distance separating the charges, ϵ_{ro} is the effective dielectric between the charges, e is the electrostatic unit of charge, and RT has its usual significance. The quantity k in eq 23 is included as a parameter defining the relation between electronic polarizability α[35] and the π superdelocalizability $S^{(E)}$. That is, it is assumed that

$$\alpha = kS^{(E)} \quad (24)$$

The ratio of the coefficients of eq 20, according to equations 21–23, is given by

$$a/b = 2571/283 = D_{ro}^3 \quad (25)$$

in which it is assumed that k is equal to 1. The bond distance is therefore

$$D_{ro} = 2.08 \text{ Å} \quad (26)$$

which is of the same order of magnitude as could be assigned to a hydrogen bond. Thus, despite the crude nature of the MO calculations on which eq 20 is based, the *relative* magnitudes of the coefficients in this equation are not unreasonable from a physical standpoint. The *absolute* magnitudes of the coefficients, however, may be greatly in error.

It should be noted that the correlation provided by eq 20 gives no indication of whether the 3-hydroxy group is functioning as a proton donor or a proton acceptor. Either mode of bonding is consistent with the correlation obtained. This work, however, provides substantiating evidence for the dominant mode of interaction of 3-HPTA derivatives with AChE and indicates a method whereby hydrogen-bonding interactions may be investigated in biological systems.

N-*sec*- and N-*t*-Alkyl Derivatives of Methoxamine and Related Compounds[1]

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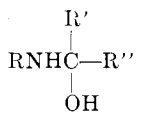
Received October 6, 1967
Revised Manuscript Received February 19, 1968

A number of N-*sec*- and N-*t*-alkyl derivatives derived from or related to methoxamine [*erythro*-α-(2,5-dimethoxyphenyl)-β-aminopropanol] have been prepared. Some of these compounds exhibited the physiological properties of "β-blockers" and antiarrhythmic agents. Several had a marked tendency to lower the blood levels of glucose and free fatty acids. *In vivo* N-*sec*-alkyl compounds were found to be degraded metabolically to the parent methoxamine (among other products) but the N-*t*-alkyl system was stable as regards this degradation. The *sec*-alkyl derivatives were prepared mainly by reductive alkylation of methoxamine, *t*-alkyl compounds from the appropriate amine and bromo ketone followed by reduction. When reductive alkylation created a third point of asymmetry, the physiologically inferior enantiomeric pair D-alkylamino-(−)-methoxamine–L-alkylamino-(+)-methoxamine was formed preferentially. Some conclusions are possible as to the spatial requirements of "receptor" sites.

Methoxamine [*erythro*-α-(2,5-dimethoxyphenyl)-β-aminopropanol] has been regarded pharmacologically as a pure α-adrenergic stimulant. Interest having been expressed as to the fashion in which this property would be altered by, *e.g.*, N-isopropyl substitution, a considerable number of such derivatives were prepared by reductive alkylation of methoxamine base in the presence of available aliphatic ketones, cycloalkanones, and aromatic aldehydes.

In these reactions, the aromatic aldehydes probably form Schiff's bases but the ketones presumably give only alkylolamines



by an equilibrium reaction. When methoxamine base was allowed to stand overnight in the presence of excess acetone before reduction, about one-third of the calculated amount of hydrogen was absorbed rapidly and the remaining two-thirds quite slowly. As might be expected, reactions with the other aliphatic ketones were much slower, presumably corresponding largely to slower formation of alkylolamine (and less favorable equilibria in that step).

The reductions with aromatic aldehydes proceeded rapidly and in good yield. There was no evidence for formation of tertiary amines which had seemed possible *a priori*. Data on the compounds of these types are presented in Tables I and II. No physiological properties of serious interest were found among the benzylamino and cycloalkylamino derivatives.

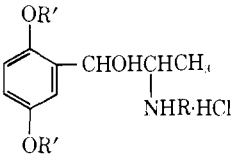
The compound first prepared, N-isopropylmethoxamine (I), was first regarded as a β-adrenergic blocker. Further investigation revealed more complicated behavior and interest centered on two properties. The first of these was the ability to restore normal sinus rhythm to hearts in which this had been disturbed by a number of stimuli (*cf.* ref, 1b, 1c, and especially 1h).

This antiarrhythmic activity was manifested by a number of the higher analogs of isopropylmethoxamine

(1) This paper reports part of a joint investigation carried out in collaboration with the Pharmacology Department of these laboratories. Detailed discussions of the pharmacological findings will be published separately. Preliminary reports that have appeared are (a) S. Norton and F. Soroko, *Fed. Proc.*, **21**, 417 (1962); (b) C. H. Ellis and S. Norton, 22nd International Congress of Physiological Sciences, Leiden, 1962; *Excerpta Med., Intern. Congr. Ser.*, **48**, 1205 (1962); (c) C. H. Ellis and S. Gross, *Fed. Proc.*, **22**, 247 (1963); (d) R. A. Salvador, K. I. Colville, L. A. Lindsay, and J. J. Burns, *ibid.*, **22**, 508 (1963); (e) K. I. Colville, L. A. Lindsay, R. A. Salvador, and J. J. Burns, *ibid.*, **23**, 542 (1964); (f) R. A. Salvador, K. I. Colville, S. A. April, and J. J. Burns, *J. Pharmacol. Exp. Ther.*, **144**, 172 (1964); (g) J. J. Burns, K. I. Colville, L. A. Lindsay, and R. A. Salvador, *ibid.*, **144**, 163 (1964); (h) C. H. Ellis, *Arch. Int. Pharmacodyn. Ther.*, **150**, 144 (1964); (i) J. J. Burns, K. I. Colville, L. A. Lindsay, S. A. April, and R. A. Salvador, *Pharmacologist*, **6**, 186 (1964); (j) J. J. Burns and L. Lemberger, *Fed. Proc.*, **24**, 298 (1965); R. A. Salvador and S. A. April, *ibid.*, **24**, 298 (1965); (k) K. I. Colville, L. A. Lindsay, and J. J. Burns, *Pharmacologist*, **7**, 178 (1965); (l) R. A. Salvador, S. A. April, and L. Lemberger, *ibid.*, **8**, 181 (1966); (m) R. A. Salvador, S. A. April, and L. Lemberger, *Fed. Proc.*, **25**, 500 (1966).

TABLE I

α-(2,5-DIALKOXYPHENYL)-β-(sec-ALKYLAMINO)PROPANOL HYDROCHLORIDES



No.	R	R′	Mp, °C[a]	Formula	Analyses	Antiarrhythmic act.[c]	Toxicity[d]
I	2′-Propyl	Me	246–247 dec	$C_{14}H_{23}NO_3 \cdot HCl$	C, H	+	High
II	2′-Butyl	Me	222–224[b]	$C_{15}H_{25}NO_3 \cdot HCl$	C, H, N	+	High
III	2′-Pentyl	Me	204–207[b]	$C_{16}H_{27}NO_3 \cdot HCl$	C, H	++	Low
IV	3′-Pentyl	Me	199–200	$C_{16}H_{27}NO_3 \cdot HCl$	C, H	++	Medium
V	3′-Methyl, 2′-butyl	Me	221–223[b]	$C_{16}H_{27}NO_3 \cdot HCl$	C, H	++	High
VI	2′-Hexyl	Me	189–192[b]	$C_{17}H_{29}NO_3 \cdot HCl$	C, H	++	Medium
VII	3′-Hexyl	Me	180–181[b]	$C_{17}H_{29}NO_3 \cdot HCl$	C, H, N	++	Medium
VIII	4′-Methyl, 2′-pentyl	Me	225–228[b]	$C_{17}H_{29}NO_3 \cdot HCl$	C, H	++	High
IX	2′-Heptyl	Me	172–173[b]	$C_{18}H_{31}NO_3 \cdot HCl$	C, H	++	High
X	3′-Heptyl	Me	176–177[b]	$C_{18}H_{31}NO_3 \cdot HCl$	C, H	++	High (h)
XI	4′-Heptyl	Me	185–186	$C_{18}H_{31}NO_3 \cdot HCl$	C, H	++	High
XII	2′-Octyl	Me	160–161[b]	$C_{19}H_{33}NO_3 \cdot HCl$	C, H		(h)
XIII	2′-Nonyl	Me	148–151[b]	$C_{20}H_{35}NO_3 \cdot HCl$	C, H	+++	Low (h)
XIV	5′-Nonyl	Me	143–145	$C_{20}H_{35}NO_3 \cdot HCl$	C, H, N	+	(h)
XV	2′-Undecyl	Me	138–139[b]	$C_{22}H_{39}NO_3 \cdot HCl$	C, H		(h)
XVI	2′-Tridecyl	Me	160–161[b]	$C_{24}H_{43}NO_3 \cdot HCl$	C, H		
XVII	2′-Heptadecyl	Me	132–133[b]	$C_{28}H_{51}NO_3 \cdot HCl$	C, H, N	++	(h)
XVIII	2′-Propyl	Et	187.5–189	$C_{16}H_{27}NO_3 \cdot HCl$	C, H, N	+++	Low
XIX	2′-Butyl	Et	182–183[b]	$C_{17}H_{29}NO_3 \cdot HCl$	C, H, N	++	Low
XX	2′-Pentyl[e]	Et	168–169[b]	$C_{18}H_{31}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H	++	High
XXI	2′-Nonyl	Et	149–150[b]	$C_{22}H_{39}NO_3 \cdot HCl$	C, H	+++	Low (h)
XXII	2′-Undecyl	Et	131–132[b]	$C_{24}H_{43}NO_3 \cdot HCl$	C, H	++	High (h)
XXIII	H	n-C_3H_7	173.5–174	$C_{15}H_{25}NO_3 \cdot HCl$	C, H, N	+	Medium
XXIV	2′-Propyl	n-C_3H_7	171–172	$C_{18}H_{31}NO_3 \cdot HCl$	C, H	+++	Low
XXV	2′-Butyl	n-C_3H_7	159–160[b]	$C_{19}H_{33}NO_3 \cdot HCl$	C, H	+	(h)
XXVI	H	n-C_4H_9	124–126	$C_{17}H_{29}NO_3 \cdot HCl$	C, H		
XXVII	2′-Propyl	n-C_4H_9	136–138	$C_{20}H_{35}NO_3 \cdot HCl$	C, H	+	High (h)

[a] The higher melting points are generally attended by decomposition. [b] These melting points were observed on analytically pure but not necessarily sterically homogeneous material. [c] +++ indicates restoration of normal sinus rhythm at a dose of 0.1 mg/kg or less; ++ indicates similar effect at 0.2–0.6 mg/kg; and + indicates similar effect at 1–5 mg/kg. Quinidine is effective in similar experiments at 8 mg/kg. [d] These toxicities have no relation to LD_{50} values as usually determined. High indicates other undesirable action in the dose range of effective antiarrhythmic action. Medium indicates undesirable action at about five times the effective dose. Low signifies no untoward effects at ten times the effective dose; *cf.* ref 1h. (h) signifies hemolysis. [e] Hemihydrate.

TABLE II

No.	N-Substituent	Mp, °C	Formula	Analyses
	N-Cycloalkyl- and N-Benzylmethoxamine Hydrochlorides			
XXVIII	Cyclopentyl	239–241	$C_{16}H_{25}NO_3 \cdot HCl$	C, H
XXIX	Cyclohexyl	240–241 dec	$C_{17}H_{27}NO_3 \cdot HCl$	C, H
XXX	2-Me-cyclohexyl	241–242[a]	$C_{18}H_{29}NO_3 \cdot HCl$	C, H
XXXI	3-Me-cyclohexyl	238–239[a]	$C_{18}H_{29}NO_3 \cdot HCl$	C, H
XXXII	4-Me-cyclohexyl	220–222	$C_{18}H_{29}NO_3 \cdot HCl$	C, H
XXXIII	Cycloheptyl	249–250	$C_{18}H_{29}NO_3 \cdot HCl$	C, H
XXXIV	Cyclooctyl	227–228	$C_{19}H_{31}NO_3 \cdot HCl$	C, H
XXXV	Benzyl	203–205	$C_{18}H_{23}NO_3 \cdot HCl$	C, H
XXXVI	*o*-Cl-benzyl	224–226	$C_{18}H_{22}ClNO_3 \cdot HCl$	C, H
XXXVII	*p*-Cl-benzyl	228–229	$C_{18}H_{22}ClNO_3 \cdot HCl$	C, H
XXXVIII	*o*-MeO-benzyl	214–215	$C_{19}H_{25}NO_4 \cdot HCl$	C, H
XXXIX	*p*-HO-benzyl	239–240	$C_{18}H_{23}NO_4 \cdot HCl$	C, H
XL	2-OH-5-Cl-benzyl	201–203	$C_{18}H_{22}ClNO_4 \cdot HCl$	C, H
XLI	3,4,5-(MeO)$_3$-benzyl	196–197	$C_{21}H_{29}NO_6 \cdot HCl$	C, H, N
XLII	3,4-(MeO)$_2$-5-Br-benzyl	198–199	$C_{20}H_{26}BrNO_5 \cdot HCl$	C, H
XLIII	3-EtO-4-OH-5-Br-benzyl	182–184[b]	$C_{20}H_{26}BrNO_5 \cdot HCl$	C, H
XLIV	α-Et-benzyl	249–250 (eff)	$C_{20}H_{27}NO_3 \cdot HCl$	C, H
	α-(2,5-Diethoxyphenyl)-β-benzylaminopropanol Hydrochlorides			
XLV	2,5-(MeO)$_2$-benzyl	145–147	$C_{22}H_{31}NO_5 \cdot HCl$	C, H
XLVI	2,5-(EtO)$_2$-benzyl	162–164	$C_{24}H_{35}NO_5 \cdot HCl$	C, H

[a] See footnote *b*, Table I. [b] Hemihydrate.

but rather irregularly. For the 2,5-dimethoxy series maximum activity was found with the 2′-nonyl homolog XIII, and this compound was seriously considered for clinical trial although intravenous (though not oral) administration produced appreciable hemolysis. The 2,5-diethoxy-N-isopropyl derivative XVIII was then found to be at least equally active while lacking hemolytic tendencies. Some other homologs were investigated. Antiarrhythmic activity persisted in the 2,5-diethoxy series through the N-2′-pentyl derivative XX without appearance of hemolysis, in the 2,5-dipropoxy series through the N-2′-butyl compound XXV, and was present also in XXVII. Hemolysis, however, was produced by XXV and XXVII, marking the limits of useful activity.

The second physiological property of interest was a blocking of the hyperlipoidemia and hyperglycemia evoked by catecholamines (**1d–1g**, **1i–1m**). This behavior was shown by I–III, XI, and XVIII but not by IV, IX, and XXVIII. The higher homologs showed no advantage over I in this effect and were, in fact, generally less potent.

Since therapeutic employment of any compound for this purpose would involve extended treatment, the metabolic fate of isopropylmethoxamine was investigated rather intensively. Initially, search was made for dehydrogenation and deamination products. Several possible neutral substances and also the aminoketone XLVII[2] were prepared for comparison. It soon became apparent, however, that most of the compound was being converted, at least in the rat, to more hydrophilic bases. The obvious mechanism for this (aside from ring hydroxylation) is alkyl group hydroxylation, a process known to be catalyzed by certain microsomal enzymes. Hydroxylation on a carbon bound to oxygen or nitrogen results in a hemiacetal or an alkylolamine either of which would be expected to

$$ArOCH_2R \longrightarrow ArOCHOHR$$
$$RNHCH_2R' \longrightarrow RNHCHOHR'$$

dissociate readily under physiological conditions.

Identification of these metabolic products accordingly required the 2- and 5-demethyl-N-isopropylmethoxamines (XLVIII and LV). The first of these was prepared quite readily by reductive alkylation of 2-demethylmethoxamine.[3] The preparation of 5-demethyl-N-isopropylmethoxamine was more complicated; the scheme of synthesis and identification is shown in Chart I. The necessary starting material, L, was prepared by a modification of the method used here previously for the corresponding acetophenone derivatives.[4] This was converted to the isonitroso ketone, LI, which was subjected to catalytic hydrogenation. This last step was rather unsatisfactory since it was difficult either to complete the hydrogenation (absorption of 4 molar equiv of H_2) or to interrupt the process with isolation in satisfactory yield of a partially hydrogenated intermediate. Eventually, a two-stage reduction with addition of acetone in the second step permitted isolation of LV identical with the material obtained by the alternate route through LIII and LIV.

When the isonitroso ketone LI was reduced with $LiAlH_4$, a high yield was obtained of a mixture of bases, presumably the *threo* and *erythro* forms. These were separated by distillation after which the fractions solidified and could be recrystallized. The *erythro* configuration was established for the β isomer (LIII) by conversion to methoxamine by acetylation, debenzylation, methylation, and hydrolysis. Reductive alkylation of LIII over platinum in the presence of acetone and 2-nonanone, respectively, afforded the N-isopropyl and N-2′-nonyl compounds LIV and LVI. These in turn were debenzylated over palladized charcoal to form the desired 5-demethyl-N-isopropylmethoxamine (LV) and also the N-2′-nonyl homolog LVII.

Compound LV was positively identified among the metabolic products of N-isopropylmethoxamine, and XLVIII with considerable probability. Methoxamine itself was also present and some of its O-demethylated derivatives.[5] The formation of methoxamine from N-isopropylmethoxamine in rats was paralleled in preliminary clinical trials by a delayed rise in blood pressure.

The above phenomenon is not acceptable in a drug for chronic administration, and therefore an attempt was made to devise a drug that would not be susceptible to N-dealkylation. Obviously a tertiary alkyl group could not be hydroxylated to an alkylolamine by a process involving only replacement of hydrogen by hydroxyl. (Hydroxylation elsewhere in the alkyl group might, of course, take place but would not result in a compound readily cleaved by simple chemical operations.) Accordingly it was decided to prepare the N-*t*-alkyl derivatives of methoxamine. Since the route employed hitherto in this project was not available for this purpose, *t*-alkylamino ketones were prepared by reaction of the *t*-alkylamines with the appropriate α-bromo ketones in acetonitrile. The amino ketone hydrochlorides were isolated without difficulty. Their catalytic hydrogenation appeared to give exclusively *erythro* amino alcohols, as is usual in such reactions. While such catalytic reductions are feasible on a small scale, they are extremely slow. It was found that reduction with $NaBH_4$ was more expeditious and satisfactory although not completely stereospecific.

The *t*-alkylamino alcohols were all active in suppressing hyperglycemia and hyperlipoidemia. Since the higher homologs showed no advantages most of the study was on N-*t*-butylmethoxamine (LXI, butoxamine). In rats there was no indication of N-dealkylation although some O-dealkylation did take place. The 2-demethyl analog LIX was prepared for comparison but was not clearly identified as a metabolite. Hydroxylation on the *t*-butyl group would, of course, form a more hydrophilic substance. Tlc revealed a rather complicated system of such materials whose components were not readily separated.[6]

Compound LIX was prepared from α-bromo-2-benzyloxy-5-methoxypropiophenone by reaction with *t*-butylamine in acetonitrile, and borohydride reduction to LVIII which was debenzylated over Pd-C. Data

(2) Prepared essentially by the method of J. F. Hyde, E. Browning, and R. Adams, *J. Am. Chem. Soc.*, **50**, 2287 (1928), from isopropylamine and 2,5-dimethoxy-α-bromopropiophenone [A. E. Ardis, R. Baltzly, and W. Schoen, *ibid.*, **68**, 591 (1946)].

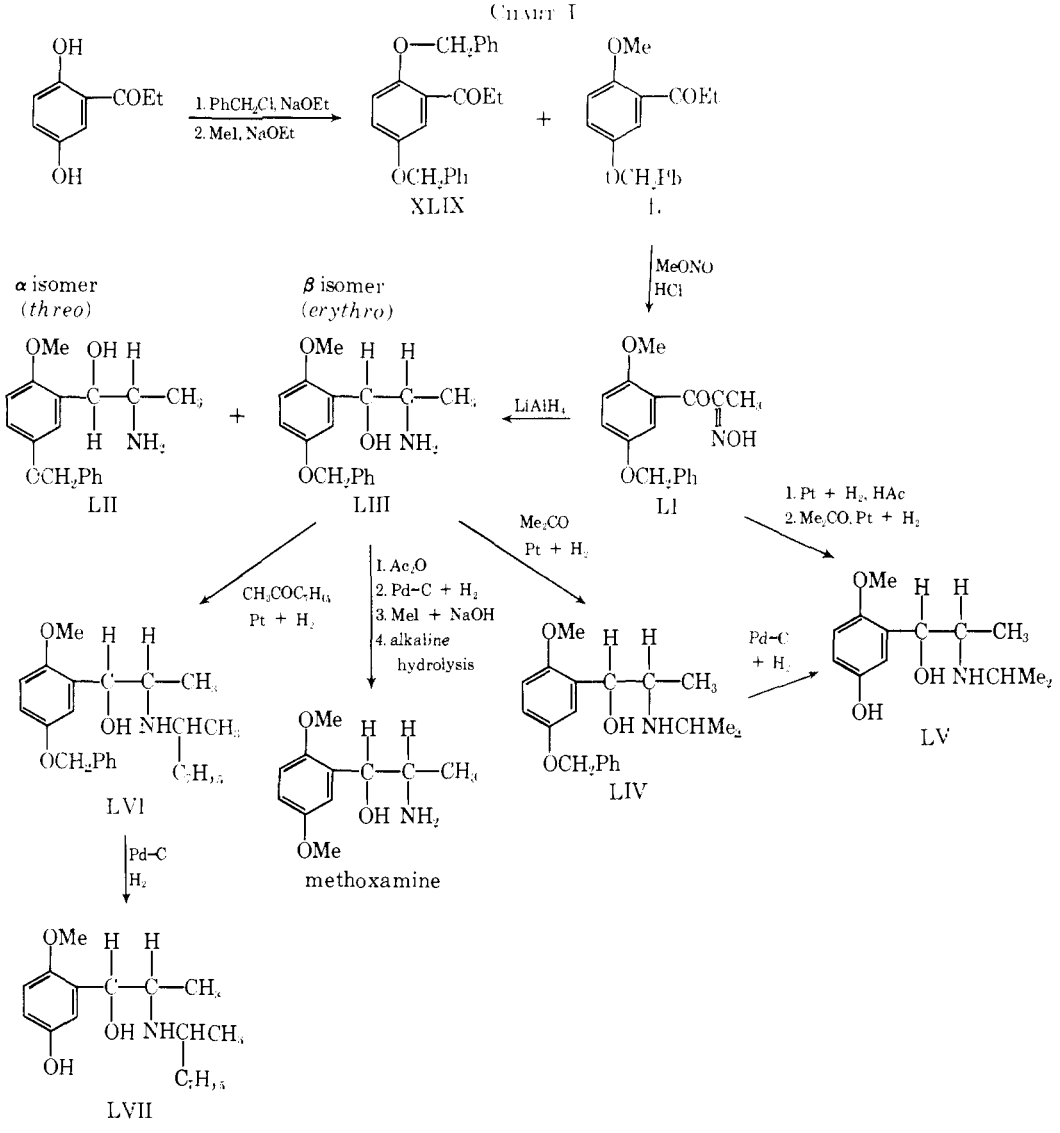
(3) W. S. Ide and R. Baltzly, *ibid.*, **70**, 1084 (1948).

(4) R. Baltzly, J. S. Buck, and W. S. Ide, *ibid.*, **72**, 382 (1950).

(5) A. Klutch and M. Bordun, *J. Med. Chem.*, **10**, 860 (1967).

(6) A. Klutch, private communication; see also ref 5.

CHART I

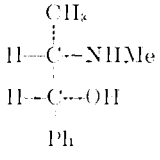


on compounds synthesized as metabolites and intermediates isolated along the way are shown in Table III. Data on the N-*t*-alkylmethoxamines and their homologs are presented in Table IV.

The *t*-alkylamino ketones were also found to have antihyperglycemic and hyperlipoidemic properties though in less degree than the amino alcohols.

Stereochemical Aspects.—Methoxamine has been considered to be the *erythro* pair of enantiomers (corresponding to ephedrine) on the basis of the method of preparation.[7] Over a period of years a number of attempts at resolution had proved fruitless. The properties of N-isopropylmethoxamine which has the same configuration suggested a means of settling this question. An approximate separation of the isomers of I through the acid tartrates proved quite easy although complete optical purity was less easily secured. The optical properties of these and of the other stereoisomers isolated in this project are shown in Table V.

Corresponding data for ephedrine and ψ-ephedrine[8,9]



are shown for comparison. It will be seen that the molecular rotations of the *erythro* isomers are reasonably close to those of the ephedrine isomers. A more complete demonstration of the *erythro* configuration would be obtained through the Welsh rearrangement,[10] by which N-acylephedrines are converted in warm dilute acid to O-acyl-ψ-ephedrines. In our series some difficulties were encountered, presumably due to increased hindrance, and conversion was most sat-

(7) R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **62**, 164 (1940); **64**, 3040 (1942). The catalytic hydrogenation under acid conditions of an isonitrosopropiophenone proceeds demonstrably through the stage of the corresponding α-amino ketone. The last stage of the hydrogenation, to the amino alcohol, is believed to be completely stereospecific although experimentally it is difficult to exclude the possibility that traces of *threo* isomer could be formed.

(8) E. Späth and R. Göring, *Monatsh.*, **41**, 335 (1920). Literature data on these rotations, in particular on ephedrine, vary considerably more than the experimental error, variations in temperature of observation, and concentrations used would seem to account for. We have taken the Späth figures more or less arbitrarily.

(9) The configuration of (−)-ephedrine has, of course, been established as shown, but since this configuration can be equally well related to L-serine and to D-phenylalanine there is no rational basis for applying D or L in a systematic fashion.

(10) (a) L. H. Welsh, *J. Am. Chem. Soc.*, **71**, 3500 (1949); (b) L. H. Welsh, *J. Org. Chem.*, **32**, 119 (1967).

TABLE III

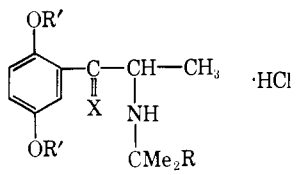
DATA ON COMPOUNDS OF CHART I AND OTHER SUBSTANCES PREPARED FOR METABOLIC STUDIES

No.	Structure	Mp, °C	Solvent for crystn[a]	Formula	Analyses
XLVII	2,5-$(MeO)_2C_6H_3COCHMeNHCHMe_2 \cdot HCl$	164–165	A-Ac	$C_{14}H_{21}NO_3 \cdot HCl$	C, H
XLVIII	2-OH-5-$MeOC_6H_3CHOHCHMeNHCHMe_2 \cdot HCl \cdot 0.5H_2O$	213–214 dec	A-E	$C_{13}H_{21}NO_3 \cdot HCl$	C, H
XLIX	2,5-$(PhCH_2O)_2C_6H_3COEt$	82–83	E-H	$C_{23}H_{22}O_3$	C, H
L	2-MeO-5-$PhCH_2OC_6H_3COEt$	41–42	E-P	$C_{17}H_{18}O_3$	C, H
LI	2-MeO-5-$PhCH_2OC_6H_3COCMe{=}NOH$	124–125	E	$C_{17}H_{17}NO_4$	C, H
LII	2-MeO-5-$PhCH_2OC_6H_3CHOHCHMeNH_2$ *threo*-base	150–153	E-P	$C_{17}H_{21}NO_3$	C, H
	threo HCl	218–219	A-Ac	$C_{17}H_{21}NO_3 \cdot HCl$	C, H
LIII	2-MeO-5-$PhCH_2OC_6H_3CHOH \cdot CHMeNH_2$ *erythro*-base	108–109	E-P	$C_{11}H_{21}NO_3$	C, H
	erythro HCl	195–196[c]	A-Ac	$C_{17}H_{21}NO_3 \cdot HCl$	C, H
LIV	2-MeO-5-$PhCH_2OC_6H_3CHOHCHMeNHCHMe_2 \cdot HCl \cdot 0.5H_2O$	223–224	H_2O	$C_{20}H_{27}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H
LV	2-MeO-5-$HOC_6H_3CHOHCHMeNHCHMe_2 \cdot HCl$	236–238	M-E	$C_{13}H_{21}NO_3 \cdot HCl$	C, H
LVI	2-MeO-5-$PhCH_2OC_6H_3CHOHCHMeNHCHMeC_7H_{15} \cdot HCl$	127–129	A-E	$C_{26}H_{39}NO_3 \cdot HCl$	C, H
LVII	2-MeO-5-$HOC_6H_3CHOHCHMeNHCHMeC_7H_{15} \cdot HCl$	164–165	M-Ac	$C_{19}H_{33}NO_3 \cdot HCl$	C, H
LVIII	2-$PhCH_2O$-5-$MeOC_6H_3CHOHCHMeNHCMe_3$	92–94[b]	E-H	$C_{21}H_{29}NO_3$	C, H
LIX	2-OH-5-$MeOC_6H_3CHOHCHMeNHCMe_3 \cdot HCl$	262–263	A-Ac	$C_{14}H_{23}NO_3 \cdot HCl$	C, H

[a] A = Absolute ethanol, Ac = acetone, E = ether, H = hexane, M = methanol, P = pentane. [b] The hydrochloride melts at 244–245° dec. [c] A hydrate melts at 153°.

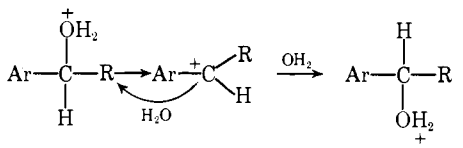
TABLE IV

N-*t*-ALKYLAMINO KETONES AND ALCOHOLS



No.	R	R′	X	Mp, °C	Formula	Analyses
LX	Me	Me	O	184–186	$C_{15}H_{23}NO_3 \cdot HCl$	C, H
LXI	Me	Me	HOH	259–260	$C_{15}H_{25}NO_3 \cdot HCl$	C, H
LXII	Me	Et	O	194–196	$C_{17}H_{27}NO_3 \cdot HCl$	C, H
LXIII	Me	Et	HOH	205–206 eff	$C_{17}H_{29}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H
LXIV	Me	Pr	O	203–204	$C_{19}H_{31}NO_3 \cdot HCl$	C, H
LXV	Me	Pr	HOH	246–247	$C_{19}H_{33}NO_3 \cdot HCl$	C, H
LXVI	Me	Bu	O	175–176	$C_{21}H_{35}NO_3 \cdot HCl$	C, H
LXVII	Me	Bu	HOH	229–230 eff	$C_{21}H_{37}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H
LXVIII	Et	Me	O	157–159 eff	$C_{16}H_{25}NO_3 \cdot HCl \cdot 0.5H_2O$	C, H
LXIX	Et	Me	HOH	229–230	$C_{16}H_{27}NO_3 \cdot HCl$	C, H
LXX	*n*-C_4H_9	Me	HOH	215.5–216.5	$C_{18}H_{31}NO_3 \cdot HCl$	C, H, N
LXXI	CH_2CMe_3	Me	O	175–176	$C_{19}H_{31}NO_3 \cdot HCl$	C, H
LXXII	CH_2CMe_3	Me	HOH	235–236	$C_{19}H_{33}NO_3 \cdot HCl$	C, H

isfactory with the N-acetyl derivatives. However, although as a preparative operation, DL-I gave about a 60% yield of *threo* isomer, and the (+)-*threo* isomer of I was obtained under Welsh conditions from (−)-I, the Welsh inversion mechanism is clearly not the only process involved. Under the conditions of the rearrangement, racemic acetylated N-isopropyl-ψ-methoxamine also gave around 30% of I (whereas N-acyl-ψ-ephedrines are not altered sterically). When refluxed 1–1.5 hr in 1 *N* HCl, both DL-I hydrochloride and the DL-*threo* hydrochloride corresponding were isomerized to the extent of 5–10%. This phenomenon could be due to solvolytic exchange in the following sense.



Such a process was rejected by Welsh[10b] as significant with the N-acylephedrine isomerization, in part, since in his system the process was stereospecific. In the methoxamine series, the *o*-methoxyl group would be expected to favor a process in which positive charge is developed on the benzylic carbon atom. The degree of isomerization found with the amine hydrochlorides is not alone capable of accounting for our observations, but the same process should be more facile in the N-acylated form which would not need to form a bivalent cation.

Although these operations do not present the elegant picture of a stereospecific conversion of the (−)-*erythro* to the (+)-*threo* isomer, they do show conversion of (−) isomer having a molecular rotation comparable to that of (−)-ephedrine into (+) isomer whose MD is also comparable to that of (+)-ψ-ephedrine.

Resolution of methoxamine itself was eventually accomplished using dibenzoyltartaric acid. This gave only a partial separation after which complete resolution was possible with D- and L-tartaric acids.

Inspection of the data of Table V shows a reasonable consistency in the molecular rotations of the optical isomers with each other and with ephedrine and ψ-

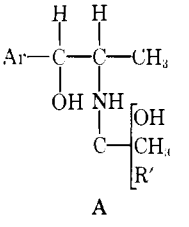
TABLE V
DATA ON OPTICAL ISOMERS

Compd HCl	Mp, °C	$[\alpha]D$,[a] deg	Concn of sdn, %[b]	MD, deg	ΔMD, deg
(−)-Ephedrine		−35.8	4	−72	199
(+)-ψ-Ephedrine		+62.8	4	+127	
(+)-Methoxamine	180.5–181.5	+28.5 ± 0.3	4	+70.6	
(−)-Methoxamine	181–182	−28.5 ± 0.3	4	−70.6	
(+)-N-Isopropylmethoxamine	242–244 dec	+22.8 ± 0.3	2	+66	
(−)-N-Isopropylmethoxamine	242–244 dec	−21.8 ± 0.5	2	−66	214
(+)-N-Isopropyl-ψ-methoxamine	167–168	+51.2 ± 0.5	2	+148	
(+)-XVIII	206–208	+25.6 ± 0.5	2	+81.3	
(−)-XVIII	206–208	−25.4 ± 0.5	2	−81.3	
(+)-N-*t*-Butylmethoxamine	261–262	+19.8 ± 0.3	4	+60.2	
(−)-N-*t*-Butylmethoxamine	259–261	−19.8 ± 0.3	4	−60.2	213
(+)-N-*t*-Butyl-ψ-methoxamine	225–226[c]	+47.5 ± 0.3	4	+153	
(−)-N-*t*-Butyl-ψ-methoxamine	227–228[c]	−47.2 ± 0.3	4	−153	
D-*sec*-Butyl-(+)-methoxamine	213–216 dec	+19.5 ± 0.8	1.5		
L-*sec*-Butyl-(+)-methoxamine	218.5–221 dec	+15.1 ± 0.3	1.7		
D-*sec*-Butyl-(−)-methoxamine	219–221 dec	−14.8 ± 0.3	3		
L-*sec*-Butyl-(−)-methoxamine	214.5–215 dec	−19.6 ± 0.3	4		

[a] Solutions made up for rotations were not thermostated but were in the range 25–27°. In all cases, observations were made promptly (within 15 min) after solutions had been made up to volume. [b] Where possible, concentrations were 4%. The isomers of N-isopropylmethoxamine and of XVIII were not sufficiently soluble to give solutions more concentrated than 2%. The available quantities of (+)-N-isopropyl-ψ-methoxamine and several of the isomers of *sec*-butylmethoxamine required operating in more dilute solutions. All solutions contained a little excess HCl (0.03 ml of concentrated or 0.5 ml of 1 *N* HCl in 25 ml). [c] These data are on the anhydrous salts. Rotations were taken on the monohydrates, (+) mp 219–223°, (−) mp 221–223° (eff), and MD is calculated on the basis of the molecular weight of the hydrate used.

ephedrine. There is a distinct tendency, as the substituents on the nitrogen atom become larger, for the molecular rotations of the *erythro* forms to become smaller and those of the *threo* isomers to become larger. The function, $\Delta M_D = M_D(+threo) - M_D(-erythro)$, is remarkably constant as between the ephedrine–ψ-ephedrine figures and those of the two methoxamine derivatives (I and LXI) for which complete data are available. The evidence is overwhelming that the configurations in the series are identical with those of the ephedrine isomers of like sign. The resolution of XVIII, which has outstanding antiarrhythmic properties, proved to be unexpectedly easy. The D-acid tartrate of the (−) isomer crystallized from solution in over 90% yield and substantially pure. As compared to DL-XVIII the (−) isomer was not demonstrably more potent in abolishing arrhythmias but its action was prolonged at least three times.[11] There are some indications that the (+) isomer has an effect antagonistic as regards its antipode.

When the compounds of Table I were screened for their effect on cardiac arrhythmias, activity showed up in a considerable number of them but no structure-activity relationships were deducible. Notably, several compounds were less active than would be expected and this peculiarity was frequently associated with the presence of asymmetry in the N-alkyl group. There was a definite possibility that the synthetic method running through the presumptive intermediate A gave exclusively or predominantly the less active of the two theoretically possible pairs of enantiomers derivable from DL-methoxamine. This could be either because one of these two pairs of configurations formed more



A

rapidly or was more stable or, since formation of A from amine and ketone is reversible, because one pair of isomers was more readily hydrogenated than the other. It has been possible to show that such a preference exists as regards II and it seems reasonable to extend this finding to the rest of the series.

A further possibility was that isolation and purification had preferentially concentrated one of the pairs of isomers. This would be more probable when the concentrations were comparable if the physical properties differed appreciably. Examination of a considerable quantity of II as the hydrochloride failed to establish homogeneity or the lack of it. (Melting points were fairly high and probably attended by decomposition.) The only unambiguous approach appeared to be to synthesize the isomers individually.

Preliminary experiments with racemic materials established satisfactory conditions for separating unreacted methoxamine from its N-*sec*-butyl derivatives

(11) The nature of the physiological test employed limits the quantitative aspect. Arrhythmias provoked by digoxin in the dog last about 15 min and are not repeatable on the same animal. Racemic XVIII abolished arrhythmias for about 5 min, (−)-XVIII, at the same dose, was effective for 15 min (the duration of the test). The time factor of 3 is therefore a minimum. In connection with this, it seems worthwhile to record an observation that may have some general significance. The hydrochlorides of (+)- and (−)-XVIII are very sparingly soluble and for injection purposes more soluble salts, preferably crystalline, would be desirable. A number of salts were prepared. The lactate and citrate are relatively soluble but do not crystallize readily. The hydrobromide (mp 214°) is not more soluble than the hydrochloride on a molar basis. The neutral sulfate (mp 243–247°) is soluble to about 4% in water and the acid phosphate ($B \cdot H_3PO_4$, mp 222°) is soluble to about 5%. The phosphate, sulfate, and D-tartrate were found to be significantly less active physiologically than the hydrochloride and hydrobromide on a molar basis. In 5% aqueous solution the phosphate gave $[\alpha]_D$ −22.4 ± 0.2° corresponding to MD −85.0 ± 0.9°. The hydrochloride has MD −81.3 ± 1.6° which is significantly less. One is led to the hypothesis that association between this amino alcohol cation and polyfunctional anions has some degree of permanence.

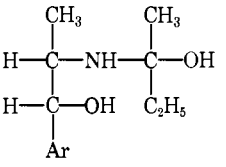
and for utilizing alkylating agent efficiently.[12] For the purpose of specific syntheses all operations were performed with the *sec*-butyl mesylates thereby avoiding the partial racemization that appears unavoidable in conversion of alcohol to bromide. Mesylate from pure D-*sec*-butyl alcohol[13] was first treated with (+)- and (−)-methoxamine bases giving the L-(+) and L-(−) isomers. After the determination of the physical properties, crystal form, etc., of these two diastereomers, similar reactions were run with L-enriched mesylate (*ca.* 80%) and the D-(+) and D-(−) isomers were obtained.

A priori it was anticipated that activity would be a function of the (−)-methoxamine portion; however, the D-(+), D-(−), and L-(+) isomers were all of about the same low activity. The L-(−) isomer was active and long acting, comparable to the (−) isomer of XVIII.

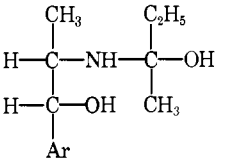
Meanwhile, a careful fractional crystallization of II as the base resulted in approximate separation into a major component crystallizing in plates and melting at 85–86° and a minor component crystallizing in needles and melting at 96–98°, in a ratio of about 3:1. Resolution of both was attempted with D-tartaric acid and the less soluble D acid tartrates were separated in both cases in sufficient quantity for identification of the corresponding hydrochlorides. The major component afforded the L-(+) isomer and the minor, the D-(+) isomer.

It was thus apparent that the reductive alkylation method had indeed produced preferentially the less active of the possible pairs of enantiomers. Knowing the rotations of the individual isomers it was possible to gain a somewhat more precise figure for this preference. Two parallel experiments were run. In the first, (+)-methoxamine was allowed to react incompletely with a large excess of DL-*sec*-butyl bromide. In the second, (−)-methoxamine was hydrogenated in the presence of butanone. The total *N*-*sec*-butylmethoxamine fractions in each experiment were isolated and rotations were determined. The rotation of the material from the alkylation experiment indicated that 70–75% of the L-(+) isomer had been formed. In the reduction experiment the product was 80–90% the D-(−) isomer. In each case about 40% of the reacted material was isolated in pure form as the hydrochloride of the predominant isomer.

On the assumption that the reductive alkylation proceeds through an intermediate alkylolamine (as A), (−)-methoxamine would give rise to the two forms B and C. Examination of Fischer–Hirshfelder models of these reveals considerably greater crowding in B than in C. Replacement of OH by H with retention of configuration would lead to the D-(−) isomer from C and to the L-(−) isomer from B. To our knowledge there is no evidence as to the mechanistic peculiarities



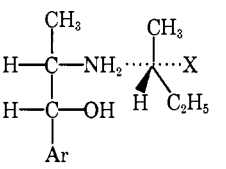
B



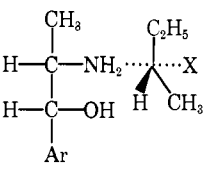
C

of such catalytic hydrogenations but there would seem to be only two obvious paths for a selective process: frontside attack with retention of configuration and backside attack with inversion. In molecules as crowded as these the latter process (as in an SN2 substitution) would seem most improbable.[14]

For the displacement reactions, the transition states of bimolecular displacements would be D and E (written for (−)-methoxamine with D- and L-*sec*-butyl-X, respectively). D has an obvious correlation with B, and E with C. E would be less crowded than D though the disparity probably would be less in these transition states than in the intermediates (B and C) whose bonds are fully covalent. This also agrees with the fact that the displacement was less selective than the reductive alkylation.



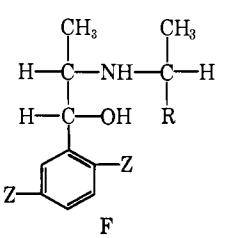
D



E

Some further correlations of the stereochemical peculiarities with the antiarrhythmic activities seem reasonable. The absolute configuration of L-*sec*-butyl-(−)-methoxamine is shown in F (Z = OMe, R = Et). The first requirement for high activity is, of course, the correct (−) configuration for the methoxamine moiety. However, the essential physiological equivalence of this isomer with the (−) isomer of XVIII (F, Z = OEt; R = Me) indicates that the magnitude of R cannot be sharply critical. Rather it is the methyl group (relatively unhindered in models) which cannot be replaced by something bulkier. This suggests that whatever the drug acts upon (receptor, enzyme surface?) has a slot which must be occupied for firm attachment but which cannot accommodate a group larger than methyl.

It is also tempting to suggest, though positive evidence is lacking, that the isolated specimen of the highly active XIII fortuitously contained a relatively high proportion of the D-(+)-L-(−) pair of isomers.



F

(12) Reactions were run with racemic methoxamine and DL-*sec*-butyl bromide and methanesulfonate in MeCN. Contrary to expectations, the mesylate was not much more than twice as reactive as the bromide. Very approximate calculations give k_{hr} (bimolecular) at reflux as 0.05 for the bromide and 0.12 for the mesylate. These figures are approximate not only because no attempt at precision was made but also because it is uncertain what form of the bimolecular equation should be employed when the basicity of the primary and secondary amine may not differ greatly.

(13) D and L are here applied as systematic notations to the isomers of *sec*-butyl alcohol. As applied to the stereo isomers of II, D-(−), D-(+), etc., are used, the D referring to the configuration of the butyl and (+) or (−) to the configuration of the methoxamine moiety.

(14) Especially since the evidence on the hydrogenations leading to I and XXIX suggests that once alkylolamine is formed its hydrogenation is rapid.

Experimental Section[15]

Reductive Alkylations.—The usual procedure for methoxamine derivatives was to dissolve methoxamine base in MeOH together with a moderate excess of the appropriate ketone, let the solution stand overnight, and then reduce it catalytically. Alternatively, methoxamine hydrochloride and an equivalent of alkali could be employed in place of the isolated base. Initially, platinized charcoal[16] was employed as catalyst. Later it was found that Pd–C and Adams' catalyst were equally satisfactory.[17] The overnight equilibration of primary amine and ketone is clearly advantageous with acetone and probably so with MeCOEt. Longer periods are undesirable probably because of slow self-condensation of the ketones with formation of traces of polymeric material. This was particularly important with the highly active cyclohexanone and for that case preliminary equilibration was both unnecessary and undesirable; freshly mixed solutions were reduced rapidly and equilibrated solutions appeared to poison the catalyst.

Operations with the higher analogs of methoxamine (2,5-diethoxy, etc.) were conducted along the same lines.

The hydrochlorides of all the compounds of Tables I and II could be recrystallized readily from H_2O, usually in the presence of a little HCl. Since such a crystallization removed any unreacted primary amine hydrochloride and inorganic impurities, H_2O was the preferred crystallization solvent.

N-Isopropylmethoxamine (I).—Methoxamine hydrochloride (25 g, 0.1 mole) was dissolved in 100 ml of MeOH. To this solution was added 5.8 g of KOH in 50 ml of MeOH and then 32 g of Me_2CO. The solution was allowed to stand overnight and then hydrogenated with 5 g of 5% Pd–C. After an initial rapid absorption of about 30 mmoles of H_2 the reduction slowed. Five hours were required for absorption of half of the calculated H_2 and about 30 hr for complete reduction. The solution was removed from the catalyst, and most of the MeOH was evaporated *in vacuo*. To the residual material were added 15 ml of concentrated HCl and 200 ml of H_2O. The solution was warmed to dissolve all solid and, on cooling, 20 g of crystals melting at 246.5–247° separated (calcd yield, 29 g). On evaporation of the filtrate to 150 ml, a further 2.2 g melting at 243–244° was obtained. The solubility of the pure hydrochloride in distilled H_2O is about 1% at room temperature. The base can be crystallized from hexane and melts at 109–110°.

N-Cyclohexylmethoxamine (XXIX).—In 40 ml of MeOH were dissolved 5.3 g (0.025 mole) of methoxamine base (mp 84.5–85.5°) and 9.8 g (0.1 mole) of freshly distilled cyclohexanone. The solution was hydrogenated with 1 g of 10% Pt–C[16] in an Adams–Parr hydrogenator. The calculated amount of H_2 was absorbed in 25 min after which time there was no further reduction. The solution was removed from the catalyst, acidified with HCl, and evaporated *in vacuo*. The residual solid was triturated with Et_2O and then crystallized from H_2O affording 7 g (85%) of pure XXIX.

N-Benzylmethoxamine (XXV).—A solution in 100 ml of MeOH of 7.5 g (35 mmoles) of methoxamine base and 4 g of distilled PhCHO was hydrogenated over 100 mg of PtO_2. The calculated amount of H_2 was absorbed in about 2 hr. The solution was filtered from the catalyst, 40 ml of 1 *N* HCl was added, and solvent was evaporated *in vacuo*. Crystallization of the residual solid from H_2O afforded 8.5 g of pure hydrochloride.

2-Methoxy-5-benzyloxypropiophenone (L) and 2,5-Bisbenzyloxypropiophenone (XLIX).—2,5-Dihydroxypropiophenone[18] (23 g, 0.2 mole) was added to 300 ml of EtOH under N_2. After an inert atmosphere had been obtained, a solution containing 0.218 mole of NaOEt in EtOH was added, giving an intensely yellow suspension of solid. To this was added dropwise with vigorous stirring 30 g (0.24 mole) of benzyl chloride over a period of 30 min. The solution was refluxed during this addition and for 2 hr further. The color faded gradually, solid disappeared, and the viscosity of the reaction mixture markedly decreased. At the end of the reflux period the pH was 8. Solid NaOH (2 g) was added and the solution was refluxed 0.5 hr longer; the pH was then 8.5. More NaOH (8 g) was added, the solution was cooled to about 40°, and 43 ml of MeI was added. The reaction mixture was stirred for 2 hr at room temperature and a further hour at 75°. Two grams more of NaOH was added and the solution was stirred overnight.

The bulk of the alcohol was removed and the material was partitioned between Et_2O and dilute alkali. The ethereal layer was dried (K_2CO_3) and evaporated; crude weight 50.5 g. The oily product was distilled through a 15-cm Vigreux column at about 0.1 mm pressure giving three fractions: (a) 8.6 g boiling at 80–81° giving a positive $FeCl_3$ test, probably in greater part 2-hydroxy-5-benzyloxypropiophenone; (b) 24.5 g, bp 148–151°; and (c) 12.4 g, bp 210–220°. Fraction c was $FeCl_3$ negative, b was weakly positive. The trace of 2-hydroxy compound in b was removed by passing through an alumina column in ethereal solution. Both fractions b and c solidified and were recrystallized to give L and LXIX, respectively.

α-(2-Methoxy-5-benzyloxyphenyl)-β-aminopropanol (LII, LIII).—2-Methoxy-5-benzyloxy-α-isonitrosopropiophenone (LI) (15 g), prepared from L by the method of Hartung and Crossley,[19] was dissolved in 150 ml of anhydrous Et_2O and added to a rapidly stirred solution of 7 g of $LiAlH_4$ in 500 ml of anhydrous Et_2O. After 2 hr of stirring at room temperature, the excess reagent was decomposed by adding 20 ml of H_2O and 3 ml of 5% NaOH solution. The ethereal layer was filtered from the precipitate, dried, and evaporated yielding 14 g (89%) of basic material. The mixed bases were distilled under high vacuum (McLeod reading 0.1–0.2 μ) through a 5-cm Vigreux column. Two fractions were obtained: (a) bp 148–149° (8.2 g), and (b) bp 160–162° (6 g). These fractions were recrystallized separately giving the bases LIII and LII, respectively.

Correlation of LIII with Methoxamine.—Four grams of the base LIII, mp 108–109°, was dissolved in 20 ml of MeCN. To this was added 7 ml of Et_3N and 3.5 ml of Ac_2O. The reaction mixture was stirred at room temperature for 1 hr and warmed over the steam bath for 1 hr further. Volatile material was then removed on the steam bath *in vacuo* and the residue was partitioned between Et_2O and H_2O. The ethereal layer was washed further with Na_2CO_3 solution and dried (K_2CO_3). Attempts to obtain crystals from ether–hexane mixtures were unsuccessful, so solvent was removed, and the total material was dissolved in MeOH and hydrogenated over Pd–C. The H_2 absorption was 14.5 mmoles (calcd 14 mmoles). After removal from the catalyst and evaporation of solvent the residue weighed 3.3 g (calcd for 5-hydroxymonoacetyl derivative, 3.35 g). This material was dissolved in 100 ml of MeOH and 3 ml of MeI was added and portions (in all, 16 mmoles) of NaOH solution. The solution was refluxed 3 hr (to neutrality), solvent was evaporated, and the residue was partitioned between Et_2O and NaOH solution. The neutral fractions (ethereal layers) were evaporated (1.3 g) and redissolved in MeOH containing 10 ml of 1 *N* NaOH solution. The reaction mixture was refluxed overnight, taken down *in vacuo*, and partitioned between Et_2O and H_2O. The ethereal layer was dried briefly (K_2CO_3) and added to an excess of EtOH–HCl solution. The solid that separated was washed with Me_2CO and recrystallized from EtOH–Et_2O. The melting point was 217° undepressed by admixture with methoxamine hydrochloride. A portion of the hydrochloride was converted to the base whose melting point was undepressed by admixture with methoxamine base.

α-(2-Methoxy-5-benzyloxyphenyl)-β-isopropylaminopropanol (LIV).—A solution was prepared of 2.43 g (8.5 mmoles) of the base LIII in 40 ml of MeOH and 15 ml of Me_2CO. The solution was allowed to stand overnight and then hydrogenated over Adams' catalyst. Hydrogen absorption was rapid at the start but slowed thereafter. The reduction was interrupted after 16 hr when the apparent absorption of H_2 was 31 mmoles. The solution was filtered, acidified with HCl, and evaporated *in vacuo*. After crystallization from H_2O, 2 g of LIV was isolated as the hemihydrate. The material in the mother liquors, after crystallization from MeOH–Me_2CO–Et_2O mixtures, yielded a small amount of slightly impure LV, mp 233–234°.

α-(2-Methoxy-5-hydroxyphenyl)-β-isopropylaminopropanol (LV).—The 2-g sample of LIV·HCl was dissolved in MeOH and hydrogenated over Pd–C. Absorption of H_2 was rapid

(15) Where in the following text and in Tables I–IV analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(16) R. Baltzly, *J. Am. Chem. Soc.*, **74**, 4586 (1952).

(17) Adams' catalyst is more convenient to handle. The supported catalysts do not reduce acetone and similar ketones and consequently permit hydrogenation to a clear stop.

(18) A. Goldweig and A. Kaiser, *J. Pract. Chem.*, [2] **43**, 86 (1890).

(19) W. H. Hartung and F. Crossley, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 363.

and, after removal of the catalyst, crystallization from MeOH–Et_2O afforded 1.5 g of pure LV.

Preparations of N-*t*-Alkyl Derivatives.—Previous operations in these laboratories in the preparation of N-methylamino alcohols have usually involved preparation of benzylmethylamino ketones and subsequent debenzylation in order to avoid handling the characteristically unstable secondary amino ketones as bases. For the present application, however, it seemed likely that use of a benzyl *t*-alkylamino intermediate would involve serious hindrance problems and 2,5-dimethoxy-α-bromopropiophenone was allowed to react directly with *t*-butylamine. Even in this instance hindrance effects were apparent and deserve some attention.

In our previous experience (*e.g.*, ref 2–4) reactions of such bromo ketones with benzylmethylamine had been very rapid. Ethereal solutions about 0.1 *M* in bromo ketone and 0.2 *M* in amine began depositing crystals of benzylmethylamine hydrobromide almost at once and precipitation was effectively quantitative within 30 min, although reaction mixtures were often allowed to stand longer than that. With *t*-butylamine under similar conditions the reaction rate was negligible. Satisfactory conditions were found to exist in MeCN, a very "fast" solvent for this type of reaction, in rather concentrated solution (about 1 *M* in bromo ketone). Once obtained, 2,5-dimethoxy-α-*t*-butylaminopropiophenone (LX) showed unusual stability for this type of compound. The base even survives distillation around 0.01 mm without much decomposition.

2,5-Dimethoxy-α-*t*-butylaminopropiophenone (LX).—2,5-Dimethoxy-α-bromopropiophenone (9 g, 0.033 mole) was dissolved in 25 g of MeCN. *t*-Butylamine (10 g) was added and the solution was allowed to stand for 21 hr. At that time some solid (*t*-butylamine hydrobromide) had separated. Absolute Et_2O (200 ml) was added and after a few minutes the solution was filtered from the separated salt which was washed with more Et_2O. The filtrate was washed with H_2O (pH *ca.* 7.5), dried (K_2CO_3), and evaporated *in vacuo*. The residue weighed 8.5 g. It was redissolved in Et_2O and added to 15 g of 10% HCl in MeOH. More Et_2O was added to incipient turbidity and crystallization was induced. The first crop weighed 5 g and melted at 181.5–183.5°. Two grams more was obtained from the mother liquors. For analysis, the solid was dissolved in 20 ml of hot absolute EtOH and an equal volume of Et_2O was added. The crystalline precipitate now melted at 184–186°.

α-(2,5-Dimethoxyphenyl)-β-*t*-butylaminopropanol (LXI). (a) By Catalytic Hydrogenation.—LX·HCl (4 g) in 40 ml of MeOH was hydrogenated over Adams' catalyst. Absorption of H_2 was complete in 4 hr. The solution was filtered, evaporated to about 10 ml, and diluted with Et_2O. The solid so obtained melted at 249–251° dec. It was further purified by recrystallization from H_2O containing a trace of excess HCl.

(b) By Borohydride Reduction.—To 3 g of LX·HCl in 15 ml of 50% EtOH, solid $NaBH_4$ was added in small portions with stirring until excess reducing agent was still demonstrable after 30 min. The solution was then acidified with HCl and boiled down to half-volume in the hood. On cooling and basification, the base precipitated as a solid that melted at 111–112° after recrystallization from Et_2O–hexane. It was then dissolved in hot dilute HCl from which the hydrochloride separated on cooling.

The other compounds of Table IV were prepared by the same general method as LX and LXI. Borohydride reduction consistently gave some isomeric amino alcohols but in small-scale preparations these were not isolated. In large-scale reductions the amount of *threo* isomer was of the order of 10%. The ketone corresponding to the amino alcohol LXX was not obtained as a crystalline hydrochloride. After reduction of a solution of the basic product, LXX·HCl crystallized readily.

Resolutions.—Compounds I, XVIII, LXI, *threo*-LXI, and methoxamine itself were resolved. The stereoisomeric *sec*-butylmethoxamines were prepared specifically, but D-*sec*-butyl-(+)-methoxamine and L-*sec*-butyl-(+)-methoxamine were also isolated by resolution. Except for the resolution of methoxamine itself all of these were done with D-tartaric acid (either in the first step or entirely). Usually the (+)-base D-acid tartrate was the salt that separated first. Compound XVIII came down as the (−)-base D-acid tartrate with high efficiency (90% of the calculated amount of salt as a trihydrate in the first crop). With *threo*-LXI also the D-acid tartrate of the (−)-base separated.

Methoxamine cannot be resolved directly with tartaric acid owing to the very low solubility of a neutral tartrate, containing both isomeric forms of base. The acid D-dibenzoyltartrate of (+)-methoxamine separates readily from Me_2CO in a rather impure form. Recrystallization is feasible by dissolving in warm 50% Me_2CO and boiling off Me_2CO until solid begins to separate. However, we have not been able to obtain optically homogeneous material by this method. Conversion of such dibenzoyltartrates to the hydrochloride followed by careful crystallization from ethanolic solution by gradual addition of Et_2O always resulted in appearance of the characteristic elongated prisms of DL-methoxamine hydrochloride. After the bulk of this had been separated, the glossy leaflets of (+)-methoxamine hydrochloride would appear. Similar operations with (−)-enriched hydrochloride from the more soluble dibenzoyltartrate fractions gave (−)-methoxamine hydrochloride. Later developments indicated that these salts were not better than about 98% of the predominant isomer. The following process proved eventually to be most advantageous.

Thirty mmoles of DL-methoxamine hydrochloride was dissolved in 50 ml of H_2O in a 500-ml wide-mouth erlenmeyer flask equipped with a stirrer. To this was added 16 mmoles of D-dibenzoyltartaric acid in 50 ml of Me_2CO and 7 ml of 2.4 *N* NaOH solution. The solution was stirred under a gentle air stream, and at intervals over 3 hr a few milliliters of Me_2CO was added to wash down the sides of the flask. Two 20-ml portions of H_2O were also added. The weight was now 95 g. The precipitated solid was filtered and dried, 5.8 g. The aqueous layer was washed with Et_2O and basified, and the base was taken into ether and converted to hydrochloride, 4.7 g. The rotation of this hydrochloride indicated that it contained 62% of the (−) and 38% of the (+) isomer.

The 5.8 g of D-enriched dibenzoyltartrate was dissolved in 100 ml of 50% Me_2CO and to it was added 8.7 mmoles of hydrochloride estimated to be two-thirds (+) isomer and 4 mmoles of D-dibenzoyltartaric acid. The evaporation and equilibration were repeated as before. The precipitate weighed 5.6 g, mp 175.5–176.5°. The hydrochloride obtained from the aqueous ayer was estimated to be 55% (+) and 45% the (−) isomer. With (+)-enriched dibenzoyltartrate of this quality it was advantageous to proceed to resolution with D-tartaric acid.

Thirteen mmoles of hydrochloride estimated to contain 11 mmoles of D and 2 mmoles of L isomer was dissolved in H_2O. To this was added 1.8 g (12 mmoles) of D-tartaric acid and the solution was warmed while 5 ml of 2.4 *N* NaOH was added. The volume was adjusted to 25 ml and the solution was allowed to cool. After 2 hr the crystalline precipitate was collected and dried, 2.5 g (7 mmoles) as the D-acid tartrate.

The above solid was redissolved in H_2O together with another batch of 6 mmoles of hydrochloride, 1 g of D-tartaric acid (6.7 mmoles), and 4.3 mmoles of NaOH solution. The volume was adjusted to 25 ml and the solution was allowed to cool. The precipitated solid weighed 4.5 g. It was recrystallized from the minimum of H_2O together with 0.7 g of D-tartaric acid, 4 g of solid melting at 162–164° being obtained.

D-Tartrate (from the above and several similar batches) (15 g) was dissolved in H_2O. The solution was basified and the base was taken into Et_2O and the solution was dried (K_2CO_3). The ethereal solution was poured slowly into a flask containing 8 g of 45% (w/w) HCl in absolute EtOH and 100 ml of Me_2CO. The hydrochloride separated as glossy leaflets which were filtered off and washed with Me_2CO, then with Et_2O; 8.7 g, mp 180.5–181.5°. Of this, 1.0742 g was dissolved in H_2O plus a drop of concentrated HCl and made up to 25 ml; α_D +2.45°, $[\alpha]_D$ +28.5 ± 0.3°. A similar sequence of crystallizations of heavily L-enriched material with L-tartaric acid *et seq.* afforded (−)-methoxamine hydrochloride.

Application of the same techniques to the resolution of ψ-methoxamine[20] was unsuccessful. The dibenzoyl tartrate that precipitated was D-enriched but in our hands did not yield hydrochloride much better than one-third D (two-thirds DL). Further operations through the very soluble D-tartrate or through the hydrochlorides afforded no material worthy of confidence.

N-Isopropylmethoxamine (I).—The (+)-base D-tartrate and (−)-base L-tartrate crystallize readily from H_2O in leaflets but in hydrated forms that melt in the vicinity of 90°. The melting points are of little value in determining steric homogeneity. The following procedure for the (+) isomer was the most successful.

(20) I. Satoda, F. Kusuda, T. Omoto, M. Kawamata, and Y. Yamamoto, *Yakugaku Zasshi*, **79**, 989 (1959); *Chem. Abstr.*, **54**, 4475 (1960).

The solid base liberated from 130 mmoles of DL hydrochloride was dissolved together with 170 mmoles of D-tartaric acid in 200 ml of H_2O. On cooling, the precipitate was collected, washed with ice–water, and dried; 28 g. Of this 1 g was soluble in 18 ml of 1% D-tartaric acid solution. The total solid was recrystallized from 90 g of H_2O containing 2 g of D-tartaric acid and yielded 13 g of tartrate with a solubility of 1 g in 21 ml of 1% D-tartaric acid solution. The second recrystallization was from 65 g of solution containing 2 g of D-tartaric acid and gave 9.5 g of solid with a solubility (as before) of 1:23. The third and fourth recrystallizations from 54 and 41 g of solution, each with 1 g of excess acid, gave 6.7 and 5.2 g, respectively, each with solubilities of 1:26.

The last portion of D-tartrate was converted to the base which was crystallized from 50 ml of hexane giving hairy crystals that re-formed as large prisms, mp 85–86°. This base was then converted to the hydrochloride and crystallized twice from H_2O, mp 242–244° dec.

Interconversions between the *erythro* and *threo* Forms of I.—The acylations of these compounds encountered difficulties probably from hindrance. The same factor may have been involved in the relative slowness of the N → O shift in aqueous acid, but low solubility could also have been responsible. No attempt was made to isolate the hydrochlorides of the O-acyl derivatives. Rather, after all the material had dissolved in aqueous phase, solvent was removed and the residue was subjected to acid-catalyzed ester exchange to remove O-acyl groups and convert all the material to amino alcohol hydrochloride.

The separation of *threo* from *erythro* isomer is easier with racemic material since the DL-*threo* hydrochloride is readily soluble in hot Me_2CO and crystallizes from the cooled solution slowly in elongated prisms. Most of the *erythro* hydrochloride can be removed first because of its low solubility in H_2O. The separation of (+)-*threo* from (−)-*erythro* hydrochloride follows similar lines but is less facile as the solubilities are closer together.

DL-N-Isopropyl-ψ-methoxamine.—Ten grams of I base was dissolved in 30 ml of MeCN together with 25 ml of Et_3N and 10 ml of Ac_2O. The solution was allowed to stand overnight after which volatile material was removed *in vacuo* in a water bath at 40-45°. The residue was taken into Et_2O and washed (H_2O, 5% NaOH, H_2O, 5% HCl, H_2O). The Et_2O was evaporated, 200 ml of 5% HCl was added, and the flask was heated under reflux. All material went into solution in about 15 min and refluxing was continued for 1 hr thereafter. The solution was taken down to dryness *in vacuo* and the residue was dissolved in 200 ml of MeOH to which 10 ml of concentrated HCl had been added. The resultant solution was allowed to stand overnight and again evaporated *in vacuo*. The residue was dissolved in 50 ml of boiling H_2O from which 3.5 g of I·HCl crystallized on cooling. The supernatant (and Me_2CO washes from the solid) were evaporated *in vacuo* and the remaining material was dissolved in 32 g of hot Me_2CO. This solution was refrigerated yielding 5.7 g of crystalline material melting at 129–132°. The solid was redissolved in 50 ml of hot Me_2CO, a little undissolved material (I·HCl) was filtered off, and Et_2O was added to crystallization. Solid (5 g) melting at 130–132.5° was obtained. The best sample, obtained from the DL-*o*-chlorobenzoyl derivative of I, melted at 129–129.5°. *Anal.* ($C_{14}H_{23}NO_3$·HCl) C, H.

The above procedure was certainly the most convenient and probably the most efficient of those investigated. The product of acetylation is probably a mixture of mono- and diacetyl derivatives. Experiments (base-catalyzed ester exchange) intended to remove the O-acetyl usually removed both acetyl groups. On consideration, it seemed best to conduct the rearrangement with the crude material. To some extent it would be expected that the ester acetyl should be removed more rapidly than the amide acetyl. Further, it is arguable that an N,O-diacetyl derivative should undergo the Welsh rearrangement as readily as the N-monoacetyl compound.

The original Welsh modification of the Schotten–Baumann reaction using benzoyl chloride or *o*-chlorobenzoyl chloride gave hardly any amide from I. Using considerable excess of reagents in repeated additions, mainly diacyl derivatives were formed: **DL-diacetyl-N-isopropylmethoxamine,** mp 121.5–122° from EtOAc–hexane [*Anal.* ($C_{18}H_{27}NO_5$) C, H], **DL-dibenzoyl-N-isopropylmethoxamine,** mp 119–120° from Et_2O [*Anal.* ($C_{28}H_{31}NO_5$) C, H], **DL-bis(*o*-chlorobenzoyl)-N-isopropylmethoxamine,** mp 165–166° from Me_2CO [*Anal.* ($C_{28}H_{29}Cl_2NO_5$) C, H].

When allowed to stand 3 days in MeOH with a trace of NaOMe, the bis(*o*-chlorobenzoyl) derivative was converted to the mono derivative, mp 170.5–172°, which could also be obtained directly by a mild acylation as described above for the acetylation. From 3 g of this N-*o*-chlorobenzoyl-N-isopropylmethoxamine 450 mg of DL-N-isopropyl-ψ-methoxamine hydrochloride was obtained in 15–20% yield.

(+)-N-Isopropyl-ψ-methoxamine.—(−)-N-Isopropylmethoxamine was acetylated and rearranged by the procedure given in detail above. The solid residue from the final evaporation *in vacuo* was extracted twice with boiling Me_2CO and unrearranged hydrochloride was collected on cooling. The mother liquors, on addition of Et_2O, deposited small prisms and rosettes of fine needles. The prisms were removed mechanically and the rosettes were dissolved in H_2O. The rotation indicated that these crystals were the desired *threo* isomer. The aqueous solution was evaporated *in vacuo* and the residue was taken up into Me_2CO, a little undissolved material (prisms) was removed, and the product was crystallized as needles on addition of Et_2O, mp 167–168°. *Anal.* ($C_{14}H_{23}NO_3$·HCl) C, H. This product (503 mg) in 25 ml of water containing 0.03 ml of concentrated HCl gave α_D + 2.06 ± 0.02°, $[\alpha]_D$ + 51.2 ± 0.5°.

Reverse Rearrangement with DL-*threo*-I.—DL-*threo* hydrochloride (6 g, 20.7 mmoles) was dissolved in 25 ml of warm MeCN. To this was added 15 ml of Et_3N and 8 ml of Ac_2O. The mixture was heated to boiling and allowed to cool. Warming was repeated twice in 5 hr and 15 ml more of MeCN was added to complete solution. After standing 24 hr the mixture was taken down *in vacuo* on a steam bath and the residue was partitioned between Et_2O and H_2O (pH *ca.* 6). The ethereal layer was washed with 1 *N* NaOH until the washings were clearly alkaline, then with H_2O and finally with 1 *N* HCl (8 ml). This acid extract yielded 0.4 g of base involatile in water-pump vacuum on the steam bath (*ca.* 2 mmoles).

The ethereal layer was evaporated *in vacuo* (8 g). To it was added 90 ml of 5% HCl, and the flask was heated under reflux. All material had dissolved after 25 min of boiling. The solution was refluxed 0.5 hr longer and then taken down *in vacuo*. The residue was dissolved in 100 ml of MeOH, and 10 ml of 15% (w/w) HCl in MeOH was added. Not all the material dissolved. The mixture was allowed to stand overnight, warmed to 55° to dissolve the solid, and allowed to stand 24 hr longer. A few large prisms were now present. The solution was refrigerated 5 hr and then decanted from the crystals which were identified as DL-I. The MeOH solution was evaporated *in vacuo* and the residue was dissolved in warm Me_2CO. Several small crops of I were obtained totalling 1.7 g (6 mmoles). A total of 3.3 g (11.3 mmoles) of DL-*threo* hydrochloride was obtained by addition of Et_2O to the Me_2CO solutions.

One-gram portions of DL-*erythro* and DL-*threo* hydrochlorides were placed in flasks with 20 ml of 1 *N* HCl, and refluxed 1.5 hr each. The comparison was not quite sound because much of the *erythro* hydrochloride remained undissolved throughout the heating period. The reaction mixtures were worked up along the lines described above. The originally *erythro* material yielded 51 mg of acetone-soluble hydrochloride (*threo*). The originally *threo* material gave 77 mg of acetone-insoluble hydrochloride (*erythro*).

N-*t*-Butylmethoxamine (LXI).—The resolution requires a considerable excess of tartaric acid (50–100%) since the least soluble salt is the DL-base neutral D-tartrate, mp 228–229°.

LXI base (41 mmoles, 11.2 g) and 65 mmoles (9.5 g) of D-tartaric acid in about 50 ml of hot H_2O gave, on cooling, well-formed needles melting about 190°. After recrystallization from 20 ml of boiling H_2O containing 2 g of excess tartaric acid, there was obtained 6 g (14 mmoles) of salt, mp 196–197.5°. The tartrate was dissolved in H_2O and the base was liberated. This was crystallized from Et_2O–pentane at 4° giving well-formed needles melting at 72–73°. The crystalline base was converted to the hydrochloride which can be crystallized from EtOH–Et_2O or from H_2O. The melting point varies with the rate of heating (253.5–255 and 261–262° have been obtained) and is not reliable. The (+) hydrochloride and DL hydrochloride do not differ appreciably in melting point but the DL hydrochloride is much less soluble (*ca.* 1% and at least 4%, respectively) in H_2O and must be a racemic compound.

The mother liquor from the separation of the (+)-base D-tartrate was basified and the base was taken into Et_2O and dried (K_2CO_3), and the solution was boiled down with hexane to about 20 ml. On cooling, fine crystals (DL-base) separated first, followed by long needles [(−)-base]. Solvent was added to dissolve the needles and the solution was decanted from the less

soluble crystals, leaving about 2 g of DL-base. The mother liquor, estimated to contain about 1.5 g of DL-base and 3.5–4 g of (−)-base, was evaporated to small volume and dissolved in 15 ml of H_2O to which 4 g of L-tartaric acid had been added. The solution was heated to boiling, and H_2O was added to a weight of 24 g and allowed to cool. The (−)-base L-tartrate that separated weighed 5.5 g (13 mmoles) and melted at 196.5–197.5°. The L-tartrate was dissolved in H_2O and the base was liberated and crystallized from hexane. It weighed 3.8 g and melted at 74°. The base in turn was converted to the hydrochloride, 3.5 g, glossy leaflets from EtOH–Et_2O; mp 259–261° dec.

threo (**Pseudo**) **Form of LXI.**—The starting material was the basic oil remaining after crystallization of LXI base from hexane when LXI was being prepared on a relatively large scale (*ca.* 1 kg) by borohydride reduction. This base formed a hydrochloride crystallizing from dilute HCl and melting at 234–235° dec. It had the same composition as LXI·HCl but the homogeneity (as the DL-*threo* isomer) was uncertain.

The oily base when dissolved in H_2O with a 50% excess of D-tartaric acid gave, from cold solutions, needles melting at 56–59°, probably hydrated and rather soluble in cold H_2O and in Me_2CO. As a consequence, the loss in washing was severe and it was expedient to keep the first filtrates separate from the washings. After several recrystallizations, material melting at 71–72.5° was obtained. Six grams of this quality was obtained from 44 g of base in three experiments but much partially separated material remained in the washings.

The base in the first mother liquors was liberated and converted to hydrochloride. The solution was dextrorotatory showing that the D-tartrate was that of the (−)-base. When the dextrorotatory solution of hydrochloride was evaporated to small volume, crystals separated and were observed to be of two types: one of irregular shape and holding onto a brownish contaminant present originally in the solution melted at 234–236° dec; the second type, nearly colorless lath-like crystals, melted at 222–224° and showed $[\alpha]D$ +47.4° (4% in H_2O). This being in the range expected for a *threo* isomer, lath-shaped crystals (6.5 g) were separated where possible from several such preparations. This material was recrystallized twice and then melted at 219–223° dec and had the composition of a monohydrate. The anhydrous form, obtained by drying in high vacuum, melted at 225–226°. The hydrate was used for rotations.

The (−)-base was recovered from the D-tartrate salt and converted to the hydrochloride which was also obtained as the monohydrate.

Small portions (0.5 g each) of the (+)- and (−)-*threo* hydrochlorides were combined in aqueous solution and allowed to crystallize. As first obtained, the salt melted at 220–223° (eff) and had the composition of a hemihydrate. On stringent drying, the melting point rose to 232–233°. This material was not clearly distinguishable from the original hydrochloride (mp 234–235° dec) but the latter may have contained appreciable amounts of *erythro* material.

Compound XVIII was resolved with minimal difficulty. The use of L-tartaric acid to purify the (+) isomer was unnecessary since the (+) and (−) hydrochlorides are less soluble (and higher melting) than the DL hydrochloride.

Stereospecific Synthesis of the Isomers of N-*sec*-Butylmethoxamine (II).—Model experiments were carried out with racemic material to determine the proper reaction conditions. In these, an excess (1.3–1.4 molar equiv) of methoxamine base was treated in MeCN with *sec*-BuBr or mesylate (*e.g.*, 10 mmoles of base plus 7 mmoles of bromide in 10 ml of MeCN). After 3 days at room temperature about 7% of the bromide had reacted (by titration). In a similar experiment at reflux for 21.5 hr, 57% had reacted. With *sec*-butyl mesylate, 8–9% of the ester had reacted after 1 week. At reflux for 22 hr, 5.7 out of 7.1 mmoles had reacted. Since a considerable portion of this reaction could have been elimination, unreacted methoxamine was separated from *sec*-butylmethoxamine. The titration of the latter gave a figure of 5.68 mmoles.

It later became apparent that in these conditions the principal reaction was between (+)-base and D reagent or (−)-base and L reagent. In the specific reactions of the (+)-base with L reagent, etc., considerable elimination may have interfered.

The separation of methoxamine from *sec*-butylmethoxamine depends upon the fact that methoxamine base is fairly soluble in H_2O and very little soluble in petroleum ether fractions. (The distribution ratio of methoxamine for hexane–H_2O is 0.004. For the system 1:1 Et_2O–hexane/H_2O, the ratio is 0.08.)

The procedure used for isolation of secondary bases was consequently to remove the solvent *in vacuo* and then to partition the residue between Et_2O and dilute alkali (two funnels in series). After the total bases were taken into the ethereal layers, these were diluted with equal volumes of hexane and washed serially with small amounts of H_2O until the washings were at about pH 8. As a guide, these washings could be titrated with standard acid. The secondary bases could next be extracted from the Et_2O–hexane layers with standard acid and the quantity of secondary base was determined approximately. The predominant isomeric hydrochlorides were isolated by fractional crystallization from aqueous solution. The procedure was complicated by the fact that earlier specimens of (+)- and (−)-methoxamine used were not in fact sterically pure and by the relatively poor yields in the reactions of D-mesylate with (−)-methoxamine and L-mesylate with (+)-methoxamine. The isolation was assisted by differences in crystalline form, the D-(+) and L-(−) salts forming rather heavy rectangular prisms while their diastereomers tended to crystallize in needles.

Separation of II into Component Racemates.—Various attempts to fractionate II·HCl had been unsuccessful. Eventually it was found that when the base was refrigerated in Et_2O–pentane solution two types of crystals appeared. A partial separation was accomplished: from 9.5 g of mixed bases 7 g of the preponderant base was obtained. This crystallized in heavy plates melting at 82–84°. The minor component crystallized in needles melting at 96–98°. This amounted to 2 g and seemed fairly pure. The major component, which was much more likely to be contaminated, was recrystallized repeatedly and two fractions, I (2.6 g), mp 86–87°, and II (2.3 g), mp 84–85.5°, were finally accepted as fairly reliable. The two specimens were resolved with D-tartaric acid. From the 96–98° base there was obtained through the D-tartrate, 120 mg of D-(+) hydrochloride, $[\alpha]D$ +19.3 ± 1°. The lower melting base was similarly resolved yielding 435 mg of L-(+) HCl, $[\alpha]D$ +15.2 ± 0.6°.

(+)-Methoxamine and DL-*sec*-Butylbromide.—Pure (+)-methoxamine (20 mmoles) (from 5.0 g of pure hydrochloride) and 13 g (0.1 mole) of DL-*sec*-BuBr were dissolved in 100 ml of MeCN. The solution was refluxed 16 hr after which most of the solvent was boiled off. The residue was dissolved in 50 ml of 50% MeOH and titrated to pH 5 (outside indicator) with standard HCl; 7.42 mmoles of acid was required. As there was a tendency for solid to separate, 5 ml of concentrated HCl was added and more H_2O and the solution was evaporated to 47 g. On cooling, 1.8 g of crystals separated (6 mmoles if hydrochloride). The filtrate was subjected to the separation described previously. The washings appeared to contain 5.1 mmoles of methoxamine. The subsequent acid extracts (containing secondary amine) were evaporated to dryness *in vacuo*, the earlier crop of crystals was added and the total solids were dissolved in 100 ml of MeOH to which 20 g of 40% (w/w) HCl in EtOH had been added. This solution was boiled for 2 hr allowing solvent to evaporate slowly (to remove any bromide present)[21] and then evaporated *in vacuo*. The residue was dissolved in H_2O with a trace of added HCl, charcoaled, filtered, transferred to a tared beaker, and evaporated to dryness on the steam bath. The weight of the residue was 2.83 g. This solid was redissolved in H_2O with 1 ml of 1 *N* HCl and made up to 50 ml αD +1.82 ± 0.02°, $[\alpha]D$ +16.1 ± 0.2°. On the basis of specific rotation of +14.7 and +19.6° for the L-(+) and D-(+) isomers, respectively, this corresponds to 70–75% of the former. The solution was evaporated to 15 g giving a first crop of flattish needles and then to 10 g giving a second crop of the same type. The two crops were combined and recrystallized from 14 g of aqueous solution. There was obtained 1 g of solid identical with the L-(+) isomer previously prepared.

Hydrogenation of (−)-Methoxamine and Butanone.—The base was liberated from 4 g (16 mmoles) of (−)-methoxamine hydrochloride and taken into Et_2O and the Et_2O was evaporated. The residue was dissolved in MeOH in a hydrogenation bottle containing 1 g of freshly prepared 10% Pt–C and 7 g of freshly distilled butanone and shaken under H_2. The absorption of H_2 was 13.7 mmoles in 140 min. The solution was allowed to stand overnight with a H_2 uptake corresponding to 4 mmoles. Shaking for 1 hr further gave an uptake of only 0.2 mmole. The solution was acidified with HCl, removed from the catalyst, and evaporated *in vacuo*. The residue was subjected to the separation as

(21) A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.*, **74**, 5231 (1952).

previously described and the dry weight of the secondary amine hydrochloride fraction was found to be 3.98 g (13 mmoles). The solid was made up to 100 ml: α_D −1.23 ± 0.02°, $[\alpha]_D$ −15.5 ± 0.2°. On the same basis of calculation as in the previous experiment this corresponds to 84.7% (reasonably, 80–90%) of the D-(−) isomer. The solution was evaporated to 31 g giving crop I, then to 14 g for II, to 7.5 g for III, and to 4 g for IV in which a different type of crystal was apparent. The first crops were recrystallized serially from 15 ml of H_2O giving crops of 1.8 g and 0.5 g, respectively, which were combined and recrystallized again from 20 g of H_2O. The product, 1.6 g, was identical with the previously prepared D-(−) isomer.

sec-Butyl mesylate was prepared by the method of Hoffmann.[22]

*sec*BuOH was resolved by literature methods[23] by fractional crystallization of the brucine half-phthalates. We were not successful in attempts to purify brucine L-*sec*-butyl acid phthalate but highly enriched L half-ester could be obtained by crystallization of racemic half-ester from material recovered from the more soluble brucine salt fractions. The oily ester remaining after no more DL ester crystallized on refrigeration was estimated by rotation (in EtOH) to be about 80% L and 20% D isomer.

Recovery of optically active alcohol from half-ester or directly from brucine salt by alkaline hydrolysis, distillation, etc., entailed, in our hands, unacceptable losses. A more convenient and efficient procedure was found to be distillation with excess benzylamine.

D-*sec*-BuOH.—D-*sec*-Butyl acid phthalate (61.5 g, 0.27 mole) was heated with 80 ml of benzylamine. A thermometer registered the temperature of the liquid and a second surmounted a 5-cm Vigreux column leading to a condenser. The receiver was protected from moisture. The internal temperature was raised during 18 min to 140°. At this point there was some refluxing (but not distillation) of liquid. During the next few minutes the internal temperature fell and after 58 min of constant heating it was 125°. Some distillation took place during this period. Heating was increased gradually over 3.5 hr until the temperature of the melt was 206° and high-boiling liquid was condensing in the lower part of the fractionating column. The condenser was rinsed with pentane into the receiving flask, the volume in the flask was increased with pentane to about 50 ml, and the distillate (which contained some water and benzylamine) was dried ($CuSO_4$). The distillate was removed from the desiccant and distilled through a short fractionating column. There was obtained 17 g of pure D-*sec*-BuOH. In several preparations by this method, yields were consistently 85–90%. Examination of the (solidified) residue in the reaction flask showed it to be mainly N,N′-dibenzylphthalamide. Benzylamine was selected for this reaction on the basis of availability and boiling point. Presumably, any other simple, primary aliphatic amine boiling well over 150° could replace it.

2-Amino-2-methylhexane[24] required for the preparation of I.XX was prepared by the Hoffmann reaction from the corresponding amide. The Jeffreys[25,26] modification of the Hoffmann reaction was most advantageous but even this variation gave inferior yields (around 50%). Considerable amounts of amide were recovered and it is suspected that hindrance slowed the initial step of N-halogenation.

Acknowledgment.—The authors wish to express their gratitude to Dr. S. W. Blackman for the many microanalyses required and to Mrs. Justina Strelitz and Messrs. Joseph Horodniak and Thomas McInerny for technical assistance.

(22) H. M. R. Hoffmann, *J. Chem. Soc.*, 1249 (1964).

(23) *Cf.* especially S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **75**, 1744 (1953).

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(25) E. Jeffreys, *Ber.*, **30**, 898 (1897); *Am. Chem. J.*, **22**, 14 (1899).

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Adrenergic Neurone Blocking Agents. III.[1] Heterocyclic Analogs of Guanoxan

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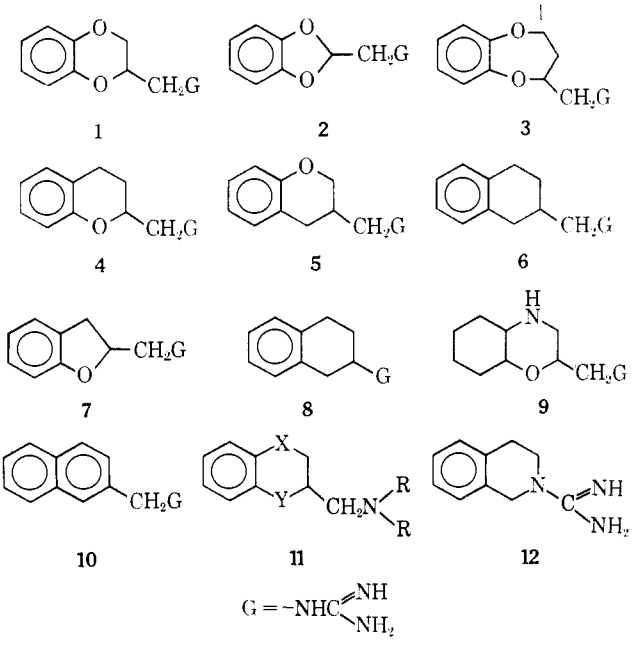
Received December 26, 1967

Analogs of guanoxan modified in the heterocyclic ring have been compared with respect to their adrenergic neurone blocking potencies, their effects *vs.* epinephrine and norepinephrine in the cat, and their antihypertensive effects in the dog.

It has been reported[2] that the antihypertensive agent guanoxan (**1**) displayed, like guanethidine, adrenergic neurone blocking properties in the cat, but in contrast to guanethidine, guanoxan also displayed a classical blockade of α receptors. The effects on these properties upon introduction of substituents to the aromatic ring[1a] or to the dioxane ring,[1b] and of modification of the side chain,[1a] have already been discussed.

This paper is concerned with the adrenergic neurone blocking activity of **2–10** in which the heterocyclic ring of guanoxan has been modified. Syntheses of most of these compounds have already been described in the literature. Additional features of interest, and details of those syntheses not already reported, are described in the Experimental Section.

Biological Results and Discussion.—Adrenergic neurone blocking activity of the compounds was measured



(1) (a) Paper I in this series: J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965); (b) paper II: A. M. Monro, G. W. H. Potter, and M. J. Sewell, *ibid.*, **10**, 880 (1967).

(2) M. J. Davey and H. Reinert, *Brit. J. Pharmacol.*, **24**, 29 (1965).