the solutions were prepared. The results are tabulated in Table II and the complete curves shown in Fig. 1.

TABLE II

ABSORPTION SPECTRA OF THE 2-PHENYL-2-HYDROXYMORPHOLINES IN HEPTANE

Morpholines	Molar Concn. × 10^4	Maxima λ,Å.	Maxima ε × 10^{-1}	Minima λ,Å.	Minima ε × 10^{-1}
(I)	15.1	2350	0.63	2260	0.59
	0.60	2350	.66	2260	.55
(II)	2.67	2550	.51	2300	.49
(III)	2.47	2350	.92	2340	.91
	1.24	2350	.98	2340	.97
ω-Dibenzylamino-acetophenone	1.50	2390	12.96	2240	10.05

Using heptane as the solvent, the spectra of (I) and (III) were observed in more dilute solutions and compared with the previous results (see Table II and Fig. 2).

The spectra of the morpholine hydrochlorides (V), (VII), (VIII), and of ω-dibenzylaminoacetophenone hydrochloride,[11] and ω-morpholinoacetophenone hydrochloride[12] were examined in absolute ethanol solution (see Table III and Fig. 3).

TABLE III

ABSORPTION SPECTRA OF 2-HYDROXY AND 2-ETHOXY-2-PHENYLMORPHOLINE HYDROCHLORIDES IN ABSOLUTE ETHANOL

Morpholines	Molar concn. × 10^4	Maxima λ,Å.	Maxima ε × 10^{-3}	Minima λ,Å.	Minima ε × 10^{-3}
V	3.67	2500	1.05	2300	0.44
VII	3.37	2570	0.31	2300	0.13
VIII	1.45	2550	0.52	2340	0.25
Acetophenones					
ω-Dibenzylamino-hydrochloride	1.54	2480	11.89	2260	5.86
ω-Morpholinohydrochloride	1.00	2480	13.70	..	..

Using absolute methanol as a solvent, the spectra of the morpholine hydrochlorides (IV) and (VI) and the dimethoxy compound (IX) were examined. A summary of the results is given in Table IV and the complete curves are shown in Fig. 4.

TABLE IV

ABSORPTION SPECTRA OF 2-HYDROXY AND 2-METHOXYMORPHOLINE HYDROCHLORIDES IN ABSOLUTE METHANOL

Morpholine	Molar concn. × 10^4	Maxima λ,Å.	Maxima ε × 10^{-3}	Minima λ,Å.	Minima ε × 10^{-3}
IV	5.32	2500	0.93	2260	0.11
VI	3.53	2605	. 26	2280	.04
IX	4.16	2500	.49	2240	.02

Summary

1. The reactions of phenacyl bromide with N-substituted ethanolamines have been studied and the desired N-phenacyl-N-substituted ethanolamines have been found to have tautomerized to their respective hemiacetal forms, the 2-phenyl-2-hydroxymorpholines.

2. Some acetal derivatives, or 2-phenyl-2-alkoxymorpholines, have been obtained from these hemiacetals.

3. Absorption spectra studies have aided in the elucidation of these structures.

4. These results confirm for the N-phenacyl-N-substituted ethanolamines the conclusions reached by Lutz, *et al.*, with the related α-(N-substituted-N-ethanolamino)-desoxybenzoins.[4]

(12) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).

LINCOLN, NEBRASKA RECEIVED JULY 17, 1948

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

Ring-Chain Tautomerism of α-(Ethylethanolamino)-acetophenone[1]

BY ROBERT E. LUTZ AND ROBERT H. JORDAN[2]

Because of the ring-chain tautomerism involved in the α-(ethylethanolamino)-desoxybenzoins,[3] and because of the interest in these compounds as possible tumor-necrotizing agents,[3,4] it seemed important to explore other series, especially simpler ones such as that based on acetophenone.[5] The present paper deals with preliminary work in this field.

α-(Ethylethanolamino)-acetophenone (I) (m. p. 52–53°) was made by condensing ethylethanolamine with phenacyl bromide.[6] It was readily con-

(1) This is the second paper dealing with ring-chain tautomerism of hydroxyalkylamino ketones. This work, except for the ultraviolet absorptions, was included in a doctorate dissertation by R. H. Jordan, University of Virginia, May, 1948. Some financial support for measurements and analyses, from a grant-in-aid by the National Cancer Institute, is acknowledged.

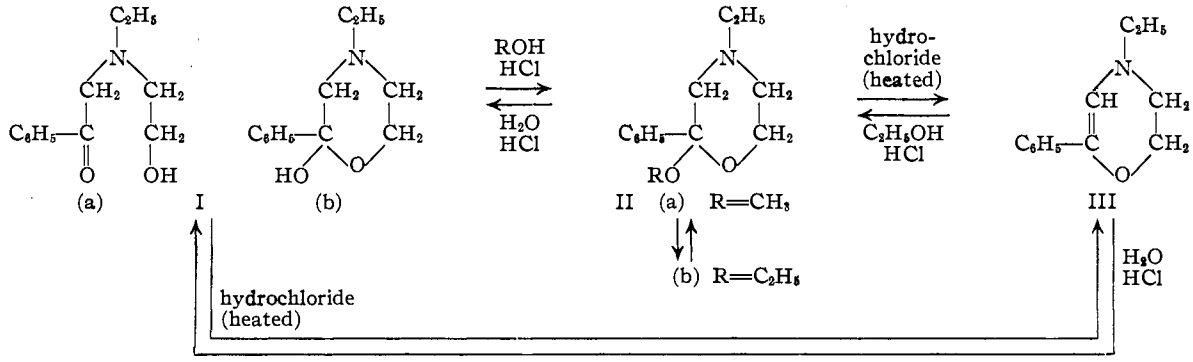
(2) Holder of Tennessee Eastman Company Fellowship, 1947-1948.

(3) (a) Lutz, Freek and Murphey, THIS JOURNAL, **70**, 2015 (1948) [an error appears in Table I, page 2016, where NR_2 for compound 612 should read $NHC_6H_4N(C_2H_5)_2$-*p*. Another typographical error appears in the last sentence of the first column of page 2020, where "δ-hydroxyl" should read α-hydroxyl]. (b) Lutz and Murphey, *ibid.*, **71**, 478 (1949); (c) Lutz, Freek and Murphey, a paper presented at the Chicago meeting of the American Chemical Society, April 20, 1948.

(4) Unpublished work of Shear, Downing, MacCardle, Hartwell, *et al.*, at the National Cancer Institute.

(5) Prior work had already been under way on the 2,4-dichloro, 3,4,5- and 2,3,5-trichloro analogs (Lutz, Jordan and Ford; results to be published shortly; *cf.* also ref. 3c).

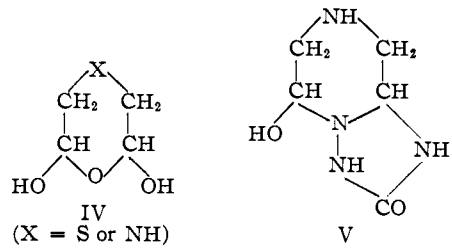
(6) (a) The hydrochloride of this compound (I) has recently been prepared by this method and converted into the *p*-ethoxybenzoyl derivative [Christiansen and Harris, U. S. Patent, 2,404,691 (July 1946); *C. A.*, **41**, 157*f* (1947)]; (b) *cf.* Brighton and Reid, THIS JOURNAL, **65**, 479 (1943).



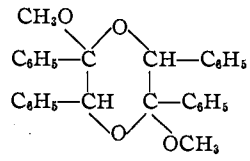
verted into the methyl and ethyl derivatives (IIa and b) by acid catalyzed alcoholysis. The conversion of the methoxy compound (IIa) into the ethoxy (IIb) was accomplished by means of ethanolic hydrogen chloride; and hydrolysis of both alkoxy compounds with dilute aqueous hydrochloric acid regenerated the original compound (I). Isopropyl alcohol did not react under these conditions.

It is noteworthy that the methoxy compound (IIa), which has not been obtained in crystalline form, was distillable under reduced pressure without loss of methanol. However, heating of either the methoxy or ethoxy compounds (II) or the parent compound itself (I), in the form of the hydrochloride or with a small amount of added hydrochloric acid, brought about elimination of the alcohol or water and gave the dehydromorpholine (the dihydro-1,4-oxazine, III). This compound was converted back into the original compound (I) by the action of hot dilute aqueous hydrochloric acid, and into the cyclic acetal (IIb) by ethanolic hydrogen chloride.[7] The reactivity of the dehydro compound in this series (III) is to be contrasted with the stability of the one obtained from α-(N-ethylethanolamino)-desoxybenzoin. The latter compound, with its stilbene double bond, seems to be stable under these conditions, is not readily hydrated to the cyclic hemiacetal nor does it react with alcohols to give the cyclic acetals.[7c]

The best known compounds showing this type of ring-chain tautomerism, of course, are the sugars and γ- and δ-hydroxyaldehydes and ketones; but special reference should be made to less well known analogs where the chain between the carbonyl group and the reacting hydroxyl is broken by an intervening hetero-element, nitrogen, oxygen or sulfur. The compounds of the type $R_2C(OH)CH_2–X–CH_2CHO$[8] and $HOCH_2CH_2–X–CH_2CHO$[9,8b] (where X = oxygen or sulfur), which doubtless involve ring-chain tautomerism, have not yet been studied adequately from this viewpoint. Related to these compounds is the dialdehydo thioethyl ether, $S(CH_2CHO)_2$, which apparently exists as the cyclic monohydrate, 2,6-dihydroxythioxane,[10] and forms the cyclic acetal, 2,6-diethoxythioxane (*cf.* IV).[11] The nitrogen analog, $NH(CH_2CHO)_2$, which appears to exist also as the cyclic monohydrate, 2,6-dihydroxymorpholine (IV),[12] is of particular interest because of the condensation with semicarbazide; the compound obtained, in view of its behavior,[13] is probably V, a possibility considered but not favored by the original authors.[12] The dimolecular product ob-



tained from benzoin by the action of methanolic hydrogen chloride also is of interest here because it seems to be the cyclic diacetal (VI),[14] formed presumably through a benzoin hemiacetal or benzoin-methyl acetal of benzoin, cyclization and completion of the methylation.



In order to decide whether the ethylethanolamino ketones are cyclic or open-chain in simple solution [apart, for example, from possible stabilization as a complex with aluminum isopropoxide],

(7) (a) *Cf.* Hill and Powell, THIS JOURNAL, **67**, 1462 (1945); (b) Paul, *Bull. soc. chim.*, [5] **1**, 971 (1934). (c) In this connection a correction must be made to ref. 3(a and c); the supposed hydration of 3,4-dihydro-1,2-diphenyl-4-ethyl-1,4-oxazine, reported in the earlier paper, appears to be an experimental error; numerous attempts since then to repeat this experiment under a variety of conditions have failed and will be described in a later paper (Lutz and Truett).

(8) (a) Parham, THIS JOURNAL, **69**, 2449 (1947); *cf.* also (b) Fuson and Parham, *J. Org. Chem.*, **11**, 482 (1946).

(9) Palomaa and Aalto, *Ber.*, **66**, 468 (1933).

(10) Coghill, THIS JOURNAL, **59**, 801 (1937).

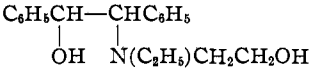
(11) Clark and Smiles, *Trans. Chem. Soc.*, **95**, 992 (1909).

(12) Wolff and Marburg, *Ann.*, **363**, 169 (1908).

(13) *Cf.* Dixon, *J. Chem. Soc.*, **61**, 509 (1892).

(14) Bergmann and Weil, *Ber.*, **68**, 1911 (1938); *cf.* also the work on dihydroxyacetone [Bertrand, *Compt. rend.*, **129**, 341 (1899); Herold, *Z. physik. Chem.*, **16**, 213 (1932)].

ultraviolet absorptions were carried out on the α-(ethylethanolamino) derivatives of acetophenone (I),[15a] desoxybenzoin[15b] and 5-chloro-2-methoxyacetophenone.[16] These compounds absorbed only very slightly in the region 240–250 mμ where ketones such as acetophenone,[17a] desoxybenzoin,[15,17b] and α-diethylaminodesoxybenzoin,[17c] show characteristic maxima. The ethyl derivative of I (the acetal IIb) and the amino-dialcohol corresponding to α-(ethylethanolamino)-desoxybenzoin (namely, VII),[15] neither of which possess a carbonyl group, show no significant absorption maxima in this range. From these facts it is to be concluded that the ethylethanolamino ketones under discussion are largely cyclic, and that the open-chain forms, if present in appreciable amounts in solution (in isoöctane), are there in concentrations probably below 3–5%.



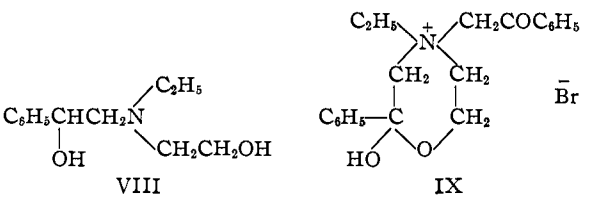
VII

It is of interest to contrast these results with those observed in the systems, —CHCH$_2$CH$_2$CH$_2$C—; the δ-hydroxyketone appears, on the basis of molar refraction, to be largely open-chain,[18a] and the δ-hydroxyaldehyde appears, on the basis of both molar refraction and ultraviolet absorption, to be largely cyclic.[7b,18b] As mentioned before[3a] the enhanced activity of the keto group in the present case (Ia) must be attributed to the heteroelement in the chain, amino nitrogen, which is at the same time alpha to the carbonyl group and comparable to the alpha hydroxyls in the ketone sugars.

That the ethylethanolamino ketones studied so far,[3] including I, exist largely in the cyclic hemiacetal forms, is indicated[3] also by the fact that they are not reduced readily by the carbonyl-specific reagent, aluminum isopropoxide, under the usually effective conditions. If the open-chain form were present in small amounts, as is perhaps indicated by the ultraviolet absorption experiments, it is possible that the cyclization is actually promoted to some extent by combination with the reagent, because of the greater acidity of the hemiacetal hydroxyl (*cf.* Ib) as compared with the alcoholic hydroxyl of the open-chain form (Ia).

It is pertinent to note in this connection that in a preliminary experiment catalytic reduction of α-(ethylethanolamino)-desoxybenzoin[19] proceeds with far greater difficulty than it does with α-(piperidyl)-desoxybenzoin[3] which is necessarily open-chain.

The amino-dialcohol (VIII) which was desired for tests and for comparison with the corresponding ketone (I), was subsequently made by standard procedure through condensation of styrene bromohydrin with ethylethanolamine. It was not obtained in a crystalline form and was characterized as the picrate.



VIII IX

As a minor by-product of the condensation of ethylethanolamine with phenacyl bromide, there was obtained the quaternary compound (IX), which is obtainable in good yield by the use of an excess of phenacyl bromide. It doubtless exists as the cyclic hemiacetal as formulated; it is easily converted by means of alcoholic hydrogen bromide into a monoethoxy derivative (the cyclic acetal). The compound (IX) is of interest in connection with the study of tumor-necrotizing agents in view of the known activity of certain phenacylpyridinium salts.[4]

The compounds I, IIb, III, VIII and IX, are being screened for pharmacological activity, and especially for tumor-necrotizing action.[4]

Further studies are in progress in the field of hydroxyalkylamino ketones and their reactions and derivatives, especially with respect to various aspects of the problem of ring-chain tautomerism. These include absorption spectral, reduction and polarographic studies.

Acknowledgment.—The ultraviolet absorption studies reported in this paper were carried out by Spencer M. King. Microanalyses were carried out by Mrs. Joyce Blume Caliga.

Experimental[20a,b]

α-(Ethylethanolamino)-acetophenone (I) [4-Ethyl-2-hydroxy-2-phenylmorpholine].[6]—A solution of 60 g. (0.3 mole) of phenacyl bromide in 200 ml. of commercial absolute ether was slowly added under stirring to 60 g. (0.82 mole) of ethylethanolamine in 100 ml. of ether. After standing for two hours, filtering, washing, drying over sodium sulfate and evaporating, the residual oil was dissolved in 80 ml. of isoöctane, filtered from a small amount of the quaternary compound (IX) (see below), and was induced to crystallize by cooling in an ice–salt-bath; 43 g. (64%); m. p. 50–51°; m. p. after recrystallization from isoöctane, 52–53°. The compound was very sensitive, especially in contact with metals; on standing overnight the melting point dropped to 48–51°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.43; H, 8.26. Found: C, 69.41; H, 8.19. Ultraviolet abs. max. in isoöctane: λ 238–242 mμ ($\epsilon \times 10^3 = 0.28$; $c = 0.001$)[14].

(15) These determinations of ultraviolet absorption were carried out in this Laboratory by Spencer M. King. (a) λ (in isoöctane) 238–242 mμ ($\epsilon \times 10^{-3} = 0.28$; $c = 10^{-3}$). (b) λ (in isoöctane) 250–258 mμ ($\epsilon \times 10^{-1} = 0.44$; $c = 10^{-3}$).

(16) The work on this series was done in this Laboratory by Gilbert Ashburn (to be published shortly).

(17) (a) λ 246–249 mμ [Scheibe, *Ber.*, **59**, 2621 (1926)]; (b) λ (in isoöctane) 239–241 mμ ($\epsilon \times 10^{-4} = 1.2$; $c = 10^{-4}$). (c) λ (in isoöctane) 241–243 mμ ($\epsilon \times 10^{-4} = 1.2$; $c = 10^{-3}$).

(18) (a) Bergmann and Miekeley, *Ber.*, **55**, 1394 (1922); (b) Schniepp and Geller, THIS JOURNAL, **68**, 1646 (1946).

(19) Lutz and Truett, reduction studies in progress.

(20 (a) Melting points are corrected. (b) The ultraviolet absorptions reported were taken with a Beckman DU quartz spectrophotometer. The solvent used was isoöctane (2,2,4-trimethylpentane) (Phillips Petroleum Co.).

The hydrochloride[6] was precipitated from ether; m. p. 125–125.5°.

Anal. Calcd. for $C_{12}H_{17}NO_2 \cdot HCl$: C, 59.12; H, 7.44. Found: C, 59.18; H, 7.42.

Recrystallization from ethanol caused partial conversion to the ethoxy compound (IIb) (demonstrated by pyrolysis of the product and identification of the ethanol generated, by micro-boiling point).

Isopropyl alcohol was found not to react with I under the various conditions which were effective with ethanol and methanol.

Treatment with aluminum isopropoxide under the usual conditions,[3a] using a large excess of reagent, in isopropyl alcohol refluxing for six hours, gave no test for evolved acetone; the recovery (crude, 80%) of pure material of melting point 51.5–52.5° was 40%.

2-Ethoxy-4-ethyl-2-phenylmorpholine (IIb).—Either of two procedures was effective. (A) A solution of I in 25:10 absolute ethanol–saturated ethereal hydrogen chloride was allowed to stand at room temperature for twelve days. The base was liberated and converted to the hydrochloride (yield 64%). (B) A solution of 24 g. of I-hydrochloride in 100 ml. of absolute ethanol with an added 5 ml. of saturated ethanolic hydrogen chloride, was refluxed for one and one-half hours. The volume was reduced to 50 ml. by distillation under reduced pressure and the hydrochloride was precipitated by ether; yield 22 g. (82.5%).

The base (liberated by alkali) crystallized on seeding. After recrystallization from petroleum ether it melted at 49–50°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.52; H, 9.00. Found: C, 71.25; H, 8.74.

The hydrochloride had to be handled under non-aqueous conditions to avoid the facile hydrolysis to I. It crystallized as rhombic plates from ethanol–ether mixtures; m. p. 144.5°.

Anal. Calcd. for $C_{14}H_{21}NO_2 \cdot HCl$: C, 61.86; H, 8.16. Found: C, 61.82; H, 8.01.

Hydrolysis to I was effected by 6 *N* hydrochloric acid (warmed, thirty min.); identified by mixture m. p.; yield 65%.

4-Ethyl-2-methoxy-2-phenylmorpholine (IIa) was prepared by (A) and (B) under IIb, using methanol. The hydrochloride was crystallized from isopropyl alcohol–ether mixture; it was hygroscopic; m. p. (dried *in vacuo*) 148–149°.

Anal. Calcd. for $C_{13}H_{19}NO_2 \cdot HCl$: N, 5.44. Found: N, 5.33.

The base did not crystallize, and was fractionated. The yield of the principal cuts was 42%; b. p. 112° (1.8 mm.); $n^{25}D$ 1.5151; d^{25}_4 1.051; $(R)D$ 62.91.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65. Found: C, 70.47; H, 8.61.

Hydrolysis (warm 6 *N* hydrochloric acid) gave I (yield 75%). **Ethanolysis** by method (B) under IIb, gave IIb (yield 64%).

4-Ethyl-2-phenyl-5,6-dihydro-1,4-paroxazin (III).—Micropyrolyses of less than 40-mg. samples of I and IIb hydrochlorides gave water and ethanol, respectively (identified by micro-boiling points[21]).

A mixture of 5 g. of I and 5 drops of concd. hydrochloric acid was heated at 175–180° until evolution of water ceased (*ca.* five minutes). The base could be distilled under reduced pressure, but a cloudy distillate was always obtained. There was evidence of change in the oil, even upon standing overnight. The hydrochloride was precipitated from an isoöctane solution of the base by ethereal hydrogen chloride; 3 g. (65%). After washing with a small quantity of acetone to remove some resinous material, it was recrystallized from acetone–ether mixture; m. p. 163.5–165.5° (dec.).

Anal. Calcd. for $C_{12}H_{15}NO \cdot HCl$; C, 63.85; H, 7.14. Found: C, 63.61; H, 7.24.

Pyrolysis of IIb under the above conditions gave III in similar yields.

Hydrolysis (hydration) by 6 *N* hydrochloric acid (warmed) gave I (60%). **Ethanolysis** (alcoholation) by (B) under IIb gave IIb (98%).

4-Ethyl-2-hydroxy-4-phenacyl-2-phenylmorpholinium Bromide (IX).—A mixture of 5 g. of I and 5 g. of phenacyl bromide was heated at 40–60° until the melt solidified (forty-five minutes); trituration and washing with ether gave 9.2 g. (94%); m. p. 183.5–184.5°. It crystallized from ethanol as short prisms; m. p. 189.5–190° (initial bath temperature 170°, heating rate 3° per minute).

Anal. Calcd. for $C_{20}H_{24}BrNO_3$: C, 59.11; N, 5.95. Found: C, 58.81; H, 5.84.

2-Ethoxy-4-ethyl-4-phenacyl-2-phenylmorpholinium Bromide was made from IX by the action of refluxing ethanolic hydrogen bromide (forty-five minutes) and precipitation by ether; yield 36% (on a 3-g. run). After recrystallization from absolute ethanol it melted at 181.5–182° (taken as above). A mixture melting point with IX showed a 5° depression below this point.

Anal. Calcd. for $C_{22}H_{28}BrNO_3$: C, 60.82; H, 6.49. Found: C, 61.05; H, 6.19.

2-Ethylethanolamino-1-phenylethanol (VII).—A solution of 24 g. (0.118 mole) of 2-bromo-1-phenylethanol (obtained in 65% yield by aluminum isopropoxide reduction of phenacyl bromide)[22] in 32 g. (0.35 mole) of ethylethanolamine, was heated at 100° for fifteen hours. The product was taken up in ether, washed, dried over sodium sulfate and obtained as an oil upon evaporation of the solvent.

The hydrochloride did not crystallize. The base was fractionated; the principal cuts of nearly constant refractive index totaled 15 g. (61%); b. p. 152–155° (1.8 mm.). Vacuum evaporation of the middle cut onto a cold-finger drip-condenser gave a pure fraction; $n^{25}D$ 1.5279.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15. Found: C, 68.69; H, 9.18.

The picrate, obtained from ethanol, was crystallized from ethanol–isoöctane mixture; m. p. 100.5–102°.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 49.31; H, 5.06; N, 12.77. Found: C, 48.96; H, 5.38; N, 12.60.

Summary

α-(Ethylethanolamino)-acetophenone shows typical ring-chain tautomerism. It is not reduced by aluminum isopropoxide. It is easily mono-alkylated under acid catalysis by methanol and ethanol but not by isopropyl alcohol. Pyrolysis of these compounds gives the dihydroparoxazine. The compounds are interconvertible.

The absence of significant ultraviolet absorption maxima in the region of 240–250° mμ shows this and other ethylethanolamino ketones to exist in the cyclic or hydroxymorpholine forms.

The corresponding amino-dialcohol, 2-ethylethanolamino-1-phenylethanol, was made through styrene bromohydrin.

The quaternary phenacyl derivative of α-(ethylethanolamino)-acetophenone was obtained; it gave a mono-ethyl derivative upon treatment with ethanol–hydrobromic acid.

CHARLOTTESVILLE, VA. RECEIVED AUGUST 10, 1948

(21) Morton, "Laboratory Technique in Organic Chemistry," Int. Chem. Series, 1938, p. 50.

(22) Lund, *Ber.*, **70**, 1520 (1937).