[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Keto-Hemiacetal Tautomerism of Some N-Phenacyl-N-substituted Ethanolamines

BY NORMAN H. CROMWELL AND KWAN-CHUNG TSOU

In a previous communication[1] the syntheses of some N-benzohydryl-N-substituted ethanolamines and derivatives were reported. The present investigation was begun with the idea of extending the preparation of such compounds to the phenacyl series. The presence of the keto group in the latter series was expected to provide for further wide variation in the structures of the various derivative types.

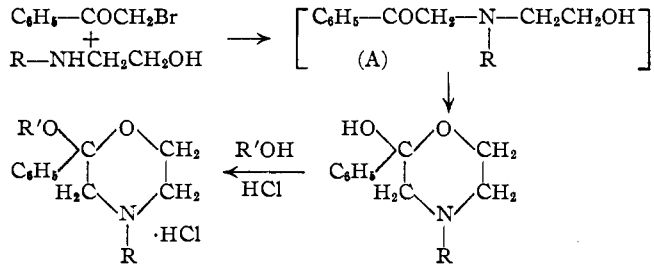
The reactions of the N-methyl, N-ethyl and N-benzyl ethanolamines with phenacyl bromide were investigated and the solid free bases, (I), (II) and (III) were isolated in fair yields. The behavior of the hydrochlorides of these bases upon attempted recrystallization from ethanol or methanol showed reaction with these solvents in such a manner as to indicate acetal formation. An inspection of the structure of an N-phenacyl-N-substituted ethanolamine (A) suggests the possibility of the formation of a six-membered ring, hemiacetal, which would, of course, be expected to form an acetal with reactive alcohols in the presence of hydrogen chloride. This phenomenon was not found for the previously investigated N-benzohydryl-N-substituted ethanolamine hydrochlorides.[1]

This problem then resolved itself into a study of the structures of the free bases (I), (II) and (III), their hydrochlorides, and their reaction products with ethanol and methanol. Helferich has made an extensive study of the analogous γ-hydroxy- and δ-hydroxy aldehydes and ketones and has reported that they undergo such cyclization to give hemiacetals which react with methyl alcohol to form acetals.[2]

Recently, Hill and Powell[3] have reported a cyclization and dehydration of N-(3,4-dihydroxyphenacyl)-N-benzoylethanolamine hydrochloride to 2-(3′,4′-dihydroxyphenyl)-4-benzoyl-5,6-dihydro-1,4-oxazine. The former compound may actually exist in the hemiacetal form.[4]

The free bases (I), (II) and (III) did not readily form either phenylhydrazones or oximes. This was the first indication that they might not contain a keto group. All three of them gave an immediate Tollens test, which is not observed with either ω-morpholinoacetophenone nor N-benzohydryl-N-benzylethanolamine.[1]

The hydrochlorides (IV) and (V) of (II) and (III), respectively, were obtained only when recrystallizations of the products were carried out very rapidly from cold methyl alcohol and dry ether, or from *t*-butyl alcohol and ether. When



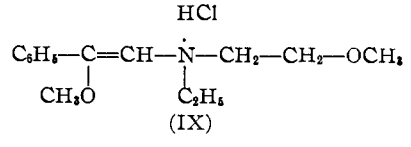
VI, R = C_2H_5, R′ = CH_3
VII, R = C_2H_5, R′ = C_2H_5
VIII, R = $C_6H_5CH_2$, R′ = C_2H_5

I, R = CH_3
II, R = C_2H_5
III, R = $C_6H_5CH_2$

these hydrochlorides were dissolved in the hot alcohols the alkoxy derivatives, such as (VI), (VII) and (VIII) resulted. These latter compounds reduced Tollens solution only after warming.

Considerable difficulty was often experienced in repeating the preparation of (VI), (VII) and (VIII), in our numerous runs of these reactions. Further reaction with the alcohol often occurred, and compounds which analysis indicated might be of the nature of (IX), discussed below, resulted. Analyses of (VI), (VII) and (VIII), as well as for (IV) and (V) were difficult to obtain because the compounds often decomposed if the usual drying techniques were used. Such difficulties prevented us from obtaining analytically pure samples of the 2-phenyl-2-alkoxy-4-methylmorpholine hydrochlorides. Although acceptable chlorine and nitrogen analysis were not difficult to obtain in these various series, it was obvious that carbon and hydrogen analyses would be required here to establish definitely the identity of these compounds.

When a sample of the alkoxy compound (VI) was allowed to stand for some time in methanol before recovering a product, a further change took place to give a dialkoxy compound which possibly is α-methoxy-β-(N-ethyl-N-(β′-methoxyethyl)-amino)-styrene (IX). Such a compound could form by a ring cleavage of (VI) by a second



(IX)

(1) Cromwell and Fitzgibbon, THIS JOURNAL, **70**, 387 (1948).

(2) Helferich, *et al.*, *Ber.*, **52**, 1123 (1919); **55**, 702 (1922); **56**, 759, 2088 (1923); **57**, 1911 (1924); **58**, 1246 (1925).

(3) Hill and Powell, THIS JOURNAL, **67**, 1462 (1945).

(4) An interesting paper by Lutz, Freek and Murphey, *ibid.*, **70**, 2015 (1948), has recently appeared which reports that ring-chain tautomerism does result with various α-(N-substituted-N-ethanolamino)-desoxybenzoins. The evidence cited was the non-reducibility of the carbonyl group in such compounds. These authors further indicated that they were studying such tautomerism in the related acetophenone series.

molecule of methanol, followed by the loss of water. This product (IX) did not react with Tollens solution until the reaction mixture was heated to boiling. After standing for several weeks (IX) underwent decomposition.

The absorption spectra studies (Table II and Fig. 1) of the free bases (I), (II) and (III), when compared with that of ω-dibenzylaminoacetophenone, offer convincing evidence that they exist almost wholly in the cyclic hemiacetal forms, as given by the 2-hydroxymorpholine structures. Acetophenone itself shows an absorption maximum of 2415–2430 Å. with a molar extinction coefficient of 12,600–16,200.[5] Thus it seems certain that if these compounds actually contained a benzoyl group (C_6H_5–CO–) they would show a strong absorption band near 2400 Å. with a molar extinction coefficient of at least 12,000.

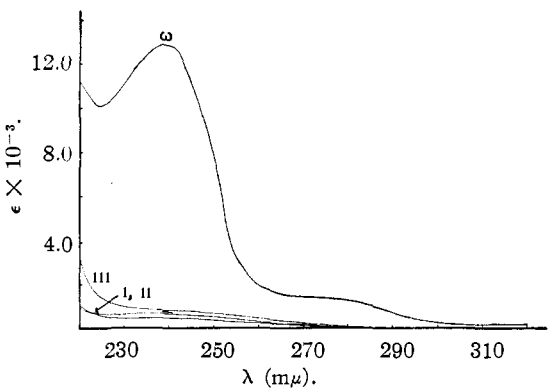


Fig. 1.—Absorption spectra of ω-dibenzyl-aminoacetophenone; of (I); of (II); and of (III) in heptane solution.

The fact that dilution had little effect on the absorption spectra (Table II, Fig. 2), indicated little tendency for (I) or (III) to exist in equilibrium with the open chain keto compounds (A) in heptane solution.

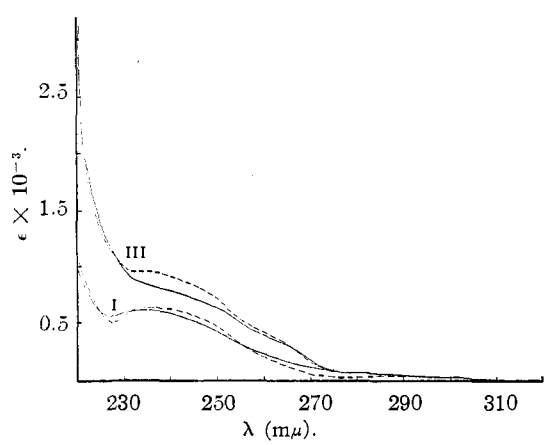


Fig. 2.—Absorption spectra dilution studies of (I) and (III): .... more dilute; — more concentrated; in heptane solution.

(5) Bielecki and Henri, *Ber.*, **47**, 1709 (1914); Morton and Sawires, *J. Chem. Soc.*, 1054 (1940).

The comparisons of the spectra of ω-morpholino- and ω-dibenzylaminoacetophenone hydrochlorides with those of the 2-hydroxymorpholine hydrochloride (V) and the 2-alkoxymorpholine hydrochlorides (VII) and (VIII), are equally convincing that these latter compounds do not contain a keto group (see Table III and Fig. 3).

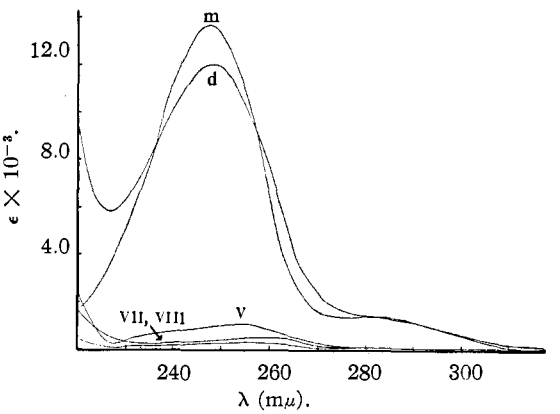


Fig. 3.—Absorption spectra in abs. ethanol: (m), ω-morpholinoacetophenone hydrochloride; (d), ω-dibenzylaminoacetophenone hydrochloride; (V); (VII); and (VIII).

The curves in Fig. 4 for the morpholine hydrochlorides (IV) and (VI) have been plotted on such a scale as to show more clearly the actual presence of weak bands for these compounds in the area expected for the keto structures. The magnitude of the molar extinction coefficients for these maxima are so low, however, that if the keto form actually exists in such solutions, it is present in very low concentrations (less than 10%). The absorption curve for the dialkoxy compound (IX) is given here, without comment, since no strictly analogous compounds were available for comparison. Styrene is known to have a maximum absorption band at 2450 A. with a molar extinction coefficient of 10,720.[6]

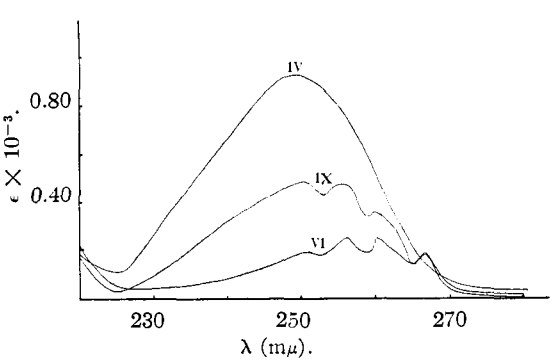


Fig. 4.—Absorption spectra in absolute methanol of (IV); (VI); and (IX).

(6) Ley and Dirking, *Ber.*, **67**, 1334 (1934).

TABLE I

PHYSICAL AND ANALYTICAL PROPERTIES

2-Phenyl-morpholines	No.	Yield, %	M. p., °C.	Formula	Percentage composition[a] Calcd. C	H	N	Cl	Found C	H	N	Cl
2-Hydroxy-4-methyl	(I)	48	53	$C_{11}H_{15}NO_2$	68.36	7.85	7.25	...	68.20	8.00	7.30	...
2-Hydroxy-4-ethyl	(II)	70	54	$C_{12}H_{17}NO_2$	...	..	6.75	...	...	..	6.57	...
Hydrochloride	(IV)	90	127	$C_{12}H_{18}NO_2Cl$	59.13	7.45	5.74	14.55	59.35	7.59	5.54	14.59
2-Hydroxy-4-benzyl	(III)	70	62	$C_{17}H_{19}NO_2$	75.80	7.11	5.20	...	75.88	7.05	5.08	...
Hydrochloride	(V)	85	144	$C_{17}H_{20}NO_2Cl$	66.77	6.59	4.58	11.60	66.33	6.79	4.54	11.67
2-Methoxy-4-ethyl Hydrochloride	(VI)	50	148	$C_{13}H_{20}NO_2Cl$	60.57	7.81	5.44	13.76	60.39	7.98	5.29	13.74
2-Ethoxy-4-ethyl Hydrochloride	(VII)	50	143	$C_{14}H_{22}NO_2Cl$	61.88	8.16	5.15	13.05	61.34	8.16	5.26	12.86
2-Ethoxy-4-benzyl Hydrochloride	(VIII)	85	151	$C_{19}H_{24}NO_2Cl$	68.35	7.24	4.19	10.62	68.70	7.40	4.15	10.58

[a] Micro analyses for carbon, hydrogen and nitrogen were carried out by the Clark Microanalytical Laboratory, Urbana, Illinois.

Herold has studied the ultraviolet absorption spectra of γ-hydroxybutyraldehyde in various solvents and has concluded that only about 10% of the free aldehyde is present.[7]

It seems evident that all of these compounds, (I) through (VIII), are essentially substituted morpholines.

Experimental

2-Hydroxy-2-phenyl-4-substituted Morpholines.—Pure phenacyl bromide (0.20 mole) was dissolved in 400 ml. of dry ether and added dropwise with stirring to 0.40 mole of the corresponding N-substituted ethanolamine dissolved in 300 ml. of dry ether. The mixture was kept at near room temperature during the addition and then allowed to stand at this temperature for twenty-four hours. The supernatant liquid was decanted or filtered from the precipitated N-substituted ethanolamine hydrobromide and washed several times with saturated salt water, dried over anhydrous calcium sulfate and evaporated. The crude solid products were recrystallized from ether–petroleum ether mixtures to give almost colorless crystalline products.

In this way (I), (II) and (III) were obtained using, respectively, N-methylethanolamine,[8] N-ethylethanolamine,[9] and N-benzylethanolamine.[1]

These morpholines (I), (II) and (III) gave only slight tests with phenylhydrazine and no solid derivatives could be isolated. All three gave an immediate silver mirror formation with Tollens solution at room temperature. They did not give isolable products from reaction mixtures of hydroxylamine. An attempted hydrogenation of (III) in absolute alcohol at room temperature using platinum oxide catalyst and 50 lb. per square inch used up no hydrogen in three hours.[4] It was not possible to obtain a benzoate of (II) employing the usual methods with benzoyl chloride.

The compounds (I), (II) and (III) were each dissolved in dry ether and treated with one equivalent of dry hydrogen chloride gas in dry ether to give almost quantitative yields of the very hygroscopic hydrochlorides.

The hydrochloride of (I) could not be handled. The crude hydrochloride of (II) melted at 112–115° but rapid recrystallization, by dissolving in cold methyl alcohol followed by the immediate addition of dry ether, or solution in warm 85% *t*-butyl alcohol, followed by the addition of ether, gave the higher melting, pure hydrochloride (IV). The crude hydrochloride of (III) melted at 131–134° but recrystallization from 90% *t*-butyl alcohol and ether gave a higher-melting, pure product (V). These hydrochlorides, like the pure bases, gave an immediate, positive Tollens test at room temperature.

2-Alkoxy-2-phenyl-4-substituted Morpholine Hydrochlorides.—Dry ether solutions of the morpholines (II) and (III) were treated with dry hydrogen chloride by cooling the solutions in an ice-bath and bubbling in the dry gas. The flocculent precipitates were filtered off, washed with dry ether and dissolved in the corresponding hot absolute alcohols, methyl and ethyl. Dry ether was added and the solutions cooled to precipitate the alkoxy compounds which were again recrystallized from the corresponding alcohols and ether mixtures to give the pure alkoxy compounds (VI), (VII) and (VIII); see Table I. Samples of these compounds for analyses were dried under vacuum at room temperature for eight hours. An excess of ether was avoided in precipitating these products since it often carried down the dialkoxy compounds of type (IX) discussed below.

These compounds gave a positive test with Tollens reagent only after the solution was warmed.

Reaction of (VI) with Methyl Alcohol.—A 10-g. sample of (VI) was dissolved in 60 ml. of dry methyl alcohol at 50° and the solution allowed to stand at room temperature for twelve hours and in the ice-chest for three days. Dry ether was added to precipitate the product which was recrystallized again from methyl alcohol and dry ether; m.p. 142°, wt., 5.4 g. A fresh sample of (IX) did not react with warm Tollens solution, but upon boiling the mixture, reaction took place.

Anal. Calcd. for $C_{14}H_{22}NO_2Cl$: C, 61.88; H, 8.16; N, 5.15; Cl, 13.05. Found: C, 61.27; H, 7.86; N, 5.07; Cl, 13.07.

Absorption Spectra Studies.—These measurements were made with a Beckman Model DU Photoelectric Quartz Spectrophotometer. At the sensitivity used, the maximum band width was one millimicron with an accuracy of 0.1% for the density measurements. The solvents used were laboratory grade absolute ethanol, methanol, and heptane-from-petroleum, purified by the procedure recommended by Weissberger.[10]

The ultraviolet absorption spectra of (I), (II), (III) and ω-dibenzylaminoacetophenone[11] were observed using heptane as the solvent. These studies were made within two hours of the time

(7) Herold, *Z. physik. Chem.*, **16B**, 213 (1932).

(8) Generously supplied by the Carbide and Carbon Chemical Corp., New York.

(9) Kindly furnished by the Smith, Kline and French Laboratories, Philadelphia, Pa.

(10) Weissberger, "Physical Methods of Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1946, p. 766.

(11) Busch and Hefele, *J. prakt. Chem.*, [2] **83**, 449 (1911).

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^{-3}	Minima λ,Å.	Minima ε × 10^{-3}
(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).