p-*Menthane-2 : 3-diols. Part IV.* The Reaction of Mercuric Acetate with (±)-Menthone and (±)-*iso*Menthone.*

By P. R. Jefferies, A. Killen Macbeth, and B. Milligan.

[Reprint Order No. 4699.]

Treatment of either (±)-menthone or (±)-*iso*menthone with mercuric acetate in acetic acid yields predominantly (±)-2-acetoxymenthone in addition to a small amount of (possibly) a (±)-4-acetoxymenthone. Reduction of this mixture of acetoxymenthones by sodium in ethanol yields (±)-*trans*-2-hydroxymenthol and possibly a (±)-*p*-menthane-3 : 4-diol; catalytic hydrogenation of the mixed hydroxymenthones yields (±)-*cis*- and (±)-*trans*-2-hydroxy*neo*menthol, and an unidentified *p*-menthane-diol.

By treatment of (—)-menthone with mercuric acetate in acetic acid, Treibs and Bast (*Annalen*, 1948, **561**, 165) prepared an optically active 2-acetoxymenthone which on hydrolysis gave a practically inactive 2-hydroxymenthone. Reduction with sodium in ethanol yielded a crystalline diol.

It was hoped that reduction of (±)-2-acetoxymenthone and (±)-2-acetoxy*iso*menthone by sodium in ethanol and catalytic hydrogenation of the corresponding hydroxy-compounds would provide another route to the (±)-*p*-menthane-2 : 3-diols, thus affording additional evidence concerning the configurations assigned by Macbeth and Robertson (*J.*, 1953, 895; Parts II and III *) to the eight epimeric (±)-*p*-menthane-2 : 3-diols.

We have repeated the reduction of acetoxy-(—)-menthone (Treibs and Bast, *loc. cit.*) and purified the resultant diol *via* its di-*p*-nitrobenzoate, m. p. 117°. Both the diol and its diester were optically inactive, racemisation apparently taking place during the sodium–ethanol reduction. Thus it is not possible to obtain the active *p*-menthane-2 : 3-diols by reactions analogous to those described above.

When (±)-menthone was added to a boiling solution of mercuric acetate in acetic acid, the characteristic crystalline mercury complex separated immediately; it was decomposed at 130° with the formation of metallic mercury and (±)-2-acetoxymenthone, which was characterised as the 2 : 4-dinitrophenylhydrazone. An identical reaction with (±)-*iso*menthone gave a product similar in physical properties to (±)-2-acetoxymenthone and forming the same 2 : 4-dinitrophenylhydrazone. Chemical reduction and catalytic hydrogenation of both products yielded menthols and *p*-menthane-2 : 3-diols corresponding to the menthone, as opposed to the *iso*menthone, series. Thus it appears that an equilibrium mixture consisting predominantly of (±)-2-acetoxymenthone is obtained from the Treibs–Bast reaction with both (±)-menthone and (±)-*iso*menthone. The isolation in small amount of what is possibly a (±)-*p*-menthane-3 : 4-diol leads us to believe that the acetoxy-group is also introduced, to a very limited extent, in the 4-position, contrary to the statement by Treibs and Bast (*loc. cit.*) that tertiary attack does not occur.

Inversion appears to take place during the mercuric acetate reaction, and might either precede the formation of the crystalline mercury complex or occur after its decomposition. Menthones are converted into their addition complexes in about 3 minutes, and measurements of rotation of the active menthones (see Table) show that inappreciable inversion of menthone and *iso*menthone occurs within this period. The inversion, catalysed by acetic acid, therefore probably occurs between 2-acetoxymenthone and 2-acetoxy*iso*menthone, and greatly favours the former.

Time of reflux with acetic acid (min.)	(—)-Menthone, α_D^{15} −25·7°		(+)-*iso*Menthone, α_D^{15} +82·1°	
	α_D^{15}	Composition, menthone–*iso*menthone	α_D^{15}	Composition, menthone–*iso*menthone
3 Min.	−22·7°	97·2%; 2·8%	+74·9°	6·7%; 93·3%
2 Hr.	+11·2°	65·8%; 34·2%	+17·6°	59·9%; 40·1%

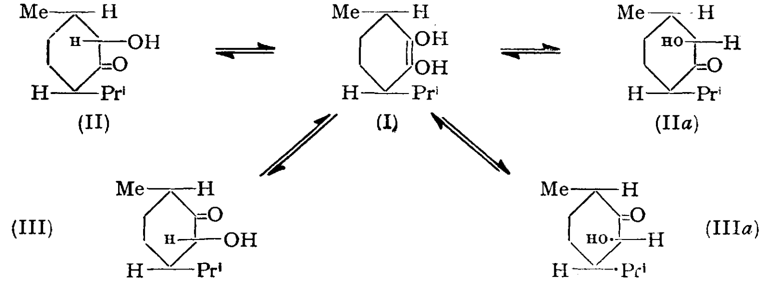
Hydrolysis of the acetoxymenthone mixtures yielded the corresponding acyloins as

---

* Parts II and III, *J.*, 1953, 3512; 1954, 701.

colourless oils of wide boiling range. Their heterogeneity may be explained by assuming inversion *via* the enolic form (I) during hydrolysis, resulting in a mixture of 2-hydroxymenthones (II ⟷ II*a*), and possibly 3-hydroxycarvomenthones (III ⟷ III*a*). The existence of (I) was shown by the isolation of its di-*p*-nitrobenzoate.

The Treibs–Bast reaction has been applied to a number of terpene ketones but the configuration of the acetoxylated products does not appear to have been established. Introduction of the acetoxy-group in the *trans*-relation to the methyl group is now shown in the case of acetoxy-menthone and -*iso*menthone, by reduction with sodium in ethanol, the main product being (±)-*trans*-2-hydroxymenthol. Hydrolysis of the acetoxy-group probably occurs simultaneously with reduction of the carbonyl group, and thus inversion at the 2-position is inhibited.



Distillation of the sodium–ethanol reduction product of the acetoxy-(±)-menthones yielded a mobile fore-run, and a very viscid oil as the main fraction, whence (±)-*trans*-2-hydroxymenthol was isolated. Chromatography of an ester prepared from the remainder of the main fraction yielded two di-*p*-nitrobenzoates of this diol and, in very small amount, of the supposed (±)-*p*-menthane-3 : 4-diol (glycol C) obtained from the peracetic acid oxidation of (±)-*p*-menth-3-ene (Macbeth and Robertson, *loc. cit.*). (±)-Menthol was isolated from the fore-run as its *p*-nitrobenzoate.

Hydrogenation of the inversion mixture of hydroxymenthones, derived from either (±)-menthone or (±)-*iso*menthone, at high temperature and pressure in presence of copper chromite, yielded, in addition to an unidentified hydrocarbon, (±)-*cis*-2-hydroxy*neo*menthol isolated as its di-*p*-nitrobenzoate by chromatography. This diol has been prepared by both Ponndorf and lithium aluminium hydride reduction of diosphenol (Part III), and the unidentified hydrocarbon is probably *trans*-*p*-menthane, produced by hydrogenolysis.

Raney nickel (activity W 7) has also been used as a catalyst for hydrogenations carried out at room temperature and pressure. The products formed were separated by chromatography of their di-*p*-nitrobenzoates into esters of a diol, $C_{10}H_{20}O_2$, of (±)-*cis*- and of (±)-*trans*-2-hydroxy*neo*menthol. A mixed di-*p*-nitrobenzoate fraction yielded the first of these esters as well as an unidentified compound. These unknown esters, which may be derived from the (±)-*p*-menthane-3 : 4-diols, are being further examined.

Hydrogenation with platinum oxide at room temperature was unsatisfactory.

EXPERIMENTAL

Unless otherwise stated, light petroleum had b. p. 60—70°, and B.D.H. alumina for chromatographic absorption was used.

Acetoxylation of (±)-*Menthone*.—(±)-Menthone (38 g.) was added to a solution obtained by dissolving mercuric oxide (53 g.) in boiling glacial acetic acid (50 ml.). Acetic acid was removed by distillation until the temperature of the mixture rose to 130°, boiling under reflux being then resumed for 2 hr. After decantation from the liberated mercury, the mixture was neutralised with sodium hydrogen carbonate solution and extracted with ether. Distillation gave a fore-fraction of menthone (10·9 g.) and a mixture of acetoxymenthones (20·8 g., 62% based on menthone used), b. p. 120·5—122·5°/6 mm., d_4^{20} 1·0204, n_D^{20} 1·4625, $[R_L]_D$ 57·2 (calc. 57·2) (Found : C, 68·4; H, 9·5. Calc. for $C_{12}H_{20}O_3$: C, 67·9; H, 9·5%).

Acetoxylation of (±)-iso*Menthone*.—(±)-*iso*Menthone (38 g.), treated as above, gave unchanged *iso*menthone (13·7 g.) and a mixture of acetoxymenthones (21·0 g., 71% based on *iso*menthone used), b. p. 102—104°/2 mm., d_4^{20} 1·0204, n_D^{20} 1·4615, $[R_L]_D$ 57·0 (calc. 57·2) (Found : C, 68·2; H, 9·4%).

2 : 4-*Dinitrophenylhydrazones* prepared from each of the above samples crystallised from light petroleum–benzene as yellow needles, m. p. 190° (Found : C, 55·0; H, 6·0; N, 13·6. $C_{18}H_{24}O_6N_4$ requires C, 55·1; H, 6·1; N, 14·0%).

Hydrolysis of the Inversion Mixture of Acetoxymenthones.—The above mixture (20 g.) was refluxed with a solution of potassium hydroxide (20 g.) in water (200 ml.) for 0·3 hr. The product was thrice extracted with ether and on distillation gave mixed (±)-2-hydroxymenthones (14·0 g., 87%), b. p. 102—114°/3·0 mm. Esterification of this (2·0 g.) with a 200% excess of *p*-nitrobenzoyl chloride in boiling pyridine for 2 hr. gave an oil which was chromatographed in petroleum–benzene (1 : 1); elution with the same solvent (500 ml.) gave the crude ester (1·0 g.) which after three crystallisations from light petroleum formed needles of the *di-*p*-nitrobenzoate* of the diol (I), having m. p. 147° (Found : C, 62·0; H, 4·9; N, 6·0. $C_{24}H_{24}O_8N_2$ requires C, 61·55; H, 5·1; N, 6·0%).

Sodium–Ethanol Reduction of the Inversion Mixture of (±)-2-Acetoxymenthones.—Metallic sodium (15 g.) was added in small portions to a solution of acetoxymenthones (12·8 g.) in boiling ethanol (140 ml.). More ethanol (80 ml.) was added during the reduction to maintain a homogeneous solution. Water (100 ml.) was then added, and the ethanol removed by fractional distillation. The aqueous residue was thrice extracted with light petroleum, and the combined extracts were washed with water and dried ($MgSO_4$). Distillation gave a mobile fore-run (2·4 g.), b. p. 70—96°/5 mm., and a viscid fraction (4·8 g.), b. p. 96—100°/5 mm. Crystals (0·2 g.) were deposited from the latter fraction, and were drained on a tile and crystallised twice from light petroleum (b. p. <40°), forming colourless prisms, m. p. 90·5°, undepressed on admixture with an authentic sample of (±)-*trans*-2-hydroxymenthol.

The non-crystalline portion (4·6 g.) of the high-boiling fraction gave a crude ester (11·7 g., 93%) on esterification with *p*-nitrobenzoyl chloride in pyridine. The ester was chromatographed in light petroleum–benzene (20 : 1) on alumina (200 g.). Elution with light petroleum–benzene (5 : 1) gave a di-*p*-nitrobenzoate (3·0 g.) as pale yellow needles, m. p. 117° (after two crystallisations from methanol). The m. p. was undepressed on admixture with an authentic sample of the di-*p*-nitrobenzoate of (±)-*trans*-2-hydroxymenthol. Hydrolysis with methanolic potassium hydroxide gave (±)-*trans*-2-hydroxymenthol, m. p. 90·5° after one crystallisation from light petroleum (b. p. <40°). Elution of the chromatogram with benzene gave pale yellow prisms (75 mg.), m. p. 137° after five crystallisations from methanol. The m. p. was undepressed on admixture with a sample of di-*p*-nitrobenzoate of a diol derived from (±)-*p*-menth-3-ene by peracetic acid hydroxylation.

Esterification of the mobile fraction (2·4 g.) of the distillate with *p*-nitrobenzoyl chloride in pyridine yielded a crude ester (3·5 g.) from which (±)-menthyl *p*-nitrobenzoate, m. p. 91° (0·5 g.), was obtained after crystallisation from methanol.

Hydrogenation of the Inversion Mixture of (±)-Hydroxymenthones.—(*a*) The above inversion mixture (5 g.) was hydrogenated at an initial pressure of 1000 lb./in.² and 200—230° for 6 hr. with copper chromite (0·5 g.; *Org. Synth.*, **19**, 31). Ether (50 ml.) was added, and the catalyst removed by filtration. The ethereal solution was dried ($MgSO_4$) and evaporated, and the product (4·3 g., 86%) esterified with *p*-nitrobenzoyl chloride in pyridine. After steam-distillation to remove hydrocarbon, the crude ester (5·0 g., 43%) was chromatographed in light petroleum–benzene (5 : 1) and on alumina (100 g.). Elution with light petroleum–benzene mixtures afforded oils, but benzene eluted a crystalline ester (0·3 g.) which, crystallised three times from methanol, formed pale yellow prisms (0·15 g.), m. p. 166° alone or mixed with the di-*p*-nitrobenzoate (m. p. 166—167°) of (±)-*cis*-2-hydroxy*neo*menthol.

(*b*) A solution of the inversion mixture of hydroxymenthones (5 g.) in ethanol (100 ml.) was hydrogenated at room temperature and pressure with Raney nickel catalyst (activity W 7; *Org. Synth.*, **29**, 28). Uptake was 90% after 4·5 hr. After removal of the catalyst, water (60 ml.) was added, and the ethanol removed by fractional distillation. The product was continuously extracted overnight with ether and isolated as a yellow oil (4·1 g., 82%) which was esterified with *p*-nitrobenzoyl chloride in pyridine. The crude ester (7·8 g., 68%), a viscid yellow oil, was chromatographed in light petroleum–benzene (10 : 1) on alumina (150 g.). The esters obtained, in order of elution, were (i) with light petroleum–benzene (10 : 1) a *di-*p*-nitrobenzoate* of a diol, $C_{10}H_{20}O_2$, which crystallised from methanol as pale yellow prisms (200 mg.), m. p. 155° (Found: C, 61·4; H, 5·7. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%); (ii) with light petroleum–benzene (4 : 1) a di-*p*-nitrobenzoate of a diol, $C_{10}H_{20}O_2$, which crystallised as short pale yellow prisms (200 mg.), m. p. 122° (Found : C, 61·3; H, 5·5; N, 6·0%). Further crystallisation from light petroleum gave a mixture of pale yellow prisms and long white needles which were separated by hand-picking. The prisms (30 mg.) had constant m. p. (155°) after four crystallisations from light petroleum; the m. p. was undepressed on admixture with a sample of the di-*p*-nitrobenzoate (i), m. p. 155°. The white needles (15 mg.) had m. p. 105° after four crystallisations from light petroleum (Found : C, 62·4; H, 5·7%); (iii) with benzene a di-*p*-nitrobenzoate, which also crystallised from methanol as pale yellow prisms (100 mg.), m. p. 165°, undepressed on admixture with an authentic sample of the di-*p*-nitrobenzoate of (±)-*cis*-2-hydroxy*neo*menthol; (iv) with benzene–ether (100 : 1) pale yellow plates (50 mg.), m. p. 166° after three crystallisations from methanol. The m. p. was undepressed on admixture with an authentic sample of the di-*p*-nitrobenzoate of (±)-*trans*-2-hydroxy*neo*menthol.

(*c*) The inversion mixture of (±)-hydroxymenthones (5 g.) in glacial acetic acid (30 ml.) containing concentrated hydrochloric acid (2 drops) was hydrogenated with platinum oxide (0·5 g.) at room temperature and pressure. Hydrogenation ceased after 3 hr., being 50% complete. After filtration, the mixture was basified with sodium hydroxide and boiled under reflux for 30 min. to hydrolyse any acetates produced during the hydrogenation. The mixture was continuously extracted with ether, and the product (4·8 g., 96%) thus isolated was esterified with *p*-nitrobenzoyl chloride in pyridine. The crude ester (7·6 g., 57%) was chromatographed in light petroleum–benzene (4 : 1) on alumina (150 g.); elution with the same solvent yielded a crystalline ester (100 mg.), m. p. 122° after four crystallisations from methanol. There was no depression of m. p. on admixture with a sample of the mixed crystals, m. p. 122°, obtained in the previous hydrogenation. Other fractions from the chromatogram could not be induced to crystallise.

We are indebted to Dr. W. G. P. Robertson for helpful suggestions, and thank Messrs. Plaimar Ltd. for a gift of menthol.

JOHNSON CHEMICAL LABORATORIES
THE UNIVERSITY OF ADELAIDE, AUSTRALIA.

[*Received, October 5th,* 1953.]