centage yields these esters were collected over a 2–5° range of boiling point. The boiling points shown in Table II represent carefully fractionated material taken for analyses.

TABLE II

ALKYL ACETOACETATES

CH_3COCH_2COOR R is	B. p., °C. (11 mm.)	d_4^{25}	n_D^{25}	M_D Calcd.	M_D Found
n-Propyl	78	0.9959	1.4205	36.38	36.63
Isopropyl[a]	69	.9835	1.4153	36.38	36.64
n-Butyl	90	.9761	1.4245	41.08	41.28
Isobutyl[b]	84.5	.9697	1.4219	41.08	41.42
s-Butyl	79.1	.9701	1.4208	41.08	41.38
t-Butyl	71.5	.9698	1.4178	41.08	41.02

Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$C_7H_{12}O_3$	58.33	58.15	8.33	8.41
$C_7H_{12}O_3$	58.33	58.44	8.33	8.46
$C_8H_{14}O_3$	60.74	60.50	8.86	8.91
$C_8H_{14}O_3$	60.74	60.89	8.86	8.87
$C_8H_{14}O_3$	60.74	60.74	8.86	8.69
$C_8H_{14}O_3$	60.74	60.42	8.86	8.81

[a] Reported by Moureu and Delange, *Bull. soc. chim.*, [3] **27**, 384 (1902), as boiling at 75–76° (15 mm.); no other physical constants are given. [b] Reported by Emmerling and Oppenheim, *Ber.*, **9**, 1097 (1876), as boiling at 202–206°; d^{28} 0.932.

In the case of phenyl acetate the residue remaining after the distillation of the ether was extracted with three 50-cc. portions of 5% potassium hydroxide, washed with water and distilled. From a run of 245 g. of phenyl acetate and 34.8 g. of sodium phenoxide 227 g. (93%) of the phenyl acetate was recovered. Acidification and ether extraction of the alkaline extract yielded 29 g. (103% based on sodium phenoxide used) of phenol.

Alcoholysis of Ethyl Acetoacetate.—In a one-liter, 3-necked flask bearing a thermometer, mercury seal stirrer and reflux condenser, were placed 68 g. (1 mole) of sodium ethoxide, 352 g. (4 moles) of ethyl acetate and 46 g. (1 mole) of ethyl alcohol and finally 130 g. (1 mole) of ethyl acetoacetate, added in small portions through the reflux condenser. The mixture, then homogeneous, was heated at 77° for thirty-two hours. The reaction product was acidified and extracted with ether according to procedure described above. The combined ester portion and ether extracts was washed once with one-half the volume of saturated sodium bicarbonate solution. The ether solution, after being dried over anhydrous sodium sulfate, was fractionally distilled. By determining the saponification equivalent of the liquid which distilled below the boiling point of ethyl acetoacetate, its ethyl acetate content was estimated to be 346 g. By distillation of the remainder there was obtained 72.2 g. of ethyl acetoacetate, and 13.5 g. of dehydracetic acid, m. p. 108–109° after one recrystallization from alcohol. The combined yield of ethyl acetoacetate and dehydracetic acid corresponds to 71% recovery of the original ethyl acetoacetate put into the reaction.

Summary

A study of the rate and extent of the acetoacetic ester condensation of various alkyl acetates by the corresponding sodium alkoxides has been made.

Methods for the preparation of the sodium alkoxides in a high state of purity are described.

The properties of a number of new alkyl acetoacetates are listed.

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Some Substituted Tetrahydroisoquinoline Hydrochlorides

BY JOHANNES S. BUCK

The physiological action of certain tetrahydroisoquinolines should prove to be of great interest on account of their relationship to such well-known compounds as tetrahydropapaverine, hydrohydrastinine, etc. The tetrahydroisoquinolines are also closely related to β-phenyethylamines, in that they may be regarded as containing the side chain $—CH_2CH_2N$ and to the benzylamines, in that they contain the group $—CH_2N$. Their relationship to the benzyl-β-phenylethylamines previously described[1] is evident, the two terminal benzene rings of the benzyl-β-phenylethylamines being represented by one shared ring in the tetrahydroisoquinolines.

(1) Buck, THIS JOURNAL, **53**, 2192 (1931).

The writer has prepared a series of methoxy-, dimethoxy-, hydroxy- and dihydroxytetrahydroisoquinolines and the corresponding N-methyl compounds, all as the hydrochlorides. Certain of the compounds also contain the pharmacologically important so-called catechol group, two hydroxy groups ortho to one another. The physiological effects are under investigation and will be described in another place.

After some trials, a method of preparation similar to that used by Decker[2] for nor-hydrohydrastinine was selected. The requisite β-phenylethylamine or β-phenylethylmethylamine

(2) Decker, German Patent 257,138; Decker and Becker, *Ann.* **395**, 342 (1913).

was condensed with formaldehyde to give the N-methylene or N-hydroxymethyl derivative, respectively. By the action of hydrochloric acid this was cyclized to the corresponding tetrahydroisoquinoline hydrochloride. Under proper conditions the method proved to be very convenient and the facile condensation and cyclization leave little to be desired. The hydroxy compounds were prepared by O-demethylating the methoxy compounds by appropriate methods.

The number of tetrahydroisoquinolines which may be prepared by the above method would appear to be limited by the necessity for having an activating group meta (3) to the side chain in the parent amine, so as to activate the position 6 in the ring of the amine, although this is not always necessary under more drastic reaction conditions.[3] Amines in which such a group was not present were not investigated, however. Two methylenedioxytetrahydroisoquinolines were also prepared by the general method in the expectation that they would be identical with nor-hydrohydrastinine and hydrohydrastinine. There are some discrepancies, however, between the properties found and those in the literature, and in all probability the present compounds are 5,6-methylenedioxy derivatives and not 6,7 derivatives. A case of this rare cyclization has been observed by Salway,[4] also with a methylenedioxy compound. On account of the bearing on certain alkaloid syntheses, this cyclization is being further investigated in detail. Tetrahydroisoquinoline and N-methyltetrahydroisoquinoline, included for completeness, were made by other methods. 6,8-Dimethoxytetrahydroisoquinoline was not prepared, as starting material was not available.

Experimental

Methoxy- and Dimethoxytetrahydroisoquinoline Hydrochlorides.—To one mole of the β-phenylethylamine was added 1.1 mole of formaldehyde (as 40% solution). Heat was evolved and the turbid liquid was then heated on the steam-bath for thirty minutes. The water was roughly removed with a pipet and 4 volumes of hydrochloric acid (23% = 2:1) was added. The whole was then evaporated on the bath to dryness and the crystalline product purified by recrystallization.

The compounds are white and well crystallized. In general they are very soluble in water, moderately to readily soluble in alcohol, soluble in concd. hydrochloric acid, sparingly soluble in ethyl acetate, and practically insoluble in ether.

(3) *Cf.* Pictet and Spengler, *Ber.*, **44**, 2030 (1911).
(4) Salway, *J. Chem. Soc.*, **97**, 1208 (1910).

Hydroxy- and Dihydroxytetrahydroisoquinoline Hydrochlorides.—The phenolic compounds were prepared by demethylating the corresponding methyl ethers. Demethylation was carried out by heating in a sealed tube for two hours at 170° with 8–10 times the weight of concd. hydrochloric acid. The acid was then removed *in vacuo* and the crude product recrystallized from hydrochloric acid until pure.

The phenolic compounds are very soluble in water, moderately to sparingly soluble in alcohol, moderately to sparingly soluble in hot concd. hydrochloric acid, and practically insoluble in ether and ethyl acetate. They are all white except the 6,7-dihydroxy compound, which has a faint buff tint.

Methoxy- and Dimethoxy-N-methyltetrahydroisoquinoline Hydrochlorides.—The formaldehyde condensation product was prepared as previously described, and cyclization carried out by heating on the bath for thirty minutes (sixty minutes for the 6-methoxy compound) with 3 volumes of concd. hydrochloric acid. After cyclization, the acid solution was made strongly alkaline with ammonium hydroxide (sodium hydroxide for the 5,6-compound) and repeatedly extracted with ether. The ether was evaporated and the residual base (in the cases of the 5,6- and 6,7-compounds) converted into the hydrochloride, which was recrystallized until pure. The base from the 6-methoxy compound required further purification *via* the picrate, which was recrystallized from acetic acid before conversion into the hydrochloride (by hydrochloric acid and the removal of the picric acid by ethyl acetate extraction).

The base of the 6,7-dimethoxy compound is readily obtained crystalline. It is very soluble in the usual solvents and is best recrystallized from a little ether. No attempt was made to crystallize the other bases.

The hydrochlorides are very soluble in water, soluble in cold concd. hydrochloric acid, readily soluble in alcohol, sparingly soluble in ethyl acetate and practically insoluble in ether.

Hydroxy- and Dihydroxy-N-methyltetrahydroisoquinoline Hydrochlorides.—Demethylation was carried out by adding to the base of the methyl ether eight times its weight of colorless hydriodic acid (d = 1.7, 52%) and then boiling the solution gently for five minutes over a free flame. Excess acid was then distilled off *in vacuo* and the hydriodide converted into the hydrochloride in the usual way, by means of silver chloride. The hydrochloride solution was evaporated *in vacuo*, the gum or crystalline residue dissolved in 90% alcohol and ether added to incipient precipitation. The crystalline product which separated was then further recrystallized, the 6-hydroxy compound from alcohol–ether, and the others from hydrochloric acid. Demethylation by means of hydrochloric acid was not successful.

The hydroxy compounds are all white except the 6-hydroxy compound, which has a faint buff tint. They are all soluble in water, moderately to sparingly soluble in alcohol, fairly to readily soluble in concd. hydrochloric acid and practically insoluble in ether and in ethyl acetate.

N-Methyltetrahydroisoquinoline Hydrochloride.—The hydrochloride does not appear to have been described.

It was prepared from the redistilled base[5] by dissolving it in concd. hydrochloric acid, concentrating the solution to crystallization and recrystallizing the product.

Methylenedioxytetrahydroisoquinoline Hydrochloride.—Homopiperonylamine was converted into the N-methylene compound as in previous cases, the heating being for fifteen minutes only. The product was cyclized by heating in a dish on the bath with 5 volumes of 20% hydrochloric acid for thirty minutes. A crystalline magma formed and the product was filtered off and recrystallized. It is soluble in water, sparingly soluble in alcohol and in concd. hydrochloric acid and practically insoluble in ether and in ethyl acetate. The melting point is above 315°, whereas that of nor-hydrohydrastinine hydrochloride is given as 255–257°[6] or 276–278°.[2]

Methylenedioxy-N-methyltetrahydroisoquinoline Hydrochloride. The N-hydroxymethyl derivative of N-methylhomopiperonylamine was prepared as in the case of the other N-methyl compounds, and was cyclized by evaporating a solution in 5 volumes of 20% hydrochloric acid to one-half its volume on the bath. The product was filtered off from the crystalline magma which formed and recrystallized.

The compound is readily soluble in water, sparingly soluble in alcohol, moderately soluble in hot concd. hydrochloric acid and practically insoluble in ether and ethyl acetate. It melts at 315° to a red liquid, while the melting point of hydrohydrastinine hydrochloride is given as 275–277°. The base melts at 96°, hydrohydrastinine at 66°.[2]

The amines used were obtained by the methods cited by Buck.[7] N-methylhomopiperonylamine was prepared by the method given for N-methylhomoveratrylamine. The isoquinoline used was a pure specimen (m. p. 24–26°) kindly supplied by the Ciba Co. The micro-analyses (Pregl) were carried out by Mr. W. S. Ide. With most of the compounds described the analyses presented unusual difficulty, as the results were very sensitive to slight variations in the burning of the sample. The properties of the tetrahydroisoquinoline hydrochlorides are given in the table.

TETRAHYDROISOQUINOLINE HYDROCHLORIDES

Substituent	Appearance	Solvent recryst.	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Unsubst.[8]	Heavy irreg. flat prisms	Aq. alc.–ether	202	$C_9H_{12}NCl$	63.68	7.13	63.52	7.40
6-Methoxy	Dull white tiny nodules	Alc.–ether	236	$C_{10}H_{14}ONCl$	60.13	7.07	60.22	7.08
5,6-Dimethoxy	Felted tiny needles	Alc.–ether	232	$C_{11}H_{16}O_2NCl$	57.49	7.02	57.66	7.14
6,7-Dimethoxy	Jagged pearly plates, needles	Aq. alc.	253	$C_{11}H_{16}O_2NCl$	57.49	7.02	57.69	7.18
Methylenedioxy	Felted tiny needles	Aq. HCl	Above 315	$C_{10}H_{12}O_2NCl$	56.19	5.66	56.22	5.80
6-Hydroxy	Dull tiny nodules	Aq. HCl	233	$C_9H_{12}ONCl$	58.20	6.52	57.98	6.64
5,6-Dihydroxy[a]	Stout ill-formed prisms	Aq. HCl	246	$C_9H_{12}O_2NCl$	53.58	6.00	53.46	6.29
6,7-Dihydroxy[a]	Small thick hexagons	Aq. HCl	262	$C_9H_{12}O_2NCl$	53.58	6.00	53.54	6.34
Unsubst. N-methyl	Felted tiny prisms	Alc.–ether	228	$C_{10}H_{14}NCl$	65.37	7.69	65.50	7.52
6-Methoxy N-methyl	Small rounded prisms	Alc.–ether	170	$C_{11}H_{16}ONCl$	61.80	7.55	61.73	7.42
5,6-Dimethoxy N-methyl	Felted tiny needles	Alc.–EtOAc	210 (*ca.*)	$C_{12}H_{18}O_2NCl$	59.11	7.44	58.93	7.58
6,7-Dimethoxy N-methyl	Small granules	Alc.–ether, alc.–EtOAc	215	$C_{12}H_{18}O_2NCl$	59.11	7.44	58.89	7.50
6,7-Dimethoxy N-methyl (base)	Small white bulky nodules	Ether	75–77	$C_{12}H_{17}O_2N$	69.51	8.28	69.61	8.59
Methylenedioxy N-methyl	Felted flat prisms	Aq. alc.	315 red liq.	$C_{11}H_{14}O_2NCl$	58.01	6.20	57.94	6.40
6-Hydroxy N-methyl	Faint buff nodules	HCl-alc.–ether, alc.–ether	236	$C_{10}H_{14}ONCl$	60.13	7.07	59.82	7.22
5,6-Dihydroxy[b] N-methyl	Cryst. powder (nodules)	Alc.–ether, aq. HCl	Froth 139, melts 255	$C_{10}H_{14}O_2NCl$	55.67	6.54	55.37	6.88
6,7-Dihydroxy[a] N-methyl	Slender flat prisms	Alc.–EtOAc, aq. HCl	276	$C_{10}H_{14}O_2NCl$	55.67	6.54	55.74	6.44

[a] Ferric chloride gives intense dark green color. [b] Ferric chloride gives transient green color.

Summary

A number of tetrahydroisoquinoline hydrochlorides containing methoxy, hydroxy, methylenedioxy and N-methyl groups have been prepared and are described. β-Phenylethylamines and β-phenylethylmethylamines were used as starting materials and the reactions employed furnish a convenient method for preparing certain tetrahydroisoquinolines.

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(5) Emde, *Ann.*, **391**, 88 (1912).
(6) Pictet and Gams, *Ber.*, **44**, 2036 (1911).
(7) Buck, THIS JOURNAL, **56**, 1607 (1934).
(8) Schmidt, *Arch. Pharm.*, **237**, 564 (1899).