2,3-Benzoxazines. IX. Synthesis and Central Nervous System Depressant Activity of Some 3,6- and 3,7-Disubstituted 1H-3,4-Dihydro-2,3-benzoxazines

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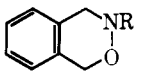
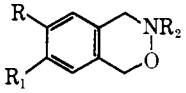
Received August 28, 1968

On the basis of the CNS depressant activity of 3-methyl-1H-3,4-dihydro-2,3-benzoxazine (Ib), a number of 3,6- and 3,7-disubstituted 1H-3,4-dihydro-2,3-benzoxazines were synthesized in order to observe the influence of the substituents on the pharmacological activity.

As a part of a systematic investigation on 1H-2,3-benzoxazines,[1] we recently described the synthesis of 1H-3,4-dihydro-2,3-benzoxazine (Ia)[2] and some N-acyl and N-alkyl[3] derivatives. Some of them possess CNS depressant activity; in particular, the N-methyl derivative Ib presents in rodents a specific activity on the behavior which has been confirmed in cats and dogs, accompanied by some autonomic side effects. A similar depressant activity on the CNS is also exhibited by a series of O-aralkylhydroxylamines.[4] On the basis of these results, we decided to further investigate this new heterocyclic structure, where the hydroxylamine function is an integral part of the ring system. This paper is primarily concerned with the synthesis and pharmacological properties of 1H-3,4-dihydro-2,3-benzoxazines with NO_2, NH_2, or Cl groups in positions 7 (II–IV) and 6 (V–VII) of the benzene nucleus and variously substituted on the nitrogen.



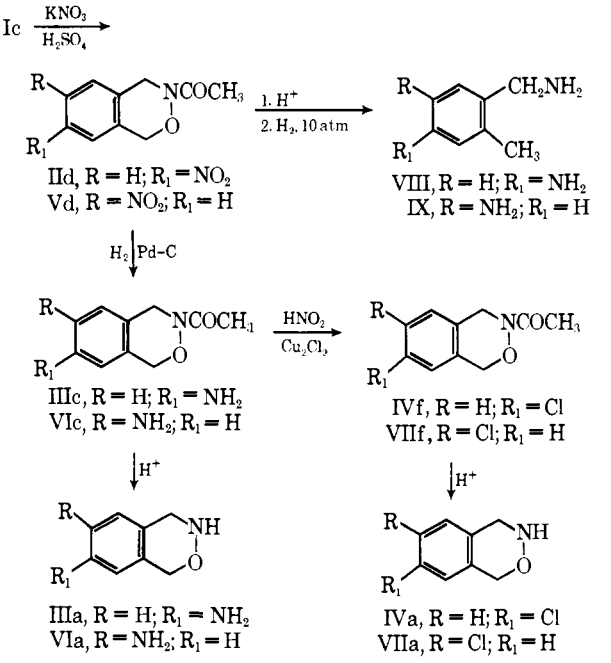
Ia, R = H
Ib, R = CH_3
Ic, R = $COCH_3$



II, R = R_2 = H; R_1 = NO_2
III, R = H; R_1 = NH_2
IV, R = H; R_1 = Cl
V, R = NO_2; R_1 = R_2 = H
VI, R = NH_2; R_1 = H
VII, R = Cl; R_1 = H

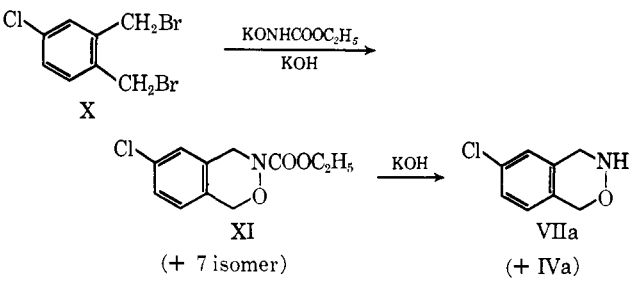
The preparation of the 7-nitro-1H-3,4-dihydro-2,3-benzoxazine (IIa) and 6-nitro isomer (Va) was carried out directly (see Scheme I) by nitrating 3-acetyl-1H-3,4-dihydro-2,3-benzoxazine (Ic);[2] the two isomers IId and Vd were separated by fractional crystallization. For the assignment of the position of the NO_2 group in the benzene ring, these compounds were deacetylated to IIa and Va, which were hydrogenolyzed to α^1,4-diamino-*o*-xylene (VIII) and α^2,4-diamino-*o*-xylene (IX),[5] respectively, recently obtained by us *via* an unambiguous route.[6] Low-pressure reduction of IId gave the 7-amino derivative IIIc, readily hydrolyzed to IIIa. IIIc was converted by the Sandmeyer reaction into the 7-chloro derivative IVf, which, refluxed in 18% HCl, gave 7-chloro-1H-3,4-dihydro-2,3-benzoxazine (IVa). The same reaction sequence, starting from Vd, afforded the corresponding 6-amino (VIa) and 6-chloro (VIIa) isomers.

SCHEME I



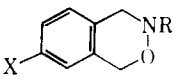
The last product can be obtained by a different pathway (see Scheme II) starting from 4-chloro-α,α'-dibromo-*o*-xylene (X), prepared in 94% yield[7] by treatment of 4-chloro-α,α'-dihydroxy-*o*-xylene[8] with dry HBr in CH_2Cl_2. Pure X was allowed to react with the K salt of N-hydroxyurethan to give 6-chloro-3-carbethoxy-1H-3,4-dihydro-2,3-benzoxazine (XI), ac-

SCHEME II



(1) Part VIII: G. Pifferi, A. Vigevani, and P. Consonni, *Gazz. Chim. Ital.*, in press.
(2) G. Pifferi, P. Consonni, and E. Testa, *ibid.*, **96**, 1671 (1966).
(3) G. Pifferi, N. Di Mola, and E. Testa, *Farmaco, Ed. Sci.*, **23**, 568 (1968).
(4) E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964).
(5) R. A. Barnes and J. C. Godfrey, *J. Org. Chem.*, **22**, 1038 (1957).
(6) G. Pifferi, P. Consonni, S. Banfi, and A. Diena, *Farmaco, Ed. Sci.*, in press.
(7) This method presents some practical advantages over the method described by D. R. Lyon, F. G. Mann, and G. H. Cookson, *J. Chem. Soc.* 662 (1947), using 4-chloro-*o*-xylene and Br_2 at 130° (40% yield).
(8) R. F. Bird and E. E. Turner, *ibid.*, 5050 (1952).

Table I
3,7-Disubstituted 1H-3,4-Dihydro-2,3-benzoxazines



Compd	X	R	Mp, °C	Cryst. solvent[a]	Yield, %[d]	Formula	Analyses
IIa	NO_2	H	168–169	A	97	$C_8H_8N_2O_4$	C, H, N
b	NO_2	NO	170 dec	A	75	$C_8H_7N_3O_4$	C, H, N
c	NO_2	CH_3	163–165	A	44	$C_9H_{10}N_2O_3$	C, H, N
d	NO_2	$COCH_3$	195–197	A	31[e]	$C_{10}H_{10}N_2O_4$	C, H, N
e	NO_2	CH_2CH_2Cl	97–98	B	98	$C_{10}H_{11}ClN_2O_3$	N, Cl
f	NO_2	CH_2CH_2OH	109–110	A	73	$C_{10}H_{12}N_2O_4$	C, H, N
g	NO_2	$COCH_2CH_3$	162–163	A	88	$C_{11}H_{12}N_2O_4$	C, H, N
h	NO_2	$CH_2CH_2OCONH_2$	139–140	A	47	$C_{11}H_{13}N_3O_5$	C, H, N
i	NO_2	$CH_2CH_2N(C_2H_5)_2$	106–110 dec	A	10	$C_{14}H_{21}N_3O_3 \cdot HCl$	N, Cl
j	NO_2	CH_2CH_2-*p*-C_5H_4N	210 dec	A	91	$C_{15}H_{15}N_3O_3 \cdot HCl$	C, H, N, Cl
k	NO_2	$CH_2CH_2C_6H_5$	120–121	A	25	$C_{16}H_{16}N_2O_3$	C, H, N
IIIa	NH_2	H	151–152	A	80	$C_8H_{10}N_2O$	C, H, N
b	NH_2	CH_3	170–171	A	65	$C_9H_{12}N_2O$	C, H, N
c	NH_2	$COCH_3$	143–144	A	79	$C_{10}H_{12}N_2O_2$	C, H, N
IVa	Cl	H	91–92	C	90	C_8H_8ClNO	C, H, N, Cl
b	Cl	NO	82–83	A	85	$C_8H_7ClN_2O_2$	C, H, N, Cl
c	Cl	$CONH_2$	206–207	A	52	$C_9H_9ClN_2O_2$	C, H, N, Cl
d	Cl	CH_3	66–67	D	56	$C_9H_{10}ClNO$	C, H, N, Cl
e	Cl	$C(=NH)NH_2$	262 dec	D	87	$C_9H_{10}ClN_3O \cdot H_2SO_4$	N, Cl
f	Cl	$COCH_3$	134	A	70[e]	$C_{10}H_{10}ClNO_2$	C, H, N, Cl
g	Cl	CH_2CH_2Cl	140 dec	D	98	$C_{10}H_{11}Cl_2NO \cdot HCl$	N, Cl
h	Cl	CH_2CH_2OH	91–93	B	72	$C_{10}H_{12}ClNO_2$	C, H, N
i	Cl	$COCH_2CH_3$	105–106	A	90	$C_{11}H_{12}ClNO_2$	C, H, N, Cl
j	Cl	$CH_2CH_2OCONH_2$	158–159	A	78	$C_{11}H_{13}ClN_2O_3$	C, H, N
l	Cl	$CH_2CH_2NC_5H_{10}$	200 dec	A	35	$C_{15}H_{23}ClN_2O \cdot 2HCl$	N, Cl

[a] A, EtOH; B, *i*-Pr_2O; C, hexane; D, EtOH–Et_2O. [b] Prepared by nitrating Ic. Yield from IIa is 90%. [c] From IIIc by the Sandmeyer reaction. Yield from IVa is 92%. [d] Most of the reactions were run only once, so the yields may be far from the optimum.

companied by small amounts of the 7-chloro isomer. Crude XI was hydrolyzed to a mixture of VIIa and of small quantities of the 7 isomer IVa. The purification of VIIa by repeated crystallization or by column chromatography was unsuccessful because of the similarity of physical properties of the two isomers (see Experimental Section).

Most of the compounds listed in Table I (7-substituted 1H-3,4-dihydro-2,3-benzoxazines) and in Table II (6-substituted 1H-3,4-dihydro-2,3-benzoxazines) are N-alkyl, N-acyl, and N-nitroso derivatives, readily obtained by general methods from the corresponding bases IIa, IIIa, and IVa (for Table I), and Va, VIa, and VIIa (for Table II), employed as starting materials. The reaction conditions employed to prepare these products and some 3-carbamyl (IVc, VIIc, Vf) and 3-guanyl derivatives (IVe, VIIe) were the same used previously in the 2,3-benzoxazine series.[2] The synthetic steps leading to a particular group of compounds consisting of 7-substituted 3-(2-hydroxyethyl)-1H-3,4-dihydro-2,3-benzoxazines (IIf, IVh) and of miscellaneous derivatives are reported in the Experimental Section.

All the 2,3-benzoxazines prepared are solids with the exception of VIId; the 7-substituted series appears to be thermally more stable than the corresponding 6-substituted one. Both series exhibit a characteristic ir absorption of variable intensity in the range 970–1100 cm^{-1} attrubuted to the C-O vibration of the heterocyclic ring.[1-3]

Pharmacology. Methods.—Compounds, dissolved in H_2O or suspended in 0.5% Methocel, were injected intraperitoneally into male 19–22-g CF1 mice. Animals were observed over a period of 5 hr for changes in behavior according to the method of Irwin.[9] Mortality was recorded over 5 days. Compounds were tested for their anticonvulsant activity in mice with the maximal electroshock method;[10] for evaluating the analgetic activity in male 150–160-g CF Wistar rats, a modified Randall and Selitto[11] method was used, in both cases by intraperitoneal administration.

Results.—Effects on behavior, righting reflex, and body muscular tone as well as approximate toxicity are summarized in Table III. In the same table results obtained with the derivative Ib and some known depressant drugs are also reported for comparison. The anticonvulsant activity was tested preliminarily for all the derivatives at a dose of about $0.2LD_{50}$. Subsequently the minimal effective dose of the compound showing some activity was determined (Table IV). The analgetic activity was tested preliminarily for all the compounds at a dose of about $0.1LD_{50}$. Only the derivatives quoted in Table V were found to increase significantly the pain threshold; the minimal effective doses are reported.

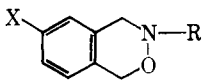
Conclusions.—A depressant activity on the CNS was found in almost all of the listed derivatives of the previously studied compound Ib, although in a lower degree. Recorded side effects such as salivation and lacrimation increase in general with the depressant

(9) S. Irwin, Gordon Research Conference on Medicinal Chemistry, New London, N. H., March 1959, p 133.

(10) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).

(11) L. O. Randall and J. J. Selitto, *Arch. Int. Pharmacodyn. Ther.*, **111**, 409 (1957).

TABLE II
3,6-DISUBSTITUTED-1H-3,4-DIHYDRO-2,3-BENZOXAZINES



Compd	X	R	Mp or bp (mm), °C	Crystn solvent[a]	Yield, %	Formula	Analyses
Va	NO_2	H	128	A	90	$C_8H_8N_2O_3$	C, H, N
b	NO_2	NO	123–125	A	96	$C_8H_7N_3O_4$	C, H, N
c	NO_2	CH_3	112–114	A	70	$C_9H_{10}N_2O_3$	C, H, N
d	NO_2	$COCH_3$	116–119	A	13.5[b]	$C_{10}H_{10}N_2O_4$	C, H, N
e	NO_2	$CH_2CH_2N(C_2H_5)_2$	164–166	D	13	$C_{14}H_{21}N_3O_3 \cdot HCl$	N, Cl
f	NO_2	$CONHC_6H_5$	185–186	A	77	$C_{15}H_{13}N_3O_4$	C, H, N
VIa	NH_2	H	155–156	A	86	$C_8H_{10}N_2O$	C, H, N
b	NH_2	CH_3	117–118	A	68	$C_9H_{12}N_2O$	C, H, N
c	NH_2	$COCH_3$	154–155	A	77	$C_{10}H_{12}N_2O_2$	C, H, N
d	NHAc	CH_3	139–140	E	57	$C_{11}H_{14}N_2O_2$	C, H, N
VIIa	Cl	H	64	C	90	C_8H_8ClNO	C, H, N, Cl
b	Cl	NO	51–52	B	90	$C_8H_7ClN_2O_2$	C, H, N, Cl
c	Cl	$CONH_2$	202–204	A	53	$C_9H_9ClN_2O_2$	C, H, N, Cl
d	Cl	CH_3	80 (0.15)[c]		75	$C_9H_{10}ClNO$	C, H, N, Cl
e	Cl	$C(=NH)NH_2$	190 dec	D	72	$C_9H_{10}ClN_3O \cdot H_2SO_4$	N, Cl
f	Cl	$COCH_3$	112–114	B	66[d]	$C_{10}H_{10}ClNO_2$	C, H, N, Cl
g	Cl	$COCH_2CH_3$	61–62	C	70	$C_{11}H_{12}ClNO_2$	C, H, N, Cl
h	Cl	CH_2CH_2-*p*-C_5H_4N	167–168	A	87	$C_{15}H_{15}ClN_2O \cdot HCl$	C, H, N, Cl

[a] A, EtOH; B, *i*-Pr_2O; C, hexane; D, EtOH–Et_2O; E, C_6H_6. [b] Prepared by nitrating Ic. Yield from Va, 85%. [c] Distilled in bulb.[12] [d] Prepared from VIc by the Sandmeyer reaction. Yield from VIIa, 88%.

TABLE III
ACTION ON BEHAVIOR

	Minimal effective dose (MED), mg/kg ip								
Compd	↓ of spon motor act.	↑ of passivity	↓ of curiosity	Ataxia	Impaired righting refl	↓ of body tone	Redn of palpebral opening	LD_{50}, mg/kg (approx)	Remarks[a]
IIa	30	100	30	60	60	60	30	350	
c	10	30	5	40	30	10	10	500	
d	30	30	30	300	100	30	30	750	
g	10	60	10	60	60	30	10	500	
h	10	60	10	60	60	30	30	500	
j	30	60	30	75	75	60	60	500	
k	10	>1000	10	200	200	30	>1000	>1000	Hyperreactivity, oo
IIIa	100	>300	100	>300	300	100	>300	300	Hyperreactivity and convulsions, ooo
b	10	75	10	45	45	30	10	>1000	Salivation and lacrimation, o
c	100	>300	100	>300	300	100	>300	300	Hyperreactivity and convulsions, ooo
IVa	30	100	30	75	75	30	30	200	
c	30	75	30	60	30	30	60	500	
d	10	60	10	60	60	10	10	500	Lacrimation, oo
i	60	100	30	100	60	60	300	500	
j	30	100	30	75	75	30	30	200	
l	30	>200	30	30	30	30	>200	200	Convulsions, ooo
Vc	30	60	30	60	60	60	60	500	Lacrimation, o
d	10	60	10	30	30	10	30	300	Lacrimation, ooo
f	30	300	30	300	300	30	300	>1000	
VId	30	60	30	60	30	60	30	>1000	
VIIa	60	60	60	60	45	60	60	200	
c	30	75	30	45	45	30	30	>1000	Lacrimation, o
d	10	45	10	30	30	10	10	500	Lacrimation, o
g	60	100	60	100	100	60	60	300	Lacrimation, o
h	60	>200	60	60	60	60	60	200	Lacrimation, hyperreactivity, o
Ib (2)	5	5	5	30	20	5	5	250	Lacrimation, o
Chlorpromazine	2	1	0.5	2	2	2	1	80	
Meprobamate	20	45	30	45	45	20	45	500	
Chlordiazepoxide	5	5–3	5–10	5–10	3–5	3–5	5	300	
Barbital	20	60	20–30	60	45	30	30	500	

[a] o, at all the tested doses; oo, only at the highest doses; ooo, only at the toxic doses.

TABLE IV
ANTICONVULSANT ACTIVITY

Compd	MED, mg/kg ip
IIa	75
c	75
h	50
j	50
IIIb	75
IVd	100
Diphenylhydantoin	3
Phenobarbital	15

TABLE V
ANALGETIC ACTIVITY

Compd	MED, mg/kg ip
IIh	50
IIIa	25
IVc	25
d	50
j	25
l	25
Morphine	1.5
Acetylsalicylic acid	40

activity. Qualitatively, taking in account that Ib had a specific activity on the behavior, only some of these derivatives can be compared with it. If the relationship between the dose level inducing passivity and those effective in reducing the righting reflex or motor coordination is taken as an index of specificity of action on the behavior, it results from Table III that only IIc, d, g, h, j, IVd, and Vf may be considered as behavioral drugs in that they increase passivity at a dose level equal to or lower than the neurotoxic ones responsible for the impairment of the coordination movements and the righting reflex.

The anticonvulsant activity found in IIa, c, h, j, IIIb, and IVd appears of no practical interest while analgetic action present in IIh, IIIa, IVc, d, j, l may be worthy of further studies.

From the point of view of the relationship between chemical structure and depressant activity the N-methyl substitution is more favorable than other alkyl or acyl substitutions. A unique exception is the N-acetyl derivative Vd. The NO_2 group in the benzene ring leads to the disappearance of the above-mentioned side effects when it is present in position 7, but not in 6 (with the exception of the very slightly active Vf). The presence of NH_2 in position 7 either abolishes the depressant activity or gives rise to a depressant compound with strong autonomic effects. Depressant activity is present in all Cl-substituted derivatives except IVl and VIIh and only the 6-substituted compounds produce autonomic side effects.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

The experimental procedures given below are representative for all compounds listed in Tables I and II. Detailed procedures are outlined where the preparations differ significantly from the general ones. The physical properties of the compounds are listed in Tables I and II. All melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer spectrophotometer Model 137, nmr spectra on a Varian A-60 spectrometer (60 Mc/sec) (TMS) (τ = 10.00 ppm).

7-Nitro-3-acetyl-1H-3,4-dihydro-2,3-benzoxazine (IId).—A solution of KNO_3 (15.2 g, 0.15 mole) in 90 ml of concentrated H_2SO_4 was added dropwise with stirring at 0° to a solution of Ic (19.5 g, 0.11 mole) in 90 ml of concentrated H_2SO_4. The temperature was kept for 30 min at 0° and for 30 min at 20°. The mixture was poured onto crushed ice and the precipitate was extracted with CH_2Cl_2; the extracts were washed (saturated aqueous $NaHCO_3$, H_2O), dried (Na_2SO_4), and evaporated to dryness. After trituration with 50 ml of EtOH, 17.3 g of a mixture of IId and Vd was collected. The two isomers were refluxed 5 min in EtOH (175 ml), then 175 ml of warm H_2O was added slowly with stirring and the mixture was allowed to cool at room temperature. The separated solid was collected and, still moist, refluxed for 5 min in 105 ml of EtOH, and the mixture was diluted again with 105 ml of warm H_2O. On cooling at room temperature, 7.6 g (31%) of IId was obtained as pale yellow crystals (mp 194–197°). An analytical sample (from EtOH) melted at 195–197° and was homogeneous on tlc; ir (Nujol, cm^{-1}), 1670 (C=O), 1530 and 1340 (NO_2), 828 and 740 (benzene ring); nmr ($CDCl_3$, τ), 7.74 (s, 3 H, CH_3), 5.03 (s, 2 H, CH_2N), 4.85 (s, 2 H, CH_2O), 2.8–1.7 (m, 3 H, aromatic H).

6-Nitro-3-acetyl-1H-3,4-dihydro-2,3-benzoxazine (Vd).—The mother liquor from IId was stored for 1 hr at 0° and the precipitate was collected to give 3.35 g (13.5%) of Vd as colorless crystals, mp 119–120°. Recrystallization from 80% EtOH did not raise the melting point and the product was chromatographically homogeneous. Comparison with IId by mixture melting point (depression) and ir spectra in $CHCl_3$ showed that it is an isomer of IId: ir (Nujol, cm^{-1}), 1670 (C=O), 1530 and 1345 (NO_2), 840, 825, and 745 (benzene ring); nmr ($CDCl_3$, τ), 7.72 (s, 3 H, CH_3), 4.99 (s, 2 H, CH_2N), 4.81 (s, 2 H, CH_2O), 2.7–1.6 (m, 3 H, aromatic H).

7-Nitro-1H-3,4-dihydro-2,3-benzoxazine (IIa).—A suspension of IId (0.5 g, 2.25 mmoles) in 10 ml of 18% HCl was refluxed for 4 hr. After concentrating, the residue was taken up with cold H_2O and the suspension was adjusted at pH 8 with saturated aqueous $NaHCO_3$. The precipitate was collected and crystallized (EtOH): ir (Nujol, cm^{-1}), 3300 (NH), 1530 and 1350 (NO_2), 838, 808, and 744 (benzene ring).

6-Nitro-1H-3,4-dihydro-2,3-benzoxazine (Va) was prepared from Vd by the same procedure as described for the 7-nitro isomer. It gave melting point depression on admixture with a sample of IIa; ir (Nujol, cm^{-1}), 3200 (NH), 1525 and 1355 (NO_2), 825, 812, and 743 (benzene ring).

Hydrogenolysis of IIa and Va. α^1,4-Diamino-*o*-xylene Dihydrochloride (VIII).—A suspension of 0.60 g (3.3 mmoles) of IIa in 70 ml of 95% EtOH and 0.8 ml of concentrated HCl was hydrogenated with 20% Pd–C (0.5 g) at 10 atm and 60° for 5 hr. After cooling, the catalyst was removed by suction and washed three times (H_2O). The filtrate and washings were evaporated to dryness and the residue was crystallized (EtOH) to give 0.45 g (65.3%) of VIII, identical with an authentic sample.[5]

α^2,4-Diamino-*o*-xylene dihydrochloride (IX), obtained from Va by the same procedure (62.5%), was identical with an authentic sample.[5,6]

7-Amino-3-acetyl-1H-3,4-dihydro-2,3-benzoxazine (IIIc).—A solution of IId (0.45 g, 2.0 mmoles) in 110 ml of EtOH was hydrogenated at normal pressure and room temperature with 0.1 g of 5% Pd–C. About 90% of the theoretical amount of H_2 was absorbed rapidly (30 min). The catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residue crystallized (EtOH); ir absorption bands were as expected.

7-Amino-1H-3,4-dihydro-2,3-benzoxazine (IIIa).—IIIc (2 g, 10.4 mmoles) was refluxed in 30 ml of 18% HCl. After cooling, IIIa·2HCl was collected and crystallized from 80% EtOH, mp 330°. *Anal.* ($C_8H_{10}N_2O$·2HCl) C, H, Cl, N. Ir absorption bands were as expected.

The corresponding **base** may be isolated by adding a saturated Na_2CO_3 solution to a cold aqueous solution of the IIIa·2HCl. The collected precipitate was recrystallized (EtOH). Ir absorption bands were as expected.

7-Chloro-3-acetyl-1H-3,4-dihydro-2,3-benzoxazine (IVf).—A solution of IIIc (1.35 g, 7 mmoles) in 15% HCl (16 ml) was diazotized at 0° with $NaNO_2$ (0.58 g) in 5 ml of H_2O. The mixture was stirred for 10 min at 0°, treated with a small amount of urea, then added to a 15% HCl solution (28 ml) of Cu_2Cl_2 (obtained from 4.7 g of $CuSO_4$·$5H_2O$). After stirring for 10 min at room temperature, the precipitate was collected, washed (H_2O), and crystallized (EtOH). Ir absorption bands were as expected.

7-Chloro-1H-3,4-dihydro-2,3-benzoxazine (IVa).—A mixture of IVf (0.3 g, 1.4 mmoles) and 6 ml of 18% HCl was heated at 100° for 2 hr, then concentrated to dryness, and the residue was crystallized (EtOH). IVa·HCl (mp 213–215°, quantitative yield) was dissolved (H_2O) and dilute $NaHCO_3$ was added. The crude base IVa was purified by crystallization. Ir absorption bands were as expected.

6-Amino- and 6-chloro-1H-3,4-dihydro-2,3-benzoxazines (VIa, VIIa) were obtained by the same procedure as IIIa and IVa, starting from Vd through VIc and VIIf, respectively.

6-Chloro-1H-3,4-dihydro-2,3-benzoxazine (VIIa) from X. Step 1. 4-Chloro-α,α′-dibromo-o-xylene (X).—To a saturated solution of HBr in CH_2Cl_2 (180 ml), 18.8 g (109 mmoles) of 4-chloro-α,α′-dihydroxy-o-xylene[8] was added slowly at 0° with stirring. After the addition, the mixture was stirred at 0° for 30 min, saturated with HBr and kept at room temperature overnight. After washing (10% $NaHCO_3$, H_2O), the organic layer was dried (Na_2SO_4), the solvent was evaporated, and the residue was crystallized from 80% EtOH to give 30.2 g (93%) of X, mp 43–45°.[7]

Step 2. 6-Chloro-3-carbethoxy-1H-3,4-dihydro-2,3-benzoxazine (XI).—To a stirred solution of 30 g (0.1 mole) of X in 120 ml of EtOH, a solution of crude N-hydroxyurethan (16 g, 80% purity) and KOH (11.3 g) in 240 ml of EtOH was added slowly. The mixture was heated under reflux for 3 hr, then cooled, and the mineral salts were filtered off. The filtrate was concentrated and the residue was taken up in Et_2O, washed (5% aqueous NaOH, H_2O), and dried (Na_2SO_4). Evaporation of the solvent left an oily residue (23.5 g) which, dissolved in C_6H_6, was chromatographed on a column of silica gel (450 g) and eluted (C_6H_6–Me_2CO, 97:3). Evaporation of the middle uniform fractions (checked by tlc) and distillation[12] gave 11 g (45%) of XI, bp 130° (0.2 mm). Tlc of this material showed that the 7-chloro isomer was a possible impurity in XI, but the purification of XI by column chromatography was unsuccessful; ir (cm^{-1}), 1710 (C=O), 1220 and 1090 (C–O), 815 and 755 (τ CH aromatic). *Anal.* ($C_{11}H_{12}ClNO_3$) Cl, N.

Step 3. 6-Chloro-1H-3,4-dihydro-2,3-benzoxazine (VIIa).—A solution of KOH (4.15 g) in H_2O (13 ml) was added to crude XI (10 g, 41 mmoles) in 82 ml of EtOH and the mixture was refluxed for 90 min. After concentrating *in vacuo*, the residue was suspended in H_2O and extracted three times (Et_2O). The combined extracts were washed (H_2O) until neutral and dried (Na_2SO_4). By adding ethereal HCl, a precipitate was obtained which, after two crystallizations (EtOH), yielded 4.78 g (56%) of crude VIIa·HCl, mp 192–195°. Further recrystallization did not raise the melting point. (A sample of pure VIIa hydrochloride obtained from pure VIIa, melted at 214° dec.) *Anal.* (C_8H_8ClNO·HCl) Cl, N.

The crude hydrochloride was suspended in ether and converted into the **base VIIa,** adding aqueous $NaHCO_3$. The organic layer, washed (H_2O) and dried (Na_2SO_4), gave after the evaporation of the solvent, a theoretical yield of an oily residue which was distilled[12] *in vacuo*, bp 115° (0.1 mm). Despite numerous attempted purifications by high-vacuum distillation and chromatography, this compound was not obtained pure and contained always small quantities of the isomer IVa.

6- and 7-Substituted 3-Alkyl-1H-3,4-dihydro-2,3-benzoxazines (IIc, IVd, Vc, VIId). General Procedure. 6-Chloro-3-methyl-1H-3,4-dihydro-2,3-benzoxazine (VIId).—To 3.55 g (21 mmoles) of VIIa in 10.5 ml of 99% HCO_2H, 2.9 ml of 38% CH_2O was added dropwise with occasional shaking and the mixture was heated at 90° for 6 hr. Excess HCO_2H was then removed *in vacuo* and the residue was taken up with H_2O and made alkaline with saturated Na_2CO_3. The oily precipitate was extracted (CH_2Cl_2), washed (H_2O), and dried (Na_2SO_4). After evaporation of the solvent, the residue was distilled. Ir absorption bands were as expected.

7- (or 6-) Amino-3-methyl-1H-3,4-dihydro-2,3-benzoxazine (IIIb, VIb).—A solution of 3.1 g (16 mmoles) of IIc (or Vc) in 250 ml of EtOH was hydrogenated at atmospheric pressure over 1.5 g of 5% Pd–C. After 30 min the theoretical amount of H_2 was consumed; the catalyst was filtered off and the solution was concentrated to a small volume. The solid product was purified by recrystallization (EtOH).

Compound VIb was transformed into the **6-acetamido derivative VId** by heating at 100° with excess Ac_2O for 2 hr. The solvent was removed *in vacuo* and the residue was crystallized (EtOH). Ir absorption was as expected.

7-Nitro-3-phenethyl-1H-3,4-dihydro-2,3-benzoxazine (IIk).—A mixture of 3.6 g (20 mmoles) of IIa and 3.4 g (24 mmoles) of K_2CO_3 in 4 g of phenethyl bromide was heated with stirring for 3 hr, while the bath temperature was allowed to rise gradually from 130 to 170°. After cooling, the dark mixture was treated with 200 ml of CH_2Cl_2 and 30 ml of H_2O, some resinous material was filtered off, and the aqueous layer was discarded. After removal of the solvent from the organic layer, the residue was slurried with warm EtOH (30 ml), filtered on carbon black, and ice cooled. The precipitate was recrystallized (EtOH). Ir absorption bands were as expected.

6- and 7-Substituted 3-Nitroso-1H-3,4-dihydro-2,3-benzoxazines (IIb, IVb, Vb and VIIb). General Procedure. 7-Nitro-3-nitroso-1H-3,4-dihydro-2,3-benzoxazine (IIb).—To a stirred suspension of IIa (0.9 g, 5 mmoles) in 5 ml of 1 *N* HCl a solution of $NaNO_2$ (0.38 g, 5.5 mmoles) in 2 ml of H_2O was added dropwise at 0° with stirring. After 1 hr at room temperature, the precipitate was collected, washed (H_2O), and crystallized (EtOH). Ir absorption was as expected.

7-Substituted 3-(2-Hydroxyethyl)-1H-3,4-dihydro-2,3-benzoxazines (IIf, IVh) and Derivatives (IIe, IIh, IIi, IVg, IVj, IVl). General Procedure. Step 1. 7-Nitro-3-(2-hydroxyethyl)-1H-3,4-dihydro-2,3-benzoxazine (IIf).—To a solution of ethylene oxide (9 g) in 300 ml of MeOH, IIa (9 g, 50 mmoles) was added at room temperature with stirring. The temperature was kept for 3 hr at 25° and for 3 hr at 50°. After standing overnight, the solvent was evaporated and the residue crystallized (EtOH). Absorption spectra (ir) were as expected.

Step 2. 7-Nitro-3-(2-carbamyloxyethyl)-1H-3,4-dihydro-2,3-benzoxazine (IIh).—Dry HCl was bubbled for 30 min into a mixture of IIf (1 g, 4.4 mmoles) and NaCNO (0.58 g, 8.8 mmoles) in 25 ml of $CHCl_3$ at 0–5° with stirring. Following an additional 15 min of stirring at room temperature without HCl, the solvent was evaporated *in vacuo* and the residue was taken up with saturated aqueous Na_2CO_3, collected on a filter, and crystallized (EtOH). Ir spectra were as expected.

Step 3. 7-Nitro-3-(2-chloroethyl)-1H-3,4-dihydro-2,3-benzoxazine (IIe).—A suspension of IIf (7.7 g, 34.4 mmoles) in anhydrous C_6H_6 was saturated with dry HCl. The benzene was decanted, the solid residue was treated with 100 ml of $SOCl_2$, and the mixture was refluxed gently for 3 hr. The excess of $SOCl_2$ was distilled off, and the residue was taken up with C_6H_6 and evaporated again to dryness. The crude product was used as such in the next step. An analytical sample was purified by crystallization (*i*-Pr_2O). Ir spectra were as expected.

IVg was obtained in a similar manner as an unstable oil and was transformed into the **hydrochloride** by adding it to ethereal HCl. The precipitate was crystallized (EtOH–Et_2O).

Step 4. 7-Nitro-3-(2-diethylaminoethyl)-1H-3,4-dihydro-2,3-benzoxazine Hydrochloride (IIi).—A mixture of IIe (1 g, 4.1 mmoles) in 8 ml of anhydrous Et_2NH was heated at 130° in a stainless bomb for 5 hr. After cooling, excess Et_2NH was allowed to evaporate *in vacuo* and the residue was treated with dilute HCl and shaken twice with Et_2O. The aqueous layer was made strongly alkaline with 50% NaOH and the precipitate was extracted (Et_2O). The extract was washed (H_2O) and dried (Na_2SO_4), and the filtrate was evaporated *in vacuo*. The oily residue was dissolved in anhydrous Et_2O and treated with a slight excess of dry HCl in ether. IIi·HCl separated as a viscous oil which, after decanting the acid solution and scratching in EtOH–Et_2O, solidified. It was purified by crystallization (EtOH). Ir spectra were as expected.

6-Nitro-3-(2-diethylaminoethyl)-1H-3,4-dihydro-2,3-benzoxazine hydrochloride (Ve) was prepared by a direct synthesis, starting from Va (0.9 g, 5 mmoles), 2-diethylaminoethyl chloride (1.05 g, 7.4 mmoles), and K_2CO_3 (1.05 g) in 5 ml of Et_2CO. The mixture was refluxed for 5 hr and worked up as described for IIi. Absorption bands of spectra (ir) were as expected.

6- and 7-Substituted 3-Acyl-1H-3,4-dihydro-2,3-benzoxazines (IId, IIg, IVf, IVi, Vd, VIIf, VIIg). Direct Synthesis. 7-Chloro-3-propionyl-1H-3,4-dihydro-2,3-benzoxazine (IVi).—To a solution of IVa (4.2 g, 24.8 mmoles) and anhydrous Et_3N (2.6 ml, 26 mmoles) in 150 ml of CH_2Cl_2, a solution of EtCOCl (2.42 g, 26 mmoles) in 20 ml of CH_2Cl_2 was added dropwise at room temperature with stirring. The reaction mixture was kept for 1 hr at 25°, then heated for 1 hr under reflux, and cooled. After washing (5% HCl, aqueous 5% $NaHCO_3$, H_2O), the organic

(12) G. Pifferi, A. De Ros, and M. Borbonese, *Farmaco Ed. Prat.*, **22**, 210 (1967).

layer was dried, the solvent was evaporated, and the residue was purified by crystallization. Ir spectra were as expected.

6- and 7-Substituted 3-Carbamoyl-1H-3,4-dihydro-2,3-benzoxazines (IVc, Vf, VIIc). General Procedure. 6-Chloro-3-carbamoyl-1H-3,4-dihydro-2,3-benzoxazine (VIIc).—To a stirred suspension of NaCNO (1.56 g, 24 mmoles) in 75 ml of anhydrous toluene, 23 mmoles of dry HCl in toluene was added dropwise at −10°. After 2 hr of stirring, a solution of VIIa (2.7 g, 16 mmoles) in 40 ml of anhydrous toluene was added and the temperature was kept at −10° for 3 hr, then at 0° overnight. The precipitate was collected, thoroughly washed (PhMe, H_2O), and crystallized (EtOH). Ir absorption bands were as expected.

6-Nitro-3-phenylcarbamyl-1H-3,4-dihydro-2,3-benzoxazine (Vf).—To a solution of Va (0.9 g, 5 mmoles) in 40 ml of anhydrous C_6H_6, phenyl isocyanate (0.65 g, 5 mmoles) was added dropwise. The mixture was allowed to stand 3 hr at room temperature, and the precipitate was collected and recrystallized (EtOH). Absorption bands of spectra (ir) were as expected.

6- and 7-Chloro-3-guanyl-1H-3,4-dihydro-2,3-benzoxazines (IVe, VIIe). General Procedure. 7-Chloro-3-guanyl-1H-3,4-dihydro-2,3-benzoxazine Sulfate (IVe).—A suspension of IVa·HCl (1.5 g, 7.25 mmoles) and cyanamide (0.31 g, 7.4 mmoles) in 30 ml of anhydrous C_6H_6 was refluxed 1 hr and the mixture was allowed to stand overnight at room temperature. The precipitate was collected (1.75 g of IVe·HCl, mp 228–230°), dissolved in EtOH (25 ml), and transformed into the corresponding sulfate by adding 0.75 ml of concentrated H_2SO_4 and 25 ml of Et_2O. Absorption bands (ir) were as expected.

6- and 7-Substituted 3-[2-(4-Pyridylethyl)]-1H-3,4-dihydro-2,3-benzoxazines (IIj, VIIh). General Procedure. 7-Nitro-3-[2-(4-pyridylethyl)]-1H-3,4-dihydro-2,3-benzoxazine Hydrochloride (IIj).—To a stirred solution of 10 mmoles of dry HCl in 45 ml of EtOH, IIa (1.8 g, 10 mmoles) was added with stirring. After 10 min at ambient temperature, 4-vinylpyridine (1.16 g, 11 mmoles) was added and the mixture was refluxed for 2 hr. After cooling overnight, the precipitate was collected and recrystallized (EtOH). Ir absorption bands were as expected.

Acknowledgment.—We are gratefully indebted to Professor P. Sensi, Professor E. Testa, and Professor G. G. Gallo for profitable discussions, to Mr. G. Tuan and Mr. A. Ripamonti for ir and nmr spectra, to Mr. S. Vecchi for chromatographic works, to Mr. A. Camp for elementary analyses, and to Dr. W. Zanichelli for assistance in the preparation of the manuscript.

The Absolute Configurations of the Pheniramines,[1a] Methyl Phenidates,[1b] and Pipradrols[1c,2]

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Received July 11, 1968

Absolute configurations of the 16 optical isomers of seven structurally related, title compounds of biological interest were determined. The pheniramines were converted to a methyl phenidate in which the relative configurations of the two asymmetric centers was established. The endocyclic center of asymmetry introduced in the process was maintained intact while the asymmetry of the exocyclic center was destroyed in the conversion to a pipradrol derivative. This was related to pipradrol by an *aufbau* sequence starting with (*R*)-(+)-piperidine-2-carboxylic acid. The absolute configurations of desoxypipradrol and thiopipradrol were established by Birch reduction and by rotatory dispersion, respectively. The antihistaminically more active acid maleates of **1a** and **1b** are stereochemically superimposable upon **1c** and all have the (*S*) configuration. The analeptically more active hydrochlorides (**25, 19, 26**) of *threo*-methyl phenidate, pipradrol, and thiopipradrol are stereochemically superimposable upon **22**. These have the (2*R*:2′*R*), (*R*), (*S*), and (*R*) configurations, respectively, but are not stereochemically superimposable upon the analeptically more active (+) acid sulfate of amphetamine.

Knowledge of the absolute configurations of biologically active compounds provides a valuable probe for investigating their modes of action and their interactions with hypothetical receptors.[4] This and the facts that the absolute configurations of the pheniramines (**1**), methyl phenidates (**9**, **25**), and pipradrols (**19**, **22**, **26**) have not been reported, that their optical isomers exhibit significant differences in activity,[5-8] and that speculation regarding the absolute configuration of **1a** and its necessarily complimentary receptor exists in the literature[9] prompted this study. Since the pheniramines, methyl phenidates, and pipradrols are structurally related, 2-substituted, six-membered, nitrogen heterocycles with an asymmetric center adjoining the heterocyclic ring, it was possible to develop and to exploit a single sequence of reactions leading to the determination of absolute configurations of the sixteen optical isomers of the seven entities (**1a-c**, **19**, **22**, **25**, **26**) of biological interest.

The salient features of the sequence are the con-

(1) (a) The antihistaminic 3-(*p*-chlorophenyl)-, 3-(*p*-bromophenyl)-, and 3-phenyl-3-(2-pyridyl)-1-dimethylaminopropanes; (b) the analeptic methyl *threo*-2-phenyl-2-(2-piperidyl)acetates; (c) the analeptic α-(2-piperidyl)-benzhydrol and the desoxy and 1,4-thiomorpholinyl analogs.

(2) Partial support was provided by National Institutes of Health (Grant No. NB-03593), U. S. Public Health Service. The authors gratefully acknowledge partial financial support from Schering and Ciba Laboratories and gifts of generous samples of the (+) acid maleate of chlorpheniramine supplied by Drs. H. Wolkoff, B. Jatul, and H. Leitzow, Schering Laboratories, of the (+) acid maleate of brompheniramine supplied by Dr. W. Schlesinger, White Laboratories, and Dr. H. Wolkoff, Schering Laboratories, of (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide supplied by Dr. L. Lachman and Mr. J. Cooper, Ciba Laboratories, and of the antipodal hydrochlorides of thiopipradrol made available by Dr. B. Belleau, University of Ottawa, and Dr. H. Leo Dickison, Bristol Laboratories.

(3) (a) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967. Abstracted from the M.S. and Ph.D. theses of A. S., Columbia University, 1965 and 1968, respectively. Recipient, Iranian Government Scholarship, 1963–1967. Regional and National First Prize Winner Lonsford-Richardson Awards, 1967, Graduate Competition. (b) Author to whom inquiries should be addressed.

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