Experimental

Benzothiazole-1-diethyl Malonate.—To 10 g. of I, prepared from malonic ester and phenyl isothiocyanate dissolved in glacial acetic acid, was added slowly the molar equivalent of bromine in acetic acid. The mixture, which became turbid from the separation of small amounts of sulfur and other decomposition products, was immediately poured into water. After three crystallizations from alcohol, the new product was obtained in small needles, m. p. 138–139°; yield approximately 5 g.

Anal. Calcd. for $C_{14}H_{15}NO_4S$: C, 57.3; H, 5.1. Found: C, 56.9; H, 5.1.

II was soluble in cold concd. hydrochloric acid, separating unchanged on dilution with water. It changed into a powder in the presence of alcoholic potassium hydroxide, which was soluble in water and which was changed by hydrochloric acid into the original substance. A precipitate was formed and bubbles of gas escaped when an ether solution of the thiazole was mixed with methylmagnesium iodide from which the same thiazole was recovered on the addition of water.

1-Methylbenzothiazole from II.—Ten grams of II was heated for two hours with concd. hydrochloric acid, the mixture was diluted with water, filtered and steam distilled until the distillate was clear. Then an excess of alkali was added and steam distillation resumed. A colorless oil with a strong pyridine-like odor resulted. Its identity with an authentic sample of 1-methylbenzothiazole was confirmed by a boiling point determination, and an analysis.

1-Benzothiazoylacetylacetone.—The thiazole prepared from acetylacetone and phenyl isothiocyanate separated from ligroin in silky needles, m. p. 155°. It was rapidly changed by hot alkali, more slowly by acid, into methyl benzothiazole.

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.8; H, 4.7. Found: C, 62.1; H, 4.5.

Summary

It has been shown that bromine converts the monothioanilide of carbethoxyethylmalonate into benzothiazoylmalonic ester, which is changed by hydrolysis into methylbenzothiazole.

MEDFORD, MASS. RECEIVED OCTOBER 9, 1939

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

3-Methyl-3,4-dihydroisoquinolines and 3-Methyl-1,2,3,4-tetrahydroisoquinolines[1]

BY WALTER S. IDE AND JOHANNES S. BUCK

Work in progress on the pharmacological effects of various substituting groups in the isoquinoline nucleus necessitated the preparation of a series of 3-methyl-3,4-dihydroisoquinolines and 3-methyl-1,2,3,4-tetrahydroisoquinolines (analogous to norhydrastinine and dihydronorhydrastinine). There are a number of scattered isoquinoline compounds with a 3-methyl group in the literature, but the methods of preparation vary widely and in many cases essential details are lacking. Most of the compounds are also substituted in the 1-position.

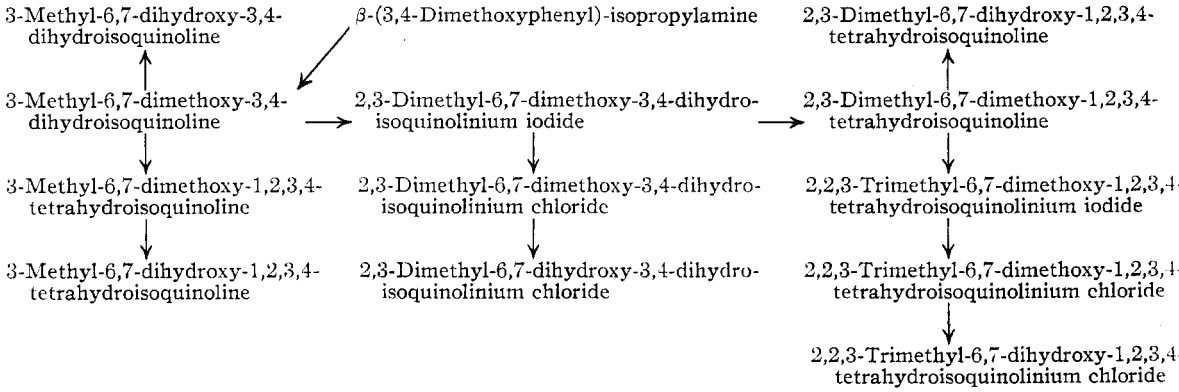
The authors therefore set out to devise a series of general reactions for the preparation of the desired 3-methylisoquinoline derivatives. By the method selected three series of compounds, containing as substituents 6,7-dimethoxyl, 6,7-methylenedioxyl and 6,7-dihydroxyl, were prepared and other series doubtless could be made in a similar way. The isoquinolines were prepared by cyclizing formyl-β-phenylisopropylamines (Bischler–Napieralski reaction). This required fairly large amounts of β-phenylisopropylamines. The methods of Mannich and Jacobsohn[2] and of Merck[3] for the preparation of these amines were not investigated since they depend on naturally-occurring materials and are therefore not general. The nitropropenyl method of Alles[4] also was not investigated. The most feasible route appeared to be a series of reactions similar to those used for phenethylamines[5,6] but attempts to prepare disubstituted α-methylcinnamic acids by the method of Bogert and Davidson[7] failed, the condensation of disubstituted benzaldehydes with methyl ethyl ketone not proceeding in the desired way. Recourse therefore was had to the Reformatsky reaction and the required α-methylcinnamic acids were prepared by condensing ethyl α-bromopropionate with the aldehyde, followed by the dehydration and saponification of the product. An alternative method used was the Claisen condensation of the aldehyde with ethyl propionate, followed by saponification. The α-methylcin-

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

(2) Mannich and Jacobsohn, *Ber.*, **43**, 189 (1910).
(3) German Patent 274,350.
(4) United States Patent 1,879,003.
(5) Buck, THIS JOURNAL, **54**, 3661 (1932).
(6) Woodruff and Conger, *ibid.*, **60**, 465 (1938).
(7) Bogert and Davidson, *ibid.*, **54**, 334 (1932).

namic acid was reduced, the product amidated and the amine obtained by a Hofmann reaction.

The production of the various isoquinoline types from the substituted β-phenylisopropylamines can be best illustrated by the chart below (for the case of the 6,7-dimethoxy compounds). The reactions are all convenient and the yields at each stage are good, for the cases examined.



Experimental

α-Methyl-3,4-dimethoxycinnamic Acid. (a) **Claisen Method.**—17.3 g. (1.25 atoms) of sodium was "atomized" (not too finely) under toluene, and the toluene decanted. To the sodium was added, in one lot, a solution of 100 g. (1 mol) of veratric aldehyde in 350 cc. (5 mols) of ethyl propionate. The reaction was carried out in a large flask fitted with an efficient reflux condenser, and provision was made for water cooling the flask. A violent reaction took place and was controlled by cooling. After the reaction had subsided, the flask was allowed to stand for two hours, and water then added under a coal-gas atmosphere; 76 cc. (1.25 mol) of concd. hydrochloric acid was added to the aqueous solution and the excess of ethyl propionate removed by steam distillation. The residual oil was extracted with ether and the ether evaporated. The crude ester was saponified by 67 g. (2 mols) of potassium hydroxide dissolved in methyl alcohol; the alcohol was then evaporated and the acid precipitated by hydrochloric acid.

The corresponding 3,4-methylenedioxy acid was prepared similarly but occasionally almost explosive carbonization took place (possibly due to the sodium being too finely atomized) and extreme caution is therefore necessary.

(b) **Reformatsky Method.**[8,9]—Eighty-three grams (0.5 mole) of veratric aldehyde and 91 g. (0.50 mole) of ethyl α-bromopropionate were dissolved in 300 cc. of benzene and 35 g. of zinc (Baker 80-mesh, granular) added. The whole was refluxed gently for about one hour, then cooled and the benzene solution decanted from the zinc. After washing with dilute sulfuric acid, the benzene solution was dried over calcium chloride, and about one-half the benzene evaporated. After cooling, 40 cc. of phosphorus oxychloride was added cautiously in portions and the whole then heated on the bath for twenty to thirty minutes. After cooling, the purple solution was washed with ice water, then with 10% sodium hydroxide, and the benzene evaporated. Saponification of the residue (methyl alcoholic potassium hydroxide) followed by removal of the alcohol and acidification gave the acid as a pasty solid.

The crude acid, fractionated from benzene, gave two compounds, about 20% being the higher-melting one. The lower-melting compound, recrystallized from alcohol, forms white needles, melting at 144°.[10]

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.83; H, 6.35. Found: C, 65.03; H, 6.57.

The higher-melting compound from alcohol, consists of a white, granular powder, melting at 232°. It is probably the *trans* isomer.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.83; H, 6.35. Found: C, 64.94; H, 6.49.

α-Methyl-3,4-methylenedioxycinnamic Acid.[11]—This acid was prepared by either of the foregoing methods. Recrystallized from benzene it forms light yellow glittering needles, melting at 200°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.05; H, 4.89. Found: C, 64.07; H, 5.11.

α-Methyl-3,4-dimethoxyphenylpropionic Acid.—This acid was prepared by a sodium amalgam reduction. The properties agreed with those described in the literature.[10]

α-Methyl-3,4-methylenedioxyphenylpropionic Acid.—This was also prepared by a sodium amalgam reduction and the properties agreed with those recorded.[11]

α-Methyl-3,4-dimethoxyphenylpropionamide.—The amide was prepared (a) by heating the ammonium salt in a stream of ammonia, for two hours at 220°, and (b) by running the acid chloride (thionyl chloride method) into aqueous ammonia containing sodium hydroxide. Recrystallized from benzene, it forms white flakes, melting at 109°.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.54; H, 7.68. Found: C, 64.77; H, 7.64.

α-Methyl-3,4-methylenedioxyphenylpropionamide.—The preparation was carried out as in the foregoing case,

(8) *Cf.* Lindenbaum, *Ber.*, **50**, 1270 (1917).

(9) *Cf.* Woodruff and Pierson, THIS JOURNAL, **60**, 1075 (1938).

(10) Tiemann and Kraaz, *Ber.*, **15**, 2070 (1882), by another method.

(11) *Cf.* Wallach and Evans, *Ann.*, **357**, 77 (1907); Lorenz, *Ber.*, **13**, 756 (1880).

TABLE I

DIHYDRO- AND TETRAHYDROISOQUINOLINE DERIVATIVES

3-Methyl-6,7-	M. p., °C.	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Dimethoxy-3,4-dihydroisoquinoline hydrochloride[a,e,m]	189	$C_{12}H_{16}O_2NCl$	59.60	59.52	6.68	6.67
Methylenedioxy-3,4-dihydroisoquinoline hydrochloride[d,f,m,u]	198	$C_{11}H_{12}O_2NCl$	58.52	58.82	5.36	5.56
Dihydroxy-3,4-dihydroisoquinoline hydrochloride[a,f,h,n]	297	$C_{10}H_{12}O_2NCl$	56.19	56.14	5.64	5.64
Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[c,e,o,v]	245	$C_{12}H_{18}O_2NCl$	59.11	59.29	7.45	7.64
Methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[d,e,o]	238	$C_{11}H_{14}O_2NCl$	58.01	58.24	6.20	6.46
Dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[c,g,i,n]	270	$C_{10}H_{14}O_2NCl$	55.67	55.51	6.55	6.80
2,3-Dimethyl-6,7-						
Dimethoxy-3,4-dihydroisoquinolinium iodide[a,e,p]	156	$C_{13}H_{18}O_2NI$	44.95	45.05	5.23	5.41
Dimethoxy-3,4-dihydroisoquinolinium chloride[a,e,t]	125–128	$C_{13}H_{18}O_2NCl$	61.03	61.06	7.09	7.44
Methylenedioxy-3,4-dihydroisoquinolinium iodide[b,e,i,p]	213	$C_{12}H_{14}O_2NI$	43.50	43.66	4.26	4.37
Methylenedioxy-3,4-dihydroisoquinolinium chloride[d,e,t]	212	$C_{12}H_{14}O_2NCl$	60.11	60.27	5.87	6.02
Dihydroxy-3,4-dihydroisoquinolinium chloride[a,e,n]	199	$C_{11}H_{14}O_2NCl$	58.01	58.27	6.20	6.35
Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[c,e,q]	232	$C_{13}H_{20}O_2NCl$	60.56	60.73	7.82	7.98
Dimethoxy-1,2,3,4-tetrahydroisoquinoline[c,g,r]	100	$C_{13}H_{19}O_2N$	70.54	70.70	8.66	8.93
Methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[c,g,q,w]	228–229	$C_{12}H_{16}O_2NCl$	59.61	59.81	6.67	6.88
Methylenedioxy-1,2,3,4-tetrahydroisoquinoline[d,e,r,x]	88	$C_{12}H_{15}O_2N$	70.20	70.19	7.37	7.38
Dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride[d,e,k,n]	266	$C_{11}H_{14}O_2NCl$	57.50	57.73	7.02	6.99
2,2,3-Trimethyl-6,7-						
Dimethoxy-1,2,3,4-tetrahydroisoquinolinium iodide[c,e,s]	232	$C_{14}H_{22}O_2NI$	46.27	46.48	6.11	6.29
Dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride[c,e,t]	239	$C_{14}H_{22}O_2NCl$	61.85	62.12	8.16	8.24
Methylenedioxy-1,2,3,4-tetrahydroisoquinolinium iodide[a,l,s]	242	$C_{13}H_{16}O_2NI$	44.95	45.26	5.23	5.22
Methylenedioxy-1,2,3,4-tetrahydroisoquinolinium chloride[c,t]	248–250	$C_{13}H_{18}O_2NCl$	61.03	61.18	7.09	7.40
Dihydroxy-1,2,3,4-tetrahydroisoquinolinium chloride[c,e,k,n]	258	$C_{12}H_{16}O_2NCl$	59.11	59.35	7.45	7.33

[a] Yellow. [b] Brown yellow. [c] White or almost white. [d] Light ivory to light tan. [e] Prisms. [f] Plates. [g] Crystalline powder. [h] Recryst. dil. HCl. [i] Recryst. aq. alcohol. [k] Recryst. methanol–ethanol. [l] Recryst. water. [m] Prepared by cyclizing the formyl amine by the method of Buck and Ide, THIS JOURNAL, **60,** 2101 (1938). [n] By demethylation of the corresponding methoxy compound with hydrochloric acid at 170° (*cf.* Buck and Ide, *loc. cit.*). [o] The dihydroisoquinoline hydrochloride was reduced hot with zinc and dilute sulfuric acid, and the product isolated via the base. [p] The 3-methyldihydroisoquinoline base, in cold benzene solution, was treated with methyl iodide. [q] By reduction (zinc and hot dilute sulfuric acid) of the 2,3-dimethyldihydroisoquinolinium iodide. [r] From the hydrochloride with aqueous potassium hydroxide. Recrystallized from hexane. [s] By the action of methyl iodide on the 2,3-dimethyltetrahydroisoquinoline in cold benzene solution. [t] Iodides were converted into chlorides in cold aqueous solution by fresh silver chloride. [u] German Patent 279,194 describes base only. [v] Prepared by different methods, German Patent 336,153 gives m. p. 232°; German Patent 280,502 gives m. p. 238° and German Patent 320,480 gives base m. p. 65–67°. [w] Prepared by different methods, German Patent 336,153 gives m. p. 230–232° and German Patent 320,480 gives m. p. 230°. [x] German Patent 320,480 gives m. p. 86°.

the chloride method being preferred. After recrystallization from benzene, the amide forms white flakes, m. p. 122°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.73; H, 6.33. Found: C, 64.00; H, 6.33.

β-(3,4-Dimethoxyphenyl)-isopropylamine.—The Hofmann reaction on the corresponding amide was carried out as usual, with 1.1 mol of sodium hypochlorite. The amide may be added dissolved in dioxane. After two distillations the amine forms a colorless, refractile liquid, with a sweet, musty odor. It boils at 154° (9 mm.) and has n_D 1.5347, d^{25}_4 1.0624. The yield was 53%.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.64; H, 8.78. Found: C, 67.79; H, 8.66.

The amine has been prepared by other methods[2,3,12] and is mentioned (no details) by Gunn, *et al.*[13]

The **hydrochloride,** recrystallized from alcohol forms a bulky white mass of ill-defined prisms, melting at 150°. Merck[3] gives m. p. 150–151°.

Anal. Calcd. for $C_{11}H_{18}O_2NCl$: C, 56.99; H, 7.83. Found: C, 56.93; H, 7.77.

(12) German Patent 247,906.

(13) Gunn, Gurd and Sachs, *J. Physiol.*, **95,** 485 (1939).

β-(3,4-Methylenedioxyphenyl)-isopropylamine.—The preparation is similar to that of the foregoing amine. After two distillations, the amine forms a slightly viscous, colorless liquid, with a faint, sweet, musty odor, boiling at 143–145° (11 mm.) and having n_D 1.5394 and d^{25}_4 1.1277. The yield was 40%.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.31. Found: C, 67.00; H, 7.00.

Other methods of preparation have been described,[2,3] and it has been mentioned by Gunn, *et al.*[13]

The **hydrochloride** forms bulky white aggregates of small rhombs when crystallized from alcohol. The melting point is 188° (*cf.* ref. 3, m. p. 183–185°).

Anal. Calcd. for $C_{10}H_{14}O_2NCl$: C, 55.67; H, 6.54. Found: C, 55.66; H, 6.60.

The salts described below were recrystallized until pure from absolute alcohol, with the addition of ether or ethyl acetate or both, unless otherwise noted. The solubilities are all very similar, the compounds being in general soluble in methyl and ethyl alcohols, very soluble in water, sparingly soluble in ethyl acetate, and practically insoluble in non-polar solvents. The melting points are corrected.

Summary

A number of 3-methyl-3,4-dihydroisoquinoline and 3-methyl-1,2,3,4-tetrahydroisoquinoline derivatives are described. The substituents are 6,7-dimethoxyl, 6,7-methylenedioxyl and 6,7-dihydroxyl. The compounds are closely related to norhydrastinine and dihydronorhydrastinine. A series of general reactions for their preparation is given.

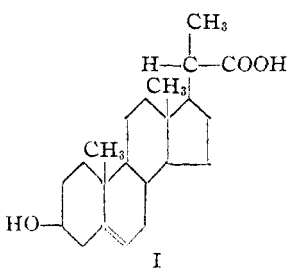
TUCKAHOE, NEW YORK RECEIVED NOVEMBER 13, 1939

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Brassicasterol. II. Degradation by Ozone

BY ERHARD FERNHOLZ AND HOMER E. STAVELY

In a previous communication[1] it was shown that completely hydrogenated brassicasterol, brassicastanol, is not identical with stigmastanol, the common hydrogenated derivative of the phytosterols stigmasterol, β-sitosterol, and α-spinasterol. This was somewhat unexpected since our analytical data favored an empirical formula with 29 carbon atoms, rather than one with 28 carbon atoms as originally proposed by Windaus and Welsch.[2] Analyses reported[1] for brassicasteryl *m*-dinitrobenzoate fitted almost equally well for a C_{28} or a C_{29} sterol but analyses for brassicastyl *m*-dinitrobenzoate definitely favored a C_{29} sterol. In spite of this, on the basis of ozonization experiments we are now forced to conclude that brassicasterol contains only 28 carbon atoms.



I

After addition of one mole of bromine to the nuclear double bond of brassicasteryl acetate, treatment with ozone and subsequent debromination, β-3-hydroxy-bisnorcholenic acid (I) was isolated, the same acid obtained by similar treatment of stigmasteryl acetate.[3] This degradation product accounts for the largest part of the molecule and leaves no doubt as to the position of the two double bonds and the hydroxyl group. Another sample of brassicasterol was ozonized under conditions favorable for the isolation of a volatile aldehyde, the other molecular fragment. A crystalline semicarbazone of the aldehyde was obtained which analyzed for six carbon atoms from the aldehyde. It is therefore conclusively proved that the empirical formula of brassicasterol is $C_{28}H_{46}O$.

A comparison of the properties of the aldehyde semicarbazones obtained by ozonizing ergosterol,[4] stigmasterol[5] and brassicasterol seems to indicate that the aldehyde from brassicasterol is slightly racemized 1-methylisopropylacetaldehyde, as shown in Table I. A mixed sample of the semicarbazone from brassicasterol with the semicarbazone of 1-methylisopropylacetaldehyde from ergosterol (m. p. 128) melted at 120–122°, showing no depression.

TABLE I

	Ethylisopropylacetaldehyde semicarbazone (from stigmasterol)	Methylisopropylacetaldehyde semicarbazone (from ergosterol)	Semicarbazone from brassicasterol
M. p., °C.	128	128	119
$[\alpha]_D$	+9°	−52°	−40°
C, %	56.14	53.46	53.65
H, %	9.95	9.62	9.70
N, %	24.58	26.74	26.76

This is noteworthy because all precautions were taken to prevent racemization and in a trial run with ergosterol no racemization occurred. The assumption that brassicasterol contains a certain amount of an isomer with the opposite configuration on C_{24} seems to offer an attractive explanation for this observation, although it is also possible that brassicasterol contains a closely related isomeric sterol with a structurally differing side chain. Our degradation experiments leave, however, little doubt that formula II must be assigned to brassicasterol, which could be called 7,8-dihydroergosterol.

(1) Fernholz and Stavely, THIS JOURNAL, **61**, 142 (1939).
(2) *Ber.*, **42**, 612 (1909).
(3) Fernholz, *Ann.*, **507** 128 (193
(4) Guiteras, Nokamiya and Inhoffen, *Ann.*, **494**, 119 (1932).
(5) Guiteras, *Z. physiol. Chem.*, **214**, 89 (1933).