The synthesis of 1,3,4,5-Tetrahydro-2,3-benzoxazepines and 1,2,4,5-Tetrahydro-3,2-benzoxazepines

G. Pifferi (1), P. Consonni, R. Monguzzi (1), and A. Omodei-Salè

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

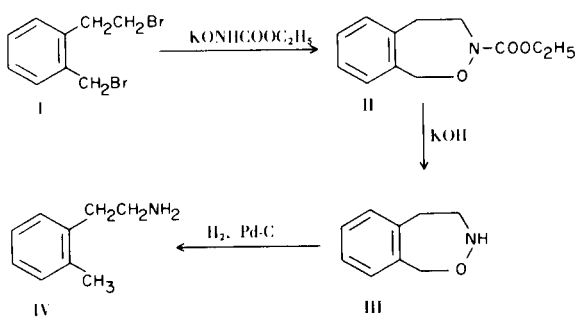
Received May 27, 1971

Condensation of *o*-bromomethylphenethyl bromide with potassium salt of *N*-hydroxyurethan afforded 3-carbethoxy-1,3,4,5-tetrahydro-2,3-benzoxazepine, which was hydrolyzed to 1,3,4,5-tetrahydro-2,3-benxoxazepine (III). The reaction of *o*-acetoxymethylphenethyl bromide (VIb) with potassium salt of *N*-hydroxyurethan in DMF, gave a complex mixture, from which *O*-[2-(*o*-acetoxymethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIIa) was separated. Subsequent desacetylation to VIIb and halogenation yielded *O*-[2-(*o*-bromomethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIIc). By treatment of VIIc with potassium hydroxide, 2-carbethoxy-1,2,4,5-tetrahydro-3,2-benzoxazepine (X) was obtained together with small amounts of 6,15-dicarbethoxy-5,6,8,9,14,15,17,18-octahydrodibenzo[*d,l*]-1,8-dioxa-2,9-diazacyclotetradecine (XI). Hydrolysis of X with potassium hydroxide gave 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII). *N*-Alkyl and *N*-acyl derivatives of III and XII were also prepared.

The discovery of a CNS depressant activity in many members of 3,4-dihydro-1*H*-2,3-benzoxazines (2) and our interest in the cyclic seven-membered hydroxylamine derivatives (3) prompted us to synthesize for biological evaluation new compounds, resulting from expansion of the 2,3-benxoxazine ring by a methylene group. We wish now to describe two synthetic routes to the unknown 1,3,4,5-tetrahydro-2,3- (III) and 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII). In this field only two 5-substituted 1,3,4,5-tetrahydro-2,3-benzoxazepine-1,4-diones (4,5), prepared by melting *o*-carboxybenzylmethyl (or phenyl) ketoximes, have been reported up to 1900, but the assigned structure has not been adequately demonstrated (6).

In accordance with a procedure which proved useful for the synthesis of the analogous benzoxazines (7a-c), *o*-bromomethylphenethyl bromide (I) (8) and the potassium salt of *N*-hydroxyurethan were condensed to the 3-carbethoxy derivative II, as shown in Scheme I.

SCHEME I

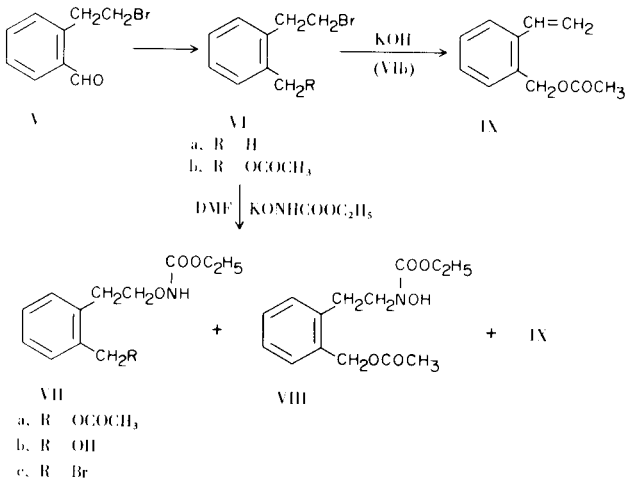


The benzylic bromine atom in I is the most reactive center and the isomer X was not detected among the condensation products. Compound II was then hydrolyzed to the free base III (pK_a 3.5 in MCS/water 4/1) by heating in an alcoholic potassium hydroxide solution or, in poorer yields, by refluxing in aqueous hydrochloric acid. The structure of the 1,3,4,5-tetrahydro-2,3-benzoxazepine (III) was assigned on the basis of ir and nmr spectra and of the results of catalytic hydrogenolysis which gave exclusively *o*-methylphenethylamine (IV) (9a,b).

A number of 3-alkyl (IIIa-g) and 3-acyl derivatives (IIIh-k) were synthesized (see Table I) for pharmacological screening. Most of them were obtained from III by conventional methods, already employed in the 2,3-benzoxazine series. Thus, methylation of III was accomplished (2) by the Eschweiler-Clarke reaction, while IIIc, IIIf and IIIg were obtained directly from III and the suitable alkyl bromide in the presence of solid sodium carbonate (10). The carbamoyl derivatives IIId and IIIe were synthesized through the β-hydroxyethyl intermediate IIIb, which was prepared by heating III with ethylene oxide in methanol according to a described procedure (7a,b). The synthesis of 3-acyl derivatives IIIi and IIIk was carried out by condensing III with the appropriate acyl chloride and triethylamine. Finally, the base III reacted easily (2,7a) with isocyanic acid and with phenyl isocyanate to give IIIh and IIIj, respectively.

In order to synthesize the isomeric compound XII, we followed the somewhat longer procedure given in Scheme

SCHEME II

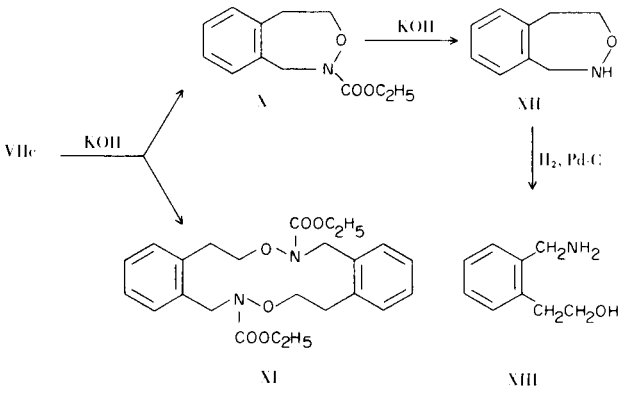


II and III. *o*-(2-Bromoethyl)benzaldehyde (V) (II) was hydrogenated at room temperature and atmospheric pressure with platinum as catalyst. The resulting alcohol VIa was then converted in good yields into the acetate VIb by warming at 100° with an excess of acetic anhydride. Condensation of VIb with the potassium salt of *N*-hydroxyurethan in dimethylformamide gave a mixture of *O*-[2-(*o*-acetoxymethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIIa), *N*-[2-(*o*-acetoxymethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIII) and the vinyl derivative IX. The last compound was separated and identified in the lower boiling fraction (see Method I) and purified by subsequent column chromatography. The formation of IX clearly derives by elimination of hydrogen bromide from VIb operated by the basic potassium salt of *N*-hydroxyurethan. This elimination was best accomplished by heating VIb in dimethylformamide at higher temperature and in the presence of a stronger base as potassium hydroxide.

The higher boiling fraction was shown, by vapor phase chromatography, to consist mainly of two isomeric materials which were isolated in a pure state by column chromatography. There are significant differences between the ir and nmr spectra of the two isomers VIIa and VIII. In particular the ir spectrum of VIIa shows a sharp band for N-H bonding at 3300 cm^{-1}, whereas VIII has a broad O-H absorption in the same region. Moreover, in the nmr of VIIa, the $C(H_2)$-CH_2-O proton triplet appears at a lower field (5.88 τ) than the $C(H_2)$-CH_2-N triplet of VIII (6.20 τ), thus substantiating the structure assignment. The formation of the two isomers VIIa and VIII can be rationalized assuming that the bromo derivative VIb can simultaneously react with either the reactive sites of the *N*-hydroxyurethan.

In order to prepare bulkier amount of VIIb, which is the key-product for the synthesis of XII, we took advantage of the reaction conditions of Method 2 (lower temperature and increased reaction time) which lead to improved yields in VIIa. Moreover, after IX was eliminated by distillation, the crude residue, containing VIIa and smaller quantities of VIII, was directly desacetylated with aqueous alcoholic sodium hydroxide and VIIb was separated from its >N-OH isomer derived from VIII.

SCHEME III



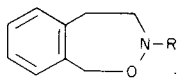
Compound VIIb was readily halogenated by dry hydrogen bromide to VIIc which, on treatment with a strong base as potassium hydroxide, effected ring closure to the corresponding 2-carbethoxy-1,2,4,5-tetrahydro-3,2-benzoxazepine (X) (Scheme III). From the residue of the distillation of X, a solid material was isolated in small amounts which showed ir and nmr absorptions similar to those of X and the same elemental analysis. The possibility that VIIc could condense bimolecularly to give XI was considered on the basis of preceding experiences on the cyclization of 2,3-benzoxazines (7a,12) and on the fact that increasing dilutions resulted in considerably lower yields. The mass spectrum, exhibiting the molecular peak with m/e = 442, clearly indicates the formation of the dibenzodioxadiazacyclotetradecine XI.

Compound X was readily hydrolyzed with potassium hydroxide at reflux temperature to 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII), a white crystalline base (pK_a = 3.2 in MCS/water, 4/1), which represents the benzylamine isomer of III. The structure XII was assigned on the basis of analytical and spectroscopic data and on the obtention of the expected *o*-aminomethylphenethyl alcohol (XIII) by catalytic hydrogenolysis of its hydrochloride.

A series of *N*-alkyl- and *N*-acyl derivatives were prepared by conventional methods from XII, employed as starting material (Table II). Since reactivity of the 3,2-benzoxazepine series was found to be parallel to that of the 2,3-benzoxazepine and 2,3-benzoxazine series, only some representative examples are reported in the experimental part. It is worth noting that the Mannich reaction

TABLE I

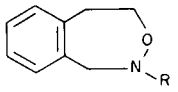
1,3,4,5-Tetrahydro-2,3-benzoxazepines (III)

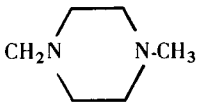
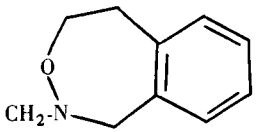


No.	R	B.p. °C/mmHg or M.p. °C (solvents)	Yield %	Formula	Analyses C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found
IIIa	CH_3	65/0.1	76	$C_{10}H_{13}NO$	73.58	73.49	8.03	8.18	8.58	8.69
IIIb	CH_2CH_2OH	115/0.1	98	$C_{11}H_{15}NO_2$	68.36	68.46	7.82	7.93	7.25	7.40
IIIc	CH_2-CH=CH_2	90/0.1	53	$C_{12}H_{15}NO$	76.15	76.20	7.99	8.15	7.40	7.50
IIId	$CH_2CH_2OCONH_2$	129-130 (EtOH-H_2O)	39	$C_{12}H_{16}N_2O_3$	61.00	60.82	6.83	7.03	11.86	11.68
IIIe	$CH_2CH_2OCSNHCH_3$	134-135 (i-Pr_2O)	8	$C_{13}H_{18}N_2O_2S$	58.62	59.02	6.81	6.75	10.52	11.00
IIIf	$CH_2CH(CH_3)_2$	90/0.1	43	$C_{13}H_{19}NO$	76.04	75.77	9.33	9.47	6.82	6.80
IIIg	$CH_2CH_2N(C_2H_5)_2$	140/0.1	27	$C_{15}H_{24}N_2O$	72.54	72.36	9.74	9.81	11.28	11.13
IIIh	$CONH_2$	159-160 (EtOH)	59	$C_{10}H_{12}N_2O_2$	62.48	62.43	6.29	6.29	14.57	14.68
IIIi	COC_2H_5	54-55 (Hexane)	84	$C_{12}H_{15}NO_2$	70.21	70.50	7.36	7.42	6.82	7.00
IIIj	$CONHC_6H_5$	114-115 (EtOH)	71	$C_{16}H_{16}N_2O_2$	71.61	71.67	6.01	6.08	10.44	10.60
IIIk	$COC_6H_2(OCH_3)_3$-3,4,5	131-132 (EtOH-H_2O)	88	$C_{19}H_{21}NO_5$	66.46	65.93	6.16	6.28	4.08	3.88

TABLE II

1,2,4,5-Tetrahydro-3,2-benzoxazepines (XII)



No.	R	B.p. °C/mmHg or M.p. °C (solvents)	Yield %	Formula	Analyses C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found
XIIa	CH_3	50/0.1	56	$C_{10}H_{13}NO$	73.58	73.14	8.03	8.31	8.58	8.22
XIIb	$C(=NH)NH_2$	197-198 (EtOH)	78	$C_{10}H_{13}N_3O \cdot H_2SO_4$	41.52	40.97	5.23	6.00	14.52	13.83
XIIc	CH_2CH_2OH	120/0.1	90	$C_{11}H_{15}NO_2$	68.37	67.73	7.82	8.01	7.25	7.32
XIId	$CH_2CH_2OCONH_2$	110-111 (i-Pr_2O)	52	$C_{12}H_{16}N_2O_3$	61.00	60.74	6.83	6.93	11.86	11.66
XIIe		130/0.1	48	$C_{15}H_{23}N_3O$	68.93	68.09	8.87	9.29	16.08	16.04
XIIf		114-115 (EtOH-H_2O)	77	$C_{19}H_{22}N_2O_2$	73.52	73.15	7.14	7.54	9.03	9.15
XIIg	$CONH_2$	171-172 (EtOH-H_2O)	59	$C_{10}H_{12}N_2O_2$	62.48	62.20	6.29	6.40	14.58	14.56
XIIh	COC_6H_4Cl-p	132-133 (EtOH-H_2O)	88	$C_{16}H_{14}ClNO_2$	66.80	66.93	4.90	4.78	4.87	4.67

with formaldehyde and *N*-methylpiperazine gave high yields of XIIe only when XII was allowed to react at 0° and in dilute conditions. Experiments at higher temperature and concentration afforded a mixture of XIIe with 2,2′-methylene-bis-(1,2,4,5-tetrahydro-3,2-benzoxazepine) (XIIf) and 4,4′-methylene-bis-(1-methylpiperazine). Compound XIIf was also obtained by treating XII with 38% formaldehyde in ethanol solution.

EXPERIMENTAL (13)

Synthesis of 1,3,4,5-Tetrahydro-2,3-benzoxazepine (III).

3-Carbethoxy-1,3,4,5-tetrahydro-2,3-benzoxazepine (II).

A suspension of 210 g. (0.75 mole) of *o*-bromomethylphenethyl bromide (I) (8) in 1360 ml. of anhydrous ethanol was treated with 182 g. of 60% *N*-hydroxyurethan potassium salt (0.75 mole). After stirring at room temperature for two hours until the *p*H became neutral, a solution of 50 g. of potassium hydroxide 85% (0.75 mole) in 680 ml. of ethanol was added and the mixture was heated under reflux for 1½ hours. The potassium bromide was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was taken up in ether (2 l.), washed with 5% aqueous sodium hydroxide and water and dried (sodium sulfate). The solvent was evaporated and the residue was distilled to yield 131 g. (79%) of II, b.p. 146-150°/1 mm. Examined by tlc the product showed 1 spot with Rf = 0.5 (benzene-acetone 8:2); ir: 1720 (C=O), 1260 and 1100 (C-O), 760 cm^{-1} (γ aromatic CH); nmr (carbon tetrachloride): 8.75 (t, 3H, CH_3-C(H_2)), 7.03 (t, 2H, CH_2-C(H_2)-N), 6.25 (t, 2H, C(H_2)-CH_2-N), 5.91 (q, 2H, CH_2-C(H_3)), 5.03 (s, 2H, CH_2-O), 3.2-2.75 τ (m, 4H, aromatic hydrogens).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.88; H, 6.94; N, 6.33.

1,3,4,5-Tetrahydro-2,3-benzoxazepine (III).

To 100 g. (0.45 mole) of 3-carbethoxy-1,3,4,5-tetrahydro-2,3-benzoxazepine (II) in 600 ml. of ethanol, a solution of 32.8 g. of potassium hydroxide in 60 ml. of water was added. A precipitate separated instantaneously which disappeared on heating at reflux temperature for 30 minutes. The solution was concentrated *in vacuo* and the residue, dissolved in 1 l. of ether, was washed with water and dried. The solution was made acidic by adding an ether solution of hydrogen chloride and the crude precipitate of *III hydrochloride* was collected: 66.3 g., m.p. 173-176°. An analytical sample, recrystallized from ethanol, melted at 186-188°; ir: 2800-2200 (NH_2^+), 1020 (C-O) and 765 cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_9H_{11}NO$·HCl: C, 58.22; H, 6.51; N, 7.55; Cl, 19.10. Found: C, 57.92; H, 6.70; N, 7.40; Cl, 18.75.

The corresponding *free base* was obtained by treating a cold solution of the crude hydrochloride (66 g.) with aqueous sodium carbonate. The base was extracted thoroughly with ether and the extracts, washed with water, were dried and evaporated. The oil residue was distilled to give 49.9 g. (74%) of III, b.p. 90° (0.4 mm.); ir: 3350 (NH), 1060 (C-O) and 765 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 6.90 (s, 4H, CH_2-CH_2-), 5.12 (s, 2H, CH_2-O), 4.14 (s, 1H, NH), 3.15-2.75 τ (m, 4H, aromatic hydrogens).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.40; N, 9.54.

Hydrogenolysis of III. *o*-Methylphenethylamine (IV) Hydrochloride.

A solution of III (1 g.) in 40 ml. of ethanol, containing 2.5 ml. of 10% hydrochloric acid, was hydrogenated with 0.5 g. of 10% Pd on charcoal at room temperature and atmospheric pressure for three hours. The catalyst was then removed by suction and the solvent was evaporated under reduced pressure. The residue was triturated with ether, collected and recrystallized from isopropyl alcohol, to yield 0.4 g. of white crystals, m.p. 223-225°, identified as IV hydrochloride (9a).

Picrate: m.p. 180-182° (from ethanol), lit m.p. for IV picrate: 175-177° (9b).

Preparation of 3-Alkyl (IIIa-g) and 3-Acyl-1,3,4,5-tetrahydro-2,3-benzoxazepines (IIIh-k).

Only a limited number of typical experiments are reported here. The remaining compounds were synthesized according to procedures which proved useful for preparing the analogues 3-substituted 3,4-dihydro-1*H*-2,3-benzoxazines (2,7a-c).

3-Isobutyl-1,3,4,5-tetrahydro-2,3-benzoxazepine (IIIf).

A mixture of 1 g. (6.7 mmoles) of 1,3,4,5-tetrahydro-2,3-benzoxazepine (III), 1.15 g. (10.9 mmoles) of anhydrous sodium carbonate and 1 g. (7.3 mmoles) of isobutyl bromide were heated for 3 hours while the temperature of the oil bath was gradually raised from 70° to 140° until the carbon dioxide evolution ceased. After cooling at room temperature, ether was added to the mixture and the inorganic salts were removed by filtration. The ether solution was washed with dilute hydrochloric acid, with water and then dried over anhydrous sodium sulfate. The filtrate was concentrated and the residue distilled to yield 0.6 g. (43%) of IIIf, b.p. 90°/0.1 mm.; ir: 1380 and 1365 (C-H isopropyl-group), 1040 (C-O), 760 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 9.07 (d, 6H, CH_3-C(H)), 8.4-7.8 (m, 1H, C(H_3)-CH-C(H_3)), 7.59 (d, 2H, CH_2-C(H)), 7.35-6.85 (m, 4H, CH_2-CH_2), 5.17 (s, 2H, CH_2-O), 3.2-2.9 τ (m, 4H, aromatic hydrogens).

3-[2-(*N*-Methylthiocarbamoyloxy)ethyl]-1,3,4,5-tetrahydro-2,3-benzoxazepine (IIIe).

To a solution of 0.5 g. (2.6 mmoles) of 3-(2-hydroxyethyl)-1,3,4,5-tetrahydro-2,3-benzoxazepine (IIIb) in 10 ml. of anhydrous benzene containing two drops of pyridine, a solution of 0.21 g. (2.85 mmoles) of methylisothiocyanate in 5 ml. of anhydrous benzene was added. After refluxing for 12 hours, the solvent was removed *in vacuo* and the residue was taken up with cold isopropyl ether. The solid was collected and recrystallized from isopropyl ether to give 56 mg. (8%) of IIIe, m.p. 134-135°; ir: 3400 (N-H), 1530 (amide II), 1340 (C=S), 1040 and 980 (C-O), 760 cm^{-1} (γ aromatic CH).

3-(3,4,5-Trimethoxybenzoyl)-1,3,4,5-tetrahydro-2,3-benzoxazepine (IIIk).

To a solution of 2 g. (13.4 mmoles) of 1,3,4,5-tetrahydro-2,3-benzoxazepine (III) and anhydrous triethylamine (1.63 g., 16.3 mmoles) in 60 ml. of methylene chloride, a solution of 3,4,5-trimethoxybenzoyl chloride (3.09 g., 13.4 mmoles) in 50 ml. of methylene chloride was added with stirring in 5 minutes. Stirring was continued for 2 hours at room temperature, then the mixture, washed with dilute hydrochloric acid, dilute sodium bicarbonate, and with water, was dried over anhydrous sodium sulfate and concentrated. The residue was crystallized from 80% ethanol to give 4.06 g. (88%) of IIIk, m.p. 131-132°; ir: 1680 (C=O), 1130 and 1000 (C-O), 855, 838 and 760 cm^{-1} (γ aromatic CH).

Synthesis of 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII).

o-Hydroxymethylphenethyl bromide (VIa).

A solution of 66 g. of *o*-(2-bromoethyl)benzaldehyde (V) (11) in 1.2 l. of ethanol and 310 ml. of water was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 7 g. of platinum oxide and of some crystals of ferrous sulfate heptahydrate. The uptake of 1 molar equivalent of hydrogen was complete in about two hours. The mixture was then filtered on charcoal and the ethanol was evaporated. The residue was taken up in water and the aqueous layer twice extracted with ether. The combined extracts were dried over sodium sulfate and concentrated. The residue was suspended in 200 ml. of hexane-isopropyl ether (1:1.5) and cooled to afford 52.5 g. (78.8%) of VIa, m.p. 61-62°. An analytical sample, recrystallized from the same solvent, melted at 62-63°; ir: 3300 (O-H), 1220 and 1050 (C-O), 750 cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_9H_{11}BrO$: C, 50.25; H, 5.15; Br, 37.15. Found: C, 50.58; H, 5.25; Br, 37.39.

o-Acetoxymethylphenethyl Bromide (VIb).

A solution of 150 g. of *o*-hydroxymethylphenethyl bromide (VIa) in 420 ml. of acetic anhydride was heated on a steam bath for two hours. After concentrating, the residue was dissolved in 50 ml. of ethanol and evaporated to dryness. The oily residue was distilled in bulb, to give 174 g. (97%) of VIb, b.p. 140°/1.5 mm. An analytical sample was redistilled at 110°/0.2 mm.; ir: 1750 (C=O), 1230 and 1025 (C-O), 760 cm^{-1} (γ aromatic CH); nmr (carbon tetrachloride): 8.03 (s, 3H, CH_3), 7.05-6.25 (m, 4H, CH_2-CH_2), 4.93 (s, 2H, CH_2-O), 2.95-2.50 τ (m, 4H, aromatic hydrogens).

Anal. Calcd. for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10; Br, 31.08. Found: C, 51.44; H, 5.20; Br, 31.40.

Condensation of VIb with the potassium salt of *N*-Hydroxyurethan. Method 1.

Separation of *O*-[2-(*o*-Acetoxymethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIIa) from *N*-[2-(*o*-Acetoxymethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIII).

To a mixture of 21 g. (0.091 mole, potassium 16.6%) of crude potassium *N*-hydroxyurethan and 10.15 g. (0.077 mole) of *N*-hydroxyurethan 80% in 320 ml. of dimethylformamide, a solution of 20 g. (0.077 mole) of *o*-acetoxymethylphenethyl bromide (VIb) in 80 ml. of dimethylformamide was added dropwise at 50°. After stirring for 30 minutes at 50° and one hour at 75°, the solvent was evaporated *in vacuo* (external bath temperature $\leqslant$ 70°) and the residue was taken up with ether. After washing with 5% sodium hydroxide and with water until neutral, the organic phase was dried over anhydrous sodium sulfate and concentrated. The oily residue (19.5 g.) was distilled and two fractions were separated.

The first fraction (9.6 g.) was collected at 80-100°/0.5 mm. and, according to spectral data and cvp chromatography, it contained mainly the *o*-vinylbenzyl alcohol acetate (IX) and a small amount of *N*-hydroxyurethan. The purification was carried out by column chromatography as described below (method 2).

The second fraction was distilled at 170-180°/0.5 mm. and weighed 7.45 g. Vapor phase chromatography showed it to contain the compounds VIIa, VIII and other impurities in the approximate ratio 4:3:3.

Two g. of this mixture were chromatographed according to a new technique (15) on 60 g. of disactivated silica gel (10% water) contained in a nylon column (column size 20 in. x 1 in.), using a mixture of benzene-ether 9:1 as eluent.

The first eluted isomer (Rf $\sim$ 0.50) was distilled in bulb to give 0.53 g. of VIIa, b.p. 170°/0.1 mm.; ir: 3300 (N-H), 1740 (C=O), 1240 and 1030 (C-O), 755 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.73 (t, 3H, CH_3-$C(H_2)$), 7.92 (s, 3H, CH_3-CO-), 6.96 (t, 2H, Ar-CH_2-$C(H_2)$), 5.88 (t, 2H, $C(H_2)$-CH_2-O), 5.78 (q, 2H, -CH_2-$C(H_3)$), 4.81 (s, 2H, Ar-CH_2-O), 2.59 (s, 4H, aromatic hydrogens), 2.05 τ (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.28; H, 6.99; N, 5.10.

The second isomer (Rf $\sim$ 0.30) was distilled in bulb yielding 0.30 g. of VIII, b.p. 170°/0.1 mm.; ir: 3300 (OH), 1740 and 1700 (C=O), 1240 and 1030 (C-O), 755 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.83 (t, 3H, CH_3-$C(H_2)$), 7.90 (s, 3H, CH_3-CO-), 6.95 (t, 2H, Ar-CH_2-$C(H_2)$), 6.20 (t, 2H, -$C(H_2)$-CH_2N<), 5.90 (q, 2H, CH_2-$C(H_3)$), 4.78 (s, 2H, Ar-CH_2-O), 3.2-2.4 τ (m, 5H, aromatic hydrogens and OH).

Anal. Calcd. for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.63; H, 7.04; N, 4.79.

Method 2. Separation of *o*-Vinylbenzyl Alcohol Acetate (IX).

A mixture of 75.2 g. of crude potassium *N*-hydroxyurethan (0.33 mole, K = 17.08%) and 35.45 g. of *N*-hydroxyurethan (80% purity, 0.27 mole) in 280 ml. of DMF was stirred at room temperature for 10 minutes. A solution of 70 g. (0.27 mole) of *o*-acetoxymethylphenethyl bromide (VIb) in 58 ml. of DMF was then added dropwise in 15 minutes. Stirring was continued for 2½ hours and for 1 hour at 75° (final *p*H = 7). The solvent was evaporated *in vacuo* (bath temperature $\leqslant$ 70°) and the residue was taken up with 3 l. of ether. After washing with 150 ml. of 5% sodium hydroxide and with water until neutral, the solution was dried over anhydrous sodium sulphate and concentrated. The oily residue was introduced in a bulb and heated gradually at 0.5 mm. to 150°. The distilled compound (35 g.) consisted mainly of *o*-vinylbenzyl alcohol acetate (IX) and *N*-hydroxyurethan (ir and nmr examination). It was dissolved in 50 ml. of chloroform and chromatographed on 350 g. of disactivated silica gel (10% water) in a nylon column (column size 28 in. x 2 in.) (15) using 400 ml. of chloroform as eluent. The first unitary fractions (rf 0.50; checking by tlc) were combined and distilled to give 11 g. of IX, b.p. 70°/0.1 mm.; ir: 1750 (C=O), 1630 (olefinic C=C), 1230 and 1025 (C-O), 775 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.02 (s, 3H, CH_3-CO-), 4.85 (s, 2H, -CH_2-O), 4.66 (two d, 1H, (H)-C=C-H cis), 4.35 (two d, 1H, (H)-C=C-H trans), 3.00 (two d, 1H, -CH=$C(H_2)$), 2.9-2.3 τ (m, 4H, aromatic hydrogens).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.71; H, 7.08.

Compound IX was also obtained from VIb according to the procedure described below.

The residue of the preceding distillation weighed 36.7 g. (48%) and could not be distilled without partial decomposition. According to nmr examination, it contained about 85% of VIIa and 10% of the isomer VIII and was used as such in the following reaction.

o-Vinylbenzyl Alcohol Acetate (IX).

To a solution of 6 g. (23 mmoles) of *o*-acetoxymethylphenethyl bromide (VIb) in 120 ml. of anhydrous dimethylformamide, 2.81 g. (42.5 mmoles) of powdered potassium hydroxide 85% were added and the mixture was stirred at 80° for 5 hours. The solvent was then distilled *in vacuo* and ether was added to the residue. After washing with water, the organic phase was dried over anhydrous sodium sulfate and concentrated. The residue was distilled with a Vigreux, collecting the fraction (1.65 g., 40%) boiling at 130°/20 mm. It was identical (by ir and nmr comparison) to the sample obtained above.

N-Carbethoxy-*O*-[2-(*o*-hydroxymethylphenyl)ethyl]hydroxylamine (VIIb).

To 36.7 g. (0.13 mole) of crude *N*-carbethoxy-*O*-[2-(*o*-acetoxymethylphenyl)ethyl]hydroxylamine (VIIa) in 320 ml. of ethanol, 138 ml. of *N* sodium hydroxide was added and the solution was left at room temperature for 16 hours. The solvent was then evaporated *in vacuo* (bath temperature $\leqslant 35°$) and the residue dissolved in ether. After washing with water, the organic phase was dried over sodium sulfate and concentrated, yielding 27 g. (88%) of VIIb which was used as such for the next reaction.

An analytical sample of VIIb was obtained by distilling in bulb, b.p. 180°/0.1 mm.; ir: 3400-3200 (OH and NH), 1740 (C=O), 1260, 1120 and 1040 (C-O), 760 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.77 (t, 3H, CH_3-$C(H_2)$), 7.4-6.8 (m, 1H, OH), 6.97 (t, 2H, Ar-CH_2-$C(H_2)$), 5.89 (t, 2H, -$C(H_2)$-CH_2-O), 5.82 (q, 2H, -CH_2-$C(H_3)$), 5.30 (s, 2H, Ar-CH_2-O), 2.66 (s, 4H, aromatic hydrogens), 1.95 τ (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.23; H, 7.33; N, 6.00.

The aqueous mother liquor and washings were combined, acidified with concentrated hydrochloric acid and thoroughly extracted with ether. The ether extracts were washed with dilute sodium bicarbonate, with water and dried over anhydrous sodium sulfate. Evaporation left 1.6 g. of an oil which was distilled at 180°/0.2 mm. According to nmr examination, it consisted of a mixture of VIIb and its -N-OH isomer in a ratio 1:1. The last isomer was not characterized.

O-[2-(*o*-Bromomethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIIc).

A solution of 53.6 g. (0.22 mole) of *N*-carbethoxy-*O*-[2-(*o*-hydroxymethylphenyl)ethyl]hydroxylamine (VIIb) in 310 ml. of methylene chloride was dropped with stirring into 1.2 l. of the same solvent saturated at 0° with dry hydrogen bromide. After the addition was complete, the solution was resaturated with dry hydrogen bromide and kept at 0° for two hours and for 40 minutes at room temperature. The solvent was then evaporated at low temperature and the residue was taken up with 500 ml. of methylene chloride and dried over anhydrous sodium sulfate. Evaporation of the solvent left a residue which was triturated with cold hexane and recrystallized from the same solvent to give 60 g. (89%) of VIIc, m.p. 70-72°; ir: 3300 (NH), 1710 (C=O), 1300 and 1030 (C-O), 775 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.77 (t, 3H, CH_3-$C(H_2)$), 6.98 (t, 2H, Ar-CH_2-$C(H_2)$), 5.95 (t, 2H, -$C(H_2)$-CH_2-O), 5.90 (q, 2H, CH_2-$C(H_3)$), 5.48 (s, 2H, CH_2-Br), 2.51 (s, 4H, aromatic hydrogens), 2.25 τ (s, 1H, NH).

Anal. Calcd. for $C_{12}H_{16}BrNO_3$: C, 47.69; H, 5.34; N, 4.63; Br, 26.44. Found: C, 47.41; H, 5.52; N, 4.40; Br, 25.98.

2-Carbethoxy-1,2,4,5-tetrahydro-3,2-benzoxazepine (X).

A solution of 19.8 g. (85%, 0.3 mole) of potassium hydroxide drops in 790 ml. of ethanol was added dropwise at room temperature to a stirred solution of 90 g. (0.30 mole) of *O*-[2-(*o*-bromomethylphenyl)ethyl]-*N*-carbethoxyhydroxylamine (VIIc) in 2.8 l. of ethanol. Stirring was continued for 4 hours, then the mixture was evaporated *in vacuo* to dryness. The residue was taken up with ether and filtered to remove the inorganic salts. The filtrate was evaporated and the residue was distilled, collecting 53.4 g. (82%) of X, b.p. 140-145°/0.2 mm. An analytical sample was redistilled at 130°/0.1 mm.; ir: 1710 (C=O), 1220 and 1010 (C-O), 760 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.78 (t, 3H, CH_3-$C(H_2)$), 6.86 (t, 2H, Ar-CH_2-$C(H_2)$), 5.84 (t, 2H, -$C(H_2)$-CH_2-O), 5.83 (q, 2H, CH_2-$C(H_3)$), 5.15 (s, 2H, Ar-CH_2-N$\subset$), 2.76 τ (s, 4H, aromatic hydrogens).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.89; H, 6.46; N, 6.50.

6,15-Dicarbethoxy-5,6,8,9,14,15,17,18-octahydrodibenzo[*d,l*]-1,8-dioxa-2,9-diazacyclotetradecine (XI).

The residue of the preceding distillation (9 g.) was dissolved in warm isopropyl ether, filtered on charcoal and concentrated to incipient crystallization. The precipitate was recrystallized from isopropyl ether yielding 2.1 g. of XI, m.p. 148-149°; ir: 1700 (C=O), 1240, 1120 and 1080 (C-O), 750 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 8.65 (t, 6H, CH_3-$C(H_2)$), 7.12 (t, 4H, Ar-CH_2-$C(H_2)$), 5.85 (t, 4H, $C(H_2)$-CH_2-O), 5.68 (q, 4H, CH_2-$C(H_3)$), 5.35 (s, 4H, Ar-CH_2-N$\subset$), 2.9-2.4 τ (m, 8H, aromatic hydrogens). The mass spectrum showed a molecular peak at m/e 442.

Anal. Calcd. for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.40; H, 6.52; N, 6.20.

1,2,4,5-Tetrahydro-3,2-benzoxazepine (XII).

A solution of 22.5 g. (0.34 mole) of potassium hydroxide in 28 ml. of water was added under stirring to a solution of 49.4 g. (0.22 mole) of 2-carbethoxy-1,2,4,5-tetrahydro-3,2-benzoxazepine (X) in 300 ml. of ethanol. The solution was refluxed for 4 hours and the solvent was removed *in vacuo*. The residue was taken up with ether, washed with water and dried over anhydrous sodium sulfate. Evaporation gave a residue which was triturated with 100 ml. of hexane-isopropyl ether (1:1) and crystallized from isopropyl ether, to yield 28.8 g. (86.8%) of XII, m.p. 87-88°; ir: 3300 (NH), 1025 (C-O) and 765 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 6.94 (t, 2H, Ar-CH_2-$C(H_2)$), 5.88 (t, 2H, -$C(H_2)$-CH_2-O), 5.76 (s, 2H, Ar-CH_2-N$\subset$), 4.33 (s, 1H, NH), 2.81 τ (s, 4H, aromatic hydrogens).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.36; H, 7.66; N, 9.59.

The *hydrochloride of XII*, prepared by addition of an ether solution of hydrogen chloride to an ether solution of the base, was purified by crystallization from ethanol, m.p. 190-192°; ir: 2800-2100 (NH_2^+), 1550 (δ NH_2^+), 1020 (C-O) and 760 cm^{-1} (γ aromatic CH).

Anal. Calcd. for $C_9H_{11}NO$·HCl: C, 58.22; H, 6.51; N, 7.55; Cl, 19.10. Found: C, 58.30; H, 6.27; N, 7.30; Cl, 19.17.

Hydrogenolysis of XII. *o*-Aminomethylphenethyl Alcohol (XIII) Hydrochloride.

A solution of XII hydrochloride (1.24 g.) in 40 ml. of ethanol was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 0.5 g. of 10% Pd-C for ten hours. The catalyst was then removed by suction and the solvent was evaporated. The residue, scratched with ether, gave a crude product which was crystallized from isopropyl alcohol, yielding 0.7 g. of XIII hydrochloride, m.p. 168-169°; ir: 3300 (OH), 3100-2400 (NH_3^+), 1600 (δ NH_3^+), 1060 (C-O), and 760 cm^{-1} (γ aromatic CH); nmr (DMSO-d_6): 7.12 (t, 2H, Ar-CH_2-$C(H_2)$), 6.30 (t, 2H, -$C(H_2)$-CH_2-O), 5.89 (s, 2H, Ar-CH_2-N$\subset$), 3.1-1.5 τ (m, 8H, aromatic and mobile hydrogens).

Anal. Calcd. for $C_9H_{13}NO$·HCl: C, 57.59; H, 7.52; N, 7.46; Cl, 18.88. Found: C, 57.90; H, 7.89; N, 7.37; Cl, 19.02.

Preparation of 2-Substituted 1,2,4,5-Tetrahydro-3,2-benzoxazepines (XIIa-h).

Only some typical experiments are reported here as examples for the whole series.

2-(4-Methylpiperazinomethyl)-1,2,4,5-tetrahydro-3,2-benzoxazepine (XIIe).

An aqueous solution of 38% formaldehyde (0.32 ml., 4.4 mmoles) was added at 0° with stirring to a solution of 0.5 g. (3.35 mmoles) of 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII) in 40 ml. of ethanol. After ten minutes, a solution of 0.36 g. (3.63 mmoles) of *N*-methylpiperazine in 5 ml. of ethanol was added dropwise and stirring was continued for 4 hours at room temperature. The solvent was then evaporated *in vacuo* (30°) and the residue was rapidly distilled to give 0.80 g. (92%) of XIIe; b.p. 120°/0.1 mm.; ir: 1010 (C-O), 760 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 7.70 (s, 3H, CH_3-N $\subset$), 7.8-7.1 (m, 8H, CH_2 of piperazine ring), 6.91 (t, 2H, Ar-CH_2-C(H_2)), 6.44 (s, 2H, $\geq$N-CH_2-N $\subset$), 5.89 (t, 2H, -C(H_2)-CH_2-O), 5.88 (s, 2H, Ar-CH_2-N $\subset$), 2.80 τ (s, 4H, aromatic hydrogens).

2,2'-Methylene-bis(1,2,4,5-tetrahydro-3,2-benzoxazepine) (XIIf).

An aqueous solution of 38% formaldehyde (0.14 g., 1.84 mmoles) was added to 0.5 g. (3.35 mmoles) of 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII) in 2.5 ml. of ethanol and the mixture was refluxed for 30 minutes. The solvent was then evaporated and the residue was crystallized from 80% ethanol, to yield 0.4 g. (77%) of XIIf, m.p. 113-114°; ir: 1040 (C-O) and 755 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform): 6.88 (t, 4H, Ar-CH_2-C(H_2)), 6.00 (s, 2H, $\geq$N-CH_2-N $\subset$), 5.83 (t, 4H, C(H_2)-CH_2-O), 5.71 (s, 4H, Ar-CH_2-N $\subset$), 2.80 τ (s, 8H, aromatic hydrogens).

2-Carbamoyl-1,2,4,5-tetrahydro-3,2-benzoxazepine (XIIg).

To a stirred suspension of 1.95 g. (29.6 mmoles) of sodium cyanate in 125 ml. of anhydrous toluene, 29 mmoles of dry hydrogen chloride in toluene solution were added dropwise at -10°. After 2 hours of stirring, a solution of 3.1 g. (20.8 mmoles) of 1,2,4,5-tetrahydro-3,2-benzoxazepine (XII) in 30 ml. of anhydrous toluene was added and stirring was continued at -10° for 3 hours. After one night in a refrigerator, the precipitate was filtered, thoroughly washed with water and recrystallized from ethanol 80%, yielding 2.35 g. (58.7%) of XIIg, m.p. 172-173°; ir: 3450 and 3200 (NH_2), 1670 (C=O), 1600 (amide II), 1010 (C-O), 770 cm^{-1} (γ aromatic CH); nmr (deuteriochloroform-DMSO-d_6 10:1): 6.82 (t, 2H, Ar-CH_2-C(H_2)), 5.80 (t, 2H, -C(H_2)-CH_2-O), 5.12 (s, 2H, Ar-CH_2-N $\subset$), 4.20 (broad s, 2H, -$CONH_2$), 2.75 τ (s, 4H, aromatic hydrogens).

Acknowledgment.

The Authors acknowledge Dr. A. Vigevani for spectroscopic data, Mr. A. Restelli for elemental microanalysis and Dr. W. Zanichelli for help during the revision of the manuscript.

REFERENCES

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

(2) G. Pifferi, P. Consonni, S. Banfi and A Diena, *J. Med. Chem.*, 12, 261 (1969).

(3) G. Pifferi and P. Consonni, *J. Heterocyclic Chem.*, 6, 111 (1969).

(4) S. Gabriel, *Ber.*, 18, 2448 (1885).

(5) J. Gottliebe, *ibid.*, 32, 966 (1899).

(6) E. Moriconi, F. J. Creegan, C. K. Donovan, F. A. Spano, *J. Org. Chem.*, 28, 2215 (1963).

(7a) G. Pifferi, P. Consonni and E. Testa, *Gazz. Chim. Ital.*, 96, 1671 (1966); (b) G. Pifferi and P. Consonni, *Il Farmaco, Ed. Sci.*, 23, 949 (1968); (c) G. Pifferi, A. Vigevani and P. Consonni, *Ann. Chim., (Rome)*, 58, 1294 (1968).

(8) J. Colonge and P. Boisde, *Bull. Soc. Chim. France*, 1337 (1956).

(9a) E. Blumerfeld, *Chem. Zentr.*, I, 1788 (1907); (b) C. G. Overberger and J. E. Mulvaney, *J. Am. Chem. Soc.*, 81, 4697 (1959).

(10) G. Pifferi, N. Di Mola and E. Testa, *Il Farmaco, Ed. Sci.*, 23, 568 (1968).

(11) A. Rieche and E. Schmitz, *Chem. Ber.*, 89, 1254 (1956).

(12) G. Pifferi and R. Monguzzi, *Boll. Chim. Farm.*, 108, 697 (1969).

(13) Melting and boiling points are uncorrected. Distillation were performed *in vacuo* using a bulb tube apparatus (14). Ir spectra were determined as liquid films or Nujol mulls on a Perkin-Elmer 137 spectrophotometer. Nmr spectra were obtained with a Varian A-60 (60 Mc/s) spectrophotometer in the solvent indicated. Chemical shifts are reported as τ (ppm) relative to TMS and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The mass spectrum was recorded with a Hitachi-Perkin Elmer RMU-60 spectrometer (single focus) at electron ionizing voltage 70 V.

(14) G. Pifferi, A. DeRos and M. Borbonese, *Il Farmaco, Ed. Pr.*, 22, 210 (1967).

(15) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).