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Ring–Chain Tautomerism of Derivatives of *o*-Hydroxybenzylamine with Aldehydes and Ketones[1]

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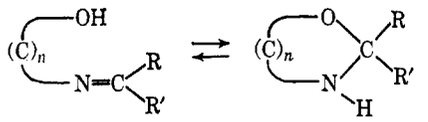
The ring–chain tautomerism of the condensation products of *o*-hydroxybenzylamine with a number of aldehydes and ketones was studied by infrared and nuclear magnetic resonance spectroscopy. Substituted benzaldehydes give rise to products which in the crystalline state are Schiff bases (chain) but which rapidly equilibrate in solution to a mixture of Schiff base and 3,4-dihydro-2H-1,3-benzoxazine (ring) tautomers. The ring–chain ratio depends on the solvent and the substituent in the benzaldehyde ring, electron-donating substituents favoring the open-chain form. For the open-chain tautomers in chloroform-*d*, the chemical shift of the intramolecularly hydrogen-bonded phenolic proton correlates linearly with the σ constant of the substituent in the benzylidene ring. Acetone, cyclohexanone, 5α-cholestan-3-one, acetaldehyde, cyclohexanecarboxaldehyde, and isobutyraldehyde, on condensation with *o*-hydroxybenzylamine, give dihydro-2H-1,3-benzoxazines which tautomerize to less than 10% in chloroform-*d* or carbon tetrachloride. Cyclopentanone gives a mixture of tautomers, and 5α-androstan-3α-ol-17-one, only the Schiff-base tautomer. Formaldehyde gives 1,3,5-tris(*o*-hydroxybenzyl)hexahydro-*s*-triazine or 3,3′-methylenebis(3,4-dihydro-2H-1,3-benzoxazine), and chloral, an adduct. Acylation products of two of the condensation products are reported.

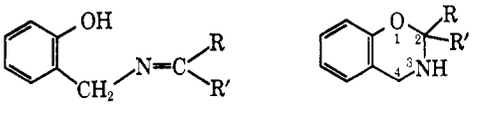
Condensation of primary β- or γ-amino alcohols with aldehydes and ketones yields either heterocycles (oxazolidines or oxazines), open-chain Schiff bases, or mixtures of these in which the components appear to be in mobile tautomeric equilibrium.[4,5] In general it has been found that aliphatic aldehydes and ketones tend to give predominantly or exclusively heterocyclic structures, whereas aromatic or α,β-unsaturated aldehydes and ketones tend to give predominantly open-chain structures. Hitherto the structures of such products have been deduced on the basis of infrared and ultraviolet absorption spectra and molecular refraction measurements.[4d] Although these methods may be definitive when unique products are obtained, they do not easily furnish quantitative data when the products are mixtures. Consequently there exists very little quantitative data concerning tautomeric equilibria of the general type I $\rightleftharpoons$ II. This type of ring–chain tautomerism has not previously been studied by nuclear magnetic resonance (nmr) spectroscopy.



I II

$n = 2$ or 3

We present here a study of some condensation products of *o*-hydroxybenzylamine with aldehydes and ketones. *A priori*, these products could be Schiff bases (III), 3,4-dihydro-2H-1,3-benzoxazines (IV), or mixtures of these. Only a few derivatives of *o*-hydroxybenzylamine have been studied[5–8] and no simple dihydro-1,3-benzoxazine lacking a substituent on the nitrogen has been characterized. Such derivatives of *o*-hydroxybenzylamine are of interest because of the structural similarities between *o*-hydroxybenzylamine and pyridoxamine, which in its role in enzymic transamination reactions is considered to form Schiff-base



III IV

(1) Taken from the Ph.D. Thesis of A. F. M., Vanderbilt University, Jan 1967. Some of this work has been reported in a communication: A. F. McDonagh and H. E. Smith, *Chem. Commun.*, 374 (1966).

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(4) (a) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1942); (b) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. Trav. Chim.*, **71**, 168 (1952); (c) E. D. Bergmann, E. Gil-Av, and S. Pinchas, *J. Am. Chem. Soc.*, **75**, 358 (1953); (d) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953); (e) E. D. Bergmann and A. Kaluszyner, *Rec. Trav. Chim.*, **78**, 315 (1959).

(5) F. W. Holly and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 1875 (1944).

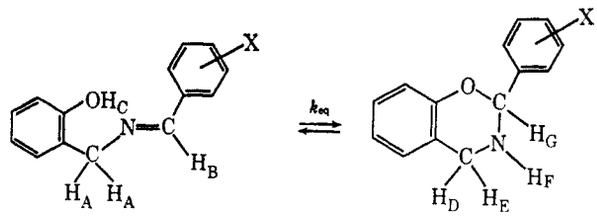
(6) B. Witkop and T. W. Beiler, *ibid.*, **76**, 5589 (1954).

(7) A. Takahashi and S. Seto, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 943 (1955).

(8) Y. Inagaki, O. Ohashi, M. Kishita, and M. Kubo, *Bull. Chem. Soc. Japan*, **38**, 1197 (1965).

TABLE I

NMR DATA AND RING–CHAIN TAUTOMER RATIOS IN CHLOROFORM-*d* FOR DERIVATIVES OF *o*-HYDROXYBENZYLAMINE WITH AROMATIC ALDEHYDES



V VI

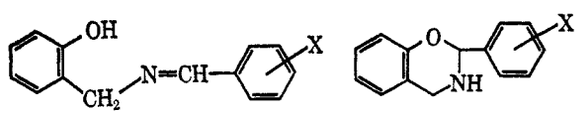
		Nmr[a]								
		Chain (V)			Ring (VI)					
Compd	X	H_A	H_B	H_C[b]	H_D[c]	H_E[c]	J_{DE}	H_F	H_G	% ring[d]
a	*p*-NO_2	5.02	1.52	1.08	5.77	6.03	17	7.8	4.13	51
b	*m*-NO_2	5.04	1.5	1.00	5.77	6.03	17	7.8	4.15	49
c	*p*-Br	5.08	1.70[e]	0.33	5.76	6.02	17	*f*	4.21	20
d	H	5.06	1.64	0.03	5.73	6.00	17	*f*	4.17	16[g]
e	*p*-$CH(CH_3)_2$	5.08	1.67	−0.15	5.73	6.00	*h*	*f*	4.19	10
f	*p*-$N(CH_3)_2$	5.13	1.82	−0.17	Not detected					

[a] Concentration 0.4 *M* with tetramethylsilane (τ 10) as internal standard. Chemical shifts in τ units; coupling constants (J) in cycles per second. [b] Broad peak. [c] Calculated (N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 42) chemical shifts from AB-type doublet of doublets. [d] At 35 ± 1°, except for Vb ⇌ VIb, for which the temperature was not measured. Precision estimated at ±3 percentage units (see Experimental Section). [e] Triplet, J = 1.4 cps. [f] Not detected. [g] Previously estimated and reported[1] as 14%. [h] Satellite peaks not detected; J = 17 cps assumed.

intermediates by condensation with α-keto acids.[9] To what extent Schiff-base derivatives of pyridoxamine exist as tautomeric ring–chain mixtures in solution is not known.

Results and Discussion

Substituted Benzaldehydes.—Condensation of *o*-hydroxybenzylamine with benzaldehyde and several substituted benzaldehydes gave stable, crystalline products which have the open-chain Schiff-base (azomethine) structures Va–g in the solid state as shown by their sharp melting points and infrared spectra. These compounds all melt over a one- or two-degree range and show infrared absorption (KBr



V VI

a, X = *p*-NO_2
b, X = *m*-NO_2
c, X = *p*-Br
d, X = H
e, X = *p*-$CH(CH_3)_2$
f, X = *p*-$N(CH_3)_2$
g, X = *o*-OH

disk) at 1620–1655 (C=N) and 2500–3400 cm^{-1} (broad, hydrogen-bonded OH). The molecular weights of four of the compounds, determined osmometrically, show them to be monomeric in chloroform at room temperature.

The nmr spectra of these compounds, with the exception of N-salicylidene-*o*-hydroxybenzylamine (Vg) which is too insoluble, were determined in chloroform-*d*. Spectral data are presented in Table I. The spectra of Va–e in chloroform-*d* show unequivocal evidence for the presence of both Schiff base (V) and the corresponding 3,4-dihydro-2H-1,3-benzoxazine tautomers (VI). In each spectrum there is a singlet at τ 5.0–5.1 arising from the methylene protons of the open-chain tautomer and also a doublet of doublets with a coupling constant of 17 cps centered at τ 5.87–5.90 from the methylene protons of the ring tautomer. The azomethine proton resonance of tautomer V is a broadened singlet or triplet at τ 1.5–1.7 and the corresponding methine proton resonance of the cyclic tautomer, a singlet at τ 4.1–4.2. In three of the spectra the NH proton resonance from the cyclic tautomer is not detectable, but in the spectra of the two nitrobenzaldehyde derivatives (Va ⇌ VIa and Vb ⇌ VIb) *both* the OH and the NH signals from each tautomer appear and simultaneously vanish on deuteriation. In agreement with these sssignments, in each spectrum the intensity ratio of the methylene to methine resonances arising from each tautomer is approximately 2:1, irrespective of the tautomer ratio. In the spectrum of the last compound in Table I, N-(*p*-dimethylaminobenzylidene)-*o*-hydroxybenzylamine (Vf), only signals arising from the open-chain tautomer were detected.

The tautomeric equilibrium appears to be rapidly established since spectra measured within 20 min of preparing the solutions did not change appreciably when measured again 12 hr later. Evaporation of these solutions give back the original Schiff bases. Equilibrium data, calculated from the relative intensities of the proton resonance signals from the ring and chain tautomers, respectively, are given in Table I. Two factors in particular limited the precision of these measurements. First, the methylene and methine signals from the cyclic tautomers (VI) are not very sharp, mainly owing to coupling with the adjacent NH proton. Second, the low solubility of several of the compounds in chloroform-*d* limited measurements to dilute solutions. The precision is estimated to be about ±3 percentage units. It is evident from the results

(9) (a) E. E. Snell and W. T. Jenkins, *J. Cellular Comp. Physiol.*, **54**, *Suppl.* 1, 161 (1959); (b) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4798 (1961).

that the greater the electron-withdrawing power of the substituent in the aromatic ring of the aldehyde moiety the greater the ring–chain ratio. A plot of log (K/K_0) for the equilibrium *vs.* the appropriate substituent constants (σ)[10] was found to be approximately linear with a slope of about +1 (Figure 1).

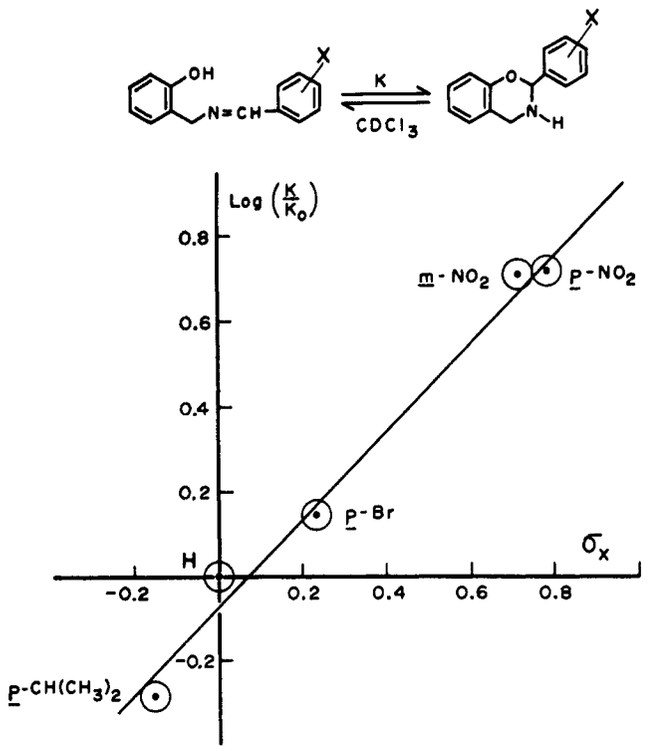


Figure 1.—Hammett plot for the ring–chain tautomeric equilibrium in chloroform-*d* of derivatives of *o*-hydroxybenzylamine with aromatic aldehydes.

The effects of solvent and concentration on the equilibria of two of the compounds were studied (Table II). Unfortunately the concentration could not be varied over a very wide range because of the insolubility of the compounds. The most soluble derivative, Ve ⇌ VIe, is the least reliable for study because of its unfavorable equilibrium constant. Over the moderate concentration ranges studied there was no change in the tautomer ratio within the experimental error. Measurements on the *p*-nitrobenzaldehyde derivative (Va ⇌ VIa) indicate that the equilibrium is markedly solvent sensitive. The data shown in Table II for acetonitrile, ethanol-d_6, and dimethyl sulfoxide are probably of little more than qualitative significance because of the poor quality of the spectra, but nevertheless the trend indicated by the numbers is believed to be correct. The change in the equilibrium position on changing from one solvent to another is not correlated by either the dipole moment, dielectric constant, or Kosower *Z* value[11] of the solvent.

An interesting aspect of the nmr data in Table I concerns the hydrogen bonding in the open-chain tautomers. When the chemical shifts (τ_{OH}) of the phenolic protons for the structures Va–f are plotted against the σ constants[10] for the corresponding benzylidene substituents the points show, with one exception,

(10) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(11) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3253 (1958).

TABLE II
CONCENTRATION AND SOLVENT EFFECTS ON RING–CHAIN EQUILIBRIA

Ve ⇌ VIe			Va ⇌ VIa		
Solvent	Concn, *M*	% ring[a]	Solvent	Concn, *M*	% ring[a]
CCl_4	0.40	13	$CDCl_3$	0.40	51
$CDCl_3$	0.97	8		0.33	51
	0.50	7		0.16	52
	0.40	10	CH_3CN[b]	0.4	40[c]
	0.36	9	C_2D_5OD[d]	0.4[e]	19
	0.25	7	$(CH_3)_2SO$	0.7	0–3[f]

[a] ±3 percentage units. [b] Noisy spectrum. [c] ±5 percentage units. Previously estimated and reported[1] as 35%. [d] Poorly resolved spectrum; broad methylene and methine peaks. [e] Supersaturated solution. [f] On the basis of a very small, broad, questionable peak at τ 6.03. Previously reported[1] as 0%.

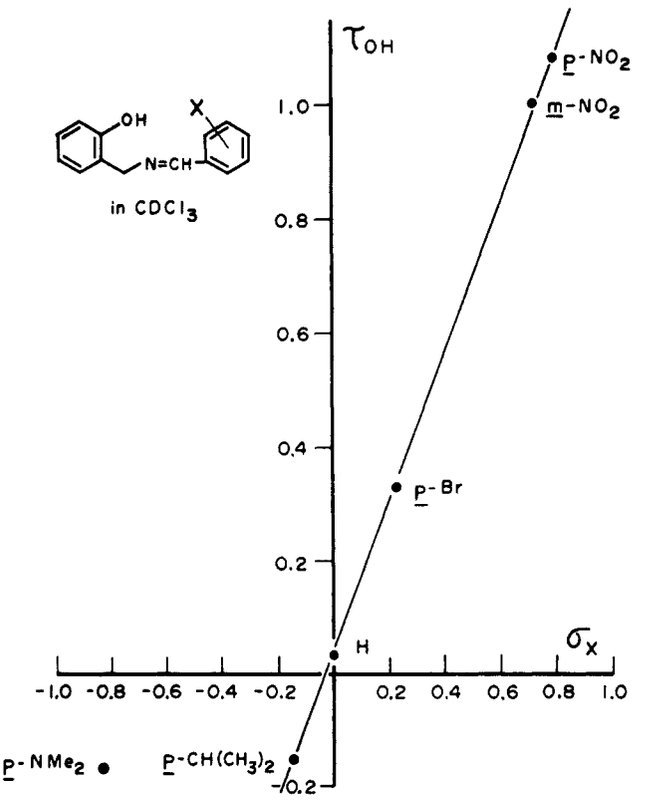
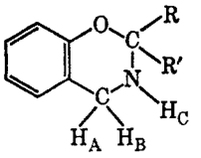


Figure 2.—Plot of phenolic proton chemical shift (τ_{OH}) in chloroform-*d* *vs.* σ constants for derivatives of *o*-hydroxybenzylamine with substituted benzaldehydes.

a good linear fit (Figure 2). The exception is the compound (Vf) with a *p*-dimethylamino substituent. In these structures the phenolic proton is intramolecularly hydrogen bonded to the azomethine nitrogen.[12] The strength of a hydrogen bond is determined by the electron density at the electron donor,[12,13] and except when the donor is an aromatic ring, the chemical shift accompanying hydrogen-bond formation is to lower field.[14] Therefore the shift of τ_{OH} to lower field down the series of compounds in Table I reflects the increased strength of the hydrogen bond as the aromatic substituent becomes less electron withdrawing. If the anomalous point is neglected, Figure 2 shows that the variation in the strength of the intramolecular hydrogen

(12) H. H. Freedman, *ibid.*, **83**, 2900 (1961).
(13) (a) A. Reiser, "Hydrogen Bonding," D. Hadzi, Ed., Pergamon Press Inc., New York, N. Y., 1959, p 443; (b) S. Forsen and B. Akermark, *Acta Chem. Scand.*, **17**, 1907 (1963).
(14) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press Inc., New York, N. Y., 1965, p 537.

TABLE III
NMR SPECTRA OF 2-SUBSTITUTED 3,4-DIHYDRO-2H-1,3-BENZOXAZINES



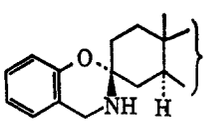
			Nmr[a]			
Compd	R	R'	H_A,H_B	H_C[b]	NCHO	Solvent
VII	CH_3	H	6.09, 6.38 (17)[c]	8.3	5.37 (quartet)	CCl_4
VIII	$CH(CH_3)_2$	H	6.04, 6.28 (17)[c]	*d*	5.67 (doublet)	CCl_4
			5.94, 6.14 (17)[c]	*d*	5.57 (doublet)	$CDCl_3$
IX	*c*-C_6H_{11}	H	6.04, 6.28 (17)[c]	*d*	5.67 (doublet)	CCl_4
X	CH_3	CH_3	6.17	8.1		CCl_4
XI	Spirocyclohexane		6.18			CCl_4
			6.11	8.0		$CDCl_3$
XII	Spiro-3-(5α-cholestane)		6.06, 6.11 (doublet)[e]	*d*		$CDCl_3$

[a] Chemicals shifts in τ units; tetramethylsilane as internal standard (τ 10). [b] When observed this signal was broad. [c] Calculated (N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 42) chemical shifts; AB-type doublet of doublets with coupling constant (J) in cycles per second. [d] Obscured by other signals. [e] See text.

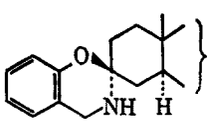
bond correlates directly with the substituent constants. Most probably the *p*-dimethylamino-substituted compound (Vf) is anomalous because of the presence of intermolecularly hydrogen-bonded structures. Baker and Shulgin[15] have shown that a linear correspondence exists between the intramolecularly hydrogen-bonded OH stretching frequency and σ substituent constants in *o*-hydroxyanils. More recently, in several studies the linear relationship between the infrared OH stretching frequency and the OH chemical shift for intramolecularly hydrogen-bonded hydroxyl groups has been demonstrated.[16] The linear relationship found here between the hydroxyl chemical shift and σ constants is therefore in agreement with expectations based on previous work in other systems.

Aliphatic Aldehydes and Ketones.—Condensation of *o*-hydroxybenzylamine with acetone, cyclohexanone, 5α-cholestan-3-one, acetaldehyde, and cyclohexanecarboxaldehyde gave sharp-melting solids whose infrared spectra lack C=N absorption and show NH absorption at 3310–3330 cm^{-1} (free NH) with, in some cases, another peak or shoulder at 3260–3270 cm^{-1} (hydrogen-bonded NH). These materials are therefore dihydro-1,3-benzoxazines (IV) in the solid state. In the liquid phase or carbon tetrachloride solution the products from acetaldehyde, cyclohexanecarboxaldehyde, and isobutyraldehyde exhibit weak absorption bands at 1680–1690 cm^{-1} indicating the presence of small amounts of the open-chain tautomers III.

The nmr spectra of these products (Table III) in chloroform-*d* or carbon tetrachloride are in agreement with the infrared diagnosis. For the three products (VII–IX) derived from aldehydes, the benzoxazine ring methylene protons give rise to an AB pattern centered at about τ 6.0–6.2 with a coupling constant of 17 cps. These protons would appear as a singlet or doublet if the structures were the corresponding open-chain tautomers. Additional evidence for the cyclic structure VIII for the condensate from isobutyraldehyde is the appearance of two doublets for the methyl protons of the isopropyl group at C-2. Similar doubling of the methyl doublet is frequently observed for an isopropyl group which is attached to an asymmetric center.[17] Since the corresponding open-chain tautomer lacks an asymmetric center, this observation provides conclusive evidence for the ring structure VIII with an asymmetric center at C-2. In three cases the NH proton was detected as a broad peak at about τ 8 which disappeared on deuteriation. Two overlapping peaks of apparently similar intensities separated by 3 cps were observed for the $ArCH_2N$ protons of the product (XII) from 5α-cholestan-3-one. This doublet did not collapse on deuterium exchange. Probably this product is an approximately equal mixture of stereoisomers corresponding to the partial structures XIIa and XIIb.



XIIa



XIIb

The nmr spectra of the products from isobutyraldehyde and cyclohexanecarboxaldehyde in carbon tetrachloride exhibit, in addition to the predominating benzoxazine proton signals, several minor peaks below τ 6. Of these the one at τ 5.45 for the isobutyraldehyde product and the one at τ 5.43 for the cyclohexanecarboxaldehyde product are assigned to the $ArCH_2N$ protons of traces of the open-chain tautomers III. It is estimated from the spectra that not more than 8% of the open-chain tautomer is present in carbon tetrachloride in either case. Only the cyclic tautomer IV was detected in the spectrum of the acetaldehyde product in carbon tetrachloride.

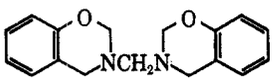
Cyclopentanone condensed with *o*-hydroxybenzylamine to give a white solid which becomes discolored on standing and is only sparingly soluble in chloroform or carbon tetrachloride. Its elemental and molecular weight analyses, broad melting point range (49°), and

(15) A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.*, **81**, 1523 (1959).
(16) (a) G. O. Dudek, *J. Org. Chem.*, **30**, 548 (1965); (b) E. A. Allan and L. W. Reeves, *J. Phys. Chem.*, **66**, 613 (1962); (c) L. W. Reeves, E. A. Allan, and K. O. Stromme, *Can. J. Chem.*, **38**, 1249 (1960).
(17) C. van der Vlies, *Rec. Trav. Chim.*, **84**, 1289 (1965); N. S. Bowman, D. E. Rice, and B. R. Switzer, *J. Am. Chem. Soc.*, **87**, 4477 (1965); H. J. Jakobsen, P. Madsen, and S.-O. Lawesson, *Tetrahedron*, **22**, 1851 (1966), and references therein.

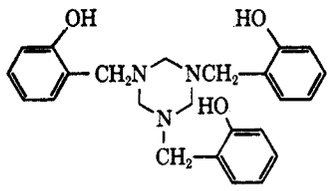
infrared spectrum, which shows absorption at 2300–3500 and 1680 cm^{-1}, indicate this product to be a mixture of ring and chain tautomers. The nmr spectrum of this mixture in carbon tetrachloride (as a saturated solution in contact with solid suspension) has peaks at τ 3.3 (aromatic multiplet, 4.0 H), 5.57 (0.64 H), 6.15 (1.40 H), and about 8 (cyclopentane envelope, 8.0 H). The sum of the relative intensities of the peaks at τ 5.57 and 6.15 corresponds to two protons. These peaks are respectively assigned to the $ArCH_2N$ protons of the open (III) and cyclic (IV) tautomers, present in the ratio of 3:7. The itinerant NH–OH proton is not detectable in the spectrum.

5α-Androstan-3α-ol-17-one condensed readily with o-hydroxybenzylamine to give a stable, crystalline Schiff base (ν_{max}^{KBr} 1700 cm^{-1}) which does not appear to cyclize to any appreciable extent in chloroform-*d*. Only one $ArCH_2N$ signal (τ 5.40) was observed in the nmr spectrum, at lower field than the methylene signal from dihydro-1,3-benzoxazines and close to the corresponding methylene resonance (τ 5.54) of the analogous Schiff base obtained by condensation of 5α-androstan-3α-ol-17-one with benzylamine.

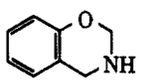
Formaldehyde.—Reaction of o-hydroxybenzylamine with a large excess of formaldehyde gave the previously reported[5] 3,3′-methylenebis(3,4-dihydro-2H-1,3-benzoxazine) (XIII), but when equimolar quantities of the



XIII



XIV

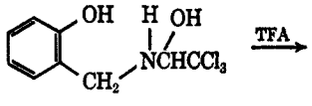


XV

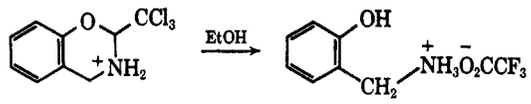
reagents were used the product was 1,3,5-tris(o-hydroxybenzyl)hexahydro-s-triazine (XIV), contaminated with a trace of XIII. The structure of XIV follows from its elemental analysis, molecular weight (osmometric in chloroform), and nmr spectrum, which has two methylene singlets at τ 6.42 and 6.15 and a phenolic proton signal at τ 0.7 which disappeared on deuterium exchange. This compound has been previously reported[7] as 3,4-dihydro-2H-1,3-benzoxazine (XV) on the basis of a Rast molecular weight determination (in camphor). However, since the trimer XIV decomposes below the melting point of camphor, presumably to its monomer,[18] the Rast method is not applicable in this case.

Reaction of the s-triazine XIV with formaldehyde in aqueous ethanol gave the methylenebisamine XIII, indicating that in solution in polar solvents the trimer XIV is in equilibrium with its monomer XV.

Chloral.—Chloral hydrate reacted with o-hydroxybenzylamine to give a white, crystalline solid which decomposes rapidly at its melting point with evolution of chloroform and which we were unable to purify by recrystallization. Its elemental analysis and infrared spectrum, which shows strong absorption at 3280 cm^{-1} and lacks C=N absorption, indicate that the major component of the product is the adduct XVI. The



XVI

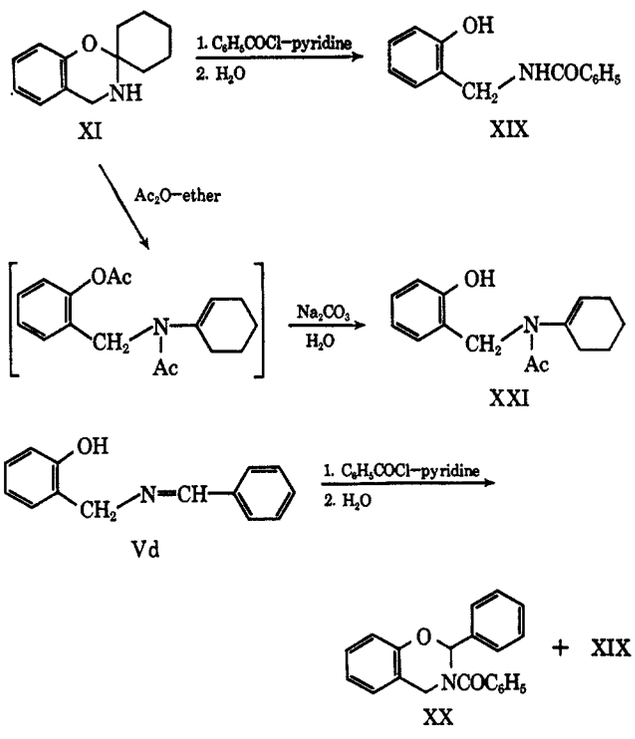


XVII XVIII

insolubility of this material precluded nmr measurements in the common solvents. Its spectrum in trifluoroacetic acid (TFA) shows an aromatic multiplet, a singlet (1 H) at τ 4.41, and an AB pair of doublets (2 H) at τ 5.04 (J = 16 cps), in addition to a minor quartet at τ 5.57, originating from the methylene protons of a small amount of o-hydroxybenzylammonium ion, and a minor unidentified singlet at τ 0.95. Therefore in trifluoroacetic acid the predominant species present is 2-trichloromethyl-3,4-dihydro-2H-1,3-benzoxazonium ion (XVII), formed by dehydration of the adduct XVI. Coupling of the ammonium protons of XVII with the adjacent methylene protons was not detected owing to their rapid exchange with the solvent. Evaporation of a trifluoroacetic acid solution of the chloral o-hydroxybenzylamine adduct and crystallization of the product from ethanol–ether gave only o-hydroxybenzylammonium trifluoroacetate (XVIII).[19]

Acylation Reactions.—Treatment of the dihydrobenzoxazine XI (Scheme I) with a slight excess of

SCHEME I



benzoyl chloride in a chloroform–pyridine mixture and dilution of the mixture with water gave, after work-up, o-hydroxybenzylbenzamide (XIX) in modest yield

(18) (a) A. M. Paquin, *Ber.*, **82**, 316 (1949); (b) P. A. Laurent, *Compt. Rend.*, **261**, 1323 (1965).

(19) Analogous reactions for ethanolamine derivatives have been reported: W. Ruske and I. Hartmann, *J. Prakt. Chem.*, **18**, 150 (1962).

(43%). On similar treatment of the Schiff base Vd there was obtained *o*-hydroxybenzylbenzamide (12%) and 2-phenyl-3-benzoyl-3,4-dihydro-2H-1,3-benzoxazine (XX) (37%). The latter displays an nmr AB pattern centered at τ 5.34 (J_{AB} = 16.5 cps) for the methylene protons and infrared absorption at 1650 cm^{-1}. Reaction of the benzoxazine XI with excess acetic anhydride in pyridine or ether and treatment of the product with aqueous base afforded N-(*o*-hydroxybenzyl)-N-(1′-cyclohexenyl)acetamide (XXI) whose structure follows from its elemental analysis and spectral properties. Its nmr spectrum has signals at τ 0.24 (phenolic OH), 4.59 (vinylic proton), 5.53 ($ArCH_2N$), and 7.97 (acetyl methyl), in addition to signals from the aromatic and cyclohexenyl methylene protons, and its infrared spectrum has a broad strong peak at 1590–1630 cm^{-1}.

Experimental Section

Melting points were determined in capillary tubes, sealed when necessary, and are corrected. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn. Except where noted otherwise, molecular weights were determined osmometrically in chloroform solution at room temperature by Galbraith Laboratories and are accurate to ±5%. Infrared absorption spectra were obtained with a Beckman Model IR-10 spectrophotometer; spectra of carbon tetrachloride solutions were obtained using a 0.2-mm sodium chloride sample cell and a sodium chloride variable-thickness compensating cell. Nmr spectra were determined with a Varian Associates A-60 spectrometer operating at 60 Mcps;[20] chloroform-*d* was used as solvent and tetramethylsilane (τ 10) as internal standard, except where otherwise indicated. Deuterium exchange of amino or hydroxyl protons was accomplished by shaking a chloroform-*d* or carbon tetrachloride solution of the sample with deuterium oxide.

Determination of Ring–Chain Tautomer Ratios.—The signals from the methylene and methine protons of each tautomer were traced onto good quality tracing paper, and the tracings were cut out and weighed. The percentage of the ring tautomer was calculated both from the relative weights of the methine signals and the relative weights of the methylene signals. The mean value of these is that which is reported. In most cases the percentage calculated from the methine protons was smaller than that calculated from the methylene protons; the deviation from the mean was usually not more than two percentage units. The accuracy of the reported values is probably within their precision, which is estimated to be about ±3 percentage units. However, large numbers of measurements were not made.

General Procedures for the Condensation of *o*-Hydroxybenzylamine[5,6] with Aldehydes and Ketones.—The condensation products (benzoxazines or imines)[21] were prepared by one of the following procedures, except where another procedure is described. **Method A.** Equimolar amounts of *o*-hydroxybenzylamine and the aldehyde or ketone were dissolved in dry benzene. The water of condensation was removed by azeotropic distillation of most of the solvent from the solution. The remaining solvent was removed at reduced pressure and the residual crude product purified by sublimation or crystallization. **Method B.** A mixture of *o*-hydroxybenzylamine and a 10% excess of the aldehyde in dry benzene was kept over Linde Molecular Sieve 4A for several hours at room temperature. The sieve was removed by filtration and washed with dry benzene. Evaporation of the combined filtrate and washings gave the crude product, which was then purified by distillation or sublimation.

N-(*p*-Nitrobenzylidene)-*o*-hydroxybenzylamine (Va) resulted (method A): yellow platelets (80%) from aqueous ethanol, mp 132–134°, ν_{max}^{KBr} 1641 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; mol wt, 256.3. Found: C, 65.42; H, 4.90; N, 10.91; mol wt, 263.

N-(*m*-Nitrobenzylidene)-*o*-hydroxybenzylamine (Vb) resulted (method A): yellow prisms (90%) from 95% ethanol, mp 128–130°, ν_{max}^{KBr} 1640 cm^{-1} (lit.[5] mp 125.5–126°).

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; mol wt, 256.3. Found: C, 65.42; H, 4.78; N, 11.05; mol wt, 248.

N-(*p*-Bromobenzylidene)-*o*-hydroxybenzylamine (Vc) resulted (method A): light yellow, rectangular plates (69%) from absolute ethanol, mp 134–135°, ν_{max}^{KBr} 1636 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}BrNO$: C, 57.95; H, 4.17; N, 4.83; mol wt, 290.2. Found: C, 58.10; H, 4.21; N, 4.90; mol wt, 291.

N-Benzylidene-*o*-hydroxybenzylamine (Vd) had mp 106–107° and ν_{max}^{KBr} 1640 cm^{-1} (lit.[5] mp 106–107°).

N-(*p*-Isopropylbenzylidene)-*o*-hydroxybenzylamine (Ve) resulted (method A): white needles (49%) from aqueous ethanol, mp 97–98°, ν_{max}^{KBr} 1633 cm^{-1}.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53; mol wt, 253.3. Found: C, 80.70; H, 7.45; N, 5.60; mol wt, 257.

N-(*p*-Dimethylaminobenzylidene)-*o*-hydroxybenzylamine (Vf) resulted (method A): yellow needles (85%) from 95% ethanol, mp 151–153°, ν_{max}^{KBr} 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.72; H, 7.22; N, 10.96.

N-Salicylidene-*o*-hydroxybenzylamine (Vg) had mp 183–184° and ν_{max}^{KBr} 1655 cm^{-1} (lit.[6] mp 183–184.5°).

2-Methyl-3,4-dihydro-2H-1,3-benzoxazine (VII) (method B) sublimed at 25° (0.005 mm) (73%): mp 34–35°; ν_{max}^{film} 3330, 3270, and 1690 cm^{-1} (very weak); $\nu_{max}^{CCl_4}$ (1.1 *M*) 3330 and 1680 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39; mol wt, 149.2. Found: C, 72.49; H, 7.32; N, 9.13; mol wt, 157.

2-Isopropyl-3,4-dihydro-2H-1,3-benzoxazine (VIII) (method B) distilled under nitrogen using a modified Claisen flask: colorless oil (86%), bp 72–75° (0.04–0.05 mm), $n^{25}D$ 1.5284, ν_{max}^{film} 3330 and 1680 cm^{-1} (weak).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.41; H, 8.56; N, 7.74.

2-Cyclohexyl-3,4-dihydro-2H-1,3-benzoxazine (IX) (method A) recrystallized from aqueous ethanol followed by sublimation at 60° (0.002 mm): white crystalline solid (60%), mp 72–73°, $\nu_{max}^{resolidified\ melt}$ 3320 and 3260 cm^{-1}, $\nu_{max}^{CCl_4}$ (0.9 *M*) 3330 and 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45; mol wt, 217.3. Found: C, 77.54; H, 8.81; N, 6.36; mol wt, 221.

2,2-Dimethyl-3,4-dihydro-2H-1,3-benzoxazine (X).—A solution of 0.59 g of *o*-hydroxybenzylamine (4.7 mmoles) in 25 ml of acetone was refluxed for 2 hr and the mixture was dried overnight with magnesium sulfate. The filtered solution was evaporated under vacuum. Two consecutive molecular distillations of the residue at 65° (0.06 mm) gave 0.64 g of X (79%), white solid, mp 56–58°, $\nu_{max}^{resolidified\ melt}$ 3320 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.90; H, 8.10; N, 8.70.

Spiro[cyclohexane-1,2′-(3′,4′-dihydro)-2′H-1′,3′-benzoxazine] (XI) (method A) sublimed at 50° (0.04 mm): white prisms (94%), mp 53–54°, $\nu_{max}^{molten\ film}$ 3335 cm^{-1}, ν_{max}^{KBr} 3310 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89; mol wt, 203.3. Found: C, 76.87; H, 8.10; N, 7.02; mol wt, 198.

Spiro[5α-cholestane-3,2′-(3′,4′-dihydro)-2′H-1′,3′-benzoxazine] (XII) (method A) recrystallized twice from absolute ethanol–ethyl acetate and once from absolute ethanol under nitrogen: tiny white needles (58%), mp 148–150°, $[\alpha]^{26}D$ +18° (*c* 2.0, chloroform), ν_{max}^{KBr} 3330 cm^{-1}.

Anal. Calcd for $C_{34}H_{53}NO$: C, 83.03; H, 10.86, N, 2.85. Found: C, 83.32; H, 10.88; N, 2.91.

Condensation Product of *o*-Hydroxybenzylamine and Cyclopentanone.—This product (method A) was molecularly distilled at 61° (0.002 mm) and then subjected to two successive sublimations at 45–50° (0.001–0.002 mm): white solid (56%), mp 57–106°, ν_{max}^{KBr} 2300–3700 (broad absorption) and 1678 cm^{-1}, decomposed on storage.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40; mol wt, 189.3. Found: C, 75.91; H, 8.02; N, 7.58; mol wt, 198.

N-(3α-Hydroxy-5α-androstan-17-ylidene)-*o*-hydroxybenzyl-

(20) We acknowledge the generosity of the National Science Foundation for a grant (GP-1683) to the Department of Chemistry, Vanderbilt University, for the purchase of this instrument.

(21) Derivatives of *o*-hydroxybenzylamine with aldehydes and ketones are named and numbered here according to the tautomer which predominates in the free state at room temperature.

amine (method A) recrystallized once from dioxane and once from absolute ethanol: white needles (46%), mp 230–232° dec, $[\alpha]^{26}D$ +36° (*c* 0.5, chloroform), ν_{max}^{KBr} 3450 (3α-OH) and 1700 cm^{-1}, τ 5.40 (NCH_2).

Anal. Calcd for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43; N, 3.54. Found: C, 78.58; H, 9.34; N, 3.70.

N-(3α-Hydroxy-5α-androstan-17-ylidene)benzylamine (method A, using benzylamine in place of *o*-hydroxybenzylamine) recrystallized once from benzene and once from absolute ethanol: white needles (53%), mp 197–211° dec, $[\alpha]^{27}D$ +44° (*c* 0.5, chloroform), ν_{max}^{KBr} 3430 (3α-OH) and 1670 cm^{-1}, τ 5.54 (N–CH_2).

Anal. Calcd for $C_{26}H_{37}NO$: C, 82.27; H, 9.83; N, 3.69. Found: C, 82.51; H, 9.90; N, 3.49.

3,3'-Methylenebis(3,4-dihydro-2H-1,3-benzoxazine) (XIII).—A solution of 0.73 g of *o*-hydroxybenzylamine (5.9 mmoles) in 25 ml of 95% ethanol was added with stirring to 5 ml of U.S.P. formalin. The mixture was stirred overnight at room temperature, diluted with 20 ml of water, and filtered. The residue was washed extensively with water, then with 50% aqueous ethanol, and dried: yield, 0.70 g, mp 155–156°. This material was sublimed at 105–110° (0.04 mm) to give 0.64 g of XIII (77%): mp 154–157°; τ 6.21 (1 H), 5.88 (2 H), 5.04 (2 H), and aromatic signals [lit.[5] mp 154–155° (from absolute ethanol)].

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; mol wt, 282.3. Found: C, 72.26; H, 6.38; N, 9.85; mol wt, 280.

1,3,5-Tris(*o*-hydroxybenzyl)hexahydro-*s*-triazine (XIV).—A mixture of 0.43 g of USP formalin and 3 ml of water was added dropwise with stirring to a solution of 0.70 g of *o*-hydroxybenzylamine (5.7 mmoles) in 20 ml of 95% ethanol. The solution was stirred for 30 min, then diluted with 15 ml of water, and stirred for 1 hr longer. The precipitate was removed by filtration, washed three times with 50% aqueous ethanol, and dried. Sublimation of this solid at 75° (0.002 mm) gave 0.014 g of XIII, mp 152–156°, mmp 152–157° with authentic XIII. There was also obtained 0.567 g of a residue, mp 140–144°. The residue was dissolved in 8 ml of boiling absolute ethanol and the solution was cooled and diluted with 1.6 ml of water. The crystals which formed were collected, washed with 50% aqueous ethanol, and dried. This material (mp 140–145°) was again subjected to sublimation and 0.013 g of sublimate was obtained. The residue (mp 143–147°) was recrystallized twice from 20% aqueous ethanol as above. Thus was obtained 0.23 g of XIV (30%), white needles, insoluble in water but soluble in 5% aqueous sodium hydroxide: mp 148–149° dec; τ 0.70 (broad singlet, 1 H, vanished on deuteriation, concentration-dependent chemical shift), 6.15 (singlet, 2 H), 6.42 (singlet 2 H), and aromatic signals (lit.[7] mp 153.5–154° for the "monomer"). This material with authentic XIII had a mixture melting point of 134–148°.

Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36; mol wt, 405.5. Found: C, 71.32; H, 7.04; N, 10.07; mol wt, 376 (Rast, 184).

The purification procedure described above is not necessary. Addition of U.S.P. formalin to a 10% excess of *o*-hydroxybenzylamine in ethanol, followed by dilution of the mixture with water gave a precipitate which after being collected, washed, and dried had mp 149–151° (92%). One reprecipitation from aqueous ethanol as described above gave XIV, mp 149–150°.

The procedure of Takahashi and Seto[7] (*viz.*, mix equivalent amounts of amine and formalin in ethanol, concentrate the mixture under vacuum, and recrystallize the residue from 80% aqueous ethanol) in our hands gave XIV with mp 148–150°, mol wt 365, and mol wt (Rast) 170, 195. Further recrystallization from boiling 80 or 95% aqueous ethanol gave lower melting crystals.

Reaction of 1,3,5-Tris(*o*-hydroxybenzyl)hexahydro-*s*-triazine (XIV) with Formaldehyde.—To a solution of 0.061 g of XIV (0.15 mmole) in 10 ml of ethanol was added 1.0 ml of U.S.P. formalin. The solution was stirred at room temperature overnight, diluted with water, and stirred for 2 hr longer. The precipitate was collected, washed with 50% aqueous ethanol, and dried. There was thus obtained 0.050 g of XIII (79%): mp 154–156°, infrared spectrum identical with that of authentic XIII; mmp 153–157° with the authentic sample.

Reaction of *o*-Hydroxybenzylamine with Chloral Hydrate.—A solution of 20.0 g of chloral hydrate (0.124 mole) in 25 ml of water was added to a stirred solution of 3.00 g of *o*-hydroxybenzylamine (0.0244 mole) in 50 ml of 95% ethanol at 35°. After a few minutes a crystalline precipitate formed. The mixture was chilled briefly in ice water and filtered. The residue, after being dried, weighed 5.75 g, mp 111–114°. This material was recrystallized rapidly from dry benzene. The white crystals were washed with petroleum ether (bp 40–60°) and dried, giving 4.92 g of a product, mp 117–118° dec, ν_{max}^{KBr} 3280 cm^{-1}. Further recrystallization of this material from benzene gave a solid with an inferior melting point.

Anal. Calcd for $C_9H_8Cl_3NO$: C, 42.81; H, 3.19; Cl, 42.12; N, 5.55; mol wt, 252.5. Calcd for $C_9H_{10}Cl_3NO_2$: C, 39.96; H, 3.73; Cl, 39.31; N, 5.18; mol wt, 270.5. Found: C, 41.02; 40.82; H, 4.08, 3.95; Cl, 38.55; N, 5.17; mol wt, 248.

The gas evolved on pyrolysis of this product was identified as chloroform by infrared (vapor) and gas–liquid partition chromatography (glpc) analysis.

Reaction of the *o*-Hydroxybenzylamine–Chloral Adduct with Trifluoroacetic Acid. *o*-Hydroxybenzylammonium Trifluoroacetate (XVIII).—To 0.46 g of adduct was added 15 ml of trifluoroacetic acid at 0°, and the solution was then allowed to warm to room temperature. After 40 min the solution was evaporated at reduced pressure and the residual brown oil was dissolved in ether. Almost immediately white crystals formed. These crystals were collected, washed extensively with dry ether, and dissolved in absolute ethanol. On dilution of the solution with ether there was obtained 0.31 g of solid XVIII: mp 140–142°; ν_{max}^{KBr} 1670 cm^{-1} (C=O); nmr (in deuterium oxide, without a reference), two singlets and one multiplet (HDO, CH_2, and aromatic) with integral ratios of 4.6:2.0:4.2, respectively; nmr (in trifluoroacetic acid), τ 5.56 (quartet, 2 H) and 1.7–4.5 (multiplet, 7 H). The latter nmr spectrum was identical with that of *o*-hydroxybenzylamine in trifluoroacetic acid.

Anal. Calcd for $C_9H_{10}F_3NO_3$: C, 45.57; H, 4.25. Found: C, 45.84; H, 4.30.

N-(*o*-Hydroxybenzyl)benzamide (XIX), prepared by hydrolysis of N-(*o*-benzoyloxybenzyl)benzamide,[22] crystallized from chloroform–petroleum ether as rhombohedral needles: mp 144–145°; ν_{max}^{KBr} 3350 (NH) and 1630 cm^{-1} (C=O); τ 0.48 (singlet, OH), 5.45 (doublet, CH_2), and 2.0–3.4 (aromatic protons and NH) (lit.[22] mp 142–143°).

Benzoylation of Spiro[cyclohexane-1,2'-(3',4'-dihydro)-2'H-1',3'-benzoxazine] (XI).—A procedure described by McCasland and Horswill[23] was used. To 0.50 g of XI (2.5 mmoles) dissolved in 2 ml of dry chloroform–benzene (2:1) was added 0.35 g of benzoyl chloride (2.5 mmoles). After the solution had stood overnight at room temperature it was diluted with 5 ml of water and 10 ml of ether. The phases were separated and the aqueous layer was extracted with three 5-ml portions of ether. The combined ether phases were washed first with 10% sodium bicarbonate solution, then with water, and finally dried with magnesium sulfate. Evaporation of this solution afforded 0.49 g of a brown oil which subsequently partially crystallized. Crystallization of this oily mass from benzene–cyclohexane gave 0.24 g of N-(*o*-hydroxybenzyl)benzamide (43%) as light brown needles, mp 143–146° (lit.[22] mp 142–143°). Recrystallization once from benzene–cyclohexane and once from benzene gave an analytical sample: mp 143–145°; infrared and nmr spectra identical with those of an authentic sample, mp 144–145°; mmp 145–146° with the authentic sample.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 74.34; H, 5.87.

Benzoylation of N-Benzylidene-*o*-hydroxybenzylamine. 2-Phenyl-3-benzoyl-3,4-dihydro-2H-1,3-benzoxazine (XX).—As described above, 0.32 g of N-benzylidene-*o*-hydroxybenzylamine (1.5 mmoles) was treated with 0.23 g of benzoyl chloride (1.7 mmoles). The crude product was 0.38 g of oil which crystallized on standing. This material was dissolved in about 6 ml of warm 95% ethanol, and this solution diluted with about 2 ml of water and cooled. There was formed 0.18 g of XX (37%) as a crystalline solid, mp 116–118°, which was removed by filtration, the mother liquors being retained for further examination (see below). The solid was recrystallized from aqueous ethanol and then from *n*-hexane. There was obtained 0.13 g of XX as white needles, insoluble in 5% aqueous sodium hydroxide: mp 118–120°; ν_{max}^{KBr} 1650 cm^{-1} (tertiary amide C=O); τ 4.84, 5.83 (AB pair of doublets, 2 H, CH_2, J = 16.5 cps) and 2.0–3.3 (multiplet, 15 H, aromatic protons and OCHN).

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 80.20; H, 5.59; N, 4.43.

On dilution of the aqueous ethanol mother liquors from above

(22) L. C. Raiford and E. P. Clark, *J. Am. Chem. Soc.*, **45**, 1738 (1923).
(23) G. E. McCasland and E. C. Horswill, *ibid.*, **73**, 3923 (1951).

with water there was obtained 0.10 g of a solid which was only partially soluble in *n*-hexane. A solution of the *n*-hexane-insoluble fraction in chloroform was filtered and on dilution of the filtrate with petroleum ether there was deposited 0.040 g of N-(*o*-hydroxybenzyl)benzamide (XIX), mp 144–145°, its identity being established by mixture melting point and infrared measurements.

Acetylation of Spiro[cyclohexane-1,2′-(3′,4′-dihydro)-2′H-1′,3′-benzoxazine] (XI). N-(*o*-Hydroxybenzyl)-N-(1′-cyclohexenyl)acetamide (XXI).—A mixture of 0.47 g of XI (2.3 mmoles) and 1.1 g of acetic anhydride (11 mmoles) in 10 ml of dry ether was allowed to stand at room temperature and then evaporated at reduced pressure. The residue was a colorless oil which did not crystallize on being scratched or cooled. The oil was mixed thoroughly with excess sodium carbonate solution and this mixture was extracted with three 10-ml portions of ether. The combined ether solutions were dried over magnesium sulfate and evaporated at reduced pressure to give 0.48 g of a colorless oil. The infrared spectrum (capillary film) of this oil showed broad absorption at 2600–3400 cm^{-1} (hydrogen-bonded phenolic OH), strong sharp absorption at 1775 cm^{-1} (ester C=O), and a broad strong peak at 1610–1660 cm^{-1} (tertiary amide C=O). The oil was taken up in warm aqueous ethanol and this solution was scratched and cooled to give 0.28 g of a crystalline solid, mp 76–112°. This solid was recrystallized, with considerable loss, twice from aqueous ethanol to give 0.064 g of XXI (11%): white platelets; mp 119–120°; ν_{max}^{KBr} 1590–1630 cm^{-1} (strong broad peak); τ 0.24 (singlet, 1 H, OH, vanished on deuterium exchange), 2.5–3.4 (multiplet, 4 H, aromatic protons), 4.59 (broad, 1 H, vinylic proton), 5.53 (singlet, 2 H, CH_2-N), and 7.6–8.7 (10–11 H, cyclohexene ring methylene protons and acetyl methyl protons with the latter as a sharp peak at τ 7.97 protruding from the methylene envelope). The product is insoluble in water and 10% aqueous sodium bicarbonate but soluble in 5% aqueous sodium hydroxide, from which it can be recovered unchanged by addition of dilute hydrochloric acid.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.52; H, 7.99; N, 5.86.

Improved yields of the same compound were obtained when the following procedure was employed. A 1.0-ml portion of acetic anhydride was added to a solution of 0.46 g of XI (2.3 mmoles) in 5 ml of dry pyridine. The solution was allowed to stand overnight at room temperature and evaporated at reduced pressure. A solution of the residual oil in 25 ml of ether was washed once with 25 ml of water and twice with 25-ml portions of saturated aqueous sodium bicarbonate, then dried over magnesium sulfate and evaporated at reduced pressure. The residue was 0.48 g of a colorless oil whose infrared spectrum (capillary film) showed two strong bands at 1770 and 1655 cm^{-1} and lacked phenolic hydroxyl or amide NH stretch absorption. Attempts to crystallize this oil by cooling, scratching, trituration with various solvents, or molecular distillation failed. This oil was dissolved in 3 ml of ethanol and 10 ml of 2.5% aqueous sodium hydroxide was added. The resultant emulsion was extracted with ether and the combined ether phases were washed with 5 ml of water and dried over magnesium sulfate. The aqueous phase and washings were combined and made acid with 1 *N* hydrochloric acid, producing an emulsion. Crystallization of the oil was induced by seeding the emulsion. The crystals were recrystallized from aqueous ethanol and 0.16 g of XXI (29%), mp 119–120°, was obtained. Evaporation of the ethanol extract obtained above and recrystallization of the residue from aqueous methanol gave a further 0.08 g of XXI (14%), mp 109–114° (impure).

Registry No.—Va, 10358-86-8; Vb, 14723-37-6; Vc, 10358-87-9; Vd, 13293-96-4; Ve, 10358-88-0; Vf, 10358-89-1; Vg, 3946-40-5; VIa, 14680-09-2; VIb, 14680-10-5; VIc, 14680-11-6; VId, 14680-12-7; VIe, 14680-13-8; VII, 14680-14-9; VIII, 14680-15-0; IX, 14746-04-4; X, 14723-39-8; XI, 14783-46-1; XII, 14746-05-5; XIII, 14723-40-1; XIV, 14746-06-6; XVI, 14680-16-1; XVII, 12125-64-3; XVIII, 14680-17-2; XIX, 14680-18-3; XX, 14680-19-4; XXI, 14723-41-2; N-(3α-hydroxy-5α-androstan-17-ylidene)-*o*-hydroxybenzylamine, 14723-42-3; N-(3α-hydroxy-5α-androstan-17-ylidene)benzylamine, 14723-43-4.

Ring–Chain Tautomerism of Derivatives of *o*-Hydroxybenzylamine with Aldehydes and Ketones. The Nuclear Magnetic Resonance Spectra of Immonium Ions[1]

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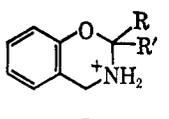
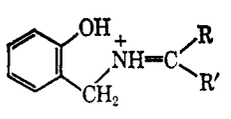
The condensation products (2-substituted 3,4-dihydro-2H-1,3-benzoxazines or the corresponding imines) of *o*-hydroxybenzylamine with several aliphatic and aromatic carbonyl compounds form immonium ions when dissolved in trifluoroacetic acid, no evidence for the cyclic tautomers being detected. The nuclear magnetic resonance spectra of these and other immonium ions are presented. The cyclic protonated 3,4-dihydro-2H-1,3-benzoxazine tautomer is preferred for ions derived from the products formed by reaction of chloral or formaldehyde with *o*-hydroxybenzylamine. 3,4-Dihydro-2H-1,3-benzoxazonium ion is generated by dissolving either 1,3,5-tris(*o*-hydroxybenzyl)hexahydro-*s*-triazine or 3,3′-methylenebis(3,4-dihydro-2H-1,3-benzoxazine) in trifluoroacetic acid; in the latter case a ternary immonium ion is also formed.

We have previously shown[4] that the condensation products of *o*-hydroxybenzylamine with aldehydes and ketones are 2-substituted 3,4-dihydro-2H-1,3-benzoxazines or Schiff bases, or mixtures of these, and that in certain cases a rapid tautomeric equilibrium exists between the two forms. A similar type of tautomerism is also possible for the protonated derivatives of these compounds. *A priori*, it is impossible to predict whether a given derivative, when protonated, will exist



I



II

as a protonated benzoxazine (I), an immonium ion (II), or a mixture of these. There has been no systematic study of this type of tautomeric equilibrium. Hydrochloride salts of tetrahydro-1,3-oxazines,[5] oxazolidines,[6]

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