as the corresponding isocyanate. The colorimetric methods cannot distinguish between bufexamac and any hydroxy derivatives of bufexamac. No evidence was, in fact, obtained for the presence of a hydroxy derivative of bufexamac as a metabolite of the drug in blood or urine.

The smallest amount of bufexamac that could be assayed following extraction with a standard deviation within the limits reported here corresponded to a concentration of about 0.6 mcg./ml. in urine or plasma. This amount is equivalent to about 2 ng./μl. injected, giving a peak height of about 60 mm. (1×10^{-11} amp. full scale deflection).

An investigation into the general applicability of the Lossen rearrangement to the analysis of hydroxamic acid derivatives of other compounds of pharmaceutical interest is currently being undertaken.

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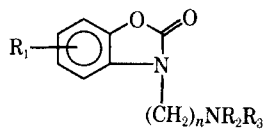
Reaction of 3-(Chloroalkyl)-2-benzoxazolinones with Amines: Formation of 3-(Aminoalkyl)-2-benzoxazolinones and 5-Substituted-2,3,4,5-tetrahydro-1,5-benzoxazepines

J. SAM, J. L. VALENTINE, and M. N. ABOUL-ENEIN

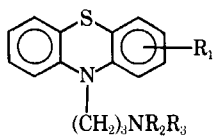
Abstract □ The reactions of 3-(chloroalkyl)-2-benzoxazolinones with various bases are described.

Keyphrases □ 3-(Aminoalkyl)-2-benzoxazolinones—preparation from 3-(chloroalkyl)-2-benzoxazolinones □ 3-(Chloroalkyl)-2-benzoxazolinones—reactions with amines □ 5-Substituted-2,3,4,5-tetrahydro-1,5-benzoxazepines—preparation from 3-(chloroalkyl)-2-benzoxazolinones □ CNS depressants, potential—3-(aminoalkyl)-2-benzoxazolinones, preparation □ IR spectrophotometry—identification, 3-(aminoalkyl)-2-benzoxazolinones □ NMR spectroscopy—identification, 3-(aminoalkyl)-2-benzoxazolinones

The observed CNS depressant activity associated with some 3-(aminoalkyl)-2-benzoxazolinones (I) (1, 2), as well as parenthetic analogy with unbranched aminopropyl side chains in the 10-position of phenothiazines (II) (3), prompted the investigation of other 3-(aminoalkyl)-2-benzoxazolinones.

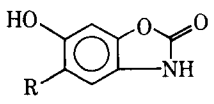


I



II

Metabolic studies by Bray *et al.* (4) on 2-benzoxazolinone and by Conney and Burns (5) on 5-chloro-2-benzoxazolinone indicated that the major urinary metabolites of both are the 6-hydroxylated compounds



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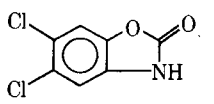
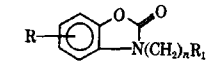


IV

(III). To determine if a hindrance of metabolic detoxication would enhance biological activity of type I compounds, 5,6-dichloro-2-benzoxazolinone (IV) was selected for further study. The introduction of the aminopropyl side chain of the phenothiazines into the 3-position of the parent system was undertaken in anticipation of obtaining interesting CNS depressants.

The preparation of I ($n = 2$ or 3) by the reaction of an appropriately substituted 2-benzoxazolinone with an aminoalkyl halide was described (1, 2, 6). Such synthetic pathways occasionally, however, involve troublesome preparations of the intermediate aminoalkyl halides, thus subjecting the overall synthetic pathways to poor

Table I—3-Substituted-2-benzoxazolinones



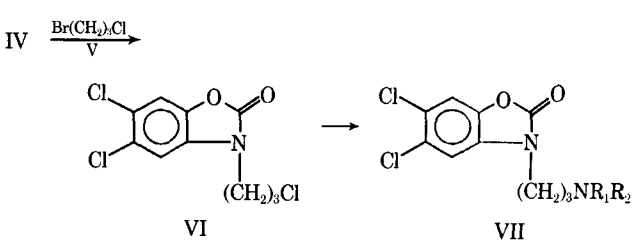
Number[a]	R	R_1	n	Method	Recrystallization Solvent[b]	Yield, %	Melting Point	Molecular Formula	Analysis, % Calc.	Found
I*a*	5,6-DiCl	$(CH_3)_2N$	3	A	E	48	62–63°	$C_{12}H_{14}Cl_2N_2O_2$	C, 49.84 H, 4.87 N, 9.05	C, 50.00 H, 5.03 N, 9.25
I*b*	5,6-DiCl	C_4H_8N[c]	3	D	E–W	63	243–245°	$C_{14}H_{17}Cl_3N_2O_2$[d]	C, 47.81 H, 4.87 N, 7.96	C, 47.92 H, 5.02 N, 7.89
I*c*	5,6-DiCl	$C_5H_{10}N$[e]	3	C	E	64	123–124°	$C_{15}H_{18}Cl_2N_2O_2$	C, 54.73 H, 5.51 N, 8.51	C, 54.91 H, 5.47 N, 8.34
I*d*	5,6-DiCl	$C_6H_{12}N$[f]	3	C	E	62	88–89°	$C_{16}H_{20}Cl_2N_2O_2$	C, 55.98 H, 5.87 N, 8.15	C, 56.17 H, 5.82 N, 8.05
I*e*	5,6-DiCl	C_4H_8NO[g]	3	C	C	53	128–129°	$C_{14}H_{16}Cl_2N_2O_3$	C, 50.76 H, 4.86 N, 8.46	C, 50.91 H, 4.75 N, 8.35
I*f*	5,6-DiCl	$C_5H_{11}N_2$[h]	3	C	I	55	101–102°	$C_{15}H_{19}Cl_2N_3O_2$	C, 52.33 H, 5.56 N, 12.26	C, 52.43 H, 5.65 N, 12.11
I*g*	5-Cl	C_4H_8N[c]	3	C	E–Et	74	194–196°	$C_{14}H_{18}Cl_2N_2O_2$[d]	C, 53.06 H, 5.71 N, 8.83	C, 52.86 H, 5.71 N, 8.63
I*h*	6-Cl	C_4H_8N[c]	3	C	E	54	220–222°	$C_{14}H_{18}Cl_2N_2O_2$[d]	C, 53.06 H, 5.71 N, 8.83	C, 53.20 H, 5.87 N, 8.67
I*i*	5-Cl	C_4H_8N[c]	2	C	E		188–190°	$C_{19}H_{18}ClN_5O_9$[i,j]	C, 46.02 H, 3.65 N, 14.12	C, 46.54 H, 4.56 N, 13.50
I*j*	5,6-DiCl	C_4H_8N[c]	2	C	E	35	273–274°	$C_{13}H_{15}Cl_3N_2O_2$[d]	C, 46.24 H, 4.44 N, 8.30	C, 46.43 H, 4.63 N, 8.11
I*k*	5-Cl	$C_5H_{10}N$[e]	2	C	E	45	268–269°	$C_{14}H_{18}Cl_2N_2O_2$[d]	C, 53.06 H, 5.71 N, 8.83	C, 53.46 H, 6.00 N, 8.78
I*l*	5-NO_2	C_4H_8N[c]	3	C	E	77	226–228°	$C_{20}H_{20}N_6O_{11}$[i]	C, 46.15 H, 3.87 N, 16.11	C, 46.05 H, 3.92 N, 15.45
XII*a*	6-NO_2	Cl	3	A	E	40	93–94°	$C_{10}H_9ClN_2O_4$	C, 46.74 H, 3.53 N, 10.91	C, 46.61 H, 3.79 N, 10.97
XII*b*	5-NO_2	Cl	3	A		61	135–140°(0.1 mm.)[k]	$C_{10}H_9ClN_2O_4$[l]	C, — H, — N, —	C, — H, — N, —
XII*c*	6-Cl	Cl	3	A	E	90	95–96°	$C_{10}H_9Cl_2NO_2$	C, 48.70 H, 3.69 N, 5.65	C, 48.22 H, 3.64 N, 5.95
XII*d*	5-Cl	Cl	2	A	E	81	84–85°	$C_9H_7Cl_2NO_2$	C, 46.19 H, 3.04 N, 6.03	C, 46.72 H, 2.83 N, 6.31
XII*e*	5-Cl	Cl	3	A,B	E	59,81	85–86°	$C_{10}H_9Cl_2NO_2$[m]	C, — H, — N, —	C, — H, — N, —

[a] IR and NMR spectra are in accordance with the structures. [b] E = ethanol, C = cellosolve, Et = ether, I = isopropyl ether, and W = water. [c] Pyrrolidino. [d] Hydrochloride. [e] Piperidino. [f] Hexamethyleneimino. [g] Morpholino. [h] *N*-Methylpiperazino. [i] Picrate. [j] Hydrochloride, m.p. 195–196° (ethanol). [k] Boiling point. [l] Characterized through II. [m] Characterized through Ig and XIV*b*.

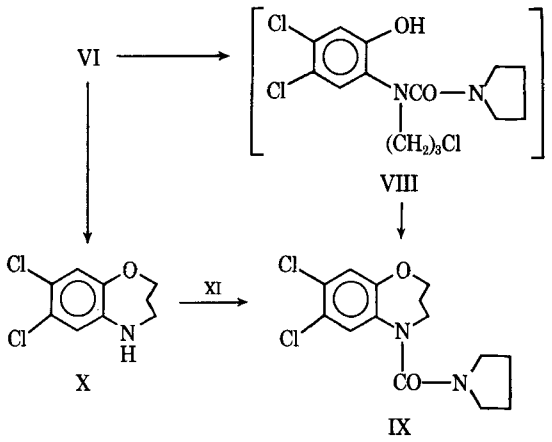
yields. One objective of the present work, therefore, was to investigate an alternate route for the preparation of I.

The use of 1-bromo-3-chloropropane (V) as an alkylating agent is well documented (7, 8). Consequently, V was utilized for the preparation of 3-(3-chloropropyl)-5,6-dichloro-2-benzoxazolinone (VI) (Scheme I). Subsequent reaction of VI with appropriate secondary amines gave VII (I, Table I).

The aminoalkylbenzoxazolinones (I) show a common IR carbonyl absorption at 1750 cm.$^{-1}$. The reaction of pyrrolidine with VI, however, gave a product insoluble in acids and showing IR absorption at 1650 cm.$^{-1}$, indicative of an amide. The IR and NMR spectra and elemental analyses were consistent with the structure of 7,8-dichloro-5-pyrrolidinocarbonyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (IX). Compound IX also was prepared by the alkaline hydrolysis of VI to X and subsequent treatment of the latter with pyrrolidinocarbonyl chloride (XI) (Scheme II).

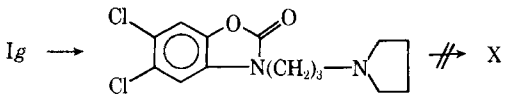


Scheme I



Scheme II

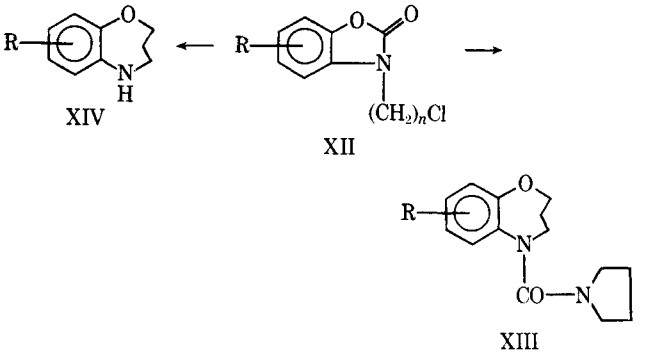
The pyrrolidino derivative (VII*b*) (I*b*, Table I) was prepared by the chlorination of 5-chloro-3-(3-pyrrolidinopropyl)-2-benzoxazolinone (I*g*) (Scheme III). Refluxing I*b* with pyrrolidine under the conditions utilized for the preparation of IX from VI resulted in the recovery of unchanged I*b*. The formation of IX from VI apparently proceeds *via* VIII and not I*b*.



Scheme III

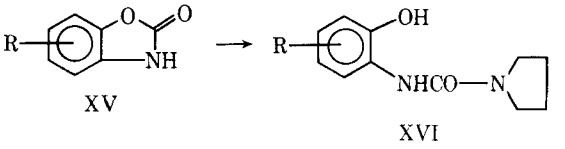
The rearrangement of 3-(3-chloropropyl)-2-benzoxazolinones (XII, $n=3$) to XIII (Table II) occurred only when a strong electron-withdrawing group (6-nitro or 5,6-dihalo) was present in the benzoxazolinone ring and only when the amine was pyrrolidine. However, XII ($n=3$) undergoes rearrangement to XIV when heated with alkali hydroxides. A similar rearrangement of 3-(β-chloroethyl)-2-benzoxazolinone (XII; R = H, $n=2$) to 2,3,4-trihydro-1,4-benzoxazine was noted by Fujii (9).

The reaction of the chloroethyl derivatives (XII, $n=2$) with amines provided the anticipated products (I, $n=2$) (Scheme IV). Moreover, the chloropropyl derivatives (II, $n=3$), containing a monohalo aromatic substituent or a 5-nitro group, also produced I ($n=3$).



Scheme IV

Further evidence that the course of the rearrangement proceeds *via* an intermediate such as VIII was obtained by treating 2-benzoxazolinones (XV) with pyrrolidine under the same experimental conditions as utilized for the preparation of IX. When R = H, rearrangement failed to occur; however, when R = 5,6-dichloro, XVI was obtained (Scheme V).



Scheme V

Attempts to prepare XIV from XIX *via* *o*-aminophenol and XVIII were unsuccessful. Efforts to cyclize XVIII by the method of Sidhu *et al.* (10) resulted only in the unsaturated derivative (XX) (Scheme VI). Attempts to cyclize XX also were unsuccessful. The results are in agreement with the report of Loudon and Ogg (11).

A number of derivatives (XXIII, Table III) of XIV were prepared and subjected to pharmacological evaluation. Except for XXIII*v*, XXIII*w*, and XXIII*x* (Table

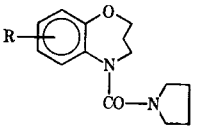
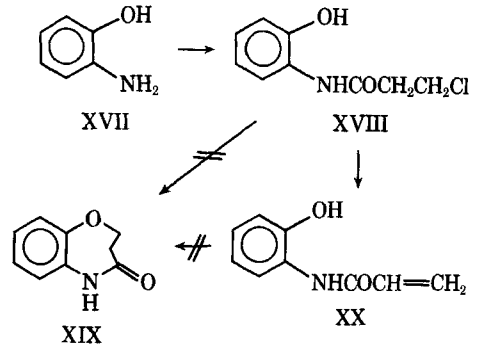


Table II—5-Pyrrolidinocarbonyl-2,3,4,5-tetrahydro-1,5-benzoxazepines

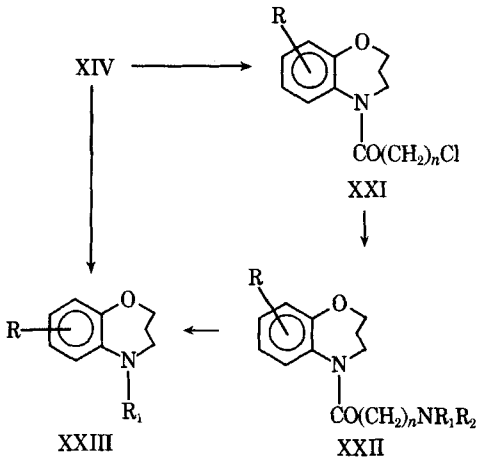
Number[a]	R	Recrystallization Solvent[b]	Method	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
XIII*a*	8-NO_2	E	A	71	148–150°	$C_{14}H_{17}N_3O_4$	C, 57.72 H, 5.88 N, 14.42	C, 57.59 H, 5.66 N, 14.48
XIII*b*	7-Cl-8-Br	E	A	67	167–168°	$C_{14}H_{16}BrClN_2O_2$	C, 46.77 H, 4.48 N, 7.79	C, 46.61 H, 4.49 N, 7.65
XIII*c*	7,8-DiCl	E–W	A,B	62,53	153–154°	$C_{14}H_{16}Cl_2N_2O_2$	C, 53.34 H, 5.12 N, 8.89	C, 53.37 H, 5.24 N, 8.71
XIII*d*	8-NH_2	E	—[c]	43	227–228°	$C_{14}H_{19}N_3O_2$	C, 64.35 H, 7.33 N, 16.08	C, 63.90 H, 7.19 N, 15.97

[a] IR and NMR spectra are in accordance with the structures. [b] E = ethanol, and W = water. [c] By platinum oxide reduction of XIII*a* in ethanol at 3 kg./cm.^{2} at room temperature.



Scheme VI

III), which were prepared directly from XIV, all were synthesized *via* XXI and XXII (Scheme VII).



Scheme VII

EXPERIMENTAL[1]

3-Substituted-2-benzoxazolinones (Table I)—References to the preparation of 2-benzoxazolinones utilized in this study are cited in the review by Sam and Valentine (12).

Method A—To a solution of 11.2 g. (0.1 mole) of potassium hydroxide in 200 ml. of ethyl cellosolve was added 0.1 mole of the appropriate 2-benzoxazolinone (XV). The mixture was stirred at room temperature for 1 hr. and thereafter heated to reflux and treated with 0.2 mole of the requisite alkyl halide. The mixture was stirred and refluxed for an additional 4 hr. The solution was filtered and then concentrated under reduced pressure. The resultant material either was distilled or recrystallized.

Method B—To a stirred and refluxing (for 1 hr.) solution of 4.6 g. (0.2 atom) of sodium and 34 g. (0.2 mole) of 5-chloro-2-benzoxazolinone in 240 ml. of absolute ethanol was added 94.6 g. (0.6 mole) of 1-bromo-3-chloropropane in one portion. Refluxing was continued for 24 hr. The reaction mixture was cooled, filtered, and evaporated under reduced pressure. An ether solution (500 ml.) of the residual material was washed with 10% potassium hydroxide (5 × 20 ml.) and water (3 × 50 ml.) and dried ($MgSO_4$). Evaporation of the ether gave a crystalline mass, which was recrystallized.

Method C—To 200 ml. of ethyl cellosolve was added 0.05 mole of the appropriate 3-(chloroalkyl)-2-benzoxazolinone (XII, Table I; also *References 1* and *9*). The mixture was stirred and refluxed until solution occurred (30 min.). In one portion, 0.1 mole of the appropriate secondary amine was added; the mixture then was refluxed for 6 hr. The solvent was distilled under reduced pressure; the resultant oily crystalline mass was treated with 500 ml. of 5% sodium hydroxide and extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated under reduced pressure. The residual solid was washed with acetonitrile and then recrystallized from a suitable solvent.

Method D—A solution of 14.0 g. (0.05 mole) of 3-(3-pyrrolidinopropyl)-5-chloro-2-benzoxazolinone (Ig) in 200 ml. of dry chloroform was treated dropwise with a solution of 4.3 (0.06 mole) of chlorine in 100 ml. of dry chloroform. Then the mixture was stirred and refluxed for 24 hr. The solvent was distilled under reduced pressure; the resultant solid was treated with 500 ml. of 10% sodium hydroxide and extracted with ether (3 × 100 ml.). The ether extract was dried (Na_2SO_4) and converted to a hydrochloride in the usual manner.

5-Pyrrolidinocarbonyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (XIIIa–XIIIc, Table II)—*Method E*—The procedure described under Method C was followed using the appropriate 3-(3-chloropropyl)-2-benzoxazolinone and pyrrolidine.

Method F—A mixture of 4.0 g. (0.019 mole) of 7,8-dichloro-2,3,4,5-tetrahydro-1,5-benzoxazepine (X) and 2.5 g. (0.019 mole) of pyrrolidinocarbonyl chloride (13) was fused in an oil bath at 200° for 4 hr. The resultant charred mass was treated with 200 ml. of 10% sodium hydroxide and extracted with ether. The ether was dried (Na_2SO_4) and then distilled under reduced pressure. The residue was washed with acetonitrile and recrystallized from ethanol: IR $\nu_{max.}^{CHCl_3}$ 1650 cm.$^{-1}$ (C=O); NMR(CCl_4) δ 1.63–2.25 (m, 6, —CH_2—), 2.91–3.14 (m, 4, —CH_2—N—CH_2—), 3.60–3.78 (t, 2, —N—CH_2—), 3.96–4.14 (t, 2, —OCH_2), and 7.12 (s, 2, aromatic protons). The product was identical in every respect to that obtained in Method E.

2-Hydroxy-4,5-dichloro-*N*-pyrrolidinocarbonylaniline (XVI)—A mixture of 20.6 g. (0.1 mole) of XV (R = 5,6-dichloro) and 14.2 g. (0.2 mole) of pyrrolidine in 200 ml. of methyl cellosolve was stirred and refluxed for 4 hr. The solvent was distilled under reduced pressure; the resulting solid was washed with 5% hydrochloric acid and then recrystallized from methyl cellosolve to give 25 g. (91%) of product, m.p. 219–221°: IR $\nu_{max.}^{KBr}$ 3400 cm.$^{-1}$ (NH) and 1650 cm.$^{-1}$ (C=O); NMR (d_5-pyridine) δ 1.55–1.78 (m, 4, —CH_2—), 3.29–3.51 (t, 4, N—CH_2), 7.23 (s, 1, aromatic proton), 8.71 (s, 1, aromatic proton), 7.90 (s, 1, NH), and 10.71 (s, 1, OH).

Anal.—Calc. for $C_{11}H_{12}Cl_2N_2O_2$: C, 48.01; H, 4.39; N, 10.18. Found: C, 48.27; H, 4.57; N, 10.12.

2,3,4,5-Tetrahydro-1,5-benzoxazepines (X, XIV*a*, and XIV*b*, Table III)—A solution of 33 g. (0.156 mole) of 3-(3-chloropropyl)-2-benzoxazolinone and 35 g. (0.625 mole) of potassium hydroxide in 400 ml. of methyl cellosolve was refluxed for 48 hr. The solvent was removed *in vacuo;* the residue was treated with 500 ml. of cold water and extracted with ether (3 × 100 ml.). The ethereal solution was extracted with 20% hydrochloric acid (3 × 30 ml.). The acidic solution was basified with 15% sodium hydroxide, extracted with ether (3 × 100 ml.), and dried ($MgSO_4$). Distillation of the ether extract gave 12.6 g. (55%) of XIV*a*, b.p. 90–94° (0.6 mm.), m.p. 51.5–52.5°: IR $\nu_{max.}^{CHCl_3}$ 3360 cm.$^{-1}$ (NH); NMR ($CDCl_3$) δ 2.00 (m, 2, —CH_2—), 3.20 (t, 2, N—CH_2), 4.05 (t, 2, O—CH_2), 3.80 (s, 1, NH), and 6.85 (m, 4, aromatic protons). The picrate was prepared in the usual manner and recrystallized from ethanol.

The procedure described here also was used for the preparation of X and XIV*b* (Table III); however, methylene chloride was used as the solvent for the extraction of X.

5-Chloroacyl-2,3,4,5-tetrahydro-1,5-benzoxazepines (XXIII*a*–XXIII*d*, Table III)—To a stirred mixture of 0.1 mole of XIV and 12 g. of anhydrous sodium carbonate in 300 ml. of dry benzene was added dropwise at room temperature 0.11 mole of the appropriate chloroacyl chloride in 50 ml. of dry benzene. The mixture was refluxed overnight, filtered, and concentrated under reduced pressure at 100°. The residue was recrystallized from benzene–methanol.

5-Aminoacyl-2,3,4,5-tetrahydro-1,5-benzoxazepines (XXIII*e*–XXIII*o*, Table III)—A solution of 0.1 mole of XXIII*a*–XXIII*d* and 0.2–0.5 mole of the appropriate amine in 80 ml. of dry benzene was heated in a sealed tube at 110–115° for 20 hr. The mixture was filtered and concentrated under reduced pressure. The residue was dissolved in 50 ml. of dilute hydrochloric acid and extracted with ether (3 × 30 ml.). The acidic solution was basified with 10% sodium hydroxide and extracted with ether (3 × 40 ml.). The extract was dried (Na_2SO_4), evaporated, and purified either by distillation or recrystallization.

5-Aminoalkyl-2,3,4,5-tetrahydro-1,5-benzoxazepines (XXIII*p*–XXIII*u*, Table III)—A solution of 0.027 mole of XXIII*e*–XXIII*o*

[1] Melting points were determined on a Fisher-Johns melting-point apparatus and are corrected. IR spectra were obtained on Perkin-Elmer 137G and 257 IR spectrophotometers. NMR spectra were determined on a Varian A-60-A spectrometer, using Me_4Si as an internal standard.

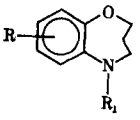


Table III—5-Substituted-2,3,4,5-tetrahydro-1,5-benzoxazepines

Number[a]	R	R′	Melting Point or Boiling Point (mm.)	Yield, %	Molecular Formula	Analysis, % Calc.	Found
X	7,8-DiCl	H	84–85°[b]	66	$C_9H_9Cl_2NO$	C, 49.56 H, 4.11 N, 6.42	C, 49.20 H, 4.59 N, 6.47
XIV*a*	H	H	90–94°(0.6) 51–52°	55	$C_{15}H_{14}N_4O_8$[c]	C, 47.62 H, 3.70 N, 14.81	C, 47.93 H, 3.84 N, 15.55
XIV*b*	7-Cl	H	115–116°(0.5) 70–72°	57	$C_{15}H_{13}ClN_4O_8$[d]	C, 43.63 H, 3.15 N, 13.57	C, 43.69 H, 3.24 N, 13.72
XXIII*a*	H	$ClCH_2CO$	101–102°[e]	94	$C_{11}H_{12}ClNO_2$[f]	C, — H, — N, —	C, — H, — N, —
XXIII*b*	H	$Cl(CH_2)_2CO$	90–91°[e]	72	$C_{12}H_{14}ClNO_2$[f]	C, — H, — N, —	C, — H, — N, —
XXIII*c*	7-Cl	$Cl\text{-}CH_2CO$	129–130°[e]	76	$C_{11}H_{11}Cl_2NO_2$[f]	C, — H, — N, —	C, — H, — N, —
XXIII*d*	7-Cl	$Cl(CH_2)_2CO$	82–83°[e]	89	$C_{12}H_{13}Cl_2NO_2$[f]	C, — H, — N, —	C, — H, — N, —
XXIII*e*	H	$(CH_3)_2NCH_2CO$	120–122°(0.1)	67	$C_{13}H_{18}N_2O_2$	C, 66.64 H, 7.74 N, 11.96	C, 66.18 H, 7.70 N, 11.85
XXIII*f*	H	$(C_2H_5)_2NCH_2CO$	128–132°(0.1)	79	$C_{15}H_{22}N_2O_2$	C, 68.67 H, 8.45 N, 10.68	C, 68.62 H, 8.06 N, 10.92
XXIII*g*	H	C_4H_8NO[g]CH_2CO	114–115°[h]	82	$C_{15}H_{20}N_2O_3$	C, 65.20 H, 7.30 N, 10.14	C, 65.11 H, 7.31 N, 10.14
XXIII*h*	H	$(CH_3)_2N(CH_2)_2CO$	128–130°(0.25)	69	$C_{14}H_{20}N_2O_2$	C, 67.72 H, 8.12 N, 11.28	C, 67.25 H, 8.09 N, 11.29
XXIII*i*	H	$(C_2H_5)_2N(CH_2)_2CO$	130–134°(0.2)	72	$C_{16}H_{24}N_2O_2$	C, 69.53 H, 8.75 N, 10.14	C, 68.94 H, 8.75 N, 10.10
XXIII*j*	H	C_4H_8N[i]$(CH_2)_2CO$	152–154°(0.45)	74	$C_{16}H_{22}N_2O_2$	C, 70.04 H, 8.08 N, 10.21	C, 69.55 H, 8.08 N, 9.56
XXIII*k*	H	C_4H_8NO[g]$(CH_2)_2CO$	154–156°(0.15)	56	$C_{16}H_{22}N_2O_3$[f]	C, — H, — N, —	C, — H, — N, —
XXIII*l*	7-Cl	$(CH_3)_2NCH_2CO$	138–140°(0.2)	74	$C_{13}H_{17}ClN_2O_2$	C, 58.10 H, 6.33 N, 10.42	C, 57.87 H, 6.49 N, 10.46
XXIII*m*	7-Cl	$(C_2H_5)_2NCH_2CO$	148–152°(0.6)	58	$C_{15}H_{21}ClN_2O_2$	C, 60.70 H, 7.08 N, 9.44	C, 60.55 H, 7.16 N, 9.27
XXIII*n*	7-Cl	$(CH_3)_2N(CH_2)_2CO$	148–150°(0.25)	84	$C_{14}H_{19}ClN_2O_2$	C, 59.46 H, 6.72 N, 9.91	C, 59.00 H, 7.07 N, 10.05
XXIII*o*	7-Cl	$(C_2H_5)_2N(CH_2)_2CO$	158–160°(0.05)	84	$C_{16}H_{23}ClN_2O_2$	C, 61.83 H, 7.41 N, 9.01	C, 62.37 H, 7.69 N, 9.54
XXIII*p*	H	$(CH_3)_2N(CH_2)_2$	100–102°(0.2)	69	$C_{13}H_{20}N_2O$	C, 70.87 H, 9.15 N, 12.72	C, 70.51 H, 9.03 N, 12.47
XXIII*q*	H	$(C_2H_5)_2N(CH_2)_2$	100–105°(0.15)	50	$C_{15}H_{26}Cl_2N_2O$[j]	C, 56.10 H, 8.16 N, 8.72	C, 56.61 H, 8.48 N, 8.70
XXIII*r*	H	C_4H_8NO[g]$(CH_2)_2$	130–134°(0.15)	60	$C_{15}H_{22}N_2O_2$	C, 68.67 H, 8.45 N, 10.68	C, 68.06 H, 8.58 N, 10.69
XXIII*s*	H	$(CH_3)_2N(CH_2)_3$	120–122°(0.06)	82	$C_{14}H_{22}N_2O$	C, 71.76 H, 9.46 N, 11.95	C, 71.51 H, 9.36 N, 11.93
XXIII*t*	H	$(C_2H_5)_2N(CH_2)_3$	116–120°(0.3)	98	$C_{16}H_{26}N_2O$	C, 73.24 H, 9.99 N, 10.68	C, 73.05 H, 10.06 N, 10.66
XXIII*u*	H	C_4H_8NO[g]$(CH_2)_3$	138–140°(0.2)	60	$C_{16}H_{24}N_2O_2$	C, 69.53 H, 8.75 N, 10.14	C, 69.87 H, 8.92 N, 9.77
XXIII*v*	H	$3,4(CH_3O)_2C_6H_3(CH_2)_2$	172–175°(0.15)	40	$C_{19}H_{23}NO_3$	C, 72.83 H, 7.40 N, 4.47	C, 72.30 H, 7.67 N, 4.36

Table III—(*continued*)

Number[a]	R	R′	Melting Point or Boiling Point (mm.)	Yield, %	Molecular Formula	Analysis, % Calc.	Found
XXIII*w*	H	$C_4H_7N_2$[k]	102–103°	97	$C_{13}H_{18}ClN_3O$[l]	C, 58.31 H, 6.35 N, 15.70	C, 58.52 H, 6.63 N, 15.84
XXIII*x*	H	NH_2	190–192°[m]	18	$C_9H_{13}ClN_2O$[m]	C, 53.86 H, 6.03 N, 13.96	C, 53.51 H, 6.44 N, 13.65

[a] IR and NMR spectra are consistent with the assigned structures. [b] Recrystallized from ethanol. [c] Picrate (ethanol), m.p. 193–194°. [d] Picrate (ethanol), 189–190°. [e] Recrystallized from benzene–methanol. [f] Characterized through their derivatives which appear in Table III. [g] Morpholino. [h] Recrystallized from ether. [i] Pyrrolidino. [j] Dihydrochloride (isopropanol), m.p. 190–201°. [k] 2-Imidazolin-2-ylmethyl. [l] Hydrochloride (isopropanol–ethyl acetate), m.p. 220–221°. [m] Hydrochloride (isopropanol).

in 100 ml. of anhydrous ether was added with stirring over 1.5 hr. to a suspension of 2.2 g. (0.057 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether. The mixture was refluxed for 3 hr., cooled to 0–5°, and treated with 10 ml. of a saturated sodium sulfate solution. The precipitate was removed by filtration and washed thoroughly with ether. The combined filtrates were dried ($MgSO_4$) and evaporated. The residue was purified by distillation.

5-(3,4-Dimethoxyphenethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine (XXIII*v*, Table III)—A mixture of 4.5 g. (0.03 mole) of XIV*a* and 4 g. of anhydrous sodium carbonate in 150 ml. of dry benzene was treated dropwise at room temperature with a solution of 7.1 g. (0.035 mole) of 3,4-dimethoxyphenylacetyl chloride (prepared from 5.9 g. of 3,4-dimethoxyphenylacetic acid and 25 ml. of thionyl chloride) in 100 ml. of dry benzene. The mixture was refluxed for 24 hr., filtered, and concentrated under reduced pressure. The residue was dissolved in 200 ml. of ether and washed with 15% sodium hydroxide (3 × 30 ml.), water (3 × 20 ml.), and 20% hydrochloric acid (3 × 30 ml.), respectively. The extract was dried (Na_2SO_4) and evaporated to give 9.8 g. of a dark-green viscous oil, which was dissolved in 100 ml. of dry tetrahydrofuran and added dropwise with stirring to a suspension of 4 g. (0.105 mole) of lithium aluminum hydride in 200 ml. of dry tetrahydrofuran. The mixture was refluxed for 24 hr. and then decomposed at 0–5° with a saturated sodium sulfate solution. The mixture was filtered and evaporated under reduced pressure. The residue (8 g.) was dissolved in 50 ml. of 20% hydrochloric acid, washed with ether (3 × 30 ml.), rendered alkaline with 15% sodium hydroxide, and extracted with ether (3 × 60 ml.). The ethereal extract was dried (Na_2SO_4) and distilled.

5-(2-Imidazolin-2-ylmethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine (XXIII*w*, Table III)—The procedure of Werner *et al.* (14) was followed. A solution of 7.5 g. (0.05 mole) of XIV*a* in 26 ml. of glacial acetic acid was treated with 1.52 g. (0.05 mole) of paraformaldehyde. The reaction mixture was stirred and cooled to 15° while adding dropwise a solution of 3 g. (0.06 mole) of sodium cyanide in 7.5 ml. of water. The temperature was raised to 45° over a 30-min. period and maintained at 45–50° for 3 hr. After cooling to 35°, 2.2 ml. of 37% formaldehyde was added; after 20 min., 6 ml. of water was added and the precipitated oil was extracted with ether (3 × 30 ml.). The ether solution was washed with 10% sodium hydroxide (3 × 20 ml.), dried (Na_2SO_4), and evaporated under reduced pressure to give 6.6 g. (69%) of the cyanomethyl derivative, b.p. 120–124° (0.25 mm.). A mixture of 6.6 g. (0.035 mole) of the nitrile, 2.6 g. (0.043 mole) of anhydrous ethylenediamine, and 0.08 ml. of carbon bisulfide was heated for 6 hr. at 128–130°. After cooling, the crystalline mass was triturated with 45 ml. of hot water and extracted with ethyl acetate (3 × 50 ml.). The extract was dried (Na_2SO_4) and evaporated to give 7.9 g. (97%) of green viscous oil, which solidified on standing to a pale-yellow crystalline mass, m.p. 102–103°. The hydrochloride was prepared in the usual manner and recrystallized.

5-Amino-2,3,4,5-tetrahydro-1,5-benzoxazepine (XXIII*x*, Table III)—To a solution of 4 g. (0.026 mole) of XIV*a* in 60 ml. of isopropanol and 50 ml. of 10% hydrochloric acid was added at 0–5° a solution of 3.2 g. of sodium nitrite in 15 ml. of water. The mixture was heated at 75° for 3 hr. and treated with another 3.2 g. of sodium nitrite. The red solution was kept at 75° for 12 hr., diluted with 100 ml. of cold water, and concentrated under reduced pressure to 100 ml. An ether extract (3 × 40 ml.) was dried (Na_2SO_4) and evaporated to give 3.2 g. of red oil (*N*-nitroso derivative), which was dissolved in 30 ml. of dry tetrahydrofuran and added dropwise with stirring into a suspension of 1.5 g. (0.04 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was heated at reflux for 3 hr., cooled, and decomposed with saturated sodium sulfate solution. After filtration and evaporation under reduced pressure, the residue was converted to a hydrochloride in the usual manner and recrystallized.

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