522. *Synthetic Studies in the Diterpene Series. Part I. Synthesis of Some Degradation Products of Methyl Totaryl Ether.**

By D. NASIPURI and A. C. CHAUDHURI.

The phenanthrene derivatives (II), (III), and (IV) are synthesised. They are identical with those obtained by Short and Wang [1] as the dehydrogenation products of methyl totaryl ether, substantiating the structure of the latter.

THE structure of totarol [1] (I) was elucidated by Short and his co-workers,[2,3] mainly by dehydrogenation of totarol and its derivatives and has been confirmed by total synthesis.[4] By milder dehydrogenation, Short and Wang [2] obtained three products (II, III, and IV) from methyl totaryl ether, none of which, however, was synthesised. Since the structure (I) does not conform to the isoprene rule, it appeared desirable to synthesise these products and the following is an account of the synthetical operations.

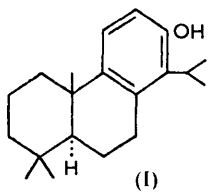
3-Methoxy-2-*iso*propylbenzonitrile [6] (VI; R = CN) was converted into the amide (VI; R = $CO{\cdot}NH_2$) by 30% hydrogen peroxide in alkali,[7] then into the iodo-compound (VI; R = I) by Hofmann degradation [8] followed by diazotisation and into the alcohol (VI; R = $CH_2{\cdot}CH_2{\cdot}OH$) by the action of ethylene oxide on the Grignard reagent of the iodo-compound in an overall yield of 15—16%. The derived bromide (VI; R = $CH_2{\cdot}CH_2Br$) was condensed with ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate (V) in the usual way, to give the product (VII) in satisfactory yield. The latter on cyclodehydration [5] and subsequent hydrolysis furnished γ-(2-carboxy-3 : 4-dihydro-6-methoxy-5-*iso*propyl-1-naphthyl)butyric acid (VIII) in about 60% yield, the dimethyl ester of which on Dieckmann cyclisation and hydrolysis gave 1 : 2 : 3 : 4 : 9 : 10-hexahydro-7-methoxy-1-oxo-8-*iso*propylphenanthrene (IX). The ketone was condensed with methylmagnesium iodide, and the resultant alcohol on simultaneous dehydration and dehydrogenation by 30% palladium–charcoal [9] afforded 2-methoxy-8-methyl-1-*iso*propylphenanthrene (IV) in good yield. The properties of this compound and the corresponding phenol and their

* Part of this work was published in *Science and Culture*, 1957, **23**, 319.

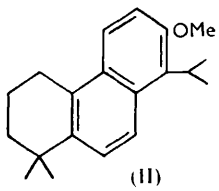
[1] Easterfield and McDowell, *Trans. New Zealand Inst.*, 1911, **43**, 55; 1915, **48**, 578.
[2] Short and Wang, *J.*, 1951, 2979.
[3] Short and Stromberg, *J.*, 1937, 516; Short and Wang, *J.*, 1950, 991.
[4] Barltrop and Rogers, *Chem. and Ind.*, 1957, 397.
[5] Bardhan and Nasipuri, *J.*, 1956, 350.
[6] (*a*) Richtzenhain and Nippus, *Ber.*, 1944, **77**, 566; (*b*) Fuson, Gaertner, and Chadwick, *J. Org. Chem.*, 1948, **13**, 489.
[7] *Org. Synth.*, Coll. Vol. II, 1st edn., p. 586.
[8] Wallis and Lane, *Org. Reactions*, Vol. III, p. 267.
[9] Linstead and Thomas, *J.*, 1940, 1127.

derivatives corresponded with those recorded by Short and Wang [1] for their compound C from methyl totaryl ether.

As a model for the synthesis of the other two compounds (II and III), we treated methyl γ-1-naphthylbutyrate with an excess of methylmagnesium iodide. Heating the resultant alcohol (XI; R = R′ = H) with polyphosphoric acid [10] gave an excellent yield of a liquid hydrocarbon, 1 : 2 : 3 : 4-tetrahydro-1 : 1-dimethylphenanthrene, which was characterised



(I)



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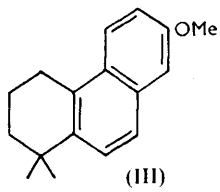

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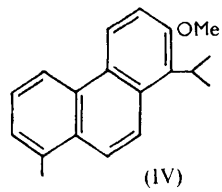
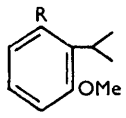


(IV)

$EtO_2C\cdot[CH_2]_3\cdot CO\cdot CHAc\cdot CO_2Et$
(V)



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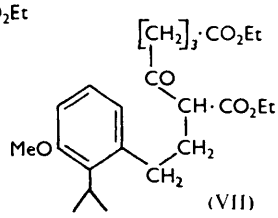
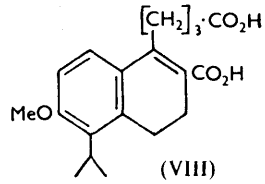
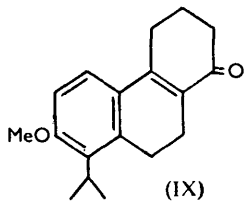


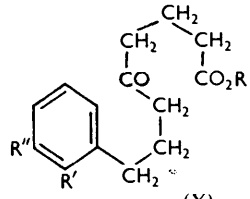
(VII)



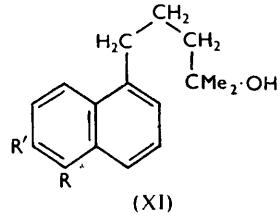
(VIII)



(IX)



(X)



(XI)

by dehydrogenation to 1-methylphenanthrene. This route was next extended to the synthesis of 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1 : 1-dimethylphenanthrene (III). Methyl 8-*m*-methoxyphenyl-5-oxo-octanoate [11] (X; R = Me, R′ = H, and R″ = OMe) was conveniently obtained by alkylation of ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate with *m*-methoxyphenethyl bromide followed by hydrolysis and esterification. The resultant methyl γ-6-methoxy-1-naphthylbutyrate afforded the phenanthrene derivative (III), identical with compound B of Short and Wang.[2] This compound was aromatised to 7-methoxy-1-methylphenanthrene, the main dehydrogenation product of methyl totaryl ether under more vigorous conditions.[2]

Finally, the keto-ester (VII) was hydrolysed to 8-(3-methoxy-2-*iso*propylphenyl)-5-oxo-octanoic acid (X; R = H, R′ = $CHMe_2$, R″ = OMe) which was converted by the same series of reactions into 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1 : 1-dimethyl-8-*iso*propylphenanthrene (II), identical with the compound A of Short and Wang.[2]

Further studies on the keto-ester (X; R′ = Pr^i, R″ = OMe) and its possible conversion into (±)-totarol by the method described elsewhere [12] are in progress.

Experimental

3-Methoxy-2-isopropylbenzamide.—3-Methoxy-2-*iso*propylbenzonitrile [6] (17·5 g.) was treated with a mixture of 30% hydrogen peroxide (80 ml.), 95% ethanol (120 ml.), and 6N-sodium hydroxide (8 ml.) at 50° for 4 hr. (cf. ref. 7). After neutralisation most of the ethanol was

[10] Ansell and Selleck, *J.*, 1956, 1238.
[11] Robinson and Thompson, *J.*, 1939, 1739.
[12] Nasipuri, *Chem. and Ind.*, 1957, 425.

removed by steam-distillation. On cooling, the heavy oil solidified. On crystallisation from benzene it gave 3-methoxy-2-*iso*propylbenzamide (10 g., 52%), m. p. 126° (Found: C, 68·6; H, 7·8; N, 7·1. Calc. for $C_{11}H_{15}O_2N$: C, 68·4; H, 7·8; N, 7·3%) (Richtzenhain and Nippus [6] give m. p. 124—125°).

3-*Methoxy*-2-iso*propylaniline*.—This amine, b. p. 135°/8 mm., was prepared according to the procedure described in *Organic Reactions* [8] in approximately 70% yield from the preceding amide by the action of 0·5N-sodium hypochlorite at 70°. The *benzoyl derivative* formed needles (from methanol), m. p. 153° (Found: C, 75·4; H, 7·1; N, 5·3. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%).

3-*Methoxy*-2-iso*propylphenethyl Alcohol* (VI; R = CH_2·CH_2·OH).—A mixture of 1-iodo-3-methoxy-2-*iso*propylbenzene (27·6 g.) prepared from the above amine by diazotisation, ethyl bromide (10·9 g.), and ether (70 ml.) was added dropwise during 30 min. to a suspension of magnesium (5·2 g.) in ether (30 ml.). Thiophen-free benzene (100 ml.) was next added and the mixture was gently heated under reflux for 2 hr. It was then cooled to 0° and ethylene oxide (10 g.) in ether (50 ml.) was gradually added with stirring and the whole left overnight. Next day the mixture was refluxed for 1 hr., then decomposed with ice and 10% sulphuric acid. The organic layer was separated, washed with water, dried (K_2CO_3), and after removal of the solvent distilled, to give 3-*methoxy*-2-iso*propylphenethyl alcohol* (13·6 g., 70%), b. p. 140—145°/3 mm. (Found: C, 74·3; H, 9·4. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%). Its 3 : 5-*dinitrobenzoate* crystallised from ethanol in light yellow prismatic needles, m. p. 103·5° (Found: C, 58·4; H, 5·2; N, 7·3. $C_{19}H_{20}O_7N_2$ requires C, 58·8; H, 5·2; N, 7·2%). The *bromide* (VI; R = CH_2·CH_2Br), b. p. 135°/3 mm. (Found: C, 56·3; H, 6·8. $C_{12}H_{17}OBr$ requires C, 56·0; H, 6·6%), was prepared [13] from the alcohol by the action of phosphorus tribromide in carbon tetrachloride in 64% yield.

Ethyl α-(3-*Methoxy*-2-iso*propylphenethyl*)-β-*oxopimelate* (VII).—The above bromide (25·7 g.) was added to a cold mixture of ethyl 4 : 6-dioxoheptane-1 : 5-dicarboxylate (27·2 g.) and ethanolic sodium ethoxide prepared from sodium (2·3 g.) and absolute ethanol (40 ml.), and the whole heated under reflux for 10 hr. The product was worked up in the usual way and on distillation gave the *ester* (VII) (17 g.), b. p. 210—215°/0·1 mm. (Found: C, 68·1; H, 8·6. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

γ-(2-*Carboxy*-3 : 4-*dihydro*-6-*methoxy*-5-iso*propyl*-1-*naphthyl*)*butyric Acid* (VIII).—The ester (VII) (5 g.) was treated with concentrated sulphuric acid (15 ml.) at −10° for 3 hr., then poured on ice. The organic matter was taken up in ether and hydrolysed with 5% ethanolic potassium hydroxide to the *acid* (VIII) (3 g., 70%) which crystallised from dilute methanol as prisms, m. p. 195° (Found: C, 68·3; H, 7·0. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·2%). The *dimethyl ester*, b. p. 210—212°/0·1 mm., (Found: C, 70·1; H, 7·9. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%), was prepared by means of methanol and concentrated sulphuric acid on the steam-bath for 6 hr.

1 : 2 : 3 : 4 : 9 : 10-*Hexahydro*-7-*methoxy*-1-*oxo*-8-iso*propylphenanthrene* (IX).—The preceding ester (3·4 g.) was heated with a suspension of sodium methoxide [from sodium (0·23 g.) and methanol (0·4 ml.)] in dry benzene (6 ml.) for 2 hr. The product was worked up in the usual way and was hydrolysed by refluxing concentrated hydrochloric acid (30 ml.), acetic acid (60 ml.), and water (5 ml.) for 30 min. in nitrogen. The mixture was diluted with water and extracted with ether. The ethereal extract was washed with sodium hydrogen carbonate solution, then with water, dried, and distilled, to give the *ketone* (IX) (1·1 g.), leaflets (from methanol), m. p. 62—63° (Found: C, 80·1; H, 8·3. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%). The *dinitrophenylhydrazone* formed red needles (from ethanol), m. p. 225° (Found: C, 64·0; H, 6·0; N, 12·3. $C_{24}H_{26}O_5N_4$ requires C, 64·0; H, 5·8; N, 12·4%).

2-*Methoxy*-8-*methyl*-1-iso*propylphenanthrene* (IV).—A solution of the above ketone (1 g.) in dry benzene (20 ml.) was added at room temperature to a stirred solution of methylmagnesium iodide prepared from magnesium (0·4 g.), methyl iodide (1·2 ml.), and ether (30 ml.). The mixture was refluxed for 4 hr., then decomposed with cold 5% sulphuric acid, and the resultant alcohol was worked up in the usual way and distilled in a high vacuum, to give a semi-solid mass (0·9 g.) which was heated with 30% palladium–charcoal (50 mg.) at 300—310° for 1 hr. (cf. ref. 9). The product (0·5 g.) recovered by means of benzene was chromatographed in light petroleum (b. p. 60—80°) through alumina. Recrystallisation from ethanol gave 2-methoxy-8-methyl-1-*iso*propylphenanthrene (IV) in plates (0·35 g.), m. p. 145° (Found: C, 86·3; H, 7·8. Calc. for $C_{19}H_{20}O$: C, 86·4; H, 7·6%). The picrate separated from ethanol in orange needles,

[13] Hewett, *J.*, 1936, 50.

m. p. 186—187° (Found: C, 60·8; H, 4·8; N, 8·5. Calc. for $C_{19}H_{20}O,C_6H_3O_7N_3$: C, 60·9; H, 4·7; N, 8·5%). The trinitrobenzene complex formed short needles (from ethanol), m. p. 207—208° (Found: C, 62·9; H, 4·9; N, 8·6. Calc. for $C_{19}H_{20}O,C_6H_3O_6N_3$: C, 62·9; H, 4·8; N, 8·8%). The phenol, m. p. 139—140° (Found: C, 86·6; H, 7·3. Calc. for $C_{18}H_{18}O$: C, 86·4; H, 7·2%), was prepared by boiling the methyl ether (IV) with pyridine hydrochloride. Short and Wang [1] give 144·5—145°, 186—187°, 208—209°, and 139—140° as the respective m. p.s.

1 : 2 : 3 : 4-*Tetrahydro*-1 : 1-*dimethylphenanthrene*.—Methyl γ-1-naphthylbutyrate (7·5 g.) in dry ether (20 ml.) was added dropwise at room temperature to methylmagnesium iodide prepared from magnesium (4 g.), methyl iodide (12 ml.) and ether (60 ml.), and reaction was completed by 2 hours' heating. The complex was decomposed by cold 10% sulphuric acid, and the ethereal layer was washed with water, dried (K_2CO_3), and evaporated at the water-pump. The crude alcohol (XI; R = R′ = H) (8 g.) was cyclised by heating with polyphosphoric acid [prepared from phosphoric oxide (8 g.) and 89% phosphoric acid (40 ml.)] at 160° for 3 hr. with stirring. The product was worked up in the usual way and distilled *in vacuo* over sodium (0·5 g.), to give 1 : 2 : 3 : 4-*tetrahydro*-1 : 1-*dimethylphenanthrene* (4·8 g., 70%), b. p. 140°/1 mm. (Found: C, 91·5; H, 8·5. $C_{16}H_{18}$ requires C, 91·4; H, 8·6%). The *picrate* crystallised from ethanol in orange-red needles, m. p. 97° (Found: C, 60·3; H, 4·9; N, 9·7. $C_{16}H_{18},C_6H_3O_7N_3$ requires C, 60·1; H, 4·8; N, 9·6%).

Dehydrogenation of 1 : 2 : 3 : 4-*Tetrahydro*-1 : 1-*dimethylphenanthrene*.—The preceding hydrocarbon (1 g.) was heated with powdered selenium (2 g.) for 10 hr. at 300—320°. The product, worked up in the usual way and crystallised from ethanol, gave 1-methylphenanthrene [14] (0·3 g.), m. p. and mixed m. p. 118—119° (picrate, m. p. 135—136°).

γ-6-*Methoxy*-1-*naphthylbutyric Acid*.—Ethyl α-*m*-methoxyphenethyl-β-oxopimelate (35 g.) was refluxed with potassium hydroxide (30 g.) in water (450 ml.) for 10 hr. The cold mixture was extracted with ether, and the alkaline solution was acidified. The organic matter was collected in ether, dried (Na_2SO_4), and after removal of the solvent, distilled, to afford 8-*m*-methoxyphenyl-5-oxo-octanoic acid (X; R = R′ = H, R″ = OMe) (12 g.), b. p. 215—220°/2 mm. The methyl ester was converted by the usual procedure [11] into γ-6-methoxy-1-naphthylbutyric acid, m. p. 149—150°.

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1 : 1-*dimethylphenanthrene* (III).—Methyl γ-6-methoxy-1-naphthylbutyrate (3 g.) was treated with excess of methylmagnesium iodide, and the product (3 g.) on cyclodehydration with polyphosphoric acid as before gave 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1 : 1-dimethylphenanthrene (1·6 g.), b. p. 155—160°/2 mm., which solidified and crystallised from methanol in needles, m. p. 56° (Found: C, 84·9; H, 8·3. Calc. for $C_{17}H_{20}O$: C, 85·0; H, 8·3%). The picrate formed red needles (from ethanol), m. p. 94° (Found: C, 59·0; H, 5·0; N, 8·8. Calc. for $C_{17}H_{20}O,C_6H_3O_7N_3$: C, 58·8; H, 4·9; N, 8·95%). Short and Wang [1] give m. p. 55·5—56° for the methyl ether and m. p. 105—106° (when heated slowly) or 94° (when heated rapidly) for the picrate. We were, however, unable to get the higher m. p. The corresponding phenol crystallised from benzene–light petroleum in needles, m. p. 134° (Found: C, 85·1; H, 8·0. Calc. for $C_{16}H_{18}O$: C, 85·0; H, 8·0%). Short and Wang [1] give m. p. 134—134·5°. The methyl ether (III) (0·7 g.) was dehydrogenated by selenium powder (1·2 g.) at 300—310° for 6 hr. and the product on crystallisation from ethanol (charcoal) gave 7-methoxy-1-methylphenanthrene,[15] m. p. 129—130° (picrate, m. p. 141—142°).

Methyl 8-(3-*Methoxy*-2-iso*propylphenyl*)-5-*oxo-octanoate* (X; R = Me, R′ = Pr^i, R″ = OMe).—Ethyl α-(3-methoxy-2-*iso*propylphenethyl)-β-oxopimelate (VII) (12 g.) was heated with potassium hydroxide (7 g.) in water (100 ml.) for 10 hr. and the product was worked up in the usual manner, to give the gummy acid (6 g.). The crude acid was esterified by refluxing methanol (50 ml.) containing 3% hydrochloric acid. The *methyl ester* was obtained as a viscous oil (5 g.), b. p. 187—190°/1 mm. (Found: C, 71·4; H, 8·9. $C_{19}H_{28}O_4$ requires C, 71·3; H, 8·8%).

γ-6-*Methoxy*-5-iso*propyl*-1-*naphthylbutyric Acid*.—The foregoing ester (5 g.) was cyclised by concentrated sulphuric acid (10 ml.) at −10° for 3 hr. The brown mixture was worked up in the usual way, to give γ-3 : 4-dihydro-6-methoxy-5-*iso*propyl-1-naphthylbutyric acid (2·7 g.), m. p. 110—115°, which was esterified without further purification. The *methyl ester* (2 g.), b. p. 180—182°/0·1 mm. (Found: C, 75·3; H, 8·9. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·6%), was dehydrogenated by sulphur (0·22 g.) at 240—250° for 2 hr., and the product hydrolysed by

[14] Haworth, *J.*, 1932, 1125.
[15] Short, Stromberg, and Wiles, *J.*, 1936, 319.

boiling it with potassium hydroxide (1 g.) in 95% ethanol (30 ml.) for 3 hr. The crude *acid* (1·8 g.) was purified by repeated crystallisation from aqueous methanol and formed thick prisms, m. p. 163—164° (Found: C, 75·5; H, 7·8. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%). The *methyl ester* had b. p. 180—182°/0·1 mm. (Found: C, 76·2; H, 8·1. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%).

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1 : 1-*dimethyl*-8-iso*propylphenanthrene* (II).—The above ester (1 g.) was treated with excess of methylmagnesium iodide in ether and the resultant alcohol was cyclised as previously described. The product (0·4 g.) was distilled at 0·01 mm. and crystallised from methanol in needles, m. p. 108—109° (0·1 g.) (Found: C, 85·3; H, 9·3. Calc. for $C_{20}H_{26}O$: C, 85·1; H, 9·2%). The trinitrobenzene complex formed orange-red needles (from ethanol), m. p. 150—151° (Found: C, 62·8; H, 5·8; N, 8·3. Calc. for $C_{20}H_{26}O,C_6H_3O_6N_3$: C, 63·0; H, 5·9; N, 8·5%).

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UNIVERSITY COLLEGE OF SCIENCE,
CALCUTTA, 9, INDIA.
[Present address (D. N.): THE UNIVERSITY, MANCHESTER, 13.] [*Received, January 22nd,* 1958.]