1·HCl (2 g) treated as above gave **33**·AcOH (0.25 g), mmp 111°, and **33** (0.6 g), mmp 106°, by fractional crystallization. The mother liquors were separated chemically to give a nonbasic part which yielded **45** (0.6 g), mmp 85° from EtOAc–petroleum ether.

b.—AcCl (1.57 g, 1 equiv) in C_5H_5N (10 ml) was added to **33** (4.58 g) in C_5H_5N (25 ml) at 0°. After 18 hr Et_2O (100 ml) was added and the solution was washed with 2 *N* HCl. The Et_2O solution gave a gum containing ester impurity (ir). MeOH (90 ml) and NaOH (10%, 5.8 ml) were added. After 2.5 hr the MeOH was evaporated *in vacuo*, Et_2O was added, and the Et_2O solution was washed with 2 *N* HCl. The Et_2O solution gave **45**, mp 86–87° from EtOAc–petroleum ether (bp 40–60°). *Anal.* ($C_{17}H_{21}NO_2$) C, H, N.

***S*-[2-Isopropylamino-1-(2-naphthyl)ethyl]isothiourea·2HCl (12).**—Compound 1 (4 g) and thiourea (1.1 g) in EtOH (150 ml) were heated under reflux for 9 hr and then the EtOH was evaporated to give **12**.

2-Isopropylamino-1-(2-naphthyl)ethanethiol (13).—Compound **12** (3.8 g), 1 *N* NaOH (65 ml), and MeOH (200 ml) were heated under reflux for 4 hr and then the MeOH was evaporated. Et_2O extraction gave **13**, converted into its HCl by Et_2O–HCl: nmr τ 2.15–2.80 (multiplet, ArH, 7), 6.25 (X part of ABX, SCH<, 1), 7.85–7.97 (multiplet, AB part of ABX, CH_2N, 2), 7.20–7.60 (septet, *i*-Pr CH, 1), 8.72 (singlet, NH and SH, 2), 9.08 and 9.13 [2 doublets, $CH(CH_3)_2$, 6].

***N*-[2-Methoxy-2-(2-naphthyl)ethyl]isopropylamine·HCl (16).**—Compound 1 (1.5 g) in MeOH (40 ml) was heated under reflux for 5 days and then most of the MeOH was evaporated. EtOAc was added to precipitate **16**: nmr τ 2.15–2.65 (multiplet, ArH, 7), 5.45–5.60 (X part of ABX, CHO, 1), 6.75 (singlet, OCH_3, 3), 6.97–7.30 (multiplet, CH_2NCH<, 3), 7.98 (singlet, NH, 1), 8.93 and 8.98 [2 doublets, $CH(CH_3)_2$, 6].

2-Isopropylamino-1-(2-naphthyl)ethylamine·2HCl (14).—Compound 1 (0.5 g) and saturated EtOH–NH_3 (20 ml) were heated in a Carius tube at 130° for 6 hr and then the EtOH and NH_3 were evaporated. NaOH (1 *N*) was added, **14** was isolated by Et_2O extraction, and converted into the HCl salt by Et_2O–HCl.

2-Isopropylamino-1-(2-naphthyl)ethyl Methyl Hydrogen Phosphate Hydrochloride (10).—Compound **17** (5.0 g), MeOH (200 ml), and 0.1 *N* HCl (100 ml) were kept at room temperature for 18 hr and then freeze dried. The solid **10** was stirred with Me_2CO to remove gummy material before crystallization (2.6 g, 47%).

2-Isopropylamino-1-(2-naphthyl)ethyl Dihydrogen Phosphate (11).—Compound **10** (0.5 g) in H_2O (2 ml) was kept for 15 min and then the solid **11** which had separated was isolated by filtration.

1-Isopropylamino-3-(1-naphthoxy)-2-propyl Dihydrogen Phosphate (30).—Compound **23** (50 mg) in H_2O (30 ml) was refluxed for 5 min, filtered, and then concentrated to 1 ml. Compound **30** separated on cooling.

Acknowledgment.—I thank Mr. B. S. Rao for his able assistance.

A New Class of Sympathetic β-Receptor Blocking Agents. 3,4-Dihydro-3-hydroxy-1,5-benzoxazocines

B. Basil, E. C. J. Coffee, D. L. Gell, D. R. Maxwell, D. J. Sheffield, and K. R. H. Wooldridge

Research Laboratories, May & Baker Ltd., Dagenham, Essex, England

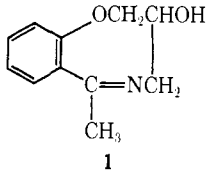
Received October 13, 1969

A series of 3,4-dihydro-3-hydroxy-1,5-benzoxazocines has been prepared one of which, 3,4-dihydro-3-hydroxy-6-methyl-1,5-benzoxazocine (1), has high sympathetic β-receptor blocking activity. The chemistry of the dihydro-1,5-benzoxazocine system is discussed.

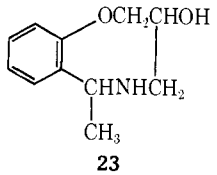
During the last few years, many sympathetic β-receptor blocking compounds have been described containing the 2-isopropylamino-1-hydroxyethyl[1] (I) or 3-isopropylamino-2-hydroxypropyloxy[2] (II) side chain or minor

$-CHOHCH_2NHCHMe_2$ (I) $-OCH_2CHOHCH_2NHCHMe_2$ (II)

variants[3] attached to an aromatic or heterocyclic nucleus. These compounds possess a number of pharmacological properties *e.g.*, β-blocking, quinidine-like, local anesthetic, and possibly hypotensive properties,[4] and we considered the possibility of synthesizing structures in which the mobility of the side chain was restricted in the hope of achieving some specificity of pharmacological action. One approach entailed linking the side chain with the aromatic nucleus to form benzoxazocines such as **1** and **23**.



1



23

In fact, 3,4-dihydro-3-hydroxy-6-methyl-1,5-benzoxazocine (**1**) was found to possess significant β-blocking properties and we report here the synthesis of this compound and 30 related analogs. Furthermore, since the 1,5-benzoxazocines represent a new heterocyclic system some of its chemical reactions are described.

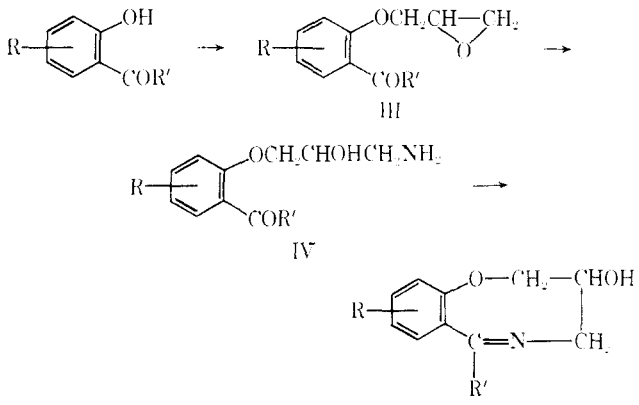
Chemistry.—Most of the benzoxazocines were prepared by treatment of the appropriate *o*-acetylphenoxypropane epoxide III with NH_3 in MeOH at room temperature.

(1) C. E. Powell and I. H. Slater, *J. Pharmacol. Exp. Ther.*, **122**, 480 (1958); R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1000 (1968); R. Howe, *ibid.*, **12**, 642 (1969); L. E. Folle and D. M. Aviado, *J. Pharmacol. Exp. Ther.*, **149**, 79 (1965); B. Levy, *ibid.*, **156**, 452 (1967); B. Levy, *Brit. J. Pharmacol.*, **27**, 277 (1966); K. Takagi, E. Osada, E. Takayanagi, and F. Taga, *Arch. Intern. Pharmacodyn.*, **168**, 212 (1967); R. C. Hill and P. Turner, *Brit. J. Pharmacol.*, **32**, 663 (1968); P. Somani, R. T. Backand, Jr., W. Murmann, and L. Almirante, *J. Med. Chem.*, **9**, 823 (1966).

(2) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, **11**, 1009 (1968); A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *ibid.*, **12**, 638 (1969); K. Saameli, *Helv. Physiol. Pharmacol. Acta*, **25**, 219 (1967); H. Brunner, P. R. Hedwall, and M. Meier, *Brit. J. Pharmacol.*, **30**, 123 (1967); B. Ablad, M. Brogard, and L. Elk, *Acta Pharmacol. Toxicol.*, **25**, *Suppl.* **2**, 9 (1967); A. S. J. P. A. M. van Miert and E. A. Huisman, *J. Pharm. Pharmacol.*, **20**, 495 (1968); D. Dunlop and R. G. Shanks, *Brit. J. Pharmacol.*, **32**, 201 (1968); K. Hermansen, *Acta. Pharmacol. Toxicol.*, **26**, 343 (1968); R. G. Shanks, T. M. Wood, A. C. Dornhorst, and M. L. Clark, *Nature*, **212**, 88 (1966).

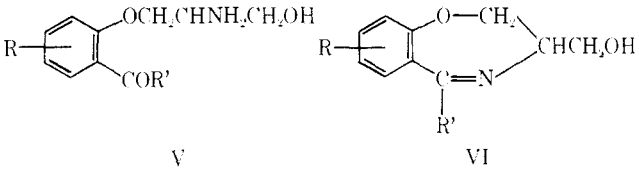
(3) H. C. Stanton, T. Kirchgessner, and T. Parmenter, *J. Pharmacol. Exp. Ther.*, **149**, 174 (1965); B. Levy, *ibid.*, **151**, 413 (1966); R. Ferrini, *Arzeim. Forsch.*, **18**, 48 (1968); P. N. Patil, A. Tye, and J. B. LaPidus, *J. Pharmacol Exp. Ther.*, **156**, 445 (1967).

(4) J. H. Biel and B. K. B. Lum, *Progr. Drug Res.*, **10**, 46 (1966).



The intermediate amino alcohol IV usually formed within 48 hr and then cyclized slowly to the benzoxazocine over a period of days. Attempts to accelerate this process always resulted in decreased yields. In a few favorable cases the overall yields from the hydroxy ketones were greater than 30% but usually they were lower, particularly with the more heavily substituted examples. In a few cases, the amino alcohol failed to cyclize and the benzoxazocine could not be isolated. No explanation of these failures could be deduced on electronic, steric, or solubility grounds. Most of the dihydrobenzoxazocines reverted to the amino alcohols on acid treatment but there were some exceptions, notably the 9-phenyl derivative, possibly due to the very insoluble nature of this compound.

There is the possibility that the epoxides might react with NH_3 to give isomeric amino alcohols V which could then cyclize to give 1,4-benzoxazepines VI. This is



unlikely by analogy[2] and on mechanistic grounds, but is positively excluded because the amino alcohol **25** derived from **1** has the expected nmr spectrum. In particular the observed spectrum clearly shows signals due to 3 protons on C adjacent to O (τ 5.7, 5.55) and 2 protons on C adjacent to N (τ 6.6) whereas the position isomer (V, R = H; R′ = Me) would be expected to show signals from 4 protons on C adjacent to O and 1 on C adjacent to N. The benzoxazocines themselves give unsatisfactory nmr spectra due to poor solubility.

Other modes of cyclizations of IV are excluded because all the products show a strong ir band at 1640 cm^{-1} characteristic of C=N, which disappears on hydrogenation (*e.g.*, in **23**).

The chemical reactions of the dihydrobenzoxazocines are indicated in Chart I.

Pharmacological Results and Discussion.—The pharmacological results reported in Tables I and II form the initial part of a screening program designed to find a compound with useful sympathetic β-receptor blocking activity unaccompanied by acute toxic effects. The chloralose-anesthetized cat preparation was used because of its reliability and stability over prolonged periods. It was not found practical to reach toxic doses in these preparations and for determination of the lethal dose mice were used.

The results in Tables I and II indicate that only a small group of dihydrobenzoxazocines (**1**, **2**, **6**, **14**, **16**, and **17**) possess appreciable β-blocking activity and that relatively minor departures from the parent compound **1** lead to total loss of activity. Moreover activity is unlikely to be due to hydrolysis to the open-chain derivatives since the primary amine **25** formed by hydrolysis of **1** has less than 0.25 the activity of the latter.

The activity of members of this class of compounds presents some points of interest in that the N function (C=N) is different from that found in other β-blocking series (*viz.*, C–NH) and the effect of nuclear substitution on activity does not parallel that in other series. Moreover it is difficult to reconcile the benzoxazocine configuration with the detailed structural requirements of some of the current theories of the mode of action of β-blocking agents at the molecular level.[5]

Experimental Section

Biological Methods.—Compounds which were soluble in H_2O were dissolved in normal physiological saline. Bases were dissolved by the addition of HCl which was subsequently neutralized (pH 5.0) with NaOH. One insoluble compound (**15**) was administered orally as a suspension.

Sympathetic β-Receptor Blocking Activity.—Cats were anesthetized with chloralose (80 mg/kg i.p.) and pentobarbitone (6 mg/kg i.p.). Heart rate was recorded continuously from the E.C.G. or pulse wave, and the blood pressure was either recorded on a kymograph with an Hg manometer, or with a pressure transducer and an electrophysiological recorder.

Intravenous doses of isoproterenol of 0.2 and 0.4 μg were given alternately at 7-min intervals. When the experimental subject was responding regularly, a low dose of the test compound was administered 3.5 min after a 0.2 μg dose of isoproterenol. The size of the next tachycardia response to 0.4 μg of isoproterenol was compared with those of the previous responses and the apparent potency of isoproterenol expressed as a per cent of control was determined as:

$$\log^{-1}\left(2 - \frac{R_2 - R_{2A}}{R_2 - R_1} \times 0.3010\right)$$

where R_1 is the size of the control response to 0.2 μg of isoproterenol, R_2 is the size of the control response to 0.4 μg of isoproterenol, and R_{2A} is the size of the response to 0.4 μg of isoproterenol after the dose of the test drug.

When the subject had recovered, a further increased dose of the test substance was given similarly. The per cent apparent isoproterenol values were plotted against the logarithm of the dose of test drug. The best line was fitted by eye and interpolated to find the dose producing a 50% apparent isoproterenol potency. This dose is called the 50% effective dose.

Syntheses.[6]—All melting points were determined on an electrothermal instrument and are corrected.

The general procedure for the preparation of benzoxazocines from *o*-hydroxyketones (See Table I) is illustrated by the following example.

DL-3,4-Dihydro-3-hydroxy-6-methyl-1,5-benzoxazocine (1).—*o*-Hydroxyacetophenone (272 g, 2.00 mol) was added to NaOEt in EtOH [from Na (46 g, 2.00 g-atom) and EtOH (2500 ml)] to give a slurry of the Na salt of *o*-hydroxyacetophenone to which was added epichlorohydrin (480 ml, 6.15 mol) during 0.5 hr. The mixture was refluxed for 3 hr, cooled, filtered, and fractionally distilled to give 1-*o*-acetylphenoxy-2,3-epoxypropane (267 g, 70%), bp 40° (1 mm).

1-(*o*-Acetylphenoxy)-2,3-epoxypropane (267 g) was added to anhydrous MeOH (1250 ml) saturated with NH_3 at −30°. The solution was allowed to warm to room temperature and was kept for 10 days, during which time colorless prisms of **1** (190 g) deposited, mp 249–250°, ir (KBr disk) 1640 cm^{-1} (C=N).

(5) B. M. Bloom and I. M. Goldman, *Advan. Drug Res.*, **3**, 121 (1966).

(6) Microanalyses were performed by Mr. S. Bance and his staff.

Chart I

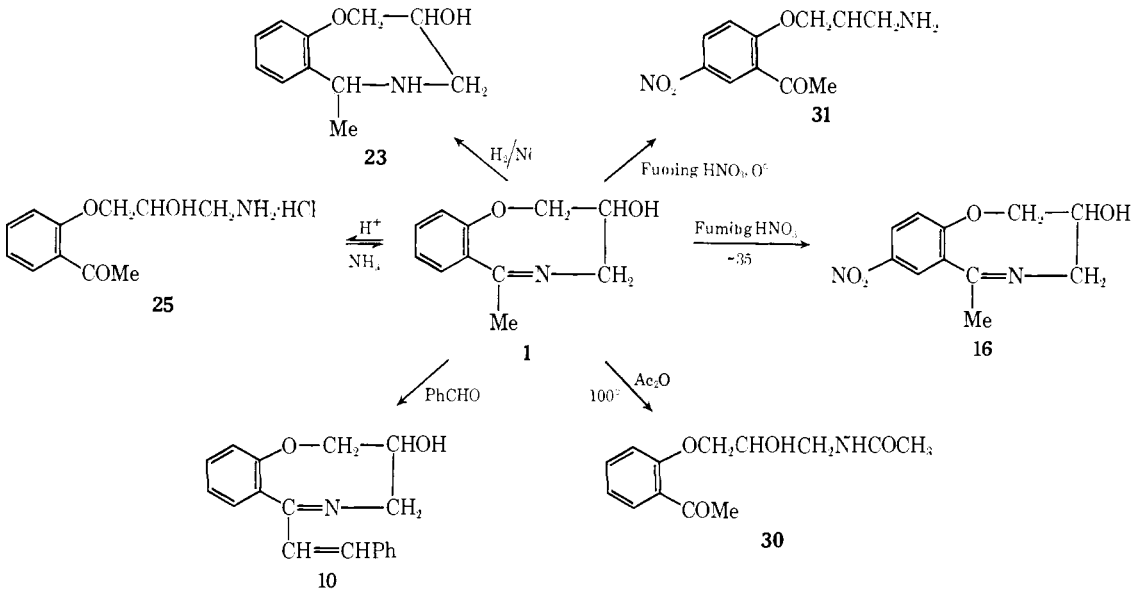
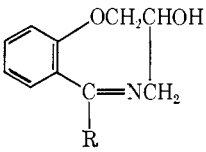


Table I

3,4-Dihydro-3-hydroxy-1,5-benzoxazocines



No.	R	Other substituent	Yield (%)[a]	Mp, °C	Formula[b]	LD_{50} (mg/kg iv) in mice	50% effective dose (mg/kg iv) in cats
1	CH_3		37.5	249–250	$C_{11}H_{13}NO_2$	>200	0.4
2	C_2H_5		23	227–229	$C_{12}H_{15}NO_2$		0.8
3	n-C_3H_7		8	170–174	$C_{13}H_{17}NO_2$	160	>2.0
4	i-C_3H_7		5	198–200	$C_{13}H_{17}NO_2$	175	>4.0
5	t-C_4H_9		2	209–212	$C_{14}H_{19}NO_2$		>1.0
6	C_6H_5		12	261–262	$C_{16}H_{15}NO_2$		0.9
7	p-$CH_3C_6H_4$		5	238–242	$C_{17}H_{17}NO_2$[d]	>200	>3.6
8	$C_6H_5CH_2$		6	212–214	$C_{17}H_{17}NO_2$	120	>2.0
9	$C_6H_5CH_2CH_2$		7	143–145	$C_{18}H_{19}NO_2$	165	>2.0
10	C_6H_5CH=CH			125[c]	$C_{18}H_{17}NO_2$[d]	160	>2.0
11	p-$NO_2C_6H_4CH$=CH			200[c]	$C_{18}H_{16}N_2O_4$[d]	150	>1.8
12	2-C_5H_4N		5	222–224	$C_{15}H_{14}N_2O_2$	200	>2.0
13	CH_3	3-CH_3	19	281–285	$C_{12}H_{15}NO_2$	>200	>1.0
14	CH_3	8-Cl	6	240[c]	$C_{11}H_{12}ClNO_2$		0.7
15	CH_3	8-C_6H_5	4	254–256	$C_{17}H_{17}NO_2$		>50 p.o.
16	CH_3	8-NO_2		173–175[c]	$C_{11}H_{12}N_2O_4$[e]	>200	0.6
17	CH_3	9-C_6H_5	15	215–217.5	$C_{17}H_{17}NO_2$		1.0
18	CH_3	8-n-C_3H_7CONH	58	288–289	$C_{15}H_{20}N_2O_3$		>1.0
19	CH_3	7,9-Cl_2	8	219–220	$C_{11}H_{11}Cl_2NO_2$	>200	>3.2
20	CH_3	8,10-Cl_2	12	163–165	$C_{11}H_{11}Cl_2NO_2$	72	>5
21	CH_3	8,10-$(CH_3)_2$	4	135–137	$C_{13}H_{17}NO_2$	50	>30
22	CH_3	9,10-C_6H_4	34	138–140	$C_{15}H_{15}NO_2$	130	>2.0
23	CH_3	5,6-H_2		95	$C_{11}H_{15}NO_2$[e, f]		>10.0
24	C_2H_5	5,6-H_2		300	$C_{12}H_{17}NO_2$[f]		>2.0

[a] Yield from hydroxy ketone. When no yield is quoted, see Experimental Section. [b] All compounds were analyzed for C, H, and N. The analytical results were within ±0.4% of the theoretical values. [c] Decomposed. [d] Hemihydrate. [e] Hydrate. [f] Hydrochloride.

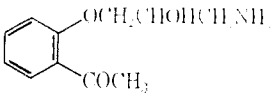
Other benzoxazocines in Table I were prepared in a similar way. In a few cases it was necessary to concentrate the reaction mixture to an oil which was extracted with 2 N HCl. The acid solution was made alkaline and extracted with EtOAc. After being kept for several days, crystals of the benzoxazocine formed.

DL-1-(*o*-Acetylphenoxy)-3-amino-2-hydroxypropanes.—In four cases (**26, 27, 28,** and **29**) the general procedure for the preparation of benzoxazocines afforded noncyclic products (see Table II).

The hydroxy ketone intermediates for the above syntheses were mostly prepared according to literature methods or were commercially available. The remainder were prepared as below.

***o*-Hydroxypivalophenone.**—Pivaloyl chloride (63.6 g, 0.53 mol) in Et_2O (100 ml) was added during 5 hr to *o*-$MeOC_6H_4MgBr$ (from 150 g of *o*-bromoanisole, 24.3 g of Mg, and 750 ml of Et_2O) at −10 to −15°. The reaction mixture was treated with 2 N HCl and the Et_2O layer was fractionally distilled to give *o*-

TABLE II



No.	Substituent	Mp, °C	Formula[a]	LD_{50} (mg/kg (vt in mice	50% effective dose (mg/kg (iv) in cats
25		60	$C_{11}H_{15}NO_3$[b]	80	>1.6
26	4-CH_3	133–135	$C_{12}H_{17}NO_3$		7.0
27	3,5-$(CH_3)_2$	129	$C_{13}H_{19}NO_3$		2.6
28	4,5-$(CH_3)_2$	155–158	$C_{13}H_{19}NO_3$		1.1
29	3,4-C_6H_4	118–123	$C_{15}H_{15}NO_3$		>5.0
	Propranolol			26	0.012

[a] All compounds were analyzed for C, N, and H. The analytical results were within ±0.4% of the theoretical values. [b] Hydrochloride.

methoxypivalophenone (47.0 g, 46%), bp 78–85° (0.4 mm). *Anal.* ($C_{12}H_{16}O_2$) OMe.

o-Methoxypivalophenone (47.0 g) in vigorously stirred anhydrous boiling pyridine (100 ml) was treated with HCl gas until no more was absorbed. The reaction mixture was then refluxed for 15 min, cooled, poured into H_2O, and extracted with Et_2O. The Et_2O solution was extracted with 2 *N* NaOH which on acidification afforded the hydroxy ketone (22.5 g, 52%), bp 115–124° (10 mm). *Anal.* ($C_{11}H_{14}O_2$) C, H.

2-Hydroxy-4′-methylbenzophenone.—Similarly *p*-tolunitrile and *o*-$MeOC_6H_4MgBr$ gave 2-methoxy-4′-methylbenzophenone (44%), mp 62°. *Anal.* ($C_{15}H_{14}O_2$) C, H. This compound was demethylated to the hydroxy ketone (33%), mp 61–63°. *Anal.* ($C_{14}H_{12}O_2$) C, H.

2-*o*-Hydroxybenzoylpyridine.—Similarly 2-cyanopyridine afforded 2-*o*-methoxybenzoylpyridine (23%), mp 77–79°. *Anal.* ($C_{13}H_{11}NO_2$) C, H, N. Demethylation gave the hydroxy ketone (80%), mp 55–56°. *Anal.* ($C_{12}H_9NO_2$) C, H, N.

DL-**3,4-Dihydro-3-hydroxy-6-styryl-1,5-benzoxazocine** (10).—Compound **1** (2.4 g), benzaldehyde (1.5 g), and piperidine (1 ml) were heated in an open vessel for 2 hr at 110–115°. The residue was crystallized (charcoal) from EtOH–petroleum ether (bp 40–60°) to give the 6-styrylbenzoxazocine (2.0 g, 55%).

DL-**3,4-Dihydro-3-hydroxy-6-*p*-nitrostyryl-1,5-benzoxazocine** (**11**) was prepared similarly at 140° in 10% yield.

DL-**3,4-Dihydro-3-hydroxy-6-methyl-8-nitro-1,5-benzoxazocine** (**16**).—Compound 1 (5 g) was added during 30 min to fuming HNO_3 (50 ml, d = 1.51) at −35°. After 10 min the solution was poured onto a mixture of ice and 2 *N* NaOH to give the 8-nitrobenzoxazocine (1.5 g, 24%).

DL-**3-Hydroxy-6-methyl-3,4,5,6-tetrahydro-1,5-benzoxazocine·HCl** (**23**).—A solution of 1 (5 g) in EtOH (150 ml) was catalytically hydrogenated (Raney Ni) at 7.03 kg/cm² at 80°. The solution was concentrated to an oil which was treated with concentrated HCl and then evaporated to dryness. Trituration with petroleum ether (bp 40–60°) afforded the hydrochloride hydrate (5 g, 78%), mp 95°. *Anal.* ($C_{11}H_{15}NO_2 \cdot HCl \cdot H_2O$) C, H, N, H_2O.

DL-**6-Ethyl-3-hydroxy-3,4,5,6-tetrahydro-1,5-benzoxazocine** (**24**), mp 148–151°, was prepared similarly. *Anal.* ($C_{12}H_{17}NO_2$) C, H. The hydrochloride had mp 300° dec. *Anal.* ($C_{12}H_{17}NO_2 \cdot HCl$) C, H, Cl.

DL-**1-Acetamido-3-*o*-acetylphenoxy-2-hydroxypropane** (**30**).—Compound **1** (5 g) and Ac_2O (50 ml) were heated at 100° for 2 hr and then cooled and poured on to H_2O to give **30** (1.35 g, 23%), mp 108–110°. *Anal.* ($C_{13}H_{17}NO_4$) C, H, N.

DL-**3-Acetoxy-3,4-dihydro-6-phenyl-1,5-benzoxazocine** (**32**).—AcCl (3 ml) was added during 10 min to **6** (3 g) in dry pyridine (70 ml) at 0°. The reaction mixture was stirred at 0° for 2 hr and poured onto ice to give **32** (3.2 g, 92%), mp 280–282°. *Anal.* ($C_{18}H_{17}NO_3$) C, H, N.

DL-**1-(*o*-Acetylphenoxy)-3-amino-2-hydroxypropane Hydrochloride** (**25**).—A solution of **1** (20 g) in 2 *N* HCl (250 ml) was made alkaline with 10 *N* NaOH and, after 60 min, extracted with Et_2O. The dried extract was treated with HCl gas to give **25** (17.5 g, 68%), mp 60°.

DL-**1-(2-Acetyl-4-nitrophenoxy)-3-aminopropyl-2-nitrate Hydrate** (**31**).—Compound **1** (5 g) was added during 30 min to fuming HNO_3 (25 ml, d = 1.51) at 0°. After a further 5 min at 0°, the solution was poured on to a mixture of ice and 2 *N* NaOH to give **31** (2.4 g, 26%), mp 251–253° dec. *Anal.* ($C_{11}H_{13}N_3O_7 \cdot HCl \cdot H_2O$) C, H, N, Cl, H_2O.

DL-**1-(*o*-Acetylphenoxy)-3-amino-2-hydroxypropane Hydrochloride** (**25**).—A solution of 1 (20 g) in 2 *N* HCl (200 ml) was kept for 8 hr, then basified with 12 *N* NaOH, and extracted with $CHCl_3$. Treatment with ethereal HCl gave **25** (17.5 g) as a hygroscopic solid, mp 60°, nmr (D_2O) τ 6.6, 2 H^+ (CH_2NH_3); 5.7, 2 H^+ (OCH_2); τ 5.55, 1 H^+ (CHOH). *Anal.* ($C_{11}H_{15}NO_3 \cdot HCl$) CHN.

Acknowledgment.—The authors wish to thank Miss J. R. Brooks, Miss H. V. Martin, Mr. J. H. Kempster, Mr. B. J. V. Mead, and Mr. G. C. Timms for technical assistance.