190. *A Ring Homologue of Tropacocaine.*

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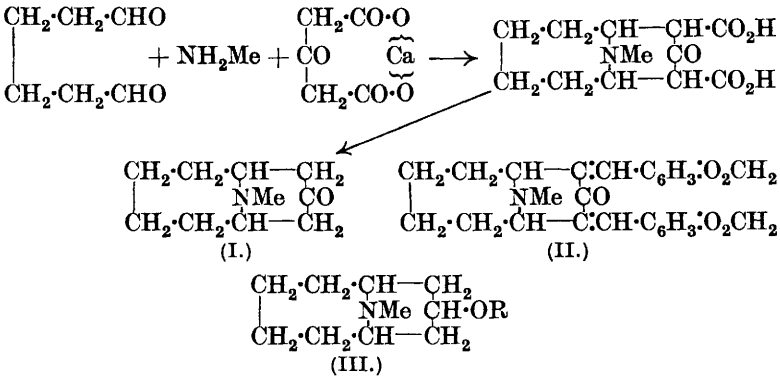
The synthesis of tropinone from succindialdehyde (J., 1917, **111**, 762) was extended to that of pseudopelletierine from glutardialdehyde by Menzies and one of us (J., 1924, **125**, 2169) and the feasibility of its further extension to adipdialdehyde was mentioned.

This dialdehyde, then not readily prepared, has recently been made accessible (Criegee, *Ber.*, 1931, **64**, 260) by the oxidation of *cyclo*hexanediol with lead tetra-acetate, a reagent introduced by Dimroth and Schweizer (*Ber.*, 1923, **56**, 1375). We have now condensed adipdialdehyde with calcium acetonedicarboxylate and methylamine and obtained duplohomotropinone (or *N*-methylhomogranatonine) (I) in a yield of approximately 18%.

This ring homologue of tropinone and pseudopelletierine is an oil,

but it forms a crystalline *picrate* and *dipiperonylidene* derivative (II) and a highly characteristic *methiodide*.



On reduction with sodium and *n*-butyl alcohol the ketone yields the related secondary alcohol, *N*-methylhomogranatoline (III, R = H), likewise an oil, of which the *picrate* was analysed. The *O*-benzoyl derivative (III, R = COPh) of this base (*picrate*, *hydrochloride*) is the substance mentioned in the title; it possesses strong local anæsthetic properties.

EXPERIMENTAL.

cis-cyclo*Hexane*-1 : 2-*diol*.—The following process, based on one due to Coleman and Johnstone, and Osterberg (" Organic Syntheses," **5**, 31—35), is a rapid method for preparing the pure compound in quantity from accessible materials; the yield, however, is not entirely satisfactory.

*cyclo*Hexene (" Organic Syntheses," **5**, 33) (83 g.) was treated gradually with a slight excess of hypochlorous acid (sodium hypochlorite solution and nitric acid), the mixture being stirred and kept below 15° by the addition of ice. The aqueous layer was then siphoned off and replaced by a solution of sodium hydroxide (40 g.) in water (250 c.c.) and after 1 hour's stirring, a little ether was added and the upper layer was dried and distilled through a short column. The crude *cyclo*hexene oxide (about 40 g., b. p. 80—160°) was refluxed for 1 hour with 1% sulphuric acid, the liquid neutralised with potassium carbonate, most of the water distilled off, the remainder evaporated on the steam-bath, and the residue extracted with hot benzene. Addition of ether to the concentrated extract at 0° gave pure *cis-cyclo*hexanediol (20—27 g.).

N-*Methylhomogranatonine* (I).—The crude adipdialdehyde (12 g.; b. p. 70—100°/12 mm.) obtained by the oxidation of *cis-cyclo*hexanediol (15·5 g.) by the method of Criegee (*loc. cit.*) was dissolved

in water (120 c.c.) and added to a solution of acetonedicarboxylic acid (48 g.) in water (240 c.c.) which had been neutralised with precipitated chalk (60 g.); aqueous methylamine (150 c.c. of 33%) was then introduced during 30 minutes with constant shaking. After a week, the mixture was acidified with concentrated hydrochloric acid (Congo-red) boiled until evolution of carbon dioxide ceased, cooled, and made alkaline. The calcium oxalate precipitated by ammonium oxalate (72 g.) was collected and washed with a little alcohol and thoroughly with ether. The brown green-fluorescent filtrate was shaken 15 times with about its own volume of ether, the base extracted in each operation being taken up in a small quantity of hydrochloric acid (3*N*). The bases were again rendered to ether and after evaporation of the dried ethereal solution the product was obtained as a brown oil. This was mixed with acetone (10 c.c.) and treated with picric acid (15 g.) in acetone (15 c.c.). Heat was evolved and, after cooling, the picrate was collected; a further quantity was recovered from the mother-liquor. N-*Methylhomogranatonine picrate* crystallised from hot water in bright yellow needles (7·5 g.), m. p. 206° (decomp.) (Found: N, 14·5. $C_{16}H_{20}O_8N_4$ requires N, 14·1%).

The free base, regenerated as an oil from the recrystallised picrate, was mixed (0·2 g.) with methyl iodide (0·2 c.c.) and methyl alcohol (3 c.c.) and kept for a week; N-*methylhomogranatonine methiodide* separated in large cubic crystals, very sparingly soluble in organic solvents. It crystallised from water at the ordinary temperature in cubes, at low temperatures in long, thin, feathery prisms, m. p. 277° (decomp.) (Found: C, 42·9; H, 6·5. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%).

Dipiperonylidene-N-*methylhomogranatonine* (II) was prepared from the crude mixture of bases (0·5 g.) by gentle heating on the steam-bath for 4 hours with piperonal (1 g.) and aqueous potash (3 drops of 50%) in alcohol (10 c.c.). After cooling, the brown solid was separated and crystallised from ethyl acetate (charcoal) and chloroform–ethyl acetate, yielding the derivative in yellow, irregular, four-sided plates, m. p. 209—210° (Found: C, 72·2; H, 6·1. $C_{26}H_{25}O_5N$ requires C, 72·4; H, 5·9%). The solution in concentrated sulphuric acid has an intense royal-blue colour and becomes green and then yellow on dilution, in every way resembling those of the dipiperonylidene derivatives of tropinone and pseudopelletierine. The light yellow hydrochloride is very sparingly soluble in dilute hydrochloric acid. This substance was also prepared from the pure base regenerated from the picrate.

N-*Methylhomogranatoline* (III, R = H).—*N*-Methylhomogranatonine, regenerated from the recrystallised picrate (3·5 g.), was

reduced with sodium (5 g.) and dry *n*-butyl alcohol (80 c.c.). The solution was made acid to Congo-red with concentrated hydrochloric acid, and the butyl alcohol distilled in steam, the liquid being simultaneously heated to diminish the volume; it was then cooled, basified, and repeatedly extracted with ether, the base being removed each time from the organic layer by shaking with a little hydrochloric acid (3*N*). Finally the combined acid solutions were rendered alkaline and the base was isolated by means of ether as an almost colourless oil (1·4 g., 95%).

The *picrate*, prepared in alcoholic solution, crystallised in clusters of small orange-yellow needles, m. p. 236—237° (decomp.), with considerable previous darkening (Found : C, 48·6; H, 5·5. $C_{16}H_{22}O_8N_4$ requires C, 48·2; H, 5·5%).

O-*Benzoyl*-N-*methylhomogranatoline* (*Duplohomotropacocaine*) (III, R = COPh).—*N*-Methylhomogranatoline (1·2 g.), benzoic anhydride (2·5 g.), and water (2 c.c.) were heated together on a boiling water-bath for 2 hours, a further quantity (1·5 g.) of benzoic anhydride was added, and the heating continued for a further 1 hour. After cooling, the mixture was diluted somewhat and made acid to Congo-red, the benzoic acid and unchanged anhydride were extracted with ether, the aqueous layer was neutralised with sodium carbonate, and the liberated base isolated by means of ether and treated with an excess of picric acid in ether–acetone. A gummy picrate separated, which solidified after 24 hours at 0° and was twice crystallised from aqueous acetone by slow cooling and constant shaking. O-*Benzoyl*-N-*methylhomogranatoline picrate* forms yellow needles, m. p. 175—177° (Found : C, 55·6; H, 5·3; N, 11·1. $C_{23}H_{26}O_9N_4$ requires C, 55·0; H, 5·2; N, 11·2%).

The recrystallised picrate was decomposed with hydrochloric acid, the picric acid removed by ether–acetone, and the base rendered to ether. The dried solution was concentrated to a small bulk, and dry hydrogen chloride led in; the *hydrochloride*, which separated as an oil, from which the solvent was decanted, was crystallised by solution in a little alcohol, cautious addition of ether until a turbidity was produced, and cooling to 0°. The salt (0·31 g.) separated in long white needles which were stable in the air, and evidently contained solvent of crystallisation, since they melted indefinitely from 50°. On drying in a vacuum desiccator, they were converted into a colourless gum, which crystallised again in moist air (Found in material dried at 110° in a high vacuum : C, 65·4; H, 7·7; N, 4·4. $C_{17}H_{23}O_2N$,HCl requires C, 65·9; H, 7·8; N, 4·5%).

A trace of this substance placed on the tongue produces a characteristic sensation of numbness. Professor J. Gunn and Mr. G. K. Elphick of the University Department of Pharmacology have kindly

undertaken the investigation of the physiological properties of the salt and have made the following interim report: "Tested on the cornea of the eye of the rabbit, the preparation (duplohomotropacocaine hydrochloride) is a powerful local anæsthetic and is approximately as effective in this respect as tropacocaine hydrochloride. The anæsthesia produced by the new agent is, however, more persistent than that produced by tropacocaine. Relative toxicity tests are in progress."

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