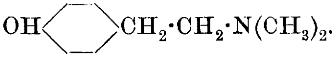
CCXXXV.—*Synthesis of Hordenine, the Alkaloid from Barley.*

By George Barger.

A few years ago Léger (*Compt. rend.*, 1906, **142**, 108) isolated from barley germs a crystalline alkaloid, which he named hordenine, and subsequently (*Compt. rend.*, 1906, **143**, 234, 916) gave the following constitution:



This constitutional formula was confirmed by Gaebel (*Arch. Pharm.*, 1906, **244**, 435), and the physiological action of hordenine was studied by Camus (*Arch. int. de Pharmacodyn. et de Thér.*, 1906, **16**, 43).

It is evident that hordenine (*p*-hydroxyphenylethyldimethylamine: α-dimethylamino-β-*p*-hydroxyphenylethane) is closely related to *p*-hydroxyphenylethylamine, a physiologically active base of somewhat wide distribution, and the author's recent synthesis of the latter base (this vol., p. 1123) suggested an attempt to prepare hordenine from it by methylation.

This attempt was not wholly successful, for although the methiodide of hordenine was readily obtained by treating *p*-hydroxyphenylethylamine with methyl iodide, it was found impossible to isolate the alkaloid itself; the reaction did not stop at the tertiary base, but resulted in the formation of the quaternary iodide, no matter what proportion of methyl iodide was employed. For the same reason it was found impossible to prepare α-dimethylamino-β-phenylethane, $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$, by direct methylation of the corresponding primary amine, for the only products formed were the primary and quaternary iodides. The same difficulty was recently encountered by Johnson and Guest (*Amer. Chem. J.*, 1909, **42**, 340).*

A suitable material for the synthesis of hordenine was, however, found in phenylethyl alcohol (benzylcarbinol), a commercial product, from which α-chloro-β-phenylethane could be prepared. The latter substance yielded, with dimethylamine, the desired α-dimethylamino-β-phenylethane. After nitration of this tertiary base, the *p*-nitro-compound was isolated as the oxalate. It was also found possible to obtain pure α-chloro-β-*p*-nitrophenylethane by distillation and crystallisation, and then to combine it with dimethylamine. On reduction the separation of the amino-compound from the unchanged nitro-compound proved difficult, since both substances are bases; the crude reaction-product was therefore diazotised, and finally yielded a small quantity of a base, identical with hordenine, prepared from malt germs.

EXPERIMENTAL.

α-Chloro-β-phenylethane, $C_6H_5{\cdot}CH_2{\cdot}CH_2Cl$.

Fischer and Schmitz have shown (*Ber.*, 1906, **39**, 2208) that, contrary to the statement of Fittig and Kiesow (*Annalen*, 1870, **156**, 245), the principal product of the chlorination of ethylbenzene is the α- and not the β-compound. They therefore used instead α-bromo-β-phenylethane, $C_6H_5{\cdot}CH_2{\cdot}CH_2Br$, which may be prepared according to Grignard's method (*Compt. rend.*, 1904, **138**, 1049). This method is, however, not very simple, and the required compound may be obtained more readily from phenylethyl alcohol (benzylcarbinol) (a commercial product, which is prepared synthetically, because it occurs in rose-oil).

By heating this alcohol with hydrogen chloride, only a small yield of the desired compound was obtainable; thionyl chloride and phosphorus pentachloride furnished a larger proportion, but the

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* The phenylethylmethylamine prepared by these authors has been obtained in the course of the present work by reduction of the condensation product of phenylacetaldehyde with methylamine, $C_6H_5{\cdot}CH_2{\cdot}CH{:}NMe$. It is, of course, also readily obtainable from α-chloro-β-phenylethane and methylamine in the manner described below for the preparation of the dimethyl derivative; its *p*-nitro-derivative was prepared from α-chloro-β-*p*-nitrophenylethane and methylamine. A number of closely related bases containing one or two phenolic hydroxyl groups will soon be described.

product was contaminated with sulphur and phosphorus compounds. The best yield was obtained with phosphorus pentachloride as follows.

Dry chloroform (100 c.c.) was poured on phosphorus pentachloride (41·7 grams), and phenylethyl alcohol (24·4 grams = one molecular proportion) was added drop by drop. Much hydrogen chloride was evolved, and the phosphorus pentachloride gradually passed into solution; the reaction was completed by warming on the water-bath for two hours. After removal of the chloroform and phosphoryl chloride, the residue distilled under atmospheric pressure at 190—200° with slight decomposition. On redistillation under 20 mm. pressure, the bulk of the product boiled at 91—92°, and was approximately pure (yield = 70 per cent.):

0·2611 gave 0·2732 AgCl. Cl = 25·8.

C_8H_9Cl requires Cl = 25·2 per cent.

α-Dimethylamino-β-phenylethane, $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_3)_2$.

Three grams of the above chloride were heated in a sealed tube with 4 c.c. (a considerable excess) of a 33 per cent. alcoholic solution of dimethylamine to 100° for several hours, and yielded 2·5 grams of the base, boiling at 198—202°. As so little was available, this substance was not further characterised, but the whole was nitrated.

*α-Dimethylamino-β-*p*-nitrophenylethane*,
$NO_2{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_3)_2$.

2·5 Grams of the compound just described were added drop by drop to 10 c.c. of nitric acid (D 1·5), cooled to −10°. On diluting with ice, rendering alkaline, and extracting with ether, a syrupy mixture of nitro-derivatives was obtained. By adding an ethereal solution of anhydrous oxalic acid to the syrup, dissolved in ether, an *oxalate* was precipitated, which, after repeated crystallisation from 95 per cent. alcohol, formed elongated leaflets, melting at 153—154°. This salt is very sparingly soluble in hot absolute alcohol, but dissolves readily in dilute alcohol. The yield was 60 per cent.:

0·2130 gave 0·3989 CO_2 and 0·1094 H_2O. C = 51·0; H = 5·7.

$C_{10}H_{14}O_2N_2,C_2H_2O_4$ requires C = 50·7; H = 5·6 per cent.

That the nitro-group is in the para-position follows from the conversion of the substance into hordenine. The same salt was obtained from α-chloro-β-*p*-nitrophenylethane and dimethylamine, as follows.

*α-Chloro-β-*p*-nitrophenylethane,* $NO_2 \cdot C_6H_4 \cdot CH_2 \cdot CH_2Cl$.

α-Chloro-β-phenylethane (13 grams) was dropped into nitric acid (50 c.c.; D 1·5), cooled by a freezing mixture. After pouring on snow, extracting with ether, and washing the ethereal solution with sodium carbonate, the residue was distilled under 18 mm. pressure. Two fractions, b. p. 165—175° and 175—179°, were collected; the second of these crystallised almost completely on cooling below 0°, and was then drained on a porous tile in the cold room. After recrystallisation from light petroleum, 3·9 grams of glassy crystals were obtained, melting sharply at 49°:

0·1354 gave 9·2 c.c. N_2 (moist) at 17° and 758 mm. N = 7·9.
0·1593 „ 0·1195 AgCl. Cl = 18·8.
$C_8H_8O_2NCl$ requires N = 7·6; Cl = 19·1 per cent.

That the crystalline nitro-compound is the *p*-compound is a priori probable; that this is indeed the case follows from its conversion into α-dimethylamino-β-*p*-nitrophenylethane, which at once yielded an oxalate, melting at 153—154°, and identical with that described above.

*Conversion of α-Dimethylamino-β-*p*-nitrophenylethane into Hordenine.*

2·7 Grams of α-dimethylamino-β-*p*-nitrophenylethane oxalate were dissolved in 10 c.c. of alcohol; 2 grams of tinfoil and 10 c.c. of concentrated hydrochloric acid were added; after rendering alkaline with excess of sodium hydroxide, and extraction with ether, 0·55 gram of the crude amino-compound was obtained as a syrup. This was dissolved in 5 per cent. sulphuric acid, and to the boiling solution the calculated quantity of sodium nitrite was gradually added. Much resin was formed; on cooling, the filtered solution was rendered alkaline with sodium hydroxide, washed with ether, sodium carbonate added, and the solution extracted with ether. The ethereal extract left, on evaporation, a small quantity of crystals (m. p. 111°) and a little resin. On again dissolving the crystals in ether, the phenolic amine was extracted with sodium hydroxide, and afterwards shaken with ether; on evaporation of the ether, yellow crystals separated, which were drained on a porous tile and recrystallised from a mixture of benzene and light petroleum. In this way a small quantity of a white, crystalline substance was obtained, melting at 117—117·5°. A specimen of pure natural hordenine melted at 117·5°, and a mixture of equal quantities of the synthetic and the natural substance at 117—117·5°.

The synthetic specimen gave Millon's reaction very intensely; it reddened phenolphthalein, was not coloured by concentrated sulphuric acid, and reduced acid potassium permanganate in the cold and ammoniacal silver nitrate on warming; in all these respects its properties were identical with those of the natural base, as described by Léger. The amount of the synthetic substance obtained was insufficient for analysis.

The natural hordenine, used for comparison, was purified by distillation, the boiling point being 173—174°/11 mm. As in the case of *p*-hydroxyphenylethylamine, distillation is by far the most convenient method of purification.

Preparation of Hordenine Methiodide from p-*Hydroxyphenylethylamine.*

Two grams of *p*-hydroxyphenylethylamine were dissolved in a little methyl alcohol, and boiled for a few minutes with a large excess (20 c.c.) of methyl iodide. After two days, glassy prisms separated, which were up to 4 cm. in length; the weight was 0·45 gram, much being left in the mother liquor. On recrystallisation from water, the quaternary iodide gave stout crystals, melting at 230—231°, and closely resembling natural hordenine methiodide, a specimen of which melted at 229—230°; on mixing the two, the melting point was 229—230°:

0·1444 gave 0·1110 AgI. I = 41·5.

$C_{11}H_{18}ONI$ requires I = 41·3 per cent.

Benzoylhordenine methiodide,

$$C_6H_5\cdot CO\cdot O\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot N(CH_3)_3I,$$

was prepared from both specimens of hordenine methiodide; in each case hexagonal leaflets were obtained, sparingly soluble in hot water, and melting at 252—254°; this was also the melting point of the mixture of the synthetic and natural substance.

Although hordenine methiodide can thus be readily prepared from *p*-hydroxyphenylethylamine, numerous attempts to synthesise the alkaloid itself by this method were unsuccessful, and the other method, described above, had to be employed.

Wellcome Physiological Research Laboratories,
Herne Hill, London, S.E.