Naphthalic Anhydride from Tetrahydro-7-methylfluoranthene-10-carboxylic Acid (IV).—A solution of 0.2 g. of the acid (IV) in 30 cc. of hot acetic acid and a solution of 2 g. of potassium dichromate in 20 cc. of water plus 0.5 cc. of concentrated sulfuric acid were mixed and heated twenty-four hours at 100°. After adding 30 cc. of water and 10 cc. of sulfuric acid, the cooled solution was extracted with three 50-cc. portions of ether. The ether was removed and the residue sublimed up to 250° at 30 mm. Recrystallization of the sublimate from ethanol gave 14 mg. (9%) of creamy-white needles of naphthalic anhydride, m. p. 271.5–272°, no depression when mixed with an authentic sample.

Summary

Indene and 1,2-dihydronaphthalene reacted with sorbic and muconic acids to give partially hydrogenated fluorene and phenanthrene derivatives. Sorbic acid also reacted with α-methylstyrene and acenaphthylene to give partially hydrogenated biphenyl and fluoranthene derivatives.

The structures of the products were proven by appropriate degradative experiments and add support to current electronic theories of the Diels–Alder reaction.

Although the yields were low (12 to 24% of pure product), the ease of isolation recommends these reactions as practical methods for the preparation of the above condensed ring systems.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Further Study of the Rearrangement Occurring during the Alkylation of 6-Methoxy-8-aminoquinoline with 1-Diethylamino-3-chloropentane[1]

BY ROBERT C. ELDERFIELD AND CHARLOTTE RESSLER

In a previous paper[2] in which the preparation of the antimalarial SN-13,431[3a] was described, the formation of isomeric substances was noted when the product of the reaction of 6-methoxy-8-aminoquinoline (VI) and 1-diethylamino-3-chloropentane (II) was examined by the Craig countercurrent distribution method. Two major components of the reaction product, present to the extent of 75–80% (compound A) and 20–25% (compound B) respectively, were partially characterized by unique distribution constants and by a citrate of B melting at 136–139°. The latter salt was identical with the citrate prepared from the major contaminant of commercial pamaquin and was given the trivial name of *iso*-pamaquin. Although no experimental evidence was offered, it was suggested that the isomeric bases might be formed by way of a cyclic intermediate (III)

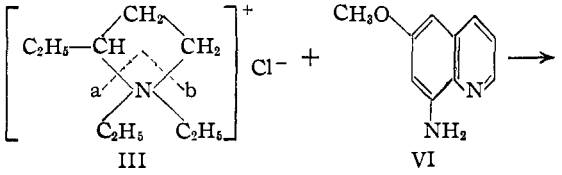
$C_2H_5CHOHCH_2CH_2Cl \longrightarrow$

$C_2H_5CHOHCH_2CH_2N(C_2H_5)_2 \longrightarrow$

I

$C_2H_5CHClCH_2CH_2N(C_2H_5)_2 \longrightarrow$

II

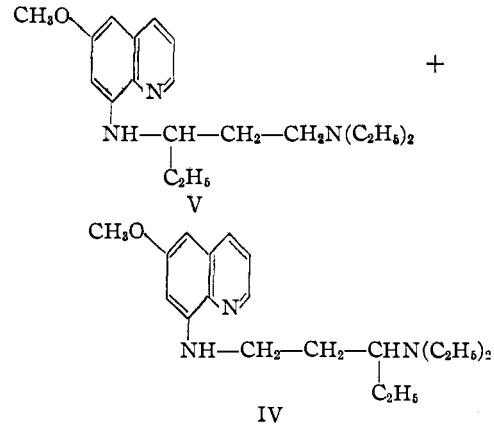


III VI

(1) This investigation was made possible by a grant-in-aid from the National Institutes of Health.

(2) Elderfield, Craig, Lauer, *et al.*, THIS JOURNAL, **68**, 1516 (1946).

(3) This Survey Number has been assigned according to the system used by Wiselogle, Survey of Antimalarial Drugs (1941–1945), J. W. Edwards, Ann Arbor, Michigan, 1946; (a) Vol. II, part 2, 1191; (b) *ibid.*, 1136.



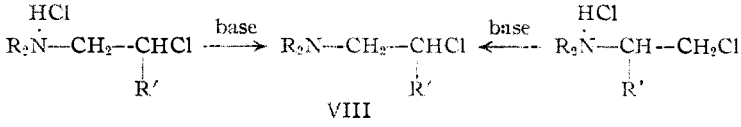
IV

Displacement by the base, VI, on bond "a" of III would lead to the isomer V while displacement on bond "b" of III would lead to the isomer IV. In the present investigation the structures previously tentatively assigned to Compounds A and B (IV and V) have been experimentally substantiated and the suggested mechanism accounting for their formation has been discussed.

In addition to the above mechanism wherein the propylenimmonium ion, III, is regarded as the effective alkylating intermediate, the possibility exists that rearrangement may also have occurred during the preparation of the amino alcohol (I) from the precursor chloro alcohol, conceivably through an analogous trimethylene oxide intermediate. Evidence that a mixture of isomers did not result in the preparation of I was obtained by a close examination of several crystalline fractions of a salt obtained in good yield from I.

Rearrangement may have also occurred during the preparation of the chloroamine (II) either at the time of its liberation from its hydrochloride or

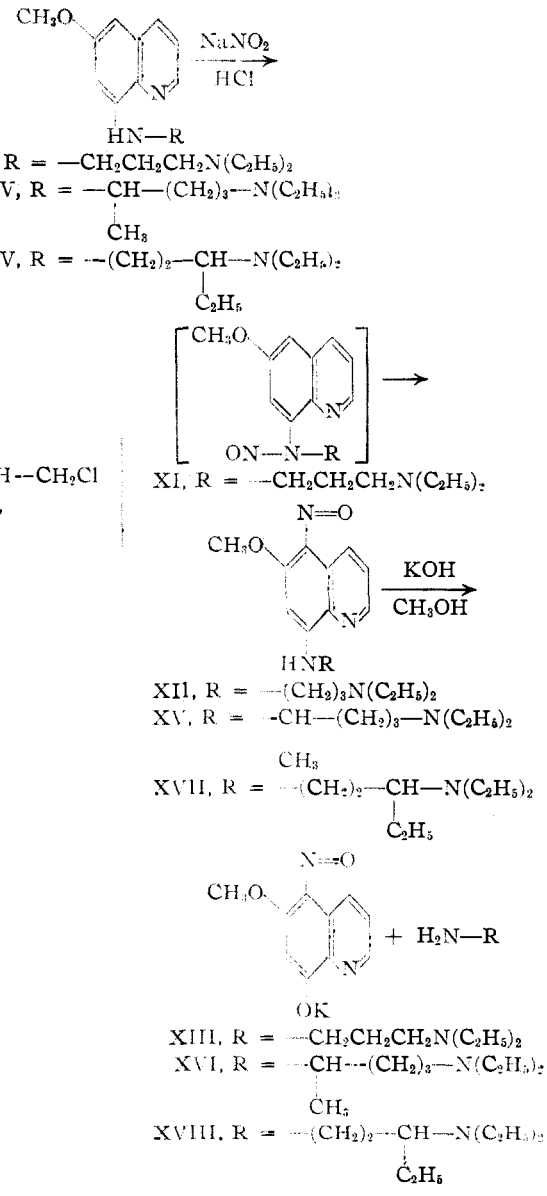
during distillation. Displacement by chloride ion on bonds "a" or "b" of the same cyclic intermediate (III) would give rise to 1-diethylamino-3-chloropentane (II) and 1-chloro-3-diethylaminopentane (VII) respectively. Alkylation of the aminoquinoline (VI) with these chloroamines would then give rise to IV and V. This possibility does not seem likely since homogeneity determinations on the chloroamine, (II), after distillation showed it to be homogeneous within 3%.[2] Further, the hydrochloride and picrate of the distilled substance are identical with the same salts obtained directly from the crude aminochloride prepared from 1-diethylaminopentanol-3 and thionyl chloride. Close examination of the picrate obtained from the distilled chloroamine base also helped to confirm the homogeneity of II. Moreover, observations elsewhere[4,5,6] on the action of base on pairs of isomeric chloroamine hydrochlorides indicate that the bases liberated possess a common structure (VIII) analogous to that of II, *e. g.*



Further indication that rearrangement did not occur in the preparation of II from I may be derived from the work of Cope, *et al.*,[7] in which the aminochlorides formed from several primary and secondary β-alkylamino alcohols were converted most probably without rearrangement back to the original aminoalcohols.

Several examples of alkylation by means of cyclic ethylenimmonium ions may be found in the literature.[5,7,8,9,10,11] Kharasch and Fuchs[12] were able to alkylate phthalimide and succinimide ions with 1,1-diethyl-2-methylpyrrolidinium bromide, although this salt failed to alkylate bases such as sodium phenylacetylide, sodamide[12] and 6-methoxy-8-aminoquinoline.[2] Alkylations of nitrogen, oxygen and sulfur by quaternary ions without involving rupture of a bond of a cyclic structure are well known.[13] As far as we are aware, no case exists in the literature in which an azetidinium ion of the type of III has either been proved or assumed to act as an alkylating agent.

The structures of IV and V were established by two degradation reactions described below, by which the side chains could be removed as identifiable substances without possibility of further rearrangement during the process. The first method used was based on the classical general procedure of Baeyer and Caro for the preparation of primary and pure secondary amines[14] according to the general equation



In order to test the reliability of this general method, it was applied to 6-methoxy-8-(3-diethylaminopropylamino)-quinoline (X). When X was nitrosated under conditions designed[15] to yield the N-nitrosoamine (XI), the latter substance was not isolated. Rather rearrangement occurred either during the reaction or in the subsequent working up and the 5-nitroso derivative (XII) was ob-

(4) Schultz and Sprague, THIS JOURNAL, **70**, 48 (1948).
(5) Kerwin, Ullyot, Fuson and Zirkle, *ibid.*, **69**, 2961 (1947).
(6) Fuson and Zirkle, *ibid.*, **70**, 2760 (1948).
(7) Cope, Nace, Hatchard, Jones, Stahmann and Turner, *ibid.*, **71**, 554 (1949).
(8) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946) and following papers.
(9) Ross, THIS JOURNAL, **69**, 2982 (1947).
(10) Schultz, Robb and Sprague, *ibid.*, **69**, 188, 2454 (1947).
(11) Clapp, *ibid.*, **70**, 184 (1948); Coleman and Callen, *ibid.*, **68**, 2006 (1946).
(12) Kharasch and Fuchs, *J. Org. Chem.*, **9**, 359 (1944).
(13) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944); Rodionov, *Bull. soc. chim. France*, [4] **39**, 305 (1926).
(14) Baeyer and Caro, *Ber.*, **7**, 809 (1874); Fischer and Hepp, *ibid.*, **19**, 2991 (1886); **20**, 2471 (1887); **21**, 684 (1888).
(15) Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, second edition, 1948, p. 317.

tained directly. The structure of XII is assigned by analogy to the behavior of ethylaniline on nitrosation and subsequent rearrangement[15] and on the basis of the known nitration of quinoline which occurs at the 5 and 8 positions. In this and subsequent similar preparations the yields of solid or oily green nitroso compounds varied between 21 and 73%. In the cases of compounds giving low yields it was found more advantageous to recycle the unnitrosated base rather than to use excess reagent because of the extreme lability of the nitroso compounds to acid as well as to base.

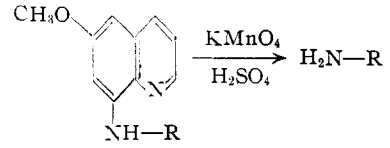
Hydrolysis of the nitroso derivative (XII) with aqueous sodium bisulfite[16] gave unreproducible results. The volatile diamine formed apparently was absorbed at times onto the voluminous sulfonated quinoline fragment. Better success attended the use of a solution of potassium hydroxide in absolute methanol. The primary-tertiary diamine was easily isolated and converted into appropriate derivatives for characterization.

By these reactions X yielded 3-diethylaminopropylamine (XIII), pure pamaquin (XIV) yielded 1-diethylamino-4-aminopentane (XVI) via the nitroso compound (XV), and Compound A (IV) yielded 3-diethylamino-1-aminopentane (XVIII) via the nitroso compound, XVII. The identification of XVIII was on the basis of identity of melting points, mixed melting points and crystal habits of the picrate, hydrochloride and hydrobromide of the diamine obtained as above with the salts of a known sample of the diamine synthesized as described below.

When the minor component (Compound B) of SN-13,431 was nitrosated under similar conditions, extensive decomposition occurred. Although the potassium salt of 5-nitroso-6-methoxy-8-hydroxyquinoline was obtained in good yield, no diamine could be isolated. Accordingly, conditions for a second degradative method were worked out.

Available evidence in the literature on the permanganate oxidation of alkyl, aryl and mixed amines is generally inconclusive. The nature of the products appears to be very sensitive to changes in experimental conditions. Diethylamine has been obtained along with other products from the oxidation of diethylaniline.[17] Knunjanz, *et al.*,[18] mention the formation of 1-diethylamino-4-aminopentane on oxidation of pamaquin with acid permanganate. Under proper conditions hydrogen peroxide effects smooth cleavage of the side-chain of pamaquin as 1-diethylamino-4-aminopentane.[19]

It has now been found that oxidation of representative 8-aminoquinoline drugs with approximate molar proportions of base, permanganate and sulfuric acid of 1:4:20 at 30° results in cleavage of the side-chain as the diamine in good yield. In this way oxidation of pamaquin (XIV) yielded 1-diethylamino-4-aminopentane (XVI). Compound A (IV) again yielded 3-diethylamino-1-aminopentane (XVIII) and Compound B (V) yielded 1-diethylamino-3-aminopentane (XIX).



XIV, R = $-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$

IV, R = $-(CH_2)_2-CH(C_2H_5)-N(C_2H_5)_2$

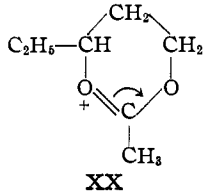
V, R = $-CH(C_2H_5)-(CH_2)_2-N(C_2H_5)_2$

XVI, R = $-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$

XVIII, R = $-(CH_2)_2-CH(C_2H_5)-N(C_2H_5)_2$

XIX, R = $-CH(C_2H_5)-(CH_2)_2-N(C_2H_5)_2$

On the basis of this verification of the structures previously assigned to Compounds A and B it appears that a rational explanation for the formation of these isomers may be found in the assumption of the formation of an intermediate azetidinium ion (III) followed by a displacement on either bond "a" or bond "b." The predominance of the rearranged product, IV, in the alkylation products also favors the picture of an SN_2 displacement by VI on the primary carbon atom (bond "b") of the intermediate. An analogous four-membered trimethylene oxide intermediate has been suggested to explain the formation of 1-hydroxy-3-acetoxypentane from 1-chloropentanol-3 and potassium acetate[20]; although the six-membered structure (XX) may also be considered a likely intermediate



XX

The possibility, although unlikely, of alternate paths to IV and V exists. Consideration of such paths forces the conclusion that, should they ex-

(16) Munch, Thannhauser and Cottle, THIS JOURNAL, **68**, 1297 (1946).

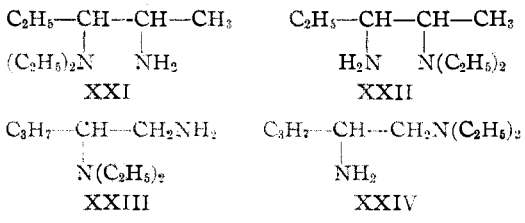
(17) Matthiessen, *Ann.*, **111**, 86 (1859).

(18) Knunjanz, Toptschijew, Tschelinzew, *Bull. Acad. Sci. (USSR)*, **7**, 153 (1934); *cf.* Ghighi, *Ann. chim. applicata*, **32**, 3 (1942) [*C. A.*, **37**, 1385 (1943).]

(19) Elderfield and Smith, unpublished work.

(20) Fourneau and Ramart-Lucas, *Bull. soc. chim. France*, [4], **27**, 550 (1920). For a critical discussion of the effects of such neighboring groups see Winstein, Chapt. 1 of "Heterocyclic Compounds," edited by Elderfield, John Wiley and Sons, New York, N. Y., 1950.

ist, the structures assigned to IV and V, and hence those of the diamines obtained from IV and V would be untenable. In order to eliminate such possibilities from further consideration, the diamines XXI–XXIV were prepared. None of these was identical with either of the diamines isolated by decomposition of IV or V.



XXI XXII

XXIII XXIV

It is interesting that alkylation of VI with 1-diethylamino-3-bromopentane[2] in contrast to the chloride (II) resulted in the formation of a drug base composed of 94% of the unrearranged product V. Apparently, the direct intermolecular displacement of the bromine by VI is favored over a competing intramolecular displacement or other reactions involving rearrangements in the case of the more active bromoamine.

As a result of the degradation experiments here presented pure pamaquin has the structure commonly assigned to it. The major contaminant of commercial pamaquin, iso-pamaquin, by its identity with the unrearranged Compound B (V) has now been shown to possess the structure previously assigned to it.[2] However, the source of iso-pamaquin in commercial preparations is undoubtedly traceable to the presence of 1-diethylamino-3-bromopentane in the commercial 1-diethylamino-4-bromopentane used.[2]

The possibility of the occurrence of rearrangements in displacement reactions on γ-haloamines, then, leaves the structure of a large number of alkylated compounds previously prepared in this manner open to question. One or more isomeric products may have been obtained, for example, in the alkylation of methyl aniline,[21] aniline,[22] piperidine, methylamine, ammonia, cyanide, diethyl malonate and acetoacetate ions, *l*-ephedrin,[23] 6-methoxy-8-aminoquinoline,[3,24,25] and 2,6-disubstituted-9-amino acridines[3b,26] by 1-dimethylamino, 1-diethylamino- or 1-piperidino-3-chlorobutane and pentane; or in the alkylation of *p*-phenetidine[27] and 2-alkoxy cinchoninate ion[28] by α,β-dimethyl-γ-dialkylaminopropyl chlorides.

(21) Schuleman, Schönhofer and Wingler, German Patent 518,207, *Chem. Zentr.*, **102**, I, 2803 (1931).

(22) Mannich and Margotte, *Ber.*, **68**, 273 (1935).

(23) German Patent 619,756, *Chem. Zentr.*, **106**, II, 3798 (1935).

(24) Magidsson and Bobyschew, *Chem. Ser. A. J. allg. Chem.*, **8** [70], 899 (1938); *Chem. Zentr.*, **110**, I, 4952 (1939).

(25) Fourneau, Trefouel, Bovet and Benoit, *Ann. Inst. Pasteur*, **46**, 514 (1931).

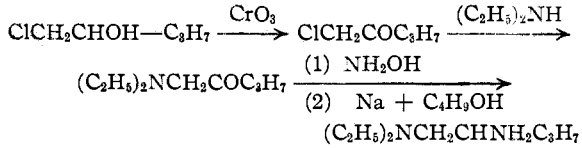
(26) Mauss and Mietzsch, I. G. Farben, A. G.; German Patents 571,449; 553,072.

(27) Schuleman, Schönhofer and Wingler, U. S. Patent 1,752,617 *Chem. Zentr.*, **101**, I, 3830 (1930).

(28) Lurje, *J. Chim. Gen.*, **9**, 287 (1939); *Chem. Zentr.*, **110**, II, 3574 (1939).

The diamines required for identification purposes in the present work were prepared by a variety of methods some of which raise points of interest. The syntheses described below may not represent the most expedient preparations of these diamines. They were chosen to circumvent particularly reactions involving displacements on chloroalkyl amines, where rearrangements similar to those discussed above may occur.

1-Diethylamino-2-aminopentane was prepared according to the following scheme from 1-chloropentanol-2.[2]



The non-identity of the observed melting point of the picrate of 1-diethylamino-2-aminopentane as here prepared with the reported melting point of the picrate of 1-amino-2-diethylaminopentane[29] removes doubt as to the structure assigned to the latter. Since this was made by the action of ammonia on 1-chloro-2-diethylaminopentane, the possibility of rearrangement through an intermediate ethyleneimmonium ion exists. In this case, at least, the product of such rearrangement does not seem to have been isolated.[29]

In the reaction of 1-diethylaminopentanone-2 with hydroxylamine according to the usual conditions for the preparation of oximes[30] two white crystalline solids, XXV and XXVI, were obtained instead of the expected oily aminoketoxime. These were separated by taking advantage of their different solubilities in alcohol or ether. The more soluble substance (XXV) furnished analytical figures agreeing with $C_5H_{10}N_2O_2$. On reduction with sodium and butyl alcohol a diaminopentane was obtained which was not definitely identified. XXV also gave a bright red precipitate with ammoniacal nickel solution. It is therefore assigned the structure of *n*-propyl glyoxime and the diaminopentane is the 1,2 derivative.

Differentiation between XXV and 2-isonitroso-1-hydroxylaminopentane, which might be expected to arise by a direct displacement of the diethylamino group in the aminoketone by a hydroxylamino group facilitated by the α-carbonyl grouping, is easily made on the basis of analytical data. It therefore appears as if the reaction here noted is analogous to that between α-halogen- or α-hydroxycarbonyl compounds and phenylhydrazine to yield osazones. Further, α-halogen carbonyl compounds yield glyoximes among other products when treated with hydroxylamine.[31,32]

A clue to the nature of XXVI as well as to the identity of XXV, is found in the work of Scholl

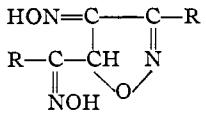
(29) Prelog, Rajner and Stern, *Helv. chim. Acta.*, **26**, 1172 (1943).

(30) Shriner and Fuson, "Identification of Organic Compounds," 2nd Ed., John Wiley & Sons, Inc., New York, 1940, p. 167.

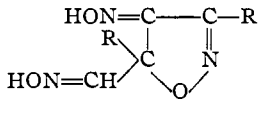
(31) Hantzsch and Wild, *Ann.*, **289**, 285 (1896).

(32) Strassmann, *Ber.*, **22**, 419 (1889).

and collaborators[33] who obtained monoximes when α-halogen ketones were treated with hydroxylamine in acid solution; in alkaline solution the principal product was the glyoxime. In addition a compound which was assigned either the structure XXVI or XXVII was found among the products of the reaction of ω-bromoacetophenone and hydroxylamine.



XXVI, R = C_6H_5
XXVIa, R = C_3H_7



XXVII, R = C_6H_5
XXVIIa, R = C_3H_7

By analogy compound XXVI is assigned either structure XXVIa or XVIIa. A definite choice between the two formulas cannot be made on the basis of existing data and awaits the results of further work on this problem.

The preparation of 1-diethylamino-3-aminopentane (XIX) was first carried out by a method outlined by Kharasch and Fuchs[12] based on earlier reports in the literature according to the equations

$$ClCH_2CH_2COCl + Zn(C_2H_5)_2 \longrightarrow$$

$$ClCH_2CH_2COCH_2CH_3 \xrightarrow[(2)\ NH_2OH \quad (3)\ Na + C_4H_9OH]{(1)\ (C_2H_5)_2NH} (C_2H_5)_2NCH_2CH_2C(NH_2)CH_2CH_3$$

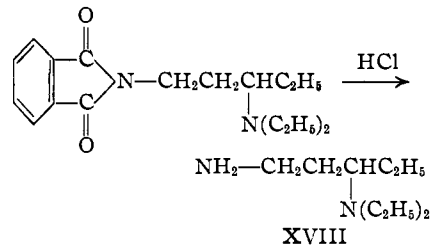
XIX

Difficulty was encountered in the preparation of β-chloropropionyl chloride which showed a strong tendency to lose hydrogen chloride on distillation unless the pressure was so low as to render condensation difficult under the usual conditions. The same difficulty accompanied by polymerization of the resultant ethyl vinyl ketone was encountered in distilling β-chlorodiethyl ketone. As a result of this experience it was found more convenient to prepare β-diethylaminodiethyl ketone by direct addition[34] of diethylamine to ethyl vinyl ketone. The diamine was then prepared by reduction of the oxime of the diethylamino ketone.

1-Amino-3-diethylaminopentane (XVIII) was prepared according to the equations

$$ICH_2CH_2CHOHC_2H_5 + KN(CO)_2C_6H_4 \longrightarrow$$

$$(CO)_2C_6H_4N{-}CH_2CH_2CHOHC_2H_5 \xrightarrow[(2)\ (C_2H_5)_2NH]{(1)\ SOBr_2}$$



XVIII

In view of the rearrangement occurring in the displacement reaction under discussion it is conceivable that the displacement by phthalimide ion on 1-iodopentanol-3 might similarly give rise to one or a mixture of isomeric 1,3-phthalimido pentanols. However, the melting points of three derivatives of XVIII were observed to be sharp, constant and non-identical with those of the corresponding salts of XIX prepared in two unequivocal ways. The melting points of the corresponding salts of XVIII and XIX when mixed were depressed in each case, confirming their non-identity. Thus, it seems most likely that XVIII possesses the structure suggested and that the displacement by phthalimide ion on 1-iodopentanol-3 proceeded without rearrangement. The preparation of XVIII was also attempted according to the reactions

$$C_3H_7CHO \longrightarrow C_3H_7CHOHCN \xrightarrow{PCl_5} C_3H_7CHCl{-}CN \xrightarrow{\text{Quinoline}}$$

XXVIII

$$C_2H_5CH{=}CH{-}CN \xrightarrow{(C_2H_5)_2NH} C_2H_5CH(N(C_2H_5)_2){-}CH_2CN \xrightarrow{Ni\text{-}H_2} \text{XVIII}$$

The chloronitrile (XXVIII) was readily prepared from the corresponding cyanohydrin according to Bruylants and Jmoudsky[35] who also report the dehydrochlorination of α-chlorobutyro- and valeronitrile on heating the substances with quinoline at steam-bath temperature. Our experience does not confirm this. The chloronitrile was recovered unchanged when treated under these conditions. However, at the reflux temperature (155–165°) a 77% yield of mixed pentenonitriles was obtained. Attempts to add diethylamine to the unsaturated nitrile failed, thus confirming the observation of Bruylants[36] that amines of larger molecular weight than dimethylamine failed to add to crotononitrile.

Attempts to characterize the primary–tertiary diamines XVI, XIX and 1-diethylamino-2-aminopentane by forming the corresponding disubstituted pentyl thioureas were unsatisfactory. When a mixture of the amine which had been dried over potassium hydroxide and distilled, and phenyl isothiocyanate was heated gently for sev-

(33) Korten and Scholl, *Ber.*, **34**, 1901 (1901); Scholl and Mathaiopoulos, *ibid.*, **29**, 1550 (1896); *cf.* also Diels and Sasse, *ibid.*, **40**, 4052 (1907); Ponzio and Avogadro, *Gazz. chim. ital.*, **53**, 311 (1923); Avogadro, *ibid.*, **56**, 713 (1926).

(34) Blaise, *Bull. soc. chim. France*, [4] **3**, 543 (1908).

(35) Bruylants and Jmoudsky, *Bull. soc. chim. Belg.*, **41**, 273 (1932); *cf.* Heim, *ibid.*, **40**, 214 (1931).

(36) Bruylants, *ibid.*, **32**, 267 (1923).

TABLE I

MELTING POINTS OF SALTS OF VARIOUS PENTANEDIAMINE DERIVATIVES

Amine	M. p., °C. Picrate	Hydrochloride	Hydrobromide
$H_2N(CH_2)_5N(C_2H_5)_2$[a]	110		
$(C_2H_5)_2NCH(CH_2)_3NH_2$[12]	138–140		
$H_2N(CH_3)CH(CH_2)_3N(C_2H_5)_2$[b]	134–135	163–164	
$H_2N(C_2H_5)CH(CH_2)_2N(C_2H_5)_2$	155.5–156.5[12]	171.5–173.5	169–171.5
Diamine from V	154–155	171.5–173.5	169–171.5
$H_2N(C_3H_7)CHCH_2N(C_2H_5)_2$	176.5–178	157.5–159	130.5–131
$(C_2H_5)_2N(C_3H_7)CHCH_2NH_2$[32]	163		
$(C_2H_5)_2N(C_2H_5)CH(CH_2)_2NH_2$	156.8–157.5	185.5–187	189.5–191
Diamine from IV	156.8–157.5	185.5–187	189.5–191

[a] von Braun, *Ber.*, **43**, 2864 (1910). [b] Drosdov and Bekli, *J. Gen. Chem.* (*U. S. S. R.*), 14, 480 (1944); Walls, *J. Chem. Soc.*, 1405 (1935).

eral minutes, hydrogen sulfide was evolved. On addition of pentane to the mixture, a good yield of thiocarbanilide was obtained.

The pentyl phenyl thiourea presumably was formed first, since reaction at room temperature gave thick, non-crystallizable oils as the sole product. These thioureas, possessing a basic tertiary amino group, appear, then, to catalyze the reaction of phenyl isothiocyanate with traces of water. This observation is in agreement with the marked acceleration by aqueous alkali in the reaction of phenyl isothiocyanate with water to yield *sym*-diphenyl thiourea.[37] Bamberger also noticed a similar catalytic decomposition of phenyl isothiocyanate by guanidine carbonate and guanidyl phenyl thiourea.

The generally accepted superiority[38] of this reagent over the corresponding isocyanate, by virtue of its insensitivity toward water, should be reconsidered, then, in characterizing certain amines.

The physical constants of salts of the diamines concerned in the above argument are summarized in Table I in which data taken from the literature have been combined with data on the new amines prepared.

Experimental[39,40]

1-Diethylaminopentanol-3, b. p. 112° (30 mm.), was prepared from the chloro alcohol as previously described.[41] The amino alcohol (1.15 g.) formed 2.99 g. of a crude **picrolonate** (98% yield) which melted at 89.5–92.5°. After several recrystallizations from acetone–pentane mixture in the cold, the tan microcrystalline powder melted at 94–95.8°. Mixed m.p's. with samples of the second and third crops (850 mg., m. p. 89–92.5°; 135 mg., m. p. 89–92°, respectively) obtained from the first recrystallization, representing almost quantitative recovery were undepressed.

Anal. Calcd. for $C_{19}H_{29}N_5O_6$: C, 53.89; H, 6.90. Found: C. 54.07; H. 6.52.

The above alcohol failed to give solid derivatives easily with picric, styphnic, toluenesulfonic, chloroauric, oxalic, or anhydrous hydrochloric acid.

1-Diethylamino-3-chloropentane (II) was prepared as previously described[2] by the chlorination of 1-diethylaminopentanol-3 with thionyl chloride. No attempt was made to fractionate the chloramine base which distilled completely at 87° (18 mm.) through a six-inch Vigreux column. Counter-current analysis[2] on several different preparations of the distilled chloramine base (II) consistently showed the presence of less than 3–6% inhomogeneity. The hygroscopic hydrochloride of the distilled base and that isolated directly from the corresponding amino alcohol on treatment with thionyl chloride melted alone and when mixed at 93–95°; reported[42] m. p. 98.5°.

Anal. Calcd. for $C_9H_{21}NCl_2$: C, 50.5; H, 9.9; N, 6.5. Found: C, 50.1; H, 9.8; N, 6.2.

Both hydrochlorides on treatment with a concentrated aqueous solution of picric acid yielded the same **picrate**; m. p. 76–77°.

Anal. Calcd. for $C_{15}H_{25}N_4ClO_7$: C, 44.3; H, 5.7. Found: C, 44.5; H, 5.7.

The **picrate**, as obtained crude in almost quantitative yield from a sample of the total distilled chloroamine base, melted at 75.5–76°. Recrystallization from ethyl acetate–hexane gave a fraction the m. p. of which (76–77°) could not be raised by further recrystallization, and second and third fractions both melting at 75–76°. Mixed m.p's. of an analytical sample with samples of the second and third fractions failed to depress.

SN-13,431—Mixture of IV and V.—The drug base was prepared in best yield according to Procedure A[43] by refluxing 130 g. (0.75 mole) of VI and 130 g. (0.73 mole) of 1-diethylamino-3-chloropentane (II)[2] in 458 ml. of absolute ethanol for sixty hours, removing the solvent and distilling. After removal of the low-boiling amino olefin and unreacted VI, 94 g. (41%) of orange-yellow viscous drug base, b. p. 175–184° (0.1 mm.), was obtained after three distillations.

Fractionation of SN-13,431.—Addition of anhydrous ether to the drug base precipitated 5% of a solid. After three recrystallizations from acetone–heptane the tan long needles melted at 152–152.5° and showed the presence of ionic chlorine.

Anal. Calcd. for $C_{19}H_{30}N_3ClO$: C, 64.8; H, 8.6. Found: C, 64.5; H, 8.2.

This corresponds to the monohydrochloride of IV or an isomer of it. It is unlikely that the quinoline nitrogen was alkylated to give a quaternary chloride since its acid solution containing nitrous acid did not couple with β-naphthol. The base of this component was shown to be identical with component (B) by the identity of their citrates, m. p. 136–137°, and picrates; m. p. 171–171.5°.

(37) Bamberger, *Ber.*, **14**, 2638 (1881).

(38) Wild, "Characterization of Organic Compounds," Cambridge University Press, Cambridge, 1st ed., 1947, p. 226.

(39) All melting points are corrected for stem exposure. All boiling points are uncorrected.

(40) Microanalyses by Miss Lois May of these laboratories and the Clark Microanalytical Laboratories, Urbana, Illinois.

(41) Fourneau and Ramart-Lucas, *Bull. soc. chim. France*, [4] **25**, 364 (1919).

(42) Hass and Huffman, THIS JOURNAL, **63**, 1233 (1944).

(43) Elderfield, Gensler, *et al.*, *ibid.*, **68**, 1524 (1946)

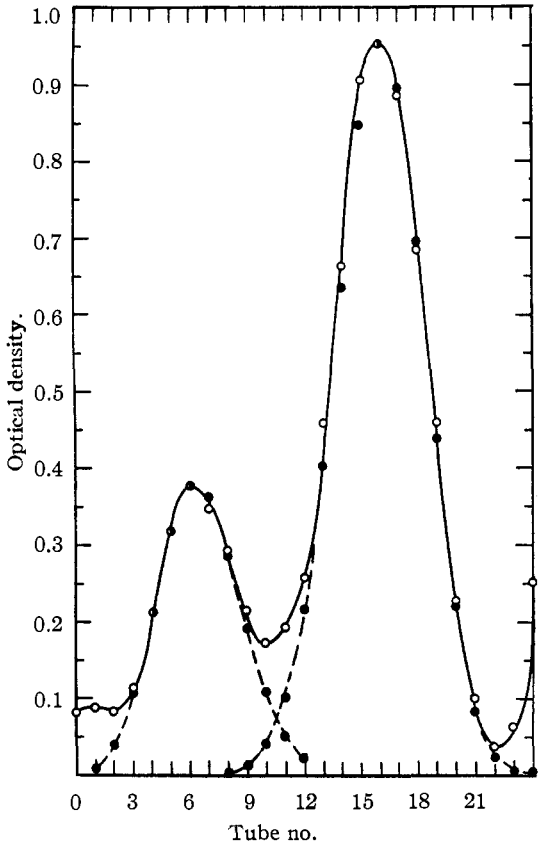


Fig. 1.—Fractionation of iso-pamaquin: isopropyl ether–citrate buffer, *p*H 5.11, concn. 0.67 mg./ml.; ●, theoretical; O, experimental.

The distribution[44] of 5.4 mg. of drug base through twenty-four plates between isopropyl ether and 1 *M* citrate buffer at *p*H 5.11 by means of the Craig machine showed the presence of three components in the ratio of 70:26:4, as indicated in Fig. 1. In Figs. 1 and 2 the conventions are those of Craig. A large-scale fractionation of the principal isomers, in 1455 ml. phases of isopropyl ether and 1 *M* citrate buffer at *p*H 5.31, at a concentration of 60 mg./ml., moving the aqueous layers, enabled 87.5 g. of drug base to be distributed through thirty plates using fifteen funnels. Fractions were cut by following concentrations spectrophotometrically at λ = 365 mμ using a Beckman quartz spectrophotometer. Upper organic layers were read after 14, 19, 24 and 30 plates.

A third component was removed as the total base of tubes 1 and 2 after 14 plates. In plates 15–19, the upper layers of tubes 3, 4, 5, 6, 7 were not equilibrated with buffer but were removed and combined as major component with the total base of tubes 8, 9, 10, 11 after 19 plates. After five more plates had been applied to tubes 12–20, component A was obtained also from the total base of tubes 12, 13, 14 and component B from tubes 21–25 (Fig. 2). Distributing the remaining tubes 15–20 through five additional plates allowed the base of tubes 15 and 16 to be combined with the major component and that of tubes 27–31 with the isomer B. The material in tubes 17, 18, 19, 20, 26 after 30 plates, comprising 7–9% of partially separated material, was set aside, and could have been further worked.

A twenty-four plate machine run in a citrate–isopropyl ether system at *p*H 4.99 on a portion of the 56 g. of com-

(44) Craig, *et al.*, *J. Biol. Chem.*, **161**, 321 (1945); **155**, 519 (1944).

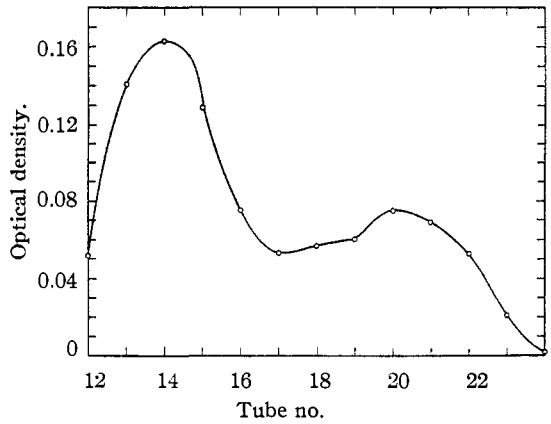


Fig. 2.—Large-scale fractionation of iso-pamaquin, redistribution of fractions 12–20 after 19 plates: system isopropyl ether–citrate buffer, *p*H 5.31, concn. 60 mg./ml.

ponent A obtained from the combined fractions above without further purification showed it to be homogeneous within 2.5% of a less basic and within 0.3% of a more basic compound (originally B). This base was characterized by a distribution constant of 11.3 at *p*H 4.75 and a dipicrate, which formed long, lustrous, deep yellow needles, m. p. 167–168°, when recrystallized from ethyl acetate.

Anal. Calcd. for $C_{31}H_{35}N_9O_{15}$: C, 48.1; H, 4.6. Found: C, 48.3; H, 4.9.

This component also formed a white, powdery **citrate** with difficulty, m. p. 116–119° dec., when recrystallized from an ethanol–ethyl acetate mixture.

Anal. Calcd. for $C_{25}H_{37}N_3O_8$: C, 59.2; H, 7.4; N, 8.3. Found: C, 59.4; H, 7.2; N, 8.4.

Component B: The combined fractions of base (12.4 g.) obtained, representing minor component, on redistribution was homogeneous within 4% of more basic and 2% of less basic material (originally component A). It is characterized by a distribution constant of 1.15 at *p*H 4.75. Its **dipicrate** formed bright orange needles, m. p. 171–171.5° dec., when recrystallized from methanol.

Anal. Calcd. for $C_{31}H_{35}N_9O_{15}$: C, 48.1; H, 4.6. Found: C, 48.2; H, 4.6.

Its citrate melted at 136–137° when recrystallized from an ethanol–ether mixture; reported[2] 136–139°. A mixed m. p. with the citrate of the major contaminant of commercial pamaquin (m. p. 135–137°) was undepressed.

Nitroso Plasmocid (XII).—A solution of 17.3 g. (0.25 mole) of sodium nitrite in 40 ml. of water was added dropwise with stirring to 72 g. (0.25 mole) of 6-methoxy-8-(3-diethylaminopropylamino)-quinoline (X)[45] in 37 ml. of concentrated hydrochloric acid and 100 g. of ice at 3°. After one and one-half hours, the reaction mixture was made slightly basic, and extracted with warm benzene. Seventeen and one-half grams of green felt-like, lustrous needles crystallized from the dried, concentrated benzene extract. The dark, oily residue (50 g.) that could not be crystallized was recovered as starting material; b. p. 170–180° (0.2 mm.); hydriodide; m. p. 191–192°. This was reworked to give a total of 41 g. (50%) of nitroso Plasmocid. After three recrystallizations from ethyl acetate, the compound melted at 144–144.2°.

Anal. Calcd. for $C_{17}H_{24}N_4O_2$: C, 64.5; H. 7.6; N, 17.7. Found: C, 64.9; H, 7.5; N, 17.7.

Its red, amorphous potassium salt decomposed at 249–250°. Diphenylamine test reagent failed to indicate the N-nitroso grouping in XII.

(45) Elderfield, Gensler, *et al.*, ref. 46, record the m. p. of Plasmocid hydriodide as 207–209°. When heated very slowly, however, this compound, like a sample of the hydriodide of the material used above, melted at 191–192°; mixed m. p. 191–192°.

Nitrosation and Hydrolysis of Pamaquin (XIV).—A solution of pamaquin base 13.5 g. (0.043 mole) obtained from 25 g. of its citrate, m. p. 125–127°, in 6.3 ml. of concentrated hydrochloric acid was treated dropwise with 15 ml. of an aqueous solution containing 3.45 g. (0.049 mole) of sodium nitrite. The mixture was stirred for one and three-quarters hours at 3°. It was then carefully made alkaline and extracted with pentane to separate out unreacted drug base. A benzene extract yielded a deep green-brown oil which could not be crystallized. This was dissolved in 10 ml. of dry methanol and refluxed for four hours with 8.6 g. of potassium hydroxide in 40 ml. of methanol. After one hour, 0.96 g. of a green powder was filtered off.

Anal. Calcd. for $C_{10}H_7N_2O_3K$: C, 49.6; H, 2.9; N, 11.6. Found: C, 49.6; H, 3.2; N, 11.8.

Recrystallized from methanol, the salt did not melt below 360°.

The reaction mixture was then acidified with ethereal hydrogen chloride, and the precipitated potassium chloride removed by filtration. The filtrate was then concentrated to dryness, and the residual red oil made alkaline and extracted with ether. The combined ether extracts, after rigorous drying with solid potassium hydroxide followed by sodium, yielded 0.77 g. of a dithiocarbamate,[46] m. p. 123–128°, on treatment with carbon disulfide. This salt was boiled with 2 ml. of concentrated hydrochloric acid for ten minutes, and the solution made basic and extracted with ether. Treatment of the ether extract with alcoholic picric acid gave a picrate, m. p. 133.5–134°, which failed to depress the m. p. of an authentic sample of 1-diethylamino-4-aminopentane dipicrate prepared here; m. p. 133.5–134°. The picrate was shaken with 4 ml. of 10% potassium hydroxide. The ether extract obtained from it gave an oil on treatment with anhydrous hydrogen chloride, which crystallized as lustrous plates from absolute ethanol, m. p. 163–164°. The m. p. of a sample when mixed with an authentic specimen of the amine hydrochloride was 162–163°.

Hydrolysis of XII: (a) A solution of 2 g. (0.0063 mole) of XII was refluxed for one-half hour in 50 ml. of methanol containing 7.05 g. of potassium hydroxide. When worked up as described above for pamaquin, 0.5 g. of the quinolinol salt and 280 mg. (22%) of a crude dithiocarbamate, m. p. 147–147.5°, reported[47] m. p. 150°, were obtained. This was converted to a picrate which formed yellow needles when recrystallized from ethanol, m. p. 194.5–195° dec.; reported[48] m. p. of 3-diethylaminopropylamine picrate, 193.5–194°. It also formed a phenyl thiourea, m. p. 116–117°; reported[49] 116–116.5°, 116.5–117°.[48]

(b) Hydrolysis was also attempted by treating 10 g. (0.032 mole) of XII with a 40% aqueous solution of sodium bisulfite[16] (19.8 g., 0.19 mole). After two hours at room temperature and one-half hour at 70°, the clear, red-brown solution was made alkaline whereupon a copious yellow precipitate appeared. This was presumably a sulfonated *p*-aminoquinolinol salt.[50] A continuous ether extraction of the solution and mixed salts yielded 2.5 ml. (62%) of a strongly basic liquid. The base was characterized as 3-diethylaminopropylamine by the phenyl thiourea; m. p. 116–117°, and picrate; m. p. 194–195°. Although the odor of the diamine was always detectable, further similar runs did not yield consistent results. The voluminous sulfonated salts apparently rendered the separation of XIII by ether extraction difficult.

Degradation of Component A: Nitrosation and Hydrolysis.—According to the method described above for Plasmocid, 15 g. (0.048 mole) of the purified drug base; k = 11.3 (pH 4.75), in 6.9 ml. of concentrated hydrochloric acid was allowed to react with 3.27 g. (0.048 mole) of sodium nitrite at 3° for fifty-five minutes. The solution was then carefully made alkaline until no further precipitation of bright green crystals occurred in the aqueous layer. Washing with a heptane–ether mixture helped in avoiding tar formation on the filter. The bright green plates (XVII) obtained in 73% yield melted at 111.5–112° after two recrystallizations from heptane.

Anal. Calcd. for $C_{19}H_{28}N_4O_2$: C, 66.3; H, 8.2. Found: C, 66.2; H, 8.5.

A solution of 2.12 g. (0.0062 mole) of XVII in 10 ml. of anhydrous methanol was refluxed with 6.9 g. (0.123 mole) of potassium hydroxide in 40 ml. of methanol. After one and one-half hours, 0.41 g. of the quinolinol salt was removed by filtration. After working up as described previously, 0.31 g. of a dithiocarbamate was obtained which was decomposed and yielded a picrate, m. p. 153.5–157.5°. After two recrystallizations from ethanol, the long, yellow, lustrous needles melted at 156.8–157.5°.

Anal. Calcd. for $C_9H_{22}N_2 \cdot C_{12}H_6O_{14}$: C, 40.9; H, 4.6. Found: C, 41.3; H, 4.7.

When a sample of this picrate was mixed with that of 1-diethylamino-3-aminopentane, m. p. 154–155°, it melted at 132–149°. When mixed with the picrate of 1-amino-3-diethylaminopentane, m. p. 156.8–157.5°, it melted at 154.5–155.5°. To characterize further the side-chain hydrolysis product, the picrate was converted to a hydrochloride, m. p. 185–186.5°, when recrystallized from ethanol–ethyl acetate. On admixture with an authentic sample of the above diamine dihydrochloride, it melted at 185–186.5°. Its dihydrobromide melted at 189.5–191° and also showed no depression when mixed with the dihydrobromide of XVIII, m. p. 189.5–191.5°.

Oxidative Degradations

Pamaquin.—The following procedure gave the optimum yield of desired diamine (XVI) in a series of experiments in which temperature and ratio of acid:oxidizing agent:base was varied. A solution of 2.08 g. (0.0132 mole) of potassium permanganate in 30 ml. of water was added with cooling to the base obtained from 1.62 g. (0.032 mole) of pamaquin citrate in 40 ml. of 10% sulfuric acid, the color being discharged almost immediately. After 1.5 hours, the solution was concentrated to dryness, made strongly alkaline, and extracted exhaustively with ether. On treatment of the dried ether extract with carbon disulfide, 160 mg. (22%) of a dithiocarbamate,[49] m. p. 136–136.5°, was obtained. This was converted to a yellow picrate, m. p. 133.5–134°. When mixed with an authentic sample of 1-diethylamino-4-aminopentane picrate, and with that of the diamine obtained from the hydrolysis of XV, its melting point remained undepressed at 133–134°.

Component A.—This base (2.0 g.) in 80 ml. of 10% sulfuric acid was similarly treated with an aqueous solution containing 4.16 g. of potassium permanganate. The ether extract obtained as above yielded 1.15 g. (30%) of a picrate, m. p. at 156.8–157.5°, after two recrystallizations from ethanol. A mixed m. p. with a sample of the picrate of XVIII prepared here, and of that obtained from the hydrolysis of XVII showed no depression.

Component B.—A solution of 1.0 g. (0.0032 mole) of the minor component base in 40 ml. of 10% sulfuric acid was similarly treated with an aqueous solution of 2.08 g. of potassium permanganate. On the addition of picric acid in alcohol to the pale yellow ether extract, obtained as described for the oxidation of XIV, 350 mg. of yellow lustrous plates was slowly deposited. These melted at 151–153° after one recrystallization from ethanol. On further recrystallization, the picrate melted constantly at 154–154.5°. A mixed m. p. with the picrate of 1-diethylamino-3-aminopentane (XIX), m. p. 154–155°, was undepressed. When a sample of this picrate was mixed with the picrate, m. p. 156.8–157.5°, of the diamine obtained from the oxidative degradation of A it melted at 134–156°.

Further identification of the diamine obtained above

(46) Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431–432 (1944). The salt-like character of this derivative and its insolubility in ethanol or acetone render it particularly useful for purification here.

(47) Schinzel and Benoit, *Bull. soc. chim. France*, [5] **6**, 501 (1939).

(48) Whitmore, Mosher, *et al.*, THIS JOURNAL, **66**, 725 (1944).

(49) Shriner and Hickey, *ibid.*, **61**, 888 (1939).

(50) *Friedländer*, **3**, 56 (1890–1894).

was provided by converting its picrate to the hydrochloride. The melting point alone and on admixture with an authentic sample of the dihydrochloride of XIX was 171.5–173.5°. Its dihydrobromide melted at 169–171.5° and also showed no depression when mixed with 1-diethylamino-3-aminopentane dihydrobromide, m. p. 169–171.5°. A mixed m. p. of the dihydrochlorides, m. p. 185–186.5° and 171.5–173.5°, of the diamines obtained from the oxidative degradations of A and B respectively was depressed to 153–182°.

1-Chloropentanone-2.—To a well-stirred mixture of 70.9 g. (0.58 mole) of 1-chloropentanol-2[2] and 75.2 g. (0.25 mole) of sodium dichromate in 44 ml. of water was added dropwise 87.4 g. of concentrated sulfuric acid diluted with 23 ml. of water. The mixture was stirred overnight. It was then diluted and extracted with ether. The washed and dried ether extract gave on distillation 58.8 g. (83%) of a clear very lachrymatory liquid, b. p. 64–66° (26 mm.); reported[51] 55–57° (15 mm.).

1-Diethylaminopentanone-2.—The above chloro ketone (58.8 g., 0.49 mole) was added dropwise to 108 g. (1.5 moles) of diethylamine in 89 ml. of absolute ethanol. A spontaneous reaction brought the solution to reflux. Heating was continued for twenty-four hours. Working up in the usual manner gave 61 g. (79%) of a basic liquid; b. p. 90–91.5° (24 mm.), which darkened almost immediately after distillation. It formed a **semicarbazone** as white needles, m. p. 103.5–104°, when recrystallized twice from *n*-heptane.

Anal. Calcd. for $C_{16}H_{22}N_4O$: C, 56.0; H, 10.4. Found: C, 56.0; H, 10.6.

1-Diethylaminopentanone-2-oxime.—A mixture of 33 g. (0.477 mole) of hydroxylamine hydrochloride, 26.8 g. (0.477 mole) of potassium hydroxide in 100 ml. of water and 50 g. (0.318 mole) of the above amino ketone was allowed to stand with stirring for three days. Ether extraction, drying, and distillation gave 2 g. of forerun and 47.4 g. (86.5%) of a slightly colored viscous liquid, b. p. 110–112° (1.3 mm.). Several redistillations gave a main fraction, b. p. 89–90° (0.3 mm.), $n^{25}D$ 1.4623.

Anal. Calcd. for $C_9H_{20}N_2O$: C, 62.7; H, 11.7. Found: C, 62.3; H, 11.2.

The oxime formed a **picrate** which crystallized from ethanol as yellow prisms, m. p. 136–136.5°.

Anal. Calcd. for $C_{15}H_{23}N_5O_8$: C, 44.9; H, 5.8. Found: C, 44.9; H, 5.8.

1-Diethylamino-2-aminopentane.—To a solution of 30.5 g. (0.18 mole) of 1-diethylaminopentanone-2-oxime in 580 ml. of refluxing *n*-butanol was added 40.1 g. (1.9 mole) of sodium. The reaction was worked up as described for XIX. On distillation considerable amounts (10 g.) of very low boiling products and 6.2 g. (22%) of a fraction b. p. 76–79° (15 mm.) were obtained. This fraction formed a **dihydrochloride**, m. p. 157.5–159°, when recrystallized from ethanol–acetone mixture.

Anal. Calcd. for $C_9H_{24}N_2Cl_2$: C, 46.8; H, 10.5. Found: C, 46.5; H, 10.8.

The **dihydrobromide**, recrystallized twice from an ethanol–ethyl acetate mixture, melted at 130.5–131°.

Anal. Calcd. for $C_9H_{24}N_2Br_2$: C, 33.8; H, 7.6. Found: C, 34.0; H, 7.6.

The **picrate** crystallized from a methanol–ethanol mixture as stout yellow needles which melted at 176.5–178°.

Anal. Calcd. for $C_{21}H_{28}N_8O_{14}$: C, 40.9; H, 4.6. Found: C, 40.9; H, 4.5.

1-Diethylaminopentanone-2 and Excess Hydroxylamine: *n*-Propyl Glyoxime (XXV), 3,5-Di-*n*-propyl-5-oximinomethylisoxazolone-4-oxime (XXVIIa).—A solution of 30.7 g. (0.195 mole) of 1-diethylaminopentanone-2 and 61.4 g. (0.9 mole) of hydroxylamine hydrochloride in 31 ml. of 10% potassium hydroxide and 31 ml. of water at a *p*H 5.5 was heated gently. After one hour, a light orange oil separated, which solidified into a white crystalline mass, m. p. 95–130°, after standing overnight. Two compounds were separable due to their difference in solubility in ethanol or ether. The fraction that was more soluble in ethanol gave 8.2 g. of soft, pearly needles, m. p. 121.5–122°, after three recrystallizations from benzene. Although base soluble, it remained undissolved in dilute hydrochloric acid.

Anal. Calcd. for $C_5H_{10}N_2O_2$: C, 46.1; H, 7.7; N, 21.5. Found: C, 46.3: H, 7.8; N, 21.0, 21.3.

The theoretical analytical values for 2-isonitroso-1-hydroxylaminopentane are: C, 45.4; H, 9.2; N, 21.2.

Four grams (0.031 mole) of the above compound was reduced with 14 g. (0.61 mole) of sodium added in portions in 200 ml. of boiling butanol. The acidified solution was steam distilled, concentrated, and basified. An ether extract of the basic solution gave an **oxalate** as white needles, m. p. 190–190.5° dec., from dilute ethanol.

Anal. Calcd. for 1,2-diaminopentane oxalate, $C_7H_{16}N_2O_4$: C, 43.6; H, 8.2. Found: C, 43.7; H, 8.4.

A yellow **picrate** was also obtained, which melted at 212.5° dec. when recrystallized from ethanol.

Anal. Calcd. for $C_{17}H_{20}N_8O_{14}$: C, 36.4; H, 3.6. Found: C, 36.7; H, 3.8.

The fraction that was less soluble in ethanol gave 7.5 g. of small, white needles, m. p. 186.5–188.5° dec. after one recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{17}N_3O_3$: C, 52.8; H, 7.5; N, 18.5. Found: C, 52.8, 52.7; H, 8.0, 7.7; N, 18.2.

This compound dissolved readily in 10% hydrochloric acid and aqueous potassium hydroxide.

1-Diethylaminopentanone-3.—To a well-stirred suspension of 30 g. (0.35 mole) of ethylvinylcarbinol[52] in 300 ml. of water containing 63.5 g. (0.24 mole) of sodium dichromate was added 95.5 g. of concentrated sulfuric acid dropwise over a period of sixty minutes at 34–35°, as described without details by Courtot and Pierron.[53] The reaction mixture was worked up immediately by extracting with ether. Hydroquinone (0.1 g.) was added and the solution dried for two hours over calcium chloride at 10°. The ethereal ketone solution was then added dropwise at 3° to 70 g. of anhydrous diethylamine. The product (21 g. or 37%) freed of 2 g. of non-basic material distilled completely at 94–96° (36 mm.); reported[53,54] b. p. 84° (13 mm.); 80° (10 mm.).[37] It formed a semicarbazone, m. p. 101–102°; reported[34] m. p. 100°. A mixed m. p. with the semicarbazone of the ketone prepared via the zinc diethyl condensation[55] with β-chloropropionyl chloride after treatment with diethylamine was undepressed.

1-Diethylamino-3-aminopentane (XIX).—1-Diethylaminopentanone-3 oxime, b. p. 107–109° (0.55 mm.) (40 g., 0.23 mole) in 750 ml. of dry *n*-butanol was reduced with 53.6 g. (2.3 moles) of sodium slices within fifty-five minutes and yielded 27.6 g. (75%) of the base XIX; b. p. 86–95° (22 mm.); $n^{20}D$ 1.4421; reported[12] b. p. 104° (37 mm.); $n^{20}D$ 1.4420. It formed a **picrate** as lemon-yellow, lustrous plates, m. p. 154–155°; reported[12] 155.5–156°, when recrystallized from ethanol.

Its **dihydrochloride** melted at 171.5–173.5° when recrystallized from ethanol.

Anal. Calcd. for $C_9H_{24}N_2Cl_2$: C, 46.8; H, 10.5. Found: C, 46.4; H, 10.2.

A dihydrobromide recrystallized from ethanol–ethyl acetate melted at 169–171.5°.

Anal. Calcd. for $C_9H_{24}N_2Br_2$: C, 33.8; H, 7.6. Found: C, 34.0; H, 7.8.

1-Phthalimidopentanol-3.—To a solution of 157.9 g. (0.755 mole) of 1-iodopentanol-3[41] in 750 ml. of refluxing

(51) Levene and Haller, *J. Biol. Chem.*, **77**, 555 (1928), prepared the chloro ketone from the alcohol by a potassium dichromate–sulfuric acid oxidation but give no preparative details except b. p. and analysis.

(52) Kohler, *Am. Chem. J.*, **38**, 511 (1907).

(53) Courtot and Pierron, *Compt. rend.*, **188**, 1501 (1929).

(54) Adamson, McQuillan, Robinson and Simonson, *J. Chem. Soc.*, 1576 (1937).

(55) Blaise and Marie, *Bull. soc. chim. France*, [4] **3**, 265 (1908).

acetone[56] was added 140 g. (0.755 mole) of potassium phthalimide in portions over a period of six hours. The suspension was stirred and allowed to reflux for fifty hours, after which 112 g. of tan solid was removed by filtration. The oily residue after removal of the solvent was dissolved in absolute ethanol, and the solution deposited on cooling 128.5 g. of a white solid, m. p. 75–77°, and 30.5 g. of a second crop (91% yield). Several recrystallizations from heptane gave rosettes of white, long needles, m. p. 77.5–79°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 66.9; H, 6.5; N, 6.0. Found: C, 67.0; H, 6.3; N, 6.1.

1-Phthalimido-3-bromopentane.—To a flask equipped with a mechanical stirrer and condenser fitted with a calcium chloride tube and immersed in an ice-water-bath was added 30 g. of 1-phthalimido-3-hydroxypentane (0.128 mole) in 11.2 g. (0.147 mole) of dry pyridine and 150 ml. of anhydrous benzene. A solution of 34.8 g. (0.167 mole) of thionyl bromide in 70 ml. of benzene was added dropwise over a period of thirty minutes. The pale orange solution containing a white solid suspension was then refluxed for two and one-half hours, during which sulfur dioxide was liberated. The viscous residue left on removal of the solvent was taken up in warm heptane. On refrigeration 29.8 g. (78.7%) of a white solid, m. p. 64.5–66° was obtained. Several recrystallizations from hexane gave long white prisms, m. p. 66.5–68°.

Anal. Calcd. for $C_{13}H_{14}NBrO_2$: C, 52.7; H, 4.8; Br, 27.0. Found: C, 52.8; H, 4.8; Br, 27.4.

1-Phthalimido-3-diethylaminopentane.—A solution of 40 g. of 1-phthalimido-3-bromopentane (0.135 mole) and 98.8 g. of anhydrous diethylamine (1.35 moles) in 200 ml. of absolute ethanol was heated at 95–105° for fifteen hours in an American Instrument bomb. The excess amine and solvent were removed on the water-bath and the residue was freed from non-basic compounds by extracting with dilute hydrochloric acid. On making the acid solution basic, extracting with ether, and distilling, 10 g. (26%) of an orange viscous oil, which distilled with some decomposition, b. p. 163–167° (0.13 mm.), was obtained. No attempt was made to improve the yield by recycling the recovered non-basic material, which was probably a mixture of unsaturated alkyl phthalimide and starting material. A **picrate** was prepared from the above base as yellow prisms when recrystallized from ethanol, m. p. 168–168.5°.

Anal. Calcd. for $C_{23}H_{27}N_5O_9$: C, 53.4; H, 5.3. Found: C, 53.1; H, 5.0.

1-Amino-3-diethylaminopentane (XVIII).—A solution of 7.9 g. of 1-phthalimido-3-diethylaminopentane (0.027 mole) in 25 ml. of concentrated hydrochloric acid was refluxed for fifteen hours. After the solution had been cooled and diluted, 4.4 g. of phthalic acid separated and was removed by filtration. The filtrate was concentrated, made strongly alkaline, and extracted with ether. The diamine was isolated from the well-dried ether extract as its **picrate.** The stout, lustrous, yellow needles were recrystallized from ethanol and melted at 156.8–157.5°.

Anal. Calcd. for $C_{21}H_{29}N_8O_{14}$: C, 40.9; H, 4.6; N, 18.2. Found: C, 41.2; H, 4.6; N, 18.0.

This salt was shaken with 20% potassium hydroxide and ether. The well-dried ethereal extract gave a **hydrobromide** on treatment with anhydrous hydrogen bromide. It melted at 189.5–191° on recrystallization from an ethanol–ethyl acetate mixture.

Anal. Calcd. for $C_9H_{24}N_2Br_2$: C, 33.8; H, 7.6. Found: C, 34.0; H, 7.5.

A **hydrochloride** was obtained as white prisms, m. p. 185.5–187.5°, when recrystallized from ethanol–ethyl acetate.

Anal. Calcd. for $C_9H_{24}N_2Cl_2$: C, 46.8; H, 10.5. Found: C, 46.8; H, 10.2.

(56) Drake, private communication, used acetone successfully as solvent in converting 1,5-dibromopentane to bromo-*n*-amyl phthalimide.

Summary

1. Optimum conditions for two methods of amine degradations have been found and applied to bases of the 6-methoxy-8-(dialkylaminoalkylamino)-quinoline type. In this way, the structures commonly assigned to Plasmocid, pamaquin, and iso-pamaquin have been verified.

2. The alkylation products resulting from the displacement by 6-methoxy-8-aminoquinoline on 1-diethylamino-3-chloropentane have been identified as 6-methoxy-8-(1-ethyl-3-diethylaminopropylamino)-quinoline and 6-methoxy-8-(3-diethylaminopentylamino)-quinoline. These are the products to be expected of a displacement on a possible cyclic 1,1,2-triethylazetidinium ion intermediate. The possibility of the four-membered ring intermediate is thereby suggested.

3. A number of pentane diamine derivatives have been synthesized.

4. The phenyl thioureas formed from these primary–tertiary diamines appear to catalyze the reaction of phenyl isothiocyanate with water.

5. An interesting side reaction in the preparation of the α-dialkylaminoketoxime, probably similar to the formation of glyoximes and isoxazolone oximes from ω-halo methyl ketones on treatment with hydroxylamine, has been observed. It involves a displacement of a diethylamino group.

6. The possibility of rearrangement similar to that encountered here opens to question the structure of a large number of alkylated compounds previously prepared by reactions involving displacements on γ halo amines.

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