6. The unstable, sirupy halogeno compounds obtained from the second octaacetate have the regular structures of the α-halogeno-acetylturanoses (VII). Inasmuch as the properties of these substances are extremely different from those of the "α-chloroacetylfructose," it has been concluded that the latter substance cannot be the stereoisomer of the unstable β-chloroacetylfructose.

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[CONTRIBUTION FROM THE EXPERIMENTAL RESEARCH LABORATORIES, BURROUGHS, WELLCOME AND COMPANY]

# HYDROXY- AND DIHYDROXYPHENYLETHYLMETHYLAMINES AND THEIR ETHERS

BY JOHANNES S. BUCK

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In an earlier paper[1] the synthesis of Epinine, 3,4-dihydroxyphenylethylmethylamine, was described. This, with two other members of the same series, has been examined pharmacologically.[2] Owing to their pressor activity, it was decided to attempt the synthesis of the remaining members of the series and to carry out a pharmacological examination of these. The compounds recorded up to the present are the unsubstituted amine, the 4-hydroxyamine and the 3,4-dihydroxyamine. Those so far not described are the 2-hydroxy, 3-hydroxy, and the 2,3-, 2,5-, 2,4-, 3,5- and the 2,6-dihydroxyphenylethylmethylamines. Of these, all but the three latter have been synthesized and are described, together with their intermediates, in the present paper. The synthesis of the 2,4-dihydroxy compound broke down at the last stage, the demethylation proceeding abnormally. This reaction will form the subject of another communication. The syntheses of the remaining two members of the series, the 3,5- and 2,6-dihydroxyamines, have not been carried out, the first owing to lack of starting material, and the second owing to difficulties caused by the powerful steric hindrance of the 2,6-groups. It is hoped to complete the series in the future. The pharmacological action will be described in another place.

## Experimental

The preparation of the hydroxyphenylethylmethylamines was carried out in all cases by a series of reactions similar to that used in the synthesis of epinine.[1]

$$(OMe)RCHO \longrightarrow (OMe)RCH{=}CHCOOH \longrightarrow (OMe)RCH_2CH_2COOH \longrightarrow$$
$$(OMe)RCH_2CH_2CONH_2 \longrightarrow (OMe)RCH_2CH_2NH_2 \longrightarrow$$
$$(OMe)RCH_2CH_2N{=}CHC_6H_5 \longrightarrow (OMe)RCH_2CH_2N(MeI){=}CHC_6H_5 \longrightarrow$$
$$(OMe)RCH_2CH_2NHMe{\cdot}HI \longrightarrow (OMe)RCH_2CH_2NHMe \longrightarrow$$
$$(OH)RCH_2CH_2NHMe{\cdot}HCl$$

[1] Buck, THIS JOURNAL, 52, 4119 (1930).

[2] Barger and Dale, *J. Physiol.*, **41**, 19 (1910).

The cinnamic acid in each case was made by the well-known Knoevenagel method, by condensation of the aldehyde with malonic acid in the presence of pyridine, piperidine being used as catalyst. On reduction with 4% sodium amalgam (excess = 4H being used), the corresponding phenylpropionic acid was produced, usually in very good yield. From the acid, the amide was made by heating in a stream of ammonia at 220–230° for two hours, the liquors, after removal of the first crop from benzene, being evaporated and the treatment repeated. Conversion to the phenylethylamine was carried out by a Hofmann reaction, the theoretical amount of sodium hypochlorite being used. Monomethylation of the phenylethylamine was done by the elegant Decker method,[3] except that the reaction mixture was heated for eighteen hours at 37° in place of the higher temperatures used by Decker. The Schiff bases and the methyl iodide addition products were used directly, the first being thick sirups and the second being too unstable to manipulate. Subsequent O-demethylation was carried out in one of two ways, either by heating with hydriodic acid (52% colorless, sp. gr. 1.7) at the boiling point, removal of excess of acid and conversion to the chloride by means of silver chloride, or by demethylating the free amine by concentrated hydrochloric acid at 180°. In the latter case the amine

INTERMEDIATES, PREVIOUSLY PREPARED AND DESCRIBED

| Compound | Yield, % | Lit. refs. | Compound | Yield, % | Lit. refs. |
|---|---|---|---|---|---|
| *o*-Methoxycinnamic acid[a,b] | 95 | 4 | 2,3-Dimethoxyphenylpropionic acid | .. | 11 |
| *o*-Methoxyphenylpropionic acid | 87 | 5, 6 | 2,3-Dimethoxyphenylpropionamide[b,e] | 84 | 11 |
| *m*-Methoxybenzaldehyde[b,c,d] | 83 | 8 | 2,4-Dimethoxybenzaldehyde[d] | .. | 12, 8 |
| *m*-Methoxycinnamic acid | .. | 9 | *Trans*-2,4-dimethoxycinnamic acid[a,b] | 97 | 13 |
| *m*-Methoxyphenylpropionic acid | .. | 10 | 2,4-Dimethoxyphenylpropionic acid | 89 | 14 |
| *m*-Methoxyphenylpropionamide[b,e,f] | 86 | 10 | 2,5-Dimethoxybenzaldehyde | 37 | 15 |
| 2,3-Dimethoxybenzaldehyde | .. | 8 | 2,5-Dimethoxycinnamic acid[a,b] | 95 | 15 |
| 2,3-Dimethoxycinnamic acid | .. | 11 | | | |

[3] Decker, *Ann.*, **395**, 390 (1913).

[4] Perkin, *J. Chem. Soc.*, **31**, 414 (1877).

[5] Perkin, *ibid.*, **39**, 415 (1881).

[6] Tiemann and Ludwig, *Ber.*, **15**, 2043 (1882).

[7] Mentioned but not described by Shoesmith and Connor, *J. Chem. Soc.*, 2230 (1927).

[8] Douetteau, *Bull. soc. chim.*, [iv] **9**, 932 (1911).

[9] Chakravarti, Haworth and Perkin, *J. Chem. Soc.*, 2265 (1927).

[10] Helfer, *Helv. Chim. Acta*, **7**, 945 (1924).

[11] Haworth, *J. Chem. Soc.*, 2281 (1927).

[12] Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).

[13] Perkin and Schiess, *J. Chem. Soc.*, **85**, 159 (1904).

[14] Will, *Ber.*, **16**, 2106 (1883).

[15] Kauffmann and Burr, *ibid.*, **40**, 2352 (1907).

NEW INTERMEDIATES

| Compound | Cryst. form | Sol. in | Yield, % | M. p., °C. | Analyses Found, % C | H |
|---|---|---|---|---|---|---|
| *o*-Methoxyphenylpropionamide[7,a] | Prisms | Bz, EtOH, $Et_2O$ | 73 | 110 | 66.61 | 7.23 |
| 2,4-Dimethoxyphenylpropionamide[e] | Prisms | Bz, EtOH, $Et_2O$ | 71 | 113 | 63.23 | 7.35 |
| 2,5-Dimethoxyphenylpropionamide[e] | Needles | EtOH | 85 | 111 | 63.24 | 6.99 |
| 2,5-Dimethoxyphenylpropionic acid[g] | Poor prisms | EtOH | 94 | 101 | 63.02 | 6.49 |

[a] Malonic acid method of preparation. [b] Method differs from that in literature. [c] B. p. 122° (22 mm.). [d] Method of Ref. 8 adapted to present compound. [e] Ammonia method of preparation. [f] Purification difficult, b. p. 180–205° (1 mm.). [g] Sodium amalgam method of preparation.

hydrochloride was obtained directly. Repeated efforts failed to give the 2,4-dihydroxyamine, the reaction taking another course and giving products of a different type.

**β-Phenylethylamines.**—The amines are all colorless, somewhat viscous liquids, which rapidly absorb carbon dioxide from the air, forming solid carbonates. With the exception of the 2,3-compound, which is miscible with water, they are rather slightly soluble in water, giving strongly alkaline solutions. They are miscible with alcohol, benzene and ether. The odors are much fainter than would be expected. The mediocre yields in some cases are doubtless due to nuclear halogenation, a not infrequent accompaniment to the Hofmann reaction.

| Amine | Odor | B. p., °C. | mm. | $n_D^{25}$ | $d_4^{25}$ | $M_D$ | Formula | Analyses Calcd. C | H | Found C | H | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2-Methoxy | Musty, amine | 117 | 9 | 1.5391 | 1.0408 | 45.49[a] | $C_9H_{13}ON$ | 71.48 | 8.66 | 71.70 | 8.88 | 65 |
| 3-Methoxy[c] | Musty, sweet | 118 | 6 | 1.5370 | 1.0385 | 45.44[a] | $C_9H_{13}ON$ | 71.48 | 8.66 | 71.43 | 8.75 | 33 |
| 2,3-Di-methoxy | Slight amine | 138 | 8 | 1.5348 | 1.0839 | 52.01[b] | $C_{10}H_{15}O_2N$ | 66.25 | 8.33 | 65.94 | 8.53 | 79 |
| 2,4-Di-methoxy | Faint amine | 140 | 1 | 1.5402 | 1.0915 | 52.08[b] | $C_{10}H_{15}O_2N$ | 66.25 | 8.33 | 66.33 | 8.41 | 31 |
| 2,5-Di-methoxy | Faint ester | 150 | 8 | 1.5399 | 1.0889 | 52.18[b] | $C_{10}H_{15}O_2N$ | 66.25 | 8.33 | 65.94 | 8.40 | 63 |

[a] Calcd. (Brühl), 45.42. [b] Calcd. (Brühl), 51.73. [c] Helfer[10] uses hypobromite.

**β-Phenylethylmethylamines.**—The amines were prepared by adding excess of 30% potassium hydroxide solution to the aqueous solution of the hydriodide. The resulting oil was extracted with ether, dried over solid potassium hydroxide, and distilled under reduced pressure. Small amounts of white crystalline material usually separate during the ether extraction. The amines form colorless, viscous liquids, slightly soluble in water, with the exception of the 2,3-compound, which is more soluble. The aqueous solutions are strongly alkaline. The amines do not form solid carbonates in the air.

| Amine | Odor | B. p., °C. | Mm. | $n_D^{25}$ | $d_4^{25}$ | $M_D$ | Formula | Analyses Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2-Methoxy | Strong amine | 115 | 9 | 1.5240 | 1.0043 | 50.38[a] | $C_{10}H_{15}ON$ | 72.68 | 9.16 | 73.04 | 9.21 |
| 3-Methoxy | Strong amine | 118 | 7 | 1.5225 | 0.9999 | 50.40[a] | $C_{10}H_{15}ON$ | 72.68 | 9.16 | 72.83 | 8.99 |
| 2,3-Dimethoxy | Faint amine | 136 | 6 | 1.5218 | 1.0471 | 56.82[b] | $C_{11}H_{17}O_2N$ | 67.64 | 8.78 | 68.02 | 9.01 |
| 2,4-Dimethoxy | Faint, musty | 136 | 4 | 1.5283 | 1.0534 | 57.07[b] | $C_{11}H_{17}O_2N$ | 67.64 | 8.78 | 67.82 | 8.87 |
| 2,5-Dimethoxy | Pract. odorless | 155 | 8 | 1.5278 | 1.0545 | 56.96[b] | $C_{11}H_{17}O_2N$ | 67.64 | 8.78 | 68.01 | 8.57 |

[a] Calcd. (Brühl), 50.23. [b] Calcd. (Brühl), 56.51.

**β-Phenylethylmethylamines—Hydriodides.**—With the exception of the 2,4-compound, which could not be crystallized, the hydriodides were recrystallized from alcohol–ether mixture. They are all white when pure, and are very soluble in water and in alcohol. The hydriodides show marked supercooling and are difficult to crystallize.

| Hydriodide | Appearance | M. p., °C. | Formula | Analyses Calcd. C | Calcd. H | Found C | Found H | Yield,[a] % |
|---|---|---|---|---|---|---|---|---|
| 2-Methoxy | Glittering rounded prisms | 101 | $C_{10}H_{16}ONI$ | 40.95 | 5.50 | 41.16 | 5.62 | 76 |
| 3-Methoxy | Glittering tiny rect. plates | 108 | $C_{10}H_{16}ONI$ | 40.95 | 5.50 | 41.27 | 5.26 | 52 |
| 2,3-Dimethoxy | Glittering prisms | 90 | $C_{11}H_{18}O_2NI$ | 40.86 | 5.62 | 41.01 | 5.60 | 82 |
| 2,4-Dimethoxy | Uncrystallizable sirup | ... | ..... | ... | .. | ... | .. | [b] |
| 2,5-Dimethoxy | Pearly plates | 137 | $C_{11}H_{18}O_2NI$ | 40.86 | 5.62 | 41.00 | 5.62 | 92 |

[a] The yields are given for unrecrystallized hydriodide. [b] Weighed as amine, 47% over both stages.

**β-Phenylethylmethylamines—Hydrochlorides.**—The hydrochlorides were prepared either by passing hydrogen chloride into an ether solution of the pure amine, or by the action of silver chloride on the hydriodide. They form bulky, pure white masses of micro crystals. Alcohol–ether mixture is the best solvent for recrystallization, as the hydrochlorides are all very soluble in cold water and in cold alcohol, but sparingly soluble in ether.

| Hydrochloride | Appearance[a] | M. p., °C. | Formula | Analyses Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| 2-Methoxy | Mesh of long thin plates | 119 | $C_{10}H_{16}ONCl$ | 59.52 | 8.00 | 59.31 | 8.05 |
| 3-Methoxy | Tiny rhombic plates | 119 | $C_{10}H_{16}ONCl$ | 59.52 | 8.00 | 59.48 | 8.08 |
| 2,3-Dimethoxy | Mesh of long thin plates | 117 | $C_{11}H_{18}O_2NCl$ | 56.99 | 7.83 | 57.11 | 7.80 |
| 2,4-Dimethoxy | Mesh of flat needle-prisms | 145 | $C_{11}H_{18}O_2NCl$ | 56.99 | 7.83 | 56.91 | 8.20 |
| 2,5-Dimethoxy | Mass of tiny needles | 110 | $C_{11}H_{18}O_2NCl$ | 56.99 | 7.83 | 56.80 | 7.60 |

[a] Under microscope, from alcohol.

**Hydroxyphenylethylmethylamines—Hydrochlorides.**—The hydrochlorides all form white crystals, very soluble in water, alcohol, acetic acid and concd. hydrochloric acid. They are very difficult to obtain in a crystalline form, the 3-hydroxy compound being particularly so. When pure, however, they are quite stable. No bases could be isolated on account of their solubility and instability. The dihydroxy compounds are powerful reduc-

ing agents. Alcohol–ether or acetone–ether mixtures are the best solvents for crystallizing the salts, as they are sparingly soluble in ether.

| No. | Hydrochloride | Appearance | $FeCl_3$ | Ammon. $AgNO_3$ | Excess NaOH |
|---|---|---|---|---|---|
| 1 | 2-Hydroxy | Thin, pearly plates | Dull violet | No redn. | Colorless, stable |
| 2 | 3-Hydroxy | Glittering plates | Pale violet | No redn. | Colorless, stable |
| 3 | 2,3-Dihydroxy | Stars of prisms | Dull green | Reduced in cold | Rapidly blackens |
| 4 | 2,5-Dihydroxy | Felted tiny plates | Transient pale green | Reduced in cold | Rapidly blackens |

| No. | Hydrochloride | M. p., °C. | Formula | Analyses Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|
| 1 | 2-Hydroxy | 148 | $C_9H_{14}ONCl$ | 57.63 | 7.53 | 57.98 | 7.49 |
| 2 | 3-Hydroxy | 89 | $C_9H_{14}ONCl$ | 57.63 | 7.53 | 57.43 | 7.60 |
| 3 | 2,3-Dihydroxy | 149 | $C_9H_{14}O_2NCl$ | 53.05 | 6.93 | 53.30 | 6.72 |
| 4 | 2,5-Dihydroxy | 128 | $C_9H_{14}O_2NCl$ | 53.05 | 6.93 | 53.23 | 7.01 |

The analyses given in this paper are all micro-analyses (Pregl). The author is indebted to Mr. W. S. Ide for these.

## Summary

The paper describes the synthesis of four of the seven previously unknown hydroxy- and dihydroxyphenylethylmethylamines. The synthesis of one of the remaining three broke down at the last stage. It has not been possible to obtain starting material to attempt the syntheses of the other two.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

# THE HALOFORM REACTION. VI. ALPHA-HALOGEN DERIVATIVES OF HINDERED KETONES

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The study of the halogenation phase of the haloform reaction has now been extended to types other than methyl ketones, and it has been found that the replacement of α-hydrogen by halogen is a fairly general reaction between hindered ketones and hypohalite solutions. This investigation has also included a study of certain unusual reactions which are apparently general for this type of compound. These reactions are (1) cleavage by alkali, (2) the dehalogenation by phenol and (3) dehalogenation by the Grignard reagent. These several phases of the work will be discussed under separate headings.

**The Halogenation.**—From the previous work[1] in this series it appears that the hindered methyl ketones are generally converted directly into the corresponding trihalomethyl compounds. In no case has the mono- or the di-halomethyl derivative been isolated as an intermediate.

[1] (a) Fuson and Walker, THIS JOURNAL, **52**, 3269 (1930); (b) Gray, Walker and Fuson, *ibid.*, **53**, 3494 (1931); (c) Fuson, Farlow and Stehman, *ibid.*, **53**, 4097 (1931); (d) Fuson, Lewis and Du Puis, *ibid.*, **54**, 1114 (1932).