[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

CYCLIZATION OF α-(β-AMINOETHYLAMINO) KETONES. PEROXIDES OF 2,3-DIPHENYL-2,3-DEHYDROPIPERAZINES[1]

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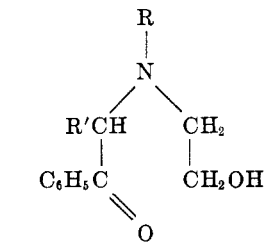
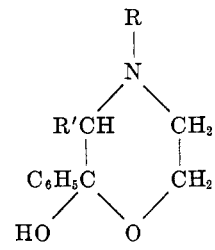
In an extension of studies on the effect of structure on the ring-chain tautomerism of the α-(β-hydroxylethylamino) ketones (1–4) (*cf.* I–II) an attempt has been made to obtain the α-(β-aminoethylamino)-α-phenylacetophenone analogs (V–VI) and related compounds for purposes of chemical and pharmacological comparisons [amino alcohols and ketones of this type have shown tumor-necrotizing activity (5–7)]. The hydroxyethylamino ketones in which the nitrogen is tertiary (I; R = alkyl, R′ = H or phenyl) have been shown generally to be in the cyclic form (II) and to give cyclic derivatives (III and/or IV); but when the nitrogen is secondary (R = H) the compounds are open-chain (I) and fail to give cyclic derivatives. The diamino ketone analogs V or VI were not obtained in either open-chain or cyclic forms because, whether or not the α-nitrogen was tertiary, dehydration occurred spontaneously (through VI) to give dehydropiperazines (XII and XV) which are analogs of III but which absorb oxygen rapidly when the NH-group is present to give peroxides (*cf.* XVII). Because of their relative stability and better melting points the mono- and di-N,N′-benzyl derivatives have been investigated the most extensively.



I



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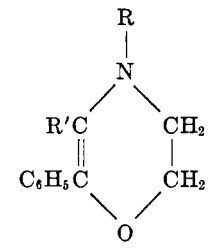

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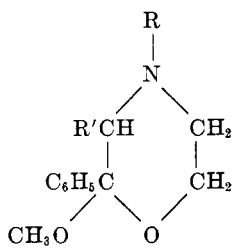

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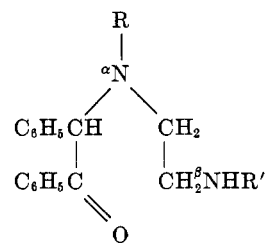
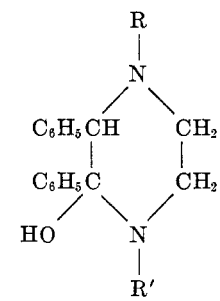


V



VI

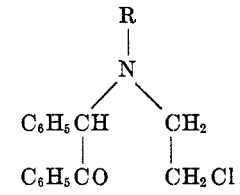
[1] This investigation was supported in part by grants-in-aid from the National Institutes of Health.

[2] Holder of the E. I. du Pont de Nemours Company Postgraduate Fellowship 1951–1952; present location, A. H. Robins Co., Inc., Richmond, Virginia.

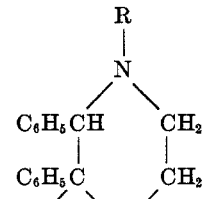
[3] Present location, Reynolds Metal Co., Richmond, Virginia.

Three different approaches to the synthesis of substituted α-(β-aminoethylamino)-α-phenylacetophenones (V–VI) were attempted.

The α-(β-chloroethylamino)-α-phenylacetophenones (VII), intermediates in two of the three synthetic approaches, were prepared by the action of thionyl chloride on the corresponding hydroxyethylamino ketones I or II. They have been assigned open-chain rather than cyclic structures corresponding to II on the basis of their ultraviolet absorptions in the 240–250 mμ range characteristic of the benzoyl group. It follows that the hydroxyethylamino ketones even when largely cyclic react with thionyl chloride in the open-chain sense. Cyclic chloro compounds (VIII) remain unknown despite repeated attempts to make them (3); they would be very reactive and may possibly be intermediates.

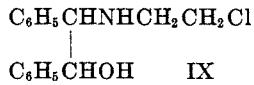


VII (a) R = H
(b) R = C_2H_5
(c) R = CH_2CH_{65}

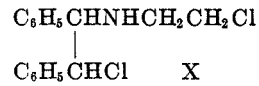


VIII

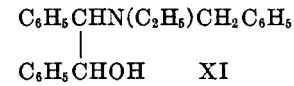
One of the chloroethylamino ketones, VIIa, was reduced to the corresponding β-chloroethylamino alcohol (IX) by aluminum isopropoxide and (more efficiently) by lithium aluminum hydride. The action of thionyl chloride on the chloroethylamino alcohol IX converted it into the dichloro amine X.



IX



X

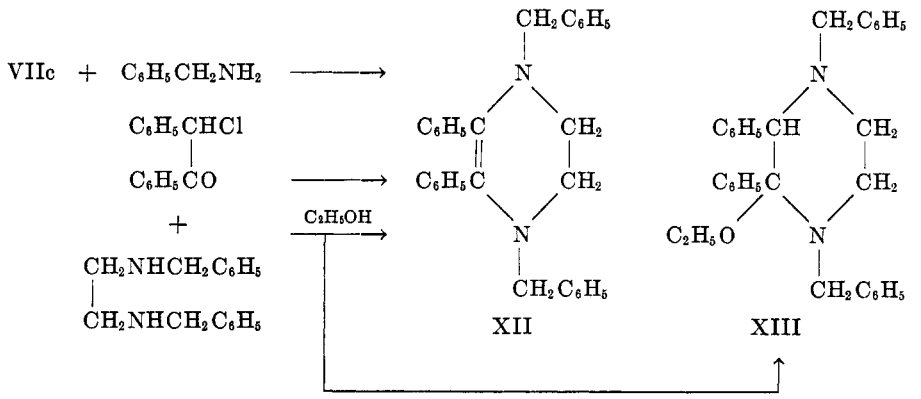


XI

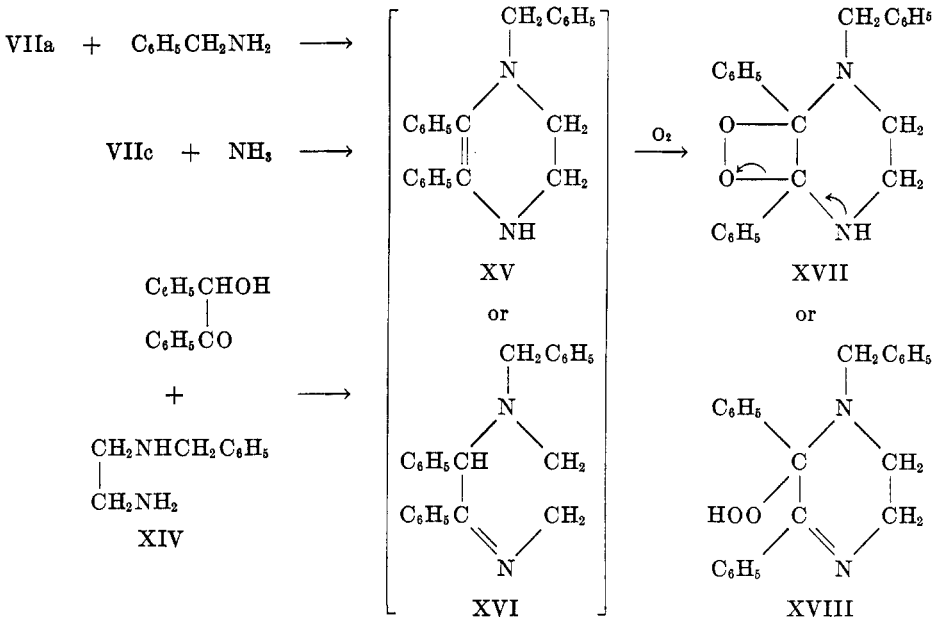
Reduction of the N-benzyl compound VIIc by excess lithium aluminum hydride proceeded with elimination of the halogen to the amino alcohol XI.

Acid hydrolysis of the N-ethyl-chloroethylamino ketone VIIb converted it back into the hydroxyethylamino ketone which exists only in the cyclic form II (R = C_2H_5; R′ = C_6H_5). Treatment of the N-benzylchloroethylaminoketone (VIIc) with sodium ethoxide to replace the chlorine by ethoxyl gave however the dehydromorpholine III (R = $CH_2C_6H_5$; R′ = C_6H_5).

The 2,3-diphenyl-2,3-dehydropiperazines (XII, XV, XXXI). The first of the three synthetic approaches to the aminoethylamino ketones V–VI involved condensation of the above chloroethylamino ketones (VII) with primary amines or ammonia. However these reactions proceeded further with cyclization and dehydration to the dehydropiperazines (XII, XV) and oxidation of the latter to the peroxide (XVII). The 1,4-dibenzyl compound XII, resulting from the condensation of the N-benzylchloroethylamino ketone (VIIc) with benzylamine, contains the stilbene system, and its ultraviolet absorption spectrum closely resembles that of *cis*-stilbene.



When ammonia reacted with the N-benzylchloroethylaminoketone (VIIc), the monobenzyl 2,3-dehydropiperazine (XV) which was presumably formed first, was unstable and absorbed a molecule of air-oxygen to give a peroxide (XVII or XVIII). The same peroxide resulted from condensation of benzylamine with α-(β-chloroethylamino)-α-phenylacetophenone (VIIa) and this reaction presumably also involved air-oxidation of the same intermediate dehydropiperazine XV.



In the second approach to the desired aminoethylamino ketones the condensation of desyl chloride with dibenzylethylenediamine in benzene solution led to the N,N′-dibenzyl dehydropiperazine described above (XII). However, when the condensation was carried out in ethanol there was obtained also 1,4-dibenzyl-

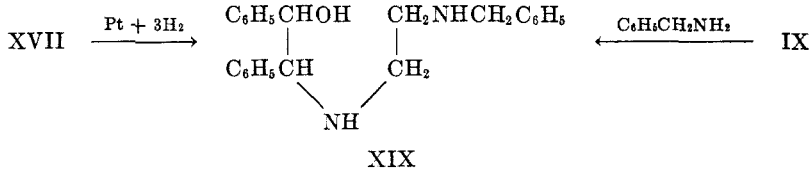
2,3-diphenyl-2-ethoxypiperazine (XIII) which is the cyclic ethyl ether of the desired diamino ketone (V or VI).

The third synthetic approach to the aminoethylamino ketones (V–VI), the Voigt reaction between monobenzylethylenediamine (XIV) and benzoin catalyzed by phosphorus pentoxide, resulted in the formation of the same peroxide XVII. It should be noted here that the intermediate diaminoketone (V; R = H, R′ = $CH_2C_6H_5$) must first be formed, and that the secondary nature of the α-nitrogen is not sufficient to prevent cyclization (through VI) as it does in the corresponding hydroxyethylamino ketone series (I → II → III; R = H).

1-Benzyl-2,3-diphenyl-2,3-dehydropiperazine peroxide (XVII or XVIII). Air-oxidations to peroxides are common among compounds which, like the dehydropiperazine XV, have the system C=C—X—H (X = N or O) (8–16). As examples, 1,2,3,4-tetrahydrocarbazole upon recrystallization gives 11-hydroperoxy-1,2,3,4-tetrahydrocarbazolenine (8), and 2-phenylskatole easily goes to 3-hydroperoxy-3-methyl-2-phenylindolenine (9) [*cf.* other types (10–16)]. These compounds generally have been assigned open-chain hydroperoxy structures of the type XVIII (17, 18) rather than cyclic peroxy structures such as XVII.

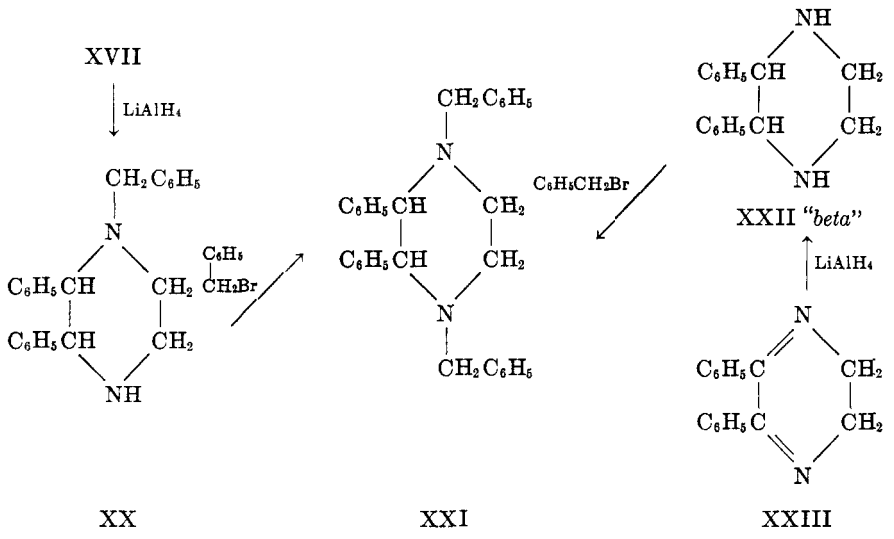
The compound presently being considered (XVII or XVIII), like other related peroxides, readily liberates iodine from acidified potassium iodide and melts with typically rapid decomposition.

Reductions. Confirmation of its peroxidic state is offered by the fact that catalytic reduction involves quantitative absorption of three molecules of hydrogen and gives 2-(N-β-benzylaminoethylamino)-1,2-diphenylethanol (XIX). The structure of the latter (and consequently the direction of ring opening of XVII if it is involved) was proven by synthesis of the reduction product XIX by condensation of the chloroethylamino alcohol IX with benzylamine.



XIX

Lithium aluminum hydride reduction of the peroxide XVII takes a course different from that of catalytic hydrogenation and produces the saturated ring compound, 1-benzyl-2,3-diphenylpiperazine (XX). In order to prove the structure of this compound by an independent synthetic approach the following sequence of reactions was performed. Lithium aluminum hydride reduction of 5,6-diphenyl-2,3-dihydropyrazine (XXIII) gave only the "*beta*" form of the two known stereoisomeric 2,3-diphenylpiperazines (XXII) which had been obtained previously by sodium-alcohol reduction of XXIII (19, 20). Compound XXII was converted by condensation with two molecules of benzyl bromide into 1,4-dibenzyl-2,3-diphenylpiperazine (XXI) which was identical with the product of condensation of 1-benzyl-2,3-diphenylpiperazine (XX) and one molecule of benzyl bromide. This series of reactions demonstrates that the peroxide (XVII) contains the piperazine nucleus intact.

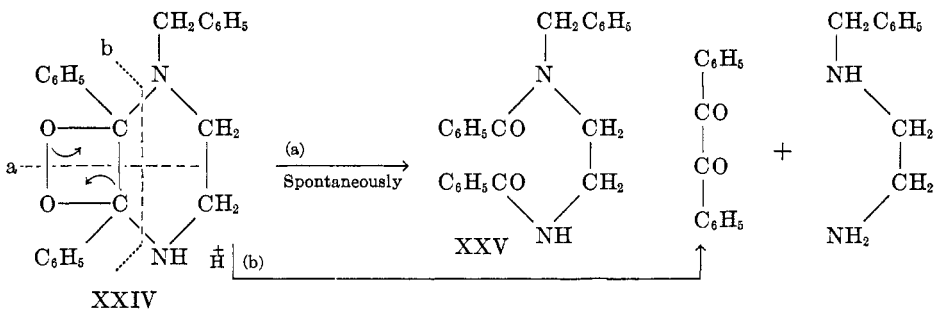


Catalytic or hydride reductions of hydroperoxy compounds such as hydroperoxy-α-phenylskatole (9) lead first to the corresponding hydroxy compounds and then to the parent compounds (*e.g.*, α-phenylskatole). In contrast the reductions of the peroxide presently being considered, XVII or XVIII, do not stop at either of these stages but continue farther to the piperazine or amino alcohol (XX, XXII, XIX). It must be assumed that here catalytic reduction (to XIX) goes stepwise through the hydroxy analog of the peroxide (V or VI; R = H, R′ = benzyl) if the ultimate opening of the piperazine ring in the observed direction is to be explained; but this behavior is not necessarily an argument for the hydroperoxy-structure XVIII and against the peroxy-ring structure XVII because the peroxy-ring in a compound of the latter type would probably open preferentially in such a way as to lead to the same end result. Lithium aluminum hydride, functioning as a strong base, might convert the peroxide XVII to an anion and thereby under the reducing conditions eliminate any difference between the two forms XVII and XVIII. The 2,3-dehydropiperazine XV, although it may be involved as in intermediate in the last stage of the reduction, is probably not reduced as such because the stilbene systems of the 2,3-dehydropiperazine XII and of the analogous dehydromorpholine (III; R = C_2H_5, R′ = C_6H_6) are not reduced by lithium aluminum hydride. Perhaps the reduction proceeds through the ketimine form XVI or its anion which might be produced under the basic activity of the reagent.

Evidence for a cyclic structure. The ultraviolet absorption spectrum of the peroxide XVII shows only a slight maximum or shoulder at 240–250 mμ (ε 3,500), the region of characteristically strong absorption by known Schiff bases of the type $C_6H_5CH{=}NH$ (21), and it is incompatible with a hydroperoxy structure of the type XVIII. The infrared absorption spectrum showed no band in the 2.87 μ region characteristic of the hydroperoxy group, and there were prominent bands

at 4.3 and at 6.1 μ.[4] Possible chemical evidence against the hydroperoxy structure is the insolubility in alkali. The cyclic structure XVII has therefore been assigned, recognizing however that probably ring-chain tautomerism (XVII $\rightleftharpoons$ XVIII) is involved, that the cyclic form may be favored by steric factors and by a relatively high acidity of the hydroperoxy group of XVII caused by the inductive effect of the adjacent tertiary-nitrogen and the phenyl group,[5] and that a certain percentage of zwitterion character may be involved and account for the low but significant absorptivity in the 240–250 mμ region.

Cleavages of the peroxide. Cleavage-isomerization of XVII takes place slowly on standing and rapidly in solution (during recrystallization) to the dibenzamide of monobenzylethylenediamine (XXV). This type of cleavage is generally characteristic of peroxides (23–27) and in some cases is acid-catalyzed (18). For example, isomerization of 11-hydroperoxy-1,2,3,4-tetrahydrocarbazolenine to the cyclic ketoamide (1-aza-8,9-benzylcyclononadi-2,7-one) is believed to involve a protonated quasi four-membered ring-intermediate resembling that pictured in the peroxide XVII. This may be analogous to the hydroxyethylamino ketone ring-chain equilibria (I $\rightleftharpoons$ II) where in some cases acid is known to favor the ring form (4). In the present case, especially in the light of the facility of the cleavage-isomerization without the aid of added acid, the reaction seems best expressed as a simple rearrangement along the lines indicated in formula XXIV(a).



XXIV XXV

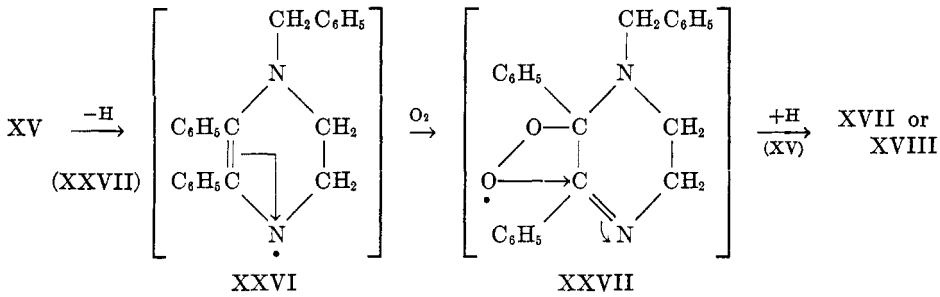
[4] The free bases of the two α-arylskatole ozonides and the corresponding peroxides show typical hydroperoxy infrared absorption bands at *ca.* 2.87 μ, whereas their salts do not absorb in this region. By itself this suppression of the hydroperoxy absorption would be consistent with cyclic peroxy structures for both types of salts. However Witkop, *et al.* (17, 18) offer other data in support of their open-chain formulations which if correct would indicate that the failure of our peroxide to absorb in the 2.87 μ region is not significant. More work in the field is to be undertaken to explore this problem in greater detail.

[5] In the indole and tetrahydrocarbazole series (17, 18) a 4-membered peroxy ring fused to the 5-membered nitrogen-containing ring is rejected by Witkop, *et al.* in favor of hydroperoxy forms analogous to XVIII; however a closely analogous 5-membered peroxy ring is postulated for the salt of the ozonide of α-phenylskatole; and a 4-membered peroxy type ring structure was postulated for an intermediate in acid-catalyzed cleavage. Analogy to the molozonide 4-membered peroxy ring structure may be cited here, and also the autoxidative cleavage of 2-butene which has been interpreted in terms of a cyclic peroxy intermediate (22). In the case in hand (XVII) the 4-membered peroxy ring is fused to a highly substituted 6-membered (piperazine) ring, an arrangement which involves less

Actually in the case of the dehydropiperazine peroxide XVII treatment with dilute acid produces a type of cleavage which is different from that described above and which results in the formation of benzil and monobenzylethylenediamine. This reaction [(b) of XXIV] may be pictured in terms of simple hydrolysis analogous to that of *tert*-butyl peroxide (28) and liberation of the two carbonyl groups.

The mechanism of formation of the peroxide XVII from the intermediate dehydropiperazine XV doubtless is analogous to that proposed for the air-oxidation of other similar systems (8, 18); it presumably involves free radicals such as XXVI and XXVII and cyclization of the latter, at this point as indicated, or in a later ionic step. Support for this mechanism is furnished by the fact that 1,4-dibenzyl-2,3-diphenyl-2,3-dehydropiperazine (XII) which does not have the required —C=C—NH— system, resists air-oxidation.

2,3-Diphenyl-1-ethyl-2,3-dehydropiperazine peroxide was obtained by the three methods described above: (a) condensation of α-(β-chloroethylamino)-α-phenylacetophenone (VIIa) with ethylamine, (b) condensation of α-N-(β-chloroethyl)-N-ethylamino-α-phenylacetophenone (VIIb) with ammonia, and (c) condensation of benzoin with monoethylethylenediamine under the Voigt conditions. This peroxide had the characteristics described for the corresponding benzyl compound (XVII) and it was assumed by analogy to have the cyclic-peroxy structure.

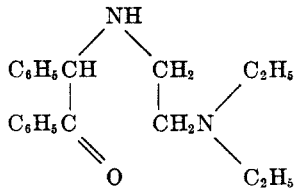


XXVI XXVII

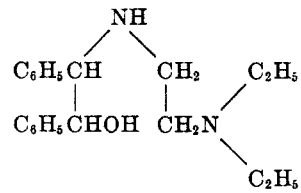
Other related air-oxidations. Condensation of diethylaminoethylamine with benzoin under the Voigt conditions gave the α-(β-dialkylaminoethylamino) ketone XXVIII which was characterized by reduction to the diamino alcohol XXIX. The diamino ketone XXVIII in the form of its salt was stable toward air-oxidation, evidently because the tertiary condition of the β-nitrogen makes cyclization impossible and thus prevents the formation of the dehydropiperazine of the type XV. It should be noted however that the air-oxidation of the free base XXVIII does occur fairly readily to give benzil. This result may be explained in terms of the sensitivity of the secondary α-monoalkylamino ketone system which in contrast to a tertiary α-dialkylamino ketone system can upon

strain than fusion with a 5-membered ring such as in the indole derivatives, and a combination of substituents such as might favor the bicyclic arrangement as it favors cyclization in the hydroxyethylamino ketone series (I to II).

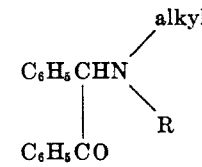
enolization give the easily oxidizable secondary enolamine system HO—C=C—NH—; such a system, like the enediol from benzoin and a hydroquinone, would be expected to undergo ready oxidation through a semiquinone-like intermediate to the equivalent of an α-diketone rather than to a peroxide. This interpretation is consistent with the fact that simpler secondary α-monoalkylamino ketones of the type XXXa are known generally to be relatively unstable as free bases, in contrast to the tertiary α-dialkylamino ketones of the type XXXb which are more stable and which in their tertiary enolamine forms HO—C=C—NR_2 could react only as ordinary monoenols.



XXVIII

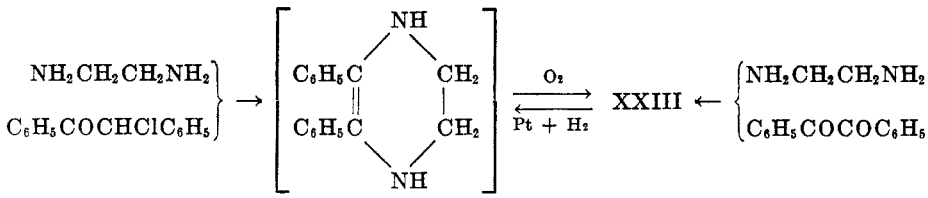


XXIX



XXX (a) R = H
(b) R = alkyl

It would be expected that in the 2,3-dehydropiperazine series where both nitrogens are secondary, as in the still unknown 2,3-diphenyl compound XXXI, air-oxidations would occur particularly readily. In fact oxidation does accompany the condensation of ethylenediamine with desyl chloride and gives rise to 5,6-dihydro-2,3-diphenylpyrazine (XXIII) which is obtainable directly by condensation of ethylenediamine with benzil. That the 2,3-dehydropiperazine XXXI actually has existence as an intermediate is shown as follows: catalytic hydrogenation of the 5,6-dihydropyrazine XXIII proceeded rapidly with quantitative absorption of one molecule of hydrogen; the color changed from the yellow of the starting material through a dark red (presumably a semiquinone-like intermediate) to the yellow of the product (presumably XXXI but which has not been isolated); then when air was admitted to the system the reverse of these color changes was observed and starting material was recovered quantitatively.

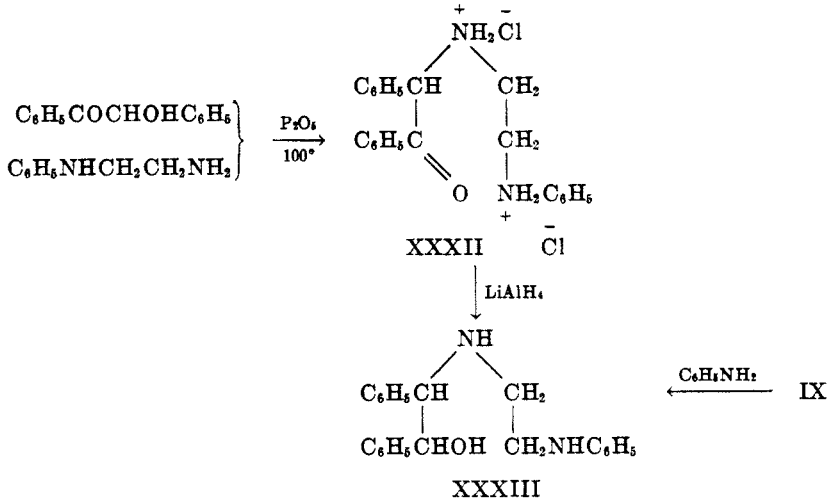


XXXI

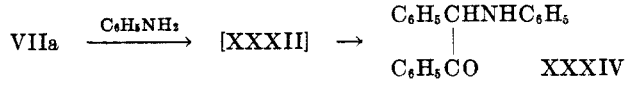
The α-[β-(*mono-N-phenylaminoethylamino*)] *ketone* (XXXII). The product of condensation of benzoin with anilinoethylamine was isolated by Gabriel and Eschenbach (29) as a dihydrochloride of empirical formula, $C_{22}H_{22}N_2O \cdot 2HCl$, and it was presumed by them to be a monohydrate of a dehydropiperazine (of the type XVI with phenyl in place of the benzyl group). In a restudy of this compound we find that the condensation is greatly improved by lowering the re-

action temperature from 150° to 100° and by using phosphorus pentoxide as catalyst.

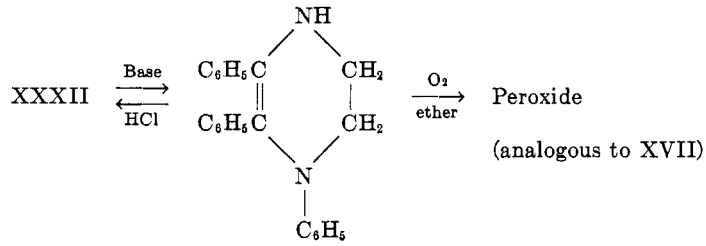
The following relationships show that the oxygen atom is chemically bound and not part of a molecule of hydrate water as originally proposed, and that the compound has the open-chain anilinoethylamino ketone structure (XXXII, analogous to V and XXVIII). Lithium aluminum hydride reduction involved two atoms of hydrogen and gave a new base which still contained the oxygen atom and which was shown to be the anilinoethylamino alcohol XXXIII by synthesis through condensation of aniline with the chloroethylamino alcohol IX.



Attempts to prepare the anilinoethylamino ketone directly by condensation of aniline with the chloroethylamino ketone VIIa were unsuccessful. The only product isolated was the α-anilino ketone XXXIV which was evidently produced by a Voigt-type reaction in which aniline displaced either the anilinoethylamino group of the expected product XXXII or the chloroethylamino group of VIIa.



The anilinoethylamino ketone dihydrochloride XXXII is readily converted into a yellow free base $C_{22}H_{22}N_2$ formulated by Gabriel and Eschenbach (29) as 1,2,3-triphenyl-3,4-dehydropiperazine (analogous to XVI). It seems more likely however that this compound is in the more stable stilbene form with the unsaturation located in the 2,3-position as indicated in formula XXXV (analogous to XV). The compound according to this formulation (XXXV) has one secondary nitrogen and contains the system —C=C—NH—. It should therefore be readily attacked by oxygen to form a peroxide which is analogous to XVII. Experiment showed this to be so.



XXXV

The ultraviolet absorption characteristics of the anilinoethylamino ketone furnishes further evidence in support of the structure XXXII. There is a very strong maximum at 246 mμ (ε 22,230). This band cannot be due to the anilino group alone which would absorb to a moderate degree in this region, and must be attributed in part to a benzoyl group. The molar absorptivity is close to double that of the anilinoethylamino alcohol XXXIII which does not contain a benzoyl group and which has normal aniline type molar absorptivity (ε 12,800 at λ_{max} 248 mμ).

Conclusions in respect to ring-chain tautomerism of aminoethylamino ketones. The two aminoethyl-tertiary-amino ketones (V: R = benzyl; R′ = H or benzyl) which must be formed as intermediates in the condensations of the chloroethyl benzyl amino ketone VIIc with ammonia or with benzylamine, evidently cyclize readily as do the analogous hydroxyethyl-tertiary-amino ketones (I to II: R = alkyl), but reaction does not stop at the hydroxypiperazine V although one ether derivative of it (XIII) has been isolated. The cyclizations presumably are facilitated by the tertiary arrangement of the α-nitrogen and/or by the strongly basic character of the β-nitrogen which is directly involved, and they are perhaps rendered irreversible by subsequent etherification to XIII or dehydration to the highly resonance-stabilized stilbenediamine XII.

The intermediate benzylaminoethyl-secondary-amino ketone V (R = H, R′ = benzyl) which is presumably formed in the condensation of the chloroethylamino ketone VIIa with benzylamine, must also cyclize immediately to a hydroxypiperazine (followed by spontaneous dehydration and air-oxidation). This result demonstrates that a tertiary α-nitrogen is not an essential requirement for ring closure as it seems to be in the hydroxyethylamino ketones I, and that in spite of the unfavorable α-nitrogen arrangement ring closure is made possible by the basic character of the β-nitrogen.

The anilinoethyl-secondary-amino ketone (XXXII) appears to occupy an intermediate position between the alkylaminoethylamino ketone V and the hydroxyethylamino ketones I. It can actually exist as the dihydrochloride, but in the form of the free base it is easily cyclized presumably through the hydroxypiperazine to the dehydropiperazine XXXV; and the latter compound can be converted back to the dihydrochloride XXXII. An important factor favoring cyclization here is the weakly basic character of the anilino β-nitrogen. Factors opposing cyclization are the appreciable steric interference of the phenyl group on the β-nitrogen, the secondary nature of the α-nitrogen, and the acid stabiliza-

tion of the open-chain form by salt formation at the β-nitrogen which should be considerably more basic in the open-chain than in the cyclic form.

EXPERIMENTAL[6]

The α-(N-β-chloroethylamino)-α-phenylacetophenones (VII) were prepared by treatment of the corresponding hydroxyethylamino ketone I or II with a large excess of thionyl chloride, heating at 70° for 20 min., evaporation of the excess reagent under reduced pressure, and work-up of the residue as outlined below.

α-(β-Chloroethylamino)-α-phenylacetophenone hydrochloride (VIIa). The hydrochloride separated from the mixture as the reaction progressed; crystallized from 95% ethanol; yield 45%; m.p. 233–235°.

Anal. Calc'd for $C_{16}H_{16}ClNO \cdot HCl$: C, 61.94; H, 5.52; Cl (ionic), 11.43.
Found: C, 61.76; H, 5.74; Cl, 11.44.

The *free base* was liberated by treatment of a sample of the hydrochloride with ether and a dilute sodium hydroxide solution. The ethereal layer was concentrated and the residual oil was crystallized from ligroin; m.p. 65–66°. The compound soon deteriorated on standing at room temperature. λ_{max} 252 mμ (ε 13,180).

Anal. Calc'd for $C_{16}H_{16}ClNO$: C, 70.19; H, 5.89.
Found: C, 70.41; H, 6.12.

α-[N-(β-Chloroethyl)-N-ethylamino]-α-phenylacetophenone (VIIb). The crude product after evaporation of the reagent, was cooled by addition of crushed ice, basified with sodium carbonate, and extracted by means of ether. Concentration of the ethereal layer gave an oil which was crystallized from ligroin using an acetone-Dry Ice bath; yield, 57%; m.p. 49–49.5°.

Anal. Calc'd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68.
Found: C, 71.51; H, 6.55.

The *hydrochloride* was prepared by treating an ethereal solution of the base with an insufficient amount of ethereal hydrogen chloride (when the equivalence point was passed the product became resinous and difficult to purify); λ_{max} 248 mμ, ε 12,320 (ethanol).

Anal. Calc'd for $C_{18}H_{20}ClNO \cdot HCl$: C, 63.91; H, 6.26.
Found: C, 63.72; H, 6.54.

Hydrolysis of 1 g. of VIIb in 10 ml. of water and 15 drops of conc'd hydrochloric acid (4 hrs. of refluxing), basification, extraction into ether, drying and precipitating with ethereal hydrogen chloride, gave 0.45 g. (43%) of 4-ethyl-2-hydroxy-1,2-diphenylmorpholine hydrochloride (II, R = C_2H_5; R′ = C_6H_5) (identified after recrystallizations from butanone-methanol by mixture m.p.).

α-[N-Benzyl-N-(β-chloroethyl)amino]-α-phenylacetophenone (VIIc) The crude product was worked up like VIIb; crystallized from 95% ethanol; yield 70%; m.p. 94.5–96°. In contrast to VIIa, this compound is relatively stable at room temperature.

Anal. Calc'd for $C_{23}H_{22}ClNO$: C, 75.91; H, 6.09.
Found: C, 76.04; H, 6.36.

The *hydrochloride* was precipitated from an acetone solution of the base by means of ethereal hydrogen chloride; recrystallized from 95% ethanol; m.p. 185–186°; λ_{max} 246 mμ, ε 11,300 (ethanol).

Anal. Calc'd for $C_{23}H_{22}ClNO \cdot HCl$: C, 69.00; H, 5.79.
Found: C, 68.97; H, 5.74.

The action of sodium methoxide. A mixture of 10 ml. of absolute ethanol containing 0.07 g. of dissolved sodium and 1 g. of VIIc, was refluxed; the initial yellow color disappeared

[6] All melting points are "corrected". Microanalyses were performed by Mrs. Carolyn McConnell, Mrs. Marion Smith, Mrs. Carolyn Jeffries, and Miss Patricia Paynter. Ultraviolet absorptions were determined by means of a Beckman DU quartz spectrophotometer using 0.00005 *molar* solutions in 95% ethanol. Infrared determinations were by means of Nujol mulls, using a Baird double beam spectrophotometer.

after 2 min.; 10 ml. of ethanol was added and refluxing was continued for another 3 min. Filtering while hot and cooling gave 0.59 g. (56%) of colorless solid, m.p. 135.5–138°, which was recrystallized from absolute ethanol, m.p. 136.5–138.5°, and identified as the dehydromorpholine III (R = $CH_2C_6H_5$; R′ = C_6H_5) by mixture m.p. with an authentic sample (3).

It is noteworthy that application of these same conditions to the hydroxymorpholine (II, R = $CH_2C_6H_5$; R′ = C_6H_5) did not give this same product.

2-(N-Benzyl-N-ethylamino)-1,2-diphenylethanol hydrochloride (XI). A solution of 9.1 g. of VIIc (base) in 500 ml. of dry ether was added over 15 min. under stirring to a suspension of 1.5 g. of lithium aluminum hydride in 200 ml. of ether, and after 30 min. water and conc'd potassium hydroxide were added. The ether layer was washed, dried over sodium sulfate and treated with ethereal hydrogen chloride. The resinous precipitate crystallized from ethanol, 1.7 g. (18.5%), m.p. 228.5–229°. It contained only ionic chlorine. No attempt was made to reduce VIIc stepwise.

Anal. Calc'd for $C_{23}H_{25}NO{\cdot}HCl$: C, 75.08; H, 7.12.

Found: C, 74.70; H, 7.41.

2-(2-Chloroethylamino)-1,2-diphenylethanol (IX). *Procedure* (*a*). A mixture of 3.1 g. (0.01 mole) of α-(β-chloroethylamino)-α-phenylacetophenone (VIIa), 8.2 g. (0.04 m.) of aluminum isopropoxide, and 100 ml. of dry isopropyl alcohol was heated under partial reflux for 4 hours while 40 ml. of distillate was collected. The excess solvent was evaporated under reduced pressure and the residue was treated with 30% aqueous sodium hydroxide. The precipitate after drying and crystallizing from ligroin gave 2.5 g. (91%); recrystallized from ethanol, m.p. 138.5–139.5°.

Anal. Calc'd for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58.

Found: C, 69.57; H, 6.62.

The *hydrochloride* was precipitated from an ethereal solution of the base by ethereal hydrogen chloride; m.p. 218–220°.

Anal. Calc'd for $C_{16}H_{18}ClNO{\cdot}HCl$: C, 61.54; H, 6.13.

Found: C, 61.15; H, 6.28.

Procedure (*b*). Ten g. (0.0322 mole) of VIIa was added in small portions to a stirred solution of 1.5 g. (0.0404 mole) of lithium aluminum hydride in 100 ml. of absolute ether. The mixture was stirred for an additional 20 minutes and was hydrolyzed with water and 50% potassium hydroxide. The ethereal layer was concentrated and the residual oil was crystallized from 95% ethanol; 7.5 g. (85%) [nearly pure; identified as IX by mixture m.p. with the sample prepared in (a) above].

2-Chloro-1-(β-chloroethylamino)-1,2-diphenylethane hydrochloride (X). A mixture of 5 ml. of thionyl chloride and 1.5 g. of IX hydrochloride on warming turned yellow and began to reflux; refluxing was continued for 10 min. Hydrolysis in ice gave a crystalline product; 1.1 g. (70%); recrystallized from absolute ethanol, m.p. 214–216° (decomp.) (a mixture m.p. with starting material showed a 30° depression).

Anal. Calc'd for $C_{16}H_{17}Cl_2N{\cdot}HCl$: C, 58.11; H, 5.49.

Found: C, 58.15; H, 5.82.

1-Benzyl-2,3-diphenyl-2,3-dehydropiperazine peroxide (XVII). *Procedure* (*a*). A mixture of 6.2 g. (0.02 mole) of VIIa hydrochloride and 20 g. of benzylamine was heated at 83° for two hours. The resulting yellow oil was taken up in ether, washed with several portions of water, and dried over sodium sulfate. Partial evaporation of the ether at reduced pressure gave 2.8 g. (39%) of nearly pure product; m.p. 117–118° (with rapid decomposition). Recrystallization from 1:1 dry acetone-absolute ethanol failed to raise the m.p.

Anal. Calc'd for $C_{28}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82.

Found: C, 77.26; H, 6.63; N, 8.11.

One run by procedure (*a*) using ethanol as solvent with refluxing for 1 hr. gave similar results (yield 33%); the dibenzoate of monobenzylethylenediamine was isolated in considerable quantity from the mother liquors.

There was no clear λ_{max} for the peroxide, but there was a shoulder defined by inflections at 235 mμ, ε 3,600 and 245 mμ, ε 3,300. On standing for 12 hrs. the 0.00005 *molar* solutions

showed a change in absorptivity with the inflections falling at 232 mμ, ε 8,800 and 245 mμ, ε 7,000, and approaching the absorptivity of N,N'-dibenzoyl-N,N'-dibenzylethylenediamine. The absorption of XVII is not far different from that of the ethoxypiperazine XIII.

Procedure (*b*). A mixture of 2 g. (0.0055 mole) of VIIc (base) and 20 ml. of absolute ethanol containing 0.055 mole of ammonia was heated at 75° under pressure for 1–2 hrs. Pouring into water, extracting with ether and processing as in procedure (*a*) gave the same peroxide XVII; 0.75 g. (42%), m.p. 114–115° (decomp.) [it analyzed correctly and gave no mixture m.p. depression with the product of procedure (a) above].

Procedure (*c*). A mixture of 16.5 g. (0.11 mole) of monobenzylethylenediamine, 21.2 g. (0.1 mole) of benzoin, and 1 g. of phosphorus pentoxide was heated at 100° for 2–3 hours. The resulting viscous mass was dissolved in 300 ml. of ether and the ethereal solution was processed as in procedure (*a*); yield of the same peroxide XVII, 15 g. (42%), m.p. 117–118° (decomp.) (it analyzed correctly and gave no mixture m.p. depression with the samples above).

Cleavage of 1-benzyl-2,3-diphenyl-2,3-dehydropiperazine peroxide (XVII) takes place to a considerable extent when the compound is allowed to stand for some time or is recrystallized from alcohol or dioxane; and it gives rise to the dibenzoyl derivative of monobenzylethylenediamine (m.p. 186–187°) which was identified by analysis and by mixture m.p. with an authentic sample prepared by condensation of monobenzylethylenediamine and benzoyl chloride in a standard Schotten-Baumann reaction [m.p. 188° (30)].

Anal. Calc'd for $C_{22}H_{22}N_2O_2$: C, 77.07; H, 6.19.

Found: C, 76.69; H, 6.64.

The absorptivity in ethanol diminished linearly from ε 18,000 at 220 mμ, through ε 10,000 at 240 mμ to ε 4,800 at 250 mμ.

Acid hydrolysis of 1-benzyl-2,3-diphenyl-2,3-dehydropiperazine peroxide (XVII). A solution of 1 g. of the peroxide (XVII) in 25 ml. of 3 *N* hydrochloric acid was heated at 100° for 10 minutes, cooled, and basified. Filtration gave benzil (identified by mixture m.p.). The filtrate when treated with excess benzoyl chloride gave the dibenzamide of monobenzylethylenediamine (30) (identified by recrystallization from ethanol, m.p. 186–187°, and by mixture m.p.). The yields were nearly quantitative.

2-[N-(β-Benzylaminoethyl)amino]-1,2-diphenylethanol (XIX). *Catalytic reduction of 1-benzyl-2,3-diphenyl-2,3-dehydropiperazine peroxide* (XVII). A suspension of 1.78 g. of XVII and 0.03 g. of platinum oxide in 100 ml. of 95% ethanol at atmospheric pressure was shaken for 24 hours; 350 ml. (3 molecules) of hydrogen was absorbed. Filtration and concentration under reduced pressure followed by crystallization of the residual oil from cyclohexane gave 1.2 g. (72%), m.p. 106.5–107.5°. The experiment was repeated on double this scale with comparable results.

Independent synthesis. A mixture of 7.6 g. (0.028 mole) of the chloroethylamino alcohol IX and 10 ml. of benzylamine was heated at 100° for 3 hours. Addition of water and crushed ice caused separation of an oil which crystallized on trituration; recrystallized from ethanol-water mixture; 8.9 g. (93%), m.p. 95–102°. Recrystallization from ligroin and 95% ethanol raised the m.p. to 106.5–107.5°. Identity was shown by analyses and mixture m.p.

Anal. Calc'd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56.

Found: C, 79.50; H, 7.64.

Lithium aluminum hydride reduction of 1-benzyl-2,3-diphenyl-2,3-dehydropiperazine peroxide (XVII). To a solution of 4.0 g. (0.1 mole) of lithium aluminum hydride in 400 ml. of absolute ether was added under continuous stirring 9.4 g. (0.026 mole) of solid peroxide XVII in small portions at such a rate as to maintain gentle refluxing. The mixture was stirred for 3 additional hours and was hydrolyzed with water and 40% potassium hydroxide; the ether layer was washed, dried over sodium sulfate, and concentrated under reduced pressure. The residue was crystallized from cyclohexane; 6.4 g. (70%) m.p. 112–113°. It was identified as 1-benzyl-2,3-diphenylpiperazine (XX) by conversion into the dibenzylpiperazine XXI by treatment with a refluxing mixture of benzyl bromide, potassium

carbonate and 95% ethanol; the product, m.p. 105.5–106°, was prepared independently according to the two schemes described below (samples were identified by mixture m.p.).

Anal. Calc'd for $C_{23}H_{24}N_2$: C, 84.11; H, 7.37.

Found: C, 84.02; H, 7.45.

"β"-2,3-Diphenylpiperazine (XXII) (19,20). Mason's procedure was repeated to obtain an authentic sample. The use of lithium aluminum hydride proved to be more satisfactory. A solution of 2.34 g. (0.01 mole) of 2,3-diphenyl-5,6-dihydropyrazine (XXIII) (19) in 250 ml. of absolute ether was added to a solution of 0.5 g. (0.013 mole) of lithium aluminum hydride in 100 ml. of absolute ether under continuous stirring and at such a rate as to maintain gentle reflux. After stirring for 4 additional hours and hydrolyzing with water and 20% potassium hydroxide, the ether layer was washed, dried over sodium sulfate, and concentrated under reduced pressure. The white solid which separated was recrystallized from cyclohexane; 2 g. (84%), identified as XXII by mixture m.p. with an authentic sample (20).

1,4-Dibenzyl-2,3-diphenylpiperazine (XXI). A mixture of 0.6 g. (0.0025 mole) of "β"-2,3-diphenylpiperazine (XXII), 0.86 g. (0.005 mole) of benzyl bromide, 1.38 g. (0.1 mole) of potassium carbonate, and 100 ml. of 95% ethanol was refluxed for 3 hours, filtered, and concentrated under reduced pressure. A solution of the residue in 250 ml. of ether was washed, dried over sodium sulfate and concentrated. The residual gum was crystallized thrice from absolute ethanol, m.p. 105.5–106°.

Anal. Calc'd for $C_{30}H_{30}N_2$: C, 86.08; H, 7.23.

Found: C, 85.61; H, 7.22.

1,4-Dibenzyl-2,3-diphenyl-2,3-dehydropiperazine (XII). *Procedure (a).* To a boiling solution of 5.3 g. (0.05 mole) of benzylamine in 50 ml. of absolute ethanol was added 9.1 g. (0.025 mole) of α-[N-benzyl-N-β-(chloroethyl)amino]-α-phenylacetophenone (VIIc) over a period of 15 minutes. The resulting orange solution was refluxed for 1 hour. Cooling in an ice-bath caused precipitation of a solid which was filtered and dissolved in ether; the ethereal solution on washing and concentrating gave 8.6 g. (83%) of nearly pure product; recrystallized from acetone; m.p. 120–121°; λ_{max} 247 mμ, ε 14,500; 330 mμ, ε 8,500; λ_{min} 232 mμ, ε 12,500; 275 mμ, ε 5,300.

Anal. Calc'd for $C_{30}H_{28}N_2$: C, 86.50; H, 6.78.

Found: C, 86.27; H, 6.61.

This compound was recovered almost quantitatively unchanged after treatment with 3 *N* hydrochloric acid at 100° for 1 hr.

Procedure (b). To a boiling solution of 24 g. (0.1 mole) of dibenzylethylenediamine in 200 ml. of benzene was added 11.5 g. (0.05 mole) of desyl chloride over a period of 30 minutes; at each addition a deep red color was produced which changed to a light orange as a white precipitate developed. The solution then was refluxed for 1 hour and cooled. The diamine hydrochloride was filtered off and the filtrate concentrated. The resulting oil was processed as in procedure (a); 4.5 g. (22%); m.p. 120–121° (identified by mixture m.p.).

Procedure (c). 1,4-dibenzyl-2-ethoxy-2,3-diphenylpiperazine (XIII). In several experiments using absolute ethanol as solvent instead of benzene [(b) above] the cyclic ethyl ether XIII was formed in addition to or instead of XII, but in the numerous reactions which were run the compound XII was usually the major product. In a typical run on 5.8 g. of desyl chloride the alcoholic solution was refluxed for 2 hours and allowed to stand overnight. The product which separated contained the base XII and was worked up by extracting by means of ether, evaporating and crystallizing from ethanol; 2.5 g. (23%).

The original ethanol filtrate of the reaction mixture was poured into excess water and the oil which separated was washed by decantation and crystallized from absolute ethanol; yield of XIII, 0.4 g. (3%); m.p. 94–96°. In one experiment (not duplicated) the yield of XIII was 48%.

Anal. Calc'd for $C_{32}H_{34}N_2O$: C, 83.08; H, 7.41; OC_2H_5, 9.74.

Found: C, 82.97; H, 7.33; OC_2H_5, 8.6.

Lithium aluminum hydride in dry ether (refluxing for 2 hrs.) was without effect on the ethyl ether XIII.

Attempts to obtain the methoxy analog of XIII by procedure (*c*) led only to XII. The action of methanolic hydrogen chloride (refluxing for 3 hrs.) caused cleavage, and the dihydrochloride of N,N′-dibenzylethylenediamine was obtained in almost quantitative yield.

The ultraviolet absorptivity of XIII dropped from a high value at 220 mμ, through ε 3,600 at 240 mμ; there was a shoulder between inflections at 258 mμ, ε 1,900 and 265 mμ, ε 1,200.

The ultraviolet absorptivity of 4-benzyl-2,3-diphenyl-2,3-dehydromorpholine (III: R = $CH_2C_6H_5$; R′ = C_6H_5) (4) was determined for comparison with XII. λ_{max} 324 mμ, ε 10,000; λ_{min} 265 mμ, ε 4,800; shoulder between inflections at 224 mμ, ε 12,500 and 230 mμ, ε 12,000.

The condensation of desyl chloride with ethylenediamine. To 30 g. (0.5 mole) of ethylenediamine at 70° was added 11.5 g. (0.5 mole) of desyl chloride over a period of 45 minutes. The mixture was poured into an equal volume of water, basified with sodium carbonate, and extracted with ether; the ethereal layer was washed, dried over sodium sulfate and concentrated. There was deposited 5.6 g. (41%); m.p. 157–160° [identified by analysis and mixture m.p. as 2,3-diphenyl-5,6-dihydropyrazine (19)].

α-(β-Diethylaminoethylamino)-α-phenylacetophenone (XXVIII). A mixture of 21.2 g. (0.1 mole) of benzoin, 17.5 g. (0.15 mole) of β-diethylaminoethylamine and 1 g. of phosphorus pentoxide was heated on the water-bath for 4 hours, cooled, digested with ether, and filtered from excess benzoin. The ethereal solution was washed, dried over sodium sulfate, and treated with ethereal hydrogen chloride which precipitated the salts. This product was digested with water (7 g. of benzil was filtered off at this point and identified). After basification and extraction with ether, evaporation of the ether and heating under reduced pressure to remove both solvent and starting diamine, the residual oil was dissolved in ether. The dihydrochloride monohydrate was precipitated by ethereal hydrogen chloride, and was recrystallized first from an isoamyl alcohol-acetate mixture (boiling out the moisture) and then from absolute alcohol-ether mixtures; 12 g. (33%), m.p. 231–234° (decomp.).

Anal. Calc'd for $C_{20}H_{26}N_2O \cdot 2HCl \cdot H_2O$: C, 59.84; H, 7.53; H_2O, 4.49.

Found: C, 60.25; H, 7.43; H_2O (by loss of weight upon drying *in vacuo*), 4.32.

Attempts to analyze the anhydrous material were not successful because of the high hydroscopicity.

2-(β-Diethylaminoethylamino)-1,2-diphenylethanol (XXIX). Reduction of 5.0 g. (0.012 mole) of the above diethylaminoethylamino ketone dihydrochloride monohydrate with 0.91 g. (0.024 mole) of lithium aluminum hydride in absolute ether in the usual manner gave 2.8 g. (75%); recrystallized from isoöctane, m.p. 103.5–105.5°.

Anal. Calc'd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03.

Found: C, 76.75; H, 9.12.

2,3-Diphenyl-1-ethyl-2,3-dehydropiperazine peroxide was prepared independently by the three synthetic approaches described above, using the corresponding N-ethyl rather than N-benzyl starting materials. Using procedure (*b*) VIIa hydrochloride was condensed with ethylamine; the yield of peroxide was 34%, recrystallized from isopropyl alcohol, m.p. 103–103.5° (with vigorous decomposition). Using VII (base) and ammonia by procedure (*b*) but at a reaction temperature of 85° for 1 hr., the yield was 43%. The yield by procedure (*c*) was 53%. All three samples melted alike and identity was shown by analyses and mixture m.p. The compound readily liberated iodine from acidified potassium iodide.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80.

Found: C, 73.05; H, 7.00.

α-[N-(β-Anilinoethyl)-amino]-α-phenylacetophenone dihydrochloride (XXXII) was prepared according to Gabriel and Eschenbach (29) but using phosphorus pentoxide as catalyst and a lower reaction temperature. A mixture of 1 g. of monophenylethylenediamine, 1.5 g. of benzoin, and 0.02 g. of phosphorus pentoxide was heated on the steam-bath for 2 hrs. The resulting syrup was dissolved in 6 ml. of 95% ethanol. Addition of 2 ml. of conc'd hydrochloric acid caused deposition of a white solid; 2.2 g. (76%); m.p. 224° (decomp.); λ_{max} 246 mμ (ε 22,230). Recrystallization caused a lowering of the melting point; therefore, a sample was prepared for analysis by triturating and washing the crude material with

ether. When admixed with a sample prepared exactly according to Gabriel and Eschenbach (29) no m.p. depression was observed; λ_{max} 246 mμ, ϵ 22,230 (abs. ethanol).

Anal. Calc'd for $C_{22}H_{22}N_2O \cdot 2HCl$: C, 65.51; H, 6.00.

Found: C, 65.32; H, 5.98.

1,2,3-Triphenyl-2,3-dehydropiperazine (XXXV). When allowed to stand in water, the above dihydrochloride XXXII was hydrolyzed and it gave a yellow base; m.p. 117° (completely clear at 140°); recrystallized from isoamyl alcohol with no change in m.p. Gabriel and Eschenbach obtained this same result and formulated this product as 1,2,3-triphenyl-3,4-dehydropiperazine (29).

When a sample of XXXV in an ether-ethanol solution was acidified by means of conc'd hydrochloric acid, the solution became dark. Seeding with XXXII was without immediate effect, but after 1 hr. crystals of XXXII were deposited (identified by mixture m.p.).

1,2,3-Triphenyl-2,3-dehydropiperazine peroxide. Dry air was bubbled for 1 hr. through a solution of 1 g. (0.0032 mole) of the compound XXXV described above, while cooling in a freezing mixture; yield of pure peroxide 0.7 g. (64%); m.p. 126° (decomp.).

Anal. Calc'd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13.

Found: C, 76.39; H, 5.94; N, 8.05.

Lithium aluminum hydride reduction of α-[N-(β-anilinoethyl)amino]-α-phenylacetophenone dihydrochloride (XXXII). One g. (0.0025 mole) of XXXII was added portionwise to a stirred solution of 0.5 g. of lithium aluminum hydride in 200 ml. of absolute ether. The mixture was stirred for 1 hr. and hydrolyzed with water and conc'd potassium hydroxide. The ether layer was washed, dried over sodium sulfate, and concentrated. The residue was crystallized from isoamyl alcohol or cyclohexane; yield 0.8 g. (96%); m.p. 133.5–135° (identified as XXXIII by mixture m.p. with the sample prepared below).

2-[N-(β-Anilinoethyl)-amino]-1,2-diphenylethanol monohydrochloride (XXXIII). A solution of 2.75 g. (0.01 mole) of 2-(β-chloroethylamino)-1,2-diphenylethanol (IX) and 2.0 g. (0.022 mole) of aniline in 20 ml. of 95% ethanol was refluxed for 2 hours. During the last half hour the monohydrochloride crystallized from the solution and was filtered and recrystallized from ethanol; 2.5 g. (68%); m.p. 226.5–227° (decomp.); λ_{max} 248 mμ, ϵ 12,800.

Anal. Calc'd for $C_{22}H_{24}N_2O \cdot HCl$: C, 71.62; H, 6.83; Cl, 9.61.

Found: C, 71.34; H, 6.78; Cl, 9.46.

The *free base* was obtained by extracting a basified suspension of the hydrochloride with ether, washing, drying, and concentrating of the ether; crystallized from 95% ethanol; m.p. 132.5–134°.

Anal. Calc'd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28.

Found: C, 79.12; H, 7.28.

The Voigt reaction between α-(β-chloroethylamino)-α-phenylacetophenone (VIIa) *and aniline.* A mixture of 2 g. (0.022 mole) of aniline, 3.1 g. (0.01 mole) of VIIa, and 10 ml. of 95% ethanol was refluxed for 12 hours, cooled, and partitioned between ether and water; the ether layer was washed, dried over sodium sulfate, and concentrated. The residue was crystallized from absolute ethanol and gave 1.7 g. (55%) of α-anilino-α-phenylacetophenone; m.p. 96.5–98°; identified by analysis, ultraviolet absorption spectrum, and m.p. [B. and F. report m.p. 97–98° (31)].

Anal. Calc'd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96.

Found: C, 83.82; H, 6.21.

This same product was obtained in 16% yield as the only recoverable product when an ethanol solution of the anilinoethylamino ketone dihydrochloride XXXII and aniline was refluxed for 6.5 hrs.

SUMMARY

Synthesis of the diamino analogs of hydroxyethylamino ketones was approached through condensations of chloroethylamino ketones with ammonia or amines, and of desyl chloride and benzoin with appropriate ethylenediamines.

Open-chain chloroethylamino ketones (new) were made by reaction of thionyl chloride with hydroxyethylamino ketones. Lithium aluminum hydride reductions of these gave corresponding alcohols with or without deletion of chlorine. Hydrolysis of one, the N-ethyl compound, regenerated the hydroxyethylamino ketone.

In the condensations using all-aliphatic diamines the diamino ketone was obtained only when cyclization of the initial product was prevented by a tertiary-β-nitrogen. With dibenzylethylenediamine only the dehydropiperazine and in one case an ethoxypiperazine were obtained. When one nitrogen in the initial product was secondary there resulted cyclization, dehydration to the dehydropiperazine and air-oxidation to the peroxide.

The peroxide is given a cyclic rather than an open-chain formulation. Reduction and cleavage of the peroxide were studied.

Evidence is offered that reduction of 2,3-diphenyl-5,6-dihydropyrazine gives an unstable dehydropiperazine related to hydroquinone.

The 1,2-diphenyl-2-anilinoethylamino ketone of Gabriel and Eschenbach (29) was reinvestigated. The dihydrochloride is now formulated as the open-chain diamino ketone and the free base as the dehydropiperazine. The latter undergoes air-oxidation to a typical peroxide.

Factors influencing the ring-chain tautomerism of α-(β-aminoethylamino) ketones are summarized. Cyclization is favored by tertiary character of the α-nitrogen and by basic and secondary character of the β-nitrogen.

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