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O,N-SUBSTITUTED HYDROXYLAMINE DERIVATIVES—VI[1]

1H-2,3-BENZOXAZINE-4(3H)-ONE AND RELATED COMPOUNDS—I

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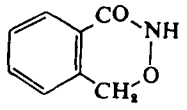
Abstract—The synthesis of a new heterocyclic compound, 1H-2,3-benzoxazine-4(3H)-one (I), by cyclization of α-aminoxy-*o*-toluic acid (VIII) is reported. Some 3-acyl, 3-alkyl- and 3-aminoalkyl-derivatives of I as well as 6-nitro-, 6-amino and 6-sulfonamido-derivatives were prepared. The physico-chemical behaviour of the compounds is reported.

IN the course of our studies on O,N-substituted hydroxylamines with potential pharmacological activity,[1] we have turned our attention to compounds containing the substituted hydroxylamine group as a part of a heterocyclic ring. More particularly, this paper deals with the synthesis of 1H-2,3-benzoxazine-4(3H)-one (I) and its 3- and 6-substituted derivatives



I

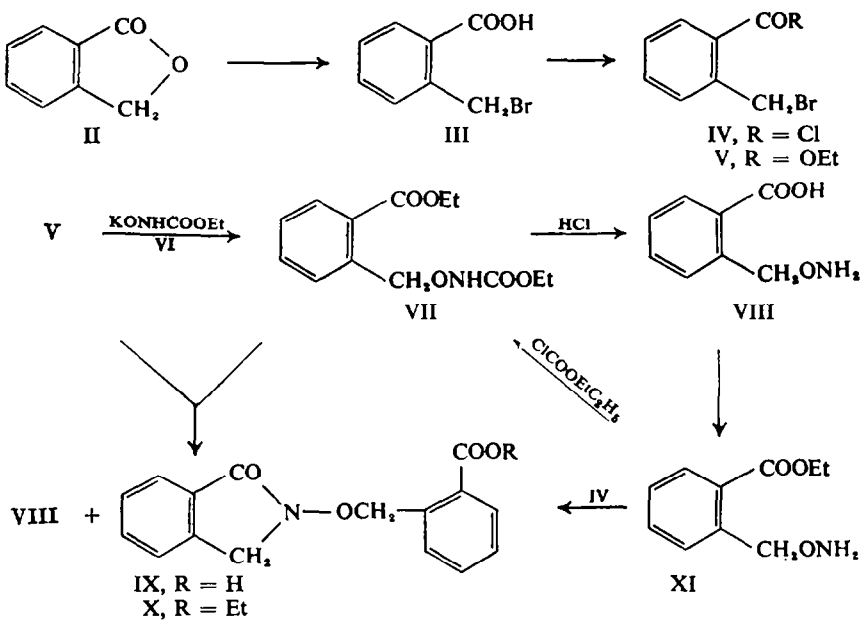
To the best of our knowledge, I and its derivatives are new.* In contrast, some of the analogous 1H-2,3-benzoxazine-1,4-(3H)-diones[2] and 1H-2,3-benzoxazine-1-ones, were reported prior to 1900.

For the synthesis of benzoxazinone (I) pthhalide (II) upon treatment with HBr in glacial acetic acid gave α-bromo-*o*-toluic acid (III). The latter was converted to its acid chloride (IV) and then to its ethyl ester (V). Compound V is not stable to heat and easily cyclizes to phthalide.[3] Therefore, V was reacted in a crude state with the K-salt of hydroxyurethan (VI): the resulting ethyl α-(carbethoxy-aminoxy) *o*-toluate (VII) was accompanied by small amounts of V as shown by TLC. The structure of VII was confirmed by synthesis from ethyl α-aminoxy-*o*-toluate (XI). Compound VII underwent decomposition during distillation; therefore, the hydrolysis of VII with HCl was carried out on the crude material: a mixture of α-aminoxy-*o*-toluic acid (VIII) and 2-(*o*-carboxybenzyloxy) 1-isoindolinone (IX) was obtained. From pure VII only VIII was isolated. Compound IX was easily separated from VIII; the ethyl ester of IX (X) appeared to be identical with a sample prepared by reaction of ethyl α-aminoxy-*o*-toluate (XI) with α-bromo-*o*-toluic acid chloride (IV).

* The structure of 4,4-bis-(*p*-hydroxyphenyl) 1H-2,3-benzoxazine-4(3H)-one was proposed by Haken Lund, *Acta Chim. Scand.* **8**, 1307 (1954) for the reaction product of phenolphthalein with hydroxylamine in alkaline solution; later on, however, Henning Lund, *Acta Chim. Scand.* **14**, 395 (1960) suggested the compound was the *p*-hydroxyanyl of *o*-(*p*-hydroxybenzoyl) benzoic acid and presented evidence for the proposed structure.

[1] E. Testa, B. J. R. Nicolaus, L. Mariani and G. Pagani, *Helv. Chim. Acta* **46**, 766 (1963).
[2] A. J. Ryer and C. B. Smith, *J. Amer. Chem. Soc.* **73**, 5675 (1951).
[3] W. Davies and W. H. Perkin, *J. Chem. Soc.* **121**, 2202 (1922).

Chart 1



α-Aminoxy-*o*-toluic acid (VIII) upon treatment with various reagents (dicyclohexylcarbodiimide, H_2SO_4, AcOH, Ac_2O)* and also by heating in toluene solution cyclized to the desired 1H-2,3-benzoxazine-4(3H)-one (I). The IR and NMR spectra of I are in accordance with the assigned structure. I is a crystalline stable compound, which is not affected by refluxing for 1 hr in 5% HCl or in 5% NaOH. However, prolonged treatment with conc hydrochloric acid led to ring cleavage and formation of VIII hydrochloride.

A number of 3-substituted derivatives of I were prepared. Treatment of compound I with fatty acid chlorides or anhydrides in pyridine gave the 3-acyl derivatives (XIIa–c). These under suitable experimental conditions may be hydrolyzed to I without cleavage of the heterocyclic ring. Compounds XII were also obtained by reaction of VIII with fatty acid anhydrides.

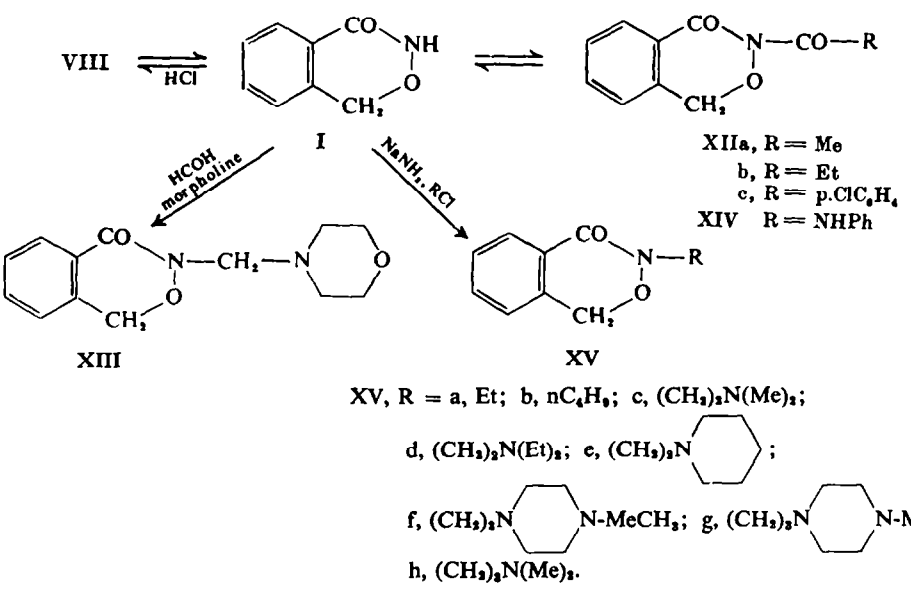
A Mannich reaction with formaldehyde, morpholine, and I gave the 3-morpholinomethyl derivative (XIII). The treatment of I with phenyl isocyanate afforded the 3-phenylcarbamyl derivative (XIV). The reaction of I with sodamide in anhydrous dioxan gave the sodium salt of I; this was reacted with alkyl halides and ω-tertiary aminoalkylhalides to give 3-alkyl- and 3-t-aminoalkyl-1H-2,3-benzoxazine-4(3H)-ones (XVa–h).

We have prepared some benzoxazine-4-ones substituted in the benzene ring. 3-Acetyl-1H-2,3-benzoxazine-4(3H)-one (XIIa) upon treatment with fuming nitric acid underwent an electrophilic substitution yielding the 6-nitro derivative (XVIa). The position assigned to the nitro group was confirmed by hydrolyzing XVIa to 6-nitro-1H-2,3-benzoxazine-4(3H)-one (XVIb) and boiling XVIb with conc hydrobromic acid; the known 6-nitrophtalide[4] was isolated. Compound XVIa was reduced

* In this case the N-acetylderivate of I was obtained.

[4] J. Tirouflet, *Bull. Soc. Sci. Bretagne Spec. N.* **26**, 7 (1951).

Chart 2



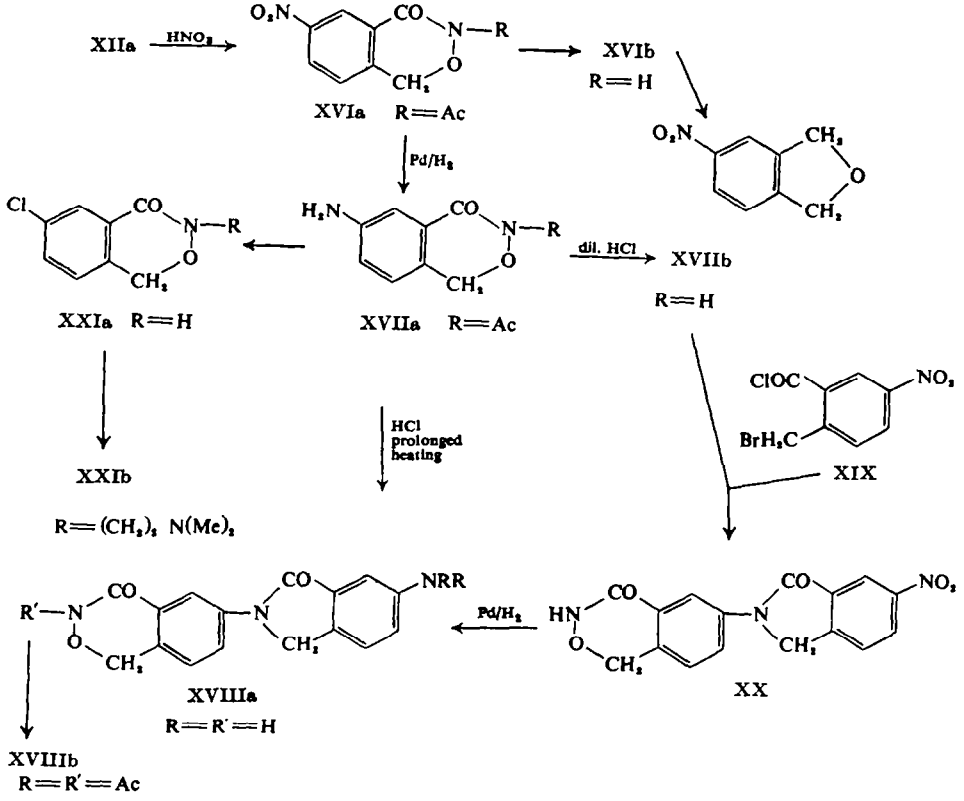
XV, R = a, Et; b, nC_4H_9; c, $(CH_2)_2N(Me)_2$;

d, $(CH_2)_2N(Et)_2$; e, $(CH_2)_2N$;

f, $(CH_2)_2N$ N-$MeCH_2$; g, $(CH_2)_2N$ N-Me;

h, $(CH_2)_2N(Me)_2$.

Chart 3



with 5% Pd–C to 3-acetyl-6-amino-1H, 2,3-benzoxazine-4(3H)-one (XVIIa), which was desacetylated to XVIIb by short heating with diluted HCl. In contrast, a ring contraction took place upon prolonged heating (7 hr) of XVIIa with HCl to give the hydrochloride of 6-(6-amino-1-oxoisoindoline-2-yl)-1H-2,3-benzoxazine-4(3H)-one (XVIIIa). The structure assigned to XVIIa was confirmed in the following manner: XVIIb was condensed with α-bromo-5-nitro-*o*-toluic acid chloride (XIX) in the presence of triethylamine and the resulting 6-(6-nitro-1-oxoindoline-2-yl)-1H-2,3-benzoxazine-4(3H)-one (XX) gave upon catalytic reduction a compound identical (analysis, mixed m.p., IR and NMR spectra) to XVIIIa. Upon treatment with acetic anhydride XVIIIa gave the triacetyl derivative XVIIIb.

The 6-chloro-derivative (XXIa) of I was obtained by the Sandmeyer reaction on XVIIa. Treatment of XXIa with β-dimethylaminoethylchloride gave XXIb.

Two 6-chlorosulfonyl-benzoxazinones (XXIIa and b) were synthesized by treatment of I and XVa with chlorosulfonic acid. Position 6 was assigned to the chlorosulfonyl group by analogy with the nitration reaction. Liquid ammonia converted XXIIa and b into the corresponding 6-sulfonamido derivatives XXIIIa and b.

All the reported benzoxazinones are under pharmacological investigation: the results will be reported later on by Maffii *et al.*

EXPERIMENTAL*

Synthesis of 1H-2,3-*benzoxazine*-4(3H)-*one* (I)

α-*Bromo*-o-*toluic acid* (III)†

To glacial AcOH (5000 ml) saturated with gaseous HBr at 5° was added, slowly, a solution of II (750 g; 5·58 moles) in glacial AcOH (1700 ml). The reaction mixture was then saturated again with gaseous HBr at 5°, stirred for 2 hr at room temp, and for 1 hr at 70°. After standing overnight, the precipitate was collected and the filtrate poured on ice-water. The diluted filtrate yielded a second crop of crystals. The combined precipitated dried at 50° under vacuum gave 72·5% yield of III, m.p. 149–150°. Concentration of the diluted filtrate yielded unreacted phthalide, yield based on reacted II was 92%. (Found: Br, 36·93. $C_8H_7BrO_2$ requires: Br, 37·17%.)

α-*Bromo*-o-*toluic acid chloride* (IV)

A mixture of III (750 g; 3·5 moles) and $SoCl_2$ (810 ml) was refluxed for 3 hr under anhydrous conditions. The excess $SOCl_2$ was removed *in vacuo*. The residue was treated with anhydrous benzene and evaporated to dryness. The oil was crystallized with hexane and the precipitate, collected by suction, washed with hexane and dried over P_2O_5. The filtrate was concentrated *in vacuo* to give an additional crop of crystals, total yield 770 g (91%); m.p. 46–48° from ligroine. (Found: Br, 34·45; Cl, 14·95. C_8H_6BrClO requires: Br, 34·23; Cl, 15·18%.)

Ethyl α-*bromo*-o-*toluate*[5] (V)

To absolute EtOH (1800 ml) at 20°, IV (768 g; 3·28 moles) was added in small portions. After standing for 24 hr at room temp, the solvent was distilled, the oily residue dissolved in ether, washed with dil $NaHCO_3$aq and dried over Na_2SO_4. The solvent was removed at low temp, yielding 712 g (89%) of V. The IR spectrum showed bands at 1730 (C=O), 1600 and 1580 (C=C) and 1260 cm^{-1}

* M.ps and b.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer spectrophotometer Mod. 137; NMR spectra were recorded on a Varian A-60 spectrometer.

† The preparation of this compound has been improved. See also Refs.[5–8].

[5] J. Salkind, *J. Russ. Physik. Chem. Gesellshaft*, **46**, 508 (1914).
[6] J. B. Shoesmith, A. C. Heterington and R. H. Slater, *J. Chem. Soc.*, **125**, 1312 (1924).
[7] E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, **17**, 1252 (1952).
[8] L. Reichel and W. Hampel, *Z. Chem.*, **3**, 190 (1963).

(C—O) in agreement with the proposed structure. This crude product was used in the next reaction. It could not be distilled (thermic dec).

Ethyl α-(carbethoxyaminoxy)-o-toluate (VII)

(*a*) *From crude* V. To a stirred suspension of crude potassium hydroxyurethan[9] (760 g) in anhydrous dimethylformamide (2400 ml), *crude* V (712 g; 2·93 moles) was quickly added. The mixture was heated for 2 hr at 70°, then concentrated *in vacuo*. Water (1100 ml) and 10% NaOHaq (175 ml) were added to the residue and the mixture was extracted with ether. The ether solution was washed with water, dried with Na_2SO_4 and the solvent evaporated. The crude oil weighed 740 g (94·5%) and was used as such in the following reaction.

A small sample distilled in a condenser bulb[10] had a b.p. of 170°/0·5 mm. IR spectrum showed bands at 3240 (NH), 1740 (C=O of ester), 1710 (C=O of carbamate), 1260 (C—O of ester), 1100 (C—O of carbamate) and 743 cm^{-1} (*o*-phenyl). (Found: N, 5·57. $C_{13}H_{17}NO_5$ requires: N, 5·28%.)

(b) *From* XI. To a stirred suspension of XI hydrochloride (1·49 g) and triethylamine (2·4 ml) in anhydrous ether (30 ml), ethyl chlorocarbonate (1 g in 10 ml of anhydrous ether) was added, dropwise. The mixture was refluxed for 3 hr, filtered, and the solvent removed *in vacuo*. The oily residue (2·3 g) easily decomposed by heating to give II. A very small sample, quickly distilled in a condenser bulb[10] showed a b.p. of 175–180°/0·8 mm and an IR spectrum identical with that of VII obtained from V. (Found: C, 58·16; H, 6·59; N, 5·40. $C_{13}H_{17}NO_5$ requires: C, 58·40; H, 6·41; N, 5·28%.)

α-Aminoxy-o-toluic acid (VIII)

(a) *From crude* VII. Compound VII (740 g; 2·77 moles) was refluxed in conc HCl (5500 ml) for 7 hr. The mixture was concentrated *in vacuo* to ½ its original volume and extracted with AcOEt to remove the unreacted product (275 g). The aqueous solution was evaporated to dryness under red. press. and the residue, dried at 100°, gave 345 g crude VIII hydrochloride, white crystals, m.p. 163–164° (dec). The latter was taken up with 1000 ml warm (45°) water and filtered from the insoluble residue (26 g) consisting of IX, m.p. 184–186° from EtOH. The IR spectrum of IX showed bands at 2800–2300 (OH), 1710 and 1670 (C=O), 748 and 740 cm^{-1} (*o*-phenyl), in agreement with the assigned structure (see also below). (Found: C, 68·09; H, 4·70; N, 4·83. $C_{16}H_{13}NO_4$ requires: C, 67·82; H, 4·62; N, 4·94%.)

The aqueous filtrate, after the separation of IX, was neutralized to pH 4·5 with a 10% NaOHaq. The precipitate was collected, washed with a small volume of cold water and dried under vacuum at 40°, yield 155 g of VIII, m.p. 112–118°. IR: 2600–2100 (NH_3^+) 1640 (NH^+); 1570 and 1385 (COO^-) and 750 cm^{-1} (*o*-phenyl). Upon concentration (cyclization) and standing of the mother liquor an additional 26 g of I m.p. 121–124° was obtained.

(b) *From pure* VII. The hydrolysis of VIII carried out as above on a sample of pure VII gave exclusively VIII. No IX could be detected even by TLC.

2-(o-*Carbethoxybenzyloxy*) 1-*isoindolinone* (X)

(a) *From* IX. Dry HCl was slowly bubbled, over a period of 5 hr, into a refluxing suspension of IX (3 g; 0·01 mole) in anhydrous EtOH (50 ml). The clear solution was concentrated *in vacuo*, the residue dissolved in AcOEt, washed with Na_2CO_3aq, dried over Na_2SO_4 and evaporated. The residue was slurried with ether and crystallized from isopropyl ether, yield: 0·9 g (27%), m.p. 89–90°. IR spectrum: 1730 (C=O), 1270 (C—O), 752 and 740 cm^{-1} (*o*-phenyl). (Found: C, 69·69; H, 5·60; N, 4·15. $C_{18}H_{17}NO_4$ requires: C, 69·43; H, 5·49; N, 4·49%.)

(b) *From* XI *and* IV. A solution of IV (2·96 g; 0·013 mole) in anhydrous benzene (20 ml) was added in about 10 min to a stirred mixture of XI (2·5 g; 0·013 mole), triethylamine (3·6 ml) and anhydrous benzene (20 ml). After the addition was completed, the mixture was refluxed for 3 hr,

* VIII hydrochloride may be purified by addition of ether to its EtOH solution: white crystals, m.p. 173–174° (dec). The compound is rather unstable and readily cyclizes with loss of water and HCl. (Found: C, 47·56; H, 5·22; N, 6·47. $C_8H_9NO_3$·HCl requires: C, 47·20; H, 4·95; N, 6·87%.)

[9] B. J. R. Nicolaus, G. Pagani and E. Testa, *Helv. Chim. Acta*, **45**, 1381 (1962).

[10] K. Ronco, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2088 (and particularly 2094) (1956).

cooled and filtered. The filtrate was washed with dil HCl, then with $NaHCO_3$aq, dried over Na_2SO_4 and evaporated. The oily residue was treated with isopropyl ether and left overnight in the refrigerator, yielding solid X (3 g). The compound was collected and recrystallized twice (from ether and from isopropyl ether), yield 1 g (25%), m.p. 89–90°. The mixed m.p. with X from IX was undepressed: the IR spectra were identical. (Found: C, 69·51; H, 5·51; N, 4·39. $C_{18}H_{17}NO_4$ requires: C, 69·43; H, 5·49; N, 4·49%.)

Ethyl α-*aminoxy*-o-*toluate* (XI) *hydrochloride*

Dry HCl was bubbled into a stirred ethanolic suspension of VIII (8 g; 0·048 mole); the mixture was refluxed for 1 hr. The gas stream was then discontinued, the solvent distilled, and the residue triturated with ether then filtered yielding XI hydrochloride (8·8 g; 80%), m.p. 113–115°. A sample, crystallized with caution from AcOEt, m.p. 116–117°. IR spectrum: 2800–2000 (NH_3^+); 1740 (C=O); 1270 (C—O) and 740 cm^{-1} (*o*-phenyl). (Found: C, 51·85; H, 6·20; N, 6·25. $C_{10}H_{13}NO_3$·HCl requires: C, 51·90; H, 6·09; N, 6·05%.)

The corresponding base XI was isolated by adding a cold Na_2CO_3aq to an ice-cold aqueous solution of the hydrochloride, extracting the separated oil with ether, drying and removing the solvent *in vacuo* at low temp. IR spectrum: 3350 (NH); 1730 (C=O) and 1265 cm^{-1} (C—O). This compound decomposed by distillation. (Found: C, 58·16; H, 6·59; N, 5·40. $C_{18}H_{17}NO_5$ requires: C, 58·40; H, 6·41; N, 5·28%.)

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

(a) *From* VIII *with acetic acid.* A suspension of VIII (174 g; 1·1 moles), in glacial AcOH (1000 ml), was heated on a steam bath for 4 hr. The cloudy solution was filtered, distilled and the residue dissolved in hot EtOH (400 ml). On cooling, I (111 g), m.p. 124–126° were obtained. The mother liquor, when concentrated under red. press., gave a second crop of crystals, m.p. 123–125°, yield 116 g (75%). Yield of 1H-2,3-benzoxazine-4(3H)-one from phthalide (II) was 24%.

(b) *From* VIII *with* N,N′-*dicyclohexylcarbodiimide.* To a solution of VIII (1·67 g; 0·01 mole) in EtOH (75 ml) was added a solution of N,N′-dicyclohexycarbodiimide (2·27 g; 0·012 mole) in EtOH (10 ml). The mixture was allowed to stand 1 day. It was concentrated to 40 ml and filtered from dicyclohexylurea. The filtrate was concentrated to dryness and the residue crystallized from EtOH to give I (1·0 g; 67%), m.p. 125–127°.

(c) *From* VIII *by heating.* Compound VIII (1·1 g; 0·006 mole) in toluene (50 ml) was refluxed in a Marcusson's apparatus for 2 hr. The solvent was distilled *in vacuo* and the residue crystallized from EtOH to give I (0·70 g; 71%), m.p. 126–128°.

Samples of I obtained as indicated under a, b and c, are identical (IR spectrum, mixed m.p.). The substance was identified as I on the basis of its IR and NMR spectra. IR spectrum: 3150 (NH); 1670 (C=O); 1610 and 1580 (C=C), 763 and 740 cm^{-1} (*o*-phenyl). NMR spectrum: τ = 4·92 ppm (CH_2); τ = 3·00–2·70 (4H ar) and τ = −0·1 ppm (NH). (Found: C, 64·29; H, 4·87; N, 9·27. $C_8H_7NO_2$ requires: C, 64·50; H, 4·69; N, 9·39%.)

Acid hydrolisis of I. A mixture of I (1 g) and conc HCl (5 ml) was refluxed for 2 hr. The resultant solution was cooled and the precipitate collected, yield 1·2 g (88%), m.p. 168–170° (dec) identified as VIII hydrochloride.

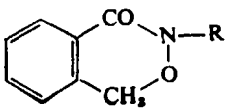
(B) 3-*Substituted derivatives of* I

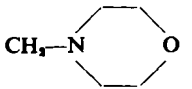
(1) 3-*Acyl*-1H-2,3-*benzoxazine*-4(3H)-*ones* (XII)

Example—3-(p-*Chlorobenzoyl*) 1H-2,3-*benzoxazine*-4(3H)-*one* (XIIc). *p*-Chlorobenzoylchloride (4·2 g; 0·024 mole) were slowly dropped with stirring into a solution of I (3·5 g; 0·023 mole) in anhydrous pyrydine (40 ml). The mixture was kept at 50° for 5 hr then cooled and diluted with ether. The precipitate was collected by suction, washed with water and dried to give XIIc (4·6 g; 70%), m.p. 169–170°, purified by recrystallization from EtOH. Compounds XIIa and b were obtained with this procedure (Table 1).

3-*Acetyl*-1H-2,3-*benzoxazine*-4(3H)-*one* (XIIa)—*from* VIII. Compound VIII (30 g; 0·18 mole) was heated in Ac_2O (100 ml) for 3 hr on a water bath. The resultant clear solution was concentrated *in vacuo* and the residue poured on warm water (50°). After 15 min, the cooled mixture filtered and the collected solid was washed with water and dried, yield 33·8 g (98·5%) of XIIa, m.p. 115–116° from EtOH (Table 1).

TABLE 1



Nr.	R	B.p.	Yield %	Formula (mol. wt.)	Analyses Found C	Found H	Found N	Required C	Required H	Required N
XIIa	$COCH_3$	115–116°	90	$C_{10}H_9NO_3$ (191·17)	62·79	4·84	7·19	62·82	4·75	7·33
XIIb	COC_2H_5	107–108°	75	$C_{11}H_{11}NO_3$ (205·19)	64·30	5·54	7·00	64·40	5·36	6·83
XIIc	COC_6H_4Cl-p	169–170°	70	$C_{15}H_{10}ClNO_3$ (287·68)	62·18	3·50	4·50	62·62	3·50	4·87
XIII		102–103°	82·5	$C_{12}H_{16}N_2O_3$ (248·27)	63·10	6·69	11·20	62·90	6·49	11·29
XIV	$CO—NH—C_6H_5$	152–153°	81·5	$C_{15}H_{12}N_2O_3$ (268·25)	67·10	4·50	10·48	67·15	4·51	10·44

(2) 3-*Morpholinomethyl*-1H-2,3-*benzoxazine*-4(3H)-*one* (XIII)

To a warm solution of I (2·9 g; 0·019 mole) and 38% formaldehyde (2 ml) in EtOH (30 ml), a solution of morpholine (2·05 g; 0·023 mole) in EtOH (50 ml) was slowly added. After the addition was completed, the mixture was refluxed for 30 min, then concentrated *in vacuo*. Upon addition of ether and cooling, a crystalline precipitate separated. This was collected by suction and dried on a water bath, yielding 4 g (82·5%) of XIII, m.p. 99–101° (Table 1).

(3) 3-*Phenylcarbamyl*-1H-2,3-*benzoxazine*-4(3H)-*one* (XIV)

To I (3 g; 0·02 mole) dissolved in anhydrous toluene (30 ml), phenylisocyanate (2·4 g; 0·02 mole) were added and the solution refluxed 5 hr. After cooling overnight, the precipitate was collected by suction, washed with petroleum ether and dried, yield: 4·4 g (81·5%) of XIV, m.p. 150–152° (Table 1).

(4) 3-*Alkyl*-1H-2,3-*benzoxazine*-4(3H)-*ones* (XV)

Example—preparation of 3-*ethyl*-1H-2,3-*benzoxazine*-4(3H)-*one* (XVa). To a solution of I (4 g; 0·027 mole) in anhydrous dioxan (40 ml), finely powdered $NaNH_2$ (0·03 mole) was added and the mixture heated for 1 hr at 70°. A solution of EtBr (4 g; 0·036 mole) in anhydrous benzene (15 ml) was then added, dropwise. The mixture was refluxed with stirring for 10 hr, cooled and the insoluble salts* removed by suction. The filtrate was washed with water, dried with Na_2SO_4 and distilled to give oily XVa (2 g; 42%), b.p. 126–130°/1 mm (air bath).[10] Following this procedure, XVb (R = n-C_4H_9) was also prepared. (Table 2).

3-(*Substituted aminoalkyl*)-1H-2,3-*benzoxazine*-4(3H)-*ones* (XVc–h). *General procedure*

Example—preparation of 3-(2-*piperidinoethyl*)-1H-2,3-*benzoxazine*-4(3H)-*one* (XVe). Finely powdered $NaNH_2$ (0·02 mole) was added to a solution of I (3·5 g; 0·023 mole) in anhydrous dioxan (50 ml). The mixture was stirred for 1 hr at 70°, then a solution of 1-(2-chloroethyl)-piperidine (3·5 g; 0·024 mole) in anhydrous benzene (20 ml) was dropped in and the mixture refluxed for 10 hr. After cooling and removing the salts by suction, the filtrate was evaporated to dryness. Ether was added to the oily residue and the solution extracted with cold dil HCl. The acid aqueous layer was made alkaline with a sat Na_2CO_3aq and extracted twice with ether. The combined ether extracts were washed with water, dried over Na_2SO_4, concentrated, and the residue was distilled in glass bulbs, yield: 4·1 g (67%) of XVe, b.p. 180° (air bath)[10] with a press of 0·8 mm. Compounds XVc–h were prepared with this procedure (Table 2).

(C) 6-*Substituted* 1H-2,3-*benzoxazine*-4(3H)-*ones*

(1) 6-*Nitro and* 6-*amino derivatives*

3-*Acetyl*-6-*nitro*-1H-2,3-*benzoxazine*-4(3H)-*one* (XVIa). TO conc HNO_3 (d = 1·52; 300 ml) cooled to −30°, XIIa (33·8 g; 0·18 mole) was added in small portions in 20 min. The temp was kept for 30 min at −30° and for 30 min at 0°. The mixture was poured on crushed ice, the precipitate collected by suction, washed with water and dried. The filtrate was extracted with AcOEt, the solvent evaporated and an additional crop of product collected. Recrystallization of the combined crops from 600 ml tetrahydrofuran yielded 33·6 g (80·5%) of XVIa, m.p. 175–176°. IR spectrum: 1700 (C=O); 1560 and 1340 cm^{-1} (NO_2). (Found: C, 50·65; H, 3·60; N, 11·62. $C_{10}H_8N_2O_5$ requires: C, 50·85; H, 3·39; N, 11·84%.)

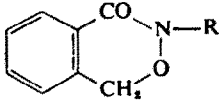
6-*Nitro*-1H-2,3-*benzoxazine*-4(3H)-*one* (XVIb). To XVIa (3·7 g; 0·015 mole) in EtOH (30 ml), 5% HCl (60 ml) was added and the suspension heated on a water bath for 2 hr. After concentrating and cooling, the precipitate was collected, yield 2·65 g (87%), m.p. 202–204° from EtOH. IR spectrum: 3150 (NH); 1665 (C=O); 1520 and 1345 cm^{-1} (NO_2). (Found: C, 49·29; H, 3·26; N, 14·18. $C_8H_6N_2O_4$ requires: C, 49·50; H, 3·09; N, 14·44%.)

6-*Nitrophthalide from* XVIb. A mixture of XVIb (0·2 g; 0·001 mole) and 48% HBr (10 ml) was refluxed for 8 hr. Water (20 ml) was added and the mixture cooled in an ice bath. The precipitate was collected by suction, washed with water and dried, yield 0·1 g (54%), m.p. 144–145°. IR spectrum: 1760 (C=O), 1520 and 1340 (NO_2) cm^{-1}. (Found: N, 8·05. $C_8H_5NO_4$ requires: N, 7·82%.) The compound was identical (IR spectrum, mixed m.p.) with an authentic sample of 6-nitrophthalide.[4]

3-*Acetyl*-6-*amino*-1H-2,3-*benzoxazine*-4(3H)-*one* (XVIIa). Compound XVIa (15 g; 0·06 mole)

* Mixture of inorganic salts and unreacted sodium salt of I.

TABLE 2. 3-ALKYL AND 3-(SUBSTITUTED AMINOALKYL)-DERIVATIVES OF 1H-2,3-BENZOXAZINE-4(3H)-ONE



XV

XV	R	B.p.	Yield %	Formula (mol. wt.)	Nitrogen % Found	Nitrogen % Required	m.p., C° from	Picrates % Found C	Found H	Found N	Required C	Required C	Required N
a	C_2H_5	126–130° (1 mm)	42	$C_{10}H_{11}NO_2$ (177·18)	7·63	7·91							
b	n-C_4H_9	126–130° (0·8 mm)	15	$C_{12}H_{15}NO_2$ (205·24)	6·71	6·82							
c	$(CH_2)_2N(CH_3)_2$	150–152° (0·8 mm)	40	$C_{12}H_{16}N_2O_2$ (220·25)	12·51	12·72	210 (dec.) (T)	48·08	4·35	15·75	48·10	4·26	15·58
d	$(CH_2)_2N(C_2H_5)_2$	152–155° (0·8 mm)	81	$C_{14}H_{20}N_2O_2$ (248·31)	11·32	11·28	158–159 (E)	50·22	5·00	14·86	50·18	5·87	14·66
e	$(CH_2)_2N$ 	180–182° (0·8 mm)	67	$C_{15}H_{20}N_2O_2$ (260·32)	10·60	10·76	192–193 (T)	51·50	5·00	14·49	51·33	4·73	14·32
f	$(CH_2)_2N$  $N-CH_3$	180–181° (0·7 mm)	45	$C_{15}H_{21}N_3O_2$ (275·35)	14·92	15·26	260–262 (dec.) (D)	44·51	3·99	17·35	44·24	3·73	17·10
g	$(CH_2)_2N$  $N-CH_3$	200–203° (0·6 mm)	55	$C_{16}H_{23}N_3O_2$ (289·36)	13·98	14·52	268 (dec.) (D)	45·20	4·12	16·67	45·05	3·91	16·87
h	$(CH_2)_2N(CH_3)_2$	150–155° (1 mm)	70	$C_{13}H_{18}N_2O_2$ (234·28)	11·77	11·96	193–196 (dec.) (T)	49·43	4·70	14·94	49·26	4·57	15·12

T = tetrahydrofuran; E = ethanol; D = dioxane.

were hydrogenated at room temp in EtOH (1000 ml) with 5% Pd–C (3 g). When the calculated quantity of H_2 was absorbed (about 1 hr), the hydrogenation was stopped. The mixture was warmed and the solvent evaporated *in vacuo* after removal of the catalyst, yield 11·2 g (86%), m.p. 168–169° from EtOH. (Found: C, 58·11; H, 5·02; N, 13·45. $C_{10}H_{10}N_2O_3$ requires: C, 58·22; H, 4·89; N, 13·58%.)

6-*Amino*-1H-2,3-*benzoxazine*-4(3H)-*one* (XVIIb). Compound XVIIa (5 g; 0·03 mole) was heated on a water bath in 5% HCl (60 ml) for 30 min. After cooling, a 50% NaOHaq was added to elevate the pH of the solution to 5, and the precipitate collected, yield 3·1 g (78%), m.p. 172–175° from EtOH. IR spectrum: 3400 and 3350 (NH_2); 3160 (NH); 1660 (C=O) and 1630 cm^{-1} (NH_2). (Found: C, 58·51; H, 5·18; N, 16·87. $C_8H_8N_2O_2$ requires: C, 58·52; H, 4·92; N, 17·07%.)

6-(6-*Amino*-1-*oxoisoindol*-2-*yl*)-1H-2,3-*benzoxazine*-4(3H)-*one* (XVIIIa)

(a) *Prolonged hydrolysis of* XVIIa. Compound XVIIa (1·5 g; 0·007 mole) was heated on a water bath *for* 7 *hr* in 5% HCl (18 ml). The product initially dissolved, then slowly precipitated. After cooling, XVIIIa hydrochloride (0·75 g; 62·5%), m.p. 340°, was obtained as a yellow powder insoluble in most organic solvents and very difficult to purify. IR spectrum: 3150 (NH); 1715 and 1670 (C=O) 1540 and 1355 cm^{-1} (NO_2). (Found: C, 12·75; S, 10·28. $C_{16}H_{13}N_3O_3$·HCl requires: N, 12·67; S, 10·68%.)

The free base (XVIIIa) was isolated by dissolving XVIIIa hydrochloride (500 mg) in 50% aqueous MeOH (375 ml) at 40°. The clear solution was adjusted to pH 5 with 0·1M NaOH. The precipitate was collected, washed with water and dried. The crude product was dissolved in warm dioxan (200 ml), the solution filtered on charcoal, concentrated *in vacuo* till cloudy, then allowed to crystallize, yield 0·25 g of XVIIIa, m.p. 283° dec. IR spectrum: 3500 and 3400 (NH_2); 3150 (NH); and approx 1680 cm^{-1} (broad) (C=O). (Found: C, 64·58; H, 4·69; N, 14·11. $C_{16}H_{12}N_3O_3$ requires: C, 65·08; H, 4·44; N, 14·23%.)

(b) *Synthesis from* XVIIb + XIX—2-*bromomethyl*-5-*nitrobenzoyl chloride* (XIX). A mixture of crude 2-bromomethyl-5-nitrobenzoic acid[8] (2·6 g; 0·01 mole) and $SOCl_2$ (20 ml) was refluxed for 3 hr. The excess of $SOCl_2$ removed *in vacuo* and the residue treated with benzene and evaporated to dryness at low temp; the last procedure was repeated 3 times. The oily residue, 2·8 g, could not be crystallized. IR spectrum: 1770 (C=O); 1535 and 1350 (NO_2), in agreement with the structure of XIX.

6-(6-*Nitro*-1-*oxoisoindol*-2-*yl*) 1H-2,3-*benzoxazine*-4(3H)-*one* (XX). To XVIIb (10 g; 0·061 mole) and triethylamine (21·5 ml; 0·15 mole) in anhydrous dioxan (370 ml) was added a solution of XIX (17 g; 0·061 mole) in anhydrous dioxan (60 ml), dropwise and with stirring. During this operation, the temp climbed to 35°. The mixture was allowed to stand for 18 hr and was stirred occasionally. The collected precipitate, washed with dioxan, water and dried, weighed 6 g m.p. 266–268° (dec). By concentrating the mother liquor, a second crop of XX, 5 g, m.p. 264–267° (dec) was obtained (total yield 55%).

The product had a very low solubility in the most organic solvents and was used without further purification. For the analysis, a small sample was recrystallized from dioxan–pyridine: m.p. 285° (dec). IR spectrum: 3150 (NH); 1715 (C=O in isoindol ring); 1670 (C=O benzoxazine); 1540 and 1355 cm^{-1} (NO_2). (Found: N, 12·78. $C_8H_{11}N_3O_5$ requires: N, 12·92%.)

6-(6-*Amino*-1-*oxoisoindol*-2-*yl*)-1H-2,3-*benzoxazine*-4(3H)-*one* (XVIIIa). A sample of XX (0·003 mole) was dissolved in warm dioxan (1500 ml) then concentrated to 500 ml. The solution was hydrogenated with 10% Pd–C (1 g) at room temp and atm press. Uptake of H_2 was essentially complete after 3 hr. The catalyst was filtered and the filtrate divided in 2 equal samples:

(1) by concentrating *in vacuo* to 25 ml and cooling 0·2 g (44% yield) of XVIIIa, m.p. 267–278° (dec) were obtained. The mixed m.p. with a sample of XVIIIa from hydrolysis of XVIIa was not depressed and the IR spectra were identical. (Found: N, 13·98. $C_{16}H_{12}N_3O_3$ requires: N, 14·23%.)

(2) by adding an ether solution of HCl, XVIIIa hydrochloride was obtained, 0·28 g m. p. 340°, identical (mixed IR spectra) with a sample of XVIIIa hydrochloride from hydrolysis of XVIIa.

3-*Acetyl*-6-[6-*diacetylamino*-1-*oxoisoindol*-2-*yl*] 1H-2,3-*benzoxazine*-4(3H)-*one* (XVIIIb). A solution of XVIIIa hydrochloride (0·3 g) in anhydrous pyridine (6 ml) and Ac_2O (3 ml) was heated on a steam bath for 4 hr and then concentrated *in vacuo* in order to remove the solvent. The residue slurried with water gave 0·3 g (78·5%) crude XVIIIb, m.p. 225–227° (dec). The compound was dissolved in warm dioxan (60 ml), filtered, concentrated to a small volume and reprecipitated with

ether, yielding 0·13 g pure XVIIIb, m.p. 235–237° (dec). IR spectrum: approx 1730 (broad) (C=O); 830 and 770 cm^{-1} (phenyl). (Found: C, 62·98; H, 4·49; N, 10·08. $C_{22}H_{19}N_3O_6$ requires: C, 62·75; H, 4·59; N, 9·98%.)

(2) *6-Chloro derivatives*

6-Chloro-1H-2,3-benzoxazine-4(3H)-one (XXIa). A solution of XVIIa (6·2 g; 0·03 mole) in 15% HCl (70 ml) was diazotized at 0° by adding a solution of $NaNO_2$ (2·5 g) in water (20 ml). The mixture was stirred for 10 min at 0°, treated with a small amount of urea to eliminate the excess of HNO_2 and then added to a 15% HCl (120 ml) of CuCl (obtained from 20 g $CuSO_4 \cdot 5H_2O$). After stirring for 10 min at room temp, the precipitate was collected, washed with water, dried and refluxed 2 hr in 10% HCl (80 ml) and EtOH (25 ml). The precipitate obtained by concentration was washed with water and dried to give 2·5 g (45%) of XXIa hydrochloride, m.p. 189–190°. Recrystallization from 70% EtOH gave 2 g, m.p. 189–192°. IR spectrum: 3150 (NH) and 1665 (C=O) cm^{-1}. (Found: C, 52·05; H, 3·78; N, 18·95. $C_8H_6ClNO_2$ requires: C, 52·32; H, 3·29; N, 19·31%.)

6-Chloro-3-(β-dimethylaminoethyl) 1H-2,3-benzoxazine-4(3H)-one hydrochloride (XXIb). Finely powdered $NaNH_2$ (0·56 g; 0·014 mole) was added to a solution of XXI (2·57 g; 0·014 mole) in anhydrous dioxan (30 ml), the mixture heated 2 hr at 70–80°, then dropwise treated with a solution of (2-chloroethyl) dimethylamine (1·81 g; 0·0168 mole) in dry benzene (15 ml). The mixture was heated 10 hr under stirring then cooled; the precipitate was removed by suction and the filtrate evaporated to dryness. The residue was taken up with cold dil HCl and the solution extracted with ether. The acidic mother liquor was basified with a conc Na_2CO_3aq then extracted with ether. The extract was dried over Na_2SO_4, then treated with an ether solution of HCl. The precipitate (XXIb hydrochloride) was collected and crystallized from EtOH–ether, yield: 2·2 g (54%); m.p. 203–204°. (Found: N, 9·60; Cl, 24·43. $C_{12}H_{15}ClN_2O_2 \cdot HCl$ requires: N, 9·56; Cl, 24·65%.)

(3) *Sulfonic acid derivatives*

6-Chlorosulfonyl-1H-2,3-benzoxazine-4(3H)-one (XXIIa). Compound I (6 g; 0·04 mole) was heated at 140° for 2 hr in chlorosulfonic acid (30 ml). The solution was then cooled and poured on crushed ice with vigorous stirring. On standing, the mixture crystallized, yield 3·8 g (35%), m.p. 178–181° (dec) from acetone. IR spectrum: 3150 (NH); 1670 (C=O); 1380 and 1180 cm^{-1} (SO_2). (Found: N, 5·48; S, 14·15. $C_8H_6ClNO_4S$ requires: N, 5·65; S, 14·32%.)

6-Chlorosulfonyl-3-ethyl-1H-2,3-benzoxazine-4(3H)-one (XXIIb). This was prepared from 3-ethyl-1H-2,3-benzoxazine-4(3H)-one (3 g; 0·017 mole) as described for XXIIa. The compound was obtained as an oil, which was extracted with trichloroethylene. The extract was washed with water, dried and the solvent evaporated, yield 4·2 g of an oil which could not be crystallized; IR spectrum: 1670 (C=O); 1380 and 1180 cm^{-1} (SO_2).

6-Sulfamyl-1H-2,3-benzoxazine-4(3H)-one (XXIIIa). Compound XXIIa (2 g; 0·0075 mole) was added to anhydrous ammonia (20 ml). After evaporation of the latter, the compound was taken up in a small amount of water, neutralized with dil HCl to pH 6 and cooled to give XXIIIa (1·5 g; 87·5%), m.p. 250° (dec) from water. (Found: N, 12·01; S, 14·23. $C_8H_8N_2O_4S$ requires: N, 12·26; S, 14·04%.)

6-Sulfamyl-3-ethyl-1H-2,3-benzoxazine-4(3H)-one (XXIIIb). A solution of crude XXIIb (3·8 g) in 10 ml of ethyl ether was added, dropwise, to anhydrous ammonia (30 ml). The mixture was allowed to stand and the dry residue taken up with ethyl ether, washed with water and dried on Na_2SO_4. The ether extract was evaporated and the residue recrystallized from EtOH to give 1·5 g of XXIIIb, m.p. 191–193°. (Found: N, 10·57; S, 12·29. $C_{10}H_{12}N_2O_4S$ requires: N, 10·52; S, 12·04%.)

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