Acid-Catalyzed Rearrangement of 2-Phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)ones (I)

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2-Phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)ones (I) were converted into 2-(*o*-hydroxyaryl)-5-phenyl-2-oxazolines (II) and 3,4-dihydro-4-phenyl-8-hydroxyisocarbostyrils (III) by concentrated sulfuric acid. The ratio of II and III is dependent upon substituents present in the aromatic ring of the parent benzoxazepinones.

2-Phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)ones synthesized from flavanones by the Schmidt reaction (3-5), are quite stable compounds in concentrated hydrochloric acid, trifluoro, and dilute sulfuric acid but readily rearranged upon treatment with concentrated sulfuric acid. 2-Phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)one (Ia) readily dissolved in concentrated sulfuric acid and was converted into two isomeric compounds, 2-(*o*-hydroxyphenyl)-5-phenyl-2-oxazoline (IIa) and 3,4-dihydro-4-phenyl-8-hydroxyisocarbostyril (IIIa) in a ratio of 10 to 1. It can be postulated that the formation of the two compounds occurs through protonation of the ring oxygen, followed by the formation of the more stable benzylic carbonium ion. The latter rearranges giving the oxazoline IIa as the major product together with the dihydroisocarbostyril IIIa.

Compound IIIa is formed by a Friedel-Crafts type electrophilic attack on the aromatic nucleus. Its formation should be facilitated by an electron-releasing substituent on the aromatic nucleus of the benzoxazepinone Ia. In order to check this hypothesis, 7-methyl-2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)one (Ib) (5), bearing a methyl group in the 7-position was subjected to the same acid treatment. The benzoxazepinone Ib, under the same conditions, was converted to the two isomeric compounds IIb and IIIb, but the ratio was 1 to 10, exactly the opposite of the previous reaction observed for the benzoxazepinone Ia. The presence of a methyl group on the aromatic ring was sufficient to enhance the Friedel-Crafts condensation. The same mechanism occurs in the reactions of cinnamanilide derivatives with sulfuric acid or polyphosphoric acid leading to the formation of 4-phenyl-3,4-dihydrocarbostyril derivatives (6,7).

Scheme I

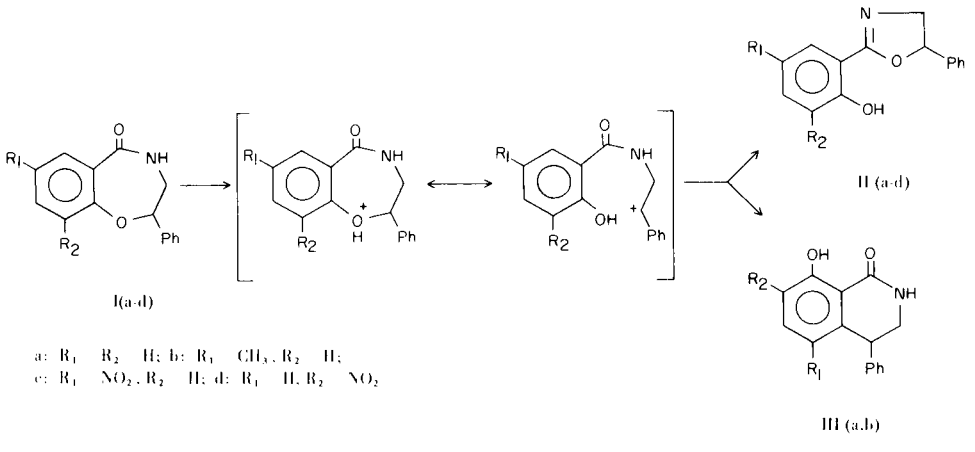


TABLE I

Rearrangement Products and Related Compounds

Compound	M.p., °C Recryst. Solv. (b.p.°C/mmHg)	OH (NH)	Aromat.	Nmr (δ) -CH-	-CH_2-	-CH_3-	Ir cm^{-1}
IIa	52-53 hexane	(a) 11.46	7.65dd (H-6′); 7.25dt (H-4′); 7.23s (Ph); 6.90dd (H-3′); 6.73 dt (H-5′) (b)	5.47q	4.38q (1H), 3.91q (1H)		(a) ν C=N 1640
IIa, *O*-Methyl	(125-128/0.005)		7.85dd (H-6′); 7.40dt (H-4′); 7.32s (Ph); 7.05-6.85m (H-3′, H-5′) (b)	5.56q	4.51q (1H), 4.01q (1H)	3.92s (OCH_3)	(c) ν C=N 1640
IIa, *O*-Acetyl	(135-138/0.005)		8.04dd (H-6′); 7.50dt (H-4′); 7.33s (Ph); 7.40-7.00m (H-3′, H-5′) (b)	5.54q	4.44q (1H), 3.91q (1H)	2.16s ($OCOCH_3$)	(c) ν C=N 1639, CO 1760
IIb	67-68 hexane	(a) 11.38	7.90d (H-6′); 7.28s (Ph); 7.11 dd (H-4′); 6.82d (H-3′) (b)	5.53q	4.46q (1H), 3.97q (1H)	2.28s (arom. CH_3)	(a) ν C=N 1640
IIc	113-114 AcOEt-hexane	13.10	8.62d (H-6′); 8.23dd (H-4′); 7.33s (Ph); 7.10d (H-3′) (b)	5.73q	4.53q (1H), 4.05q (1H)		ν C=N 1640
IId	(142-144/0.005)	11.70	8.20-7.80m (H-6′, H-4′); 7.35s (Ph); 6.88t (H-5′) (b)	5.70q	4.55q (1H), 4.00q (1H)		ν C=N 1645
IIIa	153-154 AcOEt-hexane	(d) 12.90, (6.70)	7.50-7.00m (Ph, H-6); 6.80dd (H-5); 6.47dd (H-7) (b)	4.30m	3.60m (2H)		ν NH 3350, ν CO 1650
IIIa, Diacetyl	118-120 hexane	(e)	6.85-5.90m (8H)	3.50d (1H), 3.38 bs (1H), 3.02q (1H)		1.53s, 1.85s ($OCOCH_3$, $NCOCH_3$)	ν CO 1685, 1752
IIIb	240-241 AcOEt-hexane	(d) 12.83, (8.20)	7.50-6.90m (Ph, H-6); 6.76d (H-7) (b)	4.35dd	3.87q (1H), 3.41dd (f) (1H)	1.98s (arom. CH_3)	ν NH 3350, ν CO 1650
IIIb, Diacetyl	153-154 hexane		7.60-6.80m (7H)	4.30m	4.92dd (1H), 3.65dd (1H)	2.13s (arom. CH_3) 2.34s, 2.39s ($OCOCH_3$, $NCOCH_3$)	ν CO 1682, 1750
IVa	120-122 benzene-hexane	12.13, (7.00), 3.50	7.50-6.50m (9H) (g)	4.90q	3.87q (1H), 3.42q (f) (1H)		ν OH, NH 3300, ν CO 1630
IVb	124-125 benzene-hexane	11.83, (6.80), 3.20	7.40-6.70m (8H)	4.90q	3.85q (1H), 3.40q (f) (1H)	2.23s (arom. CH_3)	ν OH, NH 3400, 3300 ν CO 1640
IVc	148-150 benzene	12.05 (9.11), 3.40	8.98d (H-6); 8.23dd (H-4); 7.40 bs (Ph); 7.03d (H-3) (b)	4.93q	3.83q (1H), 3.40q (f) (1H)		ν OH, NH 3400, 3300 ν CO 1640
Va	116-118 cyclohexane	5.16 (3H)	7.35-6.60m (9H)	4.76t	2.80d (CH-CH_2); 3.92q (benzylic-CH_2)		ν OH, NH 3500, 3300
VIa	104-106 benzene-hexane	3.50 (2H)	7.50-6.60m (9H)	4.77q	2.93q (1H), 2.63q (1H); 3.86s (benzylic-CH_2)	3.80s (OCH_3)	ν OH 3250
VIIb, HCl (h)	178-180 (dec.) ethanol	(i)	8.00-7.40 (7H)	5.30 (l)	4.97bs (benzylic-CH_2); 3.92q (CH_2-CH_3); 4.30d (CH-CH_2)	1.87t (CH_3-CH_2); 2.37s (arom. CH_3)	

(a) Solvent: carbon tetrachloride; (b) observed: J_{ortho} 8 cps, J_{meta} 2 cps; (c) film; (d) Solvent: hexadeuteriodimethylsulphoxide; (e) Solvent: hexadeuteriobenzene; (f) after addition of deuterium oxide; (g) Solvent: perdeuteriopyridine 8.20dd (H-6); (h) VIIb, trifluoroacetic acid: m.p. 200-202° (water); (i) Solvent: deuterium oxide; (l) partially covered by the signal of water, in tetradeuterio methanol: 4.65t.

TABLE II

Compound	Formula	Elemental Analysis Calcd. C	H	N	Found C	H	N
IIa	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	75.25	5.51	5.88
IIa, *O*-Methyl	$C_{16}H_{15}NO_2$	75.87	5.97	5.53	75.57	6.14	5.33
IIa, *O*-Acetyl	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.34	5.45	4.93
IIb	$C_{16}H_{15}NO_2$	75.87	5.97	5.53	75.95	6.10	5.74
IIc	$C_{15}H_{12}N_2O_4$	63.38	4.26	9.86	63.33	4.29	9.76
IId	$C_{15}H_{12}N_2O_4$	63.38	4.26	9.86	63.23	4.17	9.75
IIIa	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	75.14	5.76	5.59
IIIa, Diacetyl	$C_{19}H_{17}NO_4$	70.57	5.30	4.33	70.31	5.39	4.28
IIIb	$C_{16}H_{15}NO_2$	75.87	5.97	5.53	76.03	6.27	5.72
IIIb, Diacetyl	$C_{20}H_{19}NO_4$	71.20	5.68	4.15	71.04	5.77	4.32
IVa	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	69.71	5.87	5.60
IVb	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	70.76	6.32	5.43
IVc	$C_{15}H_{14}N_2O_5$	59.60	4.67	9.27	59.88	4.66	9.33
Va	$C_{15}H_{17}NO_2$	74.05	7.04	5.76	73.90	7.13	5.64
Va, Triacetyl	$C_{21}H_{23}NO_5$	68.28	6.28	3.79	68.00	6.31	3.69
VIa	$C_{16}H_{19}NO_2$	74.68	7.44	5.44	74.59	7.32	5.38
VIIb, HCl	$C_{18}H_{22}NOCl$	71.15	7.30	4.61	70.83	7.25	4.55 (a)
VIIb, CF_3COOH	$C_{20}H_{22}NO_3F_3$	62.98	5.81	3.67	62.75	5.84	3.42

(a) % Cl Calcd. 11.67. Found, 11.56.

This observation was confirmed by the results obtained from the acid treatment of 7-nitro-2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)one (Ic) (5) and of 9-nitro-2-phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)one (Id) (5). In the two latter cases only the oxazoline derivatives IIc and IId were obtained without any dihydroisocarbostyril derivatives. The presence of the deactivating nitro-group on the aromatic ring totally blocked the Friedel-Crafts condensation.

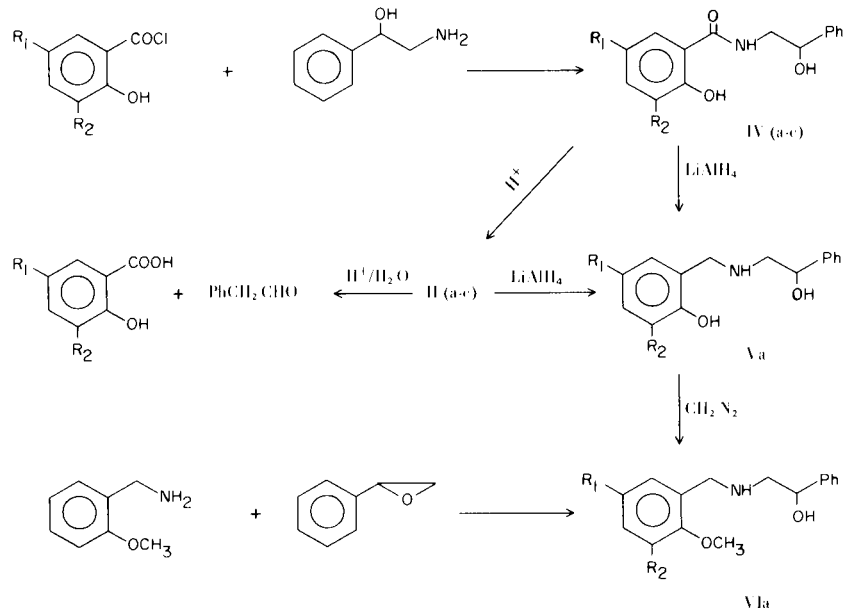
The formation of oxazoline-type compounds II(a-c) was strongly favoured by the presence of water in sulfuric acid; however, under these conditions, the conversion took place over a much longer period of time. Experiments carried out with sulfuric acid diluted with water showed that 80% sulfuric acid converted the benzoxazepinones Ia and Ib into oxazolines IIa and IIb, without formation of IIIa and IIIb in 2 hours, while 60% sulfuric acid produced the same result in two days. During both conversions, the formation of an intermediate was observed, which was identified as *N*-(β-hydroxyphenethyl)salicylamide (IVa) and *N*-(β-hydroxyphenethyl)-5-methylsalicylamide (IVb). This was confirmed by treating amides IVa and IVb, synthesized independently, with concentrated sulfuric acid. In both reactions only oxazolines IIa and IIb were obtained. Similarly 2-(2-aminophenyl)-2-oxazolines were obtained by acid cyclization of substituted 2-amino-*N*-(2-hydroxyethyl)benzamides (8,9), in agreement with the oxazoline formation from *N*-(β-hydroxyethyl)alkyl or aryl amides (10).

Scheme 1 shows the postulated mechanism of the rearrangement. As a result of this study, it appears that the benzylic carbonium ion undergoes nucleophilic attack with water giving the intermediate benzamides IV which readily rearrange to oxazoline II.

Structural Assignment.

The structure of the oxazolines II(a-d) was supported by spectroscopic data and by chemical reactions. Oxazoline IIa, in common with the other oxazolines II(b-d), gave a strong positive ferric chloride test. Moreover IIa with diazomethane gave a monomethyl derivative (negative ferric chloride test) and with acetic anhydride a monoacetyl derivative (negative ferric chloride test). Therefore, it can be assumed that II contains the phenolic OH group. Oxazolines IIa and IIb were hydrolyzed by refluxing with hydrochloric acid: the hydrolysate yielded a neutral fraction identified as phenylacetaldehyde, and an acid fraction identified as both salicyclic and 5-methylsalicylic

Scheme II



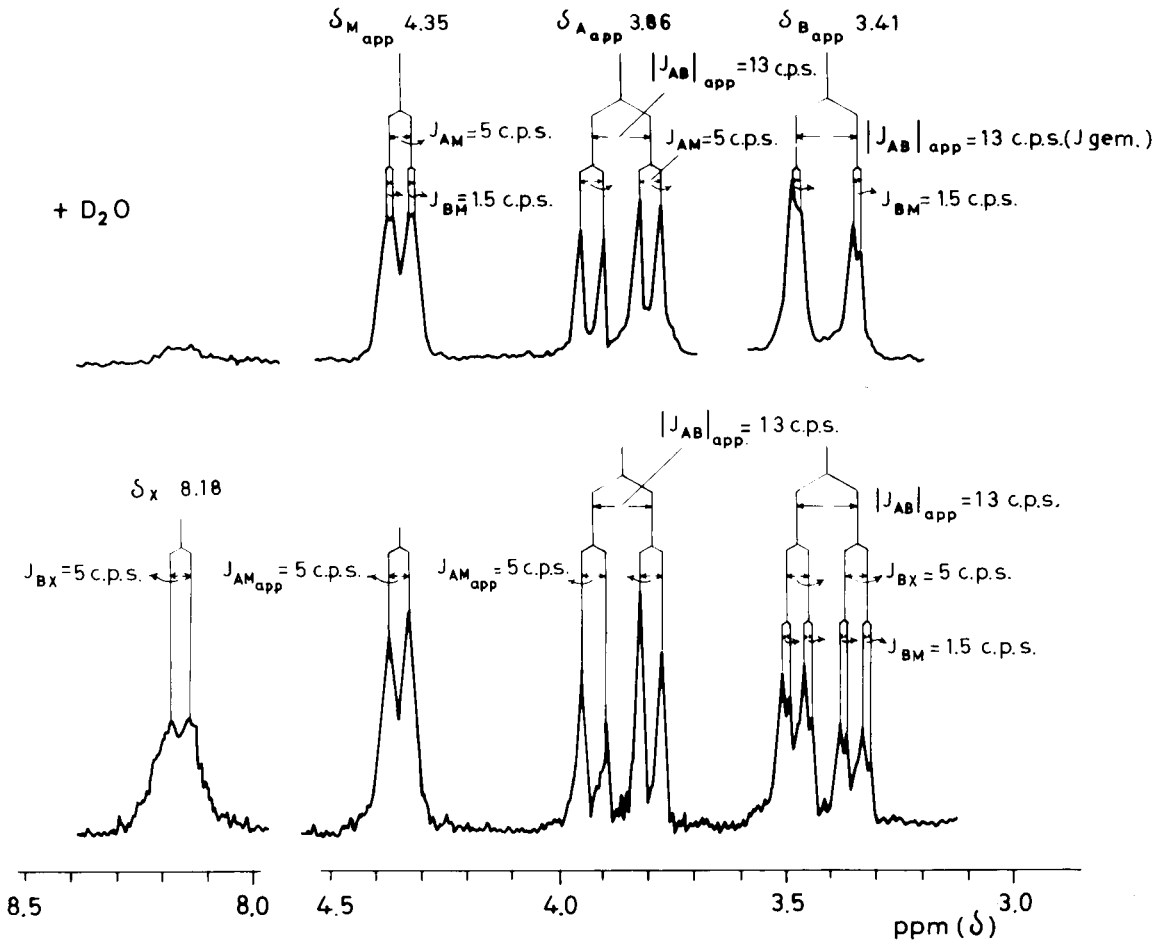


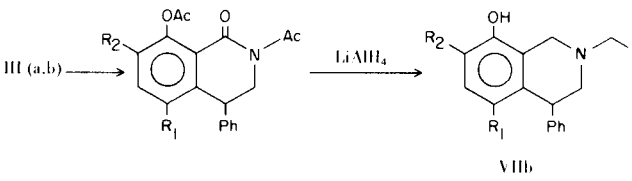
Figure 1

acid, respectively. As reported previously, *N*-(β-hydroxyphenethyl)salicylamides (IVa,b) and also IVc, prepared by the reaction between the appropriate salicyloyl chloride and 1-phenyl-2-aminoethanol, were readily converted into oxazolines II(a-c) by treatment with concentrated sulfuric acid. Oxazoline IIa, by LAH reduction, gave *N*-(β-hydroxyphenethyl)salicylamine (Va), which was identical, in all respects, to the LAH reduction-product of IVa. The methyl ether VIa, obtained by addition of diazomethane to salicylamine Va, was synthesized independently from *o*-methoxybenzylamine and styrene oxide. Spectroscopic data for all compounds reported are in agreement with the assigned structures and are reported in Table I.

The structure reported for dihydroisocarbostyrils IIIa and IIIb was derived mainly from the interpretation of nmr and mass spectra. The aromatic region of nmr spectrum of IIIa and IIIb depicts eight and seven aromatic protons, respectively. Moreover, both show no signal absorption at low field, which is generally assigned to a deshielded aromatic proton (11). This means that the aromatic proton *ortho* to the carbonyl group, H-6 in the starting benzoxazepinones, was substituted. The nmr spectrum of dihydroisocarbostyril IIIb was more useful in elucidating structure than that of IIIa. As showed in spectrum of IIIb, (Figure 1) the four proton of the sequence Ph - C(H_M) - C(H_A)(H_B) - N(H_X) - C = O are arranged in an ABMX system. The latter, on addition of deuterium oxide became an AMB system by the collapse of the signal of X (assigned to -CO-NH-) and the coupling constant J_{BX} = 5 cps.

Moreover the nmr spectrum of the corresponding diacetyl derivative shows the following parameters for the sequence Ph - C(H_M) - C(H_A)(H_X) - N(Ac) - C = O: J_{AX} = 13 cps, δ_A 3.65; J_{AM} = 4 cps, δ_M 4.30; J_{MX} = 2.5 cps, δ_X 4.92. The strong shift of the *geminal* proton (H_X) to low field is probably due to the anisotropy of the carbonyl of the acetyl group. Dihydroisocarbostyrils III(a,b) contain phenolic -OH (positive ferric chloride test) chelated with an *ortho*-carbonyl group (singlet at *ca.* 12.90 in the nmr spectrum) and with acetic anhydride gave both Ar-OAc and Ar-CO-NAc derivatives. Compounds III(a,b) are stable in acid solution and were recovered unchanged from an attempted drastic acid hydrolysis. In addition, the diacetyl derivative of IIIb was reduced by LAH to 2-ethyl-4-phenyl-5-methyl-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (VIIIb) characterized as the corresponding salts.

Scheme III



VIIIb

The mass spectra of dihydroisocarbostyrils III(a-b) and of its diacetyl derivatives show a similar pattern. In the mass spectra of IIIa and IIIb, the base peak is due to the loss of 29 amu from M^+. However, in the mass fragmentation of the corresponding diacetyl derivatives, the loss of both acetyl residue (mass 42 each) and following loss of 29 amu, generates the base peak. The spectra of the above compounds always show a fragment formed by the loss of 28 amu from the base peak. Masses 29 and 28 could be assigned to (CHO·) and CO, observed in the electron impact of phenols (12) and aromatic amides (13).

The most important fragmentations (some of which supported by appropriate metastable ions) are reported. IIIa, 239 $(M^+) \xrightarrow[-CHO\cdot]{*} 210$; IIIa, diacetyl derivative, 323 $(M^+) \xrightarrow[-CH_2=C=O]{*} 281 \xrightarrow[-CH_2=C=O]{*} 239 \xrightarrow[-CHO\cdot]{*} 210$; IIIb, 253 $(M^+) \xrightarrow[-CHO\cdot]{*} 224 \xrightarrow[-CH_3\cdot]{} 209$; IIIb, diacetyl derivative, 333 $(M^+) \xrightarrow[-CH_2=C=O]{*} 295 \xrightarrow[-CH_2=C=O]{*} 253 \xrightarrow[-CHO\cdot]{*} 224 \xrightarrow[-CH_3\cdot]{*} 209$. Additional spectroscopic data are reported in Table I.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected; ir spectra were recorded on a Perkin Elmer model 21 double beam spectrophotometer, in chloroform solution unless otherwise stated. Nmr spectra were taken using a Varian T-60 or Ha-100 spectrometer in deuteriochloroform solution unless otherwise stated. Chemical Shifts are measured in ppm (δ) with respect to TMS as an internal standard. The peaks assigned to the protons from the NH-, HO- phenolic or HO- alcoholic (Table I) disappeared after exchange in deuterium oxide. Mass spectra (MS) were obtained on a Hitachi RMU6D (single focus) instrument with ionizing potential of 70 eV. Samples were directly introduced into the ion source heated at 200°. Tlc were performed on Merck Silica Gel GF_{254}. Melting points and spectroscopic data are reported in Table I, elemental analysis in Table II.

Reactions of 2-Phenyl-2,3-dihydro-1,4-benzoxazepin-5(4*H*)ones I(a-d) with Sulphuric Acid.

a) Concentrated Sulfuric Acid.

Benzoxazepinones (Ia-d) (0.01 mole) were treated with concentrated sulfuric acid (5 ml.) and the reaction was followed by thin layer chromatography (tlc) (ethyl acetate-hexane 1:1). After the benzoxazepinone disappeared (10 minutes) the reaction mixture was poured into an ice-cooled saturated sodium bicarbonate solution and finally extracted with ethyl acetate. The combined extracts were dried (sodium sulfate), then evaporated.

Benzoxazepinone (Ia) was converted to a mixture of oxazoline (IIa) and dihydroisocarbostyril (IIIa) in 80% yield. The crude product was chromatographed on a silica gel column eluting with hexane gradually enriched with ethyl acetate. First, the oxazoline (IIa) was obtained, and then practically pure 3,4-dihydro-4-phenyl-8-hydroxyisocarbostyril (IIIa); uv λ max (ethanol) 246 sh (log ε, 3.71), 309 (log ε, 3.71) nm MS: m/e (1%), 239 (57) M^+, *210* (100), 182 (12.5), 181 (22), 165 (11), 164 (17), 153 (13), 152 (22), 105 (8), 91 (8), 77 (16), 51 (13), 44 (12), 39 (10), 28 (25), 18 (95); metastable ion 184.4 (184.74). The ratio of IIIa and IIa isomers was 1:10 (confirmed by nmr spectrum of the crude reaction product).

Benzoxazepinone (Ib) was converted to a mixture of oxazoline (IIb) and dihydroisocarbostyril (IIIb) in 95% yield. The crude product was recrystallized from ethyl acetate giving practically pure 3,4-dihydro-4-phenyl-5-methyl-8-hydroxyisocarbostyril (IIIb); uv λ max (ethanol) 245 sh (log ε, 3.72), 316 (log ε, 3.72) nm MS: m/e (1%), 253 (77), *224* (100), 209 (31), 196 (11), 195 (9), 181 (20), 178 (16), 165 (17), 152 (20), 91 (12), 77 (12), 51 (11), 39 (10), 28 (14), 18 (15); metastable ions 198.3 (198.57), 195.1 (195.20).

The ethyl acetate filtrate was then chromatographed on a silica gel column. On elution with 1% methanol in chloroform, first the oxazoline (IIb) was obtained and then an additional amount of dihydroisocarbostyril (IIIb). The ratio of the IIIb and IIb isomers was 10:1 (confirmed by nmr spectrum of the crude reaction product).

Benzoxazepinones (Ic and Id) were entirely converted to the corresponding oxazolines (IIc and IId) in about 85% yield. The crude product was further purified by recrystallization (IIc) or by distillation (IId).

b) Eighty Percent Sulfuric Acid.

The reaction was carried out on benzoxazepinones Ia and Ib as previously described for concentrated sulfuric acid. Benzoxazepinones (Ia and Ib) were completely converted to the corresponding oxazolines (IIa and IIb) respectively in 1 hour and 2 hours. The tlc (ethyl acetate-hexane 1:2) showed the disappearance of the spot corresponding to the benzoxazepinones and the appearance of a spot corresponding to the oxazolines. An additional spot, ferric chloride sensitive, intermediate between I and II appeared during conversion I(a,b) → II(a,b), corresponding to *N*-(β-hydroxyphenethyl)-*o*-hydroxybenzamides IVa and respectively IVb.

c) Sixty Percent Sulfuric Acid.

Benzoxazepinones (Ia and Ib) were converted to the corresponding oxazolines after 26 hours and 40 hours respectively through the formation of the intermediates IVa and IVb, as previously described in b).

Acid Hydrolysis of Oxazolines (IIa,b).

Oxazolines (IIa and IIb) were hydrolyzed by refluxing with 6*N* hydrochloric acid for 7 hours. The acid fractions gave salicylic acid and 5-methylsalicylic acid, identified by comparison with authentic samples (mixed m.p.'s, ir spectra). In both of these hydrolyses, phenylacetaldehyde was found in the neutral fraction and identified by comparison with an authentic sample, on gas liquid chromatography.

2-(*o*-Methoxyphenyl)-5-phenyl-2-oxazoline (IIa-OMe).

An ethereal solution of the oxazoline (IIa) was treated with an ethereal solution of diazomethane at 0°. The crude reaction product was purified by vacuum distillation.

2-(*o*-Acetoxyphenyl)-5-phenyl-2-oxazoline (IIa-OAc).

Oxazoline (IIa) (100 mg.) was acetylated with acetic anhydride (1 ml.) and pyridine (0.1 ml.) at room temperature for 24 hours. The crude reaction product was purified by vacuum distillation.

N-Acetyl-3,4-dihydro-4-phenyl-8-acetoxyisocarbostyril (IIIa, diacetyl) and *N*-Acetyl-3,4-dihydro-4-phenyl-5-methyl-8-acetoxyisocarbostyril (IIIb, diacetyl).

Dihydroisocarbostyrils (IIIa and IIIb) (200 mg.) were acetylated with acetic anhydride (5 ml.) and pyridine (0.5 ml.) by refluxing for 30 minutes. The crude reaction products were purified by recrystallization; IIIa, diacetyl derivatives; uv λ max (ethanol) 247.5 (log ε, 4.12), 287 sh (log ε, 3.42) nm; MS: m/e (1%), 323 (2) M^+, 281 (65), 239 (71), *210* (100), 182 (8), 181 (13), 165 (7), 164 (9), 153 (10), 152 (14), 131 (15), 91 (10), 77 (9), 51 (5), 43 (43), 28 (13), 18 (12); metastable ions 203.3 (203.51), 184.6 (184.74); IIIb, diacetyl derivative uv λ max (ethanol) 248 (log ε, 4.12), 295 sh (log ε, 3.45) nm; MS: m/e (1%), 337 (1) M^+, 296 (22), 295 (86), 253 (95), 225 (15), *224* (100), 209 (16), 196 (5), 181 (8), 165 (10), 152 (8), 91 (10), 77 (8), 43 (35), 32 (13), 28 (55), 18 (41); metastable ions 217.0 (217.22), 198.3 (198.57), 195.0 (195.20).

N-(β-Hydroxyphenethyl)-*o*-hydroxybenzamides (IVa-c).

To a solution of 2-hydroxy-2-phenethylamine (0.01 mole) and triethylamine (2 g.) in benzene (20 ml.), a solution of the acid chloride (0.01 mole) (salicyloyl chloride, 5-methylsalicyloyl chloride and 5-nitrosalicyloyl chloride) in benzene (10 ml.) was added. The reaction mixture was heated at 50° for 5 hours, cooled in ice, and diluted with ether. The ethereal solution was washed with 6*N* hydrochloric acid, 2*N* sodium carbonate, and finally with water V, was dried with sodium sulfate. The crude residue from the ethereal extracts was purified by column chromatography. Chromatographic elution (ethyl acetate-hexane 1:2) of the residue from the reaction with salicyloyl chloride afforded first *N*-(β-salicyloyloxyphenethyl)salicylamide, yield 30%, m.p. 157-158° (benzene); ir ν CO 1670, 1640 cm^{-1}; nmr δ: 12.07b, 10.51b (2-OH), 8.20-6.40m (aromatic 13H + NH), 6.23t (-CH-O-C=O), 3.97t (-CH_2-NH-C=O, doublet on addition of deuterium oxide).

Anal. Calcd. for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.05; H, 5.12; N, 3.83.

Then *N*-(β-hydroxyphenethyl)salicylamide IVa was obtained in a yield of 60%, practically pure.

Chromatographic elution (ethyl acetate-hexane 1:2) of the residue from the reaction with 5-methylsalicyloyl chloride afforded first *N*-(β-5-methylsalicyloyloxyphenethyl)-5-methylsalicylamide, yield 30%, m.p. 131-133° (benzene-hexane); ir, ν CO 1672, 1645 cm^{-1}; nmr δ: 11.87, 10.33s (2-OH), 7.80-6.60m (aromatic 11H + NH), 6.20t (-CH-O-CO-), 3.95t (-CH_2-NH-CO-; doublet on addition of deuterium oxide), 2.30, 2.22 s(2-CH_3).

Anal. Calcd. for $C_{24}H_{23}NO_5$: C, 71.09; H, 5.72; N, 3.46. Found: C, 71.32; H, 5.84; N, 3.73.

Then *N*-(β-hydroxyphenethyl)-5-methylsalicylamide (IVb), was obtained in a yield of 30%, nearly pure. The residue from the reaction with 5-nitrosalicyloyl chloride, recrystallized from ben-

zene, gave pure *N*-(β-hydroxyphenethyl)-5-nitrosalicylamide (IVc) (60%).

Cyclizations of *N*-(β-hydroxyphenethyl)-*o*-hydroxybenzamides (IVa-c) to Oxazolines (IIa-c).

N-(β-Hydroxyphenethyl)-*o*-hydroxybenzamides (IVa-c) (0.01 mole) were readily converted to the corresponding oxazolines (IIa-c) by treatment with concentrated sulfuric acid (5 ml.) at 10°. The crude residue was recrystallized to give pure (IIa-c). The yields were *ca.* 90%.

N-(β-Hydroxyphenethyl)salicylamine (Va).

a) This compound was obtained by LAH reduction of the oxazoline (IIa) after heating under reflux in ether solution for 12 hours.

b) An identical compound (mixed m.p., identical ir and nmr spectra) was obtained by LAH reduction of the *N*-(β-hydroxyphenethyl)salicylamide (IVa), after heating under reflux in ether solution for 12 hours.

c) The same compound was also obtained by LAH reduction of *N*-(β-salicyloyloxyphenethyl)salicylamide in the same conditions described before. The triacetyl derivative was obtained by treatment with acetic anhydride-pyridine 10:1 for 24 hours at room temperature. The crude reaction product was purified by distillation, b.p. 140-145°/0.005 mm Hg; ir (film), ν CO 1740, 1640 cm^{-1}.

N-(β-Hydroxyphenethyl)-*o*-methoxybenzylamine (VIa).

a) This compound was obtained by treatment of a methanolic solution of *N*-(β-hydroxyphenethyl)salicylamine (Va) with an ethereal solution of diazomethane. The crude reaction product was chromatographed on a silica gel column. On elution with ethyl acetate-hexane (2:1) a small amount of impurities was first obtained and then pure benzylamine (VIa), further purified by recrystallization.

b) A mixture of *o*-methoxybenzylamine (0.002 mole) and styrene oxide (0.002 mole) was heated in a sealed tube at *ca.* 90° for 2 hours. The crude reaction product was chromatographed on a silica gel column. On elution with ethyl acetate-hexane (2:1), a considerable amount of an unidentified oil was first obtained and then pure benzylamine (VIa) (30% yield) identical (mixed m.p., ir and nmr spectra) with the compound obtained in a).

2-Ethyl-4-phenyl-5-methyl-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (VIIb).

This compound was obtained in a 60% yield by LAH reduction of the *N*-acetyl-3,4-dihydro-4-phenyl-5-methyl-8-acetoxyisocarbostyril (IIIb, diacetyl), after heating under reflux in ether solution for 24 hours. The free base in ether solution gave the corresponding hydrochloride on addition of hydrogen chloride gas, and the corresponding trifluoroacetate on addition of trifluoroacetic acid. Both salts were further purified by recrystallization.

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