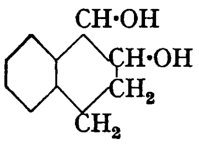
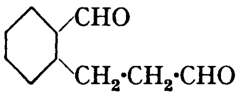
141. *Aromatic Tropane Derivatives. Part I. Derivatives of* 8 : 9-*Benz*-$\Delta^{8:9}$-*homogranatene.*

By B. K. Blount.

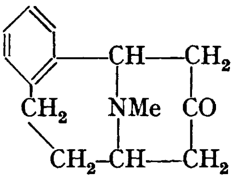
The application of Robinson's tropinone synthesis to aromatic dialdehydes should give a number of interesting new ring systems. Suitable aromatic dialdehydes can now be obtained from the corresponding glycols by oxidation with lead tetra-acetate (Criegee, *Ber.*, 1931, **64**, 260).



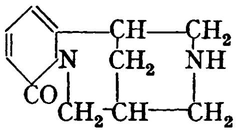
(I.)



(II.)



(III.)



(IV.)

Titration experiments of Criegee show that *trans*-tetrahydronaphthalene-1 : 2-diol (I) reacts normally with lead tetra-acetate, but the dialdehyde (II) which should be produced has not been isolated. This reaction has now been adapted to preparative purposes.

Several methods have been described for the preparation of both *cis*- and *trans*-tetrahydronaphthalene-1 : 2-diol usually designed to give one or other isomeride in the pure state. For the present purpose a mixture of both forms was equally useful, since the stereoisomerism disappears when the ring is broken, and such a mixture has been obtained by a modification of the method of Straus and Lemmel (*Ber.*, 1921, **54**, 25) with increase in yield and convenience. The initial material in this synthesis is 1 : 2-dibromotetrahydronaphthalene, which was prepared by Straus and Lemmel from Δ^1-dihydronaphthalene. These authors mention a patent of von Braun (D.R.-P. 316218) describing the preparation of this dibromide by the direct bromination of tetralin, but reject the method on account of the poor yield, and for other reasons. Von Braun specifies bromination between 100° and 140°, and if the upper limit is approached it is not surprising that the yields are unsatisfactory, for Straus and Lemmel have shown that the dibromide decomposes readily above 130°, losing hydrogen bromide and forming 1-bromo-Δ^1-dihydronaphthalene. It has now been found that a workable yield is obtained by carrying out the reaction rapidly at 95—100°, and this method is greatly to be preferred to that of Straus and Lemmel.

When oxidised in warm benzene solution with lead tetra-acetate, the glycol (I) was smoothly converted into the dialdehyde (II), isolated as an oil which was characterised as the ***dioxime***. The crude dialdehyde was condensed with calcium acetonedicarboxylate and methylamine, and, after acidification and heating, yielded 8 : 9-*benz*-$\Delta^{8:9}$-*homogranaten*-3-*one* * (III) in approximately 20% yield. It is interesting to note the similarity in ring system between this compound and cytisine (IV) (Ing, J., 1932, 2778).

The ketone (III) was reduced by means of sodium and butyl alcohol to the *alcohol* (V, R = H), to which the prefix ψ is attached since it doubtless corresponds to ψ-tropine. Benzoylation of this compound gave the analogue of tropacocaine, *benzoyl*-ψ-8 : 9-*benz*-$\Delta^{8:9}$-*homogranaten*-8-*ol* (V, R = Bz); this forms a characteristic *hydrobromide*, which is very sparingly soluble in water and displays local anæsthetic properties when placed on the tongue.

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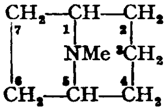
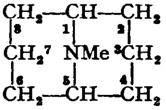
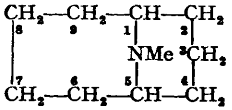
* Nomenclature in the tropane group is somewhat confused. It is proposed to refer compounds of this type to the ring systems :



Tropane

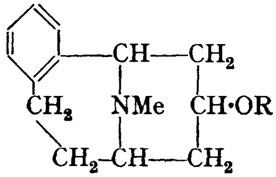


Granatane



Homogranatane

The pharmacology of these substances is being investigated by Professor Gunn and Dr. Rao of the University Department of Pharmacology.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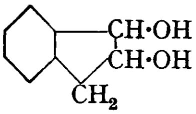
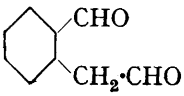
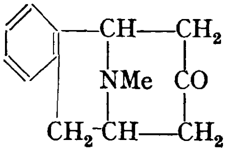

(VI.)


(VII.)


(VIII.)

It has been shown (Blount and Robinson, this vol., p. 555) that the dialdehyde (VII) can be prepared from hydrindenediol (VI), but it appeared unlikely that this compound could be used to prepare 7 : 8-benz-$\Delta^{7:8}$-granaten-3-one (VIII) in a similar way, since it should be converted preferentially into 2-methyl*iso*quinolinium hydroxide by the action of methylamine. The reaction, carried out in the usual way, gave an oil which yielded a sparingly soluble picrate identified as 2-methyl*iso*quinolinium picrate.

EXPERIMENTAL.

1 : 2-*Dibromo*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—To tetralin (135 c.c.), heated to 80° in a flask with an efficient reflux condenser, Br (120 c.c., *i.e.*, 10% excess) was added below the surface as rapidly as was possible without loss of the HBr evolved. The temp. was maintained at 95—100°, at first by occasional cooling, later by warming. Towards the end of the reaction some loss of Br was unavoidable without undue slowing of the reaction (hence the excess used). The dark brown reaction mixture began to crystallise at 0° when stirred, and petroleum (b. p. 60—80°, equal vol.) was added. After being kept at 0° over-night, the solid was collected, pressed as dry as possible, and recrystallised from petroleum (b. p. 60—80°). Yield, 80—90 g. of nearly colourless crystals, m. p. 71—72°.

Tetrahydronaphthalene-1 : 2-*diol*.—The above dibromide (87 g.), AcOK (150 g.), and AcOH (200 c.c.) were heated on the water-bath with frequent shaking for 1 hr., and then gently refluxed in an oil-bath for 12 hr. When the cooled reaction mixture was poured into H_2O, a brown oil separated, which was taken up in a little Et_2O. The extract was washed with K_2CO_3 aq. and evaporated without drying, and to the residue KOH (70 g.) in H_2O (70 c.c.) was added. Hydrolysis proceeded with evolution of heat, and was completed by warming on the water-bath for 1 hr. After collection in Et_2O, drying, and evaporation, the dark oil was distilled in a high vac. The distillate crystallised at once when mixed with hot C_6H_6, and, after cooling, was collected. Yield, about 25 g. of a colourless mixture of *cis*- and *trans*-tetrahydronaphthalene-1 : 2-diol.

β-(o-*Formylphenyl*)*propaldehyde* (II).—Tetrahydronaphthalene-1 : 2-diol (1·6 g.) was dissolved in boiling C_6H_6 (30 c.c.), a little solvent distilled off to ensure a dry solution, and cooled to about 50°. $Pb(OAc)_4$ (4·4 g.) was added gradually during 5 min., with constant shaking, and the mixture heated to boiling, cooled, and filtered from $Pb(OAc)_2$. Evaporation of the filtrate in vac. gave the *dialdehyde* as a colourless oil with an odour recalling that of acetophenone and also of the aliphatic dialdehydes. (An attempt to distil the substance in vac. caused darkening and much resinification.) The dialdehyde was dissolved in EtOH (13 c.c.), and NH_2OH,HCl (3 g.) and Na_2CO_3 (3 g.) in H_2O (13 c.c.) added. After 2 hrs.' refluxing, boiling H_2O (20 c.c.) and a little charcoal were added and the liquid was filtered. On cooling, the *dioxime* separated; recryst. from 25% EtOH aq., it formed rosettes of thick colourless needles, m. p. 116° (Found : C, 62·4; H, 6·2. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·2%).

8 : 9-*Benz*-$\Delta^{8:9}$-*homogranaten*-3-*one* (III).—The dialdehyde (from 6·4 g. of the glycol), dissolved in EtOH (60 c.c.), was mixed with a solution obtained by neutralising acetonedicarboxylic acid (10 g.) in H_2O (60 c.c.) with pptd. $CaCO_3$ (12·5 g.), and $MeNH_2$ aq. (25 c.c. of 33%) added gradually with constant shaking during 20 min. After 15 hr., the solution was made acid to Congo-red with conc. HCl and boiled until no more CO_2 was evolved. To the cooled solution, KOH aq. (rather more than equiv. to the HCl) was added, followed by $(NH_4)_2C_2O_4$ aq. (15 g.), and the liquid filtered. The ppt. was washed with EtOH and with Et_2O, and the filtrate extracted several times with the latter solvent. The basic material was removed from the extracts by means of 3*N*-HCl, recovered, and crystallised from a little EtOH, yielding the desired base, which was recrystallised from H_2O. From the H_2O mother-liquor more was re-

covered as picrate, and a further quantity was obtained by pouring the alc. mother-liquors into boiling H_2O, clarifying the solution with charcoal, and pptng. the picrate with picric acid. The latter crop was rather sticky, but was obtained almost pure by washing with acetone. 8 : 9-*Benz*-$\Delta^{8:9}$-*homogranaten*-3-*one* forms colourless six-sided plates, m. p. 125° (Found : C, 78·6; H, 7·8; N, 6·6. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%). Yield, 0·9 g. of free base, and 1·5 g. of picrate. A longer time of reaction diminished the yield. The *picrate* is sparingly sol. in most solvents, and crystallises from ethoxyethyl acetate in yellow needles, m. p. 204° (decomp.) (Found : C, 54·2; H, 4·5; N, 12·7. $C_{20}H_{20}O_8N_4$ requires C, 54·1; H, 4·5; N, 12·6%). The *hydrobromide* crystallised from EtOH, in which it is sparingly sol., in transparent oblique prisms, m. p. 235° (decomp.) (Found : Br, 26·7. $C_{14}H_{17}ON,HBr$ requires Br, 27·0%). Attempts to obtain a cryst. dipiperonylidene derivative of this base were unsuccessful. Under the usual conditions an orange-coloured amorphous product resulted, which gave the colour reactions of a monopiperonylidene compound. Reference to models indicated that there might be a stereochemical explanation for this.

ψ-8 : 9-*Benz*-$\Delta^{8:9}$-*homogranaten*-3-*ol* (V, R = H).—The above ketone (0·43 g.) was reduced by means of Na (0·5 g.) and boiling dry *n*-BuOH (10 c.c.). After acidification, and removal of the BuOH in steam, addition of NH_3 aq. pptd. the reduction product as a gum, which soon solidified. ψ-8 : 9-*Benz*-$\Delta^{8:9}$-*homogranaten*-3-*ol* exhibits a considerable tendency to separate from solution as a resin, but could be satisfactorily recrystallised from wet C_6H_6 as the *monohydrate*, short colourless prisms, which loses its water and melts indefinitely at 105—110° (Found : C, 71·7; H, 8·9; N, 6·4. $C_{14}H_{19}ON,H_2O$ requires C, 71·5; H, 8·9; N, 6·0%).

Benzoyl-ψ-8 : 9-*benz*-$\Delta^{8:9}$-*homogranaten*-3-*ol* (V, R = Bz).—The crude alcohol (from 0·43 g. of ketone), benzoic anhydride (0·5 g.), and H_2O (2 c.c.) were heated together on the water-bath. At intervals of 40 min. two further portions of benzoic anhydride (each 0·5 g.) were added, the heating being continued for 2 hr. in all. After the product had been shaken with dil. HCl aq. and Et_2O, addition of NH_3 aq. to the aq. layer gave a sticky ppt. of the *benzoyl* compound, which crystallised from EtOH aq. in colourless rhombs, m. p. 98° (Found : C, 78·7; H, 7·2; N, 4·7. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·2; N, 4·4%). Yield, 0·30 g. (47%); a further quantity was isolated from the mother-liquors as the *hydrobromide*. This salt is sparingly sol. in EtOH and H_2O, and separates from the latter in compact irregular crystals, m. p. 257° (Found : Br, 19·6. $C_{21}H_{23}O_2N,HBr$ requires Br, 19·9%). The hydrobromide proving inconveniently sparingly sol. for pharmacological work, the *hydrochloride* was also prepared : it crystallised from EtOH in small compact crystals, m. p. 258° (decomp.) (Found : N, 4·1. $C_{21}H_{23}O_2N,HCl$ requires N, 3·9%).

The condensation of homophthalaldehyde (VII) with calcium acetonedicarboxylate and methylamine was carried out in an analogous manner, and yielded finally a dark-coloured oil. A solution of this in acetone gave a sparingly sol. picrate which after several crystns. from the same solvent formed long yellow plates, m. p. 164—165°, not depressed by admixture with a specimen obtained from *iso*quinoline methiodide. Giua and Giua (*Gazzetta*, 1921, **51**, i, 313; cf. Kohn and Grauer, *Monatsh.*, 1913, **34**, 175) give m. p. 161—162°.

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