Synthesis of 4,5-Dihydro-2,4-benzoxazepin-3(1*H*)ones and 1,3,4,5-Tetrahydro-2,4-benzoxazepines

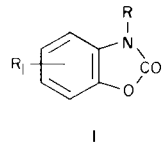
Giorgio Pifferi (1), Luigi Fontanella, Emilio Occelli, and Riccardo Monguzzi (1)

Research Laboratories of Lepetit S.p.A., Milan, Italy

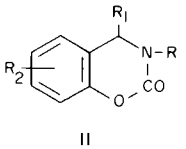
Received August 3, 1972

o-Aminomethylbenzyl alcohols (X) easily cyclize with phosgene in an aqueous alkaline medium to form 4,5-dihydro-2,4-benzoxazepin-3(1*H*)ones (IV) and with aldehydes in acidic conditions to yield 1,3,4,5-tetrahydro-2,4-benzoxazepines (V). The characteristics and chemical behaviour of these new heterocyclic ring systems are reported.

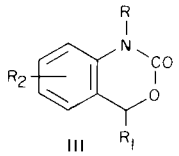
Many five and six membered benzoheterocycles containing the carbamic function -O-CO-NH- are known; it has been reported that substituted benzoxazolin-2-ones I (2), 1,3-benzoxazin-2-ones II (3a,b) and 3,1-benzoxazin-2-ones III (4a,b,c,d) exhibit interesting activity on the central nervous system. Our continuing interest in this area (5a,b,c) led us to synthesize the 4,5-dihydro-2,4-benzoxazepin-3(1*H*)ones (IV) where R_1 = H or Cl, resulting from the expansion of compounds II and III. Because of the novelty of the parent ring it also seemed interesting to prepare the analogs 1,3,4,5-tetrahydro-2,4-benzoxazepines (V).



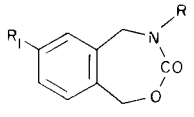
I



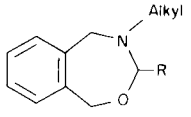
II



III



IV

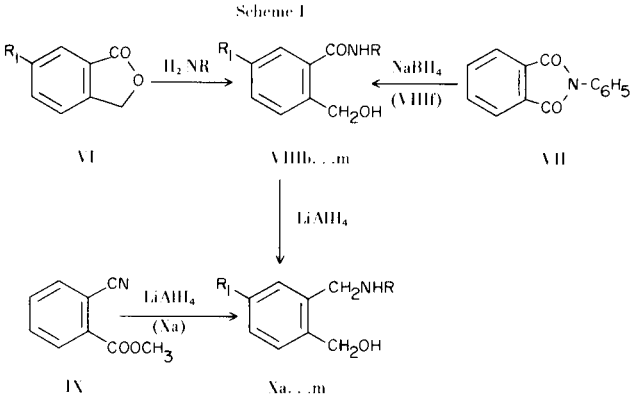


V

Preparative Methods.

Condensation of phthalides VI with primary aliphatic amines dissolved in water or benzene (Scheme I) afforded *N*-substituted *o*-hydroxymethyl benzamides (VIII); the *N*-phenyl derivative (VIIIf) was instead prepared by treating VII with sodium borohydride. Reduction of VIIIb. . .m with lithium aluminum hydride smoothly yielded *o*-aminomethylbenzyl alcohols (Xb. . .m), with the exception of Xa, which was obtained from methyl *o*-cyanobenzoate (IX) (6). The analytical data of these two classes of compounds are shown in Tables I and II.

Scheme I



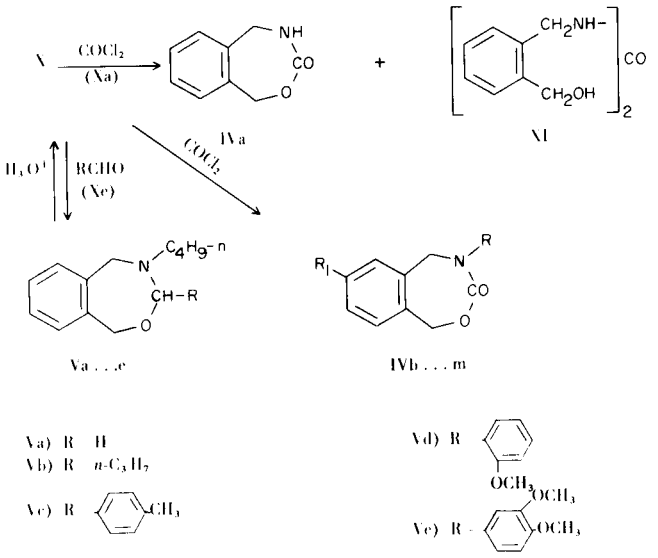
a) R = H; R_1 = H
b) R = CH_3; R_1 = H
c) R = C_2H_5; R_1 = H
d) R = *i*-C_3H_7; R_1 = H
e) R = *n*-C_4H_9; R_1 = H
f) R = C_6H_5; R_1 = H
g) R = $CH_2C_6H_5$; R_1 = H
h) R = C_2H_5; R_1 = Cl
i) R = *n*-C_3H_7; R_1 = Cl
l) R = *n*-C_4H_9; R_1 = Cl
m) R = $CH_2C_6H_5$; R_1 = Cl

When compounds of type X were allowed to react with phosgene in the presence of aqueous potassium hydroxide, the 4,5-dihydro-2,4-benzoxazepin-3(1*H*)ones (IVb. . .m) were obtained in fairly good yields. *o*-Aminomethylbenzyl alcohol (Xa) gave under the same experimental conditions a mixture of IVa and *N*,*N*′-bis-*o*-hydroxymethylbenzyl urea (XI), which were chromatographically separated (Scheme II).

The structural assignment of compounds IV rested on the analytical data (Table III), on compatible ir and nmr spectra and on the chemical behavior of IVa.

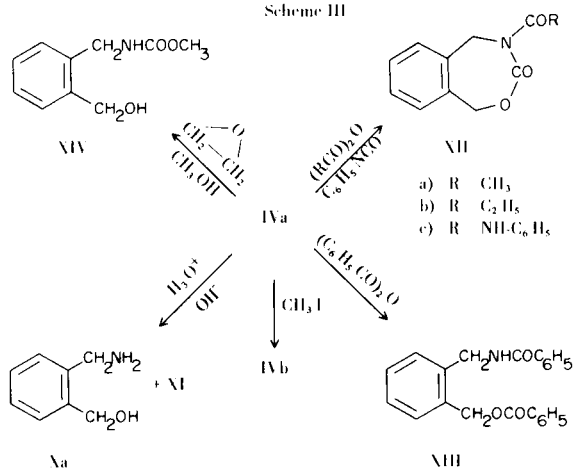
Condensation of *o*-(*n*-butylaminomethyl)benzyl alcohol (Xe) with aliphatic and aromatic aldehydes afforded the 1,3,4,5-tetrahydro-2,4-benzoxazepines (V) reported in Table IV. These compounds, which could be easily distilled or crystallized, are stable in mild aqueous alkaline

Scheme II



solution, but are rapidly decomposed by diluted mineral acids to give the starting amino alcohol.

Scheme III



Chemical Behavior of 4,5-Dihydro-2,4-benzoxazepin-3(1*H*)-one (IVa).

The reactivity and stability in acidic or basic media of IVa was investigated and it was found that the heterocyclic nucleus readily opens in warm dilute alkali to give Xa and XI, while similar treatment in hydrochloric acid affords only Xa. The acylation of IVa was also explored: this compound decomposes on reaction with both aliphatic and aromatic acid chlorides. The corresponding *N*-acyl derivatives (XIIa,b) were instead isolated by heating IVa with aliphatic anhydrides at 135° for five hours; with an aromatic anhydride such as benzoic anhydride only the ring-opened compound XIII was obtained.

Benzoxazepinone IVa reacted normally with phenyl isocyanate to yield the *N*-phenylcarbamoyl derivative (XIIc). Reaction with ethylene oxide in methanol gave methyl *o*-hydroxymethylbenzylcarbamate (XIV): surprisingly, this compound was not obtained by boiling IVa with methanol in absence of ethylene oxide. Methylation of IVa with methyl iodide was achieved with difficulty; as some starting material was still present it was necessary to purify the methylated product IVb by repeated crystallizations from ethyl ether-isopropyl ether.

EXPERIMENTAL

Melting and boiling points are uncorrected. Distillations were performed *in vacuo* using a bulb tube apparatus (7). Infrared spectra were taken on a Perkin-Elmer 137 spectrometer; liquid films or Nujol mulls were used. Nmr spectra were obtained with a Varian A-60 (60 MHz) spectrometer. Chemical shifts are reported as δ parts per million relative to internal TMS (δ = 0.00). In the nmr spectra, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

N-Substituted *o*-Hydroxymethylbenzamides (VIIIb,c,d,e,g).

These compounds were synthesized according to the method already described (8) with a slight modification; the synthesis of VIIIc is given as an example.

o-Hydroxymethyl-*N*-ethylbenzamide (VIIIc).

Phthalide (50 g.) was added to a 50% solution of 67.2 g. of ethylamine in water. The resulting suspension was refluxed for one hour. After cooling, the solid which precipitated was extracted with methylene chloride, dried, and the solvent removed by distillation. The solid residue was crystallized from isopropyl ether to yield 33.2 g. (50% yield) of VIIIc, m.p. 90-91°; ir: 3250 (ν -OH and -NH), 1640 (ν C=O), 1550 (amide II), 1030 (ν C-O), and 730 cm^{-1} (γ C-H arom.).

Compound VIIIe was obtained in the same way in 60% yield as a colorless oil which decomposes on heating; it was purified by dry column chromatography (9) by eluting with chloroform.

o-Hydroxymethyl-*N*-phenylbenzamide (VIIIf).

This compound was prepared by a method already described (10); the yield was greatly improved by using methanol instead of 2-propanol as a solvent, and acetic acid instead of hydrochloric acid to acidify the reaction mixture; m.p. 135-137° (lit. 130-132°(10)).

The chloro compounds VIIIh. . .m were prepared by reaction of 6-chlorophthalide with primary amines in benzene. The synthesis of VIIIh is given as an example.

o-Hydroxymethyl-*N*-ethyl-5-chlorobenzamide (VIIIh).

Ethylamine (40 g.) was bubbled through a suspension of 20 g. of 6-chlorophthalide in 250 ml. of anhydrous benzene; the mixture was stirred at 60° for 4 hours, and then refluxed for 30 minutes. After cooling, the solid was eliminated and the benzene solution was washed with aqueous sodium bicarbonate, dried and evaporated to dryness. The residue was crystallized from ethyl ether to give 21 g. (83%) of VIIIh, m.p. 114°.

N-Substituted-*o*-aminomethylbenzyl Alcohols (Xb. . .m).

The synthesis of Xc is described as an example.

o-*N*-Ethylaminomethylbenzyl Alcohol (Xc).

Compound VIIIc (33 g.) was added cautiously to a suspension

TABLE I

VIII

N.	R	R_1	Formula	M.p. or B.p., °C	Yield %	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
b	CH_3	H	$C_9H_{11}NO_2$	121-123 (8)	95								
c	C_2H_5	H	$C_{10}H_{13}NO_2$	90-91 (a)	50	67.00	7.31	7.81		67.02	7.43	8.00	
d	*i*-C_3H_7	H	$C_{11}H_{15}NO_2$	111-113 (8)	45								
e	*n*-C_4H_9	H	$C_{12}H_{17}NO_2$	decomposes	60	69.53	8.26	6.75		69.35	8.43	6.60	
f	C_6H_5	H	$C_{14}H_{13}NO_2$	130-132 (10)	90								
g	$CH_2C_6H_5$	H	$C_{15}H_{15}NO_2$	131-132 (10)	60								
h	C_2H_5	Cl	$C_{10}H_{12}ClNO_2$	114-115 (b)	83			6.56	16.56			6.55	16.60
i	*n*-C_3H_7	Cl	$C_{11}H_{14}ClNO_2$	79-80 (b)	80			6.15	15.59			5.90	15.31
l	*n*-C_4H_9	Cl	$C_{12}H_{16}ClNO_2$	73-74 (b)	83			5.77	14.66			5.78	14.82
m	$CH_2C_6H_5$	Cl	$C_{15}H_{14}ClNO_2$	158-160 (b)	34			5.08	12.60			5.20	12.43

(a) From isopropyl ether. (b) From ether.

of 54 g. of LAH_4 in 520 ml. of anhydrous tetrahydrofuran. The mixture was then refluxed for 6 hours, cooled to 0°, decomposed with 150 ml. of water and stirred at room temperature for 30 minutes. The solid was collected, washed with THF and the filtrate was evaporated under reduced pressure. The residual oil was dissolved in ether, filtered and made acidic with ethereal hydrogen chloride. The crude hydrochloride was dissolved in ethanol and precipitated by addition of ether to yield 19.9 g. (54%) of Xc, m.p. 135-137°; ir: 3400 (ν O-H), 2800-2300 (ν NH_2^+), 1015 (ν C-O), and 760 cm^{-1} (γ C-H arom.).

The remaining aminoalcohols were synthesized by the same procedure. The reduction of Xf, Xg, and Xd was run in 1,2-dimethoxyethane and diglyme, respectively.

4,5-Dihydro-2,4-benzoxazepin-3(1*H*)one (IVa) and *N*,*N*-Bis-(*o*-hydroxymethylbenzyl) urea (XI).

Compound Xa (5.6 g.) was added with stirring to a mixture of 20.7 g. of potassium hydroxide in 150 ml. of water and 120 ml. of toluene. Phosgene (10.4 g.) in 120 ml. of toluene was then added and the mixture was stirred for 30 minutes. The medium was kept alkaline by occasional additions of 10% aqueous potassium hydroxide. The white crystals were removed by filtration, washed with ether, dried and purified by chromatography on silica gel. The two products were eluted with chloroform containing 2% methanol. The less polar IVa was crystallized from ethanol/isopropyl ether to give 2 g., m.p. 161-162°; ir (nujol): 3250 (ν NH), 1700 and 1675 (ν C=O) [in chloroform solution one band at 1690], 1120 (ν C-O), 743 cm^{-1} (γ C-H arom.); nmr (DMSO-d_6) δ: 4.28 (d, 2H, CH_2N), 5.19 (s, 2H, CH_2O), 7.25-7.85 ppm (m, 5H, arom. H and NH).

The more polar XI was obtained from the same chromatography and was crystallized from methanol/isopropyl ether: 1.8 g., m.p. 184-186°; ir: 3350 and 3150 (ν N-H and -OH), 1640 (ν C=O), 1570 (amide II), 1040 (ν C-O), and 750 cm^{-1} (γ C-H arom); nmr (DMSO-d_6) δ: 4.29 (d, 4H, two CH_2N), 4.58 (d, 4H, two CH_2O), 5.23 (t, 2H, two -OH), 6.60 (t, 2H, two NH), 7.0-7.5 ppm (m, 8H, arom. H).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.84; H, 6.86; N, 9.50.

Compounds IV(b. . .m) were synthesized by a general method; the synthesis of IVc is given as an example.

N-Ethyl-4,5-dihydro-2,4-benzoxazepin-3(1*H*)one (IVc).

To a solution of 20.7 g. of potassium hydroxide in 150 ml. of water was added with stirring 60 ml. of toluene and then 6.4 g. of Xc. Phosgene (10.4 g.) in 70 ml. of toluene was then added and the mixture stirred for 30 minutes. The organic layer was separated and dried over sodium sulfate. Evaporation of the solvent yielded a compound which was purified by chromatography on silica gel and eluted with benzene containing 5% acetone to give 3.5 g. of IVc, b.p. 0.5/140°, which was crystallized from isopropyl ether, 3.0 g., (49%) m.p. 48-49°; ir: 1650 (ν C=O), 1080 (ν C-O), 750 and 730 cm^{-1} (γ C-H arom.); nmr (deuteriochloroform) δ: 1.12 (t, 3H, $CH_3C(H_2)$), 3.46 (q, 2H, $C(H_3)$-CH_2), 4.44 (s, 2H, Ar-CH_2-N), 5.25 (s, 2H, CH_2O), 6.9-7.5 ppm (m, 4H, arom. H).

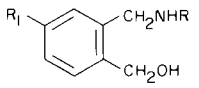
3-Substituted-*N*-butyl-1,3,4,5-tetrahydrobenzoxazepines (Va. . .e).

The synthesis of Va and Vb are described as examples.

N-Butyl-1,3,4,5-tetrahydro-2,4-benzoxazepine (Va).

Eight g. of Xe hydrochloride were added with stirring to 12 ml. of 40% aqueous formaldehyde. The mixture was stirred at room temperature for 4 hours and then made alkaline with aqueous

TABLE II



X

N.	R	R_1	Formula	M.p., °C (a)	Yield %	Calcd. N	Calcd. Cl	Found N	Found Cl
a	H	H	$C_8H_{11}NO\cdot HCl$	177-178	60 (6)				
b	CH_3	H	$C_9H_{13}NO\cdot HCl$	103-104	62	7.46	18.89	7.62	18.59
c	C_2H_5	H	$C_{10}H_{15}NO\cdot HCl$	135-137	54	6.94	17.58	6.80	17.52
d	*i*-C_3H_7	H	$C_{11}H_{17}NO\cdot HCl$	121-122	27	6.49	16.43	6.30	16.20
e	*n*-C_4H_9	H	$C_{12}H_{19}NO\cdot HCl$	98-99	30	6.09	15.43	6.03	15.70
f	C_6H_5	H	$C_{14}H_{15}NO\cdot HCl$	156-157	67	5.61	14.19	5.80	14.33
g	$CH_2C_6H_5$	H	$C_{15}H_{17}NO\cdot HCl$	176-177	56	5.31	13.44	5.17	13.27
h	C_2H_5	Cl	$C_{10}H_{14}ClNO\cdot HCl$	129-130	84	5.93	30.09	6.10	29.94
i	*n*-C_3H_7	Cl	$C_{11}H_{16}ClNO\cdot HCl$	125-127	83	5.60	28.40	5.40	28.43
l	*n*-C_4H_9	Cl	$C_{12}H_{18}ClNO\cdot HCl$	118-120	80	5.30	26.88	5.15	26.95
m	$CH_2C_6H_5$	Cl	$C_{15}H_{16}ClNO\cdot HCl$	178-180	76	4.70	23.81	4.59	23.68

(a) From ethanol/ether.

sodium carbonate and extracted with ethyl ether. Evaporation of the solvent yielded 6.7 g. of product which was purified by chromatography on silica gel with benzene containing 3% acetone as eluent. Evaporation of the solvent and distillation of the residue yielded 4.0 g. of pure Va, b.p. 0.5/100°; ir: 1030 (ν C-O), 735 cm^{-1} (γ C-H arom.); nmr (deuteriochloroform) δ: 0.87 (t, 3H, CH_3-C(H_2)), 1.0-1.6 (m, 4H, C(H_3)-CH_2CH_2), 2.48 (t, 2H, C(H_2)-CH_2-N), 4.18 (s, 2H, Ar-CH_2-N), 4.77 and 4.80 (two s, 4H, Ar-CH_2-O-CH_2), 7.21 ppm (s, 4H, arom. H).

4-*n*-Butyl-3-*n*-propyl-1,3,4,5-tetrahydrobenzoxazepine (Vb).

A solution of 9.4 g. of Xe, 7.2 g. of freshly distilled butyraldehyde and 0.1 g. of *p*-toluenesulfonic acid in 200 ml. of anhydrous toluene was refluxed in a flask equipped with a Marcusson apparatus for 5 hours. After cooling, the toluene was washed with a 5% aqueous sodium bicarbonate solution and dried. The solvent was evaporated and the residue distilled twice under reduced pressure to give 7.5 g. of Vb, b.p. 0.5/120°; ir: 1035 (ν C-O), 735 cm^{-1} (γ C-H arom); nmr (deuteriochloroform) δ: 0.6-1.9 (m, 14H, two CH_3-CH_2-CH_2-), 1.9-2.8 (m, 2H, C(H_2)-CH_2N), 4.08 (s, 2H, Ar-CH_2-N), 4.31 (t, 1H, CH), 4.72 (s, 2H, Ar-CH_2-O), 7.10 ppm (s, 4H, arom. H).

Compound Vb when treated with aqueous mineral acids gave the starting compound Xe.

N-Acetyl-4,5-dihydro-2,4-benzoxazepin-3(1*H*)one (XIIa).

Compound IVa (3.2 g.) was warmed for 5½ hours with 32 g. of acetic anhydride. The mixture was then cooled, filtered and evaporated *in vacuo* to dryness. The residue was recrystallized from 50 ml. of isopropyl ether to yield 2.06 g. (51%) of XIIa, m.p. 105-106°; ir: 1750 and 1690 (ν C=O), 1190 and 1010 (ν C-O), and 745 cm^{-1} (γ C-H arom.); nmr (deuteriochloroform) δ: 2.48 (s, 3H, CH_3), 5.10 (s, 2H, Ar-CH_2N), 5.45 (s, 2H, Ar-CH_2-O), 7.0-7.5 ppm (m, 4H, arom. H).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.35; H, 5.58; N, 6.90.

N-Propionyl-4,5-dihydro-2,4-benzoxazepin-3(1*H*)one (XIIb).

This compound was obtained using the same procedure as for XIIa, yield 55%, m.p. 78-79° (isopropyl ether).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.53; H, 6.16; N, 6.48.

N-Phenylcarbamoyl-4,5-dihydro-2,4-benzoxazepin-3(1*H*)one (XIIc).

Two g. of IVa and 1.46 g. of phenylisocyanate were warmed in boiling toluene for 5 hours. After distilling the solvent, the residue was recrystallized from isopropyl ether to give 2.62 g. (74%) of XIIc, m.p. 135-136°; ir (chloroform): 3300 (ν N-H), 1730 and 1710 (ν C=O), 1550 (amide II) and 1180 cm^{-1} (ν C-O); nmr (deuteriochloroform) δ: 5.24 (s, 2H, Ar-CH_2N), 5.55 (s, 2H, Ar-CH_2-O), 6.95-7.75 (m, 9H, arom. H), 10.7 ppm (s [large], 1H, NH).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.11; H, 5.17; N, 9.75.

Methyl *o*-Hydroxymethylbenzyl Carbamate (XIV).

A solution of 0.875 g. of IVa in 3 ml. of methanol was added to a solution of 0.8 g. of ethylene oxide in 7 ml. of methanol. The mixture was stirred for 3 hours and allowed to stand overnight at room temperature. The methanol was removed under reduced pressure and the residue was recrystallized from ethyl ether to yield 0.65 g. of XIV, m.p. 70-71°; ir: 3430 and 3330 (ν O-H and N-H), 1710 (ν C=O), 1290 and 1040 (ν C-O), and 750 cm^{-1} (γ C-H arom.); nmr (deuteriochloroform) δ: 3.07 (s [large], 1H, OH), 3.68 (s, 3H, CH_3), 4.45 (d, 2H, Ar-CH_2-N), 4.74 (s, 2H, Ar-CH_2-O), 5.4-5.9 (m, 1H, NH), 7.38 ppm (s, 4H, arom. H).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.17. Found: C, 61.54; H, 6.90; N, 7.13.

N-Methyl-4,5-dihydro-2,4-benzoxazepin-3(1*H*)one (IVb) from IVa.

Compound IVa (1.6 g.) was added to a solution of sodamide

TABLE III

IV

N.	R	R_1	Formula	B.p. or M.p., °C	Yield %	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl	Column SiO_2 Eluent
a	H	H	$C_9H_9NO_2$	161-163 (a)	38	66.24	5.56	8.58		66.05	5.68	8.66		$CHCl_3/CH_3OH$ 98/2
b	CH_3	H	$C_{10}H_{11}NO_2$	120-121 (b)	53	67.78	6.26	7.91		67.70	6.06	8.00		$CHCl_3/CH_3OH$ 98/2
c	C_2H_5	H	$C_{11}H_{13}NO_2$	48-49 (a)	49	69.09	6.85	7.33		68.95	7.05	7.20		benz./acetone 95/5
d	*i*-C_3H_7	H	$C_{12}H_{15}NO_2$	72-73 (a)	17	70.22	7.37	6.82		69.96	7.50	6.90		benz./eth. ether 95/5
e	*n*-C_4H_9	H	$C_{13}H_{17}NO_2$	145-150/0.5	46	71.20	7.82	6.39		71.00	7.79	6.40		benz./eth. ether 95/5
f	C_6H_5	H	$C_{15}H_{13}NO_2$	113-115 (c)	7	75.30	5.48	5.85		75.50	5.60	5.70		benz./acetone 97/3
g	$CH_2C_6H_5$	H	$C_{16}H_{15}NO_2$	70-72 (a)	48	75.87	5.97	5.53		75.75	5.81	5.41		benz./acetone 98/2
h	C_2H_5	Cl	$C_{11}H_{12}ClNO_2$	65-66 (d)	62			6.21	15.73			6.23	15.71	benz./acetone 98/2
i	*n*-C_3H_7	Cl	$C_{12}H_{14}ClNO_2$	60 (d)	54			5.84	14.81			5.65	14.64	benz./acetone 98/2
l	*n*-C_4H_9	Cl	$C_{13}H_{16}ClNO_2$	42-43 (d)	40			5.52	13.98			5.60	14.05	benz./acetone 98/2
m	$CH_2C_6H_5$	Cl	$C_{16}H_{14}ClNO_2$	79-80 (e)	40			4.87	12.34			5.00	12.48	benz./acetone 98/2

(a) From isopropyl ether. (b) From ether/isopropyl ether. (c) From ethanol/isopropyl ether. (d) From ether/petroleum ether. (e) From ether.

prepared from 0.25 g. of sodium in 150 ml. of liquid ammonia. The mixture was stirred for 10 minutes and then 1.7 ml. of methyl iodide in 10 ml. of ethyl ether was added. The ammonia was evaporated, 150 ml. of ethyl ether was added and the mixture was refluxed for 2 hours. The ethereal solution was washed with water, dried, and the solvent distilled. The residue was repeatedly recrystallized from ethyl ether/isopropyl ether to yield 0.25 g. of IVb, m.p. 120-121°. The mixed melting point with a sample of IVb obtained from Xb was not depressed.

o-Benzamidomethylbenzyl Benzoate (XIII) from IVa with Benzoic Anhydride.

A mixture of 0.2 g. of IVa in 2 ml. of benzoic anhydride was heated at 140° with occasional stirring for 5 hours. The benzoic anhydride was distilled *in vacuo* and the residue was recrystallized twice from benzene to give 0.1 g. of XIII, m.p. 141-142°; ir: 3260 (ν N-H), 1710 and 1630 (ν C=O), 1530 (amide II), 1270 and 1100 (ν C-O), 775, 750 and 720 cm^{-1} (γ C-H arom.); nmr (deuteriochloroform) δ: 4.77 (d, 2H, Ar-CH_2-N), 5.49 (s, 2H, Ar-CH_2-O), 7.0-8.2 ppm (m, 15H, arom. H and N-H).

Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.51; H, 5.64; N, 3.93.

Stability of IVa with Alkali and Acids.

Compound IVa (0.2 g.) was boiled for 2 hours with 5 ml. of 10% aqueous sodium hydroxide. After cooling to 0°, the mixture was filtered to give 0.05 g. of XI as fine crystals, m.p. 188-190°. The alkaline solution was extracted with ethyl ether which was in turn washed with a saturated solution of sodium chloride and dried over sodium sulfate. The ethereal solution was made slightly acidic with ethereal hydrochloric acid and filtered, yielding 0.1 g. of Xa, m.p. 178-179°.

When IVa (0.2 g.) was boiled with a 10% aqueous solution of hydrochloric acid, 0.1 g. of Xa, m.p. 178-180° was obtained.

Acknowledgements.

The authors are grateful to Mr. G. Tuan and Dr. B. Gioia for the ir and nmr spectra, and to Mr. S. Vecchi and A. Campi for the thin layer chromatography and elemental analyses.

REFERENCES

(1) Present address: Research Laboratories I.S.F. - Italseber, Milan, Italy.

(2) J. Sam, C. W. Richmond, and J. L. Valentine, *J. Med. Chem.*, **10**, 408 (1967).

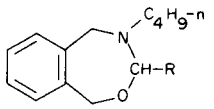
(3a) Farmitalia Patent, Netherlands Patent, 6,807,248 (1968); Farmdoc 34,921; (b) Farmitalia Patent, Netherlands Patent, 6,810,362 (1968); Farmdoc 35,992.

(4a) E. Testa, L. Fontanella, *Farmaco, Ed. Sci.*, **21**, 549 (1966); (b) F. G. Petracek, U.S. Patent, 3,280,120 (1966), *Chem. Abstr.*, **66**, 10944g (1967); (c) L. Bernardi, S. Coda, L. Pegrassi, K. Suchowsky, Belgian Patent, 704,583 (1968), Farmdoc 31,898; (d) Farmitalia Patent, Netherlands Patent, 6,710,332 (1968); Farmdoc 30,666.

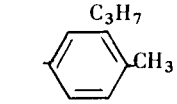
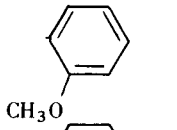
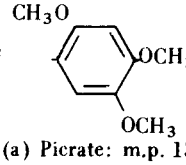
(5a) E. Testa, L. Fontanella, M. Bovara, *Farmaco, Ed. Sci.*, **18**, 815 (1963); (b) E. Testa, L. Fontanella, *ibid.*, **20**, 323 (1965); (c) G. Pifferi, E. Testa, Convegno del CNR sulla Chimica del farmaco e dei prodotti biologicamente attivi, Roma 30-31 Gennaio 1967.

(6) G. Pifferi, E. Testa, and P. Consonni, *Gazz. Chim. Ital.*,

TABLE IV



V

N	R	Formula	B.p. or M.p., °C	Yield %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	H	$C_{13}H_{19}NO$	100/0.5 mm. (a)	47	76.05	9.33	6.82	75.75	9.41	6.72
b		$C_{16}H_{25}NO$	120/0.5 mm.	62.5	77.68	10.19	5.66	77.80	10.38	5.46
c		$C_{20}H_{25}NO$	150/0.5 mm.	81.5	81.31	8.53	4.74	81.19	8.62	4.66
d		$C_{20}H_{25}NO_2$	160/0.5 mm.	61	77.13	8.09	4.50	77.06	8.21	4.34
e		$C_{21}H_{27}NO_3$	110-112 (b)	54	73.84	7.99	4.10	73.78	8.18	4.21

(a) Picrate: m.p. 138-140° (from ethanol), Calcd.: C, 52.53; H, 5.1; N, 12.89. Found: C, 52.63; H, 5.03; N, 12.85. (b) From ethyl ether/light petroleum.

96, 1671 (1966).

(7) G. Pifferi, A. De Ros, and M. Borbonese, *Farmaco, Ed. Prat.*, **22**, 210 (1967).

(8) W. Theilacker and H. Kalenda, *Ann. Chem.*, **584**, 87 (1954).

(9) B. Loew and M. M. Goodmann, *Chem. Ind.* (London), 2026 (1967).

(10) F. C. Uhle, *J. Org. Chem.*, **26**, 2998 (1961).