748. *The Synthesis of Musizin.*

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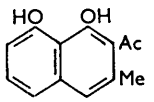
2-Acetyl-3-methylnaphthalene-1,8-diol (I) and 2-acetyl-8-methoxy-3-methyl-1-naphthol (XVI) have been synthesised and shown to be identical with musizin and 8-*O*-methylmusizin, respectively.

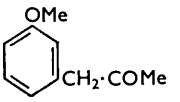
Musizin was isolated from the heartwood of *Maesopsis eminii* and, from degradation studies, assigned the structure 2-acetyl-3-methylnaphthalene-1,8-diol (I) by Covell, King, and Morgan [1] in 1961. Shortly afterwards, Murakami and Matsushima [2] reported that nepodin,[3] isolated from *Rumex nepalensis* Wall. and *Rumex japonicus* Houtt., was the same compound. We have already reported,[4] without experimental details, that the compound (I) and its 8-methyl ether (XVI) have been synthesised and shown to be identical with natural musizin and 8-*O*-methylmusizin. We now give a full account of these experiments and of some preliminary work.

[1] Covell, King, and Morgan, *J.*, 1961, 702.
[2] Murakami and Matsushima, *Chem. Pharm. Bull.* (*Japan*), 1961, **9**, 654.
[3] Hesse, *Annalen*, 1896, **291**, 305; Nonomura and Maruyama, *Kumamoto Pharm. Bull.*, 1955, **2**, 24.
[4] Horii, Hanaoka, and Tamura, *Chem. and Ind.*, 1962, 1243.

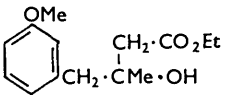
m-Methoxyphenylacetone [5] (II) was prepared by a method used for the corresponding *o*- and *p*-isomers: [6] condensation of *m*-methoxybenzaldehyde [7] and nitroethane in acetic acid in the presence of ammonium acetate,[8] followed by reductive hydrolysis of the crude nitrostyrene, gave the ketone (II) in 39% overall yield. Standard reactions gave the



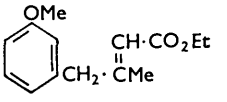
(I)



(II)

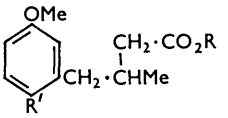


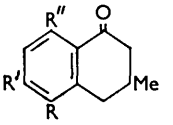
(III)



(IV)

(V: R = Et, R′ = H)
(VI: R = H, R′ = H)
(VII: R = H, R′ = Br)





(VIII: R = Br, R′ = H, R″ = OMe)
(IX: R = Br, R′ = H, R″ = OH)
(X: R = H, R′ = H, R″ = OMe)
(XI: R = H, R′ = OMe, R″ = H)
(XII: R = H, R′ = OH, R″ = H)

sequence of compounds (III)—(VII) in satisfactory yields, and cyclisation of the acid chloride of the bromo-acid (VII) with stannic chloride led to the methoxytetralone (VIII) [$\nu_{max.}$ 1672 cm.$^{-1}$ (free C=O)], which afforded the hydroxytetralone (IX) [$\nu_{max.}$ 1645 cm.$^{-1}$ (H-bonded C=O)]. The tetralone produced by cyclisation of the acid (VI) was shown not to be identical with 8-methoxy-3-methyltetralone (X) obtained by hydrogenolysis [9] of the tetralone (VIII) and, thus, must be formulated as 6-methoxy-3-methyl-1-tetralone (XI), an assignment supported by the free-carbonyl infrared absorption band at 1667 cm.$^{-1}$ shown by both the methoxy- (XI) and the hydroxy-tetralone (XII).

Acetylation [10] of the tetralone (VIII) with acetic anhydride in the presence of boron trifluoride and subsequent bromination afforded the dibromo-derivative (XIV), from which morpholine gave 2-acetyl-5-bromo-8-methoxy-3-methyl-1-naphthol (XV). Hydrogenation of this over Raney nickel in methanol containing potassium hydroxide [9] afforded 2-acetyl-8-methoxy-3-methyl-1-naphthol (XVI), identical with 8-*O*-methylmusizin (mixed melting point; infrared spectra). Finally demethylation by fusion with pyridine hydrochloride [1] produced 2-acetyl-3-methylnaphthalene-1,8-diol (I), identified with musizin by mixed melting-point determination and comparison of their infrared and ultraviolet spectra (see Table).

In early experiments, an attempt to synthesise musizin (I) by the Fries rearrangement of 1-acetoxy-8-methoxy-3-methylnaphthalene (XX) failed. The tetralone (VIII) was brominated and the resulting dibromotetralone (XVII) with morpholine gave 5-bromo-8-methoxy-3-methyl-1-naphthol (XVIII). Hydrogenation [9] over Raney nickel in methanol

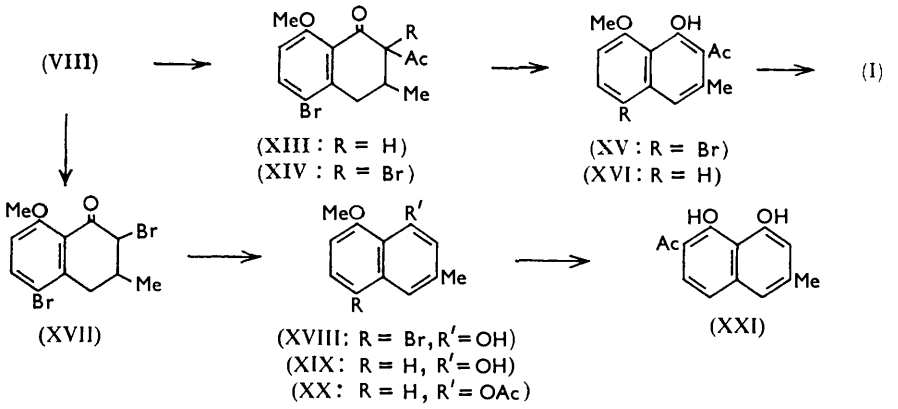
Ultraviolet and infrared absorption data for natural and synthetic musizin (I) and the Fries rearrangement product (XXI).

Compound	$\lambda_{max.}$ (mμ); log ε in parenthesis *	$\nu_{max.}$ (cm.$^{-1}$) †
Musizin (natural)	221 (4·49); 269 (4·69); 410 (3·96)	3360, 1630
,, (synthetic)	221 (4·50); 269 (4·65); 410 (3·88)	3360, 1630
Fries rearrangement product (XXI)	223·5 (4·42); 266 (4·73); 396 (3·94)	3367, 1634

* In n-hexane. † In chloroform.

containing potassium hydroxide and treatment of the resulting crude naphthol (XIX) with acetic anhydride and sodium acetate gave the acetate (XX). However, Fries rearrangement of this acetate in aluminium chloride at 150—160° gave an isomer of musizin (I); the ultraviolet spectrum of this product, resembling that of musizin, and the

[5] Cf. Béhal and Tiffeneau, *Bull. Soc. chim. France*, 1908, **3**, 317.
[6] Hoover and Hass, *J. Org. Chem.*, 1947, **12**, 501; Heinzelman, *Org. Synth.*, 1955, **35**, 74.
[7] Ick, Redemann, Wisegarver, and Alles, *Org. Synth.*, Coll. Vol. III, 1955, p. 564.
[8] Gairaud and Lappin, *J. Org. Chem.*, 1953, **18**, 1.
[9] Hermann, Leopold, and Herwig, *Chem. Ber.*, 1958, **91**, 1376.
[10] Hauser, Swamer, and Adams, *Org. Reactions*, 1954, **8**, 98.



infrared absorption at 3367 and 1634 cm.$^{-1}$ (see Table), suggest that it is similar in structure to (I) and contains a chelated nuclear acetyl group. Thus, it appears that nuclear acetylation has occurred [11] *ortho* to the 8- instead of to the 1-hydroxyl group of 3-methylnaphthalene-1,8-diol during the Fries rearrangement and that the compound must be formulated as 7-acetyl-3-methylnaphthalene-1,8-diol (XXI).

Experimental

Infrared spectra were recorded for chloroform solutions; light petroleum referred to the fraction of b. p. 60—80°. The extracts were dried over magnesium sulphate.

m-*Methoxyphenylacetone* (II).—A mixture of *m*-methoxybenzaldehyde (3·8 g.), nitroethane (3·6 g.), ammonium acetate (1·6 g.), and acetic acid (16 ml.) was heated under reflux for 2 hr., then poured into water and neutralised with sodium hydrogen carbonate. The oil that separated was taken up in ether, washed with water, dried, and recovered. Distillation yielded 1-*m*-methoxyphenyl-2-nitroprop-1-ene (3·3 g.), b. p. 128—133°/1 mm., $\nu_{max.}$ 1656, 1517, and 1321 cm.$^{-1}$.

To a stirred mixture of this product (5 g.), toluene (7 ml.), iron powder (4 g.), ferric chloride (0·15 g.), and water (12 ml.) at ~75°, concentrated hydrochloric acid (7·1 ml.) was added dropwise during 2 hr. Stirring was continued at the same temperature for an additional 30 min. The mixture was then distilled in steam. The toluene layer was separated and the aqueous layer was extracted with toluene. The combined toluene layers were washed with water, dried, and evaporated. Distillation of the residue yielded *m*-methoxyphenylacetone (2·7 g.), b. p. 107—112°/3 mm. (lit.,[5] b. p. 258—260°), $\nu_{max.}$ 1712 cm.$^{-1}$. The 2,4-*dinitrophenylhydrazone* formed orange needles (from ethyl acetate), m. p. 111—112° (Found: C, 55·85; H, 4·6; N, 16·5. $C_{16}H_{16}N_4O_5$ requires C, 55·8; H, 4·7; N, 16·3%).

Ethyl β-*hydroxy*-γ-m-*methoxyphenyl*-β-*methylbutyrate* (III).—The ketone (II) (5 g.) and ethyl bromoacetate (5·5 g.) were dissolved in anhydrous benzene (25 ml.). To 8 ml. of this solution were added zinc dust (2 g.; purified with dilute hydrochloric acid) and a small amount of iodine, and the mixture was heated with stirring on a water-bath. After a vigorous reaction had set in, the remainder of the benzene solution was added during 2 hr. Stirring and heating were continued for an additional 2 hr. The mixture was cooled and decomposed with 10% sulphuric acid. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene layers were washed with water, dried, and evaporated. Distillation yielded the *ester* (III) (4·5 g.), b. p. 143—146°/1 mm., $\nu_{max.}$ 3484 and 1704 cm.$^{-1}$ (Found: C, 66·4; H, 7·8. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%).

5-*Bromo*-8-*methoxy*-3-*methyl*-1-*tetralone* (VIII).—The hydroxy-ester (III) (4·1 g.) was heated with phosphorus oxychloride (2·6 g.) and anhydrous benzene (15 ml.) under reflux for 3 hr., then poured into water and neutralised with sodium hydrogen carbonate. The benzene layer was separated and the aqueous layer extracted with benzene. The combined benzene layers

[11] Baltzly and Phillips, *J. Amer. Chem. Soc.*, 1948, **70**, 4191; Baltzly, Ide, and Phillips, *ibid.*, 1955, **77**, 2522; Cullinane, Evans, and Lloyd, *J.*, 1956, 2222.

were washed with water, dried, and evaporated. Distillation yielded the crotonic ester (IV) (3·0 g.), b. p. 150—155°/3 mm., $\nu_{max.}$ 1709 cm.$^{-1}$.

The crotonate (3·0 g.) in absolute ethanol (45 ml.) was hydrogenated over Raney nickel (1·2 g.) at room pressure and temperature (absorption theoretical). The catalyst was filtered off and the solvent was evaporated. Distillation yielded ethyl *γ-m*-methoxyphenyl-β-methylbutyrate (V) (2·6 g.), b. p. 133—138°/1 mm., $\nu_{max.}$ 1718 cm.$^{-1}$.

This butyrate (1·5 g.), potassium hydroxide (2 g.), water (3 ml.), and ethanol (1·5 ml.) were heated under reflux for 9 hr. After removal of the ethanol, the residue was cooled, diluted with water (5 ml.), and washed with ether. The aqueous layer was acidified with concentrated hydrochloric acid, and the separated oil was extracted with ether. The extract was washed with water, dried, and evaporated, affording the oily acid (VI) (1·2 g.), $\nu_{max.}$ 1706 cm.$^{-1}$.

Bromine (1·27 g.) in chloroform (25 ml.) was added dropwise in 4 hr. to a stirred solution of the acid (VI) (1·5 g.) in chloroform (20 ml.) at 10°. Stirring was continued for an additional 30 min. at room temperature. The mixture was washed (water, 10% aqueous sodium thiosulphate, and water) and dried. Evaporation afforded oily γ-(2-bromo-5-methoxyphenyl)-β-methylbutyric acid (VII) (2·0 g.), $\nu_{max.}$ 1712 cm.$^{-1}$

A cold solution of the bromo-acid (VII) (4·2 g.) in anhydrous benzene (40 ml.) was added to powdered phosphorus pentachloride (3·0 g.). Almost complete dissolution took place in about 10 min. and the resulting solution was warmed at 50° for 15 min., then cooled to 0°. A solution of stannic chloride (3·0 ml.) in anhydrous benzene (9 ml.) was added dropwise in 15 min. and the mixture stirred for further 15 min., then decomposed with a mixture of concentrated hydrochloric acid (11 ml.) and ice–water (21 ml.). The benzene layer was separated and the aqueous layer extracted with benzene. The combined benzene layers were washed with 20% hydrochloric acid, water, 10% aqueous sodium carbonate, and water, dried, and evaporated. Distillation yielded 5-bromo-8-methoxy-3-methyl-1-tetralone (VIII) (2·4 g.), b. p. 125—127°/0·03—0·04 mm. The 2,4-*dinitrophenylhydrazone* formed reddish-orange needles (from benzene), m. p. 228—229° (Found: C, 47·9; H, 3·8; N, 12·7. $C_{18}H_{17}BrN_4O_5$ requires C, 48·1; H, 3·8; N, 12·5%).

5-*Bromo*-8-*hydroxy*-3-*methyl*-1-*tetralone* (IX).—The tetralone (VIII) (700 mg.) was heated with concentrated hydrochloric acid (26 ml.) and acetic acid (13 ml.) under reflux in a stream of nitrogen for 2 hr., then poured into ice–water, neutralised with sodium hydrogen carbonate, and extracted with ether. The extract was washed with water and dried. Evaporation afforded a brown viscous oil, which was purified by chromatography through silica gel. Elution by light petroleum yielded the tetralone (IX) (520 mg.), m. p. 45—58°. This was not recrystallised. The 2,4-*dinitrophenylhydrazone* formed orange crystals (from toluene), m. p. 257° (decomp.) (Found: C, 47·2; H, 3·2; N, 13·0. $C_{17}H_{15}BrN_4O_5$ requires C, 46·9; H, 3·4; N, 12·9%).

8-*Methoxy*-3-*methyl*-1-*tetralone* (X).—The tetralone (VIII) (300 mg.) in methanol (8 ml.) was hydrogenated over Raney nickel (200 mg.) in the presence of potassium hydroxide (110 mg.) at room pressure and temperature (theoretical in 20 min.). The catalyst was filtered off and methanol was evaporated. The residue was taken up in ether, washed with dilute hydrochloric acid and water, dried, and recovered. Distillation yielded 8-methoxy-1-tetralone (X) (100 mg.), b. p. 115—125°(bath)/0·1 mm., $\nu_{max.}$ 1669 cm.$^{-1}$. The 2,4-*dinitrophenylhydrazone* formed red needles (from ethyl acetate), m. p. 200—220° (Found: C, 58·2; H, 5·0; N, 15·2. $C_{18}H_{18}N_4O_5$ requires C, 58·4; H, 4·9; N, 15·1%).

6-*Methoxy*-3-*methyl*-1-*tetralone* (XI).—A solution of the butyric acid (VI) (0·5 g.) in anhydrous benzene (7 ml.) was treated with phosphorus pentachloride (0·5 g.), and the resulting acid chloride was cyclised by stannic chloride (0·5 ml.) in anhydrous benzene (2 ml.) as described for the tetralone (VIII). The *tetralone* (XI) was obtained as a solid, which crystallised from light petroleum as pale yellow needles (0·2 g.), m. p. 71—72° (Found: C, 75·9; H, 7·5. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%). The 2,4-*dinitrophenylhydrazone* formed red needles (from benzene), m. p. 223—224° (Found: C, 58·6; H, 5·0; N, 15·4. $C_{18}H_{18}N_4O_5$ requires C, 58·4; H, 4·9; N, 15·1%).

6-*Hydroxy*-3-*methyl*-1-*tetralone* (XII).—The tetralone (XI) (220 mg.), 48% hydrobromic acid (20 ml.), and acetic acid (3 ml.) were heated under reflux in a stream of nitrogen for 2·5 hr., then treated as described for the tetralone (IX). The *tetralone* (XII) crystallised from benzene as needles (160 mg.), m. p. 154·5° (Found: C, 74·6; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·9%).

2-*Acetyl*-2,5-*dibromo*-8-*methoxy*-3-*methyl*-1-*tetralone* (XIV).—A solution of the tetralone (VIII) (8·5 g.) in freshly distilled acetic anhydride (20 g.) was saturated with dry boron trifluoride with vigorous stirring below 0° in an ice-bath (20 min.). After saturation, the reagent was passed in at a slower rate for 30 min. to ensure maximum absorption. Stirring was continued for a total of 5 hr., during which the bath was allowed to come slowly to room temperature. A solution of sodium acetate (35 g.) in water (60 ml.) was added to the resulting reddish-brown oil, and the mixture was heated under reflux for 1 hr. The mixture was cooled and extracted with ether. The extract was washed with water, dried, and evaporated. Distillation yielded 2-acetyl-5-bromo-8-methoxy-3-methyl-1-tetralone (XIII) (4·4 g.), b. p. 140—145°/0·01—0·02 mm., $\nu_{max.}$ 1712, 1692, and 1597 cm.$^{-1}$. This gave a dark purple colour with an ethanolic ferric chloride.

Bromine (1·6 g.) in chloroform (50 ml.) was added dropwise in 4 hr. to a stirred solution of the tetralone (XIII) (3·0 g.) in chloroform (150 ml.) at $<5°$. Stirring was continued for an additional 30 min. at room temperature. The mixture was washed with water, saturated aqueous sodium hydrogen carbonate, and water, and dried. Evaporation afforded a reddish-brown oil (3·5 g.), which was chromatographed through silica gel. Elution with benzene gave yellow crystals. Recrystallisation from ether–light petroleum yielded 2-*acetyl*-2,5-*dibromo*-8-*methoxy*-3-*methyl*-1-*tetralone* (2·7 g.) as pale yellow needles, m. p. 113·5—114°, $\nu_{max.}$ 1712 and 1672 cm.$^{-1}$ (Found: C, 43·1; H, 3·65. $C_{14}H_{14}Br_2O_3$ requires C, 43·1; H, 3·6%).

2-*Acetyl*-5-*bromo*-8-*methoxy*-3-*methyl*-1-*naphthol* (XV).—A solution of the tetralone (XIV) (2·0 g.) in freshly distilled morpholine (20 g.) was stirred for 1 hr. at room temperature before being set aside overnight. The mixture was poured into water, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with 10% hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water, and dried. Evaporation afforded a yellow solid. Recrystallisation from methanol–water yielded 2-*acetyl*-5-*bromo*-8-*methoxy*-3-*methyl*-1-*naphthol* (1·3 g.) as needles, m. p. 98—98·5°, $\nu_{max.}$ 3378 and 1689 cm.$^{-1}$ (Found: C, 54·45; H, 4·3. $C_{14}H_{13}BrO_3$ requires C, 54·4; H, 4·2%).

2-*Acetyl*-8-*methoxy*-3-*methyl*-1-*naphthol* (XVI).—The naphthol (XV) (383·8 mg.) in distilled methanol (12·5 ml.) was hydrogenated over Raney nickel (400 mg.) in the presence of potassium hydroxide (500 mg.) at room pressure and temperature (absorption theoretical in 25 min.). The mixture was treated as described for the tetralone (X). The *naphthol* (XVI) was obtained as a yellow solid, which crystallised from methanol–water as white needles (276·5 mg.), m. p. 107—108°, $\nu_{max.}$ 3367 and 1686 cm.$^{-1}$ (Found: C, 72·7; H, 6·0. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%). This compound did not depress the m. p. of 8-*O*-methylmusizin, m. p. 108—109° (lit.,[1] 109—110°), kindly supplied by Dr. Morgan, and its infrared spectrum accorded with that of 8-*O*-methylmusizin throughout the range.

2-*Acetyl*-3-*methylnaphthalene*-1,8-*diol* (I).—The naphthol (XVI) (60 mg.) was fused with pyridine hydrochloride (300 mg.) at 200—210° for 15 min., then poured into water, and the resulting greenish-yellow precipitate was sublimed at 160°(bath)/20 mm., giving yellow needles (16 mg.). Recrystallisation from light petroleum yielded 2-*acetyl*-3-*methylnaphthalene*-1,8-*diol* as yellow needles, m. p. 162—163° (evacuated tube) (Found: C, 71·9; H, 5·3. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). Infrared and ultraviolet absorption data are shown in the Table. This compound did not depress the m. p. of musizin, m. p. 162—163° (evacuated tube) (lit.,[1] 164—165°), kindly supplied by Dr. Morgan, and its infrared spectrum was accorded with that of musizin for the whole range.

2,5-*Dibromo*-8-*methoxy*-3-*methyl*-1-*tetralone* (XVII).—Bromine (3·2 g.) in chloroform (80 ml.) was added dropwise in 2 hr. to a stirred solution of the tetralone (VIII) (6 g.) in chloroform (120 ml.) at 0°. Stirring was continued for an additional 30 min. at room temperature. The mixture was washed with water, saturated aqueous sodium hydrogen carbonate, and water, and dried. Evaporation afforded a yellow solid. Recrystallisation from alcohol yielded 2,5-*dibromo*-8-*methoxy*-3-*methyl*-1-*tetralone* as colourless prisms, m. p. 130—131°, $\nu_{max.}$ 1689 cm.$^{-1}$ (Found: C, 41·1; H, 3·3. $C_{12}H_{12}Br_2O_2$ requires C, 41·4; H, 3·5%).

5-*Bromo*-8-*methoxy*-3-*methyl*-1-*naphthol* (XVIII).—The tetralone (XVII) (2·2 g.) was treated with freshly distilled morpholine (22 g.) as described for the naphthol (XV). The product was obtained as a yellow solid. Recrystallisation from alcohol yielded the *naphthol* (XVIII) (1·1 g.) as pale yellow needles, m. p. 100—102°, $\nu_{max.}$ 3405 cm.$^{-1}$ (Found: C, 53·7; H, 4·1. $C_{12}H_{11}BrO_2$ requires C, 53·95; H, 4·15%).

1-*Acetoxy*-8-*methoxy*-3-*methylnaphthalene* (XX).—The naphthol (XVIII) (2 g.) in distilled

methanol (32 ml.) was hydrogenated over Raney nickel (2 g.) in the presence of potassium hydroxide (1·1 g.) at room pressure and temperature (absorption theoretical in 15 min.). The mixture was treated as described for the tetralone (X). The product was obtained as a pale yellow solid. Recrystallisation from methanol yielded 8-methoxy-3-methyl-1-naphthol (XIX) (1·1 g.) as colourless needles, m. p. 92—94° (lit.,[1] 92—93°), $\nu_{max.}$ 3401 cm.$^{-1}$

A mixture of this product (0·35 g.), fused sodium acetate (1·2 g.), and acetic anhydride (18 ml.) was heated under reflux for 18 hr., then poured into ice–water. Recrystallisation of the solid obtained from alcohol yielded 1-*acetoxy*-8-*methoxy*-3-*methylnaphthalene* (0·3 g.) as white prisms, m. p. 143—144°, $\nu_{max.}$ 1751 cm.$^{-1}$ (Found: C, 73·2; H, 6·2. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

7-*Acetyl*-3-*methylnaphthalene*-1,8-*diol* (XXI).—The acetate (XX) (500 mg.) and anhydrous aluminium chloride (1·2 g.) were fused with stirring at 150—160° for 2 hr. The mixture was decomposed with 10% hydrochloric acid. A reddish-brown solid (440 mg.) was purified by chromatography through silica gel. Elution by light petroleum afforded yellow needles (70 mg.), m. p. 115—123°. Recrystallisation from light petroleum yielded 7-*acetyl*-3-*methylnaphthalene*-1,8-*diol* as yellow needles, m. p. 124—128° (Found: C, 71·9; H, 5·6. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). Infrared and ultraviolet absorption data are shown in the Table.

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