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

1,2-Diphenyl Amino Ketones and Alcohols. Condensation of Amines With Unsymmetrically Substituted Benzoins and Related Reactions[1]

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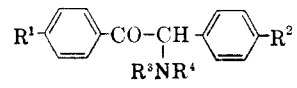
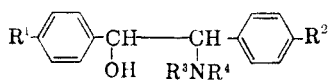
Received August 11, 1955

A number of new 1,2-diaryl amino ketones and alcohols have been synthesized for pharmacological testing. The condensation reaction between substituted benzoins and primary amines has been studied and applied to secondary amines. The results of condensation between primary amines and unsymmetrically substituted benzoins, and isomerization and *trans*-amination of unsymmetrically substituted 1,2-diaryl amino ketones, seem to be consistent with already postulated mechanisms. Distinctive aroyl ultraviolet absorption bands are used to show unequivocally or to confirm the structures of the unsymmetrically substituted benzoins, desoxybenzoins and 1,2-diaryl amino ketones.

A number of substituted amino ketones and alcohols (I and II) based on the 1,2-diphenylethane system have been found to possess tumor-necrotizing activity.[4–8] This paper deals with the preparation of new compounds of these types; and it includes a study of the Voigt reaction between amines and unsymmetrically substituted benzoins, the effect of substituents on the relative stabilities of the structurally isomeric unsymmetrically substituted amino ketones, and the use of ultraviolet absorptions to prove the structures in a simple and unequivocal manner.



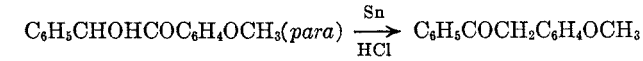
I



II

Unsymmetrically substituted benzoins needed as a starting point for many of the syntheses of amino ketones, *e.g.* 4-methoxybenzoin III, are readily obtained in the more stable of the two isomeric forms by a cyanide-catalyzed reaction between two aromatic aldehydes of widely different characters.[9,10] The production chiefly of the stable form of the unsymmetrically substituted benzoin is consistent with the generally accepted mechanism of this reaction, the reversibility of the several steps, and the predictable relative stabilities of the two types of carbonyls in the several possible products.[9,10] The less stable isomer, 4′-methoxybenzoin (V), is made by the aluminum chloride-catalyzed condensation of phenyl glyoxal and anisole,[11–13] and it can be rearranged to the stable isomer III by alcoholic potassium hydroxide or sodium cyanide, or by heat alone.[14]

The desyl halides (*i.e.* XII, XV) which constitute another starting point for synthesis can be made by the action of thionyl chloride on the corresponding benzoin or by bromination of the appropriate desoxybenzoin (*e.g.* IV). These reactions usually can be controlled so as to avoid rearrangement. A specific unsymmetrically substituted desoxybenzoin can be made consistently by the



III IV

Friedel-Crafts reaction between an arylacetyl chloride and an aromatic system. The tin-hydrochloric acid reduction of an unsymmetrical benzoin to the desoxybenzoin however may involve rearrangements,[15,16] and in our hands the stable 4-methoxybenzoin (III) upon reduction by this

(1) This work, described in a dissertation by J. W. B.,[3] was supported by a grant-in-aid from the National Institutes of Health, under recommendation by the National Cancer Institute.

(2) Present location, Monsanto Chemical Company, Nitro, West Virginia.

(3) Baker, Dissertation, University of Virginia, June 1952.

(4) Lutz, Freek, and Murphey, *J. Am. Chem. Soc.*, **70**, 2015 (1948).

(5) Lutz and Murphey, *J. Am. Chem. Soc.*, **71**, 478 (1949).

(6) Hartwell and Kornberg, *J. Am. Chem. Soc.*, **67**, 1606 (1945).

(7) Hartwell and Shear, *Am. Assoc. Cancer Research, 38th meeting*, May 16–17 (1947) [*cf. Cancer Research*, **7**, 716 (1947)].

(8) Shear, Downing, and Hartwell, *et al.*, *Am. Assoc. Cancer Research, 40th meeting*, April 16–17 (1949) [*cf. Cancer Research*, **9**, 625 (1949)].

(9) Ide and Buck, *Org. Reactions*, **4**, 269 (1948).

(10) Buck and Ide, *J. Am. Chem. Soc.*, **53**, 2350, 2784 (1931).

(11) Fuson, Weinstock, and Ullyot, *J. Am. Chem. Soc.*, **57**, 1803 (1935).

(12) Arnold and Fuson, *J. Am. Chem. Soc.*, **58**, 1295 (1936).

(13) Fuson, Emerson, and Weinstock, *J. Am. Chem. Soc.*, **61**, 412 (1939).

(14) Julian and Passler, *J. Am. Chem. Soc.*, **54**, 4756 (1932).

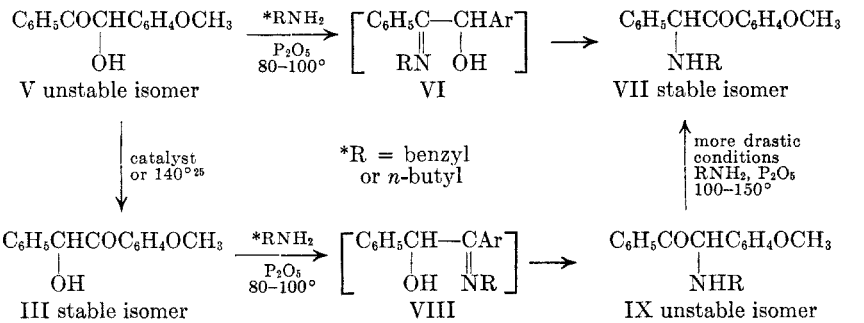
(15) Buck and Ide, *J. Am. Chem. Soc.*, **53**, 1536 (1931).

(16) Buck and Ide, *J. Am. Chem. Soc.*, **54**, 3012 (1932).

method gave the 4′-methoxydesoxybenzoin (IV) which has its carbonyl group in a different and more active position.

The structures of the unsymmetrically substituted benzoins and desoxybenzoins were determined or confirmed by the position of the ultraviolet absorption maxima of the isomers in those cases where the effect of the *para* substituent on the benzoyl group absorption was distinctive (see discussion below).

The preparation of secondary-amino ketones by the Voigt reaction between primary-amines and benzoins. In the case of the monomethoxybenzoins the reaction pattern V → VII and III → IX may



and often does hold under relatively mild reaction conditions, and it may be expressed in terms of the Cowper-Stevens mechanism involving primary attack of amine at the carbonyl group, intermediate Schiff bases of the type VI and VIII, and subsequent successive tautomerizations.[4,17] *cf.* also[18,19] One of the isomeric benzoins is unstable and under more drastic conditions may before condensation rearrange to the other (*e.g.* V to III) and thus lead to the formation of a single stable-type product or a mixture of products (*e.g.* VII or/and IX). And one of the isomeric amino ketones produced under mild conditions may rearrange to the other under the more drastic conditions (*e.g.* IX → VII). In this series the isomer of type VII containing the anisoyl group is the stable one because of the greater inherent stability of the anisoyl group as compared with benzoyl. It was partly to add to the evidence in this field that we have repeated successfully and extended the Cowper and Stevens work. The structures of the various amino ketones of the types VII and IX were demonstrated (or confirmed) by their characterizing high-intensity ultraviolet absorption bands (see below).

Benzyl and *n*-butylamines when condensed with the unstable 4′-methoxybenzoin under both controlled and drastic conditions gave in each case a single product, the amino ketone of opposite and stable type structure VII. The stable 4-methoxybenzoin (III) in reacting with these amines under controlled conditions gave in each case consistently the opposite and unstable type amino ketone IX, but under more drastic conditions gave the stable type amino ketone VII.

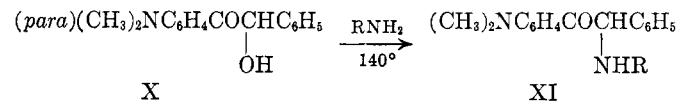
More specifically benzylamine with phosphorus pentoxide at 80° reacted with the stable 4-methoxybenzoin (III) to give the unstable amino ketone IX; at 100° using an excess of benzoin the result was the same; at *ca.* 100° using an excess of benzylamine, one run gave mainly VII and another gave IX; at 130° the stable benzylamino ketone VII was the sole product; and in a reaction begun at 80° to produce IX initially and completed at 155° the stable isomer VII was the sole product.

With excess butylamine and phosphorus pentoxide at 78° the stable 4-methoxybenzoin (III) was converted into the unstable butylamino ketone IX; at 100° a mixture of VII and IX was produced; and at 170° only the stable amino ketone VII could be isolated. Under the more drastic conditions both unstable type amino ketones IX underwent rearrangement to the stable forms VII.

When an excess of ethanolamine was condensed with the stable 4-methoxybenzoin (III) at 80° or 100° using phosphorus pentoxide as catalyst, only the stable amino ketone VII was obtained. A mixture of equimolar amounts of ethanolamine and III at 80° gave apparently a mixture of the isomers VII and IX. Without the catalyst the reaction did not go at 100° as it does with the more reactive 4,4′-dichlorobenzoin;[5] *cf.* also[19] but it did go (without the catalyst) at 140° to the stable amino ketone VII. These reactions, while they do not fully correspond to the pattern outlined above, are understandable in terms of the logical assumption that the ethanolamino ketone (IX) is more reactive or labile than the corresponding benzylamino ketone.

The reaction between amines and 4-(*p*-dimethylamino)benzoin (X) was of interest in this connection because of the high degree of stabilization of the carbonyl group by the strong *para* donor group. This benzoin, of the stable type like III, condensed with benzylamine and with ethanolamine only at the high reaction temperature of 140° to give in each case the amino ketone of the stable type XI (at this high reaction temperature no catalyst was needed, however). Possibly the

(17) Cowper and Stevens, *J. Chem. Soc.*, 347 (1940).
(18) Brown and Mann, *J. Chem. Soc.*, 858 (1949).
(19) Julian, Meyer, Magnani, and Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945).



X XI

unstable isomeric amino ketones of the type IX (as yet unknown in this series) were first formed but underwent rapid isomerization to the stable forms XI under the relatively drastic conditions required.

Piperoin which is known to be less reactive than benzoin,[20] reacted with benzylamine at 100° (with phosphorus pentoxide as catalyst); but a heating period much longer than usual was required to complete the reaction.

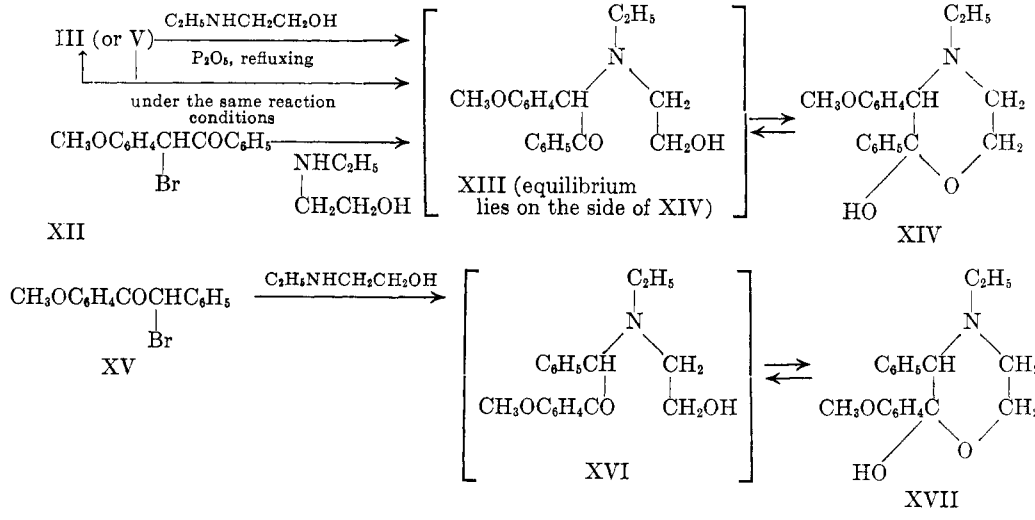
The Voigt reaction with secondary amines. There have been reports of several unsuccessful attempts to condense benzoin with the secondary amine, methylaniline.[17,21] However, under more severe than usual conditions, with consequently considerable complications due to by-products and resinification, it has now been found possible to effect the condensations of this type with methylaniline, benzylmethylamine or ethylethanolamine, at close to boiling temperatures with phosphorus pentoxide as catalyst, to give the tertiary-amino ketones. The ethylethanolamino compound was in the cyclic hydroxymorpholine form (*cf.* XIV); it was synthesized in a second and unequivocal way by the condensation of ethylethanolamine with desyl chloride.

nitrogen did not react with benzoin under these drastic conditions.

Since the above work was completed[3] Heinzelman and Aspergren[22] have reported successful Voigt condensations using the reactive cyclic secondary amines pyrrolidine and piperidine.

The less active unsymmetrically substituted benzoin, the stable 4-methoxybenzoin (III), did not react as well with secondary amines as did benzoin itself. With benzylmethylamine it gave a product which ultraviolet absorption analysis indicated to be a mixture of the two isomeric amino ketones of the types VII and IX (NHR = $C_6H_5CH_2NCH_3$). Methylaniline gave non-crystalline products, and diamylamine did not react.

Ethylethanolamine however reacted well not only with the stable 4-methoxybenzoin but also with the unstable isomer V and gave the hydroxymorpholine (XIV) which is the cyclic form of the unstable amino ketone XIII (of type IX). The structure of this compound XIV was corroborated by a second synthesis through condensation of the corresponding bromo ketone of known structure XII with ethylethanolamine; the cyclic arrangement XIV was shown by the absence of an aroyl ultraviolet absorption band. The validity of



The result of the above condensation with methylaniline was somewhat surprising because at the high temperature involved aniline itself produces the indole. On the other hand it is noteworthy that diisobutylamine with its very considerable steric hindrance toward reaction at the

the latter synthesis of the hydroxymorpholine XIV and the structural conclusions involved were supported by the analogous synthesis of the isomeric hydroxymorpholine XVII through the hydroxyethylamino ketone XVI by condensation of the isomeric bromo ketone XV with ethylethanolamine. Thus it appears that under these reaction conditions the inherently unstable primary

(20) Torrey and Sumner, *J. Am. Chem. Soc.*, **32**, 1492 (1910).

(21) Cameron, Nixon, and Basterfield, *Trans. Roy. Soc. Can.*, III, **25**, 145 (1931) [*Chem. Abst.*, **26**, 3250 (1932)].

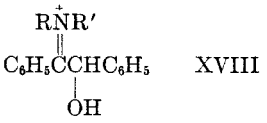
(22) Heinzelmann and Aspergren, *J. Am. Chem. Soc.*, **75**, 3409 (1953).

product of the Voigt reaction between the stable 4-methoxybenzoin (III) and ethylethanolamine, namely the hydroxyethylamino ketone XIII, does not undergo rearrangement to the more stable form XVI, and this is evidently because of prompt cyclization and consequent fixing of this arrangement in the form of the hydroxymorpholine tautomer XIV. The equilibrium XIII $\rightleftarrows$ XIV if it exists must lie so far over on the side of XIV that rearrangement through XIII to XVI and XVII becomes negligibly slow under the reaction conditions.

It might have been predicted that the unstable 4′-methoxybenzoin (V) in spite of the drastic conditions needed for condensation with ethylethanolamine would give the hydroxymorpholine based on the stable amino ketone XVI. However, there was produced the same hydroxymorpholine XIV (based on the unstable amino ketone XIII) together with a significant amount of the stable 4-methoxybenzoin III which must have resulted from rearrangement of the starting material V. Obviously rearrangement of the unstable to the stable 4-methoxybenzoin (V $\rightarrow$ III) was faster than the Voigt reaction, a conclusion which is supported by the fact that this rearrangement V to III could be readily accomplished by the action of phosphorus pentoxide and diethylethanolamine which cannot itself undergo the Voigt reaction, at a temperature much lower than that required for the condensation of V and ethylethanolamine.

Attempts to condense piperoin with ethylethanolamine, and to condense 4-dimethylaminobenzoin (X) with this amine and also with benzylmethylamine, were unsuccessful (starting materials were recovered). These failures may be interpreted in terms of somewhat lower reactivities of the substituted benzoins as compared with benzoin itself.

The mechanism of the Voigt reaction with primary amines proposed by Cowper and Stevens[17] involving Schiff bases of the benzoin carbonyl, is supported by the present studies, and it can be modified to apply to secondary amines by assuming a quaternary-nitrogen analog of the Schiff base, namely XVIII [a typical succession of steps



XVIII

has been outlined by H. and A.[22]]. It is possible to explain the fact that the secondary amines generally do not react as readily as primary amines, in terms of the steric requirements of an intermediate such as XVIII where the tetrasubstituted stilbene-like structure must involve considerably greater steric interferences with the planarity required for maximum resonance stabilization than exists in an ordinary Schiff base such as VI or its protonated form. Consistent with this viewpoint is the fact that the sterically more compact tetramethylene system of the pyrrolidyl analog of XVIII allows the reaction to go easily[22] whereas more bulky activating influence on the carbonyl or anil group open-chain substituents on nitrogen (*i.e.* diisobutyl) effectively prevent the reaction.

Incidentally it may be noted that this mechanism involves the equivalent of an enolization step which requires availability of α-hydrogen. Without an α-hydrogen the reaction could only go by direct displacement of the α-hydroxyl, but such a displacement did not occur in attempts to condense several primary amines with α-methyl and α-phenyl-benzoins.[23,24]

The mechanism of amino ketone rearrangements. The rearrangement of one unstable benzoin to the other (*e.g.* V to III) can be accomplished by merely heating.[25] The comparable rearrangement of an analogous amino ketone however, which must include migration of the nitrogen moiety, and which at times includes displacement of one amine by another, does not go as easily and requires a catalyst.[19,25–27] Examples of amino ketone rearrangements and displacements are the above-described isomerization of the benzylamino ketone XX into XIX, the conversion (*trans*-amination) of both of these isomers by the action of aniline and phosphorus pentoxide at 100° into the "stable" anilino ketone XXV, and the requirement of the much higher temperature of 160–170° for conversion of the "unstable" anilino ketone XXVI into the "stable" isomer XXV.[28]

Application of the principles discussed above under the Voigt reaction[17] seem to us to apply satisfactorily to amino ketone rearrangements. Specifically one could account for the apparently direct displacement of benzylamine by aniline at 100° by assuming intermediates and steps such as XXI–XXIV[29] and a–h, with the replacement of aniline by benzylamine at steps d–e. Similar intermediates could be written for conversion of XXVI

(23) Wayland, Dissertation, University of Virginia, 1952.

(24) Rinker (E. H.), Thesis, University of Virginia, June 1953.

(25) Cowper and Stevens, *J. Chem. Soc.*, 1041 (1947).

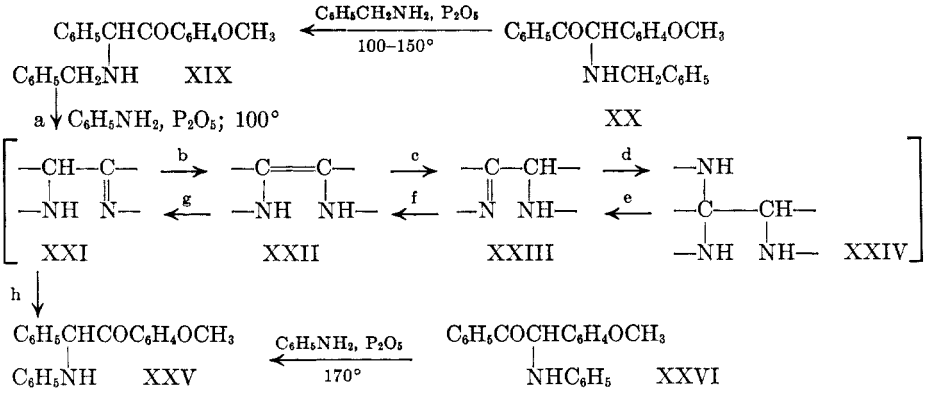
(26) Crowther, Mann, and Purdie, *J. Chem. Soc.*, 58 (1943).

(27) Verkade and Janetzky, *Rec. trav. chim.*, 62, 763, 775 (1943).

(28) Cowper and Stevens did this at 120° with aniline hydrobromide as the catalyst.[25] Other such transformations are described by Brown and Mann.[18]

(29) The isomerization mechanism can be elaborated in respect to the role of the acid catalyst.[18] It is complicated by many ramifications and many conceivable steps, by the varying facility of reversal of the steps, and by the relative stabilities of the isomeric products which become all-important only when over-all equilibrium is achieved.

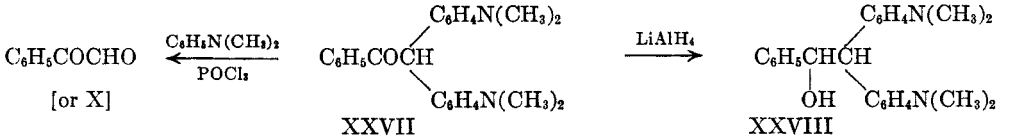
It is noteworthy in this connection that Julian, *et al.*[19] have actually isolated an enedianilide of the postulated type XXII in the reaction between desyl chloride and aniline.



into XXV at 170°. And analogous steps could be written to picture the participation of secondary amines by postulation of imonium ions of the type $\rangle C{=}\overset{+}{N}R_2$. The above explanations carry the assumptions that: although all of the steps are essentially reversible, some are not readily so; and that the benzylamino group exerts a greater to which it is *alpha* than does anilino. The nature of this mechanism entails obvious difficulties in the way of obtaining proof of the finer details and in making predictions as to the specific course of a reaction in the field.

The condensations of amines with unsymmetrically substituted desyl halides (XII, XV) produce amino ketones of corresponding structures, as if by direct displacement, at temperatures so low as to preclude likelihood of rearrangements of either the desyl halide or of the products. Possibly, in analogy with the Voigt reaction and with rearrangement of amino ketones, the mechanism involves primary attack at the carbonyl carbon followed by intramolecular displacement of the then more normally reactive bromine.

Di-(p-dimethylaminophenyl)acetophenone [XXVII,[30,31] known but desired for pharmacological testing] was made by condensation of phenylglyoxal or 4-dimethylaminobenzoin (X) with dimethylaniline,[30] and it was reduced to the corresponding alcohol (XXVIII, new) by lithium aluminum hydride.



A logical mechanism for the condensation reactions showing some analogies to the Voigt reaction involves the following steps: conversion of phenylglyoxal into the unstable 4′-dimethylaminobenzoin (unknown),[32] rearrangement to the more stable isomer X (known), attack on the carbonyl of X by a second molecule of dimethyaniline, dehydration to the enol, and ketonization to XXVII.

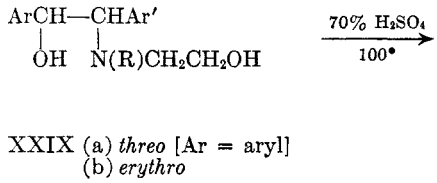
New 1,2-diaryl amino alcohols (II), desired for pharmacological testing, were made by aluminum isopropoxide or lithium aluminum hydride reduction of the corresponding amino ketones (I). In a few cases involving the ethylethanolamino ketones (I; R = C_2H_5; R′ = CH_2CH_2OH) which are cyclic (*cf.* XIV), the more powerful reagent lithium aluminum hydride was necessary. In all cases only one form of the amino alcohol was obtained and was assumed to be the "*erythro*."[4]

It should be noted that reduction of several of the compounds by aluminum isopropoxide (*e.g.* the 3,4-methylenedioxy compound) required somewhat more drastic conditions than usual. The 4-dimethylamino-α-ethanolamino ketone (XI, R = CH_2CH_2OH) did not react at all with this reagent under prolonged treatment, although lithium aluminum hydride reduced it without difficulty. The resistance here to aluminum isopropoxide reduction cannot be ascribed to cyclic structures (like XIV) because the compound shows strong aroyl type ultraviolet absorption and must therefore be open-chain. It must be attributed to the very powerful stabilizing influence of the *p*-dimethylamino group on the carbonyl, and it is consistent with the higher temperatures required to effect Voigt condensations with the corresponding benzoins (*e.g.* X).

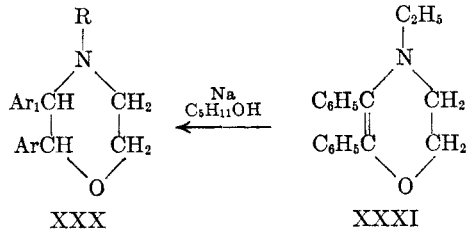
2,3-Diphenylmorpholines (XXIX). The number of carbon-substituted morpholines reported in the literature is small as compared with that of N-substituted derivatives, and no 2,3-diphenyl types are known except as the 2-hydroxy derivatives which are cyclic tautomers of the ethanolamino ketones (*cf.* XIV). One of the best preparative methods is the dehydration of the diethanolamines, and because of the availability of a number of these in the 1,2-diphenyl series it seemed worthwhile to

(30) Madelung and Oberwegner, *Ber.*, **65**, 931 (1932).
(31) Staudinger, *Ber.*, **46**, 3535 (1913).
(32) *Cf.* the analogous Friedel-Crafts reaction which stops at this stage when the aromatic hydrocarbon is used.[12-14]

prepare a few examples of this class for pharmacological testing. The method of Gilman and Wanser,[33] namely treatment with 70% sulfuric acid at 100°, gave the morpholines in good yields. As was expected both *threo* and *erythro* diethanolamines of the type XXIX gave the same morpholine XXX with elimination of stereochemical differences and formation presumably of the more stable *threo* (*trans*) 2,3-diphenylmorpholine configurations. This is consistent with the fact that in no case in the 2,3-diarylmorpholines and their 2-hydroxy derivatives (XXX or XIV) have stereoisomers been obtained.



XXIX (a) *threo* [Ar = aryl]
(b) *erythro*



XXX XXXI

In order to show that the compounds obtained were really dehydromorpholines (XXX) and not open-chain stilbenes, one of these was synthesized in a second way by reduction of the dehydromorpholine XXXI. This reduction did not go with lithium aluminum hydride and required the more effective sodium-isoamyl alcohol combination; the result appeared to be a mixture of morpholine isomers from which however was isolated the same product XXX already obtained by dehydration of the diethanolamine XXIX.

Ultraviolet absorption spectra were important and convenient in determining unequivocally the structures of the unsymmetrically substituted benzoins and the corresponding 1,2-diphenyl α-amino ketones. The identifications were based on the positions of the high-intensity absorption maxima of the aroyl group which depend on the *para* ring-substituent. The two 4'- and 4-methoxybenzoins (V and III) have benzoyl and anisoyl type absorptions, respectively, of *ca.* 245 and 280 mμ, ε = *ca.* 14,000 and 16,000 (Fig. 1); and these values compare closely with those of the 4'- and 4-methoxydesoxybenzoins (*cf.* IV) which have similar aroyl groups (Fig. 2), and with the values for the benzoyl group in benzaldehyde,[34] acetophenone,[34] and desoxybenzoin,[35] and for the anisoyl in anisaldehyde[36] and *p*-methoxyacetophenone[34] [benzene itself absorbs only very slightly at 250 mμ, ε *ca.* 200–300; [34, 36, 37] and anisole absorbs at 269 mμ, ε 1,480[31]]. It is of incidental interest here to note the low-intensity longer wave length absorption bands of the two benzoyl compounds V and IV; the bands at 272 mμ, ε 5,800, are doubtless anisole absorptions. We believe that those at *ca.* 310 mμ, ε 2,000, are not due to impurities, and are possibly due to interaction between the α-anisyl and the carbonyl groups.[38,35] Comparable longer wave length bands would of course be obscured in the anisoyl compounds.

The isomeric pair of *p*-methoxy-α-benzylamino-α-phenylacetophenones VII and IX show absorption curves which are almost identical with those of the corresponding benzoins and desoxybenzoins (Fig. 3), except that the intensity of the 310 mμ bands are suppressed to *ca.* ε 500.

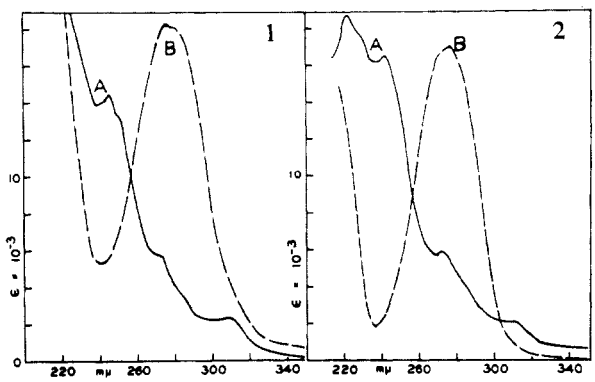


FIG. 1.—A = $C_6H_5COCHOHC_6H_4OCH_3$
B = $C_6H_5CHOHCOC_6H_4OCH_3$
FIG. 2.—A = $C_6H_5COCH_2C_6H_4OCH_3$
B = $C_6H_5CH_2COC_6H_4OCH_3$

Figure 4 shows the absorption curves of a typical ethylethanolamino ketone which is in the cyclic form XVII. The curve for the ethanolamino analog where nitrogen is secondary shows a strong maximum corresponding to an aroyl group and is therefore open-chain. In the curve for the reduced compound, the diethanolamine XXIX, this maximum is absent. The weak bands at 375–280 mμ, ε 3,500 shown by both the cyclic compound XVII and the diethanolamine, are doubtless due to the anisyl group itself, but the longer wave length band of the diethanolamine at 312 mμ, ε 1,000 is not accounted for.

The absorption curve for the 1,2-di-(3,4-methylenedioxyphenyl)-α-ethanolamino ketone is very

(33) Gilman and Wanser, *J. Am. Chem. Soc.*, **73**, 4030 (1951).
(34) Doub and Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).
(35) Alpen, Kumbler, and Strait, *J. Am. Chem. Soc.*, **72**, 4558 (1950).
(36) Morton and Stubbs, J. Chem. Soc., 1347 (1940).
(37) Platt and Klevens, *Chem. Revs.*, **41**, 301 (1947).
(38) Kumbler, Strait, and Alpen, *J. Am. Chem. Soc.*, **72**, 1463 (1950).

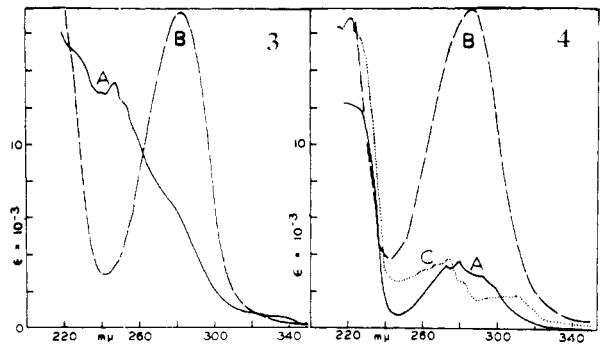


FIG. 3.—A = $C_6H_5COCHC_6H_4OCH_3$ (NHCH$_2$C$_6$H$_5$)

B = $C_6H_5CHCOC_6H_4OCH_3$ (NHCH$_2$C$_6$H$_5$)

FIG. 4.—A = $C_6H_5CH{-}C(OH)C_6H_4OCH_3$ (N, O; C_2H_5, CH_2CH_2)

B = $C_6H_5CHCOC_6H_4OCH_3$ (HCl·NHCH$_2$CH$_2$OH)

C = $C_6H_5CHCHOHC_6H_4OCH_3$ (HCl·NHCH$_2$CH$_2$OH)

similar to that of piperoin and the compound is therefore open-chain. The same holds for the corresponding 4-dimethylamino pair, except that both the intensity and wave length of the maxima are increased considerably.

EXPERIMENTAL[39]

Preparation of secondary and tertiary-amino ketones. Method 1 of Table I. From benzoins. A mixture of the benzoin, either (a) an equimolar quantity or (b) an excess of the amine, and 0.5–1.0 g. of phosphorus pentoxide per 0.1 mole of the benzoin, was heated at 80–240° for 0.5–5.0 hours and cooled to room temperature. In two cases (c) an excess of the benzoin was used. The phosphorus pentoxide catalyst (d) was omitted in several experiments and (e) toluene was used as a solvent in one instance. The crude mixture of products after cooling was worked up directly either (f) through crystallization of the free base, or (g) as the hydrochloride. The hydrochloride was prepared by dissolving the crude reaction product in ether or chloroform, removing unreacted amine by extraction either with water or dilute hydrochloric acid, drying over sodium sulfate, and precipitating by addition of ethereal hydrogen chloride. Some of the free bases which were crystalline and sufficiently stable were obtained from the hydrochlorides by treatment with aqueous sodium carbonate.

No reaction took place upon refluxing a mixture of excess ethanolamine, 4-dimethylaminobenzoin (X), phosphorus pentoxide, and boiling benzene. Likewise negative results were obtained with butylamine at temperatures less than 150° or in boiling benzene or toluene. Ethanolamine did not react with 4-methoxybenzoin (III), at 100° when the catalyst was omitted.

The formation of mixtures of isomers of some secondary-amino ketones occurred when unsymmetrically substituted benzoins were treated with primary amines in the presence of phosphorus pentoxide as catalyst. For example, a mixture of 0.025 mole of 4-methoxybenzoin (III), 0.075 mole of butylamine, and 0.25 mole of phosphorus pentoxide, upon heating in a pressure bottle at 100° for 2 hours, gave a mixture of hydrochlorides (73%) (*cf.* method 1g above). Upon recrystallization the first crop was the stable isomer. The nature and approximate composition of the residual mixture was shown by its two ultraviolet absorption bands of 254 mμ, ε 8,650 and 280 mμ, ε 8,400, which corresponded to the absorptions of the 4 and 4′-methoxyamino ketones. In each of two separate experiments at *ca.* 100° using 10% excess of benzylamine and phosphorus pentoxide as catalyst, a different isomer was isolated (no attempt was made to determine the small difference in conditions responsible for the inconsistency of these results).

In another case a mixture of isomeric amino ketone hydrochlorides (65%) was obtained by heating 0.025 mole each of 4-methoxybenzoin (III) and ethanolamine, and phosphorus pentoxide, at 80° for 2 hours. The first crop on recrystallization was stable isomer. The residual mixture showed ultraviolet absorption bands of 248 mμ, ε 10,300 and 274 mμ, ε 6,780.

In a third and similar case with III, benzylamine, and phosphorus pentoxide at 130° for 2 hours, the mixture of hydrochlorides obtained (65%) (largely the stable isomer) gave a residual mixture with maxima at 245–252 and 276–286 mμ.

The successful reactions between benzoins and secondary amines, using phosphorus pentoxide as catalyst, are given in Table I. Negative results were obtained in the following interactions: benzoin with diamyl and diisobutylamine at 140° and 180° respectively; piperoin with ethylethanolamine at 160°; 4-dimethylaminobenzoin (X) with methylaniline and with ethylethanolamine at 185° and 240° respectively; and 4-methoxybenzoin (III) with methylaniline at 240°.

Methylbenzylamine reacted with 4-methoxybenzoin at 240° to give a product which was shown by ultraviolet absorption analysis to be a mixture of the isomeric amino ketones.

The product of reaction of 0.03 mole of ethylethanolamine and 0.01 mole of 4′-methoxybenzoin (V) at 240° (2 hours) was taken up in ethanol. Upon cooling the isomeric 4-methoxybenzoin (42%) crystallized and was identified. Evaporation of the filtrate, solution of the residue in ether and addition of ethereal hydrogen chloride gave 29% of cyclic amino ketone XIV (identified by mixture m.p.).

Isomerization of 4′-methoxybenzoin (V)[24] by the action of excess diethylethanolamine with phosphorus pentoxide catalyst (100°, 2 hours) gave 92% yield of 4-methoxybenzoin III (identified by mixture m.p.).

Preparation of secondary and tertiary amino ketones. Method 2 of Table I. From desyl halides. A mixture of the appropriate desyl halide and at least two equivalents of the primary or secondary amine was allowed to stand at room temperature with such cooling as was necessary to control the normally exothermic reaction. Only occasionally was applied heating required. In a number of cases solid sodium carbonate was added to the reaction mixture to neutralize the hydrogen halide produced. The mixture usually was allowed to stand for one hour at room temperature to complete the reaction, and was treated with water and ether. The ether solution containing the product was either (a) evaporated to obtain the base or (b) treated with ethereal hydrogen chloride to give the hydrochloride. The stable bases were often obtained from the purified hydrochlorides by treatment with aqueous sodium carbonate.

Preparation of amino ketones by the action of amines on other amino ketones (trans-amination). Method 3 of Table I. A mixture of 0.01 mole of the α-amino ketone or its salt, an excess of aniline (0.1 mole), and 0.25 g. of phosphorus pentoxide, was heated at 100° under an atmosphere of nitrogen. The resulting oil was crystallized from ethanol. Negative results were obtained in the following interactions: α-phenyl-α-ethanolaminoacetophenone and ethylethanol-

(39) Analyses were by Mrs. A. B. Wilgus, Mrs. M. T. Smith, Mrs. C. M. McConnell, Mrs. C. E. Jeffries, and Clark Microanalytical Laboratory.

TABLE I

SUBSTITUTED 1,2-PHENYL-2-AMINOETHANONES

No.	Amine Group[a]	Prep. from[b]	Prep. Method[c]	Heating Time, Hrs.	Reaction Temp., °C.	Yield, %	M.P.,[d,e] °C.
			$C_6H_5COCH(N<)C_6H_5$				
1	$N(CH_3)CH_2C_6H_5$	A	1b,f	2	185	78	99–100
		B	2b	1	100	58	—
	Hydrochloride	M	—	—	—	—	222–224
2	$N(CH_3)C_6H_5$[21,40]	B	—	—	—	—	101–102
	Hydrochloride	A	1b,g	2	185	68	207–209
3	$NHCH_2CH_2OH\cdot HCl$[4]	B	2c	3	100	78	201–203[f]
4	$N(C_2H_5)CH_2CH_2OH\cdot HCl$[4]	A	1b,g	1	240	37	201–203[f]
			para-$CH_3OC_6H_4COCH(N<)C_6H_4OCH_3$-*para*				
5	$NHCH_2CH_2CH_2CH_3\cdot HCl$	C	1b,g	2	100	45	203–204
6	$NHC_6H_4N(C_2H_5)_2$-*p*$\cdot HCl$	C	1b,g	2	100	30	178–180
7	$NHCH_2CH_2OH\cdot HCl$	C	1b,g	5	100	98	187–188
		D	2c	4	30	61	—
8	$—N(C_2H_5)CH_2CH_2OH\cdot HCl$	D	2c	4	30	89	185–186
			(*3,4*)-$CH_2O_2C_6H_3COCH(N<)C_6H_3O_2CH_2$-(*3,4*)				
9	$NHC_6H_4N(C_2H_5)$-*p*$\cdot HCl$	E	1b,g	4	100	55	203–204
10	$NHCH_2CH_2OH\cdot HCl$	E	1b,g	4	100	54	193–196
11	$NHCH_2CH_2CH_2CH_3\cdot HCl$	E	1b,g	5	80	59	235–236.5
12	NHC_6H_5	E	1b,f	2	100	90	136–137
	Hydrochloride	M	—	—	—	—	220–222
			para-$(CH_3)_2NC_6H_4COCH(N<)C_6H_5$				
13	$NHCH_2CH_2OH$	F	1b,f	0.5	150	55	171–172
		F	1b,d,f	0.5	150	55	—
		F	1b,e,f	2	110	54	—
	Hydrochloride	M	—	—	—	—	214–216
14	$NHCH_2CH_2CH_2CH_3$	F	1b,f	2	150[g]	54	103–104
	Dihydrochloride	M	—	—	—	—	234–236
			$C_6H_5COCH(N<)C_6H_4OCH_3$-*para*				
15	$NHCH_2C_6H_5$	N	—	—	—	—	86–88
	Hydrochloride	G	1a,g	2	80	43	208–209
		G	1b,g	2	80	55	—
		G	1c,g	2	100	66	—
16	$NHCH_2CH_2CH_2CH_3\cdot HCl$	G	1b,f	2	80	84	220–222
17	NHC_6H_5[17]	G	1b,f	1.5	100	99	136–137
		G	1b,g	2	170	66	—
	Hydrochloride	M	—	—	—	—	202–204
18	$N(C_2H_5)CH_2CH_2OH\cdot HCl$	H	2a,c	0.5	30	88	192–194
	(cyclic)[4]	G	1b,g	1	240	12	—
		I	1b,g	2	240	29[h]	—
			para-$CH_3OC_6H_4COCH(N<)C_6H_5$				
19	NHC_6H_5[17]	I	1b,f	2	100	76	144–145
		J	3	2	100	47	—
		K	3	2	100	80	—
	Hydrochloride	M	—	—	—	—	208–209
20	$NHCH_2CH_2CH_2CH_3\cdot HCl$	L	2a,c	1	30	79	222–224
		I	1b,g	2	80	76	—
		G	1b,g	2	170[g]	30	—
21	$NHCH_2CH_2OH\cdot HCl$	G	1b,g	2.75	80	50	192–194
		G	1b,g	0.5	100	54	—
		G	1b,d,g	2	140	62	—
		I	1b,g	2	100	57	—
22	$NHCH_2C_6H_5$	L	2a,b	1	3	56	90–91
	Hydrochloride	M	—	—	—	—	218–220
		I	1b,g	2	100	51	—
		G	1b,g	2	130	33	—
		G	1c,g	4[i]	155[i]	63	—
23	$N(C_2H_5)CH_2CH_2OH$	L	2a,b	1	30	95	113–113.5
	Hydrochloride (cyclic)	L	2a,c	1	30	75	163–164

[a] This represents the nitrogen moiety. References when given are to original preparations of the known compound; the preparation described here may be similar or different. For analyses see Table III. For ultraviolet absorptivities see Table IV and Figures 1–4. [b] The compounds used in the condensations with the appropriate amines are the following: A = benzoin;

(40) Lutz, Jordan and Truett, *J. Am. Chem. Soc.*, **72**, 4085 (1950).

TABLE II

SUBSTITUTED 1,2-DIPHENYL-2-AMINOETHANOLS (II[a])

No.	NR^3R^4[a]	R^1	R^2	Prep. Method[b]	Heating Time, Hrs.	Yield, %	M.P.,[c] C.[d]
1	$NHCH_2CH_2OH$	OCH_3	H	—	—	—	126–128
	(hydrochloride)			1b	15	67	229–230
2	$NHCH_2CH_2CH_2CH_3$	OCH_3	H	1a	8	95	115.5–116.5[f]
	(hydrochloride)			—	—	—	207–208
3	$NHCH_2CH_2CH_2CH_3$	H	OCH_3	1a	9	91	115–116[f]
	(hydrochloride)			—	—	—	207–208
4	NHC_6H_5	H	OCH_3	2a	1	95	141.5–142.5
5	$NHCH_2C_6H_5$	OCH_3	H	2a	1	96	112–113
	(hydrochloride)			—	—	—	199–200
6	$N(C_2H_5)CH_2CH_2OH \cdot HCl$	OCH_3	H	2b	1	97	173–175
7	$NHCH_2CH_2OH$	OCH_3	OCH_3	—	—	—	112–113
	(hydrochloride)			1b	14	82	206–208
8	$NHCH_2CH_2CH_2CH_3$	OCH_3	OCH_3	1a	6	52	124–125
	(hydrochloride)			—	—	—	177–178
9	$NHCH_2CH_2OH$	$N(CH_3)_2$	H	2a	2	67	147–148
	(dihydrochloride)			—	—	—	196–197
10	$NHCH_2CH_2OH$	O_2CH_2[e]	O_2CH_2	—	—	—	115–116
	(hydrochloride)			1b	20	92	211–212
11	$NHCH_2CH_2CH_2CH_3 \cdot HCl$	O_2CH_2[e]	O_2CH_2	1b	20	76	234–235
12	$N(CH_3)CH_2C_6H_5$	H	H	2a	1	90	72–73
	(hydrochloride)			—	—	—	230–232

[a] The NR^3R^4, R^1 and R^2 groups are in the positions shown in formula II. For analyses see Table III. For ultraviolet absorptivities see Table IV. [b] See generalized directions in the experimental part. [c] For solvents of crystallization see Table III. [d] Melting points are "corrected". [e] O_2CH_2 = 3,4-methylenedioxy. [f] Mixtures of compounds 2 and 3 showed unequivocal mixture m.p. depressions.

amine at 100°; 2-(*p*-methoxyphenyl)-α-anilinoacetophenone (XXVI) and ethanolamine at either 100° or 175°, or ethylethanolamine at 185°.

The stability of α-(p-methoxyphenyl)-α-benzylaminoacetophenone (XXV) under heating at 160° for 2 hours was demonstrated by recovery of the material in the form of its hydrochloride [*cf.* stability of amino ketones[18,25]].

4,4'-Dimethoxydesyl bromide[42] was prepared in 84% yield by addition of bromine over a half-hour to dimethoxydesoxybenzoin in carbon tetrachloride under illumination, identified by m.p.[42] and analysis.

Preparation of amino alcohols by reduction of amino ketones. Method 1 Table II, using aluminum isopropoxide. A solution of the amino ketone or its hydrochloride and four equivalents of aluminum isopropoxide in an excess of propanol-2, was heated under partial reflux until the test for acetone in the distillate was negative. The excess solvent was distilled under reduced pressure and the residue was treated with an excess of aqueous sodium hydroxide and water. The crude amino alcohol was isolated and purified as (a) the free base or (b) the hydrochloride. The hydrochloride was prepared by dissolving the crude amino alcohol in ether, drying over sodium sulfate and addition of ethereal hydrogen chloride. The base (when stable) was liberated from the hydrochloride by means of aqueous sodium carbonate.

Three amino ketones, two of which possessed cyclic hydroxymorpholine structures, were recovered unchanged upon subjection to the above reduction conditions: namely, 2,3-di-(*p*-anisyl)-2-hydroxy-4-ethylmorpholine, 2-(*p*-anisyl)-2-hydroxy-3-phenyl-4-ethylmorpholine, and α-phenyl-α-(2-hydroxyethylamino)-*p*-dimethylaminoacetophenone.

Method 2 of Table II using lithium aluminum hydride. To an absolute ether solution of 0.5–1.0 molar-equivalent of lithium aluminum hydride was added portionwise the solid amino ketone or its hydrochloride, or an ether solution of the base when it was sufficiently soluble. The resulting mixture was stirred for 1–2 hours at room temperature. Water and dilute sodium hydroxide were added cautiously and the ether layer was washed and dried over sodium sulfate. The product was isolated (a) as the free base or (b) as the hydrochloride as described above in Method 1.

Benzoyl-bis-(p-dimethylaminophenyl)methane (XXVII) was prepared by a modification of earlier methods.[31] A solution of 13.5 g. of phenylglyoxal in 50 ml. of benzene was added dropwise over 30 minutes to a stirred mixture of 36.6 g. of dimethylaniline, 7 g. of phosphorus oxychloride, and 300 ml. of benzene. The mixture was stirred for an additional hour and allowed to stand overnight. Treatment with conc'd ammonium hydroxide, separation of the benzene layer, evaporation, and crystallization of the residue, gave 19.2 g.

B = desylchloride; C = anisoin;[41] D = $CH_3OC_6H_4COCHBrC_6H_4OCH_3$;[42] E = piperoin;[20] F = $(CH_3)_2NC_6H_4COCHOH-C_6H_5$[p];[31,43] G = $CH_3OC_6H_4COCHOHC_6H_5$; H = $CH_3OC_6H_4CHBrCOC_6H_5$;[44] I = $CH_3OC_6H_4CHOHCOC_6H_5$; J = $CH_3-OC_6H_4CH(NHCH_2C_6H_5)COC_6H_5 \cdot HCl$; K = $C_6H_5CH(NHCH_2C_6H_5)COC_6H_4OCH_3$; L = $CH_3OC_6H_4COCHBrC_6H_5$;[44] M represents the corresponding base from which the salt was made by the action of ethereal hydrogen chloride; N = the corresponding hydrochloride from which the free amino ketone was liberated by the action of bases. [c] See the three general procedures and discussions in the experimental part. Particular variations are indicated by the one or more letters following the preparation method number. [d] Solvents for recrystallization are given in Table III. [e] Melting points are "corrected." [f] Crystallized from isoöctane-methanol mixtures. [g] The reaction was carried out in a pressure bottle. [h] In the reaction a sizable amount (42%) of 4'-methoxybenzoin(III) was isolated and identified, but none of the starting material V was recovered. The yield of amino ketone was calculated from the amount of V used less the amount of III recovered. [i] Heated at 80° for 2 hours and then at 185° for an additional 2 hours. [p] The substituents are *para*.

(41) Bosler, *Ber.*, **14**, 323 (1881).

(42) Henne and Bruylants, *Bull. soc. chim. Belges*, **57**, 320 (1949) [*Chem. Abstr.*, **43**, 7922 (1949)].

(43) Jenkins, Bigelow, and Buck, *J. Am. Chem. Soc.*, **52**, 5198 (1930).

(44) Jenkins, *J. Am. Chem. Soc.*, **56**, 682 (1934).

TABLE III

ANALYSES

No.[a]	Crystallization Solvents[b]	Empirical Formula	Carbon (or Nitrogen) Calc'd	Carbon (or Nitrogen) Found	Hydrogen (or Chlorine) Calc'd	Hydrogen (or Chlorine) Found
		COMPOUNDS LISTED IN TABLE I				
1	EtOH	$C_{22}H_{21}NO$	83.77	83.31	6.71	6.70
	But.-CH_3OH	$C_{22}H_{21}NO\cdot HCl$	75.09	74.99	6.30	6.34
2	EtOH	$C_{21}H_{19}NO$	83.69	83.45	6.35	6.44
	But.-CH_3OH	$C_{21}H_{19}NO\cdot HCl$	74.66	74.37	5.97	6.14
5	But.-CH_3OH	$C_{20}H_{23}NO_3\cdot HCl$	66.01	66.26	7.20	7.18
6	Hexon.-CH_3OH	$C_{26}H_{30}N_2O_3\cdot HCl$	(6.13)	(6.37)		
7	But.-CH_3OH	$C_{18}H_{21}NO_4\cdot HCl$	61.44	61.71	6.37	6.74
8	But.-CH_3OH	$C_{20}H_{25}NO_4\cdot HCl$	63.23	63.21	6.90	7.16
9	But.-CH_3OH	$C_{26}H_{21}N_2O_5\cdot HCl$	(5.80)	(5.80)	(7.18)	(7.03)
10	But.-CH_3OH	$C_{18}H_{17}NO_6\cdot HCl$	56.92	56.94	4.78	4.72
11	But.-CH_3OH	$C_{20}H_{21}NO_5\cdot HCl$	61.30	61.56	5.66	5.93
12	EtOH	$C_{22}H_{17}NO_5$	70.40	70.13	4.57	4.53
	But.-CH_3OH	$C_{22}H_{17}NO_5\cdot HCl$	64.16	63.79	4.41	4.44
13	Acet.-EtOH	$C_{18}H_{22}N_2O_2$	72.45	72.10	7.43	7.58
	But.-EtOH	$C_{18}H_{22}N_2O_2\cdot HCl$	64.56	64.32	6.92	6.72
14	EtOH	$C_{20}H_{26}N_2O$	77.38	77.11	8.44	8.32
	But.-CH_3OH	$C_{20}H_{26}N_2O\cdot 2HCl$	62.65	62.45	7.36	7.76
15	EtOH	$C_{22}H_{21}NO_2\cdot HCl$	71.82	71.65	6.03	6.03
	But.-CH_3OH	$C_{22}H_{21}NO_2$	79.73	79.53	6.38	6.55
16	But.-CH_3OH	$C_{19}H_{23}NO_2\cdot HCl$	68.35	68.58	7.25	6.88
17	But.-CH_3OH	$C_{20}H_{19}NO_2\cdot HCl$	71.25	71.35	5.70	6.05
18	But.-CH_3OH	$C_{19}H_{23}NO_3\cdot HCl$	65.23	65.02	6.92	7.02
19	But.-CH_3OH	$C_{20}H_{19}NO_2\cdot HCl$	71.28	71.08	5.70	5.83
20	But.-CH_3OH	$C_{19}H_{23}NO_2\cdot HCl$	68.35	68.06	7.25	7.33
21	But.-CH_3OH	$C_{17}H_{19}NO_3\cdot HCl$	63.45	63.44	6.26	6.26
					(4.35)	(4.13)
22	EtOH	$C_{22}H_{21}NO_2$	79.73	79.66	6.39	6.51
	But.-CH_3OH	$C_{22}H_{21}NO_2\cdot HCl$	71.82	71.56	6.03	6.37
23	EtOH	$C_{19}H_{23}NO_3$	72.82	72.56	7.40	7.40
	But.-CH_3OH	$C_{19}H_{23}NO_3\cdot HCl$	65.23	65.40	6.92	6.93
		COMPOUNDS LISTED IN TABLE II				
1	*i*-Oct.-EtOH	$C_{17}H_{21}NO_3$	71.05	70.70	7.37	7.50
	But.-CH_3OH	$C_{17}H_{21}NO_3\cdot HCl$	63.05	63.35	6.91	6.95
			(4.33)	(4.25)		
2	70% EtOH	$C_{19}H_{25}NO_2$	76.22	76.21	8.42	8.58
	But.-CH_3OH	$C_{19}H_{25}NO_2\cdot HCl$	67.94	67.79	7.80	7.85
3	Isoöctane	$C_{19}H_{25}NO_2$	76.22	76.09	8.42	8.80
	Hexon.-CH_3OH	$C_{19}H_{25}NO_2\cdot HCl$	67.94	67.68	7.80	7.70
4	Acet.-EtOH	$C_{21}H_{21}NO_2$	78.96	78.70	6.63	6.71
5	EtOH	$C_{22}H_{23}NO_2$	79.24	79.36	6.95	7.16
	But.-CH_3OH	$C_{22}H_{23}NO_2\cdot HCl$	71.44	71.33	6.54	6.65
6	But.-CH_3OH	$C_{19}H_{25}NO_3\cdot HCl$	64.85	64.76	7.45	7.41
7	50% EtOH	$C_{18}H_{23}NO_4$	68.12	67.99	7.30	7.36
	EtOH	$C_{18}H_{23}NO_4\cdot HCl$	61.10	60.97	6.84	6.75
8	EtOH	$C_{20}H_{27}NO_3$	72.95	72.67	8.26	8.10
	Acetone	$C_{20}H_{27}NO_3\cdot HCl$	65.65	65.72	7.71	7.84
9	Acet.-EtOH	$C_{18}H_{24}N_2O_2$	(9.33)	(9.59)		
	But.-CH_3OH	$C_{18}H_{24}N_2O_2\cdot 2HCl$	57.90	57.93	7.02	7.24
10	Isoöctane	$C_{18}H_{19}NO_6$	62.60	62.60	5.55	5.89
	But.-CH_3OH	$C_{18}H_{19}NO_6\cdot HCl$	56.62	56.88	5.28	5.56
11	But.-CH_3OH	$C_{20}H_{23}NO_5\cdot HCl$	(3.56)	(3.47)		
12	EtOH-H_2O	$C_{22}H_{23}NO$	83.24	83.06	7.30	7.29
	But.-CH_3OH	$C_{22}H_{23}NO\cdot HCl$	74.66	74.37	6.84	6.65

[a] Number refers to compounds listed in Tables I and II. [b] Solvent abbreviations are: EtOH = 95% ethanol; But. = butanone; *i*-oct. = isoöctane. (2,2,3-trimethylpentane); Hexon. = methyl isobutyl ketone; Acet. = acetone. [c] Also crystallized from ethanol alone.

(54%); recrystallized from ethanol, m.p. 166.5–167.5° (it gave the correct analysis).

The yield in the corresponding reaction with X and phosphorus oxychloride in benzene (refluxing for 2 hours) was 80%.

The *dihydrochloride* was obtained from a benzene solution of the base by the action of ethereal hydrogen chloride; recrystallized from butanone-methanol mixture, m.p. 234–235°.

Anal. Calc'd for $C_{24}H_{26}N_2O\cdot HCl$: C, 66.80; H, 6.54. Found: C, 66.52; H, 6.42.

λ_{max} 254 mμ, $\epsilon \times 10^{-3}$, 30.80.

1-Phenyl-2,2-bis-(p-dimethylaminophenyl)ethanol (XXVIII) was made from the corresponding ketone XXVII in 64% yield by the above reduction method 2a; recrystallized from acetone, m.p. 183–184°.

Anal. Calc'd for $C_{24}H_{28}N_2O$: C, 79.86; H, 7.83, N, 7.73. Found: C, 79.68; H, 7.83; N, 7.86.

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA[a]

	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{min}, mμ	$\epsilon \times 10^{-3}$
	COMPOUNDS USED IN THE SYNTHESES (see list below[b])			
A	274	20.05	239	5.24
B	232;280;312	21.51; 8.87; 9.07	255;300	3.00; 8.15
C	232;277;313	18.70; 7.14; 8.70	251;291	2.64; 5.14
D	277	18.22	241	5.26
E	222;246;310	20.68;14.70; 2.28	239;303	13.84; 2.17
F	277	17.02	237	1.87
G	232;241;272	18.70;16.40; 5.88	238;270	16.23; 5.82
H	273;345	2.70;28.08	268;278	2.55; 2.47
	COMPOUNDS FROM TABLE I			
7. HCl	221;275	26.65;18.85	244	8.21
10. HCl	233;283;316	20.90; 9.46; 9.81	255;302	3.70; 8.49
11. HCl	233;283;317	20.42; 9.20; 9.63	255;302	2.93; 8.19
13.	274;345	3.54;27.70	268;279	3.45; 3.00
14.	344	27.62	269	8.55
15. HCl	230;248[d,e]	17.32;15.96	242	14.84
16. HCl	221;248	17.42;15.90	239	14.60
17.	223;248[d]	23.40;31.82	227	22.25
19.	248;280;283	15.94;19.45;19.30	234;259	12.65;12.75
19. HCl	248;284	16.05;19.40	234;259	12.62;12.80
20. HCl	221;289	13.64;17.69	244	1.65
21. HCl	220;286	18.56;17.32	243	3.76
22.	280	16.80	242	2.84
23. HCl	273;279	3.40; 3.68	246	0.72
	COMPOUNDS FROM TABLE II			
1. HCl	222;274;308	16.82; 3.81; 1.79	247;290	2.51;1.51
4.	288;249;276; 284	16.82, 15.59; 3.46; 3.44	240;272 278	14.62;3.36 3.41
7.	228;274;302	24.55; 5.42; 1.95	248;292	2.93; 1.78
7. HCl	228;274;302	23.80; 5.78; 2.21	250;290	3.54; 2.08

[a] Absorption spectra were determined by means of a Beckman DU quartz spectrophotometer, using 0.00005 *molal* absolute ethanol solutions. [b] The compounds used in syntheses of amino ketones are as follows and were essentially by the procedures for which references are given; they had the reported melting points: (A) $CH_3OC_6H_4COCH_2C_6H_4OCH_3$-*p*.[15,46] (B) $CH_2O_2C_6H_4COCHOHC_6H_4O_2CH_2$.[c,20] (C) $CH_2O_2C_6H_3COCHOHC_6H_5$.[47] (D) $C_6H_5CHOHCOC_6H_4OCH_3$-*p*.[45] (E) $C_6H_5COCHOHC_6H_4OCH_3$-*p*.[13] (F) $C_6H_5CH_2COC_6H_4OCH_3$-*p*.[15,16,45] (G) $C_6H_5COCH_2C_6H_4OCH_3$-*p*.[15,16,45] (H) $(CH_3)_2NC_6H_4COCH_2C_6H_5$-*p*.[43] [c] The O_2CH_2 group is the *3,4*-methylenedioxy. [d] Weak anisole absorption is doubtless obscured by the tailing off of the main benzoyl peak. [e] Slight shoulder at 280 mμ, ε 5,400. [p] The substitution is *para*.

threo-1,2-Diphenyl-2-ethanolaminoethanol (XXIXa) was obtained by condensation of 9.8 g. (0.05 mole) of *cis*-stilbene oxide and 4.6 g. (0.075 mole) of ethanolamine at 100° for 12 hours. Solution in ether, washing, drying, and evaporating gave 12.3 g. (96%); m.p. 119–120°; recrystallized from benzene, m.p. 120–121°.

Anal. Calc'd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.71; H, 7.22.

The *hydrochloride* was crystallized from butanone-methanol mixtures, m.p. 192–193°.

Anal. Calc'd for $C_{16}H_{19}NO_2$·HCl: C, 65.41; H, 6.86. Found: C, 65.49; H, 7.06.

threo-1,2-Diphenyl-2-ethylethanolaminoethanol (XXIXa) was prepared similarly (52%); crystallized from cyclohexanone, it had m.p. 101–102°.

Anal. Calc'd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.61; H, 8.42.

The *hydrochloride* was prepared from the pure base by the action of ethereal hydrogen chloride, m.p. 192–193°.

Anal. Calc'd for $C_{18}H_{23}NO_2$·HCl: N, 4.35; Found: N, 4.82.

Preparation of erythro-1,2-diphenyl-2-(N-benzyl)ethanolaminoethanol (XXIXb, R = $CH_2C_6H_5$)[48] was by the method described above; yield 54%, m.p. 132–133°.

2,3-Diphenylmorpholine (XXX, R = H). The red paste resulting from portionwise addition with stirring of 7.1 g of *erythro*-1,2-diphenylethanolaminoethanol (XXIXb) to 20 ml. of cold (0°) 70% sulfuric acid and heating at 100° for 3 hours, was poured into ice and neutralized with 25% sodium hydroxide. The product was isolated by extracting with ether, drying, and evaporating; 5.8 g. (54%), m.p. 70–72°; recrystallized from ethanol-water mixture and from low-boiling petroleum ether, m.p. 82–84°.

Anal. Calc'd for $C_{16}H_{17}NO$: C, 80.36; H, 7.16. Found: C, 80.29; H, 7.35.

The *hydrochloride* was precipitated from an ether solution of the pure base by ethereal hydrogen chloride and was recrystallized from butanone-methanol mixture, m.p. 271–273°.

Anal. Calc'd for $C_{16}H_{17}NO$·HCl: C, 69.68; H, 6.58. Found: C, 69.39; H, 6.51.

A sample prepared similarly by dehydration of the *threo* isomer (XXIXa) gave the same product XXX·HCl, (64%), identified by mixture m.p.

2,3-Diphenyl-4-ethylmorpholine (XXX, R = C_2H_5) was prepared both from XXIX(a) and (b) by the above procedure (yields as the hydrochlorides 69 and 61% respectively; identity shown by mixture m.p.). The base was recrystallized from ethereal-water mixture or from isoöctane, m.p. 71–72°.

Anal. Calc'd for $C_{18}H_{21}NO_2$: C, 80.86; H, 7.95. Found: C, 80.67; H, 7.78.

(45) Jenkins, *J. Am. Chem. Soc.*, **54**, 1155 (1932).

(46) Apitzsch, *Ber.*, **40**, 1803 (1907).

(47) Tiffeneau and Levy, *Bull. soc. chim. France*, [4], **49**, 725 (1931).

(48) Truett, Dissertation, University of Virginia, 1950.

Hydrochloride, crystallized from butanone-methanol mixture, m.p. 275–276°.

Anal. Calc'd for $C_{18}H_{21}NO_2$·HCl: C, 71.15; H, 7.30; Cl, 11.67. Found: C, 70.88; H, 7.41; Cl, 11.64.

Reduction of 2,3-diphenyl-5,6-dihydro-4-ethyl-1,4-oxazine (XXXI)[4] (9.3 g.) by 9.6 g. of sodium in 175 ml. of boiling isoamyl alcohol (2.5 hours), hydrolysis, and washing, and evaporation under reduced pressure, gave an oil which was taken up in ether and converted into the hydrochloride; 8 g. (75%), m.p. 185–205°. Upon recrystallization from butanone-methanol mixture it was identified by m.p. 275–276° and mixture m.p. as XXX (R = C_2H_5). The residue gave fractions of wide and varied m.p. ranges, and probably contained some of the stereoisomer.

2,3-Diphenyl-4-benzylmorpholine hydrochloride (XXX, R = $CH_2C_6H_5$) was made similarly in 65% yield by dehydration of the *erythro* dialcohol XXIXb (heating time 5 hours); crystallized from butanone-methanol mixture, m.p. 228–230°.

Anal. Calc'd for $C_{23}H_{23}NO_2$·HCl: C, 75.50; H, 6.61; N, 3.83. Found: C, 75.27; H, 6.60, N, 3.90.

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