product obtained by Jacobs (10, p. 562): 76.5%. In three following experiments the precipitate was not completely soluble in water. The soluble part was separated by leaching with generous amounts of water, bringing to dryness, and again extracting the residue with water. The yield of water-soluble material thus obtained was between 40 and 50%. The melting point of the insoluble fraction, after recrystallization from ethanol, indicated that it consisted of unchanged ketolactonecarboxylic acid (V) and hence renewed treatment of it with sodium hydroxide furnished another supply of the ketodicarboxylic acid (VI). By recrystallizing the water-soluble material from hot water, about two-thirds was recovered in the first crop as fine silky needles. The melting points of these first fractions were between 165° and 172° decomp. (uncorr.). Less pure material was obtained from the mother liquors.

Trihydroxydicarboxylic acid $C_{20}H_{30}O_7$ [*3,5,14-trihydroxyestrane-10,17-dicarboxylic acid*] (*VII*). The recrystallized ketodicarboxylic acid (VI) was oxidized in an aqueous solution with 30% hydrogen peroxide according to the procedure of Elderfield (11, p. 634). Separation from the reaction mixture of macroscopic stout glistening crystals occurred usually within 24 hours standing at room temperature. They were filtered and washed with water after at least five days standing. Five experiments were carried out with pure starting material. The melting points of the crystals obtained ranged between 255° and 270° decomp.; yields: 71.2; 67.1; 90.8; 62.6; 76.8%. No yield stated by Elderfield (11, p. 634). Somewhat impure starting material furnished crystals of the same habitus and melting point though the yields were considerably smaller. The material was recrystallized by dissolving it in a rather large amount of acetone and subsequent concentration to a smaller volume, m.p. 268–271° decomp.; $[\alpha]_D^{29} + 12.7°$ (15.0 mg. in 2.0 cc. of absol. ethanol). Elderfield (11, p. 634) states "no appreciable optical rotation."

Anal.[16] Calc'd for $C_{20}H_{30}O_7$: C, 62.79; H, 7.91.
Found: C, 62.95, 62.73; H, 7.95, 7.99.

Dimethyl ester. Since the acid is practically insoluble in ether it was dissolved in a sufficient amount of acetone. To the concentrated solution was added an excess of an ethereal solution of diazomethane. By working up as usual, the crystalline ester was obtained which was recrystallized once from acetone-ether, m.p. 185° (uncorr.).

Anal.[16] Calc'd for $C_{22}H_{34}O_7$: C, 64.35; H, 8.35.
Found: C, 64.07; H, 8.24.

B. *Preparation of 3-acetoxy-10-noretiocholenic acid* [*3-acetoxyestrene-17-carboxylic acid*] (*XIV and/or isomers XIVa, XIVb*). *Anhydrodicarboxylic acid* $C_{20}H_{28}O_6$ [*14-estrene-3,5-diol-10,17-dicarboxylic acid*] (*VIII*). In a preliminary experiment the dehydration of the trihydroxydicarboxylic acid (VII) was attempted with 5% sulfuric acid in a solution of dioxane (*cf., e.g.*, 13, p. 837). A solution of 350 mg. of the pure trihydroxydicarboxylic acid (VII) in the required amount of dioxane (30 cc.) was concentrated to a volume of 8 cc. After the addition of 88 cc. of 5% sulfuric acid the solution was heated on a water-bath for 3¼ hours and then kept at room temperature for 24 hours. Thereafter the reaction mixture was repeatedly extracted with ether, and the ether extracts washed twice with water. The first ten (a) and the following twenty-three (b) ether extracts were combined respectively. After drying with sodium sulfate they were brought to dryness: (a) resinous residue; 207 mg. (b) white crystalline residue; 136 mg. Recrystallization of the crystalline residue from acetone-ether furnished irregularly shaped plates; m.p. 275–282° decomp. The substance is very difficultly soluble in ether.

Anal.[16] Calc'd for $C_{20}H_{28}O_6$: C, 65.89; H, 7.75.
Found: C, 65.50, 65.73; H, 7.73, 7.70.

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[16] Microanalysis in April 1939 by Dr. Ing. A. Schoeller, Berlin-Schmargendorf.

The crystalline unsaturated dicarboxylic acid described above probably differs[17] from the one which was obtained in the main experiments.

The procedure of the main experiments was essentially that of Butenandt and Gallagher (12, p. 1868): Two grams of the pure trihydroxydicarboxylic acid (VII) was dissolved in 200 cc. of a 0.1 *N* solution of hydrogen chloride in absolute alcohol. This solution was concentrated at atmospheric pressure (bath temperature 90–95°) to a volume of about 25 cc. To the light yellow concentrate was added 30 cc. of water and the distillation subsequently continued *in vacuo* (50°) until a turbidity began to appear. The solution was cleared by gently warming it on a water-bath and then allowing it to stand at room temperature for two days. The first crop of crystals consisted of 0.826 g. of plates, arranged in clusters; m.p. 254–257° decomp. By further concentrating the filtrate *in vacuo* (35°) six additional precipitates (0.903 g.) were obtained. Some of them were initially soft resins which solidified on kneading with water. The remainder of the reaction product (white residue; 0.092 g.) was recovered by thoroughly extracting the final mother liquor with ether. Total material recovered: 1.821 g. In a repetition of the main experiment with 1.0 g. of trihydroxydicarboxylic acid (VII) the yields were as follows: first crop, 0.354 g., m.p. 255–256° decomp.; five additional precipitates, 0.501 g.; final ether extract, 0.046 g. Total material recovered: 0.901 g. Several of the above fractions of the two main experiments were combined, depending on their melting points, and the material then subjected to repeated recrystallizations from methanol-water (m.p. of purest fractions 261–263° decomp.; macroscopic scales; sometimes a conglomeration of prisms) or, in a few instances, from ether. The final yield from 3.0 g. starting material (VII) was divided in three groups: (a) 20 crystalline fractions melting essentially between 256° and 263°; no depression of melting points within this group; total 1.527 g. = 53.4%. The yield of 59% claimed by Butenandt and Gallagher (12, p. 1868) refers to the crude anhydro acid. (b) Five crystalline fractions; melting points between 150° and 240°; total 0.117 g. (c) Eight resinous fractions; total 0.907 g. Determination of the optical rotation with the purest crystalline fraction (m.p. 261–263°): $[\alpha]_D^{20} + 122.0°$ (15.0 mg. in 2.0 cc. of absol. ethanol); lit. (12) $[\alpha]_D^{23} + 122°$ (ethanol).

Saturated dicarboxylic acid $C_{20}H_{30}O_6$ [*estrane-3,5-diol-10,17-dicarboxylic acid*] (*IX*). A suspension of 130 mg. of platinum oxide in 5 cc. of purest glacial acetic acid was reduced by shaking it with hydrogen. After the addition of a solution of 364 mg. (1 millimole) of pure crystalline anhydrodicarboxylic acid (VIII) (m.p. between 256° and 263°) in 22 cc. of glacial acetic acid shaking was continued at room temperature (26°) for two hours after which the hydrogenation had come to a standstill. About nine-tenths of the hydrogen was absorbed within the first half hour. Total hydrogen absorption: 23.9 cc. (26°), calc'd for 1 millimole H_2: 24.5 cc. (26°).

Hydrogenations with the remainder of the pure crystalline anhydrodicarboxylic acid (VIII) furnished similar results. After the conclusion of the hydrogenations the solutions were filtered from the catalyst and immediately brought to dryness *in vacuo* (50°). The residues (from a total of 1.459 g. of starting material) were washed with water, dried, and eventually combined; yield 1.301 g.; m.p. 240–245° decomp. By concentrating the washings *in vacuo* 0.074 g. of lower-melting material and 0.065 g. of a resin were obtained. Total recovered; 1.440 g. Recrystallization of the main portion (1.301 g.) from acetone furnished

[17] When Steiger and Reichstein (13, p. 837) dehydrated 3,12,14-trihydroxyetiocholanic acid under similar conditions only a small yield of a crystalline unsaturated acid was obtained. Since it was resistant to hydrogenation either as such or in the form of the methyl ester, it is probable that the double bond in this crystalline compound is between carbon atoms 8 and 14. The major part of the reaction product was an oily unsaturated acid which was hydrogenated in the form of the methyl ester. It is likely that the oily material contained, at least partly, the double bond between carbon atoms 14 and 15. The crystalline anhydrodicarboxylic acid as obtained in our preliminary experiment (*v. supra*) possibly has the double bond between carbon atoms 8 and 14.

a number of fractions with melting points ranging between 245° and 255°. This material [total: 1.165 g; yield 79.4%; no yield stated by Butenandt and Gallagher (12, p. 1869)] was used for the subsequent reactions; m.p. of purest fraction (0.462 g.); 254–255° decomp.; $[\alpha]_D^{20.5}$ + 60.0°; $[\alpha]_D^{21.5}$ + 64.5° (15.0 mg. in 2.0 cc. of absol. ethanol); lit. (12) $[\alpha]_D^{15}$ + 35° (ethanol) for a product of m.p. 255–256° decomp.

Anal. Calc'd for $C_{20}H_{30}O_6$: C, 65.53; H, 8.26.
Found: C, 64.96, 64.97; H, 8.04, 8.27.

It may be mentioned that it was attempted to hydrogenate also the lower-melting (0.117 g.) and the resinous (0.907 g.) fractions of the anhydrodicarboxylic acid. The hydrogen absorption was 70.3 and 85.6% respectively, but only traces of material melting as high as the pure fractions could be isolated.

Estrane-3,5-diol-10,17-dicarboxylic acid 3,5-diacetate (XIII) (?). To a solution of 50 mg. of purest crystalline estrane-3,5-diol-10,17-dicarboxylic acid (IX) in 0.5 cc. of pyridine was added 0.25 cc. of acetic anhydride and the mixture allowed to stand at room temperature (21°) for 18 hours. For the destruction of anhydrides 0.25 cc. of glacial acetic acid and 0.1 cc. of water was added and the mixture heated on a water-bath (reflux condenser) for one hour. It was then brought to dryness *in vacuo* (55°), the residue taken up in ether and the ethereal solution washed with dilute hydrochloric acid and three times with water. After drying with sodium sulfate and filtering, the solution was concentrated to a small volume. When a little petroleum ether was added at room temperature, crystallization began spontaneously; rosettes of needles; yield: 35.0 mg; m.p. 219–222° (slight effervescence). From the filtrate there was obtained 8.8 mg. of crystalline material, m.p. about 200°, and 14.8 mg. of a resinous residue. Both the crystalline and the resinous material gave negative reactions with tetranitromethane. By recrystallizing the first crystalline crop from ether-petroleum ether 24.1 mg. of crystals was obtained; m.p. 223–225° (slight effervescence); $[\alpha]_D^{20}$ +56.7° (15.0 mg. in 2.0 cc. of acetone). In a repetition of this experiment crystals with a slightly lower melting point were obtained. Analyses were performed with samples from both experiments.

Anal. Calc'd for $C_{22}H_{32}O_7$(Monoacetate): C, 64.66; H, 7.90.
Calc'd for $C_{24}H_{34}O_8$(Diacetate): C, 63.96; H, 7.61.
Found: C, 63.60, 64.15; H, 7.59, 7.89.

Distillation of estrane-3,5-diol-10,17-dicarboxylic acid 3,5-diacetate (XIII) ? in a high vacuum. Thirty-five milligrams of the diacetate was distilled in a high vacuum (oil and mercury vapor pumps combined) at an oven temperature of 250–280°. The distillate (28.4 mg.) was a colorless glass which contained some rosettes of needles. The latter were removed by treating the distillate with a small volume of ether and subsequent filtering. A second crop of needles was obtained by adding some petroleum ether to the filtrate. Total crystalline material: 10.1 mg.; m.p. around 230°; no depression of m.p. in mixture with a sample of the diacetate. The non-crystalline material represented a brittle foam; wt. about 18 mg. As expected the reaction of the crystalline part with tetranitromethane was negative whereas that of the amorphous part was positive. Eventual combination of the crystalline and amorphous material and renewed high-vacuum distillation yielded a colorless glass.

Anal. Calc'd for $C_{22}H_{30}O_6$: C, 67.65; H, 7.75 [$C_{24}H_{34}O_8$(Diacetate) minus CH_3COOH].
Calc'd for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43 [$C_{24}H_{34}O_8$(Diacetate) minus CO_2].
Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73 [$C_{24}H_{34}O_8$(Diacetate) minus CH_3COOH, CO_2].
Found: C, 69.73; H, 8.62.

Estrane-3,5-diol-10,17-dicarboxylic acid 3-monoacetate (XII). A solution of 0.450 g. of recrystallized estrane-3,5-diol-10,17-dicarboxylic acid (IX) in 4.5 cc. of acetic anhydride was refluxed (metal-bath, 140–150°) for 30 minutes. To decompose anhydrides, 4.5 cc. of glacial acetic acid and 2.7 cc. of water was subsequently added and the solution heated on a water-bath for one hour. Thereafter the solvents were removed *in vacuo* (50°) and

the sirupy residue taken up in ether. This solution was extracted twice with ice-cold dilute sodium carbonate. The combined extracts were acidified by adding promptly ice-cold dilute hydrochloric acid, which caused a white flocculent precipitate to appear. The suspension was extracted three times with ether and the combined ether extracts washed several times with small quantities of water. After drying and filtering, evaporation of the ether yielded a colorless foamy glass which still retained traces of solvent; wt. 0.553 g. With tetranitromethane (in chloroform) a slight yellow color was obtained, indicating the presence of traces of unsaturated material. The substance resisted all attempts of crystallization; $[\alpha]_D^{22}$ +38.0° (15 mg. in 2.0 cc. of acetone). For analysis it was dried at 85° (slight vac.); more vigorous drying was avoided to prevent possible decomposition.

Anal. Calc'd for $C_{22}H_{32}O_7$(Monoacetate): C, 64.66; H, 7.90.
$C_{24}H_{34}O_8$(Diacetate): C, 63.96; H, 7.61.
Found: C, 64.20; H, 7.36.

The experiment was repeated twice with similar results.

3-Acetoxy-10-noretiocholenic acid [3-acetoxyestrene-17-carboxylic acid] (XIV and/or isomers XIVa, XIVb). The crude monoacetate (XII) (0.590 g.) was transferred into a high-vacuum retort by means of ether. After careful removal of the solvent a foamy glass was obtained. By gently heating it in a high vacuum to a temperature of 80–120° it almost completely liquefied or sintered. The material thus obtained weighed 0.514 g. and was considered essentially free from solvent. It was now subjected to a distillation in a high vacuum. The temperature was raised fairly quickly to about 180°, where gas evolution was observed. Subsequently it was raised slowly, within a period of one hour, to about 250°. The oven temperature was now quickly raised to about 290° and the distillation thereafter interrupted. The total weight (distillate + residue in the retort) after the distillation was 0.423 g. Calc'd for 0.514 g. starting material ($C_{22}H_{32}O_7 \xrightarrow{-H_2O,\,-CO_2} C_{21}H_{30}O_4$): 0.436 g.

The distillate (0.416 g.) was a slightly yellow brittle glass which was subjected to another distillation under practically identical conditions. This time there was no noticeable gas evolution. The loss of weight during this second distillation was only 0.015 g. which indicates that the thermal reaction had been largely completed during the first distillation. The distillate was a slightly yellow brittle glass; wt. 0.390 g.; yield: 89.5%. The substance gave a strongly positive reaction with tetranitromethane. It resisted several attempts at crystallization; $[\alpha]_D^{20}$ +74.7° (17.9 mg. in 2.0 cc. of acetone). The experiment was repeated twice with practically identical results. Analyses were performed of samples from two different experiments.

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73.
Found: C, 73.36, 72.78; H, 8.30, 8.51.

Titration: 11.2 mg. of the substance required 3.31 cc. of 0.01 *N* NaOH; Calc'd for monocarboxylic acid $C_{21}H_{30}O_4$: 3.23 cc.

3-Acetoxy-10-noretiocholenic acid chloride [3-acetoxyestrene-17-carboxylic acid chloride] (XV and/or isomers). Pure commercial thionyl chloride (Eastman) which had a slightly yellow color was purified by distilling it first over quinoline and then over linseed oil (27, p. 381). The resulting material was colorless. To 200 mg. of 3-acetoxy-10-noretiocholenic acid (XIV and/or XIVa, XIVb) was added in the cold-room 1.0 cc. of purified thionyl chloride. The mixture was allowed to stand under anhydrous conditions in the cold-room (about +2°) for a period of 50 minutes and then at room temperature (20°) for 3½ hours. The olive-green solution was brought to dryness *in vacuo* (40°) under anhydrous conditions. The resulting brown transparent resin was dried overnight in a vacuum desiccator (P_2O_5, KOH); wt. 236 mg. (calc'd 211 mg.). On repeating the experiment with more material the reaction proceeded in the same fashion. The crude acid chloride as such served for the following chemical reactions.

C. *Preparation of 10-nor-11-desoxycorticosterone acetate (XIX). 3-Acetoxy-21-diazo-10-norpregnene-20-one (XVI and/or isomers).* A solution of diazomethane in ether was pre-

pared from 5.15 g. of nitrosomethylurea (28), dried over pellets of pure potassium hydroxide, and redistilled under anhydrous conditions. To this (45 cc.) was added at a temperature of −5° an ethereal solution (5 cc.) of the crude acid chloride (XV) as obtained from 0.39 g. of 3-acetoxy-10-noretiocholenic acid (XIV). The golden-yellow mixture was allowed to stand in the cold-room (about +2°) for a period of 7 hours and then at room temperature (30–33°) for about two days. Thereafter it was concentrated to about one-third of its volume on the water-bath, filtered from a small amount of an insoluble impurity, and eventually brought to dryness *in vacuo*; amber colored, very viscous residue. It was further dried in a vacuum desiccator overnight; wt. 0.52 g. This crude and obviously not dry material was subjected to saponification.

21-Diazo-10-norpregnene-20-one-3-ol (*XVII and/or isomers*). The crude 3-acetoxy-21-diazo-10-norpregnene-20-one (XVI) (0.52 g.; not dry) was dissolved by treating it with a total of 29 cc. of methanol. A trace of a yellowish-brown impurity remained in suspension. A solution of 0.25 g. of potassium hydroxide (4 moles, calc'd on the basis of the invested 0.39 g. of 3-acetoxy-10-noretiocholenic acid) in 0.3 cc. of water and 5 cc. of methanol was added and the mixture allowed to stand at room temperature (32°) for six hours. After the addition of 0.53 g. of potassium bicarbonate dissolved in 20 cc. of water the solution was concentrated to a volume of 20 cc. *in vacuo* (45°). It was then extracted three times with ample quantities of ether, which left the above mentioned yellowish-brown impurity undissolved. The combined ether extracts were washed three times with water, dried with sodium sulfate, filtered, and brought to dryness. The residue was an amber colored foamy glass; wt. after thorough drying in a vacuum desiccator (P_2O_5; KOH) about 0.42 g.

21-Diazo-10-norprogesterone [*21-diazo-10-nor-4-pregnene-3,20-dione*] (*XVIII*). A solution of 0.85 g. of aluminum tert-butoxide (Eastman) in 25 cc. of dry benzene was separated by decantation from a trace of undissolved material and the latter washed twice with fresh benzene. By this treatment 35 cc. of a colorless and clear solution was obtained. To this was added a solution of 0.33 g. of crude 21-diazo-10-norpregnene-20-one-3-ol (XVII) in 10 cc. of dry acetone. The mixture was refluxed under anhydrous conditions on a water-bath for a period of ten hours during which time another 2 cc. of dry acetone was added. After standing at room temperature overnight much redistilled ether was added and the mixture washed twice with a rather saturated solution of potassium sodium tartrate, twice with a dil. solution of sodium carbonate, and three times with water. After drying with sodium sulfate and filtering, the solvent was removed *in vacuo* (45°). The residue was an amber colored viscous resin. On adding ether to this residue a yellow precipitate was obtained which was apparently non-crystalline. Therefore the material was again brought to dryness; yield: 0.35 g., probably not quite dry.

10-Nor-11-desoxycorticosterone acetate (*XIX*). To 0.35 g. of crude 21-diazo-10-norprogesterone was added 5 cc. of anhydrous glacial acetic acid. The solution was first heated at 95° for about 15 minutes, then, during 15 more minutes, the temperature was raised to 120–125° where it was kept for 5 minutes. Thereafter the acetic acid was removed *in vacuo* (50°). The brown, oily residue was taken up in much ether and the solution filtered from some brown by-product. The ether phase was washed with a solution of *N* sodium bicarbonate and three times with water. After drying with sodium sulfate and filtering, the ether was removed *in vacuo*. The residue was a light brown resin. Wt. after drying in a vacuum desiccator, 0.27 g.

The crude material was purified by repeated chromatographic adsorptions. For the first treatment it was dissolved in a mixture of 20 cc. of benzene and 10 cc. of petroleum ether. The solution was filtered through a column of 11 g. of aluminum oxide (aluminum oxide anhydrous, standardized for chromatographic adsorption according to Brockmann, E. Merck, Darmstadt). The original solution was passed through within two hours and the following eluates within 25 and 30 minutes each.

CHROMATOGRAPHIC FRACTIONATION I

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	20 cc. benzene + 10 cc. petr. ether (original solution)	21.4	slightly yellow oil
2	20 cc. benzene + 10 cc. petr. ether	34.6	yellow oil
3	25 cc. benzene + 5 cc. petr. ether	23.6	slightly yellow resin
4	28 cc. benzene + 2 cc. petr. ether	16.4	slightly yellow resin
5	30 cc. benzene	8.5	slightly yellow resin
6	30 cc. benzene	5.7	slightly yellow resin
7	25 cc. benzene + 5 cc. ether	23.7	yellow resin
8	20 cc. benzene + 10 cc. ether	18.3	yellow resin
9	15 cc. benzene + 15 cc. ether	8.5	yellow resin
10	10 cc. benzene + 20 cc. ether	2.0	colorless resin
11	5 cc. benzene + 25 cc. ether	1.1	colorless resin
12	30 cc. ether	1.6	colorless resin
13	30 cc. ether	12.8	yellow oil
14	25 cc. ether + 5 cc. chloroform	0.3	colorless residue
15	15 cc. ether + 15 cc. chloroform	0.8	colorless residue
16	30 cc. chloroform	7.2	yellow resin
17	25 cc. chloroform + 5 cc. methanol	34.6	whitish-brownish
18	30 cc. methanol	13.1	whitish-brownish
	Total	234.2	

In interpreting the above chromatogram it was suspected that the 10-nor-11-desoxycorticosterone acetate was present particularly in fractions 3–6. In agreement with this assumption these fractions gave a positive reaction with an alkaline solution of silver diammine. In order to secure, if possible, some more of the desired material it was decided to rechromatograph fractions 1–2 (Chromatographic Fractionation II) and fractions 7–12 (Chromatographic Fractionation III) respectively.

Fractions 1 and 2 of the first chromatogram were combined (56.0 mg.), dissolved in a mixture of 5 cc. of benzene and 20 cc. of petroleum ether and subsequently filtered through a column of 3 g. of aluminum oxide (Brockmann). The original solution was passed through within about one hour and the following eluates within 15 to 20 minutes each.

CHROMATOGRAPHIC FRACTIONATION II

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	5 cc. benzene + 20 cc. petr. ether (original solution)	13.4	colorless oil
2	5 cc. benzene + 15 cc. petr. ether	9.6	colorless oil
3	5 cc. benzene + 10 cc. petr. ether	4.9	colorless grease
4	7.5 cc. benzene + 7.5 cc. petr. ether	3.2	colorless grease
5	7.5 cc. benzene + 7.5 cc. petr. ether	2.5	colorless grease
6	10 cc. benzene + 5 cc. petr. ether	2.8	colorless resin
7	12 cc. benzene + 3 cc. petr. ether	2.7	colorless resin
8	14 cc. benzene + 1 cc. petr. ether	1.6	colorless resin
9	15 cc. benzene	0.9	colorless resin
10	15 cc. benzene	0.8	colorless residue
11	10 cc. benzene + 5 cc. ether	1.1	colorless residue
12	30 cc. ether	4.3	slightly yellow oil
13	12 cc. ether + 3 cc. methanol	1.8	whitish resin
14	15 cc. methanol	4.4	whitish yellow residue
	Total	54.0	

Fractions 7 to 12 of the first chromatogram were combined (54.3 mg.), dissolved in a mixture of 14 cc. of benzene and 6 cc. of petroleum ether, and filtered through a column of 3 g. of aluminum oxide (Brockmann). The original solution was passed through within about two hours and the eluates within 15 to 20 minutes each.

CHROMATOGRAPHIC FRACTIONATION III

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	14 cc. benzene + 6 cc. petr. ether (original solution)	1.1	colorless residue
2	14 cc. benzene + 6 cc. petr. ether	0.8	colorless residue
3	12 cc. benzene + 3 cc. petr. ether	1.2	colorless residue
4	14 cc. benzene + 1 cc. petr. ether	2.8	colorless resin
5	15 cc. benzene	3.5	colorless resin
6	15 cc. benzene	3.0	colorless resin
7	11 cc. benzene + 4 cc. ether	8.5	pale yellow resin
8	7 cc. benzene + 8 cc. ether	3.4	pale yellow resin
9	5 cc. benzene + 10 cc. ether	2.0	colorless resin
10	30 cc. ether	4.5	colorless resin
11	7.5 cc. ether + 7.5 cc. chloroform	1.6	colorless resin
12	15 cc. chloroform	4.0	yellow resin
13	12 cc. chloroform + 3 cc. methanol	10.0	whitish-yellow resin
14	15 cc. methanol	4.7	whitish residue
	Total	51.1	

The following fractions of the foregoing chromatograms were combined and the total subjected to another chromatographic purification (Chromatographic Fractionation IV): 1st. chromatogram, fractions 3–6; 2nd. chromatogram, fractions 4–9; 3rd. chromatogram, fractions 1–6; total: 75.5 mg. This material was dissolved in a mixture of 15 cc. of benzene and 15 cc. of petroleum ether. The solution was filtered through a column of 3.7 g. of aluminum oxide (Brockmann). The original solution was passed through within one hour and the eluates each within 20–25 minutes.

CHROMATOGRAPHIC FRACTIONATION IV

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	15 cc. benzene + 15 cc. petr. ether (original solution)	1.9	colorless grease
2	10 cc. benzene + 10 cc. petr. ether	10.9	colorless sticky resin
3	12 cc. benzene + 8 cc. petr. ether	5.4	colorless solid resin
4	14 cc. benzene + 6 cc. petr. ether	6.0	colorless solid resin
5	16 cc. benzene + 4 cc. petr. ether	5.7	colorless solid resin
6	18 cc. benzene + 2 cc. petr. ether	4.5	colorless solid resin
7	20 cc. benzene	3.5	colorless solid resin
8	20 cc. benzene	2.4	colorless solid resin
9	20 cc. benzene	1.5	colorless solid resin
10	16 cc. benzene + 4 cc. ether	2.8	colorless solid resin
11	12 cc. benzene + 8 cc. ether	1.8	colorless solid resin
12	8 cc. benzene + 12 cc. ether	0.9	colorless solid resin
13	20 cc. ether	1.6	colorless solid resin
14	20 cc. ether	1.6	colorless solid resin
15	15 cc. ether + 5 cc. methanol	11.5	yellowish solid resin
16	20 cc. methanol	7.4	yellowish whitish glass
	Total	69.4	

Attempts to crystallize fraction 4 from ether and petroleum ether failed. Fractions 2–9 (39.9 mg.) were combined and subjected to a distillation in a high vacuum. The oven was heated within 15 minutes to 170°, raised within 10 minutes to 230°, and eventually within 30 minutes more to 250°. The distillate was a light yellow, very viscous resin; wt.: 29.4 mg.; over-all yield based on the invested 3-acetoxy-10-noretiocholenic acid: 9.3%. A solution of the substance in methanol reduced an alkaline solution of silver diammine after short standing at room temperature; $[\alpha]_D^{21}$ +56.6° (10.3 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{22}H_{30}O_4$: C, 73.69; H, 8.44.

Found: C, 73.93; H, 8.30.

For ultraviolet absorption spectrum and physiological activity see theoretical part.

Treatment of 10-nor-11-desoxycorticosterone acetate (XIX) with hydrochloric acid (cf. 24, p. 1118; 23, p. 931). To a solution of 9.5 mg. of pure 10-nor-11-desoxycorticosterone acetate in 0.5 cc. of 95% alcohol was added 0.05 cc. of conc'd hydrochloric acid (d = 1.19). The mixture was refluxed (bath temp. about 100°) for 30 minutes and then brought to dryness *in vacuo* (40°). The residue was a red-brown resin to which was added 0.25 cc. of pyridine and 0.2 cc. of acetic anhydride. The solution was allowed to stand at room temperature (24°) for 18 hours, then brought to dryness *in vacuo* (40°) and the brown resinous residue taken up in ether. After washing the ether with N hydrochloric acid, N sodium carbonate, and water it was dried with sodium sulfate and then evaporated to dryness. The residue was a yellow resin; wt. 8.9 mg. It was purified by chromatographing it in a mixture of 1 cc. of benzene and 1 cc. of petroleum ether over 0.4 g. of aluminum oxide (Brockmann). The column was eluted with 5 cc. of benzene and then with 5 cc. of ether. The eluates were combined and brought to dryness. The residue was a colorless resin; wt. 6.6 mg.; $[\alpha]_D^{17.5}$ +50.2° (6.6 mg. in 2.0 cc. of acetone). Since this material was not distilled in a high vacuum and was hence not quite dry, the value of the optical rotation is probably a little too low. Considering this fact, the optical rotation of the 10-nor-11-desoxycorticosterone acetate appears practically unchanged after the treatment with hydrochloric acid. For the physiological activity of this material see theoretical part.

D. *Preparation of 10-norprogesterone (XXII). 3-Acetoxy-10-norpregene-20-one (XX and/or isomers).* Active zinc-copper couple was secured from 2 g. of zinc (Zinc Reagent-Merck, Mossy, cut in small pieces of 1–3 mm. size) and 0.2 g. of copper powder (Naturkupfer) according to the method of Job and Reich (29). Methylzinc iodide was prepared (22) by adding the zinc-copper couple and an iodine crystal to a mixture of 2.33 g. of methyl iodide (Eastman, pure), 0.5 cc. of dry alcohol-free ethyl acetate, and 1.0 cc. of dry toluene. The mixture was heated (reflux condenser) under anhydrous conditions in a metal-bath to 80°. Over a period of 1½ hours the temperature was gradually raised to 120° where it was kept for 45 minutes. After cooling to room temperature the mixture was diluted with 1.0 cc. of toluene. The fuming (thick white fumes) colorless solution of the organo-zinc compound was decanted from the excess metal and the latter rinsed with a few drops of toluene. To the ice-cooled solution was slowly added a solution in 1.0 cc. of dry benzene of 3-acetoxy-10-noretiocholenic acid chloride (XV and/or isomers) as prepared from 200 mg. of the free etio acid (XIV and/or XIVa, XIVb). The clear mixture was allowed to stand at room temperature (24°) for 30 minutes. After cooling with ice, water was added gradually and the resulting thick precipitate brought into solution by subsequently adding an excess of N sulfuric acid until acid to Congo. The reaction mixture was now extracted with an ample quantity of ether and the ether washed with a conc'd solution of ammonium sulfate, water, a solution of N sodium hydroxide, and eventually three times with small quantities of water (neutral ether extract). The sodium hydroxide washing and the subsequent water washings were acidified with N sulfuric acid. The precipitate was extracted with ether and the ether phase washed with water (acid-ether extract). The neutral and the acid ether extracts were dried with sodium sulfate, brought to dryness *in vacuo* (40°) and the residues dried in a vacuum desiccator (P_2O_5; KOH). Neutral residue: orange colored viscous oil; wt. 135 mg. Acid residue: brown brittle foam; wt. 68 mg.

The neutral residue (135 mg.) was subjected to chromatographic adsorption for which

purpose it was dissolved in a mixture of 10 cc. of benzene and 25 cc. of petroleum ether. The solution was filtered through a column of 6.0 g. of aluminum oxide (Brockmann). The original solution was passed through within two hours and the eluates each within 15 minutes.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	10 cc. benzene + 25 cc. petr. ether (original solution)	13.0	colorless sticky oil
2	6 cc. benzene + 14 cc. petr. ether	46.1	slightly yellow sticky oil
3	8 cc. benzene + 12 cc. petr. ether	21.1	colorless resin
4	10 cc. benzene + 10 cc. petr. ether	11.4	colorless resin
5	13 cc. benzene + 7 cc. petr. ether	6.8	colorless resin
6	17 cc. benzene + 3 cc. petr. ether	5.9	colorless resin
7	20 cc. benzene	4.6	colorless resin
8	20 cc. benzene	2.3	colorless resin
9	17 cc. benzene + 3 cc. ether	4.2	colorless resin
10	13 cc. benzene + 7 cc. ether	1.9	colorless resin
11	10 cc. benzene + 10 cc. ether	1.0	colorless resin
12	5 cc. benzene + 15 cc. ether	0.5	—
13	20 cc. ether	0.4	—
14	20 cc. ether	1.1	colorless resin
15	19 cc. ether + 1 cc. methanol	6.4	yellow resin
16	30 cc. methanol	10.6	whitish-brownish residue
	Total.....	137.3	

Fractions 2–8 of the chromatogram (98.2 mg.) were combined and subjected to a distillation in a high vacuum. The oven was heated within 10 minutes to 110°. The temperature was gradually raised to slightly above 200° within a period of one hour. The distillate was a slightly yellow viscous resin; wt. 87.5 mg.

Anal. Calc'd for $C_{22}H_{32}O_3$: C, 76.69; H, 9.37.
Found: C, 75.49; H, 8.60.

Because of this analysis the distillate was subjected to another purification by means of Girard's reagent T (betaine hydrazide hydrochloride) (30). To the available material (76.8 mg.), dissolved in 1.0 cc. of methanol, was added 110 mg. of Girard's reagent and 0.06 cc. of glacial acetic acid. The mixture was refluxed on a water-bath for one hour and then allowed to stand in the cold-room for two days. Thereafter it was cooled to −5° and subsequently about 1 g. of ice and an ice-cold solution of 0.05 g. of sodium carbonate in 1 cc. of water was added. The turbid mixture was quickly extracted twice with ether in the cold-room. The combined ether phases were washed at room temperature successively with water, a solution of *N* sodium carbonate and four times with water. After drying the ethereal solution with sodium sulfate and subsequent removal of the ether 28.6 mg. of an almost colorless resin (non-ketonic fraction) was obtained. The original aqueous phase was made acid to Congo by adding in the cold-room 1 cc. of 4 *N* sulfuric acid. The turbid mixture was extracted four times with ether at room temperature and the combined ether phases washed successively with water, a solution of *N* sodium carbonate and four times with water. From the ethereal solution there was obtained, in the usual way, 44.1 mg. of an almost colorless soft resin (ketonic fraction). The non-ketonic fraction (28.6 mg.) was subjected to another treatment with Girard's reagent under analogous conditions. This yielded 25.8 mg. of non-ketonic, and 3.3 mg. of ketonic material. Total yield of Girard separation: Invested material: 76.8 mg.; non-ketonic: 25.8 mg.; ketonic 47.4 mg. The

ketonic fraction was distilled in a high vacuum under the same conditions as described earlier in this experiment. The distillate, 44.7 mg., was a slightly yellow viscous resin; yield: 25.6%; $[\alpha]_D^{13}$ +81.2° (9.3 mg. in 2.0 cc. of acetone). The microanalysis was lost by accident.

In a repetition of this experiment it might be advisable to perform the Girard separation first and the chromatographic adsorption thereafter.

10-Norpregnene-20-one-3-ol (XXI and/or isomers). To 39.2 mg. of 3-acetoxy-10-norpregnene-20-one (XX and/or isomers), dissolved in 1.0 cc. of methanol, was added a solution of 0.1 g. of potassium carbonate in 0.5 cc. of water and 1 cc. of methanol. The mixture was refluxed on a water-bath for 1½ hours. It was made acid to Congo by the addition of dil. hydrochloric acid and the major part of methanol subsequently removed *in vacuo* (40°). The mixture was then extracted with ether and the brownish ether phase washed with a little water, a solution of *N* sodium carbonate and three times with water. After drying with sodium sulfate, evaporation of the ether furnished 29.7 mg. of an amber colored resin; yield of this crude product: 86.3%.

10-Norprogesterone (XXII). A solution of 100 mg. of aluminum tert.-butoxide (Eastman) in 1.0 cc. of dry benzene was decanted from a trace of undissolved material and the latter washed a few times with fresh benzene. Four cubic centimeters of a clear solution was thus obtained. To this was added the crude 10-norpregnene-20-one-3-ol (XXI and/or isomers) (29.7 mg.) dissolved in 1.2 cc. of dry acetone. The resulting solution was refluxed under anhydrous conditions on a water-bath for a period of ten hours during which time another 0.2 cc. of dry acetone was added. After standing at room temperature overnight an ample amount of ether was added and thereafter some *N* sulfuric acid. After separation the ether phase was washed with a dil. solution of sodium bicarbonate and three times with water. After drying with sodium sulfate and removal of the ether 30.4 mg. of a yellowish soft resin was obtained. It was purified by chromatographic adsorption for which purpose it was dissolved in a mixture of 7.5 cc. of benzene and 22.5 cc. of petroleum ether. This solution was filtered through a column of 2.0 g. of aluminum oxide (Brockmann) during a period of three hours. The eluents were passed through each within about 30 minutes.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	7.5 cc. benzene + 22.5 cc. petr. ether (original solution)	1.9	colorless resin
2	2.5 cc. benzene + 7.5 cc. petr. ether	0.6	colorless residue
3	3.5 cc. benzene + 6.5 cc. petr. ether	0.2	colorless residue
4	5 cc. benzene + 5 cc. petr. ether	1.4	colorless residue
5	7 cc. benzene + 3 cc. petr. ether	4.3	colorless resin
6	9 cc. benzene + 1 cc. petr. ether	4.1	colorless resin
7	10 cc. benzene	2.2	colorless resin
8	10 cc. benzene	0.9	colorless resin
9	8 cc. benzene + 2 cc. ether	2.4	colorless glass
10	6 cc. benzene + 4 cc. ether	0.6	colorless residue
11	4 cc. benzene + 6 cc. ether	1.7	colorless resin
12	10 cc. ether	2.1	colorless resin
13	10 cc. ether	0.2	colorless resin
14	7.5 cc. ether + 2.5 cc. methanol	5.4	light yellow glass
15	10 cc. methanol	3.0	whitish mass
	Total	31.0	

Fractions 4–8 of the chromatogram (12.9 mg.) were combined and subjected to a distillation in a high vacuum. The oven was heated within 10 minutes to 115°. The temperature was gradually raised to slightly over 200° within a period of 40 minutes. The distillate was an almost colorless (very pale yellow) soft resin; wt. 10.2 mg.; yield: 34.6%; $[\alpha]_D^{20}$ +89.3° (4.3 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{20}H_{28}O_2$: C, 79.94; H, 9.40.
Found: C, 79.12; H, 9.14.

For ultraviolet absorption spectrum and physiological activity see theoretical part.[18]

SUMMARY

Strophanthin was transformed into 10-nor-11-desoxycorticosterone acetate (XIX) and 10-norprogesterone (XXII) respectively.

The intermediate estrane-3,5-diol-10,17-dicarboxylic acid (IX) had been described in the literature previously. The steps leading to it were reinvestigated, especially as regards to yields. The 3-monoacetate of the estrane-3,5-diol-10,17-dicarboxylic acid (XII), when subjected to thermal decomposition by distillation in a high vacuum, furnished the amorphous 3-acetoxy-10-nor-etiocholenic acid which is probably a mixture of structural isomers (XIV, XIVa, XIVb). The acid chloride of the latter acid (XV and for isomers) was converted into 10-nor-11-desoxycorticosterone acetate (XIX) and 10-norprogesterone (XXII) respectively. Both compounds are resins and though they are obviously pure as to their chemical structure, they are believed to represent mixtures of stereoisomers. The extent to which carbon atoms 10, 14, and 17 may be involved in such stereoisomerism is discussed. Yields of all intermediates are given.

10-Nor-11-desoxycorticosterone acetate (XIX) was found to possess no adrenal-cortical activity when tested on a dosage level of about three times the minimal effective dose of 11-desoxycorticosterone acetate.

PHILADELPHIA, PA.

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[18] Because of the remarkable physiological activity of the isolated 10-norprogesterone, the side fractions 9–13 of the chromatogram were combined (7.0 mg.) and assayed in a single rabbit. The section of the uterine endometrium showed very slight proliferation changes. The assay was kindly performed by Dr. Willard M. Allen, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Mo. For the technique of the physiological examination *cf.* (31).

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THE PHOSPHORYLATION OF 4,4′-DIAMINODIPHENYLSULFONE AND CONVERSION OF THE PRODUCTS INTO AMIDOPHOSPHORIC ACID DERIVATIVES

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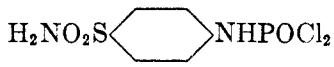
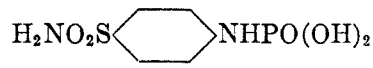
The reaction of phosphoryl chloride with sulfanilamide and related sulfonamides has been reported (1) to yield chlorophosphoryl derivatives from which could be prepared water-soluble salts of the corresponding N-phosphonic acids. The products from sulfanilamide were assigned structures I and II. The present article describes the phosphorylation of 4,4′-diaminodiphenylsulfone both in pyridine solution and by excess of phosphoryl chloride at 100°, and conversion of the products into water-soluble sodium salts.

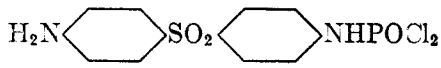


I



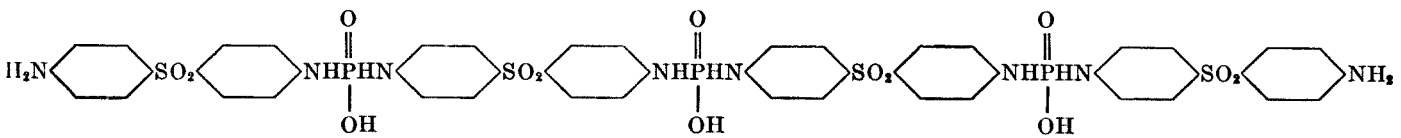
II

The reaction of phosphoryl chloride with the sulfone in dry pyridine solution should be capable of producing a variety of products according to the conditions, especially the proportion of the reactants and the temperature. This investigation has been limited to the reaction below room temperature and in the presence of an excess of the sulfone. Under these conditions the initial product of phosphorylation (III) would be expected to react with diaminodiphenylsulfone and intermediate chlorophosphoryl derivatives to form polymolecular condensation products. Isolation of the products was carried out after hydrolysis of the chlorophosphoryl derivatives in aqueous pyridine solution near 0°. Emphasis is placed on a water-soluble sodium salt, which was obtained in a yield of 45–50 g. from 120 g. of diaminodiphenylsulfone.



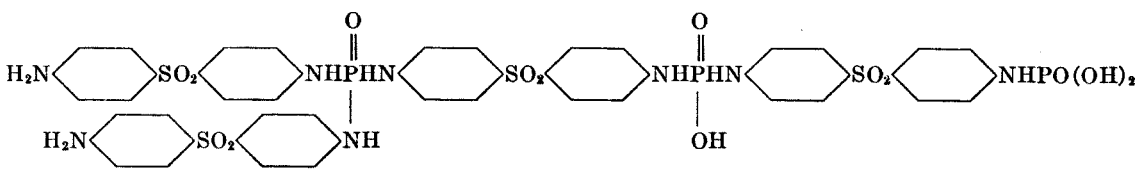
III

The proof of the homogeneity of the sodium salt and the assignment of a structure have been complicated by the failure of the salt or any of its derivatives to crystallize. However, the amorphous sodium salt has been subjected to a thorough fractional precipitation from its aqueous solution by ethanol, and the resulting purified salt used as the starting material for the preparation of the parent acid, its 2-aminoethanol salt, and *p*-dimethylaminobenzylidene derivative. The analytical data summarized in Table I are in substantial agreement with the theoretical values for the tri-diamidophosphoric acid derivative (IV), its trisodium salt, tri-2-aminoethanol salt, and di-*p*-dimethylaminobenzylidene derivative. The presence of two unsubstituted primary amino groups is shown by the formation of the di-*p*-dimethylaminobenzylidene derivative and con-

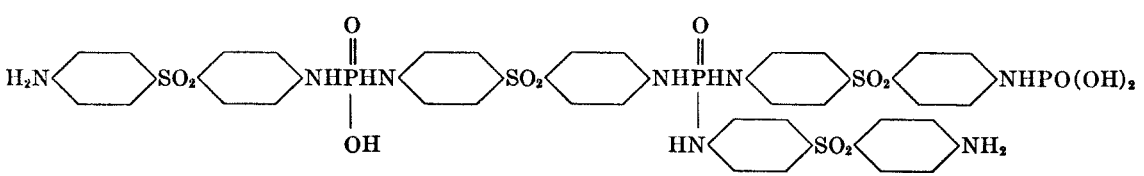


IV

N,N′-Bis(N-*p*-sulfanilylphenyl-N′-*p*-phenylsulfonylphenyldiamidophosphinico)diamidophosphoric acid



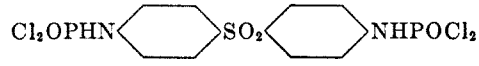
V



VI

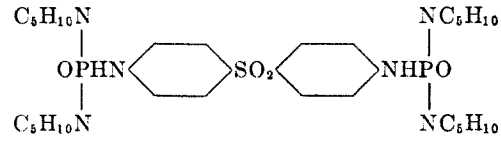
firmed by the diazotization value of both the acid and its sodium salt. The sodium content of the salt and the neutralization value of the acid correspond to the tribasicity of IV. The titration curve shown in Fig. 1 does not establish the difference in the acidic groups expected for the monoamidophosphoric acid group of V and VI which seems to justify a tentative preference for the symmetrical structure IV over the isomeric tribasic acids V and VI. In accordance with its N-phosphoryl structure the acid is hydrolyzed by *N* hydrochloric acid at 100° to produce 4,4′-diaminodiphenylsulfone, which was isolated as pure crystals in 85% yield.

The phosphorylation of diaminodiphenylsulfone with excess of phosphoryl chloride at 100° yields a crystalline chlorophosphoryl derivative. Warnat (3) has reported the preparation of a chlorophosphoryl derivative to which he ascribed structure VII but presented no analytical data. This structure has now been confirmed by the preparation of pure crystalline 4,4′-bis(dipiperidylphosphorosoamino)diphenylsulfone (VIII) through reaction of the chlorophosphoryl derivative with piperidine. The piperidyl derivative was isolated as dimorphic forms melting at 190–191° and 221–222°.



VII

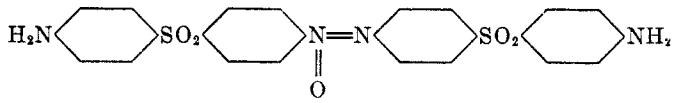
4,4′-Bis(dichlorophosphorosoamino)-diphenylsulfone



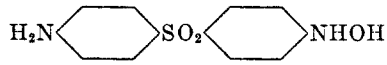
VIII

Through reaction with cold aqueous sodium bicarbonate solution the chlorine is eliminated from the molecule of the chlorophosphoryl derivative (VII) to produce an aqueous solution of sodium salts. This reaction is accompanied by cleavage of the phosphorus from a considerable portion of the phosphorylation product, as shown by the formation of diaminodiphenylsulfone. Acidification of the aqueous solution of sodium salts precipitates the phosphorylation product mixed with smaller amounts of diaminodiphenylsulfone and 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene (IX). The azoxy derivative was isolated as nearly colorless crystals melting at 245–246° (uncor.). It was characterized by an elementary analysis, determination of its diazotization value, and reduction by stannous chloride to yield 4,4′-diaminodiphenylsulfone. The compound probably is formed from 4-amino-4′-hydroxylaminodiphenylsulfone (X) in the course of the splitting of the phosphorylation product in aqueous sodium bicarbonate solution.

The phosphorylation product, after two precipitations by acidification of the aqueous solution of the sodium salt and extraction with acetone, is obtained as an amorphous powder in a yield of 20–25 g. from 100 g. of diaminodiphenyl-



IX



X

sulfone. This material, previously designated "N-phosphoryl derivative of 4,4′-diaminodiphenylsulfone," has been shown to possess antibacterial activity (4). It can be prepared regularly with approximately the same composition and properties. The substance, however, is not a pure compound. Although its sodium salt in neutral aqueous solution is substantially stable at room temperature, heating the solution at 100° liberates 25–30% of the material as a mixture composed principally of 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene and diaminodiphenylsulfone. The portion of the material stable in aqueous solution at 100° yields the sulfone and azoxy derivative through hydrolysis by *N* hydrochloric acid at 100°. The azoxy derivative, obtained in this way, may owe its origin to initially formed 4-amino-4′-hydroxylaminodiphenylsulfone, a possibility suggested by the known conversion of 4-hydroxylaminobenzenesulfonamide (5) into azoxybenzene-4,4′-disulfonamide and *p*-aminophenol by hot hydrochloric acid. The results indicate that either 4-amino-4′-hydroxylaminodiphenylsulfone or 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene is an integral part of the molecule of the phosphoryl derivative. Although the "N-phosphoryl derivative" is not a pure compound, directions for its preparation and data on its composition (see formulas XI and XII), are included on account of its antibacterial activity.

EXPERIMENTAL

Phosphorylation of 4,4′-diaminodiphenylsulfone in pyridine solution. Synthesis of the tri-diamidophosphoric acid derivative (IV). To a mechanically stirred solution of 120 g. of diaminodiphenylsulfone (1.5 molecular equivalents) in 560 cc. of anhydrous pyridine at 2–5° was added dropwise during one hour 49.6 g. of phosphoryl chloride (1.0 molecular equivalent). The ice-bath was removed and the red solution, which contained a gel in suspension, was stirred for forty-five minutes. The mixture was added gradually in the course of thirty minutes to an efficiently stirred solution of 100 cc. of pyridine in 500 cc. of ice water, the reaction flask being washed first with 15 cc. of pyridine and then with a solution of 10 cc. of pyridine in 25 cc. of water. The stirring at about 5° was continued for an additional thirty minutes, the solution left overnight at room temperature, then filtered and neutralized by sodium hydroxide solution. In order to remove pyridine, the solution was concentrated *in vacuo* (bath, 45–50°) virtually to dryness. To the thick, red sirup was added 1500 cc. of water. After being mixed thoroughly, the insoluble solid was filtered off and washed with 300 cc. of cold water. The air-dried solid weighed 87 g. This material is a mixture, the constituents of which have not yet been identified. A considerable part of it is soluble in a large volume of cold acetone. The portion insoluble in acetone consists mostly of aqueous alkali soluble material, probably IV or an unidentified amidophosphoric acid derivative. Extraction of 5 g. of the mixture with 35 cc. of cold 5% hydrochloric acid, filtration, and neutralization of the filtrate by sodium hydroxide yielded 1.7

g. of diaminodiphenylsulfone. Part of the material insoluble in 5% hydrochloric acid was soluble in sodium hydroxide solution due to the presence of an amidophosphoric acid derivative.

The crude tri-diamidophosphoric acid derivative (IV) was precipitated from the thoroughly stirred filtrate from the 87 g. of solid by the dropwise addition of 260 cc. of 19% hydrochloric acid. It was filtered immediately and washed with cold water. To a suspension of the substance in 250 cc. of water was added, with stirring, sufficient 10% sodium hydroxide solution to yield a solution of the sodium salt neutral to litmus paper. The amorphous tri-diamidophosphoric acid derivative was precipitated from the filtered solution by the addition of hydrochloric acid in amount known to be equivalent to the sodium hydroxide used for neutralization of the crude product. After the substance had been filtered off and washed with cold water, an aqueous solution of the sodium salt, neutral to litmus, was again prepared; it was kept at room temperature for twenty-four to forty-eight hours and filtered to remove a little solid material. The solution was concentrated *in vacuo* with the bath at 50° to a volume of 100 cc. and poured slowly into 1100 cc. of vigorously stirred commercial absolute ethanol, the residual sirup being transferred with the use of 25 cc. of water. The air-dried, solid sodium salt, thus precipitated, weighed 47 g. In case high humidity prevails, the substance should be dried in an evacuated desiccator over calcium chloride. An additional 2.8 g. of sodium salt was obtained by evaporation of the filtrate *in vacuo* (bath, 40–45°) to dryness, extraction of the residue with 35 cc. of cold water in portions, filtration after twenty hours to remove 1.7 g. of insoluble solid, and concentration of the aqueous solution, followed by precipitation of the salt with ethanol. A solution of the 47 g. of sodium salt in 65 cc. of water, to which had been added 135 cc. of ethanol, was kept at room temperature for several hours, and then separated from some sirup by decantation. The sodium salt was precipitated by the addition of this solution to 625 cc. of thoroughly stirred absolute ethanol. The salt, after being filtered, washed with cold absolute ethanol, and dried for several days in an evacuated desiccator over calcium chloride, weighed 34 g. The powder lost 3.6% in weight at 100° *in vacuo* and then showed: P, 8.19; S, 9.80; diazotization as compared with diaminodiphenylsulfone (2), 17%. The analytical data recorded in Table I for the trisodium salt of the tri-diamidophosphoric acid derivative were obtained after the material had been subjected to a thorough fractional precipitation from its aqueous solution by ethanol, to yield 11 g. of amorphous, slightly yellow, solid sodium salt. The salt in dilute aqueous solution apparently is stable at 100°; 0.1 g. in 2 cc. of solution in water, after being kept at 100° for thirty minutes and cooled, yielded upon addition of 2.3 cc. of 0.1 *N* hydrochloric acid 0.07 g. of the parent acid showing a neutralization value in virtual agreement with that recorded in Table I. Evidence, supplementary to the analytical data, on the purity and structure of the sodium salt was obtained by the preparation and analysis (Table I) of the parent tri-diamidophosphoric acid derivative, its 2-aminoethanol salt, and di-*p*-dimethylaminobenzylidene derivative.

The tri-diamidophosphoric acid derivative was precipitated as an amorphous solid by the addition of 4.5 cc. of *N* hydrochloric acid to a solution of 2 g. of the above carefully fractionated sodium salt in 20 cc. of water. The acid was filtered promptly and washed free of chlorine ions by cold water. The washing is facilitated by allowing the product, after being washed partially, to dry overnight at room temperature before removal of the last traces of chlorine ions. After being dried in an evacuated desiccator over calcium chloride, the slightly yellow powder weighed 1.6 g. and melted at 181–182° (uncor.). The melting point varies with the moisture content of the sample. The melting points of this amorphous acid and its two derivatives herein described are not regarded as reliable criteria of purity. The substance lost 1.8% in weight at 100° *in vacuo*; it showed no change in appearance and neutralization value as a result of the heating. The acid is soluble in cold 2-aminoethanol; it is only slightly soluble in water and the usual organic solvents. Hydrolysis by *N* hydrochloric acid at 100° yielded 4,4′-diaminodiphenylsulfone (0.1 g. of substance, suspended in 10 cc. of *N* hydrochloric acid and kept at 100° for one hour, gave a

TABLE I

TRI-DIAMIDOPHOSPHORIC ACID (IV) AND DERIVATIVES

SUBSTANCE	EMPIRICAL FORMULA	ANALYSES, %													
		Calc'd							Found[a]						
		C	H	N	P	S	Na	Diazotization	C	H	N	P	S	Na	Diazotization[b]
Tri-diamidophosphoric acid[c] (IV)	$C_{48}H_{45}N_8O_{14}P_3S_4$	48.89	3.85	9.51	7.88	10.88	—	21.1	48.41	3.94	9.38	7.77	11.07	—	24[d]
Trisodium salt	$C_{48}H_{42}N_8Na_2O_{14}P_3S_4$	—	—	9.00	7.46	10.30	5.54	19.9	—	—	8.96	7.63	10.26	5.41	16
Tri-2-aminoethanol salt	$C_{54}H_{66}N_{11}O_{17}P_3S_4$	47.60	4.88	11.31	6.82	9.41	—	—	47.15	5.05	11.30	6.99	9.50	—	—
Di-*p*-dimethylaminobenzylidene derivative[e]	$C_{66}H_{63}N_{10}O_{14}P_3S_4$	54.99	4.41	9.72	6.45	8.90	—	—	—	—	—	—	—	—	—
	$C_{66}H_{63}N_{10}O_{14}P_3S_4$ + 1.1% Cl	54.39	4.36	9.61	6.38	8.80	—	—	53.87	4.39	9.80	6.31	9.00	—	—

[a] With the exception specified, all samples were dried to constant weight at 100° *in vacuo*.

[b] Diazotization values were obtained by comparison of the samples with 4,4′-diaminodiphenylsulfone according to the method of Bratton and Marshall (2).

[c] Calc'd for IV: 2.54 cc. of 0.1 *N* NaOH solution per 100 mg. Found: 2.47 cc. (phenolphthalein).

[d] The substance, which had been dried in an evacuated desiccator over calcium chloride, was known to lose 1.8% in weight at 100° *in vacuo*.

[e] The sample contained 1.1% chlorine.

solution which, upon being cooled, filtered, and neutralized by sodium hydroxide solution, deposited crystals of the sulfone; the yield was increased to 0.072 g., or 85% by concentration of the filtrate *in vacuo* to dryness and separation of the sulfone from inorganic crystals by extraction with acetone; m.p. 175–176°, not depressed by authentic sulfone).

The titration curve for the tri-diamidophosphoric acid derivative is shown in Fig. 1. A solution of the sodium salt was prepared by the addition of 14.13 cc. of 0.1 *N* sodium hydroxide solution to an aqueous suspension of 0.5600 g. of the acid, which had been dried

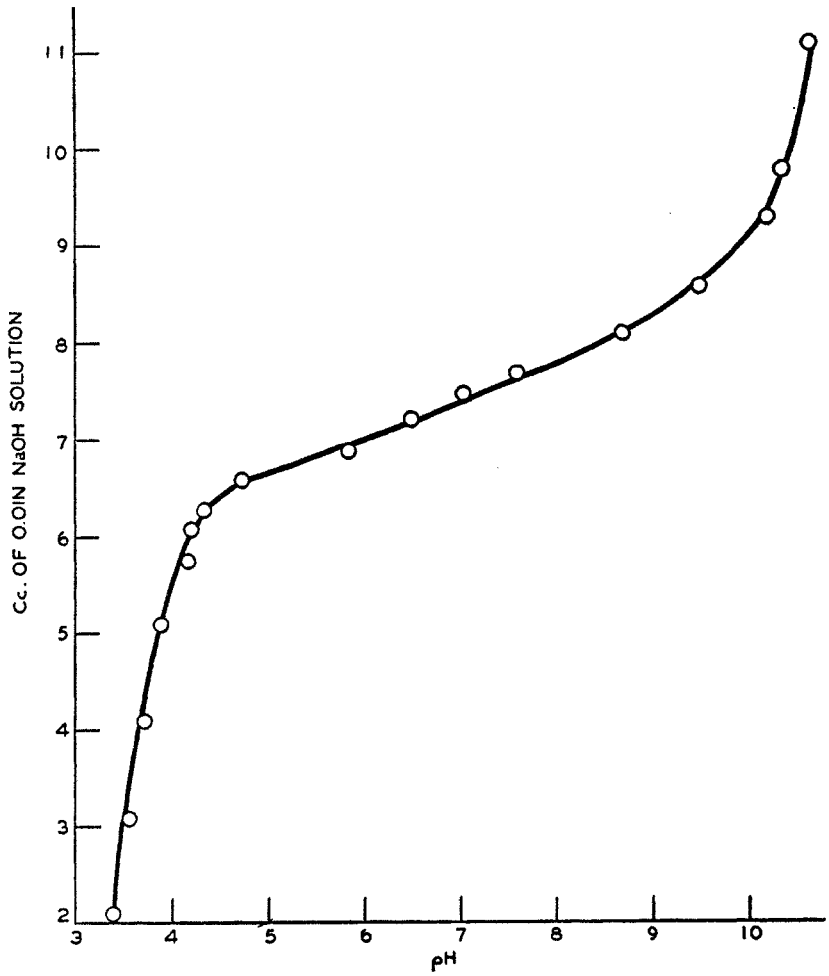


FIG. 1. TITRATION CURVE OF THE TRI-DIAMIDOPHOSPHORIC ACID DERIVATIVE

in an evacuated desiccator over calcium chloride; the solution finally was diluted with water to a volume of 35 cc. at 28°. Solutions for the *p*H determinations were prepared in one case by dilution of 2 cc. of the sodium salt solution with 3 cc. of water and for the other points by the addition of various amounts of 0.02 *N* hydrochloric acid or of 0.01 *N* sodium hydroxide solution to 2 cc. aliquots of the sodium salt solution with sufficient water to make 5 cc. (c, 0.0054 *M*). The *p*H of each solution was determined[1] at 28° with the use of

[1] Indebtedness is expressed to Dr. E. W. Emmart for the *p*H readings.

the glass electrode of a Beckman *p*H meter. A slight turbidity was observed in the solution having *p*H 4.8; the turbidity increased progressively as the *p*H became smaller.

For the preparation of the 2-aminoethanol salt the tri-diamidophosphoric acid derivative, prepared as described from 1 g. of sodium salt, was dissolved in a mixture of 4 cc. of water and 4 g. of 2-aminoethanol (b.p. 167–170°). To this solution was added, with stirring, 100 cc. of absolute ethanol. The amorphous, virtually colorless, solid precipitate was filtered, washed with absolute ethanol, and dried in an evacuated desiccator over calcium chloride; weight, 0.3 g. Additional material can be obtained from the filtrate by evaporation of the solvent *in vacuo* and precipitation by the addition of the aqueous solution of the residue to ethanol. The 0.3 g., after being dried to constant weight at 100° *in vacuo*, was used for analyses; m.p. 175–176°. Acidification of the aqueous solution of a sample which had been kept at 100° *in vacuo* for three hours precipitated the parent tri-diamidophosphoric acid derivative; m.p. 179–180°. This result confirms the salt structure of the compound dried at 100°.

The di-*p*-dimethylaminobenzylidene derivative was precipitated upon addition of 1 cc. of 24% hydrochloric acid to a homogeneous solution prepared by mixing a solution of 0.25 g. of *p*-dimethylaminobenzaldehyde in 4 cc. of absolute ethanol with a solution of 1.0 g. of the sodium salt in 2 cc. of water. The orange-colored, amorphous solid was filtered, washed first with cold water, then with absolute ethanol, and dried in an evacuated desiccator over calcium chloride; yield, 1.1 g. The substance contained 1.1% chlorine, probably retained as hydrochloride. After being dried at 100° *in vacuo*, it melted at 218–219° (uncor.). The compound is only slightly soluble in water and the usual organic solvents.

4,4′-Bis(dipiperidylphosphorosoamino)diphenylsulfone. A mixture of 10 g. of 4,4′-diaminodiphenylsulfone and 50 g. of phosphoryl chloride was heated at 100° under a reflux condenser for four and one-half hours with occasional shaking. The dark red solution, which in occasional experiments contained some solid reaction product in suspension, was kept at room temperature for a short time and then poured into 40 cc. of benzene. The sirup which was precipitated crystallized readily upon being stirred or after nucleation with crystals of the chlorophosphoryl derivative. The crystals were filtered and washed with cold benzene to remove excess phosphoryl chloride. The chlorophosphoryl derivative is only slightly soluble in benzene, chloroform, carbon tetrachloride, and petroleum ether. Although it reacts rapidly with water and consequently is unstable in the air, it can be kept for several days in an evacuated desiccator over solid sodium hydroxide with little apparent decomposition.

The freshly prepared chlorophosphoryl derivative was added in small portions, with stirring, to 100 cc. of piperidine, cooled in ice-water. After thorough mixing had been accomplished, the thick paste was left overnight at room temperature with exclusion of atmospheric moisture. The solid was then separated by filtration, washed first with 35 cc. of piperidine and finally with dry diethyl ether. It was mixed with 30 cc. of cold water, the insoluble solid filtered off, and washed with 20 cc. of water; air-dried weight, 18 g. Some unidentified amorphous material was precipitated by addition of the piperidine mother liquor to 600 cc. of water, followed by acidification with hydrochloric acid. Acidification of the water extract of the 18 g. of solid also precipitated amorphous material. The 18 g. of solid was found to contain some piperidine hydrochloride, which probably could have been removed advantageously by further extraction with water. By fractional recrystallization from mixtures of absolute ethanol and ether 9.5 g. of slightly impure 4,4′-bis(dipiperidylphosphorosoamino)diphenylsulfone melting near 180° was isolated. After completion of purification by recrystallization from a mixture of chloroform and ether the colorless, short, slender rods, dried for twenty hours in an evacuated desiccator over calcium chloride, melted at 180–181° (uncor.). The crystals lost 14.5% in weight at 100° *in vacuo* and then melted at 190–191° (uncor.). The compound is soluble in cold chloroform, ethanol, and methanol; difficultly soluble in cold acetone; slightly soluble in ether; and virtually insoluble in water.

Anal. Calc'd for $C_{32}H_{50}N_6O_4P_2S$: C, 56.78; H, 7.45; P, 9.15; S, 4.74.
Found (dried at 100° *in vacuo*): C, 56.44; H, 7.21; P, 9.20; S, 4.86.

With the use of absolute ethanol-ether as the solvent the piperidyl derivative was observed to crystallize sometimes as a second modification, prismatic needles melting at 221–222° (cor.). The pure crystals, after being dried in an evacuated desiccator over calcium chloride, lost 1.5% in weight at 100° *in vacuo* without change in the melting point. Found (dried at 100° *in vacuo*): C, 56.53; H, 7.23; P, 9.05; S, 4.88.

Reactions of 4,4′-bis(dichlorophosphorosoamino)diphenylsulfone with aqueous sodium bicarbonate solution. The reaction of 100 g. of diaminodiphenylsulfone with 500 g. of phosphoryl chloride at 100° was carried out as described. The following hydrolysis was started immediately after filtration of the crystals of the chlorophosphoryl derivative. The crude substance was added gradually during about one and one-half hours to a mechanically stirred mixture of 600 g. of sodium bicarbonate and 1400 cc. of distilled water contained in an 8-liter glass jar cooled in ice-water. After all of the substance had been added, the stirring was continued for one hour, and the mixture left overnight at room temperature to assure completion of the hydrolysis of the chlorophosphoryl derivative. The mixture was then stirred for thirty minutes, the solid thrown down by centrifugation, and a clear solution finally obtained by filtration. With the aid of centrifugation the solid was washed twice with 300 cc. portions of cold water, the washings being kept separate from the principal solution. The solid was shown to be a mixture of sodium bicarbonate and diaminodiphenylsulfone which, in one experiment, weighed 28 g. after purification. The crude phosphoryl derivative was precipitated from the principal solution by the addition of 160 cc. of 38% hydrochloric acid and from the aqueous washings by the addition of the acid in amount, usually about 120 cc., sufficient to precipitate the substance completely. The phosphoryl derivative was filtered and washed with cold water. Neutralization of the filtrate with sodium hydroxide solution precipitated some diaminodiphenylsulfone; m.p. 174–176°.

To a thoroughly stirred suspension of the phosphoryl derivative in 400 cc. of water was added sufficient 10% sodium hydroxide solution to produce a *p*H of about 9 (phenolphthalein). After being kept at room temperature for two hours, the insoluble solid was removed by filtration or centrifugation, and washed with cold water. The solid, 15–18 g., is a mixture containing diaminodiphenylsulfone and 4,4′-bis(*p*-aminobenzenesulfonyl)-azoxybenzene, the isolation of which is described below. To the light red solution was added 20% hydrochloric acid in amount known to be equivalent to the sodium hydroxide used for neutralization of the phosphoryl derivative. After the precipitate had been filtered and washed with cold water, the above described process for neutralization of the substance to *p*H 9 was repeated. The solution was kept at room temperature for an hour to allow complete separation of some fine solid. The suspension was cleared by the addition of 250 cc. of 95% ethanol, the light red solution filtered, and the phosphoryl derivative precipitated in amorphous condition as previously described. The substance was filtered, washed with 15 cc. of cold 40% ethanol, then with cold water, and dried thoroughly at room temperature. To assure freedom of the substance from diaminodiphenylsulfone and 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene, the product was suspended in 100 cc. of dry acetone, mixed thoroughly, filtered, and washed with acetone. The weight of the residue left by concentration of the acetone solution to dryness usually was about 1% of the weight of the substance extracted; in case, however, the phosphoryl derivative is not dried prior to the acetone extraction, a considerable proportion of the material is dissolved by the acetone-water mixture. After the substance had been extracted with acetone, it was dried in an evacuated desiccator over calcium chloride. In an atmosphere of excessive humidity the product should be placed in the desiccator immediately following the washing with acetone to avoid some coloration and slight gumming. The yield of gray, amorphous, hygroscopic powder was 20–25 g. This is the material used for chemotherapeutic tests (4).

The melting point of the powder, usually between 160° and 170°, was somewhat variable in different preparations. It lost 2.7% in weight at 100° *in vacuo*. Its diazotization value was about 20% compared with diaminodiphenylsulfone (2). The following analytical data[2]

[2] Thanks are expressed to Dr. B. B. Westfall, of this Laboratory, for carrying out the colorimetric phosphorus determinations.

are representative of the results of analyses of samples (dried at 100° *in vacuo*) from several preparations: C, 45.0–46.5; H, 3.9; N, 8.8; P, 9.5; S, 10.2. The substance is only slightly soluble in water and the usual organic solvents; it is more soluble in mixtures of water with acetone, ethanol, or dioxane. An aqueous solution of the sodium salt is prepared conveniently by the addition of *N* sodium hydroxide solution (1.8–2.0 cc. per g. of substance usually produces a *p*H of 6–7) to the dry powder with prompt stirring until a clear solution results; this solution can be diluted with water to any desired concentration.

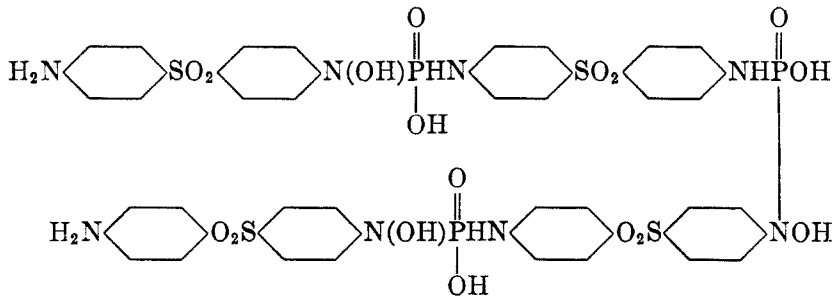
The sodium salt in neutral aqueous solution, upon being heated at 100°, liberated 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene and diaminodiphenylsulfone. A 10% solution, prepared by stirring 18 cc. of *N* sodium hydroxide solution with 10 g. of the dry phosphoryl derivative followed by dilution with 82 cc. of water, was kept at 100° for thirty minutes. A precipitate separated and after the mixture had been kept overnight at room temperature, 1.7 g. of solid was filtered off. By extraction of the solid with cold 5% hydrochloric acid, removal of the insoluble material by filtration, and neutralization of the filtrate with sodium hydroxide solution, 0.4 g. of diaminodiphenylsulfone was obtained; m.p. 175–176°, not depressed by authentic sulfone. Purification of the insoluble material as described later under 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene yielded 0.5 g. of somewhat impure azoxy derivative, which in pure condition melted at 245–246° (uncor.) alone or mixed with the authentic compound. Calc'd for $C_{24}H_{20}N_4O_5S_2$: S, 12.61. Found: S, 12.41. To the filtrate from the 1.7 g. of solid, containing the portion of the sodium salt stable in aqueous solution at 100°, was added 18 cc. of *N* hydrochloric acid. The amorphous precipitate, after being filtered, washed with water, and dried in an evacuated desiccator over calcium chloride, weighed 7.5 g. A concentrated neutral aqueous solution of the sodium salt of this material was added to 175 cc. of vigorously stirred absolute ethanol. The amorphous sodium salt, thus obtained, was precipitated four times from its aqueous solution by ethanol and dried in an evacuated desiccator over calcium chloride; weight, 3.5 g.[3] The combined filtrates from all the precipitations were concentrated *in vacuo* to dryness, and the residue extracted several times with cold water to separate the sodium salt from 1.5 g. of insoluble material from which was isolated 0.5 g. of pure diaminodiphenylsulfone. The sodium salt was isolated from the aqueous solution by concentration and precipitation by ethanol; after another precipitation 0.5 g. of sodium salt was obtained.

The parent acid was prepared from the 3.5 g. of five-times precipitated sodium salt. To a solution of the salt in 15 cc. of water was added, with stirring, 8.3 cc. of *N* hydrochloric acid. The amorphous precipitate was filtered and washed free of chlorine ions by cold water. The washing is accomplished with less loss of the product by allowing the substance, after being washed partially, to dry overnight at room temperature before removal of the last traces of chlorine ions. After being dried in an evacuated desiccator over calcium chloride, it weighed 2.3 g. and melted at 192–194° (uncor.); diazotization value as compared with diaminodiphenylsulfone (2), 19%; neutralization value (phenolphthalein), 2.37 cc. of 0.1 *N* NaOH solution per 100 mg. of substance. This material lost 2.7% in weight at 100° *in vacuo*. Found (dried at 100° *in vacuo*): C, 46.75; H, 3.79; N, 9.03; P, 7.95; S, 10.41. A sample of the acid prepared from the above 0.5 g. of sodium salt, which was isolated from the mother liquors from the 3.5 g., showed (dried at 100° *in vacuo*): C, 46.82; H, 3.74; P, 7.93; S, 10.78. The acid yields through hydrolysis by hot *N* hydrochloric acid diaminodiphenylsulfone and 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene. A suspension of 0.2 g. of the acid in 20 cc. of *N* hydrochloric acid, after being heated at 100° under a reflux condenser for one hour, gave a solution, which was filtered hot and left at room temperature. The gelatinous solid which separated was filtered, washed with 5% hydrochloric acid, then suspended in water and neutralized by sodium hydroxide solution. The solid, after being filtered, washed with water, and air-dried, weighed 0.026 g. It was

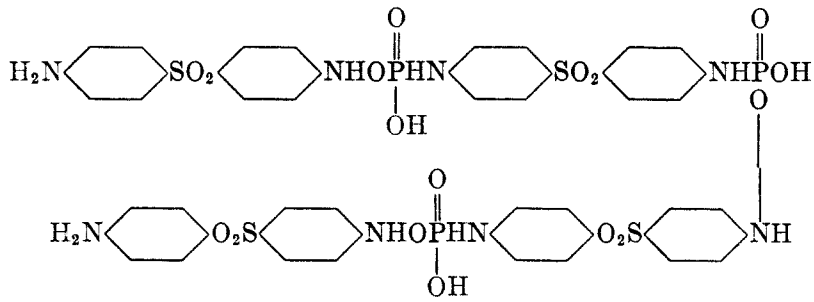
[3] In a preliminary test by Dr. E. W. Emmart this sodium salt in a concentration of 10 mg. % showed a partial inhibition of the growth of tubercle bacilli (human strain A 27) on a Difco beef medium containing 5% glycerol.

identified, after purification, as 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene by melting-point and mixed-melting-point determinations, also by resemblance to the authentic compound in appearance of the crystals and solubility. The filtrate from the crude azoxy derivative yielded 0.088 g. of diaminodiphenylsulfone, isolated by neutralization with sodium hydroxide, removal of crystals of the sulfone, concentration of the filtrate to dryness, and extraction of the residue with acetone.

Regarding the structure of the acid just described, a formula is not proposed because of the uncertain homogeneity of the material. It is noted, however, that several possible isomeric structures, illustrated by formulas XI and XII, correspond fairly well to the analytical data. Calc'd for $C_{48}H_{45}N_8O_{17}P_3S_4$: C, 46.98; H, 3.70; N, 9.13; P, 7.57; S, 10.45; diazotization, 20.2%; neutralization, 2.44 cc. of 0.1 *N* NaOH solution per 100 mg. of substance.



XI



XII

4,4′-Bis(p-*aminobenzenesulfonyl*)*azoxybenzene*. A mixture (15–18 g.) of the azoxy derivative with diaminodiphenylsulfone and other material was obtained as described under the reactions of 4,4′-bis(dichlorophosphorosoamino)diphenylsulfone with aqueous sodium bicarbonate solution. The mixture was stirred thoroughly with 75 cc. of 5% hydrochloric acid at room temperature. The insoluble solid was filtered off, washed first with 5% hydrochloric acid and finally with water. Neutralization of the filtrate by sodium hydroxide solution precipitated about 7 g. of crystalline diaminodiphenylsulfone. The insoluble solid, after being suspended in 75 cc. of water, neutralized by sodium hydroxide, filtered, washed with water, and air-dried, weighed 7–8 g. The azoxy derivative crystallized readily as needles or elongated plates from a solution of this material in pyridine to which water had been added to turbidity; yield, 1.5 g.; the remainder of the material was amorphous. The compound was purified by several recrystallizations from a mixture of pyridine and water, activated carbon being used when needed to assist in decolorization. The air-dried crystals retain pyridine, which is not removed by washing the crystals with water. Crystals of the pure azoxy derivative are almost colorless, and melt at 245–246° (uncor.) either

in the air-dried condition or after being dried to constant weight at 100° *in vacuo*. Prolonged heating at 100° *in vacuo* was found to lower the melting point in the case of certain samples which were shown by diazotization to be somewhat impure, although the air-dried material had a melting point near that of the pure compound. Samples for analysis were dried at 100° *in vacuo*. The compound is readily soluble in cold pyridine, soluble in acetone and 2-ethoxyethanol, and somewhat soluble in methanol; it is virtually insoluble in water and only slightly soluble in the majority of the common organic solvents. It failed to dissolve completely in molten camphor (1:20). On account of its slight solubility in hydrochloric acid the azoxy derivative reacts with nitrous acid only slowly under customary conditions of diazotization with starch-potassium iodide indicator. For analysis sufficient acetone was added to yield a homogenous solution (0.0810 g. of substance dissolved in 21 cc. of acetone, to which was added 31 cc. of water and 4.5 cc. of 19% hydrochloric acid, required at 2–5° 6.10 cc. of sodium nitrite solution, or 48.2% of the amount, 12.65 cc., consumed under the same conditions by 0.0810 g. of diaminodiphenylsulfone); calculated, 48.8%.

Anal. Calc'd for $C_{24}H_{20}N_4O_5S_2$: C, 56.68; H, 3.96; S, 12.61.
Found: C, 56.70, 57.03; H, 3.99, 4.10; S, 12.44.

4,4′-Diaminodiphenylsulfone is a product of the reduction of the azoxy derivative by stannous chloride. To a suspension of 0.345 g. of air-dried crystals, or 0.277 g. calculated to the dry basis, in 5 cc. of 50% aqueous acetic acid was added 0.9 cc. of 38% hydrochloric acid. After the crystals had been dissolved at steam-bath temperature, 0.8 g. of stannous chloride dihydrate was added, and the mixture kept at 100° under a reflux condenser for three hours. The nearly colorless solution upon being cooled to room temperature deposited some gelatinous solid, which was filtered, washed first with 50% acetic acid containing some hydrochloric acid, and finally with 5% hydrochloric acid. The solid in aqueous suspension was neutralized by sodium hydroxide, filtered, washed with water, and air-dried. This substance, 0.16 g. melting near 220°, was identified after recrystallization as unreacted azoxy derivative. An additional 0.03 g. was obtained from the reduction solution by dilution with an equal volume of water; the total starting material recovered was thus about 50% of the amount used. The reduction solution was treated with hydrogen sulfide, the tin sulfide filtered, and washed with water. After removal of excess hydrogen sulfide by aeration, the solution was concentrated *in vacuo* to about 5 cc., then diluted with 15 cc. of absolute ethanol, and the concentration *in vacuo* continued to dryness. The residue was transferred to a funnel with the aid of absolute ethanol. 4,4′-Diaminodiphenylsulfone was isolated both from the insoluble crystals, 0.04 g., and from the ethanol filtrate. The latter was concentrated *in vacuo* to dryness, the residue (0.2 g.) dissolved in 7 cc. of water, and the solution neutralized by sodium hydroxide, 0.02 g. of 4,4′-diaminodiphenylsulfone melting at 174–175° being precipitated. The 0.04 g. of crystals was suspended in 2 cc. of water and the mixture neutralized by sodium hydroxide, 0.03 g. of 4,4′-diaminodiphenylsulfone melting at 175–176° being produced. The identification was confirmed by the determination of the diazotization value of the product. The yield of the sulfone was about 37% on the basis of the azoxy derivative reacting.

Indebtedness is expressed to Dr. G. W. Raiziss, of the Dermatological Research Laboratory, Division of Abbott Laboratories, for the gift of some diaminodiphenylsulfone.

SUMMARY

The phosphorylation of 4,4′-diaminodiphenylsulfone in pyridine solution under specified conditions, followed by hydrolysis of the chlorophosphoryl derivative, yields an amorphous tribasic acid. The elementary composition of the acid and of three amorphous derivatives, its trisodium salt, tri-2-amino-

ethanol salt, and di-*p*-dimethylaminobenzylidene derivative, indicates the condensation of four moles of diaminodiphenylsulfone with three moles of phosphoryl chloride. The acid is represented as a tri-diamidophosphoric acid derivative. Confirmation of the amidophosphoric acid type of structure results from hydrolysis of the compound by hot hydrochloric acid to produce diaminodiphenylsulfone in high yield.

The crystalline chlorophosphoryl derivative, prepared by Warnat by phosphorylation of the sulfone with excess of hot phosphoryl chloride, is shown to be 4,4′-bis(dichlorophosphorosoamino)diphenylsulfone through its reaction with piperidine to yield crystalline 4,4′-bis(dipiperidylphosphorosoamino)diphenylsulfone, isolated as dimorphic forms melting at 190–191° and 221–222°.

4,4′-Bis(dichlorophosphorosoamino)diphenylsulfone is converted by aqueous sodium bicarbonate solution into a mixture of products consisting principally of the sodium salt of an amorphous phosphoryl derivative (4), diaminodiphenylsulfone, and crystalline 4,4′-bis(*p*-aminobenzenesulfonyl)azoxybenzene having the melting point 245–246°. Evidence is presented which indicates that the molecule of the phosphoryl derivative is constructed of 4-amino-4′-hydroxylaminodiphenylsulfone combined through phosphorus with 4,4′-diaminodiphenylsulfone.

BETHESDA, MD.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

THE STRUCTURE OF TURANOSE[1]

C. S. HUDSON

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In a recent article (1) it was shown that an application of the physico-chemical principles of stereochemistry to certain compound sugars can be used to correlate the structures of such sugars by the rigorous method of identity or non-identity. In illustration, reference was made to the known (2) reduction products of turanose, one of which has been designated by Pacsu, Wilson, and Graf (3), on reasonable evidence, as 3-α-D-glucopyranosido-D-sorbitol (characterized as its nonaacetate, m.p. 116.5° and $[\alpha]_D^{20}$ +70.9° in chloroform), and the other as 3-α-D-glucopyranosido-D-mannitol (characterized as its nonaacetate, m.p. 142° and $[\alpha]_D^{20}$ +89.3° in chloroform). The reduction of maltose, the structure of which is 4-α-D-glucopyranosido-D-glucose beyond reasonable doubt (4), leads to 4-α-D-glucopyranosido-D-sorbitol, the so-called maltitol [characterized (5) as its nonaacetate, m.p. 86–87° and $[\alpha]_D^{20}$ +84° in chloroform]. Maltose has been transformed (6) to its crystalline epimer, epimaltose, which is accordingly 4-α-D-glucopyranosido-D-mannose. At the time when my article was published epimaltose had never been reduced. It was shown from exact theoretical considerations that its reduction product, 4-α-D-glucopyranosido-D-mannitol, must be identical with the known 3-α-D-glucopyranosido-D-mannitol of Pacsu and Rich (2) from the reduction of turanose, if the postulated structure of turanose is correct, because the substitution of mannitol at either of the equivalent positions 3 or 4 must give one and the same substance by the exact mathematical principles of symmetry. 3-Methyl-D-mannitol and 4-methyl-D-mannitol, for illustration, are only alternative names for one substance. The reduction of epimaltose has now been performed and it has been found that the crystalline nonaacetate of epimaltitol (4-α-D-glucopyranosido-D-mannitol) is indeed identical with the product (3-α-D-glucopyranosido-D-mannitol) which Pacsu and Rich first prepared from turanose. The identity of this substituted mannitol from maltose and from turanose proves that the substituent is the same; in maltose this substituent is the pyranose form of D-glucose by methylation evidence (4), and it is of the *alpha* configuration by the evidence from enzyme action and from rotatory relationships (4); accordingly, the substituent in turanose must likewise be α-D-glucopyranose. Maltose and turanose cannot carry this common substituent at the same numbered carbon atom in their free glucose or fructose moiety, because, if such were the case, one and the same α-D-glucopyranosido-D-sorbitol would result from the reduction of maltose and turanose, which is contrary to the facts [see preceding data and the formulas (I) to (VII)]; therefore, the identity of the α-D-glucopyranosido-D-mannitol from maltose and from turanose proves that the common substituent is at differently numbered carbon

[1] Presented before the Organic Colloquium of Columbia University in the City of New York, May 3, 1944.

atoms which become equivalent in mannitol. *Since maltose is 4-α-D-glucopyranosido-D-glucose, turanose must be 3-α-D-glucopyranosido-D-fructose, because 3 is the equivalent position to 4 in mannitol. The result establishes the structure of turanose with the same degree of assurance as applies to the generally accepted structure of maltose.*

Preparation of epimaltose (4-α-D-glucopyranosido-β-D-mannose) from maltose octaacetate. A solution of 10 g. of pure β-octaacetylmaltose (m.p. 160–161° and $[\alpha]_D^{20}$ +62.6° in chloroform) in 34 cc. of glacial acetic acid was cooled in an ice-bath and 22 cc. of cold hydrobromic acid in glacial acetic acid (containing 30–32% hydrogen bromide) was added. After the solution had stood in the ice-bath for thirty minutes, 15 cc. of ethylene dichloride was added and the mixture poured into 250 cc. of ice and water. The layers were separated and the aqueous portion was extracted with two additional 10-cc. portions of ethylene dichloride. The combined extracts were washed with ice-water until free of acid, dried over "drierite" for one hour and concentrated *in vacuo* to a dry sirup (11 g.). The sirupy acetobromomaltose was dissolved immediately in 55 cc. of glacial acetic acid, 55 cc. of water was added and the solution was cooled to 5°. Five drops of 0.5% chloroplatinic acid in 50% acetic acid was added, followed by 22.5 g. of zinc dust, and the mixture was vigorously stirred for two hours, keeping the temperature at 0° to +5°. The solution was filtered and diluted with an equal volume of water, which caused clouding and the slow deposition of sirupy material. After standing two days in the refrigerator, the mixture, which had not crystallized, was extracted with four 10-cc. portions of ethylene dichloride. The extract was washed with dilute bicarbonate solution and water, concentrated *in vacuo* to a thick sirup and dried by reconcentration with two 25-cc. portions of absolute alcohol. The dry sirup, which weighed 7.5 g., was dissolved in 50 cc. of absolute methanol, the solution was cooled to 0°, and 10 cc. of 0.610 *N* barium methoxide solution added. After the solution had stood in the refrigerator at 5° overnight, the equivalent amount of *N* sulfuric acid was added and the barium sulfate removed by filtration. The filtrate was concentrated *in vacuo* to a dry sirup (4 g.), which was taken up in water and diluted to 25 cc. A 2-cc. aliquot, upon titration with a solution of bromine in water containing 8.55 mg. per cc., consumed 8.5 cc., which corresponds to 1.75 g. of maltal in the total solution. The remaining 23 cc. of solution was treated with 82 cc. of ethereal perbenzoic acid solution containing 0.0286 g. per cc. (3 molecular equivalents) and the mixture was shaken at 5° for two hours. The layers were separated and the aqueous fraction extracted with three 25-cc. portions of ether. The aqueous portion was concentrated *in vacuo* to dryness, 10 cc. of glacial acetic acid was added and, upon scratching, crystallization was induced. After standing two days at room temperature the crystals were removed by filtration and washed with glacial acetic acid and finally with ether. The yield was 1.15 g. (23%). The sugar was recrystallized by dissolving in one part of warm water, adding 5 parts of warm alcohol, filtering through decolorizing carbon and adding an additional 5 parts of warm alcohol to the filtrate. On seeding and cooling, the material crystallized as short rods with pointed ends, which melted with decomposition at 213–215° and mutarotated in aqueous solution $[\alpha]_D^{20}$ +99° (two min.) → 115° (sixty min. constant value), in good agreement with the values reported by Haworth, Hirst, and Reynolds (6) (m.p. 215–216° and $[\alpha]_D^{20}$ +97° → 115°) for epimaltose.

Reduction of epimaltose to 4-α-D-glucopyranosido-D-mannitol and conversion to the nonaacetate. To a solution of 1.5 g. of epimaltose dissolved in 50 cc. of water was added 0.6 g. of Raney nickel and the solution was reduced at 100° with hydrogen under 100 atmospheres pressure for six hours. The catalyst was removed by filtration and the solution, which did not reduce Fehling solution, was concentrated *in vacuo* to a thick sirup. The sirup was dried by reconcentration with two 5-cc. portions of absolute alcohol and one 10-cc. portion of pyridine. The dry sirup was acetylated by dissolving in 10 cc. of pyridine, adding 10 cc. of acetic anhydride, and allowing the mixture to stand twenty-four hours at room temperature. The acetate crystallized readily when the solution was poured into 200 cc. of ice and water, and was recovered by filtration. The yield was 2.2 g. Extraction of the mother

liquor with chloroform gave an additional 0.1 g. of the acetate; total yield, 2.3 g. (72%). The material was recrystallized from 20 parts of 95% alcohol, separating as rosettes of needles showing the specific rotation $[\alpha]_D^{20}$ +90.8° in chloroform (*c*, 1.2 g./100 cc. solution) and m.p. 142–143°[2]. A mixed melting point with 3-α-D-glucopyranosido-D-mannitol nonaacetate prepared from turanose (see next section) also gave 142–143°.

Anal. Calc'd for $C_{30}H_{42}O_{20}$: C, 49.86; H, 5.86; CH_3CO, 53.6.
Found: C, 49.90; H, 5.86; CH_3CO, 53.3.

The nonaacetate (0.6 g.) was hydrolyzed by refluxing with 0.2 *N* sulfuric acid (50 cc.) for ten hours; the sulfuric acid was removed as barium sulfate by reaction with the theoretical amount of barium carbonate, the acetic acid was removed by distillation *in vacuo*, and the glucose by fermentation with yeast. The aqueous solution upon concentration to dryness, followed by acetylation of the crystalline residue of D-mannitol with acetic anhydride and fused sodium acetate, gave 0.3 g. (83%) of D-mannitol hexaacetate which, after recrystallization from 10 parts of alcohol, showed the specific rotation $[\alpha]_D^{20}$ +25.1° in chloroform and m.p. 123°. A mixed melting point with an authentic sample of D-mannitol hexaacetate gave no depression of this value.

Preparation of 3-α-D-glucopyranosido-D-mannitol nonaacetate from turanose. A solution of 11.0 g. of recrystallized turanose ($[\alpha]_D^{20}$ +75.8° in water, equilibrium) in 100 cc. of water was agitated in a bomb with Raney nickel (2.0 g.) and hydrogen under a pressure of 67 atmospheres for six hours at 100°; the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to a dry sirup, which was dissolved in 50 cc. of pyridine and acetylated by the addition of 50 cc. of acetic anhydride. After standing for thirty hours at 25°, the solution was poured into one liter of ice-water and the precipitated nonaacetate was separated by filtration and recrystallized from 20 parts of alcohol; yield 10.6 g. (46%). This product was nearly free from the isomeric substituted sorbitol, and was brought to constant rotation readily by one recrystallization. The pure substance melted at 142–143°, in agreement with the value of Pacsu and Rich. Its rotation was $[\alpha]_D^{20}$ +90.8° in chloroform (*c*, 1.4 g./100 cc. solution), which is only slightly higher than the value of these authors (+89.3°)[3]. It gave correct analytical values for carbon, hydrogen, and acetyl. D-Mannitol, identified as the hexaacetate, was obtained by its hydrolysis with acid. In crystalline appearance it is indistinguishable from the nonaacetate in the epimaltose series, and the two substances are identical beyond question. They were examined by Mr. George L. Keenan, who has reported that "the microscopic examination of the samples of D-glucosido-D-mannitol nonaacetate prepared from turanose and from maltose, respectively, showed that they were identical, with the following optical crystallographic properties: The habit is colorless rods, showing parallel extinction and positive elongation in parallel polarized light (crossed nicols). In convergent polarized light (crossed nicols) faint interference figures indicate that the substance is biaxial. The minimum refractive index (n_α) shown crosswise on rods is 1.470, and the maximum refractive index (n_γ) is 1.490, shown lengthwise on rods (both ±0.002). The intermediate index, (n_β), could not be determined."

The nonaacetate of 3(*syn.* 4)-α-D-glucopyranosido-D-mannitol is readily soluble in chloroform and pyridine. It dissolves in boiling acetone and crystallizes at 0° as short individual fine needles. From solution in hot amyl alcohol it crystallizes on cooling as clusters of radial elongated prisms which exhibit well the end and side faces. It is only slightly soluble in boiling hexane or carbon disulfide. It is nearly insoluble in cold water but sufficiently soluble in hot water to permit its recrystallization, as individual acicular prisms.

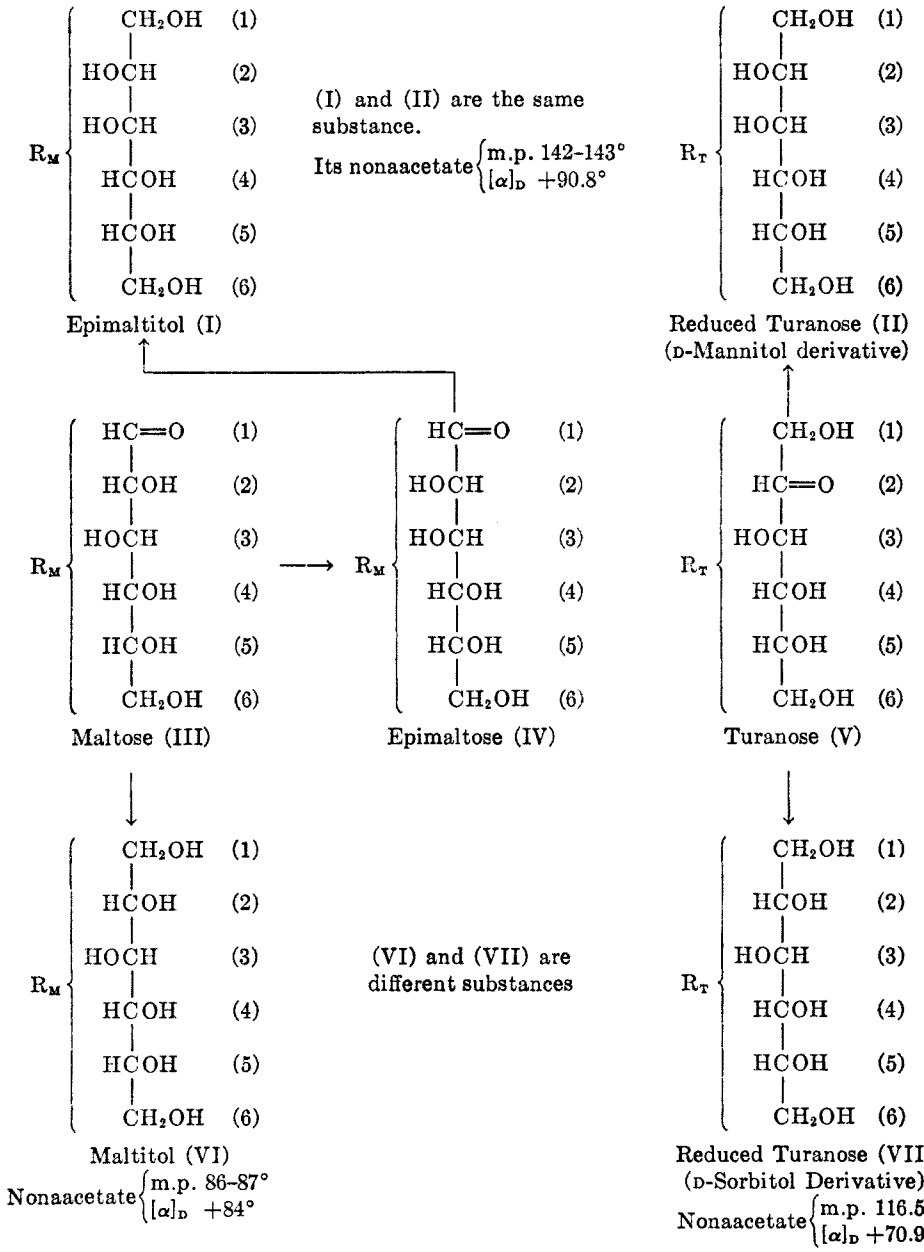
In this laboratory 3(*syn.* 4)-α-D-glucopyranosido-D-mannitol is more conveniently prepared from turanose than from maltose through epimaltose, because an abundant supply of melezitose, the source of turanose, is on hand. During a protracted drought in the

[2] The measurements, by Dr. Willard T. Haskins, were +90.99° (*c*, 1.2) after the first and +90.80° (*c*, 1.2) after the second recrystallization.

[3] The measurements, by Dr. Raymond M. Hann, were +90.71° (*c*, 1.7) after the first and +90.77° (*c*, 1.4) after the second recrystallization.

DIAGRAM ILLUSTRATING THE RELATIONSHIP BETWEEN TURANOSE AND MALTOSE

(R_M indicates in a general way the D-glucosido component of maltose, and R_T that of turanose. One OH becomes O when a position of union is specified.)



summer of 1943 in the vicinity of Charlottesville, Virginia, an unusually large amount of honey-dew was collected by bees. Through the cooperation of Mr. Harold E. Booth, whose

apiary is near Charlottesville, we obtained about six hundred kilograms of honey-dew honey, much of which was a magma of crystals of melezitose, and from it a supply of about sixty kilograms of the crystalline trisaccharide was prepared by Laboratory Technician Harry W. Diehl. The source of the honey-dew was not observed, but in view of earlier studies (7) it seems likely that it came from *Pinus virginiana*.

Independent evidence concerning the positions of union in maltose and turanose. In the foregoing proof of the structure of turanose, the generally accepted structure of maltose which has come from the evidence supplied by methylation studies, enzyme actions, and rotatory relationships, has been predicated. It seems worthy of notice that the new data showing the identity of the D-glucosido-D-mannitol from maltose and turanose lead to a new and independent proof for the 4-position of union in maltose. Referring to the schematic formulas I to VII, I have mentioned that this identity proves rigorously that the D-glucosido substituent is the same in the two disaccharides ($R_M = R_T$), and that in consequence the non-identity of the derived D-glucosido-D-sorbitols proves that the position of union is not at the same numbered carbon atom in maltose and turanose and must therefore be at respective positions which become equivalent in mannitol. In the general case that is represented by the formulas, there are three such pairs of equivalent positions in (I) and (II), namely, 1,6, 2,5, and 3,4. Introducing at this stage the fact that both maltose and turanose form osazones, it is evident that in maltose the union cannot be at its carbon 1 or 2 and therefore not at 6 or 5 in turanose, and that in turanose it cannot be at carbon 1 or 2 and therefore not at 6 or 5 in maltose. Only the third pair of positions (carbons 3 and 4) is not excluded; the union in maltose must be at one of these positions and the union in turanose must be at the other. To distinguish further, additional evidence must be introduced. The degradation of maltose has been shown (8) to lead to a D-glucosido-D-arabinose which forms a crystalline osazone, the existence of which proves that the union in maltose cannot be at its carbon 3 (which becomes the carbon 2 of D-glucosido-D-arabinose); the union in maltose is thus limited to its position 4, and in consequence the union in turanose is restricted to its position 3. The distinction between positions 3 and 4 for the maltose union also follows from the fact (4) that the hydrolysis of fully methylated maltose yields, as one product, 2,3,6-trimethylglucose, a result which excludes position 3 for the union.

The normal character of the phenylosazones of turanose and maltose. It has been assumed in the preceding paragraph that the phenylosazones of turanose, maltose, and D-glucosido-D-arabinose have an atom of nitrogen attached to each of their carbon atoms of positions 1 and 2. This normal osazone structure is now proved by the following data for the turanose and maltose osazones, and there can be little doubt that it also holds for the osazone of D-glucosido-D-arabinose. Turanose osazone has been converted by the action of copper sulfate solution to phenylturanosotriazole (9), which crystallizes well. The acid hydrolysis of phenylturanosotriazole yields D-glucose and phenyl-D-glucosotriazole, the normal structure of which has been established previously (9).

The phenylosazone of maltose undergoes the usual reaction with copper sulfate solution but the phenylmaltosotriazole has not crystallized; however, the acid hydrolysis of the reaction product produces crystalline phenyl-D-glucosotriazole in good yield, which proves the presence of phenylmaltosotriazole in the reaction product and shows the normal character of maltosephenylosazone.

Phenylturanosazone (*10*). A mixture of 4 g. of turanose, 2 cc. of water, and 1 cc. of phenylhydrazine was warmed on the steam-bath until solution was complete. To the cooled solution was added 3.5 cc. of phenylhydrazine and 4 cc. of glacial acetic acid, and the mixture returned to the steam-bath for one hour. At the expiration of this time, 40 cc. of warm 60% alcohol was added and, upon cooling, a rapid crystallization of the osazone occurred. The osazone was recovered by filtration and washed with absolute alcohol followed by ether to yield 4.2 g. (69%) of lemon-yellow needles. The osazone is soluble in hot water and separates on cooling as jelly-like particles, but water is not a satisfactory solvent for its purification. It was recrystallized from 15 parts of 95% alcohol with good recovery, as needles which melted with decomposition at 200–205° and rotated $[\alpha]_D^{20}$ +24.5° → +33.0° (24 hours, constant value) in a mixture of 4 parts of pyridine and 6 parts of absolute ethyl alcohol (*c*, 0.82). In methyl cellosolve solution it rotated $[\alpha]_D^{20}$ +44.3° → +48.5° (24 hours, constant value; *c*, 0.80).

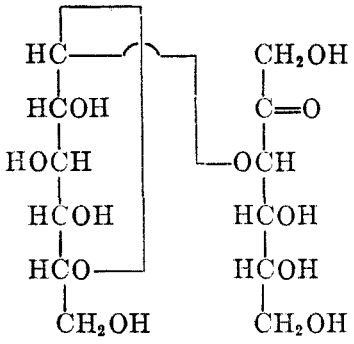
Anal. Calc'd for $C_{24}H_{32}N_4O_9$: C, 55.37; H, 6.20; N, 10.8.
Found: C, 55.32; H, 6.00; N, 10.6.

Phenylturanosotriazole (*9*). A solution of 15 g. of phenylturanosazone in 300 cc. of hot water was placed on the steam-bath and a solution of 22 g. of copper sulfate pentahydrate in 150 cc. of hot water was added. The mixture turned a deep cherry-red at once and in a short time (15 min.) a red precipitate had formed and the solution had become green. After thirty minutes from the time of addition of the copper solution, the solution was cooled, filtered, and the copper removed as sulfide. The clear light yellow filtrate was neutralized with 45 g. of barium carbonate and the insoluble material removed by filtration. The filtrate was extracted with five 50-cc. portions of ether to remove the aniline and the aqueous portion was concentrated *in vacuo* to a thick sirup. The sirup was dissolved in 60 cc. of warm alcohol, filtered to remove a slight turbidity and diluted with 65 cc. of ether. Upon cooling and scratching, the product crystallized as large prisms; yield 8.9 g. (72%). The osotriazole was recrystallized from 10 parts of alcohol and when pure showed the melting point 193–194° and rotated $[\alpha]_D^{20}$ +74.5° in aqueous solution (*c*, 0.90).

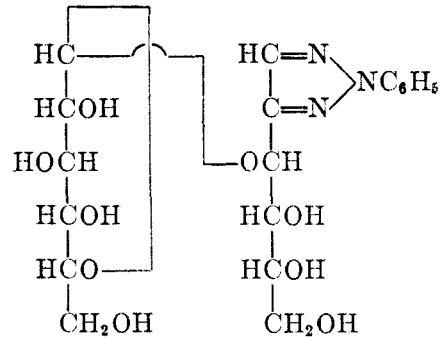
Anal. Calc'd for $C_{18}H_{25}N_3O_9$: C, 50.58; H, 5.90; N, 9.83.
Found: C, 50.52; H, 5.87; N, 9.76.

Acid hydrolysis of phenylturanosotriazole. A solution of 2.0 g. of phenylturanosotriazole in 100 cc. of 0.5 *N* hydrochloric acid was heated in a boiling water-bath at 99° for six hours. After cooling to 5° for several hours, the needle crystals of phenyl-D-glucosotriazole were removed by filtration and washed with cold water; yield 1.17 g. (94%); m.p. 195–196°; rotation $[\alpha]_D^{20}$ −81.3° in pyridine solution (*c*, 0.83). Pure phenyl-D-glucosotriazole melts at 195–196° and rotates −81.5° in pyridine solution (9). The aqueous filtrate from the osotriazole precipitate was neutralized with 10 g. of silver carbonate, filtered, the excess silver removed as the sulfide, and the clear filtrate from the sulfide precipitate concentrated *in vacuo* to a thick sirup. The sirup was taken up in 5 cc. of warm methanol, filtered to remove a slight turbidity, and reconcentrated to a thin sirup which, upon addition of an equal volume of glacial acetic acid, crystallized; yield 0.50 g. (60%). The crystals were shown to be D-glucose by their equilibrium rotation $[\alpha]_D^{20}$ in aqueous solution (*c*, 0.81), which was +52.5°.

In conclusion, there are recorded the formulas for the structures of turanose (VIII) and phenylturanosotriazole (IX) that have been established.



Turanose
3-[α-D-Glucopyranosido]-
D-fructose (VIII)



Phenylturanosotriazole
Phenyl-3-[α-D-glucopyranosido]-D-
glucosotriazole (IX)

Thanks are expressed to Dr. Raymond M. Hann and Dr. Willard T. Haskins for assistance in the experiments, to Dr. Arthur T. Ness for the microchemical analyses, to Mr. Harry W. Diehl for preparing the melezitose from which the turanose was made, and to Mr. George L. Keenan for supplying the optical crystallographic data.

BETHESDA, MD.

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[CONTRIBUTION FROM DIVISION OF DAIRY RESEARCH LABORATORIES, BUREAU OF DAIRY INDUSTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

EVIDENCE OF THE EXISTENCE OF BISULFITE COMPOUNDS OF SUGARS

H. H. BROWNE

Received March 6, 1944

In connection with an investigation into the possibility of fermenting the lactose in cheese whey to glycerol, in analogy to the much publicized (at one time) molasses fermentation, it was considered desirable after certain preliminary experiments to investigate the reaction of sodium bisulfite upon lactose, and, incidentally, upon other sugars, since many of the investigators claimed to have used alkali bisulfites to combine with acetaldehyde, the formation of which in addition to glycerol had been postulated as a product of this fermentation.

While the bisulfite compounds of some aldehydes have been investigated fairly thoroughly and in some cases have been put to use industrially, those of the sugars have received comparatively little attention except in connection with the wine industry. Rocques (1) seems to have been the first to report upon the glucose compound, which Kerp (2) claimed to have isolated, and from solutions of it to have determined the dissociation constant for various concentrations by methods similar to those described in this paper. About the same time Farnsteiner (3) determined the bound bisulfite for some ten sugars in one concentration with bisulfite of approximately constant concentration. Years later Tomoda and Taguchi (4) repeated certain features of the work of both of the last two mentioned workers, and showed also that raffinose, sucrose, and D-fructose did not react.

Nothing was published on the sugar-bisulfites by the workers on the glycerol fermentation, and in fact some of them used the term "sulfite" and "bisulfite" interchangeably and as a rule did not specify what sugar they were trying to ferment.

General information on these compounds would be of help in developing methods of control in following the fermentation. There is also the possibility that it would yield information relative to sugar structures in general.

METHODS

The sodium bisulfite and sugars used were obtained through commercial channels, the purity of the sugars being determined polarimetrically. The manufacturers' designations of purity for materials in Table VI were accepted; the "sodium bisulfite" was found upon analysis to be the meta-bisulfite, whose anion it will be recalled dissociates in solution according to the equation $S_2O_5^{=} + H_2O \rightleftharpoons 2HSO_3^-$.

All solutions were made up in sugar (1/10 dilution) flasks, generally by adding a "10% sugar solution" to the main volume mark, then using this volume to dissolve the required weights of "bisulfite" (the sugar and bisulfite must not be dissolved together), the resulting solution then being returned to the flask and

made up to the "10%" mark with water. The final solution would then contain 100/110 of the original sugar concentration, and 100/110 (of 1.10) of the bisulfite as weighed. The bisulfite was used in quantities varying from 0.5 g. to 30 g. per 100 ml. of the final solutions. The maximum concentration of sodium bisulfite was limited to 30 g./100 ml. due to the fact that this quantity increases the volume of 100 ml. of the sugar solutions approximately by 10 ml. All solutions were stored at 20° for about 20 hours before titrations and polarimetric readings were made at this temperature, although equilibrium was apparently established in less than two hours.

The analytical procedure adopted was to titrate the "free" bisulfite with 0.1 normal iodine solution, previously standardized against arsenious oxide, by running the solution into 50 ml. of the iodine solution (diluted with about 200 ml. of water). "Bound" bisulfite was computed from the difference between the bisulfite originally added and "free" bisulfite. It may be noted that the value so computed is somewhat high due to the fact that there is a slight loss of sulfur dioxide when the sugar solution is added to the dry bisulfite. Polarimetric readings were made in a S. & H. saccharimeter equipped with a dichromate filter and using a 200-mm. tube. Iodine is not known to oxidize aldoses in acid solution, and in fact in control tests it took generally about 24 hours for the sugar solutions to reduce 1 drop of the standard iodine solution.

The titrations and rotations for lactose, D-glucose, maltose, D-galactose, and D-mannose for different concentrations of bisulfite are given in Tables I to V inclusive.

It will be noted that with each sugar there is a progressive lowering of the rotation and a correspondingly lower reducing value per unit concentration with increasing added bisulfite, so that the logical assumption was that the sugar and bisulfite had combined.

The proof of the existence of an equilibrium constant would be evidence of the validity of this premise.

The constant K for the monomolecular reaction on $AB \rightleftharpoons A + B$, *i.e.*, $K = \frac{[A]\,[B]}{[AB]}$, was first computed by using the values with lactose: $[A]$ = concentration of free bisulfite determined by titration, $[B]$ = concentration of free lactose = originall actose − bound bisulfite, $[AB]$ = bound bisulfite = original bisulfite − free bisulfite. When the values of this so-determined $[B]$ were plotted against the observed rotation α, a nearly straight line resulted whose slope was approximately equal to .01, or $[B] = k\,\alpha$, which conforms to the quantitative expression for simple polarization of sugars. The resulting inference is that only part of the sugar is optically active. In order to express $[B]$ in terms of α and a constant, use was made of the standard relations: $[\alpha] = \frac{\alpha}{2c}$, moles/liter $= \frac{1000c}{M}$, and degrees $S = \frac{[\alpha]}{.3462}$, this last term used as if applicable to sugars other than sucrose, and $[\alpha]$ was treated as a constant, independent of the sugar concentration. After properly combining, etc., the value of the constant k for any sugar is given by $\frac{173.1}{M\,[\alpha]}$, and for lactose = .00913. All symbols have their customary meaning.

In the case of $[AB]$, since there was no suitable direct method for determining that, resort was had to one of three indirect methods; 1st, using the difference between the bisulfite added and the bisulfite found, which equals the bound bisulfite; 2nd, using the difference between the sugar added and the sugar found, which equals the bound sugar; 3rd, using the arithmetical mean of the 1st and 2nd method. While each method has its own advantages or disadvantages, in any case it is desirable to compute the constant for all sugars in the same way. The results of the 1st method should equal those of the 2nd in the ideal case where no sulfur dioxide is lost and where the bisulfite does not enter into any other reaction than the monomolecular one postulated.

It may be said that in the 3rd method there is the apparent advantage that any losses of sulfur dioxide will raise the $[AB]$ computed from the titration and lower that computed from the optical rotation so that their effects are opposite and their average should closely approximate the true condition. Where the differences between the two terms are not too great, as in the lower bisulfite concentrations, this method would be best, but as will be seen in the case of maltose particularly, both the differences ([bound sugar] − [bound bisulfite]) and ratios $\left(\frac{\text{[bound bisulfite]}}{\text{[bound sugar]}}\right)$ are too great to ignore. Where the first method was used for both $[B]$ and $[AB]$, greater variations in the K values were found than in the method adopted.

The writer in all cases has used the 2nd method, with computed K's in a column in Tables I–V, each table representing a different sugar—the different columns are self-explanatory. This constant is, of course, a composite one, taking in the equilibria between the bisulfite constituents, between the different forms of the sugars, and that between all of them combined.

As may be seen in Tables I–V, the values of K in most cases show remarkable agreement in spite of the many equilibria involved, but the value for glucose is not in agreement with that of Kerp (2) who found various values for various concentrations of his solid compound in aqueous solution, which this writer believes would indicate more than one reaction, *i.e.* the value was not that of a constant.

As somewhat of a check upon this idea, values were computed for other reactions such as $A_2B \rightleftharpoons 2A + B$, and $A_3B_2 \rightleftharpoons 3A + 2B$ with indifferent results, although it is very possible that other reactions do take place.

More corroborative evidence that this is an equilibrium reaction with the aldehyde grouping of the sugars is as follows: since it may be calculated from dissociation data that the bisulfite ion ceases to exist at about pH 9.0 the solutions were made alkaline (blue to thymolphthalein) with strong sodium hydroxide, keeping them ice-cold, then made colorless with a drop or two of glacial acetic acid, and polarized. It was found that the polarization values always went back to approximately the equivalent of what they would have been if no bisulfite had been added. This is also evidence that the sugar has not been irreversibly altered to any extent by the bisulfite.

While the writer believes that it would be of some interest to use this reaction on other sugars in some sort of systematic way, such as the comparison of epimers (touched upon with one pair in this paper); following down a D or L series; check-

TABLE I

Lactose Hydrate (U.S.P.)

$[\alpha] = +52.6° = +151.9°$ S, (B. of S.). "Free" sugar = 0.00913 α. "Free" HSO_3^- = 2.4985/V. pH range on polarized solutions = 2.88–4.00. Author's sample = +151.3° S.

α	Titration = V	Sodium bisulfite			Sugar		K
		added	"free"	"bound"	"free"	"bound"	
°S.	ml.	M/l	M/l	M/l	M/l	M/l	
27.5		0.0		0.0	0.2511	0.0	
26.9	118.2	.0288	0.0211	.0077	.2456	.0055	0.946
26.5	58.0	.0577	.0430	.0147	.2419	.0092	1.135
26.2	45.4	.0721	.0550	.0171	.2392	.0120	1.100
25.7	35.6	.0962	.0701	.0261	.2346	.0165	1.001
24.9	23.3	.1442	.1074	.0368	.2273	.0238	1.025
22.3	11.5	.2884	.2182	.0702	.2036	.0475	0.935
18.8	5.4	.5769	.4626	.1143	.1716	.0795	0.999
16.1	3.55	.8562	.7038	.1614	.1470	.1041	0.993
13.9	2.56	1.1538	.9759	.1779	.1269	.1242	0.997
12.5	2.02	1.4422	1.236	.206	.1141	.1370	1.029
9.3	1.21	2.3076	2.064	.244	.0849	.1662	1.053
8.2	0.98	2.8840	2.549	.335	.0749	.1762	1.083

TABLE I-A

Lactose Hydrate

13.6	—	0.0	—	0.0	0.1242	—	—
12.3	20.37	.1442	0.1226	.0216	.1125	0.0119	1.161
10.9	10.02	.2884	.2494	.0390	.0995	.0247	1.005
9.1	4.92	.5769	.5080	.0689	.0831	.0411	1.025
6.8	2.35	1.154	1.064	.090	.0621	.0621	1.064
4.6	1.14	2.037	2.192	.116	.0420	.0822	1.121
3.5	0.73	3.461	—	—	.0319	.0923	—

TABLE II

D-Galactose

$[\alpha] = +80.5° = +232.5°$ S (Mfgrs'). Author's sample = +237° S. "Free" sugar = 0.01193 α

α	Titration = V	Sodium bisulfite			Sugar		K
		added	"free"	"bound"	"free"	"bound"	
°S.	ml.	M/l	M/l	M/l	M/l	M/l	
43.1	—	0.0	—	—	0.5141	0.0	—
41.1	—	.0240	—	—	.4903	.0238	—
40.2	257	.0481	0.0097	0.0384	.4796	.0345	0.1362
37.8	162	.0721	.0154	.0567	.4509	.0632	.110
37.3	117	.0962	.0213	.0749	.4450	.0691	.1371
34.4	74	.1442	.0337	.1105	.4104	.1037	.1336
26.4	26.4	.2884	.0946	.1938	.3150	.1991	.150
18.2	9.9	.5769	.2523	.3246	.2171	.2970	.184
13.6	5.0	.8652	.4997	.3655	.1622	.3519	.232
11.2	3.0	1.1538	.8328	.3210	.1336	.3805	.292

TABLE III

D-GLUCOSE (ANHYD.)

$[\alpha] = +52.5$ (Mfgrs') $= +151.6°$ S. Author's sample $= +152.9°$S. "Free" sugar $= 0.0183\ \alpha$

α	TITRATION $= V$	SODIUM BISULFITE			SUGAR		K
		added	"free"	"bound"	"free"	"bound"	
°S.	ml.	M/l	M/l	M/l	M/l	M/l	
27.8	~	0.0	—	0.0	0.5087	0.0	—
26.9	89.6	.0481	0.0278	.0203	.4922	.0165	0.820
25.6	44.5	.0962	.0561	.0401	.4685	.0402	.655
23.1	29.3	.1442	.0852	.0590	.4227	.0860	.420
22.9	21.8	.1924	.1146	.0778	.4190	.0897	.530
21.7	17.3	.2405	.1444	.0961	.3971	.1116	.512
21.2	13.8	.2884	.1810	.1074	.3879	.1208	.577
16.1	6.6	.5769	.3785	.1984	.2946	.2141	.438
12.2	3.8	.8652	.6575	.2077	.2232	.2855	.516
9.3	2.9	1.1538	.8615	.2923	.1702	.3385	.433

TABLE IV

MALTOSE HYDRATE

$[\alpha] = +131° = +378.4°$ S (Mfgr's). Author's sample $= +378.9°$ S. "Free" sugar $= 0.00366\ \alpha$

α	TITRATION $= V$	SODIUM BISULFITE			SUGAR		K
		added	"free"	"bound"	"free"	"bound"	
°S.	ml.	M/l	M/l	M/l	M/l	M/l	
68.9	—	0.0	—	0.0	0.2521	0.0	
67.5	34.0	.0962	0.0734	.0228	.2470	.0051	3.55
65.9	17.0	.1924	.1469	.0455	.2412	.0109	3.25
64.7	10.9	.2884	.2292	.0592	.2368	.0153	3.55
63.9	5.1	.5769	.4899	.0870	.2339	.0182	6.30
62.6	3.4	.8652	.7348	.1304	.2291	.0230	7.33
61.7	2.5	1.1538	.9994	.1544	.2258	.0263	8.14

TABLE V

D-MANNOSE

$[\alpha] = +14.2°$ (B. of S.) $= +41.0°$ S. Author's sample $= +41.5°$ S. "Free" sugar $= 0.0668\ \alpha$

α	TITRATION $= V$	SODIUM BISULFITE			SUGAR		K
		added	"free"	"bound"	"free"	"bound"	
°S.	ml.	M/l	M/l	M/l	M/l	M/l	
7.55	—	0.0	—	—	0.5043	0.0	
6.6	20.7	.2884	0.1205	0.1679	.4409	.0634	0.93
6.3	13.0	.5769	.1922	.3847	.4208	.0835	.97

ing paired hexoses of the same type, such as maltose, gentiobiose, and cellobiose (paired glucoses), etc., but due to their scarcity, it is not altogether feasible at this time, although some carbohydrates have been tried against sodium bisulfite to see whether they did react. Results are tabulated in Table VI.

Referring to Table VI, it will be seen that there is no evidence of addition to mannitol which has no aldehyde group, but there is this evidence in rhamnose, which has no primary alcohol grouping but does have the aldehyde group.

TABLE VI

EFFECT OF 30% CONCENTRATION OF $NaHSO_3$ SOLUTIONS UPON ROTATION OF CARBOHYDRATES AND DERIVATIVES IN 9.09 G./100 ML. SOLUTION (UNLESS OTHERWISE NOTED)

NAME	MFGR'S DESIGNATION	CHANGE	REMARKS
		°S.	
Amygdalin	—	+0.7	Readings on 4.5 g./100 ml. solution. Deposited crystals of amygdalin when regular 9.09% solution was used.
Mannitol	—	0	
γ-Galactolactone	C.P. anhyd.	+3.9	Readings on 4.5 g./100 ml. solution, and slowly changing with time.
δ-Gluconolactone	Practical	−0.9	
L-Rhamnose	—	−3.5	
Melezitose	—	−1.0	
Trehalose	—	0	

DISCUSSION

In the light of the above findings, and those of previous workers, it is to be regretted that many text book writers ignore these compounds, or even deny their existence, as did Pringsheim (5).

As will be seen from the tables, some values of the "constant" justify that term better than others, that of lactose being the best and that of mannose the worst. It would appear that the proportionality constant in the expression "free sugar $= k\alpha$" plays a large part in this, but not the only part. On the whole, mannose and maltose, due to their small change in rotation with change in bisulfite concentration, the first probably because of its low $[\alpha]$, the latter because of its large dissociation constant, are the least informative when treated with bisulfite. Conversely, with galactose, with a concentration of 0.25 g./100 ml. of bilsulfite, there is a loss of rotation of 2° S.

SUMMARY

Data are presented as evidence of the existence of sugar-bisulfite compounds; the rotation in sugar solutions containing the bisulfite-ion is taken to be directly

proportional to the concentration of the "free" sugar. The sugars worked with were: lactose, D-glucose, D-galactose, maltose, and mannose.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE STATE UNIVERSITY OF IOWA]

THE POLYMERIZATION OF HOMOLOGS OF ETHYLENIMINE (1)

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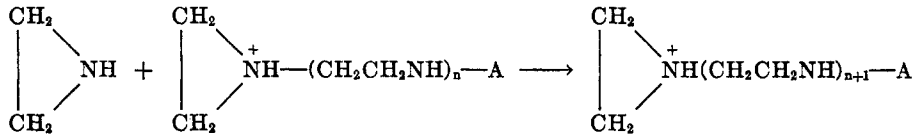
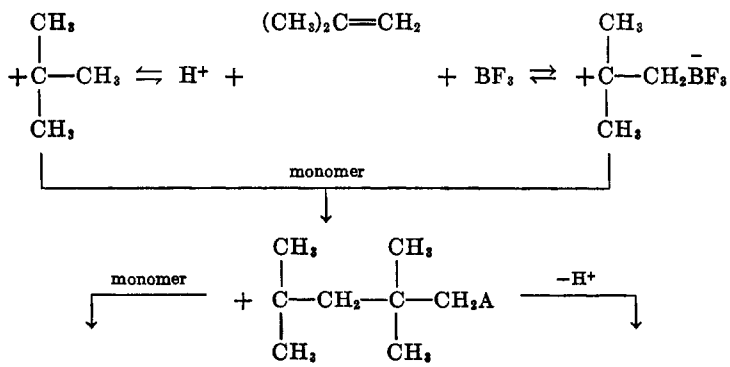
In the first paper of this series the authors reported reasons for considering the polymerization of ethylenimine (I) to be a bimolecular reaction of monomer with ethylenimmonium (and substituted ethylenimmonium) ions (II). This is is symbolized below; A may be hydrogen, boron fluoride, alkyl, etc.



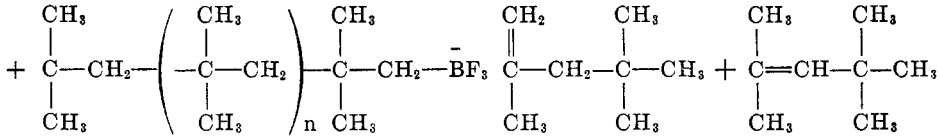
I II

This is contrary to the conclusions of Kern and Brenneisen (2) who consider the isolation of low molecular weight products to indicate condensation polymerization. The isolation of dimers and trimers of typical vinyl monomers under conditions causing polymerization is so rare (3) that such isolation is commonly accepted as contraindicating an addition mechanism. An alternative conclusion (3) is that the dimerization and polymerization occur by different mechanisms.

With full appreciation of the vast differences in behavior of dimerization and polymerization, the author would like to question both of the above conclusions and subscribe to the view previously expressed (4) that the mechanisms are the same to the extent of having a common intermediate, environmental conditions determining at each stage which course the reaction takes. For example in the case of isobutylene there is the common intermediate (III) (where A may be —H or $—BF_3^-$) if one may apply to the polymerization the mechanism of polar catalysis developed by Williams (5) and accept for the dimerization the picture of Whitmore (6).



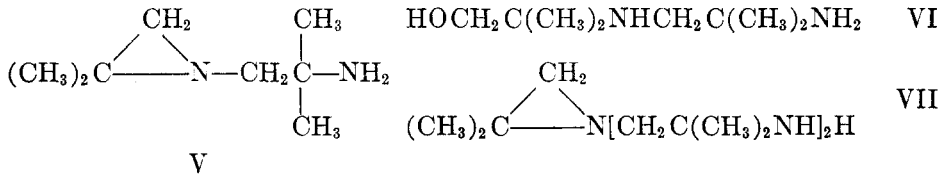
III



IV

With isobutylene it may not be possible to find a single set of conditions yielding both polymer and dimer, although some of the factors influencing the two reactions are known. For example, it has been pointed out (7) to the author that the lower the temperature the greater may be the stability of the intermediate (III) [and the higher homologs (IV)] toward loss of a proton (termination). This would seem to be a probable explanation for the extremely large polyisobutylenes obtained at very low temperatures (8). With monomers having less pronounced polymerization tendencies, such as the alkylenimines, it is possible to select conditions such that polymer, dimer, and trimer can be isolated in the same experiment. The author can find no acceptable alternative to believing that these are products of a common mechanism.

In the present work 2,2-dimethylethylenimine (IV) was polymerized in aqueous solution with hydrochloric acid. Contrary to the behavior of polyethylenimine, poly-2,2-dimethylethylenimine is soluble in ether and insoluble in water. The polymerization mixture was extracted with ether and distilled giving a low yield of three distinct intermediates and a good yield of purified waxy polymer. Nitrogen analyses and boiling points indicated the three intermediates to be a dimer (V), a hydrolyzed dimer (VI), and a trimer (VII).



V

VI

VII

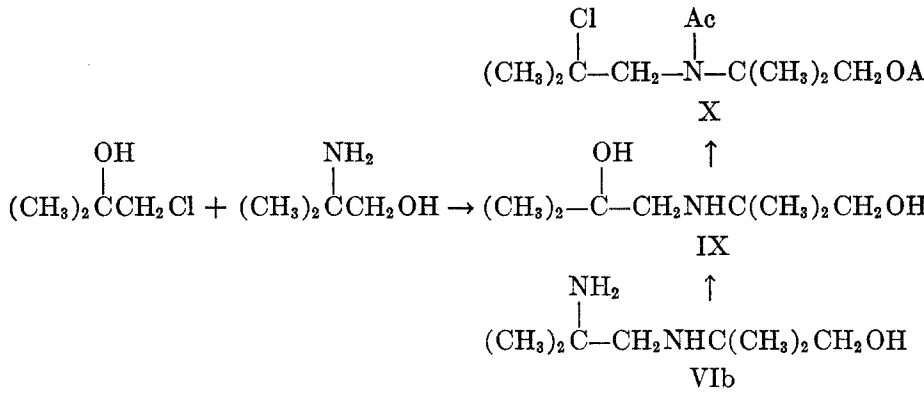
In assigning structures to these products consideration was given to the isolation by Cairns (9) of 1-amino-2-methyl-2-propanol from the sulfuric acid hydrolysis of 2,2-dimethylethylenimine. This would suggest that a mechanistic critical point lies between the secondary imine and tertiary imine structure, since Gabriel and Ohle (10) found 1,2-propylenimine to be cleaved to β-bromoisopropylamine. Preference of the primary carbon over the secondary, as in the latter case, would indicate an inversion mechanism while preference of tertiary over primary, as in the former case, would indicate an ionization mechanism (11).

Hughes and Ingold (11) have, however, demonstrated that a shift to a stronger attacking anion or donor molecule may institute bimolecular inversion with structures which undergo the ionization mechanism in the presence of less strongly nucleophilic reagents. In this connection it is to be noted that the immonium nitrogen exerts (through the carbon which is not to be severed from the nitrogen) an inductive effect favoring inversion. The two mechanisms are diagrammed in Figure 1.

The hydrolyzed dimer (VI) was synthesized by the reaction of β-chloro-*tert*-butylamine hydrochloride and 2-amino-2-methyl-1-propanol. The former was made by the action of thionyl chloride on the hydrochloride of the latter. The product of this synthesis and the hydrolyzed dimer gave identical phthalyl acetyl derivatives (VIII). This synthesis could yield either of the isomers (VIb) or (VIc); however, since the structure of the 2-amino-2-methyl-1-propanol is fixed, the uncertainty in this synthesis is different from the uncertainty in the structure of the hydrolyzed dimer which thus must be of the structure (VIb). The hydrolyzed dimer could have the structure (VIc) only if there were an S_N1 mechanism in dimerization and S_N2 in hydrolysis; however, this is impossible since S_N2 is favored with increasing donor or anionoid power and water is a poorer donor or base than the imine.

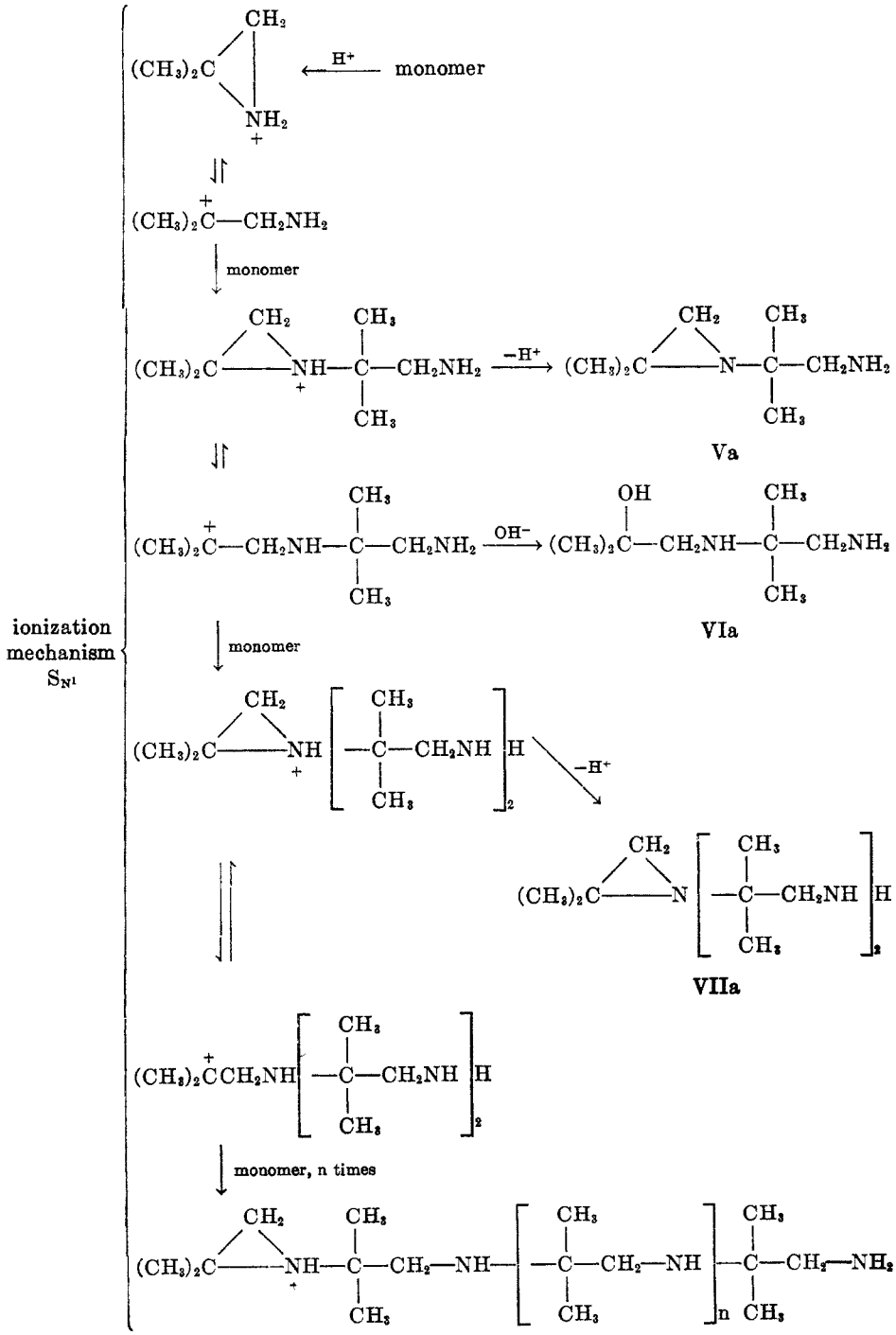
From the compound (VIb) the dimer (Vb) was obtained by the Wenker method (12) and the oxalates found to be identical. That the imine could be prepared substantiates the structure assigned, since Adams and Cairns (13) found that 1-amino-2-methyl-2-propanol could not be converted to 2,2-dimethylethylenimine by the Wenker method.

In order to confirm the structure of the hydrolyzed dimer (VIb) it was synthesized by an alternative route. Isobutylene chlorohydrin was condensed with 2-methyl-2-amino-1-propanol, yielding the amino glycol (IX). That no rearrangement of the isobutylene chlorohydrin had occurred during the reaction was indicated by the conversion of the amino glycol with acetic anhydride, hydrogen chloride, and acetyl chloride to the chlorodiacetyl derivative (X) By the method of Harvey and Caplan (14) for alkylating urea with tertiary alcohols in the presence of concentrated sulfuric acid, the amino glycol (IX) was caused to react with urea and the product hydrolyzed to (VIb), identified by comparison of the phthalyl acetyl derivatives.



The conclusion that aliphatic 1,2-alkylenimines tend to polymerize by the inversion mechanism is supported by rough rate comparisons made with a group of alkylenimines in the present work. It was found that 1,2-alkylenimines having a primary carbon in the imine ring polymerize about as readily as ethylenimine while the others polymerize much less easily. It is not possible to say

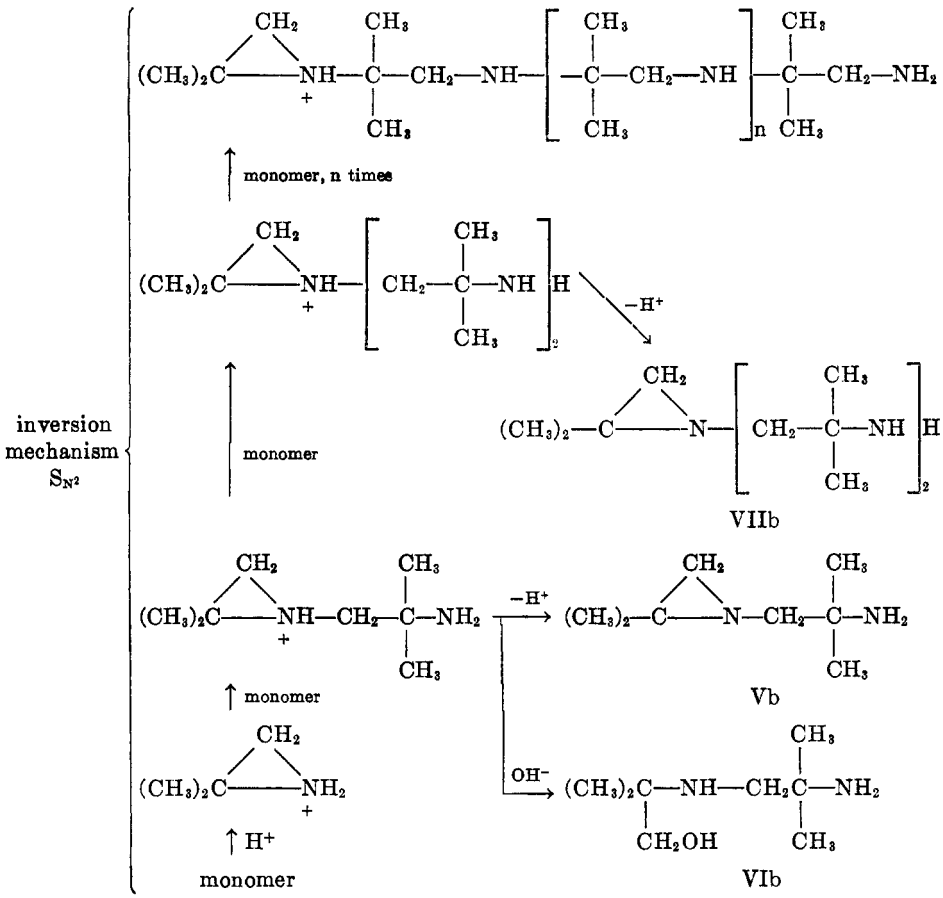
FIGURE 1a


ionization mechanism S_{N^1}
monomer
H^+
$-H^+$
OH^-
monomer, n times
Va
VIa
VIIa

as yet which mechanism and consequently which carbon is preferred with imines having both a secondary and a tertiary carbon in the ring.

The imines used were ethylenimine (15), 1,2-propylenimine (16), 1,2-butylenimine (17), 2,2-dimethylethylenimine (9) [readily prepared by the Wenker method (12) from ethanolamine, 1-amino-2-propanol, 2-amino-1-butanol, and 2-amino-2-methyl-1-propanol, respectively], *trans*-2,3-butylenimine, 2,2,3-trimethylethylenimine, and 2,2-dimethyl-3-*n*-propylethylenimine (the last prepared

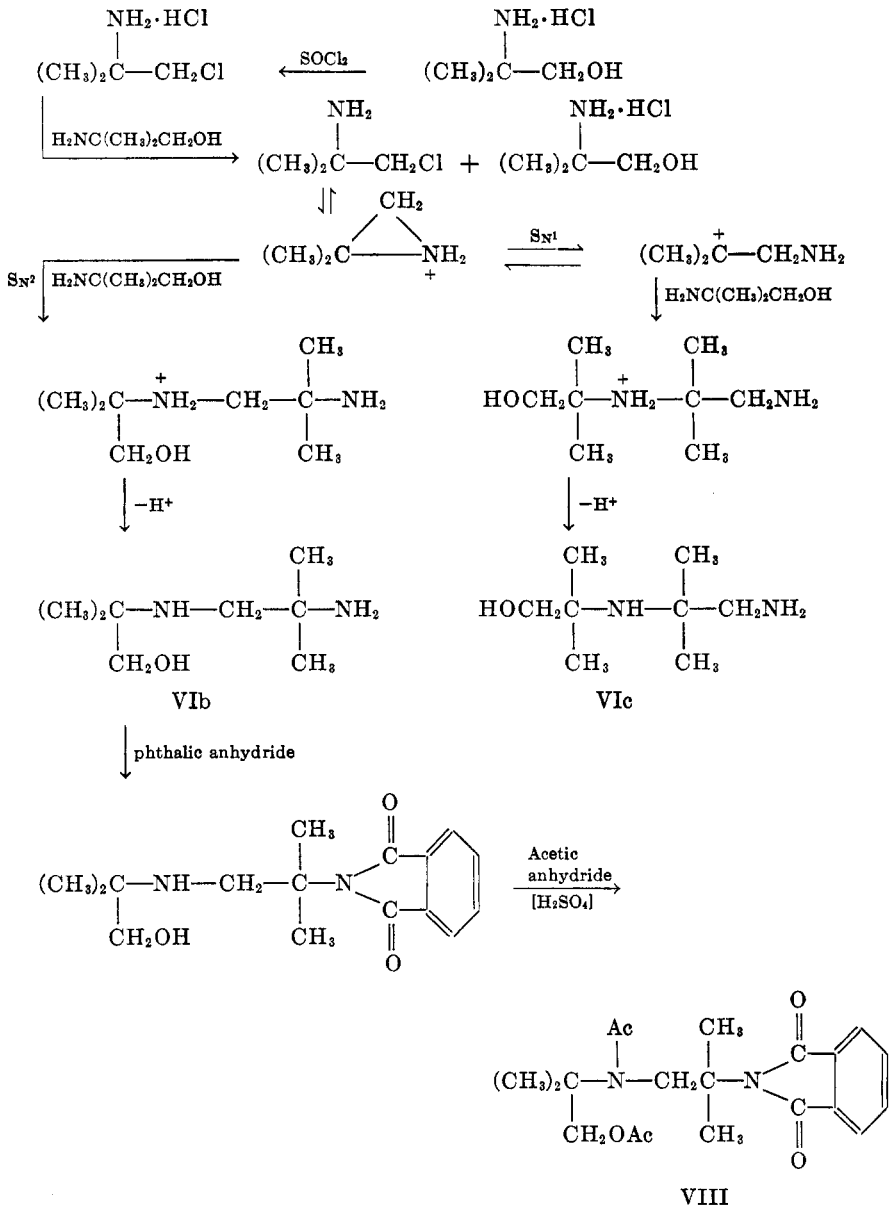
FIGURE 1b



from 2-amino-2-methyl-3-hexanol). For the preparation of 2,3-butylenimine and 2,2,3-trimethylethylenimine the nitro alcohols, 3-nitro-2-butanol and 3-nitro-3-methyl-2-butanol were prepared after the method of Hass and Vanderbilt (18) and hydrogenated according to Johnson and Degering (19) to the corresponding amino alcohols. The only 1,3-alkylenimine studied was trimethylenimine which was prepared in very poor yield by the reduction of N,N-trimethylene-*p*-toluenesulfonamide according to the method of Howard and Marckwald (20).

Cyclopropylamine, although not an alkylenimine, was included in the study because of the "resemblance in chemical behavior of cyclopropane and its

FIGURE 2



derivatives to the corresponding olefinic compounds" (21). The cyclopropylamine was prepared by a Hofmann degradation of cyclopropane carbonamide

following the directions of Lipp, Buchkremer, and Seeles (22) for the isolation of cyclopropylurethan. The polymerization of cyclopropylamine by boron fluoride yielded ammonia and a product low in nitrogen and was probably in part due to the formation of the readily polymerizable cyclopropene (23).

The 3-amino-2-butanol was not readily separated by fractional distillation into two pure diastereoisomeric amino alcohols. The higher and more nearly constant boiling 3-amino-2-butanol was converted by the Wenker method mainly to *trans*-2,3-butylenimine, identified as the benzenesulfonimide (24). When the cis- and trans-2,3-butylenimines are available in sufficient quantity it will be interesting to compare the polymers. That from the former should be a meso-polymer of irregular structure; that from the latter, of regular structure.

A good method of determining the rates of polymerization of the alkylenimines is lacking. If the polymerization is not too complete the extent of polymerization can be determined fairly accurately by evaporation, using aqueous potassium hydroxide to quench the polymerization except where polymerization was carried out at 150° and hence could be quenched by cooling. The calibration of viscosity change is an easier method which suffers, however, from the neglecting of the effect of variation in the degree of polymerization. The change in refractive index in aqueous solution has been followed (1) with ethylenimine and 1,2-propylenimine and the refractometer readings followed the same curve in the case of 2,2-dimethylethylenimine, but the data could not be calibrated in the latter case since the polymer which slowly precipitates is water-insoluble (ether-soluble). Trimethylenimine, 2,3-butylenimine, and 2,2,3-trimethylethylenimine underwent no refractive index change under the same conditions.

With 5 mole per cent boron trifluoride etherate, which has been used as a polymerization catalyst by Hanford and Stevenson (25), at 150° during twenty-four hours, the primary 1,2-alkylenimines were completely polymerized and trimethylenimine about three-fourths polymerized; 2,3-butylenimine was less than half polymerized as was 2,2-dimethyl-3-*n*-propylethylenimine. With 10 mole per cent boron trifluoride etherate at 150° during one hundred fifty hours, *trans*-2,3-butylenimine was completely polymerized, and 2,2,3-trimethylethylenimine, 2,2-dimethyl-3-*n*-propylethylenimine, and cyclopropylamine were less than half polymerized. With 3 mole per cent alcoholic hydrogen chloride at 150° for twenty-four hours the primary alkylenimines were completely polymerized and *trans*-2,3-butylenimines about three-fourths polymerized.

The polymers obtained were probably of low molecular weight, being viscous liquids or gums except for poly-2,2-dimethylethylenimine which was waxy.

EXPERIMENTAL PART

Preparation of the monomers.[1] The monomers used with the exception of trimethylenimine and cyclopropylamine were prepared by the Wenker (12) method with the results reported in Table I. The available amino alcohols used for the preparation of the imines were ethanolamine, 1-amino-2-propanol (isopropanolamine), 2-amino-1-butanol, and 2-amino-2-methyl-1-propanol; some 2-amino-2-methyl-3-hexanol was also obtained.[2]

[1] Some of the monomers were prepared by Mr. Alexander May working in this laboratory.

[2] The 2-amino-2-methyl-3-hexanol was kindly supplied by Commercial Solvents Corp.

For the preparation of 2,3-butylenimine and 2,2,3-trimethylethylenimine, 3-nitro-2-butanol and 3-nitro-3-methyl-2-butanol were prepared in ten-mole runs after the method of Hass and Vanderbilt (18) and hydrogenated[3] by the directions of Johnson and Degering (19). Hydrogenation at low pressure with platinum oxide gave higher yields (50%) than were obtained with nickel at high pressure (30%), a considerable tar resulting (this is a combined crude yield for the 3-amino-2-butanol).

3-Nitro-2-butanol; yield 77%; b.p. 74–76° at 3 mm.; n_D^{20} 1.4420.

3-Nitro-3-methyl-2-butanol; yield 75%; b.p. 78–80° at 3 mm.; n_D^{20} 1.4428; n_D^{25} 1.4416. *Anal.* Calc'd for $C_5H_{11}NO_3$: N, 10.49. Found: N, 10.52.

3-Amino-2-butanol; 116–119° at 185 mm.; n_D^{25} 1.4445; yield 16% after refractionation in 30-in. Fenske column; lower fraction 85–105° at 185 mm.; n_D^{25} 1.4425; yield 3%.

3-Amino-3-methol-2-butanol; yield 30%; 63–65° at 15 mm.; n_D^{25} 1.4434; d_{25}^{25} 0.9153.

The 3,5-dinitrobenzoate of 3-nitro-3-methyl-2-butanol was prepared and crystallized from benzene, m.p. 202–203°.

Anal. Calc'd for $C_{12}H_{13}N_3O_8$: N, 12.84. Found: N, 13.12.

The hydrochloride of 3-amino-3-methyl-2-butanol melted at 172–174°.

Anal. Calc'd for $C_5H_{14}ClNO$: Cl, 25.29. Found: Cl, 25.75.

The oxalate of the 3-amino-2-butanol was prepared in alcohol and melted at 211–212°.

TABLE I

ALKYLENIMINES

IMINE	YIELD, %	B.P., °C	n_D^{25}	LIT.	d_{25}^{25}	% N FOUND	% N CALC'D
Ethylenimine	32	55–56	1.4123	(10)			
1,2-Propylenimine	65	63–64	1.4095	(11)			
1,2-Butylenimine	46	88–89	1.4165	(17)			
trans-2,3-Butylenimine	47	75–76	1.4070		0.7887	20.37	19.70
2,2-Dimethylethylenimine	68	69–70	1.4050	(9)			
2,2,3-Trimethylethylenimine	19	83–85			0.8020	15.82	16.44
2,2-Dimethyl-3-*n*-propylethylenimine	57	128–129	1.4240			12.59	12.37

Anal. Calc'd for $C_{10}H_{24}N_2O_6$: N, 10.44. Found: N, 10.51.

From the lower-boiling 3-amino-2-butanol, b.p./185 mm. 85–105°, n_D^{25} 1.4425, which was obtained impure and in the lesser amount of a combined 26% yield, an oxalate of m.p. 199–200° was obtained. Mixtures of the two oxalates gave intermediate melting points.

Anal. Calc'd for $C_{10}H_{24}N_2O_6$: N, 10.44. Found: N, 10.58.

The acid oxalates, which were readily interconvertible with the corresponding normal oxalates, were more soluble and melted at 164–165° and 135–145°, respectively.

From the 3-amino-2-butanol boiling at 116–119°, 185 mm., in a 30-in. Fenske column there was obtained by the Wenker method an impure lower-boiling imine, presumably the *dl*-2,3-butylenimine, b.p. 65–76°; n_D^{25} 1.4074; 17% yield and the *trans*-2,3-butylenimine, b.p. 76–77°; n_D^{25} 1.4105; 30% yield. The latter imine yielded the *trans*-2,3-butylenbenzenesulfonimide (24), m.p. 77–77.5°, after immediate pressing out on clay plate and one recrystallization from aqueous alcohol. If the Schotten-Baumann benzoylation was carried out with 10% instead of 5% sodium hydroxide, the product formed an oil crystallizing on dilution and melting at 230°.

After the method of Adams and Leffler (26) *meso*-2,3-butanediol (technical)[4] was con-

[3] The author is indebted to Dr. H. R. Snyder for carrying out some of the reductions in Organic Chemical Manufactures at the University of Illinois.

[4] Kindly supplied by Dr. G. E. Ward, Northern Regional Research Laboratory, U. S. D. A., and by the Heyden Chemical Corporation.

verted by hydrogen chloride to 2,3-dichlorobutane (57%) and 2,3-butylene chlorohydrin (15%); b.p./30 mm. 52–54°; d_4^{25} 1.0602 found; d^{25} 1 0610 reported (27) for *erythro*-2,3-butylene chlorohydrin. This was converted to the oxide, b.p. 53–55°; d_{25}^{25} 0.8008 found; d_{25}^{25} 0.8053 reported (28) for *trans*-2,3-butylene oxide; yield 55%. The oxide was treated with aqueous ammonia, yielding 3-amino-2-butanol; b.p. 150–160°; n_D^{25} 1.4435; 5% yield; oxalate 214–214.5°.

Trimethylenimine was prepared from N,N-trimethylene-*p*-toluenesulfonamide[5] which was reduced according to the directions of Howard and Marckwald (20) with sodium and isoamyl alcohol; yield 14%; b.p. 59.5–60.5°; n_D^{25} 1.4282.

Cyclopropylamine was prepared by the degradation, in the manner of Lipp, Buchkremer, and Seeles (22) of cyclopropane carbonamide[5] to the urethan in 73% yield. The urethan was hydrolyzed to cyclopropylamine hydrochloride, m.p. 85–86°, in a yield of 74% and the free cyclopropylamine liberated in 70% yield, b.p. 49–49.5°, n_D^{20} 1.4195.

Isolation of intermediates in polymerization of 2,2-dimethylethylenimine. 2,2-Dimethylethylenimine (42 g., 0.59 mole) freshly distilled was dissolved in 274 cc. of water, chilled to 10° and treated with 15.2 cc. of hydrochloric acid (5.121 *N*). The solution became turbid after two days at 25° and a white, flocculent precipitate had formed after three days. This precipitate was basic, contained a trace (less than 1.0%) of chlorine, was soluble in ether and in hot alcohol, m.p. 54–56°, η_{rel} 1.073 for a 1% solution in chloroform.

After eight days 100 cc. of 40% sodium hydroxide solution was added to free that part of the product existing as the hydrochloride and the gummy precipitate extracted with ether. A portion of the extract, dried with magnesium sulfate, was treated with ethereal hydrogen chloride forming a white, thready precipitate which could be dried and powdered.

Anal. Calc'd for $C_4H_{10}ClN$: Cl, 32.96. Found: Cl, 33.6.

The ether was distilled from the extract and the residue heated in a Claisen flask at a bath temperature of 175° and 1 mm. pressure for six hours; the distillation temperature rose gradually to 120° and then fell. The yellow residue solidified to a wax on cooling, yield 20 g.; η_{rel} 1.085 (1% in chloroform).

Anal. Calc'd for $(C_4H_9N)_n$: N, 19.70. Found: N, 19.70.

The distillate was redistilled in a 10-cc. modified Claisen flask yielding three fractions:

Fraction 1. (formula V) b.p. 67–80° at 23 mm., 1.5 g., n_D^{25} 1.4357, non-viscous; evolved nitrogen from nitrous acid.

Anal. Calc'd for $C_8H_{18}N_2$: N, 19.70. Found: N, 20.6.

Fraction 2. (formula VI) b.p. 95–100° at 2 mm., 4 g., n_D^{25} 1.4516, viscous.

Anal. Calc'd for $C_8H_{20}N_2O$: N, 17.45. Found: 17.15.

Fraction 3. (formula VII) b.p. 120–140° at 2 mm., 4 g., n_D^{25} 1.4593, viscous.

Anal. Calc'd for $C_{12}H_{27}N_3$: N, 19.70. Found: N, 19.14.

From fraction 1 was obtained an oxalate, m.p. 167–168°.

Anal. Calc'd for $C_{10}H_{20}N_2O_4$: N, 12.05. Found: N, 14.0.

From fraction 2 was obtained a phthalyl acetyl derivative (XIII) after the method of Hanford and Stevensen (25), m.p. 180–181°.

Anal. Calc'd for $C_{20}H_{26}N_2O_5$: N, 7.48. Found: N, 7.93.

β-Chloro-tert-butylamine hydrochloride. 2-Amino-2-methylpropanol hydrochloride (75 g., 0.6 mole), m.p. 195–196°, prepared from 2-amino-2-methylpropanol and alcoholic hydrogen chloride, was refluxed overnight with 300 cc. (500 g., 4.2 moles) of thionyl chloride. The thionyl chloride was distilled under reduced pressure and the product recrystallized from alcohol, m.p. 205–207°; yield 58 g., 65%.

Anal. Calc'd for $C_4H_{11}Cl_2N$: Cl, 49.23. Found: Cl, 48.6.

Less drastic treatment of the starting material caused very incomplete chlorination.

Reaction of β-chloro-tert-butylamine and 2-amino-2-methylpropanol. β-Chloro-*tert*-butylamine hydrochloride (54 g., 0.375 mole) was added to 94 g. (1.05 mole) 2-amino-2-methyl-

[5] The N,N-trimethylene-*p*-toluenesulfonamide and the cyclopropane carbonamide were prepared by Dr. G. H. Coleman and Dr. Chester M. McCloskey in Organic Chemical Manufactures at the State University of Iowa.

propanol and the viscous solution, which became somewhat warm, was heated overnight at 100°. The mixture was then dissolved in water, chilled, treated with 100 cc. of 40% sodium hydroxide solution, and extracted twice with 200 cc. of ether and twice with 200 cc. of chloroform. The extracts were dried with "Drierite", and after distillation of the solvent the residue was distilled through a 6-in., all-glass column packed with glass helices. There was recovered 40.5 g. 2-amino-2-methylpropanol, b.p./27 mm., 83–87° and obtained 29.5 g. of viscous product, b.p./18 mm. 110–130°; 50% yield. This product was redistilled yielding 12 g. of viscous liquid, b.p./1 mm. 80–82°, n_D^{25} 1.4637, and 9 g. of viscous liquid, b.p./1 mm. 90–120°, n_D^{25} 1.4700.

From the former fraction, 2-(β-aminoisobutylamino)-2-methyl-1-propanol, was obtained a phthalyl acetyl derivative (VIII) (27) of m.p. 179–180°; mixed melting point 179–180° with the phthalyl acetyl derivative from fraction 2 (VI) of the intermediates isolated from the polymerization of 2,2-dimethylethylenimine.

N-(β-aminoisobutyl)-2,2-dimethylethylenimine. 2-(β-Aminoisobutylamino)-2-methyl-1-propanol, b.p./7 mm. 105–110° (45 g., 0.28 mole) was converted to N-(β-aminoisobutyl)-2,2-dimethylethylenimine by sulfuric acid (58 g., 0.56 mole) in the Wenker method; yield 11 g., 28%, b.p. 23 mm. 40–45° (in 6-in. all-glass column), n_D^{25} 1.4398. The oxalate, prepared in absolute alcohol in the cold, melted at 160–161°; mixed melting point with oxalate of fraction 1 isolated from polymerization of 2,2-dimethylethylenimine was 163–165°. Recrystallization by heating or precipitation from water yielded a product melting at 195–205°.

The imine reacted vigorously with alcoholic hydrogen chloride yielding a crystalline hydrochloride which was recrystallized from aqueous alcohol, m.p. above 250°.

Anal. Calc'd for $C_8H_{20}Cl_2N_2$: Cl, 32.95. Found: Cl, 30.2.

Attempted preparation of N-[β-(β-aminoisobutylamino)isobutyl]-2,2-dimethylethylenimine. The second product from the reaction of β-chloro-*tert*-butylamine with 2-amino-2-methyl-1-propanol, presumably 2-(β-aminoisobutylamino)isobutylamino-2-methyl-1-propanol, (30 g., 0.13 mole) was converted by sulfuric acid (0.40 mole) to the imine by the Wenker method; yield 6.5 g. of b.p./2 mm. 115–130°, n_D^{25} 1.4663 and 5 g. of b.p./2 mm. 130–140°, n_D^{25} 1.4688. The former reacted vigorously with alcoholic hydrogen chloride, yielding a gum which was converted to a solid by shaking with absolute ether and which softened over a wide range.

Anal. Calc'd for $C_{12}H_{30}Cl_3N_3$: Cl, 32.95. Found: Cl, 29.4.

Reaction of isobutylene chlorohydrin and 2-amino-2-methyl-1-propanol. To 2-amino-2-methyl-1-propanol (445 g., 5.0 mole) refluxing in all-glass apparatus isobutylene chlorohydrin (274 g., 2.52 mole) was added dropwise. After refluxing overnight the solution was treated in the cold with excess 25% potassium hydroxide and the aqueous layer extracted with six 100-cc. portions of chloroform. The chloroform extracts were combined with the upper layer and the mixture distilled through a 6-in. all-glass heated still head packed with glass helices, yield 271 g., 67%, of 2-(β-hydroxyisobutylamino)-2-methyl-1-propanol, (IX), b.p./3 mm. 120–130°; n_D^{25} 1.4580.

The chlorodiacetyl derivative (X) of the above amino glycol was prepared by the reaction of acetic anhydride (51 g., 0.50 mole) with the 2-(β-hydroxyisobutylamino)-2-methyl-1-propanol (80 g., 0.50 mole), followed by the introduction of 18 g. (0.50 mole) of hydrogen chloride and the addition of 100 g. (1.28 mole) of acetyl chloride. The product was distilled through a 6-in. all-glass still head with some decomposition, yield 47 g., 37%, b.p./7 mm. 140–150°.

Anal. Calc'd for $C_{12}H_{22}ClNO_3$: Cl, 13.76. Found: Cl, 13.97.

Attempted reaction of this product with potassium phthalimide suspended in butyl alcohol yielded only phthalimide.

Conversion of 2-(β-hydroxyisobutylamino)-2-methyl-1-propanol to 2-(β-aminoisobutylamino)-2-methyl-1-propanol. After the method of Harvey and Caplan (14) for the alkylation of urea with a tertiary alcohol, urea (35 g.) was added to 130 cc. of sulfuric acid (conc'd) with mechanical stirring and cooling to keep the temperature below 30°. To the solution was added 75 g. of 2-(β-hydroxyisobutylamino)-2-methyl-1-propanol at a rate such that the

temperature was kept between 20–25°. Near the end of the addition stirring was nearly impossible.

After standing overnight the solution was poured on one liter of ice and neutralized to Congo red with 6 *N* sodium hydroxide. The sodium sulfate was filtered and the solution evaporated on the steam-bath with mechanical stirring and a purified air jet. The residue was filtered when nearly dry and washed with chloroform and alcohol (abs.). The combined filtrates were evaporated and the viscous residue dissolved in 200 cc. of water and heated overnight on the steam-bath with 200 cc. of 50% potassium hydroxide solution, an effervescence of ammonia occurring. The upper red layer was separated and the aqueous layer extracted three times with ether. The combined extracts and upper layer were distilled, yielding a first fraction, 19 g., b.p./1 mm. 50–55°, n_D^{25} 1.4350, a second fraction, 4.5 g., b.p./1 mm. 82–83°, n_D^{25} 1.4526, and a third fraction, 9 g., b.p./9 mm. 110°, n_D^{25} 1.4543, this last fraction being recovered 2-(β-hydroxyisobutylamino)-2-methyl-1-propanol.

From fraction 2 was obtained a phthalyl acetyl derivative after the method of Hanford and Stevenson (25) which melted at 179–180°, mixed m.p. with the phthalyl acetyl derivative of fraction 2 of the intermediates isolated from the polymerization of 2,2-dimethylethylenimine, 179–180°.

Tests of the polymerizability of the monomers. Evaporation of polymer solution gave a rough estimation of the concentration as indicated in the following experiment. A 4.483-g. portion of a 6.56% solution of polyethylenimine in ethylenimine, having a viscosity relative to pure ethylenimine of 1.90, was treated with a solution (2.257 *N*) containing 0.6212 g. of potassium hydroxide, distilled to dryness and baked on a steam-bath in a modified Claisen flask connected to an aspirator. There was a 0.9236 g. residue of constant weight, which would indicate an initial concentration of 6.75% after correction for the potassium hydroxide.

The tests of Table II were run in sealed tubes placed inside metal tubes and immersed in an oil-bath for the runs at 150°. After the run the tubes were chilled, opened, and the contents dissolved in 20 cc. of absolute alcohol. The solutions were placed in tared Petri dishes and evaporated to constant weight in a vacuum oven at 10 mm. and 50°. The boron trifluoride etherate was prepared according to the directions of Hennion, Hinton, and Nieuwland (29). The tests were run with 0.1-mole portions for the most part; where this was not the case the amount of catalyst was changed to keep a constant mole ratio of catalyst to monomer in a given experiment. The weights on evaporation after polymerization were corrected for the weight of catalyst, and in the case of runs at room temperature, for the weight of potassium hydroxide added to arrest polymerization. In the tests with cyclopropylamine, *trans*-2,3-butylenimine, and 2,2-dimethylethylenimine, the product was heterogeneous, having gummy precipitated polymer with a non-viscous upper layer with the first, a viscous upper layer with the second, and a white wax with the third.

A considerable amount of ammonia was evolved on opening the cyclopropylamine tube and this test blew up in several earlier experiments. The product was lower in nitrogen (13.43%) than would be calculated (19.3%) by assuming all of the catalyst to be retained.

Some further tests were made with cyclopropylamine sealed in 2-cc. portions in tubes with various catalyst and at the end of the test the cyclopropylamine recovered by distillation with the yield indicated.

In the last case most of the cyclopropylamine was converted to a brown layer above the water. This was viscous, basic, and mainly undistillable; yield 68%. A chloroform solution of this product yielded no precipitate on treating with alcoholic hydrogen chloride. The residue on evaporation had η_{rel} 1.008 (1% in water) and hence was probably not a polymer.

While 2,2-dimethylethylenimine underwent a refractive index change in aqueous solution parallel to the changes reported (1) with ethylenimine and propylenimine, the curve could not be calibrated with the 2,2-dimethylethylenimine because the polymer, somewhat slow to precipitate, was only slightly soluble in water. Trimethylenimine, 2,3-butyleni-

mine and 2,2,3-trimethylethylenimine underwent no refractive index change under the same conditions.

TABLE II

POLYMERIZATION EXPERIMENTS

MONOMER	INITIAL WT., G.	EXTENT POLYM. APPEARANCE	FINAL WT., G.	APPROX. PERCENTAGE POLYM.	η_{rel} FOR 1 % IN $CHCl_3$
5 MOLE PER CENT BORON TRIFLUORIDE ETHERATE, 24 HRS. AT 150°					
Ethylenimine	4.3	complete	7.4	100	1.084
Propylenimine	5.7	complete	6.0	100	1.134
1,2-Butylenimine	7.1	complete	7.3	100	1.115
trans-2,3-Butylenimine	7.1	medium	6.4	75	1.075
cis(impure)-2,3-Butylenimine	7.1	medium	3.1	50	1.045
2,2-Dimethylethylenimine	7.1	complete	7.4	100	1.103
2,2-Dimethyl-3-*n*-propylethylenimine	4.0	low	3.2	50	1.035
Trimethylenimine	1.68	complete	1.28	75	1.100
10 MOLE PER CENT BORON TRIFLUORIDE ETHERATE, 120 HRS. AT 150°					
2,2,3-Trimethylethylenimine	3.0	low	1.00	30	
2,2-Dimethyl-3-*n*-propylethylenimine	11.3	medium	4.43	39	
Cyclopropylamine	5.7	low	2.45	43	
trans-2,3-Butylenimine	3.56	complete	4.32	complete	1.114
3 MOLE PER CENT ALCOHOLIC HYDROGEN CHLORIDE, 24 HRS. AT 150°					
Ethylenimine	4.3	medium	4.5	100	1.052
Propylenimine	5.7	complete	6.0	100	1.093
1,2-Butylenimine	3.6	complete	4.0	100	1.085
trans-2,3-Butylenimine	1.58	medium	1.5	75	1.068
2,2-Dimethylethylenimine	7.0	complete	7.0	100	1.089

TABLE III

CYCLOPROPYLAMINE EXPERIMENTS

CATALYST	DURATION AND TEMPERATURE	% YIELD RECOV. MONOMER
None	36 hrs. at 150°	91
Cyclopropylamine hydrochloride 0.287 g.	36 hrs. at 150°	53
Potassium persulfate 0.155 g. and 0.2 cc. water	90 hrs. at 150°	77
Ascaridole, 0.5 cc.	90 hrs. at 150°	82
Benzoyl peroxide, U.V.L.	95 hrs. at 60°	93
Boron trifluoride, 0.0287 g.	36 hrs. at 150°	18
Perhydrol, 1.0 cc.	90 hrs. at 150°	slight

Trimethylenimine which had been converted to a syrup by heating at 150° for 15 hrs. with boron trifluoride was low in nitrogen content and had a low viscosity; η_{rel} 1.014, 1% in water.

Anal. Calc'd for $(C_3H_7N)_n$: N, 24.53. Found: N, 10.03.

A waxy residue from the distillation of trimethylenimine was dialyzed in a sack of non-

waterproofed "Cellophane" on a shaker with water circulated by distillation. The residue on evaporation (low yield) was still low in nitrogen (14.51%).

Likewise 2,2,3-trimethylethylenimine was somewhat difficult to polymerize. A portion heated 138 hrs. at 100 with 3.84 mole per cent boron trifluoride developed a viscosity relative to the monomer of approximately 48. This may be compared to the partly polymerized 2,3-dimethylethylenimine (obtained after six days at room temperature with 10 mole per cent boron trifluoride etherate) which had a viscosity relative to the monomer of 1.87 and was shown by evaporation to be 32% polymerized. Another portion of 2,2,3-trimethylethylenimine heated 6 days at 70° with 14.5 mole per cent of 2-methyl-2-aminoisobutylsulfuric acid and allowed to stand six months became about as viscous as did an ethylenimine test with 1.8 mole per cent β-aminoethylsulfuric acid in six days at room temperature.

Some β-chloroethylamine was polymerized by warming at 40° for three hours. The viscous mass which had a low relative viscosity (η_{rel} 1.006 for 1% aqueous solution) was benzoylated, yield 30% of brown powder, η_{rel} 1.033 (1% in chloroform); softening point (Dennis) 88°.

Anal. Calc'd for $(C_9H_9NO)_n$: N, 9.52. Found: N, 9.08.

Some polymerization tests were run for the purpose of checking the effect of monomer and catalyst concentration variation. In the first group varying amounts of 3 *N* alcoholic hydrogen chloride were added to 1-cc. portions of ethylenimine in test tubes. Some increase in viscosity was observable in the last three tubes after two days. After a week the polymerization was arrested by solution in alcohol, treatment with 5 cc. of 3 *N* potassium hydroxide, and evaporation in Petri dishes in a vacuum oven at 50° and 10 mm. The residue was corrected for the weight of the potassium hydroxide, 0.62 g.

cc. HCl	CORRECTED RESIDUE	% POLYMER	cc. HCl	CORRECTED RESIDUE	% POLYMER
0.012	0.34	41	0.06	0.68	82
.02	.44	53	.07	.76	91
.03	.53	64	.08	.80	96
.04	.59	71	.09	.79	95
.05	.65	78	.10	.84	101

When a preparative scale run was made with 200 times the amounts of one of the middle tests the heat was not dissipated and the reaction blew up.

With variation in the monomer concentration also the following tests were made over two days at room temperature.

ETHYLENIMINE, CC.	ABSOLUTE ALCOHOL, CC.	3 *N* ALC. HCl CC.	CORRECTED RESIDUE	% POLYM.
2	none	0.20	0.667	40.2
2	1	.20	.705	42.5
2	2	.20	.867	52.3
2	3	.20	.845	50.9
2	4	.20	.707	42.7
2	5	.20	.321	19.4

Some aqueous polymerizations were run with the proportions and duration found by the refractive index method (1) to produce quarter-life polymerization of ethylenimine.

ETHYLENIMINE, CC.	WATER, CC.	HCl (5.121 *N*), CC.	TIME, MIN.	CORRECTED RESIDUE, G.	% POLYM.	η_{rel} 1%
2.50	47.5	2.5	102	0.22	10.5	
5.00	45.0	2.5	150	0.42	10.1	1.012
7.50	42.5	2.5	206	1.38	22.2	1.016
10.00	40.0	2.5	252	2.65	32	1.040

A similar experiment was run with 2,2-dimethylethylenimine except that the solutions were made up to 50 cc. in volumetric flasks with aqueous alcohol (50% by volume) and all were interrupted after six hours.

2,2-DIMETHYLETHYLENIMINE, CC.	HCl (5.121 *N*), CC.	CORRECTED RESIDUE	% POLYM.
2.50	2.5	0.29	11.5%
5.00	2.5	.43	8.6
7.50	2.5	.60	8.0
10.00	2.5	.51	5.1

Ethylenimine (9.5 g., 0.221 mole) was polymerized with β-aminoethylsulfuric acid (0.5 g., 0.0035 mole) made in absolute ether and dried. After twenty-four hours a white precipitate clung to the walls of the vessel; most of the contents remained fluid but slowly thickened over two months to a honey-like liquid. This product was dialyzed to negligible conductivity and the concentration determined by evaporation of a sample and baking of the residue to constant weight on a steam-bath at reduced pressure; yield 3.5 g., 37%; η_{rel} 1.082 for 1% solution. The dialyte was evaporated to a 5 g. clear gummy residue of η_{rel} 1.041 for 1% solution.

The osmotic pressure of solutions of the dialyzed polyethylenimine was determined in an apparatus[6] similar to that used by Flory (30) except made of steel since solutions of the polymer attack brass. The glass-metal connections consisted of ground joints fixed with polyethylene glycol phthalate and metal stopcocks were used instead of needle-valves. "Cellophane", 600 PT, non-waterproofed was used as a membrane. The values obtained at 25.0° and the relative viscosities, all in water solution, are given below constant levels were reached in three days. A 0.1% aqueous solution of polyethylene oxide ("Carbowax 4000" Carbide and Carbon Chemical Corp.) produced a Δh of 0.50 cm.

C, %	Δh, CM.	π/c	η_{rel}
0.50	6.53	13.05	1.026
0.10	2.65	26.5	1.004
0.05	0.43	8.62	—

More work will be required to interpret these results but the polymer is apparently of lower molecular weight than "Carbowax 4000".

2,2-Dimethylethylenimine was the only polyimine obtained as a solid. The author was unable to duplicate the preparation by Ulrich and Harz (31) of a solid polyethylenimine by

[6] The apparatus was constructed by Mr. J. G. Sentinella, Physics Department, State University of Iowa.

polymerization with β-chloroethylamine and could not obtain a solid polyethylenimine except if it contained a large amount of salt-forming catalyst. To separate 5-cc. portions of ethylenimine were added 0.050 g. of β-chloroethylamine hydrochloride, 0.050 g. of β-chloroethylamine hydrochloride and 0.050 g. of sodium bisulfate, 0.050 g. of sodium bisulfate, 5 drops of β-aminoethylsulfuric acid, 6 drops of β-chloroethylamine (prepared by evaporation of an ethereal solution under reduced pressure), and to the last, 6 drops of β-chloroethylamine and 0.050 g. of sodium bisulfate. The tests yielded gummy polymers but no solid was formed in a month.

SUMMARY

1. The polymerization of 2,2-dimethylethylenimine has been shown to involve cleavage between the nitrogen and the primary carbon atom. The dimer and hydrolyzed dimer have been isolated and shown by synthesis to be N-(β-aminoisobutyl)-2,2-dimethylethylenimine and 2-(β-aminoisobutylamino)-2-methyl-1-propanol, respectively.

2. A group of alkylenimines was prepared and a rough comparison of their polymerization tendencies made; only those having a three-membered ring including at least one primary carbon polymerized readily.

3. The conclusion is drawn that the bimolecular inversion mechanism suggested in the preceding paper is applicable to homologs of ethylenimine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

ATTEMPTED PREPARATION OF POLYVINYLAMINE (1)

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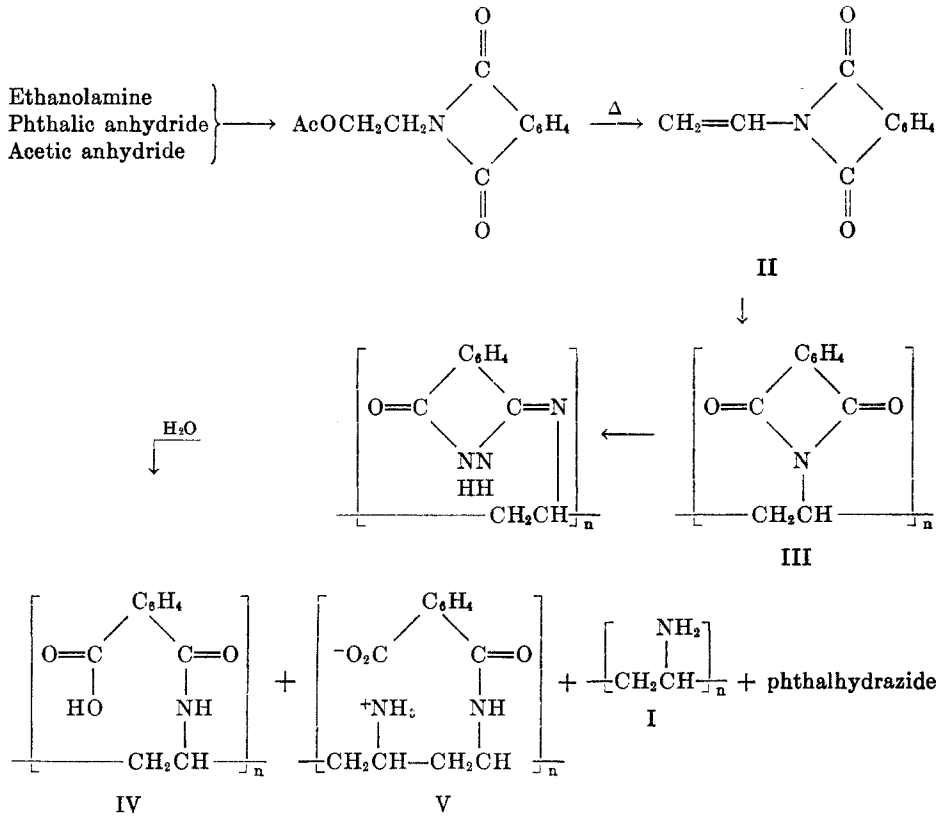
Like polyvinyl alcohol, polyvinylamine I is a desirable polymer for theoretical work because of high chemical reactivity and the possibility of correlating the structure of those polymers from which it might be made and those to which it might be converted. Like polyvinyl alcohol, polyvinylamine must be made indirectly since vinylamine does not exist.

Promising from the point of view of conversion to polyvinylamine is the work of Hanford and Stevenson (2) regarding the preparation and polymerization of



N-vinylimides. The preparation (3) of N-vinylphthalimide II from ethanolamine was selected as more suitable for laboratory work. Since Hanford and

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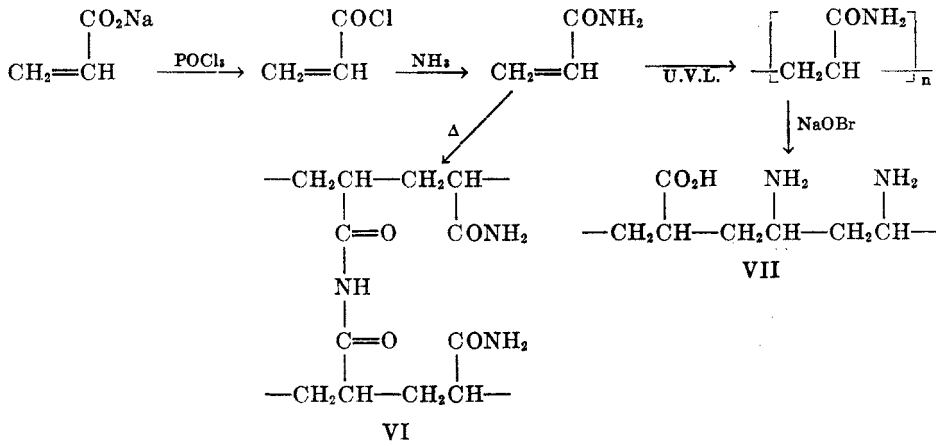
Stevenson (3) had pointed out the difficulty of obtaining complete hydrolysis of polyvinylphthalimide III, the hydrazine method of Ing and Manske (4) was employed, yielding however neither polyvinylamine nor the polyphthalamic acid IV but apparently the copolymer V.

Polynitroethylene, which might be expected to yield polyvinylamine on reduction, was obtained by Wieland and Sakellarios (5) as a white, high-melting powder by the polymerization of nitroethylene with alkali, water or light. [Homologs of nitroethylene are described by Nightingale and Janes (6) and by Schwarz and Nelles (7)]. Since nitroethylene, as well as the nearer homologs, is extremely irritating, and the dehydration of β-nitroethanol is difficult to control, the method of Riley and McBee (8) for the chlorination of anhydrous nitroethane in the β-position appeared to be a better source. On the addition of the chlorinated nitroethane to aqueous sodium bicarbonate dehydrochlorination and polymerization occur (9). The polynitroethylene so obtained in the present work was a brown powder running somewhat low in nitrogen and which could not be successfully reduced.

Another possible source of polyvinylamine would be the hypobromite degradation of polyacrylamide. Staudinger and Urech (10) pointed out that thermal polymerization of acrylamide yields an insoluble, cross-linked product VI presumably of imide structure (ammonia being evolved) and for this reason he

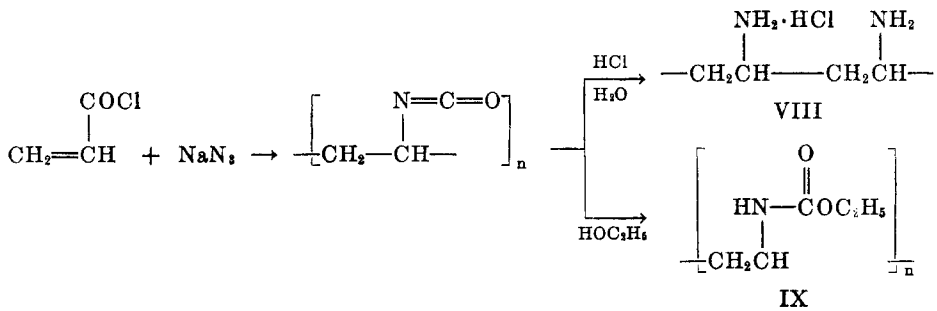


abandoned hypobromite degradation. The present authors found that the ultraviolet irradiation of an alcoholic solution containing acrylamide and benzoyl peroxide yields a water-soluble polyacrylamide which is a white powder. Hypobromite degradation of this product, followed by dialysis, yielded a basic gummy product VII of reduced nitrogen content, giving to its water solution considerable foaming tendency.

The previously undescribed polyvinylisocyanate was investigated as a source of polyvinylamine. The reaction of acrylyl chloride with sodium azide and spontaneous Curtius rearrangement (11) to vinylisocyanate was incomplete in

butyl ether. By distillation some acrylyl chloride could be recovered together with a trace of vinylisocyanate (12). Although acrylyl chloride is difficult to polymerize by itself, the constituents of this distillate copolymerized over the period of a day. The residue from the reaction mixture contained precipitated polyvinylisocyanate, which was extracted from the salts with dimethylformamide and precipitated in absolute ether as a tan, high-melting powder running slightly low in nitrogen.

When carried out in dimethylformamide the reaction was more complete, and yielded a polyvinylisocyanate of the correct nitrogen content although less completely soluble. In this solvent the reaction, once initiated, was more vigorous and required more temperature control. Due to the low solubility of polyvinylisocyanate in any aqueous medium, direct hydrolysis was difficult. Heating with concentrated hydrochloric acid yielded a water-soluble, solid, hygroscopic hydrochloride VIII, low in chloride content (as is the hydrochloride of polyethylenimine). This presumed hydrochloride could not be converted to polyvinylamine. Stirring at room temperature with freshly precipitated silver oxide



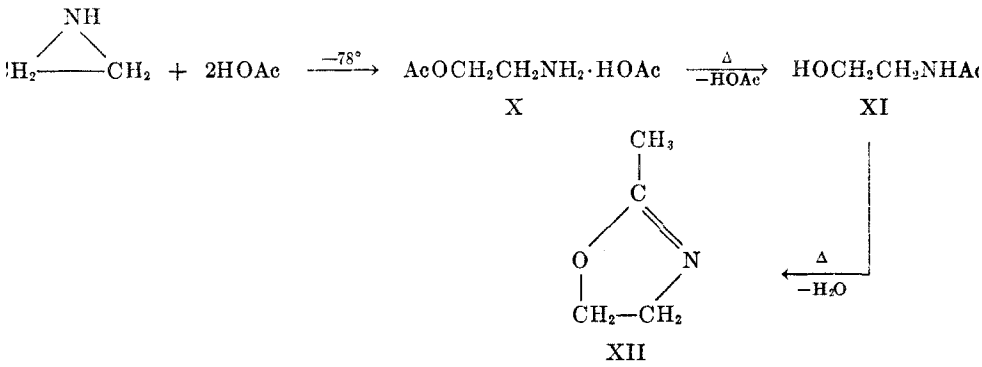
in alcohol resulted in oxidation. Treatment with aqueous sodium hydroxide and dialysis yielded a product of no increase in nitrogen content, ammonia being evolved during the alkali treatment.

A polyurethan was believed to have been obtained by long refluxing of polyvinylisocyanate with alcoholic hydrogen chloride. The water-soluble product had the nitrogen content of ethyl N-polyvinylcarbamate IX, but the nitrogen content was unaffected by saponification, followed by dialysis and evaporation.

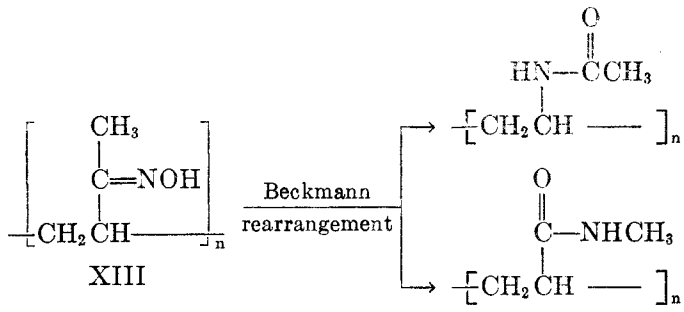
An alternative source considered for vinylisocyanate was the pyrolysis of β-acetoxyethylisocyanate, to be prepared from β-acetoxyethylammonium acetate X by the reaction with phosgene in the manner of Hanford (13). β-Acetoxyethylammonium acetate was found by the present workers to be produced when ethylenimine is treated with excess glacial acetic acid at −78° and the mixture allowed to warm slowly to room temperature. On heating, the salt loses acetic acid and rearranges to N-β-hydroxyethylacetamide XI, identified by comparison with a synthetic sample and by conversion to 2-methyl-Δ^2-oxazoline XII after the method of Wenker (14).

Due to the non-solubility in inert solvents and the low thermal stability of X, no volatile products were obtained from the reaction with phosgene.

The fifth source of polyvinylamine which was investigated was the Beckmann rearrangement of polyvinyl methyl ketoxime XIII, previously prepared by Marvel and Levesque (15). The present authors found it desirable to carry out the polymerization of the vinyl methyl ketone in concentrated dioxane solution in order to ensure obtaining a soluble polymer. The inhibition of vinyl methyl ketone polymerization by acetic acid as reported by Lange and Horn (16) was confirmed. It was hoped to facilitate the rearrangement by conversion of the



polyoxime to the picryl ether, since Chapman and Howis (17) found picryl ethers of oximes to rearrange spontaneously. Only slight acylation with picryl chloride or with *p*-bromobenzenesulfonyl chloride could be obtained; therefore it was attempted to carry out the rearrangement directly with acetyl chloride and phosphorus pentachloride. Saponification and steam distillation of the reaction product yielded a small amount of base which was neither ammonia nor methylamine and since the residue was very much lower in nitrogen, it was indicated that hydrolysis of the apparently unrearranged polyoxime had occurred.



Since the success of a reaction on a polymer often depends on finding the right conditions (particularly the right solvent), it was thought worth while to report

these attempts, although unsuccessful, in the hope that they will enable some other investigator to modify them, and thus successfully complete the synthesis.

EXPERIMENTAL PART

Vinylphthalimide. After the method of Hanford (3) β-phthalimidoethyl acetate[3] (30 g. 1.29 moles) was charged into a separatory funnel electrically heated with wires embedded in a hardened asbestos and sodium silicate paste. This funnel was connected by a rubber stopper to a 20-mm. Pyrex tube packed with pieces of Pyrex rod and heated by a slanting 13-in. combustion furnace to 560–575°. The receiver was a 1-liter flask connected with the pyrolysis tube by a ground joint and bearing a side arm leading to a hood.

The melted β-phthalimidoethyl acetate was dropped into the pyrolysis tube at one drop per second. The brown pyrolysate was vacuum distilled at 18 mm. to remove acetic acid and the residue was distilled through a 6-in. all-glass column packed with glass helices, b.p./0.5 mm. 115–120° or b.p./2.5 mm. 128–130°. The distillate solidified to a yellow solid which was recrystallized from alcohol; m.p. 85–86°; yield 225 g. or 90%.

Polymerization of vinylphthalimide. Vinylphthalimide (100 g., 0.58 mole) was mixed with 0.05 g. of benzoyl peroxide ("Lucidol") and heated in a test tube at 100° for 24 hours, yielding a hard, transparent, orange solid, soluble in phenol and in dimethylformamide.[4]

In one case the polymer was dissolved in 1 kg. of redistilled phenol and the steam-heated solution aspirated during two days into mechanically stirred water in a 3-liter five-necked flask (18), the polymer being collected on towelling. The white solid was stirred overnight with distilled water and after air-drying was readily powdered; yield 30%; η_{rel} 1.406 (1% in dimethylformamide); softening point 227° (Dennis).

Anal. Calc'd for $(C_{10}H_7NO_2)_n$: N, 8.09. Found: N, 8.90.

It was found more satisfactory to precipitate the polymer by aspirating a solution of 100 g. of polyvinylphthalimide in 800 g. of warm dimethylformamide into 4 liters of stirred ether contained in a beaker in a good hood. The ether volume was maintained by additions. The white powder which formed was washed with ether and dried, yield 61%, and the dimethylformamide recovered in good yield from the ether; η_{rel} 1.387 (1% in dimethylformamide); softening point 232° (Dennis).

Anal. Calc'd for $(C_{10}H_7NO_2)_n$: N, 8.09. Found: N, 9.70.

Reaction of polyvinylphthalimide with hydrazine. The reaction of polyvinylphthalimide with hydrazine was much more rapid in the absence of alcohol, used as a diluent by Ing and Manske (4). Polyvinylphthalimide (20 g.) dissolved readily in 100 cc. of 85% hydrazine hydrate on warming. A portion of the resulting syrup was evaporated to a white powder which was washed with dioxane; this product had η_{rel} 1.35 for a 1% aqueous solution; m.p. 152° (Dennis).

Anal. Calc'd for $(C_{10}H_9N_3O)_n$: N, 22.44. Found: N, 24.78.

A solution of the above syrup in 100 cc. of water was refluxed two days, no phthalhydrazide forming. A portion was evaporated to a white powder of unchanged nitrogen content (24.09%), η_{rel} 1.454; softening point 135–170° (Dennis).

Acidification (in one experiment with conc'd sulfuric acid, in another with conc'd hydrochloric acid) produced a precipitate, drying to a white powder, yield 19 g.; softening point 225° (Dennis). This product was soluble in alkali; η_{rel} 1.196 for a 1% solution in 4% sodium hydroxide solution.

Anal. Calc'd for $(C_{12}H_{14}N_2O_{13})_n$ (a one-to-one copolymer of N-vinylphthalamic acid and vinylamine): N, 12.01, Found: N, 15.95.

The filtrate from the above contained hydrazine sulfate (or chloride) washed from the

[3] The authors are indebted to Dr. G. H. Coleman and Mr. Ronald Pyle for preparing the compound in Organic Chemical Manufactures at the State University of Iowa.

[4] The authors are indebted to Dr. W. W. Beck, Ammonia Department, duPont Experimental Station, for supplying dimethylamine and a sample of dimethylformamide.

above precipitate with hot water. The viscosity was low (η_{rel} 1.02) and dialysis (which was carried out in a shaker with water circulating by distillation and with non-waterproofed "Cellophane" bags) produced a precipitate (4 g.) of basic gum of medium nitrogen content (17.63%).

To 23 g. of the partly hydrolyzed polyphthalamic acid was added 200 cc. of dilute (one-to-one) hydrochloric acid and the mixture heated overnight on the steam-bath. There was a 13-g. insoluble residue of phthalhydrazide, recrystallized from water, m.p. 335° (Dennis) η_{rel} 1.022 for 1% solution in 4% sodium hydroxide solution.

Anal. Calc'd for $C_8H_6N_2O_3$: N, 17.28. Found: N, 17.71.

The filtrate had appreciable viscosity, η_{rel} 1.267 (relative to water) but dialysis left only a 0.2-g. neutral residue of low nitrogen content (3.89%).

The partly hydrolyzed polyphthalamic acid (7 g.) slowly dissolved with shaking in 30 cc. of 50% potassium hydroxide, becoming warm. On cooling, there formed a 4.5-g. precipitate which was water-soluble; η_{rel} 1.073 for 1% aqueous solution. Dialysis and evaporation left a 0.2-g. tan alkaline residue of medium nitrogen content (13.65%).

Concentration of the alkaline solution yielded a 6.5-g. second crop η_{rel} of 1.101 for a 1% solution in 4% sodium hydroxide and dialysis of this yielded on evaporation a 0.1-g. tan, alkaline powder of slightly higher nitrogen content (16.54%).

Reaction of vinylphthalimide with hydrazine. Vinylphthalimide (50 g., 0.29 mole) was dissolved on warming in 450 cc. of absolute alcohol and hydrazine hydrate (11 g., 85%, 0.18 mole) added. On cooling, a slightly yellow crystalline precipitate formed, yield 28 g., m.p. 110–112° with puffing, which decolorized bromine in dimethylformamide solution.

Anal. Calc'd for $C_{10}H_9N_3O$: N, 22.44. Found: N, 21.3.

On hydrolysis with dilute hydrochloric acid and treatment of the distillate with 2,4-dinitrophenylhydrazine there was obtained in low yield after six crystallizations, acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 162–163°, mixed m.p. 163–165°.

From the initial reaction a second crop (10 g.) was phthalhydrazide, and this resulted as a sole product when 95% alcohol was used as the solvent.

On standing three months the product melting at 110–112° changed to a high-melting material shrinking only slightly at 110°; however, the viscosity (1% in dimethylformamide) was unchanged, η_{rel} 1.035. A sample of the product melting at 110–112° heated in a test tube in an oil-bath at 130° slowly sintered and vinylphthalimide sublimed from the residue, which had unchanged viscosity. A sample (6 g.) of the product melting at 110–112° was dissolved in 300 cc. of ethylene glycol monoethyl ether ("Cellosolve") with 0.5 g. of benzoyl peroxide and placed under ultraviolet light for several days, forming a slight precipitate. The filtrate had the viscosity 1.031, relative to "Cellosolve".

A sample (5 g.) of the product melting at 110–112° was mixed well with 0.5 g. of benzoyl peroxide and heated overnight in a test tube in an oil-bath at 140°. The product was washed with alcohol, leaving a sandy residue, 3.5 g., of η_{rel} 1.045 for 1% solution in dimethylformamide.

Preparation of polynitroethylene. Dry nitroethane was chlorinated and dehydrochlorinated with simultaneous polymerization (8, 9). The nitroethane was dried by distillation from phosphorus pentoxide under reduced pressure in a modified Claisen flask with an ice-cooled glass coil for condensation, b.p./26 mm. 49–54°, yield 85% of yellow product turning light brown on storage over phosphorus pentoxide in the ice box. Distillation from phosphorus pentoxide at atmospheric pressure is attended by decomposition.

Chlorination proceded slowly when the flask was surrounded by three 300-watt non-frosted bulbs. For example, ninety-six hours was required for two-thirds the theoretical weight increase in the chlorination of 163 g. (2.2 moles) of anhydrous nitroethane containing 32 g. of phosphorus pentoxide. The heat of the light bulbs was dissipated with a fan. The rate could be increased by a factor of three in a flask surrounded at 1 cm. distance by six 300-watt non-frosted bulbs in 10-in. reflectors but to prevent decomposition it was necessary to cool by mechanical stirring and with two cold fingers sealed into the reaction flask.

A sulfuric acid trap connected to the gas outlet from the reaction flask was practically

unchanged in weight. Distillation of the chlorinated mixture is contraindicated, since decomposition to the intensely irritating nitroethylene occurs.

The above solution of β-chloronitroethane in nitroethane was added in small portions to 2.5 liters of 1 *M* sodium bicarbonate solution which was well stirred. The evolution of carbon dioxide was vigorous and a brown solid precipitated, the solution becoming warm. The reaction was apparently incomplete when carried out below 5°, a brown gum with irritating odor being obtained. After the dehydrochlorination, the solution was acidified with hydrochloric acid and then stirred with dilute hydrochloric acid overnight (a procedure which increased the nitrogen content 1.4% in absolute value). The product was readily powdered on drying, yield 48 g.; η_{rel} 1.076 (1% in "Cellosolve"); decomposition point 175° (Dennis).

Anal. Calc'd for $(C_2H_3NO_2)_n$: N, 19.18. Found: N, 17.3.

Solution in "Cellosolve" containing 10% *n*-butylamine (which improved the solubility), and precipitation in water (yield 55%) did not lighten the color or raise the nitrogen content.

Reduction of polynitroethylene. A solution of 15 g. (0.20 base mole) of polynitroethylene in 90 cc. "Cellosolve" and 10 cc. of *n*-butylamine was slowly and incompletely hydrogenated under low pressure with platinum oxide catalyst, about half the theoretical amount of hydrogen being absorbed in fifty hours. Precipitation of the filtered solution in water yielded a 12-g. dark, neutral residue of lowered nitrogen content (13.64%), softening point above 320°, η_{rel} 1.141 (1% in "Cellosolve" and 10% butylamine). Evaporation of the filtrate yielded a 3-g. gummy, neutral residue, converted to a tan powder by suspending in alcohol and pouring into ether. This product also had lowered nitrogen content (12.99%); η_{rel} 1.068 (1% in "Cellosolve"), softening point 90° (Dennis).

Polynitroethylene (100 g.) dissolved in 800 cc. of "Cellosolve" containing 50 cc. of *n*-butylamine and 30 g. of Raney nickel was hydrogenated at 25 atm. The reaction mixture became warm but cooled on shaking overnight. Although less than the theoretical amount of hydrogen was absorbed there was no further absorption on steam heating. Precipitation in water yielded 60 g. of black neutral powder. The filtrate, which foamed badly under reduced pressure, was evaporated in an air-jet on a steam-bath with mechanical stirring, yielding 17 g. of black gum of lowered nitrogen content (13.50).

Polynitroethylene (10 g., 0.137 base mole) was dissolved in 85 g. of "Cellosolve" containing 5 g. of diethylamine. To the solution was added 20 cc. of water, 46.7 g. (0.714 mole) of granulated zinc, and 119 cc. of hydrochloric acid (conc'd). The mixture was warmed on the steam-bath an hour until the zinc dissolved. Sodium hydroxide was added to precipitate most of the zinc salts which were filtered and the filtrate dialyzed; yield, 3 g. of black hygroscopic powder of η_{rel} 1.063 (1% in water) and lowered nitrogen content (5.85); m.p. above 300°.

Preparation of acrylamide. Acrylamide was prepared from acrylyl chloride after the method of Moureu (19), the acrylyl chloride being prepared from sodium acrylate and phosphorus oxychloride in the manner of the same investigator.

Acrylic acid (60% aqueous solution) was converted to sodium acrylate at 0° with an alcoholic paste of sodium hydroxide, since neutralization with aqueous sodium hydroxide yielded the polymeric salt. The sodium acrylate was washed with acetone and dried in air after a preliminary drying in an oven at 100°. In the oven sudden and rapid charring occurs when the product is dry.

To a paste of 200 g. (2.13 moles) of sodium acrylate in 400 g. of heavy mineral oil was slowly added at 0° 170 g. of phosphorus oxychloride, a vigorous reaction occurring. When the addition was completed the mixture was refluxed one hour on a steam-bath and then distilled with a metal-bath, the bath temperature being gradually raised to 300° and maintained at this temperature until no further distillate was obtained. To the distillate was cautiously added 5 g. of sodium acrylate which decomposed any excess phosphorus oxychloride. This distillate was then redistilled in a 6-in. all-glass column packed with glass helices; b.p. 74–75°, yield 80%. All operations with acrylyl chloride were conducted in the hood since it is very irritating.

In 1 liter of dry benzene was dissolved 100 g. of acrylyl chloride and with water-cooling dry ammonia was bubbled through the solution until no odor of acrylyl chloride was evident. The solution was heated to boiling and filtered through a heated Büchner funnel. The precipitate was digested with three 1-liter portions benzene and filtered. From the combined filtrate on cooling large flakes of acrylamide formed, yield 62 g., 80%, m.p. 84–85°.

Polymerization of acrylamide. To a solution of 25 g. (0.35 mole) of acrylamide in 100 cc. of alcohol was added 0.1 g. of benzoyl peroxide ("Lucidol"). The solution was placed under a Hanovia ultraviolet light; precipitation of polymer began in twenty-six hours and was complete after four days, no acrylamide being recoverable. The alcoholic filtrate was neutral. The white solid was filtered, dried, and powdered; it was completely water-soluble; η_{rel} 1.80 (1% in water); K value (20), 53.9; softening point 188° (Dennis).

Anal. Calc'd for $(C_3H_5NO)_n$: N, 19.71, Found: N, 19.3.

An insoluble polyacrylamide was obtained by thermal polymerization with benzoyl peroxide. With 25 g. of powdered acrylamide was mixed 0.06 g. of benzoyl peroxide and the mixture heated at 111° for three hours, the powder melting to a yellow gummy mass which turned into a horny yellow solid. The solid could be powdered in a ball mill and was insoluble in all the common solvents.

Hypobromite degradation of polyacrylamide. In a cold solution of sodium hydroxide (400 cc., 40%) was dissolved 18 g. (0.25 mole) of polyacrylamide and 40 g. (0.25 mole) of bromine was slowly added while the solution was stirred vigorously and maintained below 0°. After the addition the solution was warmed at 80° until a test with acidified potassium iodide was negative. Schotten-Baumann benzoylation followed by slight acidification (not to the point of precipitation of benzoic acid) yielded 1 g. of brown powder, η_{rel} 1.082 (1% in 0.5 *N* hydrochloric acid), amphoteric in behavior and containing both nitrogen (12.1%) and chlorine (39.3%).

Bromination at 0° without excess alkali yielded an incompletely brominated precipitate (9 g. from 18 g. of polyacrylamide).

Anal. Calc'd for C_3H_4BrNO: Br, 53.29. Found: Br, 19.9.

This was soluble in 30% potassium hydroxide but after two hours at 75° still contained bromine on precipitation by acidification.

Polyacrylamide (27 g., 0.38 base mole) was dissolved with mechanical shaking in 750 cc. of water and added at 5° to a stirred mixture of potassium hypobromite made from 22.4 g. (0.40 mole) of potassium hydroxide in 200 cc. of water and 61 g. (0.38 mole) of bromine. The red solution was poured into 1 liter of hot 50% potassium hydroxide and the colorless solution heated two days on the steam-bath, turning yellow. The solution was dialyzed after the filtration of potassium bromide which crystallized on cooling. There formed in the dialysis a 2.0-g. neutral precipitate of lowered nitrogen content (11.29%) and evaporation yielded a 3-g. alkaline, brown powder of lowered nitrogen content (9.72%).

In another experiment the hot alkali treatment was shortened to one-half hour, yielding after dialysis and evaporation 2.5 g. (from 5 g. of polyacrylamide) of neutral, yellow powder of lowered nitrogen content (14.98%). The 1% solution after dialysis had η_{rel} 1.131 but after evaporation the product was insoluble.

Reaction of sodium azide with acrylyl chloride. To 300 g. (4.6 moles) of sodium azide, activated with hydrazine according to the directions of Nelles (21), suspended in 2 liters of purified and freshly distilled butyl ether was added 317 g. (3.5 moles) of acrylyl chloride. The 5-liter three-necked reaction vessel was provided with a separatory funnel, mercury-sealed stirrer, and "Dry-ice" trap; the addition of the acrylyl chloride required one hour while the mixture was stirred at a bath temperature of 90°. Stirring at this temperature was continued overnight, the contents of the trap having been returned to the flask; however, nitrogen evolution was quite slow after two hours. Only 45 liters of nitrogen, representing a 52% yield, had been collected by this time in a carboy connected to the trap.

The stirrer was removed and the mixture distilled to dryness at 22 mm. with two "Dry-ice" traps in series connected to the receiver. The butyl ether recovered was redistilled through a 24-in. Vigreux column and the low fraction, b.p./17 mm. 22–40° combined with

the contents of the traps. The combined volatile products were fractionally distilled in a 6-in. column (all-glass) packed with glass helices. There were obtained four fractions: a small fore-run of ethyl ether which had adhered to the sodium azide, a small fraction (5 g.) which on redistillation boiled at 48–50°, n_D^{25} 1.3735, a 7-g. impure intermediate fraction, and 62 g. (20%) of recovered acrylyl chloride, b.p. 70–80°.

A white solid which precipitated from the 48–50° fraction was indicated to be a copolymer of vinylisocyanate and acrylyl chloride.

Anal. Calc'd for $(C_3H_3NO)_n$: N, 20.37. Found: N, 16.4.

Likewise from the distilled butyl ether a white solid precipitated during several days, yield 10 g.; it is indicated that copolymerization of acrylyl chloride and vinyl isocyanate proceeds under conditions that do not cause polymerization of acrylyl chloride.

Anal. Calc'd for $(C_3H_3NO)_n$: N, 20.37. Found: N, 7.80.

A portion of the impure vinylisocyanate was precipitated from ether with ammonia gas. The precipitate was steam distilled from an acidified solution into a "Dry-ice" trap containing alcohol. From the distillate the 2,4-dinitrophenylhydrazone of acetaldehyde was isolated, m.p. 166–167° after six recrystallizations, mixed m.p. with known sample 165–166°. No urea could be isolated, a polymer having been formed.

From the residue of salts there was obtained on repeated extraction with dimethylformamide, clarification by centrifuging, and precipitation by spraying into absolute ether a tan powder, polyvinylisocyanate, yield 75 g., 30%, η_{rel} 1.060 (1% in dimethylformamide).

Anal. Calc'd for $(C_3H_3NO)_n$: N, 20.37. Found: N, 18.90.

The polyvinylisocyanate turned brown at about 200° (Dennis bar) and a sample heated in a test tube in an oil-bath at 200° for one hour shrank to a brown dried coating; a sample heated in a test tube in a free flame gave off liquid and gas decomposition products, in both cases however the residues were completely soluble in dimethylformamide.

Several Curtius reactions were run in dimethylformamide since the polyvinylisocyanate is insoluble in butyl ether and coats the sodium azide. No volatile products were obtained in the dimethylformamide but the nitrogen evolution occurred at a higher temperature (about 90° instead of 60°). If external heating was employed the polymer was mainly insoluble. Runs made without external heating lost nitrogen violently when the acrylyl chloride addition was rapid or when the reaction mixture was placed on a steam-bath after the acrylyl chloride addition. A suspension of polyvinylisocyanate in dimethylformamide was obtained; after precipitation in ether the polymer could be only partially redissolved. The insoluble fraction ran closer to the theoretical nitrogen content.

Anal. Calc'd for $(C_3H_3NO)_n$: N, 20.37. Found: (for soluble fraction) N, 16.17; (for insoluble fraction) N, 20.01.

Hydrolysis of polyvinylisocyanate. Polyvinylisocyanate (21 g.) made in butyl ether was dissolved by heating overnight on a steam-bath with concentrated hydrochloric acid. The dark solution was evaporated and dried in a vacuum desiccator. It could then be converted (by solution in absolute alcohol and precipitation into a large excess of absolute ether) into a brown hygroscopic powder which was soluble in dilute hydrochloric acid but not in water.

Anal. Calc'd for $(C_2H_6ClN)_n$: N, 17.61; Cl, 44.58. Found: N, 27.1; Cl, 28.9.

It was attempted to liberate the polyvinylamine by stirring the above product in alcoholic solution overnight with excess freshly precipitated and carbonate-free silver oxide. Separation from silver oxide (and metallic silver) by centrifuging and alcohol-extracting left a 6-g. *acidic* residue of decreased nitrogen content (18.7%); this residue was water-soluble and could be dried to a brown powder.

Polyvinylisocyanate (100 g.) made in dimethylformamide was dissolved by stirring overnight at 100° with concentrated hydrochloric acid. The dark solution was made alkaline below 50° (some ammonia evolved) and dialyzed. Evaporation yielded 7 g. of hygroscopic black powder insoluble in absolute alcohol: η_{rel} 1.022 (1% in water); softening point 240° (Dennis).

Anal. Calc'd for $(C_2H_5N)_n$: N, 32.53. Found: N, 14.33.

Alcoholysis of polyvinylisocyanate. Polyvinylisocyanate (18 g.) made in butyl ether was slowly dissolved by refluxing thirteen days with 500 cc. of absolute alcohol. A poor yield (8 g.) of urethan was obtained by pouring into absolute ether since the product tended to be gummy until dry and several reprecipitations were necessary to obtain the tan powder; η_{rel} 1.062 (1% in dimethylformamide); softening point 90° (Dennis); η_{rel} 1.040 (1% in water).

Anal. Calc'd for $(C_5H_{10}NO_2)_n$: N, 12.06. Found: N, 13.34.

In another experiment polyvinylisocyanate (61 g.) was subjected to long refluxing with alcoholic hydrogen chloride yielding a soluble product similar to that above and an alcohol-insoluble, water-soluble second product, yield 22 g.

Anal. Calc'd for (C_2H_6ClN): Cl, 44.58. Found: Cl, 53.10.

Polyvinylisocyanate (10 g.) made in dimethylformamide was partially dissolved in alcoholic dimethylformamide (10 cc. of abs. alcohol to 100 cc. of dimethylformamide) and the mixture refluxed three days in an oil-bath. There was a 5-g. insoluble residue; precipitation of the filtrate in absolute ether yielded 3 g. of brown, water-soluble powder: η_{rel} 1.151 (1% in water).

Anal. Calc'd for $(C_5H_{10}NO_2)_n$: N, 12.06. Found: N, 18.71.

Polyvinylisocyanate (10 g.) made in dimethylformamide was refluxed with 250 cc. of dry pyridine and 20 cc. of absolute alcohol four days in an oil-bath. There was a 7-g. powdery, water-soluble, neutral precipitate of medium nitrogen content (15.08%) and evaporation of the filtrate left a gummy residue converted by stirring with ligroin to 1 g. of brown powder.

Anal. Calc'd for $(C_5H_8N_2O)_n$ (a polyurea): N, 24.99. Found: N, 26.64.

The polyurethan (7 g.) described first was saponified, dissolving on shaking two days with 200 cc. of 25% potassium hydroxide. The odor of ammonia was strong on opening the bottle. Dialysis yielded 2 g. of brown powder of medium nitrogen content (13.31%); softening point 280° (Dennis).

Reaction of ethylenimine with acetic acid. To 11 g. (0.25 mole) of ethylenimine cooled to −78° and stirred by hand was added dropwise 30 g. (0.50 mole) of glacial acetic acid. The mixture was allowed to warm slightly to facilitate mixing and chilled again, becoming totally solid in a few minutes. This product melted on slowly warming to room temperature as the "Dry-ice" disappeared but no exothermic polymerization occurred such as did occur when acetic acid was added slightly more rapidly. An acid oxalate was prepared in alcoholic solution but contained twice the theoretical nitrogen content indicating contamination with polyethylenimine oxalate.

To 5 g. of the ethylenimine-acetic acid reaction product was added 7.5 g. of powdered phthalic anhydride and the mixture refluxed one hour. The water produced was distilled under reduced pressure and the residue which solidified was twice recrystallized from absolute alcohol; yield 2 g.; m.p. 85.5–86°; mixed m.p. with known β-phthalimidoethyl acetate 86–87°.

In a 25-cc. modified Claisen flask 20 g. of the above reaction product of ethylenimine with acetic acid was distilled until 9 g. of acetic acid was obtained at 115°. The residue was then distilled at 20 mm., yielding 7 g., b.p./20 mm. 175–177°, of product with an amide odor and which gave no precipitate with alcoholic oxalic acid. On redistillation, the product retained an alkaline reaction to litmus; b.p./4 mm. 154–155°; n_D^{20} 1.4572, and was mainly N-β-hydroxyethylacetamide.

The alkaline reaction was presumably due to some conversion to 2-methyl-Δ^2-oxazoline and the conversion was completed after the method of Wenker (14) by heating 10 g. with a Rose metal-bath to 260–280°, the vapor temperature not rising above 160°. The 5 cc. of distillate was dried with solid potassium hydroxide and redistilled in a 10-cc. modified Claisen flask, yielding 3 cc. of distillate, b.p. 123–125°, with a strong amine odor; b.p. 124–125° reported (19) for 2-methyl-Δ^2-oxazoline. This product yielded a picrate recrystallized from alcohol, m.p. 160–161° found, m.p. 159–160° reported (19).

After the general method of White (22), 24.4 g. (0.25 mole) of ethanolamine hydro-

chloride, m.p. 79–80°, was dissolved in 500 cc. of methanol and shaken three hours with 41.7 g. (0.25 mole) of silver acetate and acetic anhydride. After filtration of the silver chloride the product was distilled at 20 mm. pressure but decomposed violently before distillation was completed. Similar results were obtained when the reaction of β-chloroethylamine hydrochloride and silver acetate was attempted.

A successful synthesis of N-β-hydroxyethylacetamide was obtained by the addition of 17 g. (0.16 mole) of acetic anhydride in small portions to 20 g. (0.33 mole) of ethanolamine in 150 cc. of methanol. The mixture was evaporated at 90° and distilled in a 50-cc. modified Claisen flask, b.p./2 mm. 140–143°; yield 16.5 g., 97%; n_D^{20} 1.4720. The product gave an alkaline reaction to litmus.

Reaction of phosgene with the ethylenimine and acetic acid reaction product. According to the directions of Hanford (13) for the preparation of isocyanates from salts of primary amines, a solution of 40 g. (0.405 mole) of phosgene in 225 cc. of toluene was treated with 26 g. of the ethylenimine and acetic acid reaction mixture prepared as described above. The cold mixture was shaken and phosgene introduced. The viscous ethylenimine and acetic acid reaction product swelled but did not dissolve even when the solution was heated two hours on the steam-bath with phosgene passing in.

The toluene was distilled under reduced pressure with a cold trap in the line. The combined contents of the trap and receiver were fractionally distilled but contained only toluene. The residue from the phosgene reaction was a viscous water-soluble liquid presumably a reaction product with polyethylenimine; yield 6 g.

To obtain an indication of the proportion of β-acetoxyethylammonium acetate and polyethylenimmonium acetate in the ethylenimine and acetic acid reaction mixture, a portion (15 g.) was dissolved in 44 cc. of benzenesulfonyl chloride and added in portions and with vigorous shaking to 200 cc. of 20% sodium hydroxide. An alkali-insoluble white powder, presumably polyethylenimine benzenesulfonamide, was obtained, m.p. 68° (Dennis bar); yield 9.5 g. or practically quantitative; η_{rel} 1.035 (1% in dimethylformamide).

Anal. Calc'd for $C_8H_9NO_2S$: N, 7.65. Found: N, 6.11.

Beckmann rearrangement of polyvinyl methyl ketoxime. Vinyl methyl ketone was prepared in 10–15% yield by the method of Wohl and Prill (23), a few modifications being necessary to obtain even this yield. The formalin was ice-cooled during the initial neutralization with alkali. In the distillation of the unreacted acetone the use of a fractionating column was essential and it was necessary to remove the last traces of acetone by distilling at about 60 mm. until the boiling point of water at the particular pressure was reached. The pyrolysis of the methylolacetone was carried out in 600-g. portions. During drying of the crude vinyl methyl ketone a few drops of glacial acetic acid was added to keep the solution faintly acidic during the five dryings with sodium sulfate. This was followed by drying with "Drierite" and the dried ketone was distilled at 130 mm., b.p. 33–35°, in a fractionating column with a "Dry-ice" trap and manostat in the line.

The vinyl methyl ketone was polymerized after the method of Marvel and Levesque (15) except that an insoluble product was obtained unless the polymerization was carried out in 75% solution in dioxane with 0.5% benzoyl peroxide and removed from the heating-bath after about three hours at 55° and before gelation. Polymerization was 38% complete as determined by evaporation of a sample. Acetic acid was an inhibitor as reported by Lange and Horn (16) since the addition of one drop of glacial acetic acid to 6.4 g. of vinyl methyl ketone containing 0.5% benzoyl peroxide prevented polymerization during four days at 55°.

Polyvinyl methyl ketoxime (15) was prepared from the incompletely polymerized mixture with excess hydroxylamine the reaction product of the monomer remaining soluble. The polyoxime was soluble in dilute strong alkali or acid; no other solvents were found.

In 10 cc. of 0.5 *N* sodium hydroxide was dissolved 1 g. of polyvinyl methyl ketoxime and in small portions 2.9 g. of picryl chloride and 1.4 cc. of 0.5 *N* sodium hydroxide were added with vigorous shaking. On dilution with 25 cc. of water a red precipitate formed, yield 2.7 g. of water-washed orange powder.

Anal. Calc'd for $(C_{10}H_8N_4O_7)_n$: N, 18.92. Found: N, 17.10.

Attempts to carry out the reaction in acetone and in dioxane suspension resulted in products with lower nitrogen content.

A solution of 1 g. of polyvinyl methyl ketoxime in 20 cc. of 0.5 *N* sodium hydroxide was diluted with 80 cc. of water and 20 cc. of dioxane and in small portions with shaking 100 cc. of 0.5 *N* sodium hydroxide and a solution of 5.2 g. of *p*-bromobenzenesulfonyl chloride in 70 cc. of dioxane. A precipitate was filtered, yielding 0.5 g. of tan powder.

Anal. Calc'd for $(C_{10}H_{10}BrNO)_n$: Br, 33.30. Found: Br, 3.12.

Polyvinyl methyl ketoxime (2 g., 0.023 base mole) was refluxed nineteen hours with acetyl chloride (20 cc., 0.28 mole) and phosphorus pentachloride (2 g., 0.01 mole). The acetyl chloride was distilled and the residue refluxed twelve hours with 71 cc. of 15% sulfuric acid. The mixture was made alkaline and steam distilled into 25 cc. of 0.9321 *N* hydrochloric acid, only 2.09 milliequivalents of base distilling. Repetition of the sulfuric acid hydrolysis yielded an additional 0.24 milliequivalents of volatile base. The hydrochloride was evaporated and the amine liberated in the cold and treated with phenylisothiocyanate. The oily product would not crystallize on seeding with phenylthiourea or N'-methyl-N-phenylthiourea, and was perhaps the derivative of hydroxylamine.

The residue from the hydrolysis amounted to 0.8 g. of tan powder insoluble in alkali and low in nitrogen (6.17%).

SUMMARY

1. Several polymers, polyvinylphthalimide, polyacrylamide, polynitroethylene, and polyvinyl methyl ketoxime have been prepared, as well as the monomers, using procedures available in very brief form only. A water-soluble polyacrylamide was obtained.

2. Polyvinylisocyanate, previously undescribed, was prepared by the Curtius reaction and alcoholysis and hydrolysis studied.

3. β-Acetoxyethylammonium acetate, containing polyethylenimmonium acetate, was shown to have been obtained from ethylenimine and acetic acid but could not be converted to β-acetoxyethylisocyanate.

4. Attempts at the hydrazine-hydrolysis of polyvinylphthalimide, hypobromite degradation of polyacrylamide, and Beckmann rearrangement of polyvinyl methyl ketoxime did not meet with success.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XIV. METHOXYL DERIVATIVES OF PHENYLPROPANOLAMINE AND 3,5-DIHYDROXYPHENYLPROPANOLAMINE (1)

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Mescaline, 3,4,5-$(CH_3O)_3C_6H_2CH_2CH_2NH_2$, one of the numerous bases isolated from the mescal button by Heffter (2) and later by Späth (3), possesses interesting psychological effects, usually producing supernatural and colorful visions and euphoric state of mind (4, 5, 6, 7). The relationship of mescaline to the pressor compounds depends on its structure rather than on its physiological behavior. It has been reported by Raymond-Hamet (8), Grace (9), Geesink and Jager (10), and De Nito (11) that mescaline fails to produce a rise in blood pressure in dogs, rabbits, and cats.

In view of the unique responses, which must be attributed to the presence of the three vicinal methoxyl groups on the pressor active molecule, β-phenethylamine, it was thought to be of interest to synthesize and study other compounds of this type. Unfortunately, mescaline itself is quite toxic and damaging to the tissues. Since the introduction of an alcoholic hydroxyl group into the β-phenethylamine skeleton reduces the toxicity of the molecule, the correspondingly substituted hydroxymescaline may be expected to be less toxic. Because the arylpropanolamines exhibit substantially the same pharmacodynamic behavior as do the corresponding arylethanolamines and also are more easily synthesized, a 3,4,5-trimethoxyphenylpropanolamine, 3,4,5-$(CH_3O)_3C_6H_2CH(OH)CH(NH_2)CH_3$, was prepared. In an extension of this study, other methoxyl derivatives of phenylpropanolamine were prepared.

Methoxyl ring substituted pressor amines have been investigated by Hjort (12) on N-methyl-β-phenethylamine having mono- and di-methoxy nuclear substitutions. In the phenylpropanolamine series, Hartung, Munch, Miller, and Crossley (13) have synthesized and studied 2-methoxy-, 4-methoxy-, and 2,4-dimethoxy-phenylpropanolamines. In general, the methylation of hydroxyl groups on the nucleus seems to increase the toxicity and decrease the pressor activity.

Schaumann (14) and Tainter (15) attribute to the *m*-hydroxyl group on a pressor molecule a "sympathicotropic" effect, in contrast to the *p*-hydroxyl group which exhibits more of a "musculotropic" effect. It occurred to us that it would be of interest to learn what the physiological responses would be if both available meta positions were occupied by hydroxyl groups. With this in mind, the 3,5-dihydroxyphenylpropanolamine was prepared.

The synthesis of these products depends on first obtaining the appropriate ketone, AR-CO-CH_2CH_3. This ketone is then converted into the corresponding oximino-ketone, AR-CO-$C(NOH)CH_3$, which in turn is reduced catalytically to the amino alcohol, AR-$CH(OH)CH(NH_2)CH_3$, and isolated as the hydrochloride.

EXPERIMENTAL

Preparation of ketones. 3,4,5-Trimethoxy- and 3,5-dimethoxy-4-hydroxypropiophenones. Gallic acid was methylated according to the method described by Mauthner (16) using dimethyl sulfate and alkali. This was then converted to the corresponding nitrile following the sequence of procedures outlined by Hurd and Winberg (17). After drying over phosphorus pentoxide, the 3,4,5-trimethoxybenzonitrile, m.p. 91°, was allowed to react with ethylmagnesium bromide at the refluxing temperature of toluene, following the general procedure given for the isobutyl derivative by Haller and Schaffer (18), and Hurd and Winberg. 3,4,5-Trimethoxy-, melting at 52°, and 3,5-dimethoxy-4-hydroxypropiophenone, melting at 109°, were obtained in yields of 55.8% and 14.2%, respectively. The melting points reported in the literature were 51–52° for the former and 109–110° for the latter (19, 20).

3,4-Dimethoxypropiophenone. Propionylcatechol was prepared following the method of Miller, Hartung, Rock, and Crossley (21). This ketone was then methylated according to the standard method with dimethyl sulfate in alkaline solution. The yield of 3,4-dimethoxypropiophenone, m.p. 62–63°, was 43% of the theoretical amount.

3,5-Dimethoxypropiophenone. This ketone, m.p. 33.5° (literature, 32.5°, 34–35°), was prepared in good yields by following the method of Suter and Weston (22), starting from benzoic acid.

Preparation of isonitroso ketones. By employing the general nitrosation procedure of Hartung and Munch (23), the foregoing ketones were converted into their corresponding isonitroso ketones. The appropriate ketone was dissolved in a suitable amount of ether, dry hydrogen chloride was bubbled through the stirred solution and an equimolar quantity of freshly distilled *n*-butyl nitrite was slowly added. After completion of the nitrosation reaction the ethereal solution was extracted with dilute alkali and the alkaline extract slowly stirred into concentrated hydrochloric acid containing ice. The crystals which separated out were removed, dried, and recrystallized from the proper solvents. The experimental data on the various oximino ketones are shown in Table I.

Catalytic reduction. It has been found (24) that in those cases where the aromatic portion of the isonitroso ketone molecule is substituted by a phenolic hydroxyl, or its methyl ether, the reduction stops at the amino ketone stage; the resulting compound may be isolated and purified as its salts, and then reduced to the corresponding amino alcohol in aqueous solution.

(a) *Amino ketones.* The reduction of the isonitroso ketones to the amino ketones was carried out exactly in the manner described elsewhere (23, 24, 25), using both the normal and active palladinized charcoal catalyst.[1] The absorption of hydrogen stopped when approximately two equivalents were taken up. The catalyst was removed, and the clear filtrate placed in a vacuum desiccator over concentrated sulfuric acid and calcium chloride. The product was isolated as its hydrochloride salt. The aqueous solution of all of the amino ketones reduced Fehling's solution, and all melted with decomposition or effervescence, forming a red melt. The amino ketones synthesized are described in Table II.

[1] The activity of palladium-charcoal catalysts depends greatly on their method of preparation, the previous history of the catalyst, and also on the type of charcoal used. Since the investigations with these catalysts have not yet reached the stage where results merit publication it may be well at this time to indicate that a much more active palladium-charcoal catalyst may be obtained if it is prepared in sodium acetate solution. For example, in a hydrogenator, 3 g. of Nuchar (Industrial Chemical Sales, N. Y. C.), 0.3 g. of palladium chloride, and 100 cc. of 1 *N* sodium acetate solution were shaken until no more hydrogen was taken up; the catalyst was then filtered off, washed with distilled water, finally once with ethanol, and was kept in a vacuum desiccator over concentrated sulfuric acid for at least overnight before use. A catalyst so prepared is frequently active where the normal catalyst is much less active, or inert (26).

(b) *Amino alcohols.* Using a fresh catalyst, the amino ketone salts in aqueous solution were further reduced to the corresponding amino alcohols. After the removal of the catalyst, the clear filtrate was evaporated to dryness over concentrated sulfuric acid and calcium chloride. The residue was dissolved in the least quantity of absolute alcohol and white crystals (except 3,5-dimethoxy-4-hydroxyphenylpropanolamine which was tan colored) were forced out by dilution with dry ethyl ether, except in the case of 3,5-dimethox-

TABLE I

ISONITROSO KETONES

AR = AR—CO—C(NOH)—CH_3	PURIFICATION SOLVENT	M.P., °C (UNCOR.)	YIELD, %	NITROGEN[a]	
				Calc'd, %	Found, %
3,4,5-Trimethoxyphenyl-	Toluene	145–146	80		
3,5-Dimethoxy-4-hydroxyphenyl-	Benzene	160–164	37	5.85	5.80 5.82
3,4-Dimethoxyphenyl-	95% Ethanol	163	82	6.28	6.20 6.23
3,5-Dimethoxyphenyl-[b]	Benzene or 20% Ethanol	107–108	74		

[a] All nitrogen analysis was made by Kjeldahl (Hengar technique).

[b] Prepared by Bockmühl, Ehrhart, and Stein, German Patent, 613,215, May 14, 1935; *Chem. Abstr.*, 29, 5602 (1935).

TABLE II

AMINO KETONES

AR = AR—CO—CH(NH_2·HCl)—CH_3	M.P., °C (COR.)	YIELD, %	NITROGEN	
			Calc'd, %	Found, %
3,4,5-Trimethoxyphenyl-	248–249 dec.	71	5.08	5.01 4.99
3,5-Dimethoxy-4-hydroxyphenyl-	209.4 dec.	75	5.36	5.34 5.47
3,4-Dimethoxyphenyl-	214.2 dec.	63	5.70	5.65 5.68
3,5-Dimethoxyphenyl-	204.5 dec.	71	5.70	5.66 5.64

yphenylpropanolamine hydrochloride, where a 50% mixture of isopropyl and ethyl ethers was used. These amino alcohol salts are summarized in Table III.

The amount of nitrogen for the reduction product from the hydrochloride of 3,5-dimethoxy-4-hydroxyphenyl-α-aminoethyl ketone was found to be 7.80, 7.77, and 7.51%; calculated for the corresponding amino alcohol, 5.32%. However, in view of the previous supporting data, (a) that the amino ketone absorbed the theoretical one equivalent of

hydrogen, (b) that the product does not reduce Fehling's solution, and (c) that the nitrogen analysis was correct for the amino ketone, it is believed that the desired amino alcohol was actually formed. However, during the process of isolation it must have undergone change, and accordingly characterization and analysis could not be made. Due to lack of product and intermediate these conclusions have not been substantiated.

Demethylation of 3,5-dimethoxyphenylpropanolamine. In a Carius tube, 2.0 g. (0.008 mole) of 3,5-dimethoxyphenylpropanolamine hydrochloride and 10 cc. of concentrated hydrochloric acid were placed, and the tube was sealed and wrapped in towels. It was placed in the steam-bath for a period of six to eight hours. After thorough cooling, the tube was carefully opened, and the dark brown mixture emptied into an evaporating dish and the excess hydrochloric acid removed under vacuum over sodium hydroxide pellets. The resulting syrupy residue was finally dried over phosphorus pentoxide under vacuum. In this manner, almost quantitative yield of a tan colored product was obtained. A portion of this product was dissolved in the least quantity of pure *n*-butyl alcohol and a white precipitate forced out with dry ethyl ether. After centrifuging, the solvent was decanted

TABLE III

AMINO ALCOHOLS

AR = AR—CHOH—CH—CH_3 / $NH_2 \cdot HCl$	M.P., °C (COR.)	YIELD, %	NITROGEN	
			Calc'd, %	Found, %
3,4,5-Trimethoxyphenyl-	221.0–221.5	70	5.05	5.01 5.07
3,5-Dimethoxy-4-hydroxyphenyl-	96 dec.	60	5.32	See "Amino Alcohols"
3,4-Dimethoxyphenyl-	212.6–213.0	80	5.65	5.54 5.67
3,5-Dimethoxyphenyl-	169.5–170.0	66	5.65	5.60[a] 5.65

[a] This product has been previously prepared by Bockmühl, Ehrhart, and Stein, as melting at 165–167°. Since the product obtained here melted above that previously described, it was analyzed to confirm its composition.

and the white residue dried over phosphorus pentoxide. The product was very hygroscopic. An aqueous solution gave a dark violet coloration with ferric chloride test solution and did not reduce Fehling's solution. The melting point showed unusual behavior. The product did not liquefy, but passed from the crystalline state to the frothing stage without change of color at 195–200°. It decomposed to a carbonaceous mass at a temperature above 250°. Kjeldahl: nitrogen calculated for $C_9H_{13}O_3N \cdot HCl$, 6.38%; nitrogen found, 6.15 and 6.25%.

SUMMARY

1. For the purpose of eventual pharmacological study a mescaline analog of phenylpropanolamine was synthesized.

2. Also to permit a more comprehensive study of the effect of methoxyl substitution in the phenyl nucleus of phenylpropanolamine, several additional new compounds were prepared, the complete list being: 3,4,5-trimethoxy-, 3,4-dimethoxy-, and 3,5-dimethoxy-4-hydroxyphenylpropanolamines.

3. In view of the unique physiological properties conferred on a molecule containing a single *meta* hydroxyl substitution, it appeared desirable to prepare a molecule containing two hydroxyl groups on its meta positions. The 3,5-dihydroxy compound was prepared by demethylation of 3,5-dimethoxyphenylpropanolamine hydrochloride.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

NEW SYNTHESES OF PICENE

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In this paper the synthesis of picene by two closely related new methods and of 5-methylpicene, 13-methylpicene, and 13-picenol[1] is reported.

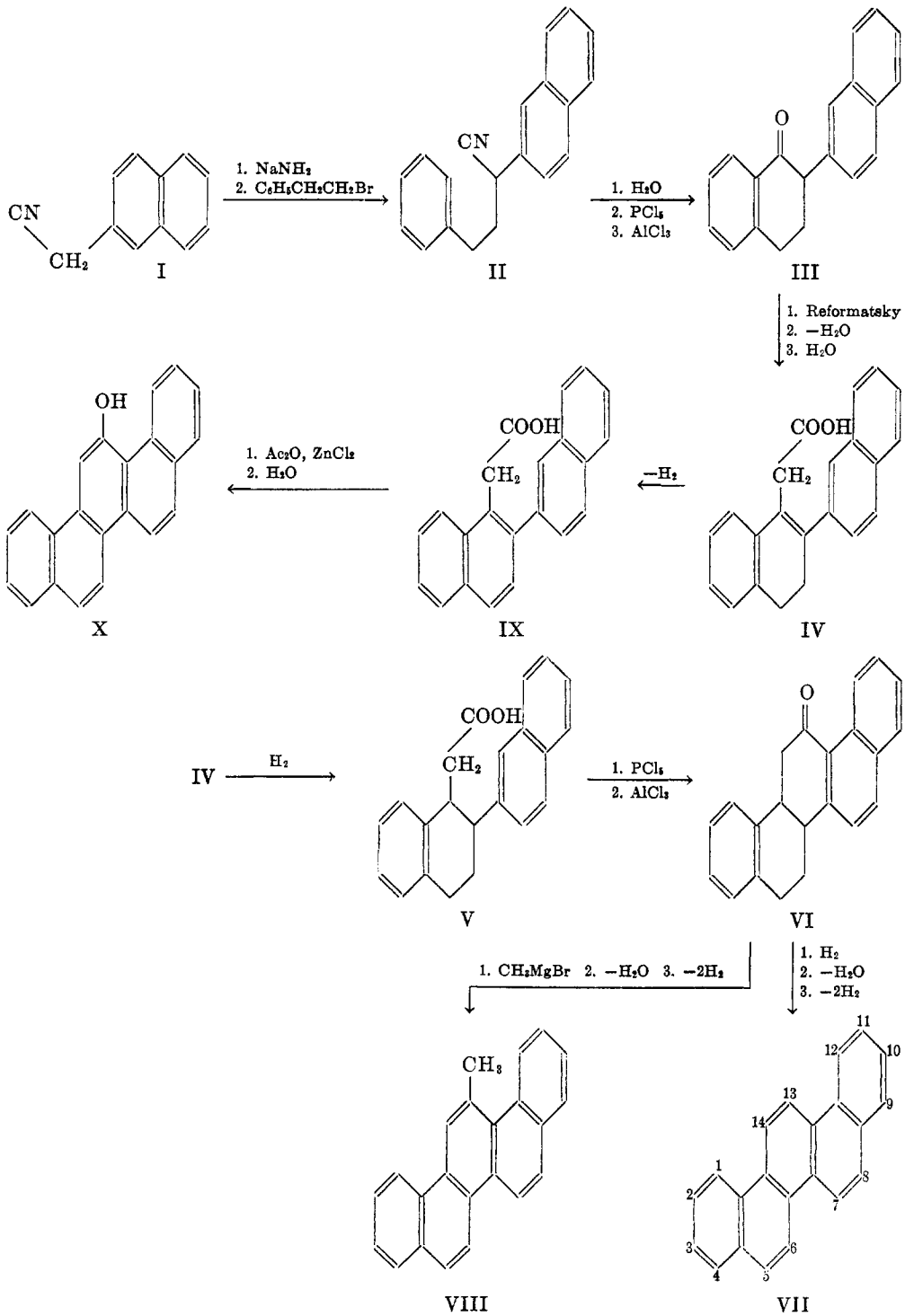
The synthesis of picene and its derivatives is of interest in connection with attempts to determine the structure of hydropicene triterpenoids by dehydrogenation (1). Most of the previously reported syntheses (2) of picene involve an intramolecular cyclization requiring prolonged treatment with aluminum chloride. Yields are very poor and the structure of any methylated picenes thus prepared must be regarded as not absolutely certain in view of the known lability of alkyl groups in Friedel-Crafts condensations (3). Indeed, one synthesis of picene definitely involves the loss of a methyl group (2 e). For these reasons it was decided to study the synthesis of picene by new methods which would be generally applicable to the preparation of any mono- or poly-substituted picene, and which would use only reactions leading undeniably to expected products. The two syntheses reported herein are closely related to the chrysene syntheses previously developed in this laboratory (4, 6).

2-Naphthylacetonitrile, I, was produced from 2-naphthylmethyl ketone *via* the thiomorpholide (5), hydrolysis to 2-naphthylacetic acid, conversion to the amide, and dehydration. In the modified Willgerodt reaction (5), it was found that more than one equivalent of sulfur and of morpholine was required to secure highest yields. The alkylation of I to II went well as in similar cases (6). Hydrolysis and ring closure to III, followed by Reformatsky reaction, dehydration and hydrolysis to IV went without trouble. The position of the double bond in IV is assumed. The reduction of IV to V was difficult of accomplishment but was finally carried out with sodium amalgam in dilute aqueous alcoholic solution. The remaining steps require no comment except that it was easier to secure the final hydrocarbons, VII and VIII when sulfur rather than palladium-on-charcoal was used as dehydrogenating agent.

13-Picenol was easily obtained by dehydrogenation of the methyl ester of IV, followed by hydrolysis to IX, cyclization to the acetate (7) of X, and hydrolysis to X.

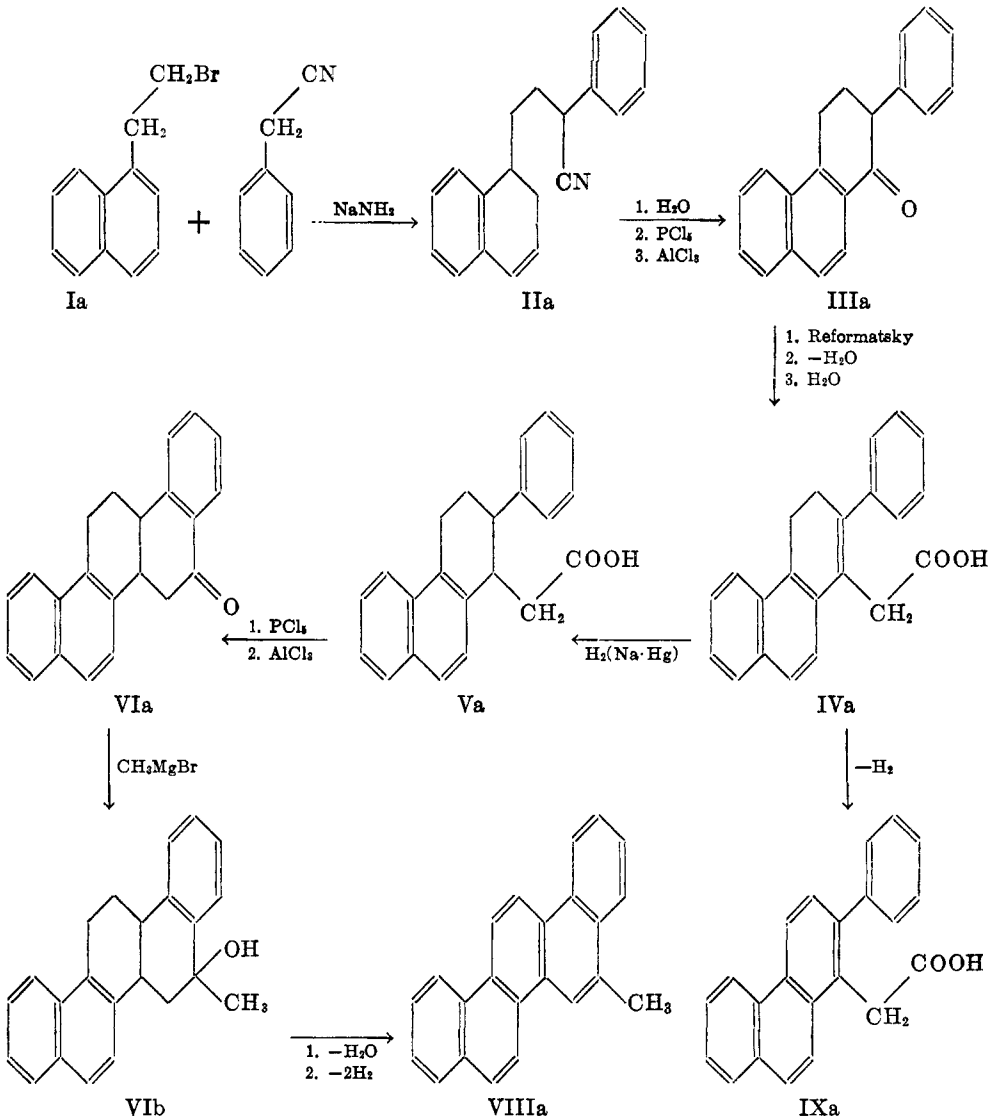
The alkylation of benzyl cyanide with I proceeded well as in other cases (6). Hydrolysis of IIa and ring closure of the resulting acid yielded the ketone IIIa which, after Reformatsky reaction dehydration, and hydrolysis, yielded IVa. As a check on the structure of IIIa, it was reduced to the corresponding alcohol which was dehydrated and dehydrogenated to 2-phenylphenanthrene, XI, a new hydrocarbon which was characterized by oxidation to 2-phenylphenanthraquinone, XII. The position of the double bond in IVa is assumed. The acid, IXa, was obtained by dehydrogenation of the methyl ester of IVa, followed by hydrolysis. The cyclization of acids IVa and IXa by procedures similar to those

[1] Chemical Abstracts numbering.



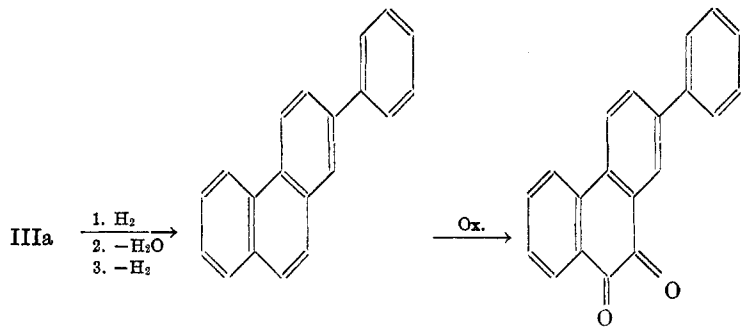
Synthesis of 13-Substituted Picenes

used in a previous case to prepare dihydrochrysenol (4) and chrysenol yielded mixtures of compounds which undoubtedly contained the nucleus of XIII in addition to the picene nucleus. For this reason, and also because of the difficulty of reducing IVa to Va without simultaneously getting more highly hydrogenated acids, this synthesis was abandoned.[2] Later, however, when it was found

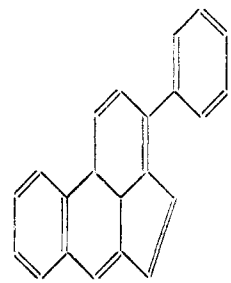


Synthesis of 5-Methylpicene[2]

[2] All of the reactions through the preparation of IVa and Xa were completed during 1939 and 1940 before the synthesis of 13-methylpicene was started. Part of this time the author was working at Yale University on a grant from the Jane Coffin Childs Memorial Fund for Medical Research (1939) and later (1940) as the Elizabeth Clay Howald Scholar at The Ohio State University.



XI XII



XIII

practical to reduce IV to V by sodium amalgam, this synthesis was resumed, and IVa was reduced to Va in the same way. The remaining steps occasioned no trouble.

The picene obtained in both syntheses melted at 366.0–366.5° corr. in a Pyrex sealed-tube and proved identical to a sample of picene previously synthesized (2a) by M. Orchin.

EXPERIMENTAL[3]

Thiomorpholide of 2-naphthylacetic acid. A mixture of 373 g. (2.2 moles) of 2-naphthyl methyl ketone, 105 g. (3.3 moles) of sulfur, and 290 g. (3.3 moles) of morpholine was heated in a good hood at gentle reflux for 14 hours and at brisk reflux for 2 hours and was poured while still hot into 1.2 l. of warm alcohol. On cooling, a yield of 534 g. (89.6%) of pale buff crystals, m.p. 100–106° was obtained. When only theoretical amounts of sulfur and morpholine were used (5) the yield varied from 53% to 65%. For hydrolysis to the acid there was no advantage in purification of the crude crystals.

2-Naphthylacetic acid. In the best of several experiments a mixture of 388 g. of thiomorpholide, 800 cc. of acetic acid, 120 cc. of concentrated sulfuric acid, and 180 cc. of water was refluxed for 5 hours and poured into 6 l. of water. Considerable tar remained in the reaction flask. After standing overnight, the solid was collected, washed with water, and

[3] All melting points corrected. Melting points above 250° were taken in an apparatus described by Bergstrom, *Ind. Eng. Chem. Anal. Ed.*, **9**, 340 (1937) with the calibrated thermometer described by Newman, *J. Am. Chem. Soc.*, **62**, 1686 (1940). The pressure recorded for all vacuum distillations is not accurate to greater than ±0.5 mm. All microanalyses marked[a] by J. E. Varner;[b] by J. A. Curtiss;[c] by D. Lester;[d] by G. Beatty;[e] by Arlington Laboratories;[f] by J. Walker.

digested with a solution of 150 g. of sodium hydroxide in 3 l. of water. A dark insoluble substance was removed by filtration and crude 2-naphthylacetic acid precipitated as a cream colored solid by acidification. After washing with water, drying, and digesting with several portions of benzene-petroleum ether, the acid was obtained as a purplish tinged solid, m.p. 138–141°, in 89.5% yield. On one crystallization from benzene it melted at 142.2–143.0°, but yields of amide were just as good when crude acid was used.

2-Naphthylacetamide. In a typical experiment, 50 g. of acid was converted into the acid chloride by heating with 57 g. of phosphorus pentachloride in 150 cc. of benzene. The solvent and phosphorus oxychloride were removed under reduced pressure, the acid chloride was dissolved in 100 cc. of dry acetone, and this solution was added slowly with efficient stirring to 300 cc. of concentrated ammonia. After diluting with one liter of water, the amide was collected, washed with water, and oven-dried to yield 47–48 g. of purplish amide, m.p. 198–202°. On recrystallization from alcohol the amide melted at 202–204.6° but darkened on melting. This preparation worked as well on a large scale (361 g.).

2-Naphthylacetonitrile, I. In the best of several experiments 20 g. of crude amide was added to 20 g. of phosphorus pentoxide under benzene. The pasty mass was heated to reflux in a glycerine bath for 36 hours with stirring. After decanting the clear benzene layer, the residue was cautiously treated with water and the ether-soluble organic matter added to the benzene solution. After washing with alkali, the nitrile, I, b.p. 145–150° at 2 mm., was obtained in 76.5% yield as a crystalline solid. Recrystallization from dilute alcohol with almost no loss gave a white nitrile, m.p. 85.6–86.2° (8). In larger runs the yield was often less, mainly because of mechanical difficulties.

α-(2-Naphthyl)-γ-phenylbutyronitrile, II. To a slowly stirred suspension of 19.5 g. of sodium amide[4] in 400 cc. of dry sulfur-free benzene was added during one hour 79 g. of I. The evolution of ammonia was brisk and the solution turned blood-red. After refluxing for two hours and cooling somewhat, a large amount of crystalline orange-brown solid was suspended in a dark solution. Upon the slow addition of 90 g. of β-phenethyl bromide much heat was generated. After the vigorous reaction had subsided the mixture was refluxed for 6 hours. The reaction mixture was washed with water and the solvent removed. Fractionation at 2 mm. yielded 86 g. (67%) of II as a viscous orange-yellow oil, b.p. 210–230°. From the forerun 5 g. of I was recovered. The nitrile II crystallized from dilute alcohol to give colorless small crystals, m.p. 62.8–64.0° but for further work the crude nitrile was used.

Anal. Calc'd for $C_{20}H_{17}N$: C, 88.5; H, 6.3; N, 5.2.
Found[5]: C, 89.1, 88.8; H, 6.5, 6.4; N, 5.3, 5.1.

α-(2-Naphthyl)-γ-phenylbutyric acid. In the best of several experiments a mixture of 86 g. of II, 350 cc. of acetic acid, 20 cc. of water, and 30 cc. of concentrated sulfuric acid was refluxed for 46 hours in an all glass system. After cooling, the mixture was diluted with water and extracted with ether. After thorough washing with water, the ether layer was extracted many times with dilute potassium carbonate solution. The crude acid obtained on acidification was dried and crystallized from benzene-petroleum ether. In all, 81.3 g. (88.5%) of crystalline acid was obtained. A portion recrystallized for analysis melted at 122.6–124.0°.

Anal. Calc'd for $C_{20}H_{18}O_2$: C, 82.7, H, 6.3.
Found[5]: C, 82.6, 82.8; H, 6.1, 6.3.

From the neutral fraction of the above hydrolysis mixture was isolated a small amount of colorless crystals, m.p. 147.8–149.0°. This compound was proved by analysis to be di-β-

[4] The author is indebted to Drs. A. L. Henne and K. Greenlee for directions for the preparation of sodium amide in liquid ammonia. These directions, shortly to be published in "Inorganic Synthesis", John Wiley and Sons, Inc., New York, made possible the conversion of a pound or more of sodium into finely granulated sodium amide in a few hours working time.

phenethyl-2-naphthylacetamide, arising from incomplete hydrolysis of a small amount of dialkylation product in the preceding step.

Anal. Calc'd for $C_{28}H_{27}NO$: C, 85.5; H, 6.9; N, 3.6.
Found[a]: C, 85.4, 85.2; H, 7.0, 6.8; N, 3.5, 3.4.

2-(2-Naphthyl)-1-keto-1,2,3,4-tetrahydronaphthalene, III. In the best of several experiments, 58 g. of acid was converted into the acid chloride with 42 g. of phosphorus pentachloride in 300 cc. of benzene. After removal of the solvent and phosphorus oxychloride under reduced pressure, the acid chloride was dissolved in 400 cc. of S-free benzene and treated with 27.5 g. of aluminum chloride during ½ hour with no attempt at cooling. When all of the aluminum chloride had been added, the mixture was heated rapidly to reflux and refluxed ½ hour. After pouring on ice, the solvent was removed by steaming and the solid ketone collected and dissolved in acetone. All solids were removed by filtration and the acetone displaced by alcohol from which the ketone largely crystallized as pale buff plates. The ketone remaining in the mother liquor was distilled, coming over at about 250° at 3 mm. In all, 47.5 g. (87.5%) of good ketone was obtained, m.p. 142.8–144.2°. To get colorless ketone it was necessary to vacuum distil, but if the crude reaction product was distilled without a previous crystallization, losses were greater. A sample recrystallized for analysis from alcohol formed fern-like white crystals, m.p. 143.8–144.6°.

Anal. Calc'd for $C_{20}H_{16}O$: C, 88.2; H, 5.9.
Found[b]: C, 87.8, 88.0; H, 6.0, 6.1.

The oxime, m.p. 158.6–159.4°, was prepared by heating with hydroxylamine hydrochloride in pyridine.

Anal. Calc'd for $C_{20}H_{17}NO$: C, 83.6; H, 6.0; N, 4.9.
Found[b]: C, 83.2, 83.1; H, 6.0, 5.8; N, 4.8, 4.8.

2-(2-Naphthyl)-3,4-dihydro-1-naphthaleneacetic acid, IV. The Reformatsky reaction between 54.4 g. of III, 35 g. of methyl bromoacetate, 16 g. of zinc, and 400 cc. of dry S-free benzene proceeded slowly and was completed by refluxing for two hours. The organic reaction product was dehydrated by heating at 190–240° for one hour with a crystal of iodine. After saponification with alcoholic potassium hydroxide, the acid and neutral reaction products were separated to yield 17.1 g. (31.5%) of starting ketone and 37.4 g. (60%, or 87% if allowance is made for recovered ketone) of acid. The acid fraction yielded 24 g. of crystalline acid, IV, m.p. 177.0–178.6°. A sample regenerated from the methyl ester and recrystallized from benzene for analysis melted at 178.0–178.6°.

Anal. Calc'd for $C_{22}H_{18}O_2$: C, 84.1; H, 5.8.
Found[b]: C, 83.9, 83.8; H, 5.9, 5.8.

By converting the non-crystalline acid fraction into methyl esters, distilling (b.p. about 250° at 4.5 mm.), and saponifying, additional crystalline acid, m.p. 177.0–178.6°, was obtained. A similar isomerization has been reported previously (9) and has been noticed frequently in other cases I have encountered. The methyl ester of IV crystallized as colorless needles, m.p. 99–101°, from benzene-methanol.

Anal. Calc'd for $C_{23}H_{20}O_2$: C, 84.1; H, 6.1.
Found[b]: C, 83.7, 83.8; H, 6.4, 6.2.

2-(2-Naphthyl)-1-naphthaleneacetic acid, IX. A mixture of 5.80 g. of the methyl ester of IV and 0.566 g. of sulfur was heated at 220° for one hour and then at 250° for one-half hour. The product was crystallized from hot propyl alcohol using decolorizing charcoal (Darco G-60) to give 4.70 g. (85.5%) of the methyl ester of IX. A sample recrystallized twice from benzene-methanol for analysis melted at 107.2–108.6°. On saponification the free acid, IX, was obtained in quantitative yield as colorless needles, m.p. 191.0–192.6°.

Anal. Calc'd for $C_{23}H_{18}O_2$: C, 84.6; H, 5.6.
Found[b]: C, 84.5, 84.3; H, 5.4, 5.5.
Calc'd for $C_{22}H_{16}O_2$: C, 84.6; H, 5.2.
Found[b]: C, 84.1, 84.0; H, 5.0, 5.2.

13-Picenol acetate and 13-picenol, X. A mixture of 2.14 g. of IX, 5 cc. of acetic acid, 5 cc.

of acetic anhydride, and a few small crystals of anhydrous zinc chloride was refluxed for one hour and was then diluted with a few drops of water. On cooling, 1.49 g. (65%) of white crystals, m.p. 207–208° was obtained. The purest sample of 13-picenol acetate melted at 208.5–209.2°.

Anal. Calc'd for $C_{24}H_{16}O_2$: C, 85.7; H, 4.8.
Found[b]: C, 86.1, 85.9; H, 4.8, 4.7.

On hydrolysis with dilute aqueous-alcoholic potassium hydroxide by refluxing for 30 minutes, this acetate was converted in high but undetermined yield to 13-picenol, X. Because of decomposition on melting, the melting point of X was not sharp, the material sintering near 275° and melting near 286°. In spite of several attempts, X was not obtained colorless, a pale buff color being present.

Anal. Calc'd for $C_{22}H_{14}O$: C, 89.8; H, 4.8.
Found[b]: C, 89.9, 89.8; H, 5.0, 4.9.

2-(2-Naphthyl)-1,2,3,4-tetrahydronaphthaleneacetic acid, V. The reduction of IV to V proved difficult and has not really been efficiently done to date. Catalytic hydrogenation over Adams platinic oxide catalyst at low hydrogen pressure or over catalyst 37KAF (10) in dioxane at 200° and 1800 lbs. initial pressure proved unsatisfactory. Reduction was successfully accomplished by stirring an alkaline solution of the sodium salt of IV in aqueous alcohol over an excess of 1.5–2% sodium amalgam for a period of from 4 days to 18 days. Frequent additions of dilute acid were made to neutrality. This caused precipitation of acid but this slowly redissolved on reaction of the sodium amalgam and was replaced by a nacreous precipitate of the sodium salt. When the reduction mixture was worked up the precipitate and the filtrate were worked up separately but later combined as there was no great difference. The acid mixture proved difficult to separate into any homogeneous fractions and for further work crude mixtures were used. There was isolated a small amount of unsaturated acid, IV, m.p. 176.4–177.2°, and of a pure isomer of V, m.p. 160.4–162.4°.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.4.
Found[b]: C, 83.8, 83.8; H, 6.1, 6.0.

Picene, VII. The acid chloride was made from 3.3 g. of crude acid mixture, V, in the usual way using phosphorus pentachloride, and this was cyclized in chlorobenzene solution at 40° for one hour using 1.5 g. of aluminum chloride. After hydrolysis, the benzene solution of the products deposited 1.00 g. (32%) of a mixture of ketones, VI. A small amount of a pure isomer of *13-keto-5,6,6a,13,14,14a-hexahydropicene*, m.p. 194.6–195.6°, was isolated as pale orange prisms.

Anal. Calc'd for $C_{22}H_{18}O$: C, 88.6; H, 6.1.
Found[b]: C, 88.4, 88.4; H, 5.8, 5.6.

The material remaining in the mother liquors after the original crystallization was vacuum distilled to yield 1.58 g. (51%) of ketone as a clear dark straw colored viscous liquid. This was dissolved in toluene and reduced with aluminum isopropoxide (11) for six hours. A benzene solution of the dehydrated (simple heating) reaction products deposited a small amount (0.113 g.) of almost colorless needles which on recrystallization melted at 297–307°. This compound gave fair analyses for a tetrahydropicene.

Anal. Calc'd for $C_{22}H_{18}$: C, 93.6; H, 6.4.
Found[b]: C, 93.3, 93.2; H, 5.5, 5.6.

The remaining product was heated up to 350° over 23% palladium-charcoal (12) for 4 hours and was then vacuum distilled to yield 1.05 g. (71%) of crude picene, VII. After decolorization with charcoal (Darco G-60) in xylene followed by vacuum sublimation at 300° and 2 mm. and crystallization from xylene there was obtained pure white glistening leaflets of picene, m.p. 366–366.5°, with an intense blue-violet fluorescence in ultraviolet light and even in indirect daylight. A mixed melting point with other synthetic picene (2a) showed no depression.

13-Methylpicene, VIII. A somewhat different fraction of crude acid, V, (4.90 g.) was cyclized as above and the crude ketone vacuum distilled to yield 3.2 g. (69%) of a mixture of

crystals and oil. The crystals, separated from a benzene solution, amounted to 0.53 g. and were saved for attempted isolation of pure ketone isomers. Of the remaining oil 1.71 g. was treated in ether solution with an excess of methylmagnesium bromide. The carbinol fraction thus obtained was heated at 240° with 0.37 g. of sulfur for 2 hours and was then vacuum distilled to yield 1.35 g. of a yellow crystalline solid. Crystallization from benzene yielded 0.98 g. (58%) of crude 13-methylpicene, VIII, m.p. 187–199°. Decolorization with charcoal (Darco G-60) followed by recrystallization from benzene-alcohol yielded pure VIII, m.p. 203.6–204.4°, as fine colorless needles having a blue-violet fluorescence in ultraviolet light.

Anal. Calc'd for $C_{23}H_{16}$: C, 94.5; H, 5.5.
Found[b]: C, 94.4, 94.5; H, 5.4, 5.2.

The addition compound with two molecules of *s*-trinitrobenzene formed orange-red needles, m.p. 178.4–179.0°.

Anal. Calc'd for $C_{35}H_{22}N_6O_{12}$: C, 68.9; H, 3.8; N, 8.3.
Found[b]: C, 69.0, 68.8; H, 3.7, 3.7; N, 8.2, 8.3.

5-Methylpicene Synthesis

β-(1-Naphthyl)ethyl bromide, Ia. β-(1-Naphthyl)ethanol was prepared in 76% yield from 1-naphthylmagnesium bromide and ethylene oxide (13). Only material boiling constantly at 148° at 1.5 mm. was taken. A mixture of 150 g. of β-(1-naphthyl)ethanol and 220 cc. of 48% hydrobromic acid was refluxed for 1 hour and then concentrated until 190 cc. of distillate had been collected. The organic layer of the distillate was returned to the residue together with 60 cc. of 48% hydrobromic acid. After refluxing 1 hour, 60 cc. of liquid was distilled. The bromide layer was then separated, washed with water and 80% sulfuric acid, and finally vacuum distilled to yield 185.5. g. (90.5%) of Ia (14), b.p. 135–137° at 1–1.5 mm.

α-Phenyl-γ-(1-naphthyl)butyronitrile, IIa. In the best of several experiments 63 g. of pure benzyl cyanide in 100 cc. of benzene was added to a stirred suspension of 22 g. of sodium amide[4] in 300 cc. of benzene. A brownish-red color was produced, some heat was evolved, and a little ammonia was given off. After 5 minutes 119 g. of Ia was added in several portions. Much heat and ammonia were evolved and a solid began to precipitate. After about half of the bromide had been added the color lightened to light brown. After refluxing for 4 hours and standing at room temperature overnight, the product was worked up as for compound II to yield 99 g. (73%) of IIa, a yellow viscous oil, b.p. 218–219° at 2 mm. This compound was not analyzed but hydrolyzed directly to the acid.

α-Phenyl-γ-(1-naphthyl)butyric acid. In the best of several experiments 103 g. of nitrile, IIa, 700 cc. of acetic acid, and 130 cc. of 50% sulfuric acid were refluxed for 63 hours, during the last hour of which 300 cc. of acetic acid was distilled. The remainder was diluted with water and the organic product taken into warm benzene and well washed with water. The acid was then extracted with aqueous potassium hydroxide. From the benzene solution a small amount of the *amide* was obtained as rosettes of fine white needles, m.p. 124.6–125.4°. On acidification of the alkaline extract, the free acid was taken into benzene and crystallized to yield 100.0 g. (91%) of white needles, m.p. 106–107°. A sample purified for analysis melted at 107.2–108.2°.

Anal. Calc'd for $C_{20}H_{18}O_2$. C, 82.7; H, 6.3.
Found[c]: C, 82.7; H, 6.3.
Calc'd for $C_{20}H_{19}NO$. N, 4.8.
Found[d]: N, 4.8, 4.9.

1-Keto-2-phenyl-1,2,3,4-tetrahydrophenanthrene, IIIa. In the best of several experiments the acid chloride, prepared from 100 g. of acid in benzene using 73 g. of phosphorus pentachloride, in 200 cc. of benzene was treated with 49 g. of aluminum chloride added slowly with cooling and stirring. At first the color became deep red-brown and hydrogen chloride was evolved. After stirring at room temperature for one hour an orange complex suddenly separated, the color became much lighter and the mixture went solid. This mixture was then scraped into ice and hydrochloric acid and the benzene was removed by

steaming. The solid was collected, dried, and crystallized from benzene. These crystals were vacuum distilled, boiling at 259° at 4.5 mm., and the distillate was crystallized from toluene-alcohol to yield 85.3 g. (91%) of IIIa, m.p. 176–177°. A sample recrystallized for analysis formed colorless plates, m.p. 177.4–177.8°.

Anal. Calc'd for $C_{20}H_{16}O$: C, 88.2; H, 5.9.
Found[c]: C, 88.2; H, 5.9.

2-Phenylphenanthrene, XI, and related compounds. A solution of 8.2 g. of IIa in 100 cc. of isopropyl alcohol containing 1 g. of dissolved aluminum (15) was refluxed for 10 hours during which acetone and alcohol were allowed to distil slowly and also 100 cc. of isopropyl alcohol was added to the reaction. The reaction mixture was hydrolyzed with dilute hydrochloric acid and the solution of secondary alcohol in dry benzene was treated with dry hydrogen chloride. The solution became milky. After all reaction with hydrogen chloride ceased and the solution had been dried with calcium chloride an attempt was made to alkylate malonic ester according to the procedure of Bachmann (11). However, no acid fraction was obtained on hydrolysis. From the crystalline neutral fraction, 1.6 g. (21%) was removed for the purification of 2-phenyl-3,4-dihydrophenanthrene, m.p. 150.6–151.0° and its characterization as dipicrate, deep red needles, m.p. 144.5–145.6°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.7; H, 6.3.
Found[c]: C, 93.7; H, 6.3.
Calc'd for $C_{32}H_{22}O_{14}N_6$: C, 53.8; H, 3.1.
Found[c]: C, 53.9; H, 2.9.

The remaining 5.4 g. (70%) of dihydrophenylphenanthrene was heated with 0.65 g. of sulfur at 235–240° for 1 hour. After removal of unreacted sulfur by refluxing a benzene solution with mercury, 4.72 g. (88%) of 2-phenylphenanthrene, XI m.p. 195–197°, was isolated by crystallization from benzene. A sample purified for analysis melted at 196.6–197.2°. The molecular compound with 2 molecules of *s*-trinitrobenzene formed bright yellow small needles, m.p. 156.4–157.4°.

Anal. Calc'd for $C_{20}H_{14}$: C, 94.5; H, 5.5.
Found[c]: C, 94.7; H, 5.5.
Calc'd for $C_{32}H_{20}O_{12}N_6$: C, 56.5; H, 3.0; N, 12.4.
Found[c]: C, 55.9; H, 2.9; N, 12.4, 12.3.

On oxidation with chromic oxide in acetic acid 2-phenylphenanthrene was converted in good yield into 2-phenyl-9,10-phenanthrenequinone, XII deep red needles, m.p. 220–221° with previous sintering and decomposition. The phenazine derivative, yellow needles, m.p. 285–287°, uncorr., was prepared with *o*-phenylenediamine.

Anal. Calc'd for $C_{20}H_{12}O_2$: C, 84.5; H, 4.3.
Found[c]: C, 83.9; H, 4.2.
Calc'd for $C_{26}H_{16}N_2$: C, 87.6; H, 4.5; N, 7.9.
Found[f]: C, 87.6; H, 4.4; N, 7.6.

2-Phenyl-3,4-dihydro-1-phenanthreneacetic acid, IVa. In the best of several experiments, 13 g. of sandpapered zinc foil (16) was added to a hot solution of 36.8 g. of ketone, IIIa, and 33.4 g. of ethyl bromoacetate in 350 cc. of toluene and 150 cc. of benzene. The reaction proceeded immediately but sluggishly so that external heating was required to maintain reflux. After four hours, the mixture was cooled and treated in the usual fashion. On concentration of the toluene-benzene solution of the products, 14.0 g. of unreacted ketone crystallized. The remaining product was dehydrated by heating near 220° with a small amount of iodine and the resulting mixture was vacuum distilled at 230–250° and 1 mm. After saponification with alcoholic potassium hydroxide, the products were separated into acidic and neutral fractions. From the neutral fraction there was isolated a further 2.3 g. of starting ketone, IIIa, making a total of 16.3 g. (44.3%) of recovered ketone. From the acid fraction was isolated 13.5 g. (31.8% or 57% on ketone consumed) of crude acid. Crystallization from toluene-alcohol yielded 11.5 g. of colorless acid, IVa, m.p. 226–228° (decomp.). The melt bubbled copiously just at and above its melting point. Evidently decarboxylation was occurring for the fact that this acid gave good analytical figures rules out solvation.

Anal. Calc'd for $C_{22}H_{18}O_2$: C, 84.1; H, 5.8.
Found[f]: C, 84.3; H, 5.6.

2-Phenyl-1,2,3,4-tetrahydro-1-phenanthreneacetic acid, Va. A hot suspension of 8.08 g. of pulverized acid, IVa, in 30 cc. of alcohol was diluted to 450 cc. with water, a milky solution being formed. This solution was stirred continuously for 32 days with an amalgam prepared from 12 g. of sodium and 100 cc. of mercury. After the first day, a nacreous white precipitate of sodium salts was formed. Each day dilute hydrochloric acid was added until the solution was about neutral. Frequently considerable amounts of organic acid were precipitated by these additions of acid. By the next day, however, the precipitated acids had redissolved in the alkali produced by the action of the sodium amalgam. The quantity of nacreous precipitate seemed to increase with time. At the end of 32 days there still remained considerable sodium in the amalgam. The suspension was decanted from the amalgam and filtered. The acids liberated from the precipitate and filtrate were treated separately but were found to be essentially the same and were united. A total of 7.48 g. (92%) of colorless crystalline acid, a mixture of stereoisomeric acids, m.p. 170–215°, was obtained. The separation of pure compounds from this mixture proved exceedingly difficult and absolutely pure isomers were not obtained. However, a low-melting racemate, m.p. 173–176°, and a higher-melting one, m.p. 205–226°, were separated.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.5; H, 6.4.
Found[b]: (low-melting isomer) C, 83.4; H, 6.4 (high-melting isomer). C, 83.1, 83.0; H, 6.5, 6.4.

Picene. The acid chloride from 1.48 g. of acid, Va, in 10 cc. of chlorobenzene was treated with 0.63 g. of anhydrous aluminum chloride. There was immediate darkening and evolution of hydrogen chloride. After five minutes a dark yellow crystalline complex separated. The mixture was heated to 55° during five minutes and then cooled and treated with water and acid. Benzene was added and the organic layer was well washed with acid and alkali and the solvents removed under reduced pressure. The resulting ketone was not isolated but reduced to the secondary alcohol using aluminum isopropoxide in toluene (11). The product thus obtained was heated for 2 hours from 240° to 340° with 0.281 g. of sulfur. The crystalline residue was sublimed at 300° under reduced pressure and the sublimate was crystallized from xylene, yielding 0.72 g. (55%) of picene, m.p. 355–360° uncorr. in a sealed Pyrex tube. By decolorization using carbon (Darco G-60) in boiling xylene, followed by sublimation and recrystallization pure picene (see above) was obtained.

5-Methylpicene. To a benzene solution of the ketone prepared as above from 2.73 g. of acid, Va, was added an excess of methylmagnesium bromide. After the initial vigorous reaction the mixture was left at room temperature for one hour and was then decomposed with dilute acid. After standing for twelve hours in benzene, 0.54 g. (20%) of the expected carbinol, VIb, crystallized and was collected. After crystallization from benzene-alcohol it separated as stout colorless prisms, m.p. 169–170°.

Anal. Calc'd for $C_{23}H_{22}O$: C, 87.9; H, 7.1.
Found[b]: C, 87.9; 87.8; H, 7.2, 7.4.

No attempt was made to secure more of this carbinol but the filtrate from the crystals was treated a second time with methylmagnesium bromide. The entire mixture thus obtained, but omitting the crystalline carbinol, was heated with 0.43 g. of sulfur at 240–280° for 1 hour and was then vacuum distilled. The crystalline distillate, 1.33 g., was crystallized to yield 0.995 g. (40%) of crude 5-methylpicene, m.p. 243–251°. After decolorization with charcoal, sublimation, and crystallization from toluene, 5-methylpicene was obtained as almost colorless stout needles, m.p. 251.6–252.2°, having strong blue-violet fluorescence in ultraviolet light.

Anal. Calc'd for $C_{23}H_{16}$: C, 94.5; H, 5.5.
Found[b]: C, 93.8, 93.9; H, 5.6, 5.8.

The di-*s*-trinitrobenzene derivative, m.p. 215.4–216.2°, crystallized in orange red fine needles.

Anal. Calc'd for $C_{35}H_{22}N_6O_{12}$: C, 68.9; H, 3.8; N, 8.3.
Found[b]: C, 68.8, 68.9; H, 3.8, 3.9; N, 8.3, 8.2.

SUMMARY

The synthesis of picene, 5-methylpicene, 13-methylpicene, and 13-picenol and the necessary intermediates is described.

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STUDIES ON THE LEUCKART REACTION

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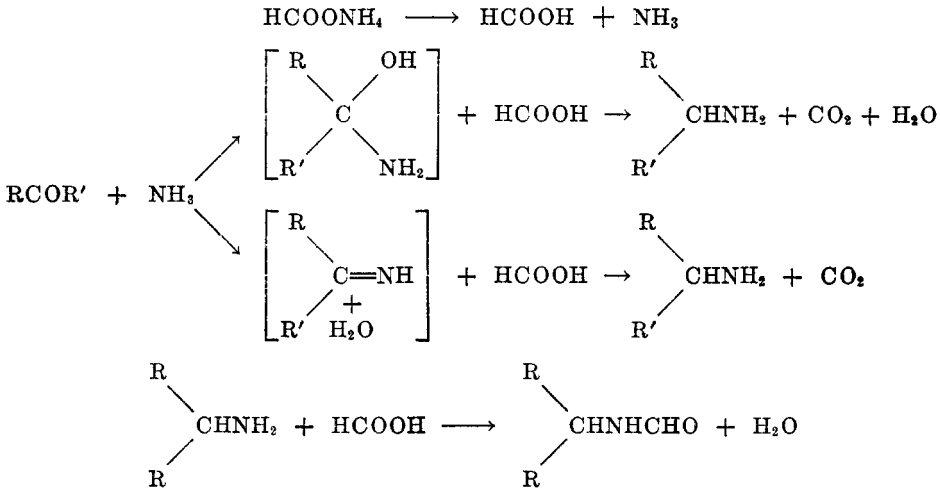
In 1885, Leuckart (1) first described the conversion of certain aldehydes and ketones to the corresponding amines by heating with excess ammonium formate. Wallach (2) applied the method to a number of alicyclic and terpenoid ketones, as well as certain aldehydes, and showed its general application. Despite the excellent results reported by Wallach, the reaction had found little use by others until Ingersoll (3) and his co-workers published a review of the method and reported the synthesis of a series of substituted α-phenethylamines by an improved modification of the procedure. Since the appearance of this publication, other workers have been stimulated to use the reaction in the preparation of a number of amines with varying success.

Although the exact mechanism has not been definitely established, the reaction has been studied by Wallach (2) and Ingersoll (4) and explained by the following steps: (a) The ammonium formate dissociates into ammonia and formic acid at the temperature of the reaction; and (b) ammonia adds to the carbonyl group or condenses to form the corresponding imine. (c) The formic acid then acts as a reducing agent to remove the hydroxyl or reduce the imino group; and (d) if in excess, may form the formyl derivative which is subsequently hydrolyzed to the free amine.



Formamide (90–95%) may be substituted for ammonium formate and probably hydrolyzes in the reaction to undergo the same steps as above. Wallach (2), and more recently Nabenhauer (5), has shown that dialkylammonium formate reacts with aldehydes and ketones to give the corresponding tertiary amines,

without the formation of an intermediate formyl derivative. These observations lend support to the suggestion of an initial dissociation of the reactive agent. Ingersoll (4) has indicated recently that the presence of formic acid increases the yield when formamide is used as the reagent. Wallach has used formic acid in some of his experiments without indicating its effect upon the yields which he obtained.

Needing a supply of various aralkylamines we have used the Leuckart reaction in their preparation and have had an opportunity to study some of the experimental conditions which influence the yield of the desired product. Following Ingersoll's suggestion (3), Johns and Burch (6) used formamide as the reactive agent, but they reported yields of 10–20% less than those of Ingersoll. In order to study the effect of the reagent upon the yield of amine, we ran a series of

TABLE I

EFFECT OF VARIATION IN THE LEUCKART REAGENT ON THE CONDENSATION WITH 3-PHENYL-2-BUTANONE. ACID HYDROLYSIS OF FORMYL DERIVATIVE

RUN NO.	LEUCKART REAGENT	TEMP. °C.	TIME, HRS.	YIELDS		
				Amine, %	Unreacted Ketone, g.	Tar, g.
1	Formamide[a]	170–180	22	27		
2	Formic acid and ammonia (5 moles each)	175–185	21	45		
3	Formamide[a] and formic acid (2.5 moles added in portions)	170–180	22	47		
4	Formic acid and ammonia (5 moles each)	170–180	14	47	3	3
5	Formamide[a] and formic acid (2.5 moles added in portions)	170–180	15	45	3	4
6	Formamide[a] and formic acid (2.5 moles added all at once)	170–180	15	48	3	3
7	Formic acid and ammonia	160–170	7	50	2	0.5
8	Formamide[a] and water (85 g.)	160–170	7	16	25	1

[a] Five moles of Eastman's material used.

experiments on the condensation of formamide with 3-phenyl-2-butanone in which the source or preparation of the formamide was varied. The reactions were carried out using a ratio of five moles of reagent to one mole of ketone (3) and the formyl derivative was hydrolyzed in concentrated hydrochloric acid by refluxing for eight hours. The reagent from formic acid and ammonia was prepared according to the procedure of Novelli (7) except for the variations in temperatures as noted in the tables. Table I shows the yield of α,β-dimethylphenethylamine obtained by using the various reagents. An examination of Table I shows that the use of formamide gave a lower yield of product than that obtained from ammonia and formic acid. The addition of formic acid to formamide increased the yield to that obtained from the ammonia and formic acid reagent. It did not appear to make much difference whether the formic acid was added in portions during the condensation or all at once at the beginning of

the reaction. The addition of water to the formamide did not increase the yield of the product. The influence of formic acid upon the formamide reagent lends further support to Wallach's explanation of the reaction mechanism and may account for the low yields obtained by Read and co-workers (8) in converting carvomenthone to carvomenthylamines with dry ammonium formate at 130°, and for the need of Leuckart to heat the reagents in a sealed tube at 210–240°.

Various experimental conditions have been used in carrying out the Leuckart reaction. Ingersoll (3) heated his reaction mixture at 160–185° until the distillation of water had ceased, at which time the temperature had reached 175–185°, maintaining this temperature from three to ten hours longer. Johns and Burch (6) refluxed the ketone with formamide for thirty hours; while Novelli (7) carried out the condensation at 190–230° for four to eight hours. In order to determine the effect of temperature on the yield of product, three experiments were run on 3-phenyl-2-butanone, using the reagent from ammonia and formic acid, in which the temperature of the reaction was varied, although all were

TABLE II

EFFECT OF TEMPERATURE ON THE LEUCKART REACTION WITH 3-PHENYL-2-BUTANONE. TIME: FIFTEEN HOURS. ACID HYDROLYSIS OF FORMYL DERIVATIVE

RUN NO.	TEMPERATURE, °C.	YIELD		
		Amine, %	Unreacted Ketone, g.	Tar, g.
9	190–200	23	8	5
4	170–180	47	3	3
10	160–170	50	3	1
CONDENSATION WITH PHENYLACETONE. TIME: SIX HOURS				
11	160–170	26	0.5	7
12	140–150	25	1.0	7

heated for fifteen hours. In two experiments with phenylacetone the reaction mixture was heated for six hours. The results are shown in Table II. It is evident that the yield was influenced by the temperature at which the condensation was carried out and in these experiments the yield was twice as much at 160–170° as at 190–200°.

The effect of varying the time of heating when carrying out the condensations at various temperatures is shown in Table III. A yield of 50% was obtained when the condensation was carried out at 190–200° for five hours, while a yield of only 23% was obtained after heating for fifteen hours. The reaction may be heated for fifteen hours at 160–170° without a reduction in yield, although the same results were obtained by heating for as short a period as four hours. Similar results were obtained in the condensations with phenylacetone, although the yield from the reactions were somewhat lower.

At least two procedures have been described for the hydrolysis of the formyl derivative to the corresponding amine. In one, 30% sodium hydroxide solution was used and in the other concentrated hydrochloric acid was the hydrolytic

agent. The effect of various concentrations of these two hydrolytic agents on purified N-formyl-α,β-dimethylphenethylamine is shown in Table IV. At the same time, a study was made of the variation in time and experimental conditions on the hydrolysis of the formyl derivative from the reaction mixture without subsequent purification. These results are summarized in Table V and inspection

TABLE III

EFFECT OF TIME ON THE LEUCKART CONDENSATION WITH 3-PHENYL-2-BUTANONE. TEMPERATURE: 190–200°. ACID HYDROLYSIS OF FORMYL DERIVATIVE

RUN NO.	TIME, HRS.	YIELD		
		Amine, %	Unreacted Ketone, g.	Tar, g.
9	15	23	8	5
13	5	50	1.5	0.5
14	3	47	2.0	0.5
TEMPERATURE: 160–170°				
10	15	50	3.0	1.0
7	7	50	2.0	0.5
15	4	48	2.0	0.5
CONDENSATION WITH PHENYLACETONE. TEMPERATURE: 160–170°				
16	8	26	0.5	7
11	6	26	0.5	7
17	3	22	0.5	8

TABLE IV

EFFECT OF TIME AND REAGENTS ON THE HYDROLYSIS OF N-FORMYL-α,β-DIMETHYLPHENETHYLAMINE

RUN NO.	HYDROLYTIC REAGENT	TIME OF HYDROLYSIS, HRS.	YIELD OF AMINE, %
18	Conc'd. Hydrochloric acid	8	59
19	10% " "	8	75
20	10% " "	1	67
21	30% Sodium hydroxide	8	0[a]
22	10% " "	8	71
23	6.6% " "	8	76

[a] Seventeen grams of unreacted formyl derivative was recovered.

shows that the best yield was obtained by hydrolyzing the formyl derivative directly in the reaction mixture with concentrated hydrochloric acid.

Having developed a satisfactory procedure for the reaction with 3-phenyl-2-butanone, it seemed desirable to study the effect of different ketones in the reaction at 160–170° under these same experimental conditions. The results obtained in this series of experiments are summarized in Table VI. In all cases the formyl derivatives were hydrolyzed in the reaction mixture with hydrochloric acid.

A review of the data brings out the interesting observation that 3-phenyl-2-butanone gave a yield of 58% of product, while with phenylacetone a yield of only 26% resulted. This may be due to the ease of resinification of the phenylacetone, as indicated by the increased amount of tar obtained. Propiophenone

TABLE V

EFFECT OF TIME AND EXPERIMENTAL CONDITIONS OF HYDROLYSIS ON THE LEUCKART CONDENSATION WITH 3-PHENYL-2-BUTANONE. REACTION TEMPERATURE: 160–170°. TIME: 7 HOURS

RUN NO.	EXPERIMENTAL CONDITIONS FOR HYDROLYSIS	TIME OF HYDROLYSIS, HRS.	YIELD	
			% Amine	Unreacted Ketone, g.
18	Formyl derivative isolated, purified and hydrolyzed with conc'd hydrochloric acid	8	39	
19	Same as above but hydrolyzed with 10% hydrochloric acid	8	53	
24	Formyl derivative isolated without purification and hydrolyzed in conc'd hydrochloric acid	8	48	2
25	Formyl derivative separated as crude oil and hydrolyzed in conc'd hydrochloric acid	8	50	2
26	Formyl derivative separated as crude oil and hydrolyzed in conc'd hydrochloric acid	4	45	2
27	Formyl derivative hydrolyzed in reaction mixture with conc'd hydrochloric acid	8	58	2
28	Formyl derivative hydrolyzed in reaction mixture with 10% sodium hydroxide	8	0[a]	3

[a] Thirty-four grams of formyl derivative isolated.

TABLE VI

EFFECT OF KETONE ON THE LEUCKART REACTION AT 160–170°. ACID HYDROLYSIS OF FORMYL DERIVATIVE IN REACTION MIXTURE

RUN NO.	KETONE	TIME, HRS.	YIELD		
			Amine, %	Unreacted Ketone, g.	Tar, g.
11	Phenylacetone	6	26	0.5	7
27	3-Phenyl-2-butanone	7	58	2	1
28	Propiophenone	7	65	0	3
29	Laurophenone	30	64	0	0
30	Benzophenone	9	80	—	0
31	*p*-Methylcaprophenone	9	63	—	0
32	*p*-Methyllaurophenone	30	0	26	—
35	8-Pentadecanone	15	40		

was converted to the amine in a yield of 65% and laurophenone in a yield of 64%, although the reaction with laurophenone required thirty hours. *p*-α-Aminododecyltoluene was not isolated from *p*-methyllaurophenone even though the reaction was continued for thirty hours. Unreacted ketone was the only definite product

recovered. Such a marked effect of the methyl group upon the lauryl derivative is surprising, particularly in view of the fact that *p*-methylcaprophenone gave a yield of 63%. However, three separate runs led to the same negative results.

The aliphatic ketone, 8-pentadecanone, gave a 40% yield of 8-aminopentadecane after heating for fifteen hours. These results indicate that the Leuckart reaction may be used to prepare amines in satisfactory yields from a large number of ketones with only a slight modification of the experimental conditions.

Substitutions in the ammonium formate had considerable influence upon the yield of the products from the reaction. The results of experiments with the Leuckart reagent prepared from various substituted amines are recorded in Table VII. Methylamine and formic acid converted phenylacetone to N,α-dimethylphenethylamine in a yield of 43%, while ammonia and formic acid produced a yield of only 26% of α-methylphenethylamine under the same conditions. In condensations with 3-phenyl-2-butanone, ammonia and formic acid gave a

TABLE VII

EFFECT OF SUBSTITUTION IN THE LEUCKART REAGENT ON THE REACTION AT 160–170°. ACID HYDROLYSIS OF FORMYL DERIVATIVE IN REACTION MIXTURE

RUN NO.	KETONE	LEUCKART REAGENT	TIME, HRS.	YIELD		
				Amine, %	Unreacted Ketone, g.	Tar, g.
11	Phenylacetone	Formic acid and ammonia	6	26	0.5	7
36	"	Formic acid and methylamine	7	43	1.0	2
37	"	Formic acid and *n*-butylamine	6	5	20	4
38	3-Phenyl-2-butanone	Formic acid and ammonia	7	58	2	1
39	"	Formic acid and methylamine	6	41	4	0
40	"	Formic acid and *n*-butylamine	24	16	9	2
29	Laurophenone	Formic acid and ammonia	30	64	0	0
42	"	Formic acid and dimethylamine	28	0	75	

higher yield of product than methylamine and formic acid. When butylamine and formic acid were used both phenylacetone and 3-phenyl-2-butanone gave a lower yield of the amines than was obtained with either ammonia or methylamine and formic acid. Attempts to carry out the condensation using dimethylamine with laurophenone proved unsuccessful.

These data indicate that the higher alkyl substituted ammonium formates are more difficult to condense with the ketones, and it may be desirable to use higher temperatures in these reactions. This aspect of the problem needs further investigation.

EXPERIMENTAL

All melting points reported are uncorrected.

The following procedures are typical examples of the experiments reported in the preceding tables.

α,β-Dimethylphenethylamine. To a three-necked flask, equipped with a dropping-fun-

nel, thermometer, and down-directed condenser, was added with care 105 g. (1.72 moles) of 28% ammonia and 88 g. (1.72 moles) of 90% formic acid. The temperature of the solution was raised to 160° by distilling out water, and 51 g. (0.344 mole) of 3-phenyl-2-butanone was added at one time. The temperature was maintained at 160–170° for seven hours and any ketone which distilled was returned to the flask at intervals. The formyl derivative was hydrolyzed in the reaction mixture by refluxing for eight hours with 120 cc. of concentrated hydrochloric acid. After standing overnight, the mixture was diluted with 200 cc. of water and extracted with 100 cc. of benzene[1] to remove water-insoluble material. The aqueous solution was treated with a little charcoal (Norit), made alkaline with ammonia and the oil thus produced extracted with benzene. The benzene solution was washed three times with water, dried with sodium sulfate and the benzene removed by distillation under reduced pressure. The residue gave 30 g. (58%) of α,β-dimethylphenethylamine, boiling at 66–69° at about 1 mm., n_D^{25} 1.5146.

α-Aminododecylbenzene. Following the above procedure, 89.5 g. (0.344 mole) of laurophenone was added to the ammonium formate mixture and the temperature maintained at 160–170° for thirty hours. The formyl derivative was hydrolyzed by refluxing for eight hours with 120 cc. of concentrated hydrochloric acid. After standing overnight, 200 cc. of water was added and the compact crystalline mass of hydrochloride salt broken up. The α-aminododecylbenzene hydrochloride was collected on a Büchner funnel and washed three times with small portions of cold water. To a hot alcoholic solution of the crude hydrochloride, an excess of 28% ammonia was added and after dilution with cold water, the free amine was extracted with benzene. The benzene extract was distilled and the α-aminododecylbenzene collected at 170–172° (1–2 mm.) (n_D^{25} 1.4903) yield 64%. The hydrochloride prepared from this amine melted at 118–118.5°.

Unreacted laurophenone was the only product isolated from the reaction of dimethylamine and formic acid in the above procedure.

SUMMARY

1. A study has been made of some of the factors affecting the Leuckart reaction.

2. The use of formamide in the reaction gave a lower yield of primary amine than that obtained from the use of ammonia and formic acid. The addition of formic acid to formamide increased the yield obtained, while the addition of water had no effect.

3. In the condensation of the reagent from ammonia and formic acid with 3-phenyl-2-butanone, a reaction temperature of 160–170° for fifteen hours or a temperature of 190–200° for three to five hours gave the best yields of primary amine. A longer period of heating at the higher temperature reduced the yield. Similar results were obtained in the condensation with phenylacetone, although the yields were lower.

4. In the hydrolysis of the formyl derivative to the corresponding amine the best yield was obtained by hydrolyzing directly in the reaction mixture with concentrated hydrochloric acid.

5. A series of ketones were converted to the corresponding primary amines by the Leuckart reaction at 160–170° under the same experimental conditions. All gave excellent results except *p*-methyllaurophenone which failed to react even when heated for thirty hours.

6. Alkyl substituted ammonium formates were more difficult to condense with

[1] Two grams of unchanged ketone and one gram of tar were recovered from the benzene.

the ketones and attempts to carry out the condensation of dimethylamine and formic acid with laurophenone were unsuccessful.

GLENOLDEN, PA.

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[CONTRIBUTION NO. 23 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LAROCHE, INC.]

PIPERIDINE DERIVATIVES. PART 1. LOBELAN AND RELATED COMPOUNDS

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Lobelan, 1-methyl-2,6-diphenethylpiperidine (Ia), the parent alkaloidal base from which the chief alkaloids of *Lobelia inflata*, lobeline, lobelanidine, and lobelanine can be considered to be derived, contains inherent in its structure di-(γ-phenylpropyl)methylamine (IIa). Similarly, lobelanidine (Ib) inherently contains the corresponding secondary alcohol (IIIa). The di(phenylalkyl)alkylamines of the structure II, in which n is 2 or 3 and m is 1 to 3 and R is an alkyl group, are characterized by interesting and, in some cases, powerful physiological action. Such compounds have been synthesized by Külz *et al.* (1) with variations such as branching of the alkylene chain and substitution in the phenyl nuclei. These compounds are said to exhibit spasmolytic activity. One of them, di-(γ-phenylpropyl)ethylamine hydrochloride (IIb), has been introduced into medicine as papaverine substitute (2).

Blicke *et al.* (3) have recorded a similar study with some further variations, notably in the use of a cyclohexyl group in the place of phenyl groups, and di-(β-cyclohexylethyl)methylamine is stated to be a powerful spasmolytic substance. An extensive pharmacological report on it has been made (4). It is of interest that Kindler (5) finds di-(β-phenylethyl)amines to have a high killing activity against paramecia and other organisms. There seems, to be, however, no report on the corresponding tertiary amines of the structure II in this respect.

Külz and Rosenmund (6) claim that di-(ω-phenyl-ω-hydroxyalkyl)alkylamines (III), where the hydroxyalkyl chain may be branched and contains not more than 3 carbon atoms and R is hydrogen or alkyl, have a respiratory stimulating effect. This is not surprising in view of the relationship of the amines III to lobelanidine. Furthermore, it might be pointed out that the phenylalkylamines II ($n = 2$, $m = 2$) are inherently contained in derivatives of the opium alkaloid papaverine. This alkaloid and its tetrahydro derivative have a direct spasmolytic action on smooth muscle and in view of the structural relationship, the physiological action of II is not surprising. Rosenmund *et al.* (1) appear to have proceeded in their syntheses from this concept.

There seems to be no indication in the literature that the lobelia alkaloids themselves are characterized by spasmolytic action, and in view of the activity of the compounds of the structure IIa in this respect, it was thought of interest to investigate further lobelan and some of its new derivatives.

The direct synthesis of lobelan itself has not been previously reported, although it has been made by a partial synthesis from lobelanidine (7). The methiodide of lobelan has been prepared by Wieland *et al.* (8) by the reduction of 2,6-di-

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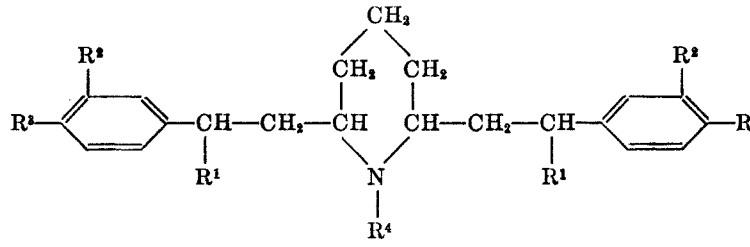
styrylpyridine with sodium and alcohol to 2,6-diphenethylpiperidine, separation of the *cis* and *trans* isomers formed and alkylation of the former with methyl iodide. We have found a convenient method for obtaining lobelan in the following route, adapted from the method employed by Winterhalder and Scheuing (9) for the synthesis of lobeline.



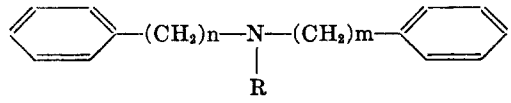
I

	R^1	R^2	R^3	R^4
Ia	H	H	H	CH_3
b	OH	H	H	CH_3
c	H	H	H	H
d	H	H	H	C_2H_5
e	H	H	H	C_3H_7
f	H	H	H	CH_2CH_2OH
g	H	H	OCH_3	H
h	H	H	OCH_3	CH_3
i	H	H	OCH_3	C_2H_5
j	H	H	OCH_3	C_3H_7
k	H	OH	OCH_3	H
l	H	O—CH_2—O		H
m	H	H	OCH_3	CH_2CH_2OH

2,6-Distyrylpyridine (V, R = H), treated with methyl *p*-toluenesulfonate, yields 1-methyl-2,6-distyrylpyridinium *p*-toluenesulfonate (VI, R = H). This quaternary compound can be hydrogenated catalytically using platinum, palladium-carbon, or Raney nickel. The absorption of five molecules of hydrogen occurs readily and 1-methyl-2,6-diphenethylpiperidine (VII, R = H) is obtained. The melting point of the hydrochloride (195–196°) was found to be identical with that of the hydrochloride obtained from the natural alkaloid.

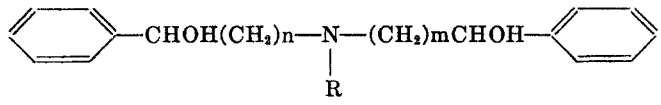
Because of the asymmetry of the carbon atoms 2 and 6 in the compounds VII, *cis* (*meso*) and *trans* (*dl*) stereoisomeric forms could form. Lobelan is known to be the *meso* form and in this synthesis no other form was isolated, but the mother

liquors in the last step were not thoroughly investigated. In the case of the compound VII (R = OCH_3), two isomeric forms were isolated. That occurring in the greatest quantity easily forms a hydrochloride and other salts. Oxidation of this form to obtain scopolic acid (*meso* form) by the known methods was not successful. *p*-Methoxybenzoic acid can be easily isolated, but apparently the conditions required to destroy the saturated side chain are vigorous enough to degrade the piperidine ring.



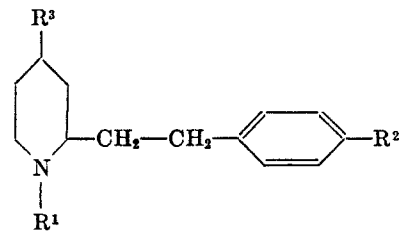
II

IIa n = 3, m = 3, R = CH_3
b R = C_2H_5, n = 3, m = 3



III

IIIa n = 2
m = 2



IV

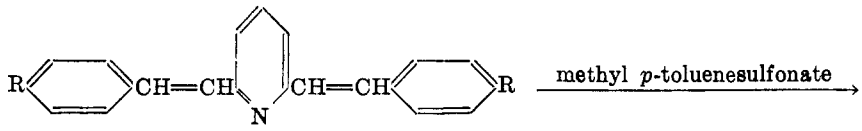
	R^1	R^2	R^3
IVa	C_2H_5	H	H
b	CH_3	H	$CH_2CH_2C_6H_5$
c	C_2H_5	OCH_3	$CH_2CH_2C_6H_4OCH_3(p)$
d	CH_3	H	CH_3
e	C_2H_5	H	$CH_2CH_2C_6H_5$

In the case of the other form only a viscous oil was obtained. Attempts to resolve the material with *d*-tartaric, *d*-malic, or *d*-dibenzoyltartaric acid failed, as crystalline salts were not obtained. A crystalline hydrochloride, m.p. 60°, was prepared.

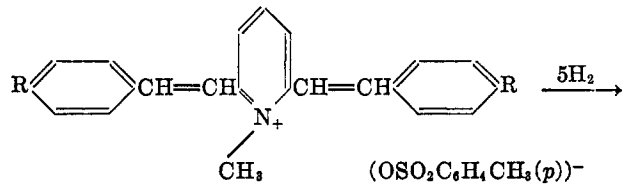
By an analogous reaction scheme, the variously substituted derivatives of lobelan (Ic, d, e, f, g, h, i, j, k) can be prepared.

Similarly, 2,4-disubstituted piperidines of structures IVb, c, d, e were prepared from 2,4-dimethylpyridines. One of these compounds, 1-methyl-2,4-di-(β-phenethyl)piperidine, is interesting as an isomer of lobelan. The 2-substituted piperidine, IVa, was obtained from 2-picoline.

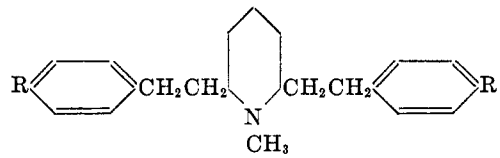
As an alternative synthesis, the styrylpyridines can be hydrogenated catalyti-



V R = H, OCH_3



VI



VII

cally to corresponding phenethylpiperidines and then alkylated. This route is not so convenient, since considerable formation of quaternary compounds occurs and several crystallizations are necessary to separate tertiary amines from them. Compound If was prepared by this route by reaction of 2,6-diphenethylpiperidine with ethylene chlorohydrin. This material was also prepared by the reaction of 2,6-distyrylpyridine with β-benzyloxyethyl-*p*-toluenesulfonate and hydrogenation of the resulting quaternary compound. In this case the benzyl group also suffers hydrogenolysis. Attempts to combine β-methoxyethyl- and β-ethoxyethyl-*p*-toluenesulfonates with 2,6-distyrylpyridine failed.

Attempts to prepare 2,6-di-(2-furylidene)pyridine by refluxing furfural with 2,6-lutidine in acetic anhydride were unsuccessful.

The hydrochlorides of the final compounds are not very soluble in water. Other salts of the most promising compound from the physiological standpoint, namely, 1-methyl-2,6-di(*p*-methoxyphenethyl)piperidine, were prepared. Of these the ethanesulfonate proved the most satisfactory, having a solubility of 6.7% in water at 25°, as compared with 0.6% for the hydrochloride.

PHARMACOLOGICAL RESULTS

The pharmacological work on the compounds described was carried out by Dr. R. H. K. Foster, of the Pharmacological Laboratories, Hoffmann-LaRoche, Inc., and will be described in detail elsewhere. In general, the compounds show both a neurotropic and musculotropic action. The neurotropic activity of the most favorable compound, Ih, is about one-tenth of that of atropine, whilst the musculotropic action is at least 7 times that of papaverine when tested against histamine-stimulated intestinal strips. Lobelan, Ia, itself has a slighter neuro-

tropic effect and a similar musculotropic activity. However, the relative safety (therapeutic index/therapeutic index of standard compound) by both subcutaneous and intravenous routes is 2.5 for lobelan and 5–6 for Compound Ih, when that of papaverine is given as unity.

As was expected from the relationship of the compounds to lobeline, the compounds show in part considerable analeptic activity. This was determined as the respiratory percentage increase in minute volume using a constant amount (2 mg./kg.) in morphinized rabbits. In this respect, increasing the size of the N-substituent decreases the activity; the most potent compound being Ig, which was more active than lobeline. The activity of Ih was of the same order as lobeline.

When tested for broncholytic action on isolated guinea pig lung stimulated with histamine, the effect of Ih was about one-twentieth of that obtained with adrenalin. On intact cats, the effect was of the same order.

EXPERIMENTAL RESULTS

The general procedures used were similar throughout the series and, therefore, the preparation of one or two members only of each group of intermediates is described. The characteristics of the intermediates and final products are given in Tables I, II, and III.

2,6-Distyrylpyridine. 2,6-Distyrylpyridine was prepared according to Shaw (10), or more conveniently, by adopting the method of Clemo and Gourlay (11), used for the preparation of 4-styryl-2-methylpyridine. This procedure was also used for the preparation of 2-styrylpyridine and 2,4-distyrylpyridine; a further example is the preparation of

2,-6Di-(p-methoxyphenethenyl)pyridine. Twenty-four grams of 2,6-lutidine, 60 g. of anisaldehyde, and 50 g. of acetic anhydride were refluxed together for sixty hours. The reaction mixture completely solidified on cooling. It was transferred to a suction filter and washed with alcohol. The filtrate and washings yielded only a negligible amount of the di-substituted material. The substance was recrystallized from benzene; yield 36 g.; m.p. 181–182°. The mother liquors contain considerable amounts of 2-(*p*-methoxyphenethenyl)-6-methylpyridine. After removal of the solvents, the residue refluxed with a further 30 g. of anisaldehyde and 50 cc. of acetic anhydride gave a further 10 g. of the desired product. Total yield 61% of theory.

2,6-Di-(p-methoxyphenethyl)piperidine. 2,6-Di(*p*-methoxyphenethyl)piperidine was obtained by dissolving 1.9 g. of the above compound in 20 cc. of glacial acetic acid and hydrogenating in the presence of two per cent Adams catalyst at atmospheric pressure. After filtration and evaporation *in vacuo*, the residue was crystallized from absolute alcohol; m.p. 154–155°. The free base was dissolved in ether, hydrogen chloride gas passed into the dry ether solution when immediate crystallization of the hydrochloride took place. It was recrystallized from alcohol, m.p. 209–211°.

2,6-Di-(p-methoxyphenethenyl)pyridine methyl-p-toluenesulfonate. Ninety grams of 2,6-di(*p*-methoxyphenethenyl)pyridine were heated in an oil-bath with 53 g. of methyl *p*-toluenesulfonate at 160–180° for eight hours. The product, after cooling, was washed on a filter with cold acetone and recrystallized from methanol; yield 130 g., m.p. 242–244°.

cis-1-Methyl-2,6-di-(p-methoxyphenethyl)piperidine hydrochloride. Twenty-two grams of the quaternary ammonium compound described above was dissolved in a mixture of 50 cc. of absolute alcohol and 50 cc. of glacial acetic acid and hydrogenated at 50 lbs. pressure in the presence of 1–2% Adams platinum oxide catalyst. The theoretical absorption of H_2 occurred in about fifty minutes. The catalyst was filtered off and the solvent removed by evaporation in vacuum, mixed with saturated sodium carbonate solution and taken up with warm benzene, washed with water, dried over K_2CO_3, and dry hydrochloric acid gas passed into the solution. On standing, the crystalline hydrochloride separated and was

recrystallized from the minimal amount of methanol or acetone. The melting point of the hydrochloride was 176–178°, and the yield was 8.4 g. The above reduction can also be performed with Raney nickel at 50–1000 lbs. pressure.

cis-1-Methyl-2,6-di-(p-methoxyphenethyl)piperidine base can be obtained by neutralizing 10 g. of the aqueous solution of the hydrochloride to phenolphthalein, extracting with ether, washing with water, and drying over solid KOH. On removal of the ether, the material crystallizes. The product was recrystallized from minimal amounts of petroleum ether. The melting point is 73–74°, yield 8.6 g.

TABLE I

PYRIDINE DERIVATIVES

COMPOUND	APPEARANCE	M.P. °C. UNCORR.	CRYSTALLIZED FROM	EMPIRICAL FORMULA AND M.W.	ANALYSIS N	
					Found	Calc'd
2,6-Di-(*p*-methoxyphenethenyl)-	Yellow needles	183–186	Ethanol-benzene	$C_{23}H_{21}NO_2$ 343.2	4.34	4.08
2-(*p*-Methoxyphenethenyl)-6-methyl-	Small yellow needles	59–62	Ether	$C_{15}H_{15}NO$ 225.2	6.33	6.22
2-(*p*-Methoxyphenethenyl)-6-methyl- hydrochloride	Bright yellow crystals	103–108	Aqueous HCl	$C_{15}H_{15}NO \cdot HCl$ 261.7	5.9	5.35
2-(3,4-Methylenedioxyphenethenyl)-6-methyl	Colorless crystals	114–116	Ethanol	$C_{15}H_{13}NO_2$ 239.2	6.06	5.83
2,6-Di-(3-hydroxy-4-methoxyphenethenyl)-	Yellow crystals	147–148	Ethyl acetate	$C_{23}H_{21}NO_4$ 375.2	3.76	3.73
2,6-Di-(3,4-methylenedioxyphenethenyl)-	Yellow crystals	195–196	Benzene	$C_{23}H_{17}NO_4$ 371.2	3.68	3.77
2,4-Distyryl-	Colorless crystals	174	Ethanol	$C_{21}H_{17}N$ 283.2	4.90	4.95
2,4-Di-(*p*-methoxyphenethenyl)-		205	Ethanol	$C_{23}H_{21}NO_2$ 343.2	3.95	4.08
2,4-Di-(*p*-methylenedioxyphenethenyl)-	Yellow crystals	215	Ethanol	$C_{23}H_{17}NO_4$ 371.2	3.87	3.77

The *lactate* was prepared by mixing molecular parts of lactic acid and the ether-alcohol solution of the free base. On evaporation to dryness, a thick, colorless syrup remained which was decomposed by water yielding the free base.

The *tartrate* was obtained by mixing an alcohol solution of 0.5 mole of tartaric acid with an alcohol-ether solution of 1.0 mole of base. On removal from the solvent and standing in a desiccator over P_2O_5, the material crystallized. Recrystallized from ethyl acetate, the compound melted at 124–125°. It is soluble in water to the extent of about 1.6%.

The *citrate* was prepared in the same manner as the tartrate, using $\frac{1}{3}$ mole of citric acid per mole of base. The product was recrystallized from benzol; m.p. 149–150°. It is soluble in water to the extent of about 0.2%.

The *ethanesulfonate* was prepared by treating 1 mole of the base with 1 mole of ethanesulfonic acid in absolute alcohol and evaporating to dryness. A white crystalline product remained which was recrystallized from benzene (or ethyl acetate); m.p. 119–120°. The

ethanesulfonate is very soluble in alcohol and soluble to the extent of about 6.7% in water at room temperature.

cis-1-Methyl-2,6-di-(β-phenethyl)piperidine (lobelan). Four and five-tenths grams of 2,6-distyrylpyridine methyl-*p*-toluenesulfonate was suspended in methyl alcohol and hydrogenated using 2% Adams platinum oxide catalyst at atmospheric pressure. The hydrogenation was complete after three hours. The catalyst was filtered off, the solvent removed in vacuum, and the remaining oil, which showed no tendency to crystallize, was taken up in ether, and dry hydrochloric acid gas introduced. The colorless, oily precipitate which separated crystallized after standing for a few hours in the ice-box and was crystal-

TABLE II

PYRIDINIUM *p*-TOLUENESULFONATES

COMPOUND	APPEARANCE	M.P. °C UNCORR.	CRYSTALLIZED FROM	EMPIRICAL FORMULA AND M.W.	N	
					Found	Calc'd.
2,6-Distyryl-N-methyl	Yellow crystals	232–234	Methanol	$C_{29}H_{27}NO_3S$ 469.2	2.78	2.98
2,6-Distyryl-N-ethyl	Yellow cubes	205–206	Ethanol	$C_{30}H_{29}NO_3S$ 483.2	2.78	2.90
2,4-Distyryl-N-methyl	Yellow crystals	201	Methanol	$C_{29}H_{27}NO_3S$ 469.2	2.86	2.98
2,4-Distyryl-N-ethyl	Yellow crystals	230–232	Ethanol	$C_{30}H_{29}NO_3S$ 483.2	2.92	2.90
2,6-Dimethyl-N-methyl	Yellow needles	110–120	Ethanol-petroleum ether	$C_{15}H_{19}NO_3S$ 293.1	4.87	4.77
2,6-Di-(*p*-methoxyphenethenyl)-N-ethyl	Yellow needles	140–145	Ethanol	$C_{32}H_{33}NO_5S$ 543.3	2.02	2.58
2,6-Di-(*p*-methoxyphenethenyl)-N-benzyloxyethyl	Bright yellow needles	201–203	Ethanol	$C_{39}H_{39}NO_6S$ 650.3	2.16	2.16[a]
2,6-Di-(phenethenyl)-N-propyl	Bright yellow needles	204–205	Ethanol	$C_{31}H_{31}NO_3S$ 497.2	2.20	2.82
2,6-Di-(methoxyphenethenyl)-N-methyl	Yellow crystals	228–230	Methanol	$C_{31}H_{31}NO_5S$ 429.2	5.77	5.97
2-Styryl-N-ethyl	Yellow crystals	142	Ethanol	$C_{22}H_{23}NO_3S$ 381.2	3.12	3.68

[a] Calc'd: C, 72.08; H, 6.05. Found: C, 72.02; H, 6.11.

lized from alcohol; m.p. 195–196°. This melting point is identical with that found for the hydrochloride of the material prepared by Wieland *et al.* (7), by the reaction of phosphorus trichloride on lobelanidine and reduction of the dichlorolobelan so formed.

When palladium black was used as a catalyst, saturation of the side-chain only occurred.

Our thanks are due to Dr. E. Flint for assistance in the preparation of 2,4-substituted derivatives of piperidine, and to Mr. L. Berger for the preparation of the salts of 1-methyl-2,6-di-(β-*p*-methoxyphenethyl)piperidine. The microanalyses were performed by Dr. A. Steyermark of the Microchemical Division of these laboratories.

TABLE III

Piperidine Derivatives

Compound hydrochloride[a]	Comp. no.	Appearance	M.P., °C	Crystallized from	Empirical formula and M.W.	Analysis					
						N		C		H	
						Found	Calc'd	Found	Calc'd	Found	Calc'd
2,6-Diphenethyl-1-methyl (lobelan) (8)	I a	Colorless hexagonal prisms	195–196	Ethanol	$C_{22}H_{29}N \cdot HCl$ 343.7	4.24	4.07	79.29	76.81	8.93	8.80
2,6-Diphenethyl (norlobelan)	I c	Long colorless needles	192–194	Ethanol ether	$C_{21}H_{27}N \cdot HCl$ 329.7	4.43	4.25				
2,6-Diphenethyl-1-ethyl	I d	Colorless plates	187–188	Alcohol	$C_{23}H_{31}N \cdot HCl$ 357.7	4.16	3.92				
2,6-Diphenethyl-1-propyl	I e	Colorless shining plates	174–176	Acetone ether	$C_{24}H_{33}N \cdot HCl$ 371.7	4.70	3.77				
2,6-Diphenethyl-1-β-hydroxyethyl	I f	Colorless crystals	180–182	Ethanol ether	$C_{23}H_{33}NO \cdot HCl$ 375.7	3.75	3.75				
2,6-Di-(*p*-methoxyphenethyl) base		Colorless crystals	154–155	Ethanol	$C_{23}H_{31}NO_2$ 353.2	3.58	3.98				
2,6-Di-(*p*-methoxyphenethyl)	I g	Colorless	209–211	Ethanol	$C_{23}H_{31}NO_2 \cdot HCl$	4.01	3.59				
2,6-Di-(*p*-methoxyphenethyl)-1-methyl	I h	Colorless cubic crystals	176–178	Ethanol	$C_{24}H_{33}NO_2 \cdot HCl$ 403.7	3.92	3.47				
2,6-Di-(*p*-methoxyphenethyl)-1-methyl base		Colorless cubes	73–75	Light petroleum ether	$C_{24}H_{33}NO_2$	3.83	3.81	76.18	78.43	9.09	9.05
2,6-Di-(*p*-methoxyphenethyl)-1-methyl tartrate		Colorless fine needles	124–125	Ethyl acetate	$(C_{24}H_{33}NO_2)_2 \cdot C_4H_6O_6$	3.30	3.17	70.81	70.56	8.36	8.20
2,6-Di-(*p*-methoxyphenethyl)-1-methyl citrate		Colorless prisms	149–150	Benzene	$(C_{24}H_{33}NO_2)_2 \cdot C_6H_8O_7$	3.08	3.02	69.90	69.95	7.99	8.05

2,6-Di-(*p*-methoxyphenethyl)-1-methyl ethanesulfonate		Colorless prisms	119–120	Benzene or ethyl acetate	$C_{24}H_{33}NO_2 \cdot C_2H_6SO_3$	2.81	2.93	65.44	65.38	8.33	8.23
2,6-Di-(*p*-methoxyphenethyl)-1-ethyl	I i	Colorless prismatic crystals	184–186	Acetone ether	$C_{25}H_{35}NO_2 \cdot HCl$ 417.7			72.10	71.82	9.00	8.68
2,6-Di-(*p*-methoxyphenethyl)-1-β-hydroxyethyl	I m	Colorless needles	209–211	Ethanol	$C_{25}H_{35}NO_3 \cdot HCl$ 433.7	3.14	3.23				
2,6-Di-(hydroxymethoxyphenethyl)	I k	Colorless prismatic crystals	225–240 decomp.	Ethanol ether	$C_{23}H_{31}NO_4 \cdot HCl$ 421.7	3.25	3.32				
2,6-Di-(3,4-methylenedioxyphenethyl)	I l	Colorless prisms	215–216	Ethanol	$C_{23}H_{27}NO_4 \cdot HCl$ 417.7	3.59	3.35	66.64	66.1	7.3	6.74
2,4-Diphenethyl-1-methyl (isolobelan)	IV b	Colorless prisms	58–61	Acetone ether	$C_{22}H_{29}N \cdot HCl$ 343.7	4.36	4.07				
2,4-Diphenethyl-1-ethyl	IV e	Colorless crystals	155–156	Ethanol petroleum ether	$C_{23}H_{31}N \cdot HCl$ 357.7	4.20	3.92				
2,4-Di-(*p*-methoxyphenethyl)-1-ethyl	IV c	Colorless crystals	—	—	$C_{25}H_{35}NO_2 \cdot HCl$ 417.7	3.37	3.35				
2-Phenethyl-1-methyl	IV a	Colorless crystals	250	Ethanol ether	$C_{15}H_{23}N \cdot HCl$ 253.7	5.88	5.52				
2-Phenethyl-1,4-dimethyl	IV d	Colorless needles	194–196	Benzene petroleum ether	$C_{15}H_{23}N \cdot HCl$	5.77	5.52				

[a] Except where otherwise stated.

SUMMARY

1. Nine derivatives of 2,6-di(phenethyl)piperidine (norlobelan), including lobelan, have been synthesized by the reduction of the corresponding 1-alkyl-2,6-distyrylpyridinium *p*-toluenesulfonates.

2. Three derivatives of 2,4-di(phenethyl)piperidine and two derivatives of 1-methyl-2-phenethylpiperidine have been synthesized by an analogous method.

3. The compounds examined for spasmolytic activity showed powerful myotropic and neurotropic effects.

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

THE PREPARATION OF 4-CARBETHOXY-3-METHYL-5-ALKYL-2-CYCLOHEXEN-1-ONES AND 3-METHYL-5-ALKYL-2-CYCLOHEXEN-1-ONES

E. C. HORNING, M. O. DENEKAS, AND R. E. FIELD

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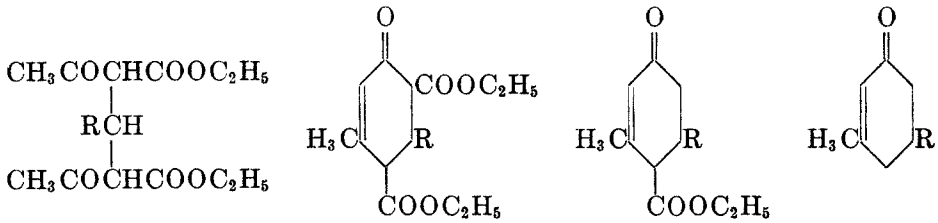
In studying certain examples of alicyclic-aromatic isomerizations, it was necessary to prepare a series of 3-methyl-5-alkyl-2-cyclohexen-1-ones (IV). For their preparation Knoevenagel's methods were used, in which an aliphatic aldehyde is condensed with two moles of ethyl acetoacetate to yield a *bis*-ester (I), followed by cyclization to a keto diester (II) and removal of the two carbethoxyl groups to give the ketones (IV). The carbethoxyl groups of 4,6-dicarbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones (II) have in some cases been removed one at a time, yielding successively 4-carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones (III) and 3-methyl-5-alkyl-2-cyclohexen-1-ones (IV); it is also possible to carry out the reaction sequence in a single operation yielding ketones IV from *bis*-esters I.

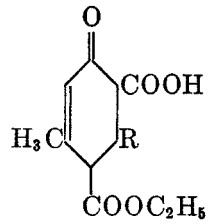


I II III IV

It was found that Knoevenagel's procedures for preparing the ketones (IV) possessed several unsatisfactory features when alkyl groups higher than methyl were involved. In the course of developing an improved general method for obtaining the ketones (IV), we have found an improved general method for preparing the keto esters (III) from *bis*-esters (I), and have also modified the procedure for obtaining 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one (II, R = CH_3) from the *bis*-ester (I, R = CH_3).

The ring closure of the *bis*-esters (I) occurs readily under both acid and alkaline conditions. To obtain 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one (II, R = CH_3), Knoevenagel (2) found it best to carry out the cyclization of the *bis*-ester (I, R = CH_3) (obtained from acetaldehyde) by means of hydrogen chloride in ether, but he encountered extensive decomposition during distillation of the produce *in vacuo*. If hydrochloric acid is added to an ether-benzene suspension of recrystallized *bis*-ester, a smooth cyclization results and 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one (II, R = CH_3) can be isolated readily and with little decomposition on distillation.

It was found that when the crude *bis*-esters (I) were maintained under reflux in glacial acetic acid containing sulfuric acid that a copious evolution of carbon dioxide occurred and 4-carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones (III), in which the alkyl group was methyl, ethyl, *n*-propyl, isopropyl, and *n*-hexyl, were formed in 52–71% yields. Selective removal of the 6-carbethoxyl group has been accomplished previously in several instances by heating *bis*-esters (I) with water at 140°, or with one equivalent of sodium ethoxide in alcohol.



V

We believe this reaction in acetic acid-sulfuric acid involves first a ring closure to the keto diester II, followed by an ester-interchange with acetic acid to yield a keto ester acid (V) which then decarboxylates immediately to yield the keto ester III. No attempt, however, has been made to prove that the removal of the ester group occurs by ester-interchange rather than by hydrolysis. In either case the equilibrium (interchange or hydrolysis) is driven to completion as a result of the decarboxylation. Presumably the 4-carbethoxyl group could also be removed by the same type of reaction, but the rate at which this occurs appears to be extremely slow when compared to the rate at which the 6-carbethoxyl group may be removed.

The products from this reaction were used in crude form for the preparation of the ketones IV. Saponification with aqueous alcoholic sodium hydroxide served to hydrolyze the remaining carbethoxyl group, and decarboxylation resulted on acidification of the solution. Yields of 56% to 78% of 3-methyl-5-alkyl-2-cyclohexen-1-ones (IV) were obtained, in which the alkyl group was methyl, ethyl, *n*-propyl, isopropyl, and *n*-hexyl. Knoevenagel's methods for preparing these ketones involved prolonged heating of the crude condensation products (*bis*-esters) with acid (20% sulfuric acid) or alkali (10–15% sodium or potassium hydroxide). When these methods were applied to higher homologs of acetaldehyde, the yields were low and subject to wide variation.

This procedure for removing a carbethoxyl group from a β-keto ester may be capable of extension; the effect of acetic acid-sulfuric acid on similar compounds derived from aromatic aldehydes is being investigated.

EXPERIMENTAL

Condensation of aldehydes with ethyl acetoacetate. The condensation of freshly distilled propionaldehyde, *n*-butyraldehyde, isobutyraldehyde, and *n*-heptaldehyde with ethyl acetoacetate was carried out with equivalent molar amounts in the fashion described for acetaldehyde. The condensation product from acetaldehyde was a solid; from higher aldehydes it was a viscous oil which was used as obtained.

In each of three 500-cc. flasks was placed 210 cc. (210 g., 1.6 mole) of ethyl acetoacetate. The flasks were chilled in an ice-salt bath and 45 cc. (34 g., 0.77 mole) of acetaldehyde was added to each flask. The contents were cooled to 0° and there was added to each flask, with shaking, 2 cc. of piperidine in 5 cc. of ethanol. The flasks were kept in an ice-salt bath for six hours, and the contents then combined and placed in a refrigerator. The mixture was kept in a refrigerator for three days, and a piperidine-ethanol mixture (3 cc. of piperidine, 5 cc. of ethanol) was added each day during this time. Crystallization usually occurred near the end of this period, but to ensure completeness of the reaction the mixture was allowed to stand for one day longer at room temperature. The product was usually used in crude form, although a recrystallization was necessary to provide material for the preparation of 4,6-dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one. The crystallization was carried out as rapidly as possible from a water-alcohol mixture, using 450 cc. of ethyl alcohol (95% denatured) and 300 cc. of water. The crystallized material was washed with cold, diluted alcohol and then air dried. The product was a colorless powder, m.p. 75–77.5°; yield, 390–405 g. The reported m.p. is 79–80° (1), but no further purification was attempted.

4,6-Dicarbethoxy-3,5-dimethyl-2-cyclohexen-1-one. Ten cubic centimeters of conc'd hydrochloric acid was added to a suspension of 390 g. of recrystallized *bis*-ester (I, R = CH_3) in 400 cc. of ether and 100 cc. of benzene, and the mixture shaken well. An additional 50 cc. of benzene was added and the mixture was allowed to stand for fifteen hours at room temperature. The solvents were removed, and the residue distilled *in vacuo* after the addition of about 50 cc. of toluene to facilitate the removal of water; yield, 292 g.; b.p. 188–190° at 19 mm. [reported (2) b.p. 225–230° at 35 mm.].

The yellow-orange *2,4-dinitrophenylhydrazone* was recrystallized from ethanol; m.p. 126.5–127.5°.

Anal. Calc'd for $C_{20}H_{24}N_4O_8$: C, 53.57; H, 5.39.
Found: C, 53.40; H, 5.48.

4-Carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-one (III). Crude *bis*-esters (I) from homologs of acetaldehyde were added to the acetic acid-sulfuric acid solution and the procedure described for the methyl analog was then followed. Yields, properties, and references are in Table I, together with the melting points of the 2,4-dinitrophenylhydrazones. The keto esters (III) all gave dark enol colors with ferric chloride in aqueous alcohol.

The yield of crude *bis*-ester (I, R = CH_3) obtained from acetaldehyde as described was was melted on a steam-cone and poured into a mixture of 600 cc. of acetic acid and 40 cc. of conc'd sulfuric acid. About 10 g. of clay boiling chips was added, and the mixture was refluxed for one hour; during this time there was a vigorous evolution of carbon dioxide. The mixture was poured with (mechanical) stirring into 2 l. of ice-water, and the layers separated with the aid of ether. The organic layer was stirred with 1200 cc. of water and neutralized by the slow addition of solid sodium carbonate, and the solutions again separated. The ethereal solution of the crude material was used for the preparation of 3,5-dimethyl-2-cyclohexen-1-one. In order to isolate 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one, the ether solution was washed with 5% sodium hydroxide solution, with 2% aqueous acetic acid, dried (anhydrous sodium sulfate), and distilled under reduced pressure through a short column. The fraction boiling at 135–155° at 10 mm. was fractionated through a Widmer column (12 inch); yield, 234 g. (52%); b.p. 137–138° at 9 mm.

3-Methyl-5-alkyl-2-cyclohexen-1-one (IV). The ethereal solution containing crude 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one, obtained as described, was heated gently under reduced pressure until the ether was removed. There was added 1140 cc. of water, 60 cc. of alcohol (95%), and 130 g. of sodium hydroxide. The mixture was heated on a steam-cone, with shaking, until the ester dissolved. The solution was heated under reflux for 15 minutes, and then acidified carefully with sulfuric acid, using a solution of 100 cc. of conc'd sulfuric acid in 200 cc. of water. This was carried out slowly while cooling the flask with a stream of water. The acid was added to the *hot* solution at a rate compatible with the ensuing vigorous evolution of carbon dioxide. The acidified mixture was boiled under reflux for 15 minutes, allowed to cool, and the layers separated. The crude product

was diluted with ether, washed with two 100 cc. portions of 5% sodium hydroxide solution, and then with 100 cc. of 5% aqueous acetic acid. The ethereal solution was dried (anhydrous sodium sulfate) and distilled under reduced pressure. There was obtained 160 g. (56%) of 3,5-dimethyl-2-cyclohexen-1-one, b.p. 84–86° at 9 mm. [reported, 23% (6), 83% (9), 63–83% (11), no yield given (12, 13)].

The procedure for the methyl analog was followed generally, but the amount of alcohol used during the saponification for higher homologs was increased by 60 cc. for each carbon atom in the side chain, with a corresponding decrease in the amount of water. The amount of sodium hydroxide was increased to 200 g. for the isopropyl compound.

When higher aldehydes were used the results were:

5-ethyl: 66%; b.p. 98–102° at 9 mm. (12, 14, 15).

5-n-propyl: 78%; b.p. 110–113° at 9 mm. (12, 16).

5-isopropyl: 71%; b.p. 120–122° at 15 mm. (10, 13, 17).

5-n-hexyl: 73%, b.p. 154–155° at 11 mm. (10, 13, 18).

TABLE I

4-CARBETHOXY-3-METHYL-5-ALKYL-2-CYCLOHEXEN-1-ONE

5-ALKYL	B.P., °C	YIELD, %	2,4-DINITROPHENYLHYDRAZONES				
			M.P., °C	Calc'd, %		Found, %[f]	
				C	H	C	H
Methyl[a]	137–138 (9 mm.)	52	133 –134	54.25	5.36	54.16	5.43
Ethyl[b]	146–149 (10 mm.)	61	120 –121.5	55.37	5.68	54.99	5.87
n-Propyl[c]	144–148 (10 mm.)	64	110.5–111.5	56.43	5.98	56.63	6.18
i-Propyl[d]	148–151 (10 mm.)	61	109 –110.5	56.43	5.98	56.19	6.13
n-Hexyl[e]	183–186 (10 mm.)	71	109 –110	59.17	6.77	59.00	6.84

[a] (3, 4, 5, 6). [b]Analytical data indicated less than analytical purity, not improved on further fractionation. Calc'd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 67.37; H, 8.66. [c]*Anal.* Calc'd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.36; H, 9.12. [d](7). [e](8). [f]By a semimicro method following Elving and McElroy [*Ind. Eng. Chem., Anal. Ed.*, **13**, 660 (1941)].

SUMMARY

Improved preparative methods for obtaining 4-carbethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones and 3-methyl-5-alkyl-2-cyclohexen-1-ones from aliphatic aldehydes and ethyl acetoacetate by way of Knoevenagel's condensation have been developed.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF BRYN MAWR COLLEGE AND THE UNIVERSITY OF MICHIGAN]

ALICYCLIC-AROMATIC ISOMERIZATIONS. 2,5-DIMETHYL-3-ALKYLPHENOLS FROM 3-METHYL-5-ALKYL-2-CYCLOHEXEN-1-ONES THROUGH THE MANNICH REACTION

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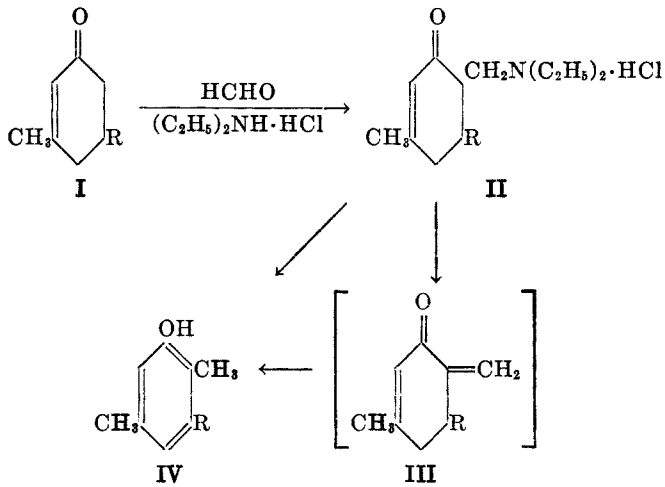
The isomerization of an alicyclic compound to an aromatic structure offers a relatively little used route for the preparation of many aromatic compounds (1). As part of a study of the preparation of phenols by this type of synthesis, we have prepared 2,5-dimethyl-3-alkylphenols from the readily available 3-methyl-5-alkyl-2-cyclohexen-1-ones as shown in formulas I–IV.



The first step, a Mannich reaction, was carried out in one of the usual fashions (2), employing the ketone, paraformaldehyde, and diethylamine (or dimethylamine) hydrochloride in absolute alcohol solution. Deamination of the Mannich salts was carried out by pyrolysis of the hydrochlorides at temperatures in the vicinity of 200°. The pyrolysis proceeded rapidly and afforded a distillate from which it was possible to isolate 2,5-dimethyl-3-alkylphenols (IV), where the alkyl group was methyl, ethyl, *n*-propyl, isopropyl, and isobutyl. The yields, however, were low at best and decreased with increasing chain length of the alkyl group.

Although it was not found possible to isolate crystalline Mannich salts, the fact that phenols were obtained indicated that the Mannich reaction was, at least in part, successful. It is not known whether the phenols were produced by direct deamination of the Mannich salts (II), or by the isomerization of intermediate methylene ketones (III) under the influence of hydrogen chloride present during the pyrolysis. An attempt was made to obtain evidence for III as a possible

intermediate by carrying out a deamination and catalytic isomerization on the free Mannich base obtained from 3,5-dimethyl-2-cyclohexen-1-one and dimethylamine hydrochloride. The base, isolated by distillation, was heated with a palladium-charcoal catalyst; dimethylamine was evolved and 2,3,5-trimethylphenol was isolated from the mixture. That the catalyst was necessary was evidenced by the fact that no phenol was formed when charcoal alone was used. It therefore appears likely that in this case the reaction proceeded through catalytic isomerization of the methylene ketone (III, R = CH_3) produced by deamination of the base. The yield obtained by this method, however, was lower than that obtained through pyrolysis of the hydrochloride.

In view of the connection of 2,3,5-trialkylphenols with Vitamin E studies, other routes for preparing these phenols from cyclohexenones are being studied.

EXPERIMENTAL

Mannich reaction on 3-methyl-5-alkyl-2-cyclohexen-1-one. The required ketones may be obtained from aliphatic aldehydes and ethyl acetoacetate according to Knoevenagel (3) or through an improved procedure (4). A mixture of 0.30 mole of the ketone, 15.0 g. (0.50 mole) of paraformaldehyde, 32.6 g. (0.30 mole) of diethylamine hydrochloride, two drops of conc'd hydrochloric acid, and 50 cc. of absolute alcohol was maintained under reflux in a nitrogen atmosphere for forty minutes to one hour, the longer time being employed for the higher ketones. The mixture was poured into 200 cc. of water containing 5 cc. of conc'd hydrochloric acid; unchanged ketone was removed with ether (ketone recovery *ca.* 20–25%) and the aqueous solution was made alkaline with 120 cc. of 20% sodium hydroxide solution. The oil which separated was removed, the solution was extracted once with ether, and the organic layers were combined. Fifty cubic centimeters of ethanol was added to the ethereal solution and hydrogen chloride was passed into the solution until the color became light yellow. The addition of 200 cc. of ether precipitated a syrup which was washed with ether by decantation. This syrupy mixture of hydrochlorides was subjected to pyrolysis. Attempts to isolate a crystalline Mannich salt by addition of ether to the original alcohol solution, or by removal of unreacted diethylamine from the dried basic reaction products by warming under reduced pressure, followed by treatment with hydrogen chloride in ether, were unsuccessful.

The effects of experimental variations were determined in the case of 3,5-dimethyl-2-cyclohexen-1-one. Employment of larger amounts of paraformaldehyde or of diethylamine hydrochloride or both did not increase the ultimate yield of phenol. When a three-fold excess of ketone (0.90 mole) was used without added solvent, and the mixture heated on a steam-cone for 30 minutes, the yield of phenol was lowered and a solid by-product (1.6 g., m.p. 164–166°) whose structure has not been elucidated, was also isolated from the pyrolysis products.

Reduction of the time of reflux to much less than 30 minutes, or prolonging it unduly (several hours) beyond the hour period, resulted in a lowered yield of phenol. When the reaction time was increased to 14 hours, no phenol was obtained after pyrolysis. The yield of phenol was slightly lower when dimethylamine hydrochloride was substituted for diethylamine hydrochloride.

A number of attempts were made to isolate the Mannich base from 3,5-dimethyl-2-cyclohexen-1-one and dimethylamine hydrochloride. This base is the lowest in molecular weight in the series, and presumably should have the lowest boiling point in the group. Distillation under reduced pressure of the Mannich base from 3,5-dimethyl-2-cyclohexen-1-one and dimethylamine hydrochloride was accompanied by extensive decomposition; the boiling ranges observed were wide and variable, and the product darkened rapidly. One fraction, b.p. 115–125° at 10 mm., was treated with Pd-charcoal (described later) to yield

2,3,5-trimethylphenol. Prolongation of the reaction time resulted in basic oils which distilled in small part or not at all. Attempted distillation of bases from higher homologs resulted in practically complete decomposition.

Pyrolysis. The mixture of hydrochlorides, obtained as described, was separated from the major portion of the solvents by decantation, and was placed in a 125-cc. distilling flask. The solvent was removed (aspirator) and the flask was heated slowly in an air-bath, under reduced pressure (aspirator). As the temperature rose, a slow distillation was observed; decomposition set in at 170° (thermometer in the mixture). The pyrolysis was practically complete at 200–210°, but the temperature was carried to 230–235° with a slight increase in pressure to about 40 mm. (to avoid extensive distillation of diethylamine hydrochloride). The pyrolysis proper required only about ten minutes.

TABLE I

2,5-DIMETHYL-3-ALKYLPHENOLS

3-ALKYL	M.P., °C	YIELD		FORMULA	CALC'D, %		FOUND, %	
		g.	%		C	H	C	H
Methyl	93.5–94.5[a]	4.0	10	$C_9H_{12}O$	—	—	—	—
Ethyl	71–72	3.3	7	$C_{10}H_{14}O$	79.95	9.39	79.78	9.46
n-Propyl	72.5–73.5	1.9	4	$C_{11}H_{16}O$	80.44	9.82	80.41	9.79
Isopropyl	78–79.5	2.1	4	$C_{11}H_{16}O$	80.44	9.82	80.38	9.89
Isobutyl	61–62	0.2	0.4	$C_{12}H_{18}O$	80.84	10.16	80.68	9.97

[a] Literature values vary from 93° to 95°.

TABLE II

4,6-DIBROMO-2,5-DIMETHYL-3-ALKYLPHENOLS

3-ALKYL	M.P., °C	FORMULA	CALC'D, %		FOUND, %	
			C	H	C	H
Methyl	149–150[a]	$C_9H_{10}Br_2O$	—	—	—	—
Ethyl	67–68	$C_{10}H_{12}Br_2O$	38.99	3.93	39.02	4.09
n-Propyl	61.5–62.5	$C_{11}H_{14}Br_2O$	41.02	4.39	41.21	4.50
Isobutyl	60.5–61.5	$C_{12}H_{16}Br_2O$	42.88	4.80	43.02	4.96

[a] In agreement with the literature.

The distillate was dissolved in 40–50 cc. of low-boiling petroleum ether, and the solution was washed with 5% hydrochloric acid, and with two 30-cc. portions of 10% sodium hydroxide solution. The combined alkaline extracts were saturated with carbon dioxide and the phenol which separated was removed by filtration. (The solution remaining after alkaline extraction contained small amounts of liquid products whose composition was not investigated.) 2,3,5-Trimethylphenol was steam distilled and then sublimed. Higher phenols were first pressed on a clay plate and then sublimed. The yields and properties of the phenols are given in Table I.

4,6-Dibromo-2,5-dimethyl-3-alkylphenols. The dibromo derivatives of the phenols, prepared by bromination at room temperature in carbon tetrachloride, were obtained as colorless needles (with the exception of the isopropyl compound, which was an oil) after recrystallization from aqueous alcohol or sublimation. Melting points are in Table II.

Deamination and aromatization of a Mannich base. Ten grams of a basic oil, b.p. 115–125° at 10 mm., obtained by distillation *in vacuo* of basic reaction products from the Mannich reaction of 3,5-dimethyl-2-cyclohexen-1-one and dimethylamine hydrochloride, was

heated with 1 g. of Pd-charcoal catalyst (5) for 30 minutes at 200–240°. There was a copious evolution of dimethylamine. From the resulting tar it was possible to isolate 0.6 g. of 2,3,5-trimethylphenol. Heating a second portion of the same basic oil with charcoal alone under the same circumstances led to a tar from which no phenol could be isolated.

SUMMARY

3-Methyl-5-alkyl-2-cyclohexen-1-ones have been subjected to a Mannich reaction and the resulting products have been deaminated and aromatized by pyrolysis to yield 2,5-dimethyl-3-alkylphenols. The alkyl groups were methyl, ethyl, *n*-propyl, isopropyl, and isobutyl.

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(5) HARTUNG, *J. Am. Chem. Soc.*, **50**, 3370 (1928). See also *J. Am. Chem. Soc.*, **66**, 888 (1944), footnote 7.

ERRATA

Butz and Butz, "The Synthesis of Condensed Ring Compounds. IX." *J. Org. Chem.*, **7,** 199 (1942).

Page 226, Reference (12) Alder and Stein, *Angew. Chem.*, **50,** 519 (1937), should read (13) Alder and Stein, *Angew. Chem.*, **50,** 512 (1937).

Reference (13) Alder and Stein, *Ann.*, **501,** 265 (1933) should read (12) Alder and Stein, *Ann.*, **501,** 265–267 (1933); ref. 12, p. 519.

Fuson and Robertson, "The Addition of Methylmagnesium Iodide to *t*-Butyl Mesityl Diketone", *J. Org. Chem.*, **7,** 466 (1942).

Page 469, insert after first paragraph:

Anal. Calc'd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68.
Found: C, 77.65; H, 8.78.

Fuson, Denton, and Best, "Highly Hindered Stilbenes", *J. Org. Chem.*, **8,** 64 (1943).

Page 69, insert after paragraph headed *"2-Phenyl-1-(triisopropylphenyl) ethylene":*

Anal. Calc'd for $C_{23}H_{30}$: C, 90.13; H, 9.87.
Found: C, 90.29; H, 9.94.

Hurd, Cashion, and Perletz, "Consideration of General Methods for the Formation of Ketenes", *J. Org. Chem.*, **8,** 367 (1943).

Page 369, line 2, and page 371, lines 11 and 7 from the bottom, "2-acetoxypropionyl bromide" should read "α-bromopropionyl bromide".

Fuson and Soper, "Quinoxaline Formation and the Ortho Effect", *J. Org. Chem.*, **9,** 193 (1944).

Page 197, line 12, "3,5-Dinitro-2,4,6-triisopropylphenylglyoxylic acid" should read "3-Nitro-2,4,6-triisopropylphenylglyoxylic acid". Line 16, "dinitroglyoxylic acid" should read "mononitroglyoxylic acid".