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

Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino)desoxybenzoins. Steric and Electronic Effects[1]

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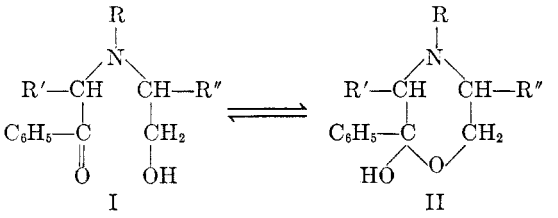
A new series of substituted α-(β-hydroxyethylamino)desoxybenzoins, involving secondary amino nitrogen, have been synthesized for the purpose of studying steric effects on the ring-chain tautomerism of ethanolamino ketones. Substitution of an *alpha* hydrogen of the β-hydroxyethyl group by a methyl, ethyl, phenyl, or benzyl, produced progressive changes from dominance of the chain form in the equilibrium to dominance of the cyclic form. In the α-methyl compounds where the equilibrium was evenly balanced substitution of *para*-chlorine and *para*-methoxyl in the benzoyl group produced marked shifts of the equilibrium toward and from the cyclic forms respectively. Similar *para*-substitutions in the adjacent α-phenyl group were found to be inconsequential and showed that the equilibrium shifts had been caused primarily by electronic effects upon the carbonyl group activity. The above results have demonstrated the major importance of steric effects in determining whether or not cyclization occurs and the real but relatively secondary importance of electronic effects on the activity of the benzoyl group. Chemical studies of the cyclic compounds include dehydration to dehydromorpholines and subsequent oxidation to peroxides.

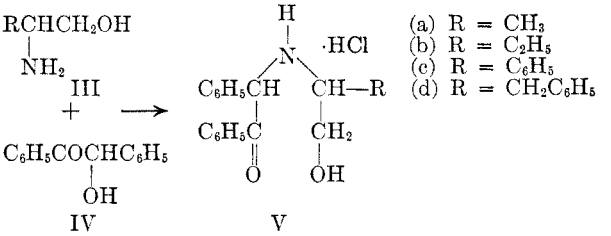
This investigation was undertaken to determine the effects of sterically active substituents and electronic activation and deactivation of the carbonyl group, on the ring-chain tautomerism of the α-(β-hydroxyethylamino)desoxybenzoins (*cf.* I–II). It is part of a broad study of chemical and pharmacological properties of this class of compound.[3,4,5]



I II

The hydroxyethylamino ketones in which the nitrogen is tertiary (I; R = alkyl, R′ = H or phenyl, R″ = H) have been shown to exist predominately in the cyclic form (II) and to give cyclic derivatives. However, when the nitrogen is secondary (R = H) the compounds generally exist in the chain form (I) and fail to give cyclic derivatives.[6] The introduction of electron-attracting or -releasing groups in the phenyl of the benzoyl group has caused no noticeable alteration of the ring-chain relationships in the cases so far studied. Compounds of the type (I-II) where nitrogen is secondary (R = H), containing bulky substituents (R″ = alkyl or phenyl), now have been prepared under the expectation that these types might involve ring-chain relationships intermediate between the extremes of the open-chain compounds (III, R = H, R′ = H or phenyl, R″ = H) and the cyclic types (II, R = alkyl) where nitrogen is tertiary. This expectation proved to be warranted.

Preparations of the hydroxyethylamino desoxybenzoins of the type V were accomplished through the Voigt condensation between benzoin and the appropriate amino alcohol (III) using phosphorus pentoxide as catalyst. The bases were not obtained in crystalline form and the compounds were isolated and handled as the hydrochlorides.



IV V

(a) R = CH_3
(b) R = C_2H_5
(c) R = C_6H_5
(d) R = $CH_2C_6H_5$

The preparation of the various intermediate amino alcohols (III) was achieved through lithium aluminum hydride reduction of the corresponding amino acids or amino acid ester hydrochlorides by modification of an earlier procedure.[7]

Steric effects. The first compound of the new series to be studied was α-(1-ethyl-2-hydroxyethylamino)desoxybenzoin (Vb) which was isolated and handled as the hydrochloride. The ultraviolet absorption spectrum of this compound showed a maximum at 246 mμ, ε 3,980. If it existed in solution as the chain tautomer (*cf.* I) there would be expected a characteristic benzoyl type absorptivity of *ca.* ε 9,000 at 245–250 mμ such as is exhibited by reference compounds of the type α-(2-hydroxyethylamino)desoxybenzoin hydrochloride (I; R = R″ = H, R′ = phenyl).[5] On the other hand if it

(1) This work was initiated under and received part of its support from a research grant from the Eli Lilly Company.

(2) Holder of the E. I. du Pont de Nemours Company Postgraduate Fellowship, 1954–1955.

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

(4) Lutz and Jordan, *J. Am. Chem. Soc.*, **71**, 996 (1949).

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

(6a) One exception to this generalization is the amino ketone, 2-(ethanolamino)-1,3-diphenylpropanone (I, R,R′′= H, R′ = benzyl) which apparently exists largely in the cyclic form (II) [(b) McConnell, *Thesis and Dissertation*, University of Virginia (1950)].

(7) Vogl and Pohm, *Monatsh.*, **83**, 541 (1952).

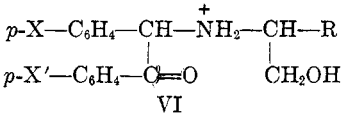
existed in solution chiefly as the cyclic tautomer (*cf.* II), the absorptivity at 245–250 mμ would be much lower and comparable to that of reference compounds such as α-[N-ethyl-N-(β-hydroxyethyl)-amino]desoxybenzoin hydrochloride (ε 700–1300 at 240–250 mμ).[5] The observed absorptivity was intermediate between these extremes and indicated that at high dilution in ethanol the compound, both in the form of the hydrochloride and as the free base, exists as a well balanced ring-chain equilibrium mixture.

From calculations based on the assumption that the molar absorptivities of the ring and of the chain forms approximate those of the reference compounds of analogous structures cited above, it can be concluded that the ring-chain equilibrium ratios in the series of compounds Va–d are of the following orders: for Va, 10–90; Vb, 50–50; Vc, 85–15; Vd, 90–10 (see Table I). Thus a full range of effects on the position of the ring-chain equilibrium has been demonstrated. With increasing bulk at the position *alpha* to the amino group, the equilibrium between the cyclic and chain tautomers is shifted toward predominance of the cyclic tautomer. In the limiting case, Vd, the steric effect reaches a maximum and the compound is predominately cyclic. In α-(2-hydroxyethylamino)desoxybenzoin (I, R = R″ = H, R′ = phenyl), the steric effect is at a minimum and the compound is exclusively open-chain.[8] With the methyl, ethyl, and phenyl analogs, intermediate steric effects are involved and considerable quantities of both the open-chain and cyclic tautomers are present in well blanced equilibrium mixtures.

The factors responsible for the aforementioned shifts in equilibrium may best be understood upon examination of molecular models of cyclic and chain tautomers of the various α-(β-hydroxyalkylamino)-desoxybenzoins. In each case, it is found that those structural features promoting a high percentage of chain tautomer in the equilibrium mixture produce a higher degree of freedom of group rotation in the chain than in the cyclic tautomer, and the chain arrangement appears to be relatively the more comfortable one. In those compounds possessing a high percentage of cyclic tautomer at equilibrium, a significantly greater number of steric repulsions are found in scalar models of the chain tautomer, than in models of the cyclic tautomer, and a relief of steric strain clearly occurs on cyclization. As a specific example of some of the kinds of effects involved and evident upon examination of scalar models, the chain tautomer of the N-benzyl compound (Vd) which has been shown to exist predominantly in solution in the cyclic form, involves strong steric interactions between the benzyl group (R), the *alpha*-phenyl group of the desoxybenzoin moiety, and the amino hydrogen; in the cyclic tautomer, the magnitude of these particular steric repulsive forces is greatly lessened, particularly by the elimination of the rigidity of the benzoyl group. It should be noted that the presence of the hydroxyl and keto groups in the same molecule is not itself enough to overcome the usually effective barriers to intermolecular hemiketal formation, and that for predominance of the cyclic form there is required

TABLE I

ULTRAVIOLET ABSORPTIONS AND APPROXIMATE POSITIONS OF RING-CHAIN EQUILIBRIA OF HYDROXYETHLAMINO KETONE HYDROCHLORIDES IN 5×10^{-5} *Molar* 95% ETHANOL



VI

Compound	R	X	X′	λ_{max}, mμ[a]	ϵ_{max}[a]	Approx. equilib. conc'n, % Cyclic	Chain
Va	CH_3	H	H	245[b]	8,460	10	90
Vb	C_2H_5	H	H	246[c]	3,980	50	50
Vc	C_6H_5	H	H	246[d]	2,300	85	15
Vd	$CH_2C_6H_5$	H	H	245[e]	1,680	90	10
VIa	C_2H_5	Cl	Cl	261	1,700	95	5
VIb	C_2H_5	OCH_3	OCH_3	285	17,300	5	95
VIc	C_2H_5	OCH_3	H	245	4,020	50	50
VId	C_2H_5	H	OCH_3	285	17,270	5	95
VIe	CH_3	Cl	Cl	263	1,860	90–95	5–10
VIf	CH_3	OCH_3	OCH_3	284	17,110	3–5	95–97
VIg	C_6H_5	Cl	Cl	260	1,430	97	
VIh	C_6H_5	OCH_3	OCH_3	285	7,690	55	45
VIi	$CH_2C_6H_5$	Cl	Cl	261	1,310	99	
VIj	$CH_2C_6H_5$	OCH_3	OCH_3	285	3,240	95–97	3–5

[a] λ_{min} (ε); [b] 228 (3,040); [c] 225 (2,120); [d] 227 (1,400); [e] 224 (1,270).

(8) This compound is considered to be exclusively chain in nature because there is no evidence, either spectral or chemical, to indicate the presence of any percentage of the cyclic tautomer. In the cases where the term "predominately" is employed, there is evidence which indicates the presence of both tautomers.

an interplay of steric repulsions which will increase the probability and decrease the strain of close proximity of the hydroxyl to carbonyl and thereby favor the ring form.

Electronic effects. The ring-chain tautomeric equilibrium is shown above to be sensitive to small changes in the nature of the compounds as evidenced by the steric effects cited. If the equilibrium is sufficiently sensitive and delicately balanced it should respond to influence by *para* substituents in the phenyl group which would either enhance or diminish the activity and rigidity of the benzoyl group of the chain form. To test this prediction the series of compounds VIa–j was synthesized and studied. Syntheses were achieved by means of the Voigt reaction and approximate equilibrium compositions were assigned on the basis of spectral analyses in the same manner as for the compounds Va–d.

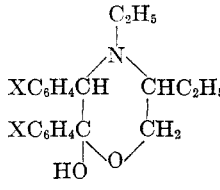
Examination of the results summarized in Table I shows that in the cases of the *alpha*-methyl and ethyl compounds (VIa–f) chlorine substituted in the *para* position of the benzoyl groups has sufficiently enhanced the activity of the benzoyl groups by electron withdrawal so that the equilibria are shifted and involve predominately the cyclic compounds. Substitution of electron-releasing methoxyl groups produces deactivation of the benzoyl groups and equilibrium mixtures consisting predominately of the chain tautomer.

These shifts in equilibria may be attributed solely to the effect of the electronically-active substituent in the *para* position of the benzoyl group. In order to exclude the possibility that the *para* substituent in the *alpha*-phenyl of the desoxybenzoin moiety would exert an appreciable effect on the equilibrium, the two unsymmetrical monomethoxydesoxybenzoins VIc and d were synthesized by the Voigt reaction employing the unsymmetrical benzoins, 4- and 4′-methoxybenzoin.[cf.9] The spectrum of the α-(*p*-methoxyphenyl) compound (VIc) was essentially identical to that of the unsubstituted parent compound (Vb) while the spectrum of the *para*-methoxyacetophenone (VId) was identical to that of the dimethoxy compound (VIb). These studies indicate that electronically-active substituents on the *alpha*-phenyl have no effect on the equilibrium position, and that the observed effects are actually totally attributable to modification of the activity of the benzoyl group by the *para* substitution in that group. While the effects of *para* substituents are thought to be principally electronic rather than steric it is recognized that there are steric implications in terms of the resonance effects of these substituents on the rigidity and maintenance of planarity of the benzoyl group.

Electronic modification of those ethanolamino ketones (VIg–j) carrying the relatively bulky phenyl and benzyl groups *alpha* to the amino groups where the equilibria are on the side of the cyclic forms, produced comparatively little change. Activation of the benzoyl group by *para*-chloro substituents produced only a slight shift of equilibrium toward the cyclic form in the case of the largely cyclic *alpha*-phenyl compound (VIg), and no discernible shift in the case of the *alpha*-benzyl compound (VIi) which in its original unsubstituted form (Vd) was predominately cyclic. A significant shift of equilibrium toward the chain form was produced in the case of the *alpha*-phenyl compound by deactivation of the benzoyl group by substitution of *para*-methoxyl (VIh), but in the case of the benzyl compound (VIj) the shift was negligible (VIj). These shifts in the equilibrium positions are much smaller in magnitude than those in the analogous methyl and ethyl series where the effect is very striking. Thus it is to be concluded that while both steric hindrance by bulky groups and electronic modification of the activity of the benzoyl group produce shifts in equilibria, electronic modification is relatively far less effective, and that the electronic effect becomes important when the ring-chain equilibrium is delicately balanced as it is in the cases of α-methyl and α-ethyl series (Va and b).

It should be noted that the effects of *para*-chlorine and of *para*-methoxyl on the position of the ring-chain equilibrium are analogous to the effects of these two substituents on the activity of benzaldehyde toward cyanide addition where the equilibrium is shifted toward or away from the cyanohydrin,[10a] respectively. Furthermore these effects, which are roughly equal but opposite, are qualitatively consistent with the *sigma* constants of +0.226 for *para*-chlorine and −0.268 for *para*-methoxyl.[10b]

Previous studies have indicated that the presence or absence of an alkyl group on the amino nitrogen is a dominant factor in the equilibrium distribution of chain and cyclic tautomers. To demonstrate the validity of this generalization in the present series, Vb and VIb were converted to the corresponding N-ethyl compounds (VIIa and b) by the action of ethyl iodide. These tertiary amino compounds were shown to be predominately cyclic by their absorption spectra. Thus the presence or absence of an alkyl group on the nitrogen is still to be regarded as a dominant factor governing the equilibrium position.



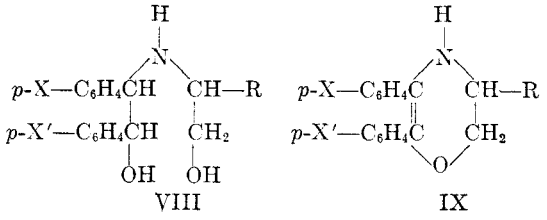
VII (a) X = H (b) X = OCH_3

Chemical studies. Certain chemical criteria of the chain or cyclic nature of a compound of the type under consideration have been applied previously.

(9) Lutz and Baker, *J. Org. Chem.*, **21**, 49 (1956).

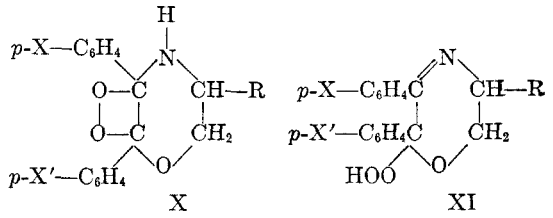
Compounds which exist predominately in the chain form are easily reduced with aluminum isopropoxide and are not dehydrated by the action of mineral acids. Compounds which exist predominately in the cyclic form with as little as 3–5% chain form present at equilibrium, have been found to resist reduction with aluminum isopropoxide but are readily dehydrated to dihydroöxazines by the action of mineral acids.[3,4,5] In the present series of compounds where equilibria have been shown by spectral analyses, it was believed that if the equilibria were not too unbalanced the compounds should give reactions characteristics of both chain and cyclic tautomers.

Aluminum isopropoxide reductions of compounds Va–d and VIa–j to give dialcohols of the general type VIII were successful in all but five instances. All of the compounds were successfully reduced by means of lithium hydride. Absorption spectral analysis had indicated that the five compounds which were resistant toward the action of aluminum isopropoxide (Vd, VIa,g,i,j) existed to the extent of 95% or more in the cyclic form.



The action of mineral acids on compounds of the series Va–d and VIa–j would be expected to yield dihydroöxazines of the type IX. It was recognized that the oxazines so formed, containing the system C=C—N—H, would be susceptible to peroxide formation by air oxidation.[10] In order to minimize the formation of such peroxides during dehydration air was excluded from the reaction mixture. Improved yields resulted. Dehydrations of the amino ketones Va–d and VIa–j to dihydroöxazines were successful in all but three cases, VIb,d and f. The reaction mixture from the dehydration of one of these, VIj, failed to crystallize, however, but the presence of the dehydration product (IXj) was shown by conversion to and isolation of the peroxide. Each of the three compounds which failed to give a dehydration product (VIb,d and f) was a dimethoxydesoxybenzoin which had been shown by absorption spectral analysis to contain negligible amounts of the cyclic tautomer. It would appear that in these types there is a definite correlation between resistance to dehydration to the dehydroöxazine and the difficulty of the primary cyclization to the hydroxymorpholine.

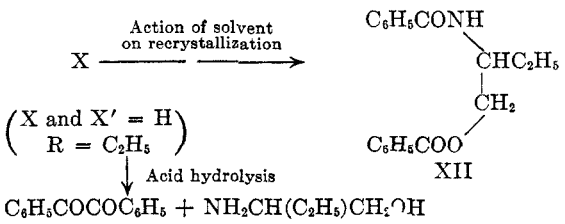
The morpholine peroxides. The dihydroöxazines of the type IX were susceptible to air oxidation, and on exposure to air they rapidly turned to oils. This suggested the possibility that stable peroxides of the type X or XI were formed and might be isolated. These peroxides were subsequently obtained in crystalline form by either of two procedures, the action of oxygen on the dihydroöxazines which had been isolated, or dehydration of the ethanol amino ketones in the presence of oxygen (without isolation of the dihydroöxazines).



The above peroxides (X or XI) were unstable and analyzed correctly only when freshly prepared. They were shown to be true peroxides by their characteristic liberation of iodine from acidified potassium iodide and by their vigorous decomposition on melting. The mechanism of formation of these peroxides is presumably like that previously proposed for the formation of dehydropiperazine peroxides.[11]

Open chain and cyclic structures, X and XI, are possible. In analogy with the dehydropiperazine peroxides and the spectral evidence given, it is believed that the peroxides in the present series are cyclic (X).[11b] Examination of scalar models with special reference to the steric effects favoring cyclization, which are described above, supported this view.

The reactions of the peroxides proved to be consistent with the results obtained in the analogous piperazine peroxides. Recrystallization of 3-ethyl-5,6-diphenyl-2,3-dihydro-1,4-oxazine peroxide (X) gave a noncrystalline product (XII) which was identified by acidic hydrolysis as the benzamide of 2-aminobutylbenzoate. Hydrochloric acid hydrolysis of XI yielded a mixture of benzil and 2-aminobutanol. Similar oxidative and acidic cleavages of peroxides have been observed in the piperazine series[11] and were attributed to the cyclic nature of the peroxides or cyclizability of the hydroperoxy forms.



(10) Lapworth, *et al.*, *J. Chem. Soc.*, 2533 (1928); 1976 (1931). (b) Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(11) Lunsford, Lutz, and Bowden, *J. Org. Chem.*, **20**, 1513 (1955); *cf.* references listed there.

TABLE II

α-(1-ALKYL-2-HYDROXYETHYLAMINO)DESOXYBENZOIN HYDROCHLORIDES

Compound	Reactants[a]	Yield,[b] %	M.p., °C.	Formula	Analyses Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
Va	AE	58	188–189.5	$C_{17}H_{20}ClNO_2$	66.77	66.51	6.54	6.50
Vb	BE	55[c]	193–195	$C_{18}H_{22}ClNO_2$	67.59	67.57	6.93	6.92
Vc	CE	64	200–202	$C_{22}H_{22}ClNO_2$	71.82	71.74	6.03	6.21
Vd	DE	61	190–192	$C_{23}H_{24}ClNO_2$	72.33	72.31	6.33	6.42
VIa	BF	57	195–197	$C_{18}H_{20}Cl_3NO_2$	55.61	55.64	5.19	5.34
VIb	BG	68	166–167	$C_{20}H_{26}ClNO_4$	63.23	62.98	6.90	6.64
VIc	BH	71	181–182	$C_{19}H_{24}ClNO_3$	65.23	65.18	6.91	6.86
VId	BI	68	191.5–193	$C_{19}H_{24}ClNO_3$	65.23	65.04	6.91	6.83
VIe	AF	49	181–183	$C_{17}H_{18}Cl_3NO_2$	54.49	54.70	4.84	5.06
VIf	AG	64	158–160	$C_{19}H_{24}ClNO_4$	62.37	62.28	6.61	6.48
VIg	CF	70	210–211	$C_{22}H_{20}Cl_3NO_2$	60.49	60.62	4.62	4.90
VIh	CG	63	189–190	$C_{24}H_{26}ClNO_4$	67.36	67.32	6.12	6.10
VIi	DF	52	198–199.5	$C_{23}H_{22}Cl_3NO_2$	61.28	61.14	4.92	4.99
VIj	DG	68	174–176	$C_{25}H_{25}ClNO_4$	67.49	68.10	6.39	6.53

[a] A = 2-aminopropanol, B = 2-aminobutanol (Commercial Solvents Corporation), C = 2-amino-2-phenylethanol, D = 2-amino-3-phenylpropanol, E = benzoin, F = 4,4′-dichlorobenzoin, G = 4,4′-dimethoxybenzoin, H = 4-methoxybenzoin, I = 4′-methoxybenzoin. [b] The following solvents were employed in recrystallization: methanol–butanone, Va, b, VIa, e, f, h, i; 95% ethanol, Vc, VIj; methanol–ethyl acetate, Vd, VIc, d; methanol-ether, VIb; methanol–acetone, VIg. [c] The yield was reduced to 32% when the preparation was carried out without an atmosphere of nitrogen.

EXPERIMENTAL[12]

The *amino alcohols* were prepared by modifications of the methods of Vogl and Pohm[7] and Karrer.[13]

A suspension of 10 g. of lithium aluminum hydride and 0.10 mole of the amino acid in 200 ml. of dry tetrahydrofuran was gently refluxed for four to six hours with constant stirring. The mixture was allowed to cool to room temperature, treated with water to destroy excess hydride, hydrolyzed with 10% potassium hydroxide and extracted with ether. The ethereal extract was washed, dried over sodium sulfate, and concentrated under reduced pressure to an oil. The product was obtained either by vacuum distillation or crystallization. When the amino acid ester hydrochloride was employed as reactant, the reaction mixture was stirred at room temperature. The following amino alcohols were prepared.

2-Aminopropanol was prepared from alanine ethyl ester hydrochloride: b.p. 72–74° at 16 mm.; yield 64%. The *picrate* melted at 114–115°; (A. and P.[14] m.p. 114–115.5°).

2-Amino-2-phenylethanol was prepared from α-aminophenylacetic acid: b.p. 99–102° at 1.8 mm.; yield 45%. The *hydrochloride* melted at 137–138° (G. and C.[15] m.p. 137–138°).

2-Amino-3-phenylpropanol was prepared from phenylalanine: recrystallized from benzene, m.p. 67–68° (K. P. and S.,[13] m.p. 67–68°); yield 45%. A preparation employing phenylalanine ethyl ester hydrochloride gave the product in 60% yield.

The α-(1-alkyl-2-hydroxyethylamino)desoxybenzoin hydrochlorides V and VI were prepared by the Voigt reaction in a manner essentially identical to that employed by previous workers in this field.[3,9,16] The only significant departure was the use of a nitrogen atmosphere throughout the reaction. This condition served to minimize oxidation of reactants and products and gave significantly increased yields.

In a typical preparation, a mixture of 0.30 mole of the required benzoin, 0.33 mole of the appropriate amino alcohol, and 3.0 g. of phosphorus pentoxide was heated under an atmosphere of nitrogen for four to six hours on a water-bath. The reaction mixture was allowed to cool, stirred with water, and extracted with either ether or chloroform. The extract was washed, dried over sodium sulfate, decanted, and acidified with ethereal hydrogen chloride. The precipitated product was separated by filtration or decantation, and recrystallized from a suitable solvent. Reactants, yields, solvent of crystallization, melting point and analytical data for these compounds are presented in Table III.

Attempted liberation of the free bases gave non-crystalline products and large amounts of the benzils. In no case was a crystalline free base obtained.

α-[N-Ethyl-N-(1-ethyl-2-hydroxyethyl)amino]desoxybenzoin (VIIa). A solution of 3.2 g. (0.01 mole) of Vb was neutralized with cold 10% sodium carbonate and extracted with ether. The ethereal solution was washed, dried, and reduced in volume to an oil which was dissolved in 10 ml. of hot absolute ethanol. The ethanolic solution was mixed with 0.01 mole of pyridine and 0.01 mole of ethyl iodide and was refluxed for three hours. Chilling and addition of absolute ether precipitated pyridine hydriodide which was removed by filtration. The filtrate was washed, dried, and evaporated. The residual oil was crystallized from 95% ethanol; 1.1 g. (35%); recrystallized from 95% ethanol; m.p. 91–92°.

Anal. Calc'd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09. Found: C, 76.87; H, 8.34.

The *hydrochloride* was precipitated from an ethereal solution of the free base by ethereal hydrogen chloride and was recrystallized from a methanol–acetone mixture, m.p. 176–178°.

Anal. Calc'd for $C_{20}H_{25}NO_2 \cdot HCl$: C, 69.05; H, 7.53. Found: C, 69.01; H, 7.40.

The ultraviolet absorptivity showed a maximum at 245 mμ, ε 1,370 and a minimum at 229 mμ, ε 1,080.

(12) All melting points are "corrected." Microanalyses were performed by Mrs. Carolyn Jeffries, Miss Patricia Paynter, and Miss Y. Mai Lai. Ultraviolet absorption spectra were determined by means of a Beckman DU quartz spectrophotometer using 4–7 × 10^{-5} *molar* solutions in 95% ethanol. Infrared determinations were by means of chloroform solutions, using a Baird double beam spectrophotometer.

(13) Karrer, Portmann, and Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

(14) Adams and Pavlic, *J. Am. Chem. Soc.*, **69**, 3039 (1947).

(15) Gabriel and Colman, *Ber.*, **47**, 1866 (1914).

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

TABLE III

PART A. 2-(1-ALKYL-2-HYDROXYETHYLAMINO)-1,2-DIPHENYLETHANOL HYDROCHLORIDES (VII)

R	X, X′	Yield,[a] %	M p., °C.	Formula	Analyses: Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
CH_3	H	77[a,c]	177–178	$C_{17}H_{21}NO_2 \cdot HCl$	66.23	66.63	7.21	7.18
CH_3	OCH_3	81[a,d]	183–184	$C_{19}H_{15}NO_4 \cdot HCl$	62.03	61.09	7.12	7.38
	Free base[e]		103–104.5	$C_{18}H_{25}NO_4$	68.86	68.91	7.60	7.61
CH_3	Cl	51[a,f]	188–189	$C_{17}H_{19}Cl_2NO_2 \cdot HCl$	54.20	54.06	5.35	5.56
C_2H_5	H	84[a,c]	192–194	$C_{18}H_{23}NO_2 \cdot HCl$	67.17	67.03	7.52	7.52
	Free base[g]		110–112	$C_{18}H_{23}NO_2$	75.75	75.51	8.12	8.34
C_2H_5	Cl	77[b,h]	184–186	$C_{18}H_{21}Cl_2NO_2 \cdot HCl$	56.32	56.53	5.68	5.52
C_2H_5	OCH_3	73[a,d]	191–192	$C_{20}H_{27}NO_4 \cdot HCl$	62.90	62.78	7.39	7.45
C_2H_5	OCH_3, H[k]	78[a,g]	194–196	$C_{19}H_{25}NO_3 \cdot HCl$	64.85	65.07	7.45	7.68
C_2H_5	H, OCH_3[k]	80[a,g]	185–187	$C_{19}H_{25}NO_3 \cdot HCl$	64.85	64.47	7.45	7.49
C_6H_5	H	54[a,c]	204–205.5	$C_{22}H_{23}NO_2 \cdot HCl$	71.43	71.60	6.54	6.81
C_6H_5	Cl	95[b,c]	214–216	$C_{22}H_{21}Cl_2NO_2 \cdot HCl$	60.22	60.44	5.05	5.08
C_6H_5	OCH_3	60[a,i]	203–205	$C_{24}H_{27}NO_4 \cdot HCl$	67.04	67.26	6.56	6.69
$CH_2C_6H_5$	H	69[b,g]	185–187	$C_{23}H_{25}NO_2 \cdot HCl$	71.95	71.90	6.83	6.82
$CH_2C_6H_5$	Cl	94[b,c]	197–199	$C_{23}H_{23}Cl_2NO_2 \cdot HCl$	61.00	61.03	5.34	5.39
$CH_2C_6H_5$	OCH_3	84[b,i]	192–194	$C_{25}H_{29}NO_4 \cdot HCl$	67.63	67.76	6.81	6.88
	PART B. 3-ALKYL-5,6-DIPHENYL-2,3-DIHYDRO-1,4-OXAZINES (VIII)							
CH_3	H	41[g]	91–93	$C_{17}H_{17}NO$	81.24	81.08	6.82	6.81[p]
CH_3	Cl	52[g]	87–88.5	$C_{17}H_{15}Cl_2NO$	63.76	63.79	4.72	4.91
C_2H_5	H	58	101–102	$C_{18}H_{19}NO$	81.47	81.63	7.22	7.04[q]
C_2H_5	Cl	43[g]	96–98	$C_{18}H_{17}Cl_2NO$	64.63	64.49	5.13	5.08
C_2H_5	OCH_3, H[k]	49[g]	99–100	$C_{19}H_{21}NO_2$	77.26	77.20	7.17	7.08
C_6H_5	H	55[j]	110–112	$C_{22}H_{19}NO$	84.31	84.23	6.11	6.23
C_6H_5	Cl	50[d]	103–105	$C_{22}H_{17}Cl_2NO$	69.12	69.34	4.48	4.41
$CH_2C_6H_5$	H	56[j]	104–105	$C_{23}H_{21}NO$	84.37	84.29	6.47	6.43[s]
$CH_2C_6H_5$	Cl	57[g]	97–99	$C_{23}H_{19}Cl_2NO$	69.70	69.93	4.83	4.99
$CH_2C_6H_5$	OCH_3	44[d]	100–102	$C_{25}H_{25}NO_3$	77.49	77.63	6.50	6.58
	PART C. 3-ALKYL-5,6-DIPHENYL-2,3-DIHYDRO-1,4-OXAZINE PEROXIDES (IX)							
CH_3	H	68[l]	107–108	$C_{17}H_{17}NO_3$	72.06	71.80	6.05	6.01[t,u]
CH_3	Cl	53[j]	121–122	$C_{17}H_{15}Cl_2NO_3$	57.97	57.69	4.29	4.03
C_2H_5	H	51[m]	98–100	$C_{18}H_{19}NO_3$	72.70	72.48	6.44	6.71[v,w]
C_2H_5	Cl	44[j,n]	110–111	$C_{18}H_{17}Cl_2NO_3$	59.03	58.83	4.68	4.51
C_6H_5	H	57	107–108	$C_{22}H_{19}NO_3$	76.50	76.34	5.54	5.69[u,x]
C_6H_5	Cl	61	96–97	$C_{22}H_{17}Cl_2NO_3$	63.78	63.52	4.14	4.38
C_6H_5	OCH_3	43[j]	124–126	$C_{24}H_{25}NO_5$	71.09	70.84	5.72	5.64
$CH_2C_6H_5$	H	67[o]	100–101	$C_{23}H_{21}NO_3$	76.86	76.74	5.89	5.79[y]

[a] Procedure I was employed and was successful in all but the five cases indicated: [b] in each of these five cases, [b] the attempted reduction of the amino ketone hydrochloride by Procedure I was unsuccessful (no positive test for acetone in the distillate was obtained during reaction periods of 89–96 hours and a minimum recovery of 91% of the starting materials was obtained); Procedure II was employed successfully in these cases. The products were crystallized from the solvents indicated: [c] Methanol–butanol mixture; [d] isopropyl alcohol; [e] benzene; [f] ethanol–ether mixture; [g] 95% ethanol; [h] ethanol–ligroin mixture; [i] 50% ethanol; [j] absolute ethanol. Unless otherwise indicated all solvents were anhydrous. [k] Where one group is indicated in this column, it represents both X and X′; where two are given, the first represents X, the second X′. In four cases the yields by Procedure II were respectively, [l] 28%, [m] 43; [n] 31%; [o] 43%. [p] λ_{max} 228, 325 mμ, ε 11,040, 9,450; λ_{min} 265 mμ, ε 4,280. [q] λ_{max} 230, 322 mμ, ε 11,280, 9,400; λ_{min} 266 mμ, ε 4,830. [r] λ_{max} 228, 324 mμ, ε 11,150, 9,760; λ_{min} 265 mμ, ε 5,020. [s] λ_{max} 230, 322 mμ, ε 11,350, 9,470; λ_{min} 266 mμ, ε 4,830. [t] λ_{max} 242 mμ, ε 3,970; λ_{min} 231 mμ, ε 3,840. [u] The infrared absorption spectrum showed transparency in the region of 2.8 μ. [v] λ_{max} 240 mμ, ε 4,020. [w] The infrared absorption spectrum showed a sharp band at 4.3 μ, but transparency in the region of 2.8 mμ. [x] λ_{max} 242 mμ, ε 3,900. [y] λ_{max} 240 mμ, ε 3,880.

α-N-Ethyl-N-(1-ethyl-2-hydroxyethyl)amino-4,4′-dimethoxydesoxybenzoin hydrochloride (VIIb) was prepared by the above described ethylation procedure. The free base was not isolated. The hydrochloride was prepared directly in 41% yield; crystallized from 95% ethanol, m.p. 168–169°.

Anal. Calc'd for $C_{22}H_{29}NO_4 \cdot HCl$: C, 64.77; H, 7.41. Found: C, 64.63; H, 7.42.

The ultraviolet absorptivity was determined: λ_{max} 286 mμ, ε 2,100, λ_{min} 266 mμ, ε 1,070.

The *2-(1-alkyl-2-hydroxyethylamino)-1,2-diphenyl ethanols* (VIII) were prepared from the corresponding amino ketones (V and VI) by either of two general methods. *Procedure I.* A mixture of 0.03 mole of the amino ketone hydrochloride, 0.1 mole of aluminum isopropoxide, and 350 ml. of dry isopropyl alcohol was heated under partial reflux until the distillate no longer gave a positive test for acetone. The excess solvent was removed under reduced pressure and the residue was treated with 10% sodium hydroxide. The alkaline mixture was extracted with ether and the ethereal extract was washed, dried over sodium sulfate, decanted, and acidified with ethereal hydrogen chloride. The precipitated product was crystallized from a suitable solvent until a constant melting point was obtained.

Procedure II. The amino ketone hydrochloride (0.025 mole) was added in one portion with continuous stirring to a chilled solution of 1.5 g. (0.039 mole) of lithium aluminum hydride in 250 ml. of absolute ether. After the initial vigorous reaction had subsided, the mixture was allowed to

warm to room temperature and was stirred for two hours. The mixture was hydrolyzed with water and 10% sodium hydroxide solution. The ether layer was separated and the hydrochloride was prepared as above.

The *free bases* were liberated by treating ethereal suspensions of the hydrochlorides with 20% sodium carbonate. The ethereal layer was washed, dried, and concentrated in volume to an oil which was crystallized.

3-Alkyl-5,6-diphenyl-2,3-dihydro-1,4-oxazines (IX). A solution of 5 g. of the amino ketone hydrochloride in 75 ml. of glacial acetic acid was heated to 80° in an atmosphere of nitrogen. Five drops of concentrated sulfuric acid were added and heating was continued for one hour. The solution was neutralized with 10% sodium carbonate and immediately was extracted with ether. The ethereal extract was washed, dried over sodium sulfate, and concentrated. The resulting thick oil was dissolved in 95% ethanol and crystallization was affected by chilling. One or two recrystallizations were sufficient to give material of analytical purity.

It was necessary throughout the preparation to minimize the contact of the compounds and their solutions with the atmosphere. In contact with the atmosphere, the compounds are oxidized to an oil or tar in one to three days. Oxidation is appreciably slower in an inert atmosphere or under a vacuum.

The *attempted dehydrations* of the amino ketones VIf, VIb, and VId by means of sulfuric acid or conc'd hydrochloric acid were unsuccessful. The only crystalline material isolated was unreacted starting material. The attempted dehydration of VIh by the above method gave a semi-crystalline product which immediately became discolored and resinous. All further attempts at crystallization were unsuccessful.

3-Alkyl-5,6-diphenyl-2,3-dihydro-1,4-oxazine peroxides (X). *Procedure I.* A solution of 0.01 mole of the dihydroöxazine (IX) in 300 ml. of dry ether was cooled in an ice-salt mixture. Dry oxygen was passed into this mixture for two hours. The colorless precipitate was separated by filtration and washed with cold dry ether.

Procedure II. A mixture of 3.0 g. of the amino ketone hydrochloride and five drops of conc'd hydrochloric acid was heated for 15 minutes at a temperature 10° below the melting point of the compound, and then for an additional five minutes at a temperature 20° higher. The mixture was neutralized with 10% sodium carbonate and was extracted with ether. The ethereal layer was washed and dried over sodium sulfate. Partial evaporation of the ether produced colorless crystals which were removed by filtration and washed on the filter with cold dry ether. In some instances, no recrystallizing solvent was used as it was found that recrystallization failed to raise the melting point and gave a poor return of material.

The peroxides decomposed vigorously on melting, and the melting points varied slightly with the rate of heating. The peroxides showed the common property of liberating iodine from acidified potassium iodide.

The *attempted preparations* of crystalline peroxides (X: R = C_2H_5, X = OCH_3, X′ = H; R = $CH_2C_6H_5$, X = X′ = Cl; R = $CH_2C_6H_5$, X = X′ = OCH_3) from the corresponding dihydroöxazines and ethanol amino ketone hydrochlorides by procedures I and II were unsuccessful. The reaction products were oils which could not be crystallized. Each of the oils exhibited peroxide character in liberating iodine from acidified potassium iodide.

Acidic hydrolysis of 3-ethyl-5,6-diphenyl-2,3-dihydro-1,4-oxazine peroxide (X). A solution of 1.2 g. of the peroxide and 10 ml. of 6 *N* hydrochloric acid was heated on a water-bath for ten minutes. The mixture on cooling and filtering gave 0.7 g. (84%) of benzil which was identified by mixture melting point with an authentic sample. The clear filtrate was neutralized with an ice-cold 10% sodium carbonate solution and was extracted with ether. The ethereal extract was washed, dried over sodium sulfate, and acidified with ethereal hydrogen chloride. The resulting precipitate was filtered, dried, and heated with 2.5 ml. of benzoyl chloride at 100° for two hours. The mixture was heated with 20 ml. of nitrobenzene at 120–125° until the evolution of hydrogen chloride ceased, and on cooling there was produced a solid which was recrystallized from a mixture of ethanol, ethyl acetate, and petroleum ether; 0.7 g. (78%). The product was identified as 2-aminobutylbenzoate hydrochloride by mixture melting point with an authentic sample of this compound.[17]

In an identical experiment, 3-ethyl-5,6-di-*p*-chlorophenyl-2,3-dihydro-1,4-oxazine peroxide (X, R = C_2H_5, X = X′ = Cl) gave a 74% return of 4,4′-dichlorobenzil[18] and a 79% return of 2-aminobutanol as 2-aminobutylbenzoate hydrochloride.

Cleavage of the peroxide (X). A 3.0-g. sample of the peroxide was recrystallized twice from 95% ethanol with recovery of 0.4 g. The ethanolic mother liquors were evaporated under reduced pressure at 50° to give an oil which could not be crystallized. Hydrolysis of the oil gave a crystalline solid which was identified by mixture melting point as benzoic acid: 1.5 g. (0.012 mole). The acidic filtrate was treated as above and gave 1.29 g. (0.0056 mole) of 2-aminobutylbenzoate hydrochloride (identified).

5-Ethyl-2,3-di-p-methoxyphenyl-morpholine hydrochloride. The dehydration of dialcohols of this general type under much more drastic conditions has been recently reported.[9]

An ethereal suspension of 2-(1-ethyl-2-hydroethylamino)-1,2-di-(*p*-methoxyphenyl)ethanol hydrochloride (VIII, R = C_2H_5, X = X′ = OCH_3) was acidified with ethereal hydrogen chloride. The mixture was reduced in volume on a water-bath. The crystalline product was recrystallized from a mixture of methanol and ether and melted at 275–276.5° (evac. tube).

Anal. Calc'd for $C_{20}H_{25}NO_3 \cdot HCl$: C, 66.01; H, 7.20. Found: C, 65.84; H, 6.96.

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(17) Ullyot, U. S. Patent 2,463,831, March 8, 1949; *Chem. Abstr.*, **43**, 4696 (1949).

(18) Gomberg and Van Natta, *J. Am. Chem. Soc.*, **51**, 2238 (1929).