185. *Stereochemistry of Metabolic Diols from Naphthalene and Anthracene.*

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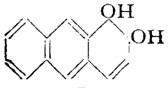
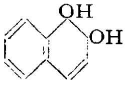
Resolution of *trans*-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-diol, through the *diesters* of *lævo*-menthoxyacetic acid, affords the *dextro-trans*- and *lævo-trans*-diols. The former of these is identical with the product obtained by hydrogenating the *lævo*-1 : 2-dihydronaphthalene-1 : 2-diol which was isolated by Young (*Biochem. J.*, 1947, **41**, 417) from the urine of rats dosed with naphthalene and which, accordingly, has the *trans*-structure.

(±)-*cis*- and (±)-*trans*-1 : 2 : 3 : 4-Tetrahydroanthracene-1 : 2-diols have been synthesised and characterised. The properties of the (±)-*trans*-diol correspond with those described by Boyland and Levi (*ibid.*, 1935, **29**, 2679; cf. Booth and Boyland, *ibid.*, 1949, **44**, 361) for the hydrogenation product of the (±)-metabolite which is formed when anthracene is fed to rats or rabbits.

Boyland and Levi (*Biochem. J.*, 1935, **29**, 2679) showed that anthracene, fed to rats and rabbits, is converted in part into lævorotatory and inactive forms, respectively, of the diol (I). Young (*loc. cit.*) isolated a lævorotatory form of the diol (II) from the urine of rats dosed with naphthalene. According to Booth and Boyland (*ibid.*, 1949, **44**, 361), the respective diols (I) and (II) are obtained in each case as a mixture of an optically active and an inactive form, the dextrorotatory predominating in the metabolites from rabbits, the lævorotatory in those from rats. Theoretically the diols can exist in *cis*- and *trans*-modifications and to each modification there will be *dextro*-, *lævo*-, and inactive forms. It is of interest in relation to the mechanism of biological oxidation to determine the stereochemical form(s) of these metabolites, and when the present investigation was begun the only guide was provided by the work of Boyland and

Shoppee (*J.*, 1947, 801), who inferred a *cis*-configuration for the metabolites (I) from the rapidity with which these diols were oxidised by lead tetra-acetate. Recently, however, in view of the negative response to Criegee's reagent for *cis*-diols (*viz.*, triacetylosmic acid, cf. Criegee, Marchand, and Wannowius, *Annalen*, 1942, **550**, 99), Booth and Boyland (*loc. cit.*) have preferred the *trans*-configuration for the anthracene metabolites and have supported the same configuration for the naphthalene metabolites by extensive evidence which in part anticipates our own.


(I.)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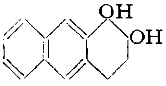
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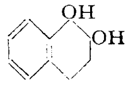
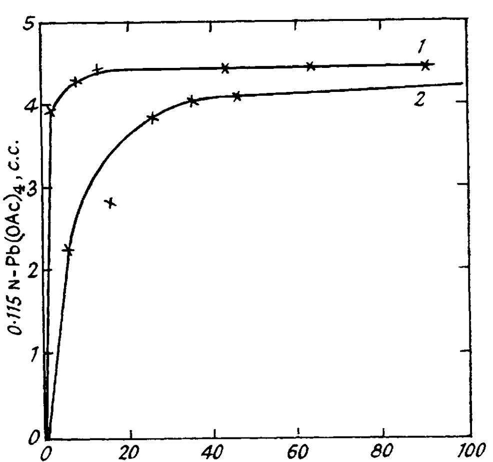

(IV.)

The metabolites (I) and (II) are readily hydrogenated to the tetrahydro-diols (III) and (IV) respectively (Boyland and Levi, *loc. cit.*; Young, *loc. cit.*), and it was the aim of the present investigation to secure for reference and for optical resolution the *cis*- and *trans*-forms of these (±)-tetrahydro-diols. Straus and Rohrbacher (*Ber.*, 1921, **54**, 40) obtained the (±)-diol (IV) in *cis*- and *trans*-forms respectively by oxidation of 1 : 2-dihydronaphthalene with potassium permanganate and by stepwise hydrolysis of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydronaphthalene. These are satisfactory methods of preparation, and confirmation of the configurations assigned follows from (*a*) the results of applying to 1 : 2-dihydronaphthalene well-authenticated modern methods for *cis*- or *trans*-hydroxylation of a double bond (cf. Experimental), (*b*) tests with potassium triacetylosmate (cf. Experimental), and (*c*) the relative rates of oxidation by lead tetra-acetate determined by Criegee, Kraft, and Rank (*Annalen*, 1933, **507**, 159).

Oxidation of 1/4000 *mol. of* (1) cis- *and* (2) trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene with lead tetra-acetate.*



Resolution of *trans*-1 : 2 : 3 : 4-tetrahydronaphthalene-1 : 2-diol was effected through *diesters* produced by acylation with *lævo*-menthoxyacetyl chloride (cf. Wilson and Read, *J.*, 1935, 1269). The esters were separated by fractional crystallisation from light petroleum and on hydrolysis afforded the dextro-trans- and lævo-trans-*diols* (IV). The former diol was found to be identical in m. p. and specific rotation with a dextrorotatory specimen of the hydrogenated metabolite, which was kindly supplied by Professor L. Young: the m. p.s of the diacetates were also identical and were unaffected by admixture of the two samples. Attempts to resolve the *cis*-diol (IV) by the same means or through esters of *lævo*-menthylglycine (cf. Clark and Read, *J.*, 1934, 1775) were unsuccessful because of failure to obtain the esters in crystalline form.

For the synthesis of the *cis*- and *trans*-1 : 2 : 3 : 4-tetrahydroanthracene-1 : 2-diols (III), 2-anthrol was hydrogenated under pressure in the presence of copper chromite to an easily separable mixture of 9 : 10-dihydro- and 1 : 2 : 3 : 4-tetrahydro-2-anthrol. Von Braun and Bayer (*Annalen*, 1929, **472**, 105) reported the dehydration of the latter compound by distillation of the phenylurethane, but a more satisfactory method consists in heating the tetrahydroanthrol with fused potassium hydroxide. 1 : 2-Dihydroanthracene, so obtained, was converted, by treatment with osmium tetroxide in benzene–pyridine and subsequent hydrolysis of the ester complex, into the *cis*-diol (III), and the corresponding *trans*-diol was prepared (*a*) by hydrolysis of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydroanthracene *via* 1(or 2)-*bromo*-2(or 1)-*hydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene*, (*b*) together with some *cis*-diol, by oxidation of 1 : 2-dihydroanthracene with lead tetra-acetate.

The configuration assigned to these two diols is implicit in their respective methods of preparation and is confirmed by the fact that the isomer designated *cis*, alone of the pair, induces a colour change in the test with potassium triacetylosmate. Further confirmation is afforded by the relative rates of oxidation by lead tetra-acetate (see Fig.), the *cis*-isomer showing the expected higher rate. It will be observed that in each case oxidation of the diol corresponds to the consumption of one molar proportion of lead tetra-acetate, and in this respect there is correspondence with the data recorded by Boyland and Shoppee (*loc. cit.*) for oxidation of the *lævo*- and inactive metabolites (I). These authors are consequently in error in interpreting their results as showing the consumption of two moles of lead tetra-acetate with concurrent (or consecutive) oxidation of the diol grouping and of the *meso*-positions in (I). It is in any case clear that analogy between the *meso*-positions in anthracene and the corresponding positions in (I) is unsound.

Attempts to resolve the *cis*- and *trans*-diols (III) were unsuccessful, but the m. p.s of the synthesised (±)-*trans*-isomer and of the derived diacetate closely correspond with those reported by Boyland and Levi (*loc. cit.*) for the hydrogenated (±)-metabolite and its diacetate.

EXPERIMENTAL.

(±)-cis-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (IV).—(i) 1 : 2-Dihydronaphthalene (1 g.) (Bamberger and Lodter, *Ber.*, 1890, **23**, 208) was added to a solution of osmium tetroxide (2 g.) in dry ether (40 c.c.). After 7 days the solution was evaporated to dryness and the residue was refluxed for 3 hours with a solution of sodium sulphite heptahydrate (8 g.) in water (40 c.c.) and ethanol (20 c.c.). After filtration (hot) and removal of most of the alcohol, (±)-*cis*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (IV) was recovered in chloroform; it had m. p. 101° (from benzene) (Straus and Rohrbacher, *loc. cit.*, give m. p. 100—101°).

(ii) To 3·25 c.c. of a dried solution of hydrogen peroxide (5 c.c.; 90% by weight) in *tert.*-butyl alcohol (50 c.c.) were added, at 0°, 1 : 2-dihydronaphthalene (1 g.) and a solution of osmium tetroxide (0·1 g.) in *tert.*-butyl alcohol (10 c.c.). After 8 days at 0° the solution was concentrated under reduced pressure and the tarry residue was extracted with boiling water. The brown oil obtained by concentration of the aqueous extracts afforded, on recovery from benzene, the (±)-*cis*-diol (IV), m. p. 99—100°.

(±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—To a dried solution of hydrogen peroxide (0·5 g.) in *tert.*-butyl alcohol (2 c.c.) were added at 0° 1 : 2-dihydronaphthalene (2 g.) and a solution of selenium dioxide (0·06 g.) in *tert.*-butyl alcohol. After 8 days at 0° concentration afforded (±)-*trans*-diol (IV), m. p. 112° (from benzene) (Straus and Rohrbacher, *loc. cit.*, give m. p. 112—113°).

Criegee, Marchand, and Wannowius (*loc. cit.*, 1942) reported *trans*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene (IV) to be exceptional (like *trans-cyclo*hexane-1 : 2-diol) in forming a diester with potassium triacetylosmate. Booth and Boyland (*loc. cit.*), without comment on this point, state that the reagent provides the usual distinction between these *cis*- and *trans*-diols. Re-examination showed that there is a marked difference in behaviour between the two forms: the *cis*-form gave immediately a rapid change from blue through green and red to brown, whereas with the *trans*-form no immediate change was perceptible, but after 30 minutes the blue had been replaced by a purple colour.

Resolution of (±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Attempts were first directed to the formation of a monoester (cf. Wilson and Read, *J.*, 1935, 1269) by the addition of freshly distilled (—)-menthoxyacetyl chloride (23·4 g., 1·4 mols.) (*Org. Synth.*, **23**, 52) to a cooled solution of the (±)-*trans*-diol (IV) (12·6 g., 1 mol.) in pyridine (100 c.c.). After 16 hours at room temperature the solution was poured into water, and an ethereal extract, thoroughly washed in turn with dilute hydrochloric acid, dilute sodium hydroxide, and water, and dried (Na_2SO_4), afforded a viscous oil which partly solidified when rubbed with light petroleum (b. p. 60—80°). This solid (24·5 g.), however, was found to contain unchanged diol and accordingly was treated as above with a further quantity of (—)-menthoxyacetyl chloride (29·9 g.; 1·8 mols.). The resulting solid (33 g.) was separated by fractional crystallisation from light petroleum (b. p. 60—80°) into a less soluble *diester* (A), m. p. 116—117°, $[\alpha]_D^{21}$ —21° (*c*, 1·0 in chloroform) (Found: C, 73·6; H, 9·2. $C_{34}H_{52}O_6$ requires C, 73·4; H, 9·3%), and a more soluble *diester* (B), m. p. 101—102°, $[\alpha]_D^{21}$ —170° (*c*, 1·0 in chloroform) (Found: C, 73·4; H, 9·3%). The nature of these compounds as diesters (not conclusively shown by analysis—calc. for $C_{22}H_{32}O_4$: C, 73·3; H, 8·9%) was supported by the observed consumption of 8·41 c.c. of 0·4095N-methanolic potassium hydroxide ($\bumpeq$ 2 moles) in hydrolysis of 0·9679 g. of ester (A). The diester (A) (8 g.) was heated under reflux for 3 hours with 2·5% methanolic potassium hydroxide (90 c.c.). Removal of the alcohol and recovery with ether afforded (—)-trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, m. p. 114—115° (from benzene), $[\alpha]_D^{21}$ —134° (*c*, 1·0 in chloroform) (Found: C, 73·4; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%). When a solution of the diol (213 mg.) in pyridine (4 c.c.) was treated at 0° with acetic anhydride (1 c.c.) and, after 12 hours, poured into ice and dilute sulphuric acid, the corresponding *diacetate*, m. p. 66—67° [from light petroleum (b. p. >120°)], was obtained: $[\alpha]_D^{21}$ +126° (*c*, 1·0 in chloroform) (Found: C, 67·8; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·4%). Similar treatment of the diester (B) afforded (+)-trans-1 : 2-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, m. p. 114—115° (from benzene), $[\alpha]_D^{21}$ +132° (*c*, 1·0 in chloroform), $[\alpha]_D^{21}$ +64° (*c*, 0·5 in ethanol), $[\alpha]_{5461}^{21}$ +44° (*c*, 0·5 in ethanol) (Found: C, 73·2; H, 7·1. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%), and its *diacetate*, m. p. 66—67° [from light petroleum (b. p. >120°)], $[\alpha]_D^{21}$ —125° (*c*, 1·0 in chloroform) (Found: C, 67·7; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·4%).

Young (*loc. cit.*) records for the (+)-hydrogenated metabolite (II) m. p. 115°, $[\alpha]_D^{23}$ +62° (*c*, 0·5 in ethanol), and a specimen kindly supplied by Professor Young did not depress the m. p. of (+)-*trans*-1 : 2-dihydroxy-1 : 2 : 3 : 4-tetrahydronaphthalene and afforded a diacetate identical in micro-m. p. and mixed micro-m. p. with (—)-*trans*-1 : 2-diacetoxy-1 : 2 : 3 : 4-tetrahydronaphthalene.

1 : 2 : 3 : 4-*Tetrahydro-2-anthrol*.—2-Anthrol (10 g.) (Lagodzinski, *Annalen*, 1905, **342**, 68) in ethanol (100 c.c.) was hydrogenated in the presence of copper chromite (1 g.) at 200°/122 atm. for 7 hours. The crystalline solid, recovered from the filtered solution, was dissolved in ether and freed from 9 : 10-dihydro-

2-anthrol (m. p. 129°; cf. von Braun and Bayer, *loc. cit.*) by shaking the solution with 20% sodium hydroxide. 1 : 2 : 3 : 4-Tetrahydro-2-anthrol, recovered from the washed ethereal solution, had m. p. 142° (from ethanol) (Found : C, 85·1; H, 6·8 Calc. for $C_{14}H_{14}O$: C, 84·9; H, 7·1%) (von Braun and Bayer, *loc. cit.*, give m p. 148°).

1 : 2-*Dihydroanthracene.*—1 : 2 : 3 : 4-Tetrahydro-2-anthrol (4 g.) was heated for 1 hour with freshly fused potassium hydroxide (4 g.) at 180—210°. The product, recovered from ether, was sublimed at 100—120°/2 mm., and had m. p. 147—148° (from ethanol) (von Braun and Bayer, *loc. cit.*, record m. p. 150°) (Found : C, 93·4; H, 6·7. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%).

(±)-cis-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene* (III).—A solution of 1 : 2-dihydroanthracene (1·42 g.) in dry ether (10 c.c.) was added to a solution of osmium tetroxide (2 g.) in ether (100 c.c.) and pyridine (1·4 c.c.). After 16 hours the precipitate was collected and heated under reflux for 1 hour with a solution of sodium sulphite heptahydrate (8·1 g.) in water (40 c.c.) and ethanol (20 c.c.). After filtration (hot) and removal of most of the ethanol, the *diol* crystallised and had m. p. 133—135° (from benzene) (Found : C, 78·7; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). When a solution of the diol (125 mg.) in pyridine (2 c.c.) was treated at 0° with acetic anhydride (0·5 c.c.) and, after 12 hours at room temperature, was poured into iced water, the corresponding *diacetate*, m. p. 122° [from light petroleum (b. p. 60—80°)], was obtained (Found : C, 72·1; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%).

(±)-trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene* (III).—(i) To a solution of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydroanthracene (2 g.) [m. p. 105—106° (from light petroleum, b. p. 60—80°); von Braun and Bayer, *loc. cit.*, record m. p. 102°] in acetone–water (4 : 1), kept at 50—60°, magnesium carbonate (1 g.) was added during 2·5 hours. The brown oil, obtained after filtration (hot) and removal of acetone, was extracted and dried in ether affording, on concentration, 1(or 2)-*bromo*-2(or 1)-*hydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene*, m. p. 102—103° [from light petroleum (b. p. 60—80°)] (Found : C, 60·6; H, 4·8. $C_{14}H_{13}OBr$ requires C, 60·6; H, 4·7%). This compound (0·5 g.) was heated under reflux for 1 hour with potassium hydroxide (0·15 g.) in water (10 c.c.). The *diol* recovered from ether had m. p. 162—163° (from benzene) (Found : C, 78·4; H, 6·8. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

(ii) 1 : 2-Dihydroanthracene (10 g.) was added to a solution of lead tetra-acetate (24 g.) in acetic acid (400 c.c.) and the mixture was heated at 80—90° for 1 hour. The cooled solution was poured into water, from which extraction with ether and recovery from the washed and dried ethereal extract gave an oil. This was hydrolysed by being heated under reflux (15 minutes) with potassium hydroxide (33 g.) in ethanol (500 c.c.). Subsequent dilution with water, removal of most of the ethanol, and recovery in ether afforded a mixture of *cis*- and *trans*-diols (III), which was separated by fractional crystallisation from benzene, the *trans*-form being the less soluble.

When a solution of the *trans*-diol (III) (118 mg.) in pyridine (2 c.c.) was treated with acetic anhydride (0·6 c.c.) and, after 12 hours at room temperature, was poured into iced water, the corresponding *diacetate*, m. p. 85—87° [from light petroleum (b. p. 60—80°)], was obtained (Found : C, 72·5; H, 6·2. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). Hydrolysis of this diacetate regenerated the *trans*-diol, m. p. 162° [Boyland and Levi, *loc. cit.*, record m. p. 162° for the (±)-hydrogenated metabolite (II) and m. p. 84° for its diacetate].

Rate of Oxidation of cis- *and* trans-1 : 2-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydroanthracene with Lead Tetra-acetate.*—To a solution of the diol (53 mg.) in acetic acid (10 c.c. distilled over chromium trioxide) kept at 18—19° by immersion in a thermostat, were rapidly added 10 c.c. of a standard solution of lead tetra-acetate, the time of addition being noted. At intervals, samples (1 c.c.) were withdrawn and run into a potassium iodide–sodium acetate buffer solution, and the liberated iodine was titrated against standard sodium thiosulphate. The results are given in the figure.

The *cis*-diol (III) produced an immediate change from blue to green; the *trans*-diol caused no change in the colour of potassium triacetylosmate.

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance (to W. F. W.) and to Professor Leslie Young for a sample of his reduced metabolite from naphthalene. Micro-analyses were carried out by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, December 28th,* 1949.]