This substance has a transition in the solid about 5.7° below the melting point. Equilibrium in the transition was attained very slowly and the methyl bromide could be superheated or supercooled one or two-tenths of a degree above or below the transition point, 173.75 ± 0.15°K.

The melting point was found to be 179.44 ± 0.05°K., the boiling point 276.66 ± 0.05°K., the heat of transition 113.4 ± 1 cal./mole, the heat of fusion 1429 ± 2 cal./mole, and the heat of vaporization 5715 ± 6 cal./mole.

Vapor pressure measurements have been made on liquid methyl bromide and the results have been represented by the following equation

liquid methyl bromide, 203 to 278°K. (0°C. = 273.10°K.)

$$\log_{10}P(\text{Int. cm. Hg}) = -(1541.437/T) + 8.49274 - 0.00424740T + 1.7599 \times 10^{-6}T^2$$

The density of methyl bromide gas at 298.10°K. and one atmosphere was found to be 3.9739 ± 0.0009 grams/liter.

The entropy of methyl bromide (ideal gas) at one atmosphere and at the boiling point, 276.66°K., has been calculated from calorimetric data to be 57.86 ± 0.10 cal./deg. per mole and compared with the value 57.99 obtained from spectroscopic data.

The good agreement indicates that it is correct to use the third law value in thermodynamic calculations. It also gives more experimental substantiation to the assumption made in the calculation of potential barriers in compounds containing methyl groups, namely, that the entropies of these compounds may be obtained correctly from low temperature calorimetric data.

The experimental entropy (ideal gas) at 298.10°K. is 58.61 cal./deg. per mole, and the spectroscopic value (ideal gas) is 58.74 cal./deg. per mole.

BERKELEY, CALIF. RECEIVED JUNE 15, 1938

[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

2-Alkyl-1,2,3,4-tetrahydroisoquinoline Hydrochlorides[1]

BY JOHANNES S. BUCK AND WALTER S. IDE

With a view to carrying out a detailed pharmacological examination of the effects of various 2-alkyl groups on the action of tetrahydroisoquinolines, three series of 2-alkyl-1,2,3,4-tetrahydroisoquinolines were prepared. One series has no nuclear substituents, the second carries 6,7-dimethoxy groups and the third has 6,7-dihydroxy groups. Hydrochlorides were chosen for pharmacological reasons. In no case was a substituent present in the 1-position.

The preparation of the unsubstituted compounds was carried out substantially according to the method of Wedekind, *et al.*[2] and offered no particular difficulties. However, a general method was required for future work, and Wedekind's procedure could not be applied to the substituted derivatives, owing to the relative inaccessibility of substituted isoquinolines. Attempts were made to N-alkylate homoveratrylamine by the Decker[3] method with a view to cyclizing the alkylated amines,[4] but these did not succeed with alkyl groups larger than ethyl, the alkiodides of the Schiff bases being non-crystalline and the homogeneity of the secondary amine being therefore in doubt. However, some 2-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was made by this route, from ethylhomoveratrylamine.

Direct alkylation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[5] with ethyl iodide gave considerable amounts of quaternary compound and unchanged material, with some of the desired 2-ethyl derivative.[6] The method, however, was regarded as unsatisfactory. Similar objections apply to the use of toluene sulfonic esters.[7] Attempts to alkylate by means of α-bromo acids[8] gave only the hydrobromide of the starting material.

Finally, 6,7-dimethoxy-3,4-dihydroisoquinoline was investigated. This readily formed crystalline

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories. The pharmacological data were contributed by this group.

(2) Wedekind and Oechslen, *Ber.*, **34**, 3986 (1901); Wedekind and Ney, *ibid.*, **42**, 2138 (1909); **45**, 1298 (1912).

(3) Decker and Becker, *Ann.*, **395**, 362 (1913).

(4) *Cf.* Buck, THIS JOURNAL, **56**, 1769 (1934).

(5) Forsyth, Kelly and Pyman, *J. Chem. Soc.*, **127**, 1659 (1925), but prepared from homoveratrylamine by the method of German Patent 257,138 (*cf.* ref. 4.).

(6) *Cf.* German Patent 270,859.

(7) *Cf.* Földi, *Ber.*, **55**, 1535 (1922).

(8) *Cf.* Bischoff and Mintz, *ibid.*, **25**, 2314 (1892).

TABLE I

2-ALKYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl	Felted tiny prisms	227	$C_{10}H_{14}NCl$	65.37	7.69	65.41	8.06
Ethyl	Felted tiny rectangular prisms	213	$C_{11}H_{16}NCl$	66.81	8.16	67.06	8.28
n-Propyl	Meshed small rectangular prisms	242	$C_{12}H_{18}NCl$	68.06	8.57	68.19	8.67
n-Butyl	Felted tiny prisms	190	$C_{13}H_{20}NCl$	69.14	8.94	69.21	8.96
n-Amyl	Matted tiny obscure crystals	191	$C_{14}H_{22}NCl$	70.11	9.26	70.35	9.45
Isopropyl	Tiny rectangular plates	215	$C_{12}H_{18}NCl$	68.06	8.57	68.35	8.95
Isobutyl	Matted minute obscure crystals	205	$C_{13}H_{20}NCl$	69.14	8.94	69.25	9.12
Isoamyl	Thin flat prisms	229	$C_{14}H_{22}NCl$	70.11	9.26	70.24	9.60

alkiodides which could be reduced to the 2-alkyl-1,2,3,4-tetrahydro derivatives, which, in turn, could be demethylated to give the corresponding dihydroxy compounds. The series of reactions is convenient and the yields are good, and the possibility of the presence of secondary amine and quaternary compound has been eliminated. The substituted hydrochlorides described below were made by the foregoing route.

Experimental

2-Alkyl-1,2,3,4-tetrahydroisoquinoline Hydrochlorides.—This series of compounds was prepared by the reduction of the isoquinoline alkiodides, following the double reduction technique of Wedekind, *et al.*[2] The product was recovered from the steam distillate as hydrochloride and was recrystallized from alcohol–ether until pure. The hydrochlorides all form white crystalline compounds, readily soluble in alcohol (with which they are often solvated) and in water, and insoluble in ether and in ethyl acetate. The three isoalkyl hydrochlorides have a saline taste, the others quinine-like tastes. The *n*-butyl and *n*-amyl compounds have a numbing effect. The properties of the hydrochlorides are described in Table I. The 2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride was checked against a specimen prepared by sodium–alcohol reduction.[4]

The majority of the isoquinoline alkiodides and reduced bases are described by Wedekind, *et al.*,[2] but hydrochlorides, although sometimes mentioned, are not described. The isobutyl compound, not obtained by the above authors, was prepared in small yield by reaction of equimolecular amounts of isoquinoline and isobutyl iodide, and, after steam distilling, reducing the residual oil in the usual way. The *n*-amyl compounds were not attempted by Wedekind, *et al.* The present authors are indebted to the Ciba Company for the isoquinoline used.

Isoquinoline *n*-amyl iodide, recrystallized from alcohol–ether, forms small, lemon-yellow prisms, soluble in alcohol, methanol and water, insoluble in ether and ethyl acetate, and melting at 139° (corr.).

Anal. Calcd. for $C_{14}H_{18}NI$: C, 51.39; H, 5.55. Found: C, 51.35; H, 5.64.

2-Alkyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochlorides.—6,7-Dimethoxy-3,4-dihydroisoquinoline was prepared from formylhomoveratrylamine (homoveratrylamine formate heated for one and one-half hours at 210°) by cyclization with phosphorus oxychloride, the experimental details being practically the same as those used by Haworth[9] for the 5,6-dimethoxy compound. The alkiodides were prepared by dissolving equimolecular amounts of the dihydroisoquinoline and alkyl iodide in twice the volume of benzene and allowing the solution to stand in a warm place until no further reaction was evident. The alkiodides were filtered off and recrystallized from alcohol–ether or alcohol–ethyl acetate. Their properties are described in Table II. The isobutiodide was not obtained, only the hydriodide of the starting material being isolable, and hence 2-isobutyl compounds are missing in Tables II, III and IV.

Reduction of the alkiodides was carried out by means of zinc powder and dilute sulfuric acid on the water-bath.[9] After filtration and cooling the sulfate of the product crystallized out and was filtered off and the base liberated by sodium hydroxide and extracted by ether. Alternatively, the reduction mixture was made strongly alkaline and extracted with ether. After drying the extract over solid potassium hydroxide, the hydrochloride was precipitated by hydrogen chloride, filtered off, dried *in vacuo*, and recrystallized from methanol with ether or ethyl acetate. The hydrochlorides form white, crystalline compounds, moderately to readily soluble in alcohol, more soluble in methanol, readily soluble in water, and insoluble in ether and ethyl acetate. The tastes are not intense or distinctive. The compounds are described in Table III. The 2-methyl compound, prepared by cyclization, has been previously described.[4] Pyman also has prepared this compound, together with the 2-ethyl and 2-*n*-propyl derivatives (the latter as picrate), from laudanosine or papaverine.[10]

2-Methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochlorides.—The dihydroxy compounds are prepared readily by demethylating the corresponding dimethoxy hydrochlorides with hydrochloric acid (two hours at 165° in a carbon dioxide-filled tube), evaporating the solution to dryness *in vacuo*, and recrystallizing the residue from methanol with ether or ethyl acetate. The solubilities, etc., of the hydrochlorides are practically the same as those of the dimethoxy compounds. The properties are given in Table IV. The corresponding 2-methyl compound has been described previously.[4,11] The hydrochlorides have no distinctive taste.

(9) Haworth, *J. Chem. Soc.*, 2281 (1927).
(10) Pyman, *ibid.*, **95**, 1266, 1738 (1909).
(11) Pyman, *ibid.*, **97**, 264 (1910).

TABLE II

2-ALKYL-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINIUM IODIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl	Orange-yellow small glittering prisms	186.5	$C_{13}H_{18}O_2NI$	44.95	5.23	44.84	5.41
n-Propyl	Straw-yellow small glittering plates	158	$C_{14}H_{20}O_2NI$	46.53	5.58	46.72	5.79
n-Butyl	Straw-yellow thin glittering needles	152	$C_{15}H_{22}O_2NI$	47.98	5.91	48.01	5.87
n-Amyl	Lemon-yellow small glittering prisms	123	$C_{16}H_{24}O_2NI$	49.34	6.22	49.40	6.24
Isopropyl	Golden-yellow glittering prisms	201 (gas)	$C_{14}H_{20}O_2NI$	46.53	5.58	46.45	5.76
Isoamyl	Lemon-yellow small glittering prisms	134.5	$C_{16}H_{24}O_2NI$	49.34	6.22	49.43	6.31

TABLE III

2-ALKYL-6,7-DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl	Tiny nodules of minute prisms	246	$C_{13}H_{20}O_2NCl$	60.56	7.83	60.49	7.97
n-Propyl	Bulky aggregates of obscure crystals	223	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.93	8.16
n-Butyl	Bulky masses of tiny spherules	224	$C_{15}H_{24}O_2NCl$	63.02	8.47	62.93	8.68
n-Amyl	Chalky masses of obscure flakes	232	$C_{16}H_{26}O_2NCl$	64.07	8.75	64.12	9.05
Isopropyl	Chalky masses of obscure plates	268 (dec.)	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.91	7.98
Isoamyl	Aggregates of flakes	254	$C_{16}H_{26}O_2NCl$	64.07	8.75	64.30	8.94

TABLE IV

2-ALKYL-6,7-DIHYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Alkyl group	Appearance	M. p., °C. (corr.)	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl	Small meshed needle prisms	223	$C_{11}H_{16}O_2NCl$	57.49	7.02	57.38	6.93
n-Propyl	Tiny rosets of prisms	240	$C_{12}H_{18}O_2NCl$	59.11	7.45	58.99	7.47
n-Butyl	Powder of fragmentary prisms	202	$C_{13}H_{20}O_2NCl$	60.56	7.83	60.77	7.83
n-Amyl	Small nodules of flat prisms	187.5	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.79	8.37
Isopropyl	Small stout spindles and clusters	253	$C_{12}H_{18}O_2NCl$	59.11	7.45	59.10	7.35
Isoamyl	Small nodules of minute prisms	208	$C_{14}H_{22}O_2NCl$	61.85	8.16	61.99	8.30

Note on Pharmacology.[12]—Complete results will be published elsewhere, but it can be stated that the nuclear-unsubstituted compounds show a slight depressor effect and that they are relatively strong sympatholytics. The M. E. D. (dogs) ranges from 1 to 10 mg./kg. and L 50 (mice) from 70 to 185 mg./kg.

The first of the series of dimethoxy compounds, 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, is a rather poor depressor, the M. E. D. (dogs) being 1 to 2 mg./kg. and L 50 (mice), 52 mg./kg.

The corresponding dihydroxy compound, 2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, is a relatively powerful pressor, the M. E. D. (dogs) being 1 to 2 mg./kg. and L 50 (mice), 280 mg./kg.

(12) *Cf.* Laidlaw, *Biochem. J.*, **5**, 243 (1911); Hjort, deBeer and Fassett, *J. Pharmacol.*, **62**, 165 (1938).

Summary

A series of 2-alkyl-1,2,3,4-tetrahydroisoquinoline hydrochlorides is described, together with the corresponding 6,7-dimethoxy and 6,7-dihydroxy derivatives. Some 2-alkyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodides are included, and preliminary pharmacological data are given.

TUCKAHOE, NEW YORK RECEIVED JUNE 16, 1938