Tetrahedron. Vol. 24, pp. 4923 to 4932 Pergamon Press 1968. Printed in Great Britain

1H-2,3-BENZOXAZINE AND DERIVATIVES—III[1]

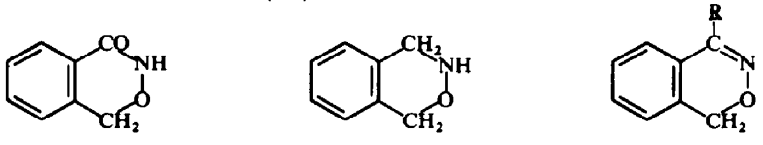
G. PIFFERI, P. CONSONNI and E. TESTA

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

(*Received in the UK* 17 *December* 1967; *accepted for publication* 15 *January* 1968)

Abstract—The synthesis of 4-substituted 1H-2,3-benzoxazines is reported. The key-product, namely 4-chloro-1H-2,3-benzoxazine (IV), was obtained by reaction with PCl_5 of 1H-2,3-benzoxazine-4(3H)one (I)[2] in addition to the 3-[4-(1H-2,3-benzoxazinyl)]-1H-2,3-benzoxazine-4(3H)one (V). By hydrolysis of IV with 20% HCl the heterocyclic ring was split giving the α-aminoxy-*o*-toluic acid hydrochloride (VII). The reaction of IV with MeSNa or KCN gave the 4-methylthio (VIII) and 4-carbamyl (IX) derivatives, respectively. By saponification of IX with alcoholic KOH, 1H-2,3-benzoxazine-4-carboxylic acid (X) was obtained; on heating of X in H_2SO_4, the 1H-2,3-benzoxazine (XI) was isolated and characterized as the hydrochloride, picrate and methiodide. By condensation of the chloride of acid X (XIII) with aliphatic, aromatic and heterocyclic amines the corresponding amides were obtained. Ethyl, phenyl, alkylaminoalkyl esters, hydrazide and two heterocyclic hydrazide derivatives of X were also prepared.

IN 1966, two new heterocyclic compounds, 1H-2,3-benzoxazine-4(3H)one (I)[2] and 1H-3,4-dihydro-2,3-benzoxazine (II),[1] were prepared, together with many of their derivatives, and submitted to systematic biological screening as potentially active

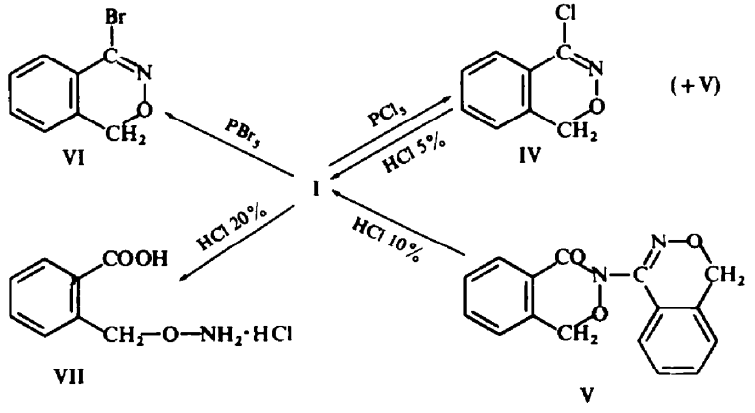


I II III

drugs. We have now turned our attention to 1H-2,3-benzoxazines (III), and the results are reported.

The key-compound for the synthesis of 1H-2,3-benzoxazines is 4-chloro-1H-2,3-benzoxazine (IV), obtained by chlorination of 1H-2,3-benzoxazine-4(3H)one (I).[2]

CHART 1



Systematic investigation of the reaction conditions was needed before IV could be prepared from I in consistently good yields. The best results have been obtained on using phosphorus pentachloride in chloroform, as the chlorinating agent: a mixture of IV and V was formed by heating, while at 0° with an excess of PCl_5 only IV was isolated in an 85% yield.

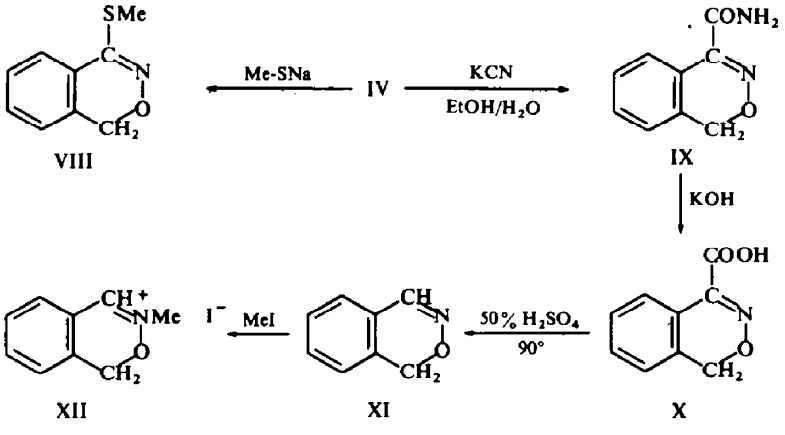
The structure of 3-[4-(1H-2,3-benzoxazinyl)]-1H-2,3-benzoxazine-4(3H)one (V) has been assigned on the basis not only of the analytical data and of the IR and NMR spectra reported in the experimental part, but also on the results of its decomposition in acid to 1H-2,3-benzoxazine-4(3H)one (I). It is interesting to observe the difference in behaviour between IV and 1-chlorophthalazine;[3] the latter, through hydrolysis with very dilute hydrochloric acid, supplies good yields of 2-(1-phthalazinyl)-1(2H)-phthalazinone,[4] which represents the phthalazine analogue of V, unexpectedly obtained by us in an anhydrous medium.

4-Chloro-1H-2,3-benzoxazine is a neutral oil and like 1-chlorophthalazine very resistance to aqueous alkali, in fact IV is recovered unaltered, even after heating for 1 hr with 10% NaOH on a steam-bath. Hydrolysis of 4-chloro-1H-2,3-benzoxazine with dilute HCl leads exclusively to I, while 20% HCl opens[2] the benzoxazine ring with formation of α-aminoxy-*o*-toluic acid hydrochloride (VII), also obtained from I under these conditions.

The use of phosphorus pentabromide has made it possible to transform I into the corresponding 4-bromo-1H-2,3-benzoxazine (VI). The yields were very poor and this was due to the reduced stability of the 4-bromo as compared with the 4-chloro derivative. Attempts to obtain 4-iodo-1H-2,3-benzoxazine, by exchange of the halogen (Cl, Br) in position 4 with sodium iodide, did not give a positive result. Compound IV reacts easily with sodium methanethiolate giving excellent yields of 4-methylthio-1H-2,3-benzoxazine (VIII) which forms an interesting compound for further studies.

4-Chloro-1H-2,3-benzoxazine (IV), on reaction with potassium cyanide in 75% EtOH, forms directly 4-carbamyl-1H-2,3-benzoxazine (IX). In no test was the 4-cyano-derivative isolated. Amide IX, after a two-day saponification in alcoholic

CHART 2



alkali at room temperature, yielded 1H-2,3-benzoxazine-4-carboxylic acid (X). This compound is unstable, even at room temperature, and was therefore immediately used in the crude state for the subsequent reactions. A small quantity was purified by crystallization for analytical purposes. Production of acid X permitted the synthesis of many derivatives as well as the parent member of the series being investigated. In fact, on heating at 90° in 50% H_2SO_4, 1H-2,3-benzoxazine-4-carboxylic acid rapidly loses CO_2 giving 1H-2,3-benzoxazine (XI) which was isolated as the hydrochloride. By making a cold aqueous solution of the hydrochloride alkaline, the free base is obtained, and this, being heat-sensitive, was purified by rapid distillation under vacuum.[8] The structure of XI has been confirmed by analysis; by the NMR spectrum which demonstrates the presence of a methylene signal with a chemical shift (τ = 4·69 ppm) characteristic of the benzoxazine ring, the presence of 5 hydrogens, four on the benzene ring and one on the double bond, and finally, the absence of mobile hydrogens; by the variation of the UV spectrum with pH indicating the presence of an ionizable group connected with the chromophore, whose p*Ka* determined spectrophotometrically is 6·9. Moreover, the product, on treatment with methyl iodide, gives a mono-methiodide, indicating the presence of a tertiary nitrogen and, on treatment with strong alkalies, it opens to *o*-cyano-benzyl alcohol. The IR spectrum of XI is abnormal as it shows a band at 3300 cm^{-1} which, however, is interpreted as an overtone of the $\nu_{C=N}$ situated at 1660 cm^{-1} (Fig. 1).

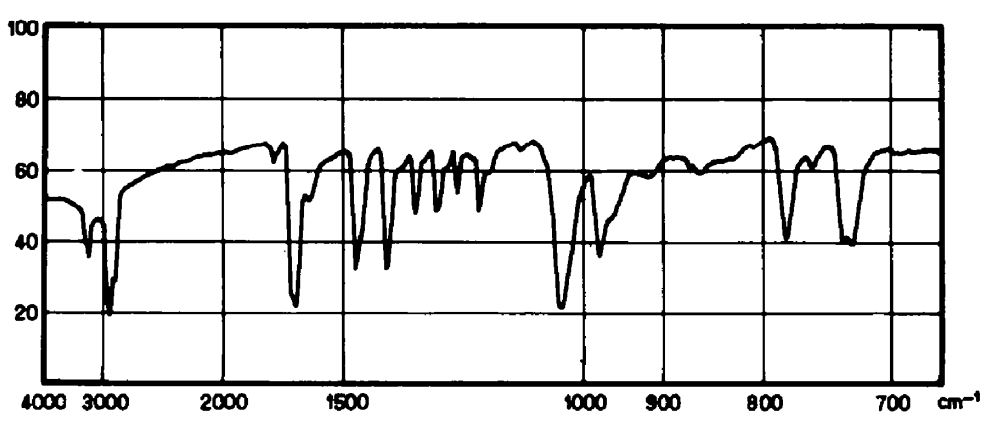
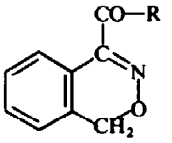
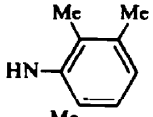
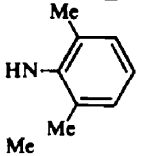
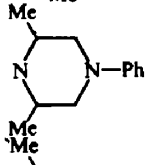
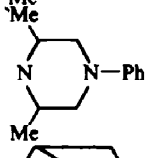


Fig 1. .

1H-2,3-Benzoxazine-4-carboxylic acid (X) was transformed with thionyl-chloride at room temperature into the acid chloride XIII, which is unstable and immediately reacted with a series of aliphatic and aromatic amines [(a) ethylamine; (b) diethylamine; (c) β-diethylaminoethylamine; (d) 2,3-dimethylaniline; (e) 2,6-dimethylaniline; (f, g) *trans*- and *cis*-2,6-dimethyl-1-phenylpiperazine;[5,6] (h) 3-methyl-3,8-diazabicyclo[3.2.1]octane[7]]. By means of a general method which involved heating two moles of amine with one of acid chloride XIII in anhydrous benzene, the respective amides (XIV) (a . . . h) were obtained, and their analytical and physico-chemical data are given in Table 1.

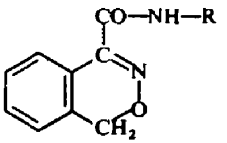
TABLE 1 1H-2,3-BENZOXAZINE-4-CARBOXYAMIDES (XIV)

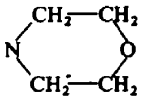
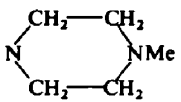


XIV	R	m.p. °C	Yield %	Formula	Found C	Found H	Found N	Required C	Required H	Required N
a	HNEt	77–78[a]	58	$C_{11}H_{12}N_2O_2$	64·63	6·10	13·59	64·69	5·92	13·72
b	NEt_2	76–77[a]	72	$C_{13}H_{16}N_2O_2$	67·04	7·10	11·56	67·22	6·94	12·06
c	$NH-(CH_2)_2NEt_2$	136–137[b]	60	$C_{15}H_{21}N_3O_2 \cdot HCl$	57·48	7·50	13·34	57·77	7·11	13·48
d		153–154[a]	53	$C_{17}H_{16}N_2O_2$	72·65	6·09	10·03	72·84	5·75	9·99
e		41–142[a]	58	$C_{17}H_{16}N_2O_2$	72·58	5·95	10·20	72·84	5·75	9·99
f		144–145[a]	64	$C_{21}H_{23}N_3O_2$	72·14	6·58	11·82	72·18	6·63	12·03
g		130–132[c]	56	$C_{21}H_{23}N_3O_2$	71·88	6·97	12·14	72·18	6·63	12·03
h		259–260[a]	40	$C_{16}H_{19}N_3O_2 \cdot HCl$	60·00	6·18	12·93	59·71	6·28	13·06

[a] From EtOH; [b] From isopropanol; [c] from isopropyl ether.

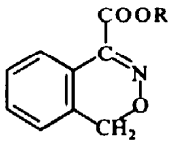
TABLE 2. HYDRAZIDES OF 1H-2,3-BENZOXAZINE-4-CARBOXYLIC ACID (XV)



XV	R	m.p. °C (from)	Yield %	Formula	Found C	Found H	Found N	Required C	Required H	Required N
a	NH_2	114–115[a]	75	$C_9H_9N_3O_2$	56·44	4·90	21·68	56·54	4·75	21·98
b		147–148[a]	38	$C_{13}H_{15}N_3O_3$	60·00	6·00	16·23	59·76	5·79	16·08
c		156–157[b]	40	$C_{14}H_{18}N_4O_2$	60·97	6·85	20·19,	61·29	6·61	20·43

[a] From EtOH; [b] From EtOH isopropylether.

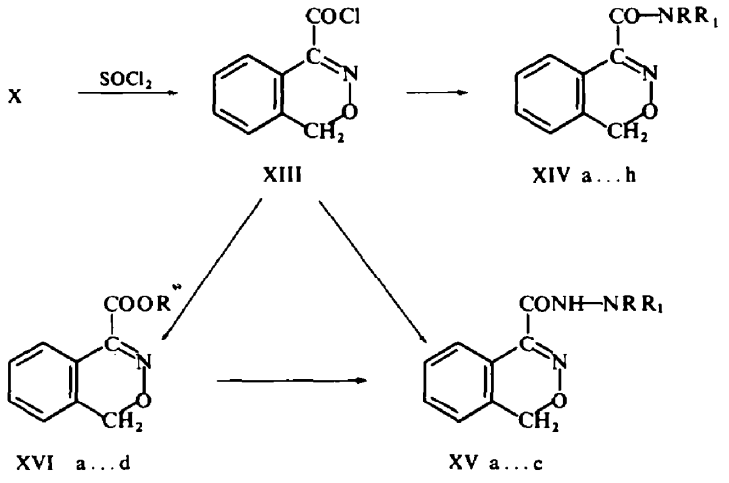
TABLE 3 ESTERS OF 1H-2,3-BENZOXAZINE-4-CARBOXYLIC ACID (XVI)



XVI	R	B.p. °C/mm or m.p. °C	Yield %	Formula	Found C	Found H	Found N	Required C	Required H	Required N
a	Et	120/0·2	75	$C_{11}H_{11}NO_3$	64·15	5·33	7·10	64·38	5·40	6·83
b	Ph	108–109[a]	60	$C_{15}H_{11}NO_3$	70·99	4·57	5·37	71·14	4·37	5·53
c	$(CH_2)_2NEt_2$	140–141[b]	27	$C_{15}H_{20}N_2O_3 \cdot HCl$	57·58	7·02	8·78	57·59	6·77	8·95
d	$(CH_2)_3NEt_2$	157–158[a]	32	$C_{16}H_{22}N_2O_3 \cdot HCl$	59·00	7·25	8·40	58·80	7·09	8·57

[a] From EtOH; [b] From EtOH–ether.

CHART 3



Likewise, compound XIII reacts with N-aminomorpholine and 1-amino-4-methylpiperazine, giving the hydrazides XVb and c respectively (Table 2). The hydrazide of 1H-2,3-benzoxazine-4-carboxylic acid (XVa) has been prepared by reaction of 4-carbethoxy-1H-2,3-benzoxazine (XVIa) with alcoholic hydrazine. Compound XVIa was obtained in excellent yields, by treatment of XIII with warm ethanol. The phenyl ester XVIb and the basic esters XVIc and d required, by contrast, more drastic experimental conditions, and were prepared by warm condensation of XIII with the sodium derivatives of the respective alcohols (Table 3).

The chemical and biological study of 1H-2,3-benzoxazines is being continued.

EXPERIMENTAL*

4-Chloro-1H-2,3-benzoxazine (IV). To a cold soln of I (29·9 g; 0·20 mole) in 3 l. anhyd $CHCl_3$, 125 g (0·60 mole) PCl_5 were added and the mixture was stirred at 0° for 3 hr and at room temp for 30 min. At the end of the reaction period, inorganic salts were removed by filtration and the filtrate was washed with $NaHCO_3$ aq, with water and dried over Na_2SO_4. Distillation of the $CHCl_3$ soln gave 28·6 g (85%) of IV, b.p. 125–130°/2 mm. (Found: C, 57·00; H, 3·67; N, 8·05; Cl, 21·13; O, 9·59. C_8H_6ClNO requires: C, 57·33; H, 3·61; N, 8·36; Cl, 21·15; O, 9·54%); IR: 1540 (C=N), 768 (aromatic CH) and 990, 860 cm^{-1} (not assigned).

3-[4-(1H-2,3-*Benzoxazinyl*)]1H-2,3-*benzoxazine*-4(3H)*one* (V). A mixture of I (119·4; 0·80 mole) and 183·5 g (0·88 mole) powdered PCl_5 in 1·7 l. anhyd $CHCl_3$ was refluxed for 30 min. The soln was then evaporated *in vacuo* and the residue taken up in ether and cooled in ice. The crystalline product was collected and recrystallized from EtOH, to give 45 g of V, m.p. 137–138°. (Found: C, 68·55; H, 4·31; N, 9·80; O, 17·27%); $C_{16}H_{12}N_2O_3$ requires: C, 68·56; H, 4·32; N, 10·00; O, 17·13); IR: 1685 (C=O), 1535 (C=N) and 745 cm^{-1} (aromatic CH). NMR ($CDCl_3$): 4·88 and 4·64 τ (s's, 4H, methylene hydrogens), 3·0–1·7 τ (m's, 8H, aromatic hydrogens).

The filtrate was shaken with $NaHCO_3$ aq, with water, then dried over Na_2SO_4 and the solvent evaporated, to give 63·67 g of crude IV.

* M.ps and b.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer spectrophotometer, Model 137; NMR spectra on a Varian A-60 spectrometer with TMS as internal reference (τ = 10·00 ppm).

1H-2,3-*Benzoxazine*-4(3H)one (I)

(1) *Hydrolysis of* IV. Compound IV (0·5 g) in 10 ml of 5% HCl was heated on a steam-bath for 7 hr. After cooling, the ppt was collected and recrystallized from EtOH, yield: 0·4 g (90%), m.p. 124–126°. The m.p. was not depressed by admixture with an authentic sample of I.[2]

(2) *Hydrolysis of* V. A suspension of V (50 g) in 500 ml of 10% HCl was refluxed for 2 hr and after standing overnight in a refrigerator, the ppt was collected, yield: 47 g of I, m.p. 124–125°.

α-*Aminoxy-o-toluic acid* (VII) *from* IV. Compound IV (0·5 g) in 10 ml 20% HCl was refluxed for 1 hr, the resulting soln was cooled and the ppt collected, yield: 0·4 g (66%), m.p. 168–170° dec, identified as VII hydrochloride.[2] The same product VII was obtained by hydrolysis of I with conc HCl.

4-*Bromo*-1H-2,3-*benzoxazine* (VI). A soln of I (3 g, 0·02 mole) in 50 ml of $CHCl_3$ was added to 9·47 g (0·02 mole) PBr_5 dissolved in 50 ml anhyd $CHCl_3$. After 20 min at room temp, the mixture was worked up as described for the chloro derivative; the residue from ether was quickly distilled according to a new technique[8] collecting the fraction (1·5 g, 35%) boiling at 108–110°/0·7 mm. Compound VI, obtained as an oil, was unstable. (Found: N, 6·60; Br, 37·51. C_8H_6BrNO requires: N, 6·60; Br, 37·68%); IR: 1540 (C=N) and 770 cm^{-1} (aromatic CH).

4-*Carbamyl*-1H-2,3-*benzoxazine* (IX). A mixture of 42 g (0·25 mole) of IV and 32·5 g (0·5 mole) KCN in 380 ml 75% EtOH was heated for 4 hr at 130° in a one liter Parr apparatus. Thereafter, the reaction mixture was concentrated at 40° under *vacuum*, the residue diluted with ether and washed with a sat NaCl aq. The ether soln was dried (Na_2SO_4) and evaporated to dryness *in vacuo*; the residue was crystallized upon addition of a small amount of warm isopropyl-ether, then cooled, yield: 20·7 g (46·4%), m.p. 125–129°. An analytical sample, recrystallized from EtOH, melted at 128–129°. (Found: C, 61·35; H, 4·75; N, 15·95. $C_9H_8N_2O_2$ requires: C, 61·36; H, 4·58; N, 15·90%); IR: 3350, 3150 (NH_2); 1640 (C=O); 1600 (NH_2); 1530 (C=N) and 755 cm^{-1} (aromatic CH).

1H-2,3-*Benzoxazine*-4-*carboxylic acid* (X). Compound IX (26·4 g, 0·15 mole) was added to a soln of 19·8 g (0·30 mole) 85% KOH in 300 ml EtOH and allowed to stand for 2 days with occasional stirring. The ppt obtained was collected by suction and washed with EtOH. The filtrate concentrated to 150 ml *in vacuo* (30°), was kept in a refrigerator overnight and an additional crop of crystals collected. From the mother liquor evaporated to dryness and diluted with water, 5·6 g of IX was recovered. The combined ppts of crude K-salt were dissolved in 90 ml H_2O, some insoluble material (unreacted carbamyl-derivative IX) filtered off (3·1 g, m.p. 127–129°) and the filtrate acidified with 10% HCl. The ppt was extracted with ether, washed with water and dried over Na_2SO_4; evaporation at low temp gave 16·5 g (62%) of crude X. This compound was unstable: a small sample was recrystallized from isopropyl-ether, m.p. 88–89·5°. (Found: N, 7·61; $C_9H_7NO_3$ requires: N, 7·91%); IR: 2800–2100 (OH); 1720 (C=O); 1540 (C=N); 1200 (C—O); 740 cm^{-1} (aromatic CH).

The stable cyclohexylammonium salt of X was prepared by adding cyclohexylamine in molar proportion to an ether soln of the acid X. The collected ppt was recrystallized from EtOH–ether, m.p. 130° dec. (Found: C, 65·06; H, 7·58; N, 10·07. $C_{15}H_{20}N_2O_3$ requires: C, 65·19; H, 7·30; N, 10·14%).

1H-2,3-*Benzoxazine hydrochloride* (XI). To 10 ml 50% H_2SO_4 heated at 90°, 1·06 g (5 mmole) of X was added and the soln was kept at 90–95° for 10 min. A vigorous CO_2 evolution was observed. After cooling in an ice-bath, 30 ml 20% Na_2CO_3 aq were added and the mixture extracted with ether. The ether extracts were thoroughly washed with a sat NaCl aq, dried on Na_2SO_4 and filtered. By adding an ether soln of HCl, a gummy ppt was obtained which after decantation of the solvent was dissolved in a small amount of EtOH and the soln diluted with 10 vols ether. The ppt, after recrystallization from EtOH, melted at 193–194° (0·52 g, 51%). (Found: C, 56·67; H, 4·90; N, 8·20; Cl, 21·18. $C_8H_7NO \cdot HCl$ requires: C, 56·65; H, 4·76; N, 8·26; Cl, 20·90%); IR: 3000–2000 (NH^+), 1670 (C=N), 1620 (NH^+) and 740 cm^{-1} (aromatic CH); NMR (DMSO-d_6) = 4·02 τ (s, 2H, methylene hydrogens), 2·5–1·0 τ (m's, 5H, aromatic hydrogens and CH=), ~ −1 τ (broad s, ~ 1H, HCl); UV: in 0·1 N HCl, λ_{max} = 244, 282, 288 (sh) mμ; in 0·1 N NaOH, λ_{max} 236, 275, 282 mμ.

1H-2,3-*Benzoxazine* (XI—Base). The corresponding *free base* was obtained by adding $NaHCO_3$ aq* to an ice-cold aqueous soln of the hydrochloride. The resulting turbid mixture was immediately extracted 3 times with ether, the combined extracts dried on Na_2SO_4 and distilled *in vacuo* at 30°. A small amount of water was removed by dissolving the crude base in benzene and subsequent distillation of the azeotropic H_2O-benzene mixture *in vacuo*. The residue was quickly distilled at 85°/0·15 mm by a new technique.[8] The base solidified on standing; m.p. 53–55° (picrate, m.p. 222° dec from EtOH). (Found: C, 71·95; H,

* With NaOH aq the base partially opened to *o*-cyano-benzyl alcohol.

5·45; N, 10·30. C_8H_7NO requires: C, 72·16; H, 5·30; N, 10·52%); IR: see Fig. 1; NMR ($CDCl_3$): 4·69 τ (s, 2H, methylene hydrogens), 3·0–2·0 τ (m's, 5H, aromatic hydrogens and CH=).

1H-2,3-*Benzoxazine methiodide* (XII). To a soln of 0·25 g of XI in 2 ml MeOH, 1 ml MeI was added and the mixture refluxed for 90 min. After distillation of the solvent, the residue was triturated with ether, collected and crystallized from EtOH, yield: 0·14 g; m.p. 194–195°. (Found: N, 4·91; I, 46·35; $C_9H_{10}INO$ requires: N, 5·09; I, 46·13%).

4-*Methylthio*-1H-2,3-*benzoxazine* (VIII). A soln of 10 mmole of IV and 11 mmole of sodium methanethiolate (from NaOEt and MeSH) in 7 ml EtOH was refluxed for 30 min, then evaporated to dryness. The residue, diluted with ether, was shaken with water and the ether soln dried on Na_2SO_4. After evaporation of the solvent, the oil was distilled *in vacuo*,[8] yield: 1·55 g (86·5%), b.p. 120°/0·7 mm. (Found: N, 7·62; S, 17·84; C_9H_9NOS requires: N, 7·82; S, 17·89%).

Derivatives of 1H-2,3-*benzoxazine-4-carboxylic acid*

1H-2,3-*Benzoxazine-4-carboxylic acid chloride* (XIII). A soln of 3·54 g (0·02 mole) of X in 35 ml $SOCl_2$ and 1 ml pyridine was allowed to stand 18 hr at room temp, then evaporated under reduced press at 30° and the residue was taken up with anhyd benzene, filtering off the solid residue. The clear benzene soln was evaporated to dryness *in vacuo* at low temp, yielding 3·5 g of XIII; this crude product was used in the next reactions. An analytical sample recrystallized from hexane melted at 59–61°. (Found: N, 7·40; Cl, 18·02. $C_9H_6ClNO_2$ requires: N, 7·16; Cl, 18·13%); IR: 1765 (C=O), 1525 (C=N) and 764 cm^{-1} (aromatic CH). A small amount was distilled[8] without decomposition, b.p. 110°/0·2 mm.

Amides of 1H-2,3-*benzoxazine-4-carboxylic acid*

General procedure (XIVa..h)—trans-4-(4-*phenyl*-2,6-*dimethyl*-1-*piperazinyl-carbonyl*)-1H-2,3-*benzoxazine* (XIVf). A soln of 0·98 g (5 mmole) of XIII in 40 ml anhydrous benzene was added dropwise under stirring to a soln of 1·9 g (10 mmole) *trans*-2,6-dimethyl-4-phenyl-piperazine[6] in 20 ml benzene at room temp. The mixture was stirred for 1 hr at 20–25°, for 1 hr at 65–70° to complete the reaction, and then cooled. After washing with 5% AcOH, with $NaHCO_3$ aq and water, the benzene layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue, after trituration with ether, was recrystallized from EtOH, yield: 1·06 g of XIVf, m.p. 142–144°; IR: 1650 (C=O); 1550 (C=N); 765 and 700 cm^{-1} (aromatic CH). Compounds XIVa, b, f, g, h, were prepared according to this procedure (Table 1). Compound XIVc was washed with water, instead of AcOH; compounds XIVd and XIVe with 5% HCl. The hydrochlorides of XIVc and XIVh were obtained by treating the crude base in anhyd ether with dry HCl and crystallizing them from appropriate solvents.

Hydrazides of 1H-2,3-*benzoxazine-4-carboxylic acid* (XVa . . . c)

1H-2,3-*Benzoxazine-4-carboxylic acid hydrazide* (XVa). A soln of 6 g (0·029 mole) of XVIa (s.u.) and 2·78 ml (0·088 mole) anhyd hydrazine in 60 ml abs EtOH was refluxed for 90 min, the solvent and the excess of hydrazine evaporated *in vacuo*, and the residue crystallized from hot EtOH, yield: 4·2 g (75%); m.p. 110–112°; IR: 3300–3370 (NH); 1670 (C=O); 1610 (NH); 1550 (C=N) and 763 cm^{-1} (aromatic CH). 4-(4-*Methyl*-1-*piperazinylcarbamyl*)1H-2,3-*benzoxazine* (XVc). To a soln of 1·15 g (10 mmole) 4-methyl-1-aminopiperazine in 20 ml anhyd benzene, 0·098 g (5 mmole) crude XIII in 40 ml anhyd benzene was added slowly. After the addition the mixture was stirred for 2 hr at room temp and for 1 hr at 70°. The reaction mixture was then cooled, the ppt filtered off and the filtrate evaporated to dryness *in vacuo*. Recrystallization from isopropyl ether yielded 0·55 g (40%) of XVc m.p. 153–154°; IR: 3300 (NH), 1680 (C=O); 1540 (C=N) and 758 cm^{-1} (aromatic CH).

4-[1-*Morpholinylcarbamyl*]-1H-2,3-*benzoxazine* (XVb). The compound was prepared according to the above procedure.

Esters of 1H-2,3-*benzoxazine-4-carboxylic acid* (XVIa . . . d)

Phenyl-1H-2,3-*benzoxazine-4-carboxylate* (XVIb). A soln of 0·58 g (3 mmole) of XIII in 20 ml anhyd benzene was added dropwise to a stirred suspension of 0·35 g (3 mmole) NaOPh in 20 ml benzene. The reaction mixture was then stirred for 30 min at room temp, the inorganic salts were filtered off and washed with benzene and the filtrate evaporated *in vacuo*. The residue was crystallized from EtOH (charcoal) to give 0·46 g (60%) of XVIb, m.p. 108–109°; IR: 1740 (C=O), 1540 (C=N); 1200 (C–O) and 747, 690 cm^{-1} (aromatic CH).

Diethylaminoethyl-1H-2,3-*benzoxazine-4-carboxylate hydrochloride* (XVIc). Sodium (0·75 g, 25 mmole)

was heated with 180 ml anhyd toluene and 10 ml abs EtOH until completely dissolved, then 3·24 g (27 mmole) diethylamino-ethanol was added at 50° with stirring and the EtOH removed by azeotropic distillation. The mixture was then cooled at 20° and a soln of 4·9 g (25 mmole) of XIII in 130 ml toluene was added dropwise. After stirring for 2 hr, at 20° and an additional hr at 70°, the mixture was cooled, the toluene suspension was washed with water and dried on Na_2SO_4. After removal of the solvent, the residue was treated with an ether soln of HCl and the ppt collected. After recrystallization from EtOH–ether it melted at 140–141°; IR: 2600–2350 (NH^+); 1730 (C=O), 1530 (C=N), 1215 (C—O) and 790 cm^{-1} (aromatic CH).

Diethylaminopropyl 1H-2,3-*benzoxazine-4-carboxylate hydrochloride* (XVId). This derivative was obtained with a procedure similar to that employed for XVIc.

Ethyl 1H-2,3-*benzoxazinecarboxylate* (XVIa) was obtained directly from XIII and EtOH.

Acknowledgements—The Authors wish to thank Dr. G. G. Gallo, Dr. C. R. Pasqualucci and Dr. Vigevani for the physico-chemical determinations, Miss Dr. G. Pelizza and Mr. A. Restelli for the analytical and microanalytical work and Miss Dr. W. Zanichelli for assistance in compilation of the manuscript.

LITERATURE

[1] Part II. G. Pifferi, P. Consonni and E. Testa, *Gazz. Chim. Ital.* **96**, 1671 (1966).
[2] G. Pifferi and E. Testa, *Tetrahedron* **22**, 2107 (1965).
[3] G. M. Atkinson, C. W. Brown and J. C. E. Simpson, *J. Chem. Soc.* 1081 (1956).
[4] G. M. Badger, I. J. McCarthy and H. J. Rhodda, *Chem. & Ind*, 964 (1954).
[5] G. G. Gallo and A. Vigevani, *J. Heterocyclic Chem.* **2**, 418 (1965).
[6] G. Cignarella, L. Mariani and E. Testa, *Gazz. Chim. Ital*, **96**, 325 (1966).
[7] G. Cignarella, E. Occelli and E. Testa, *Ann. Chim.* **53**, 944 (1963).
[8] G. Pifferi, A. De Ros and M. Borbonese, *Il Farmaco, Ed. Pr.* **22**, 210 (1967).