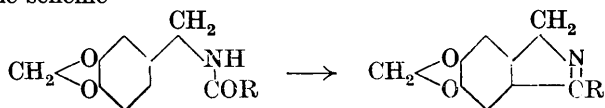


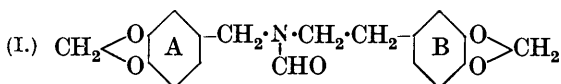
CCCL.—*Facile Ring-closure to a Derivative of Dihydroisoquinoline contrasted with the Difficulty of Analogous Formation of a Derivative of isoIndole.*

By JACQUES MALAN and ROBERT ROBINSON.

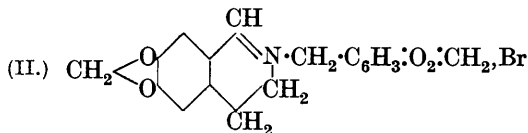
EXAMPLES of the production of *isoindole* derivatives by a reaction analogous to the Bischler-Napieralski synthesis of *dihydroisoquinolines* have not been recorded, and our own attempts to dehydrate aceto- and benzo-piperonylmethylamides in accordance with the scheme



have been fruitless. Such negative results are often attributable to various fortuitous causes, *e.g.*, unsuitable conditions, impure or too pure reagents, but, in the course of some preliminary synthetical experiments in the *isoquinoline* group of the alkaloids, we encountered a case free from such objections, and one that proves that the difficulty experienced in closing the *isoindole* ring is not fortuitous. The complex formamide (I) might give either a five-membered or a six-membered heterocyclic ring on dehydration, but, actually, a substance containing the latter is the only product of the action of phosphoryl chloride on the amide. The constitution of the



quaternary ammonium salt obtained was proved by an independent synthesis. Interaction of methylenedioxydihydro*isoquinoline* and piperonylmethyl bromide yielded the bromide (II), which was



convertible into a *picrate*, *pseudo-cyanide*, and an *anhydro-base-nitromethane* derivative identical, each to each, with the same series obtained from (I).

One of the factors controlling the direction of the ring closure is doubtless the field associated with the positive charge of the nitrogen atom, which is probably in the ammonium state under the conditions of the reaction. This field is evidently more intense over nucleus (A) than over nucleus (B), and as it should tend to inhibit union of the nuclear carbon with that of the $-\text{CHO}$ group, itself kationoid, an adequate explanation of the formation of the *isoquinoline* derivative is forthcoming. For a similar reason, the formation of *isoquinoline* derivatives from substances of the form $\text{Ar} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{N} \cdot \text{CO} \cdot$ should be more facile than from substances of the form $\text{Ar} \cdot \text{CH}_2 \cdot \text{N} \cdot \text{CH}_2 \cdot \text{CO} \cdot$, provided that the carbonyl group has an approximately equal reactivity in each case. Several illustrative cases have been recorded (Mannich and Kuphal, *Arch. Pharm.*, 1912, 250, 539).

EXPERIMENTAL.

Piperonylmethylamine Derivatives.—Piperonylmethylamine, b. p. $172^\circ/50$ mm., was obtained in 70% yield by the reduction of piperonaldoxime by means of zinc dust in boiling 50% acetic acid solution (Mannich and Kuphal, *Ber.*, 1912, 45, 314). The *chloroplatinate* crystallises from much hot water in orange needles [Found :

Pt, 27.7. $(C_8H_9O_2N)_2, H_2PtCl_6$ requires Pt, 27.6%]. The *picrate* crystallises from water in yellow needles, m. p. 198°. *Piperonylmethyltrimethylammonium iodide*, $CH_2O_2 \cdot C_6H_3 \cdot CH_2 \cdot NMe_3I$, obtained by the action of an excess of methyl iodide on the base, crystallises from alcohol in minute, yellow prisms, m. p. 219° (decomp.) (Found : C, 41.0; H, 5.1; I, 38.7. $C_{11}H_{16}O_2NI$ requires C, 41.1; H, 5.0; I, 39.2%).

Benzylidenepiperonylmethylamine, $CH_2O_2 \cdot C_6H_3 \cdot CH_2 \cdot N \cdot CHPh$, readily obtained by condensation of the base with benzaldehyde, crystallises from aqueous alcohol in colourless needles, m. p. 51—52° (Found : C, 75.5; H, 5.7. $C_{15}H_{13}O_2N$ requires C, 75.3; H, 5.4%); its *picrate* crystallises from alcohol in light yellow needles, m. p. 206°.

2-Carbomethoxyveratrylidenepiperonylmethylamine,

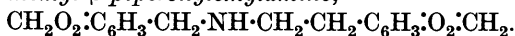


is obtained by heating methyl opianate and piperonylmethylamine in molecular proportion at 150°. It crystallises from alcohol in flocculent masses of colourless, microscopic needles, m. p. 181° (Found : C, 63.2, 63.8; H, 4.8, 5.0; N, 4.1. $C_{19}H_{19}O_6N$ requires C, 63.8; H, 5.0; N, 4.1%). An interesting transformation of this substance occurs under the influence of sodium methoxide in hot methyl-alcoholic solution. The elements of methyl alcohol are eliminated and the neutral product crystallises from methyl alcohol in glistening, hexagonal prisms, capped with pyramids, m. p. 159° (Found : C, 66.1, 66.4; H, 4.9, 4.9; N, 4.5. $C_{18}H_{15}O_5N$ requires C, 66.5; H, 4.6; N, 4.3%). The most natural hypothesis is that this substance is *4-hydroxy-5:6-dimethoxy-3-piperonylisoquinoline*, but its properties are somewhat at variance with such a view. For example, the action of boiling methyl iodide gives rise to an *iodide*, m. p. 172° (Found : C, 36.8, 36.3; H, 4.1, 4.0; I, 41.7; and, for instance, $C_9H_{12}O_2NI$, piperonylmethylmethylamine hydriodide, requires C, 36.8; H, 4.1; I, 43.3%). Evidently the molecule has been broken up, and this is difficult to reconcile with the *isoquinoline* formulation. A by-product in the preparation of piperonylmethylamine is *di(piperonylmethyl)amine*, b. p. 230°/50 mm., which crystallises from alcohol in silky needles, m. p. 114°. The foregoing experiments were made by Miss B. Dobson in these laboratories in 1910.

Acetopiperonylmethylamide crystallises from benzene in colourless needles, m. p. 103° (Found : C, 62.2; H, 5.3. $C_{10}H_{11}O_3N$ requires C, 62.2; H, 5.7%). Attempts to dehydrate this substance, and similar trials with benzopiperonylmethylamide, m. p. 117° (Mannich and Kuphal, *loc. cit.*), by means of phosphoryl chloride, phosphoric anhydride, sulphuric acid, zinc chloride and stannic chloride failed, the amides being either recovered unchanged or converted into dark violet substances that could not be purified.

It is relevant to mention here that the ring closure of *phenacyl veratrate*, $C_6H_3(MeO)_2 \cdot CO \cdot O \cdot CH_2 \cdot CPh$, to an *isocoumarin* derivative has been unsuccessfully attempted. The ester is obtained in good yield by the interaction of ω -bromoacetophenone and silver veratrate in boiling alcoholic solution. It crystallises from alcohol in well-defined, elongated prisms, m. p. 122° (Found: C, 68.0; H, 5.4. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

Piperonylmethyl- β -piperonylethylamine,

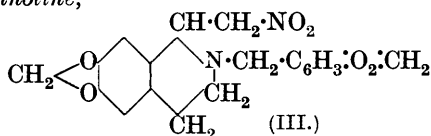


—A warm solution of piperonylidene- β -piperonylethylamine (22 g.) (Decker and Becker, *Annalen*, 1913, **395**, 342) in absolute alcohol (500 c.c.) was added as quickly as possible through a long reflux condenser to sodium (35 g.) in a flask immersed in an oil-bath at 140° . When all the sodium had passed into solution, the mixture was cooled and added to water (2000 c.c.). On keeping, colourless crystals separated (15 g.). The base crystallises from light petroleum (b. p. 40 – 60°) in needles, m. p. 53° (Found: C, 68.0; H, 5.7. $C_{17}H_{17}O_4N$ requires C, 68.2; H, 5.7%). It is readily soluble in alcohol or benzene. The *hydrochloride* is very sparingly soluble in dilute hydrochloric acid and crystallises from much boiling water in flocculent masses of colourless needles. The *nitroso*-derivative, obtained in the usual way, crystallised from alcohol in clusters of minute, colourless needles, m. p. 127 – 128° . The *dinitro*-derivative, prepared in acetic acid solution, crystallised from alcohol in colourless, diamond-shaped plates, m. p. 134 – 135° . The *N-formyl* derivative was obtained by refluxing (oil-bath at 180°) a mixture of the base (5 g.) and anhydrous formic acid (25 c.c.) for 2 days. The emulsion obtained on the addition of water resolved into crystals and the solid was purified by trituration with dilute acetic acid (yield, 70%). The substance, which is readily soluble in most organic solvents, crystallised with difficulty from light petroleum in colourless, microscopic prisms, m. p. 89 – 90° (Found: C, 65.8; H, 5.3. $C_{18}H_{17}O_5N$ requires C, 66.0; H, 5.2%).

6 : 7-Methylenedioxy-2-piperonylmethyl-3 : 4-dihydroisoquinolinium Picrate and Bromide (II).—(A). A mixture of formopiperonylmethyl- β -piperonylethylamide (5 g.) and phosphoryl chloride (30 g.) was heated on the steam-bath for 20 minutes and then added to crushed ice. Picric acid (4 g.) was added to the filtered solution and the pasty, yellow mass of the picrate was collected and obtained crystalline by rubbing under alcohol. The derivative crystallised from boiling acetone in microscopic, transparent, yellow rhombs, m. p. 184 – 185° (yield, 7.2 g.) (Found: C, 53.4; H, 3.4; N, 10.5. $C_{24}H_{18}O_{11}N_4$ requires C, 53.5; H, 3.3; N, 10.4%). (B). Solutions of 6 : 7-methylenedioxy-3 : 4-dihydroisoquinoline (3.5 g.) and of

piperonylmethyl bromide (4.4 g.) in benzene (20 c.c. each) were mixed and then heated for 10 minutes on the steam-bath. The yellow crystals (6.8 g.) deposited on cooling separated from alcohol in minute, yellow needles, m. p. 230° (Found: Br, 21.0, 20.4. $C_{18}H_{16}O_4NBr$ requires Br, 20.5%). The salt is sparingly soluble in water, more readily in alcohol, giving pale yellow solutions exhibiting a blue fluorescence. The addition of picric acid to an alcoholic solution gave the picrate, m. p. 184—185°, which was identified by direct comparison with the product obtained in (A).

6 : 7-Methylenedioxy-1-nitromethyl-2-piperonylmethyl-1 : 2 : 3 : 4-tetrahydroisoquinoline,



—The carbinol from 6 g. of the above-described bromide was extracted with ether, the extract dried with potassium carbonate, and the solvent removed. All these operations should be conducted expeditiously. The residue was dissolved in alcohol (20 c.c.), and nitromethane (1 g.) in alcohol (5 c.c.) introduced. After heating on the steam-bath for a few minutes, the mixture was cooled; the crystals that separated were obtained, after three recrystallisations from alcohol, in short, colourless prisms, m. p. 124—125° (Found: C, 61.5; H, 4.9. $C_{19}H_{18}O_6N_2$ requires C, 61.6; H, 4.9%). The picrate was similarly treated and gave the same derivative with nitromethane; a mixture of the two specimens had m. p. 124—125°.

6 : 7-Methylenedioxy-1-cyano-2-piperonylmethyl-1 : 2 : 3 : 4-tetrahydroisoquinoline (III with CN instead of CH_2NO_2).—When potassium cyanide is added to an aqueous solution of the bromide or of the chloride (derived from the picrate by addition of dilute hydrochloric acid and removal of the picric acid with ether), a curdy, white precipitate is thrown down: this rapidly becomes crystalline. The substance crystallises from alcohol in hexagonal plates, m. p. 151° (Found: C, 67.8; H, 4.8. $C_{19}H_{16}O_4N_2$ requires C, 67.9; H, 4.8%), and has the properties of a pseudo-cyanide. It is insoluble in cold 7% sulphuric acid and, on warming, a yellow solution is obtained and hydrogen cyanide liberated. It dissolves in concentrated hydrochloric acid to a colourless solution and after dilution the unchanged base may be precipitated by ammonia. On heating, however, a yellow solution is obtained.