Eight- and Higher-membered Ring Compounds. Part XI. Alkyl Derivatives of Di-, Tri-, and Tetra-salicylides.*

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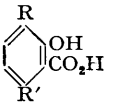
The use of tri-*o*-thymotide as a reagent for the resolution of racemates with which it forms crystalline inclusion compounds has prompted the investigation of related substances. Intermolecular dehydration of 3-*tert.*-butyl-6-methyl-, 3 : 6-dimethyl-, 3-phenyl-, 3-methyl-6-*iso*propyl-, and 6-methyl-4-*iso*propyl-salicylic acids has given products of the type of di-, tri-, and tetra-salicylide, but none of them gave crystalline inclusion compounds.

TRI-*o*-THYMOTIDE (III; R = Pr^i, R′ = Me), prepared by intermolecular dehydration of *o*-thymotic acid (I; R = Pr^i, R′ = Me) (Part VI, Baker, Gilbert, and Ollis, *J.*, 1952, 1443), is of unusual interest. Steric interaction between the carbonyl-oxygen atoms and the *iso*propyl groups prevents the molecule from assuming a planar configuration, and it takes up enantiomorphous, pyramidal forms, possessing three-fold axes of symmetry. Tri-*o*-thymotide forms many crystalline inclusion compounds, some of which, *e.g.*, the complexes with *n*-hexane and benzene, are spontaneously resolved (Powell and Newman, *J.*, 1952, 3747). More importantly, crystallisation of tri-*o*-thymotide with a racemic adduct may effect simultaneous resolution of both substances, thus providing a method of resolution (of, *e.g.*, 2-bromobutane) which is independent of the chemical nature of the substance to be resolved and, unlike the classical method of resolution, requires no previously optically active material (Powell, *Nature*, 1952, **170**, 155) [cf. the resolutions of 2-chlorooctane by repeated crystallisation of its adduct with urea (Schlenk, *Analyst*, 1952, **77**, 870)].

It is possible that other substances, related to tri-*o*-thymotide, may form inclusion

* Part X, *J.*, 1952, 3163.

compounds with a different range of adducts, some of which may undergo spontaneous resolution. With the object of adding to the scope of the new method, we have, therefore, prepared anhydro-derivatives of several acids related to *o*-thymotic acid, in particular 3-*tert.*-butyl-6-methylsalicylic acid (I; R = Me, R′ = Bu^t). In a trianhydro-compound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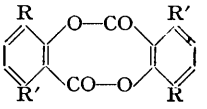
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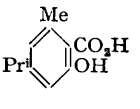
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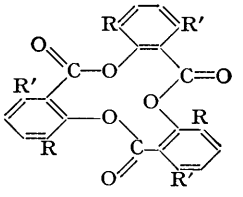

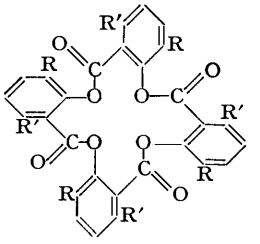

(IV)

of this acid (III; R = Me, R′ = Bu^t), the steric interference between the carbonyl-oxygen atoms and the *tert.*-butyl groups would cause a greater departure from planarity, and therefore a greater difference between the enantiomorphous forms, than in the case of tri-*o*-thymotide. There was the possibility, therefore, that it might exist in more stable enantiomorphous forms than tri-*o*-thymotide, and might be a better resolving agent.

2-*tert.*-Butyl-5-methylphenol was most conveniently prepared (50% yield) from *m*-cresol by reaction with *tert.*-butyl alcohol and anhydrous ferric chloride at room temperature (Nazarova and Tsukervanik, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 1151); with zinc chloride as condensing agent at 100° (Stockelbach, U.S.P. 1,982,180) we obtained a 45% yield, and the product was difficult to purify. The descriptions of 2-*tert.*-butyl-5-methylphenol do not entirely agree. Tchitchibabine (*Bull. Soc. chim.*, 1935, **2**, 502) describes it as a hygroscopic solid, m. p. 23°, giving a monohydrate, m. p. 37°; Stockelbach records a labile form, m. p. 34—35°, and a stable form, m. p. 23·1°; "Koppers Technical Bulletin" C-2-130 (1952, Koppers Co., Inc., U.S.A.) gives m. p. 22·7°, and a hydrate with $\frac{1}{4}H_2O$, m. p. 37°. We find that the anhydrous compound has m. p. 23°, and that it slowly absorbs moisture from air and first liquefies and then solidifies, giving finally a hydrate, m. p. 37°, analysis of which agrees best with $\frac{1}{3}$ molecule of water.

Carboxylation of 2-*tert.*-butyl-5-methylphenol by the Kolbe reaction according to Lespagnol and Bar (*Bull. Soc. chim.*, 1938, **5**, 1360) gave a 30% yield of 3-*tert.*-butyl-6-methylsalicylic acid (I; R = Bu^t, R′ = Me), but the modification now described gives an 85% yield. Distillation of the *O*-acetyl derivative of this acid gave acetic acid, and, as the only other isolable product, di-(3-*tert.*-butyl-6-methylsalicylide) (II; R = Bu^t, R′ = Me). This dianhydro-compound was also obtained as the only product of the dehydration of the free acid with phosphorus oxychloride or phosphoric anhydride in xylene. Under all these three conditions, *o*-thymotic acid gives a mixture of di- and tri-*o*-thymotide.

3 : 6-Dimethylsalicylic acid (I; R = R′ = Me), m. p. 195°, had been previously prepared by oxidation of 4 : 7-dimethylcoumaranone (Stollé and Knebel, *Ber.*, 1921, **54**, 1220), but it has now been prepared directly from 2 : 5-dimethylphenol by the Kolbe reaction. The nature of the product, m. p. 137°, obtained by Oliveri (*Gazzetta*, 1882, **12**, 166) by heating 2 : 5-dimethylphenol and sodium in carbon dioxide, and claimed to be 3 : 6-dimethylsalicylic acid, remains obscure. When dehydrated with phosphorus oxychloride 3 : 6-dimethylsalicylic acid gave di- and tri-(3 : 6-dimethylsalicylide) (II and III; R = R′ = Me). Di-(3 : 6-dimethylsalicylide) was obtained by distillation of the *O*-acetyl derivative of the acid.

3-Phenylsalicylic acid (I; R = Ph, R′ = H) when treated with phosphorus oxychloride gave only tetra-(3-phenylsalicylide) (IV; R = Ph, R′ = H).

3-Methyl-6-*iso*propylsalicylic acid [*o*-carvacrotic acid (I; R = Me, R′ = Pr^i)] was prepared from carvacrol by Kolbe's method in 80% yield. Distillation of the *O*-acetyl derivative of the acid gave di-(3-methyl-6-*iso*propylsalicylide) (II; R = Me, R′ = Pr^i), and treatment of the free acid with phosphorus oxychloride gave a mixture of di- and tri-(3-methyl-6-*iso*propylsalicylide) (II and III; R = Me, R′ = Pr^i). Dehydration of the acid with phosphoric anhydride in xylene again gave the di- and tri-anhydro-derivatives, and 1% of tetra-(3-methyl-6-*iso*propylsalicylide) (IV; R = Me, R′ = Pr^i).

3-Methyl-5-*iso*propylphenol gave an acid by the Kolbe reaction which is assumed to be 6-methyl-4-*iso*propylsalicylic acid (V) because the alternative structure, 4-methyl-6-*iso*propylsalicylic acid, is less likely for steric reasons. Distillation of the *O*-acetyl derivative of (V) gave di-(6-methyl-4-*iso*propylsalicylide), and dehydration of the acid (V) with either phosphorus oxychloride or phosphoric anhydride gave tri-(6-methyl-4-*iso*propylsalicylide).

Hydrolysis of all the foregoing anhydro-derivatives regenerated the original acids. None of them formed inclusion compounds with ethanol, chloroform, benzene, or *m*-xylene, solvents which all give crystal complexes with tri-*o*-thymotide (for other inclusion complexes formed by compounds of the salicylide type, see Part III, Baker, Gilbert, Ollis, and Zealley, *J.*, 1951, 211).

Experimental

Molecular weights were determined ebullioscopically in benzene (unless otherwise stated) in the Menzies–Wright apparatus as described by Baker, Ollis, and Zealley (Part II, *J.*, 1951, 208).

2-Hydroxy-3 : 6-dimethylbenzoic Acid (3 : 6-Dimethylsalicylic Acid) (I; R = R′ = Me).—2 : 5-Dimethylphenol (200 g.) in xylene (1500 c.c., dried over sodium) was heated in an oil-bath at 140—150° for 32 hr. whilst a rapid stream of carbon dioxide was bubbled through. During the first 10 hr. of this period, sodium (85 g.) was added in small pieces, and more xylene (in all *ca.* 1 l.) was added from time to time to keep the volume constant. Sodium was destroyed in the cooled mixture by the addition of 90% ethanol (*ca.* 480 c.c.), the mixture shaken with water (1600 c.c.), and the aqueous layer acidified. The precipitated acid was collected, washed, and crystallised from a mixture of ethanol (720 c.c.) and water (900 c.c.) (charcoal), giving 2-hydroxy-3 : 6-dimethylbenzoic acid as faintly coloured needles, m. p. 195° (71 g., 24%) (Stollé and Knebel, *loc. cit.*, give m. p. 195°) (Found: equiv., 167. Calc. for $C_8H_9O{\cdot}CO_2H$: equiv., 166). 2 : 5-Dimethylphenol (53 g.) was recovered from the xylene solution.

Di- and Tri-(3 : 6-dimethylsalicylide) (II and III; R = R′ = Me).—2-Hydroxy-3 : 6-dimethylbenzoic acid (20 g.), redistilled phosphorus oxychloride (37 g.), and xylene (120 c.c.) were heated on the water-bath for 12 hr., water (200 c.c.) was added, and the mixture shaken. The solid (A) was collected, washed, and dried (11·0 g.; m. p. 235—241°), and after 2 days the xylene filtrate had deposited a solid (B) (2·0 g.; m. p. 182—206°). The xylene was finally washed with 3% aqueous sodium carbonate, dried, evaporated under reduced pressure, and treated with warm ethanol, giving a solid (C) (0·6 g.; m. p. 222—238°); the alcoholic filtrate was evaporated, and the residue crystallised from light petroleum (b. p. 80—100°), giving solid (D) (0·3 g.; m. p. 201—209°). Solids (A), (B), and (C) were separately crystallised from benzene–light petroleum (b. p. 80—100°), and solid (D) from ethanol. *Tri-(3 : 6-dimethylsalicylide)* (III; R = R′ = Me) was obtained from (A) and (C) as fine needles (9·0 g.), m. p. 254—255° (Found: C, 73·2; H, 5·1%; *M*, 440. $C_{27}H_{24}O_6$ requires C, 73·0; H, 5·4%; *M*, 444). From ethanol, chloroform, or dioxan it crystallises as platelets or needles, m. p. 255°. After melting or crystallisation from benzene and either sublimed at 200°/10^{-4} mm. or heated at 160°/0·5—1 mm., its m. p. was 290—291° (Found: C, 73·2; H, 5·4%) but, on keeping, the m. p. reverted to 255°. Curiously, the m. p. of the material crystallised from ethanol was not affected by heating at 160°/0·5—1 mm. *Di-(3 : 6-dimethylsalicylide)* (II; R = R′ = Me) was obtained from (B) and (D) as hexagonal prisms (1·5 g.), m. p. 211—212° (Found: C, 73·2; H, 5·4%; *M*, 292. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%; *M*, 296). Distillation of the *O*-acetyl derivative of 3 : 6-dimethylsalicylic acid, as described for 6-acetoxy-2-*tert.*-butyl-5-methylbenzoic acid (p. 2045), gave di-(3 : 6-dimethylsalicylide) in 33% yield.

Hydrolysis of di-(3 : 6-dimethylsalicylide) with boiling 2N-aqueous sodium hydroxide for 6 hr., or of tri-(3 : 6-dimethylsalicylide) with boiling ethanolic potassium hydroxide for 4 hr., gave 2-hydroxy-3 : 6-dimethylbenzoic acid in 86% and 92% yields, respectively. When the two salicylides (0·5 g.) were each boiled for 1 hr. with benzylamine (3 c.c.) and ammonium chloride (0·1 g.), the mixtures treated with dilute hydrochloric acid, and the solids recrystallised 5 times from dilute ethanol, *N-benzyl-2-hydroxy-3 : 6-dimethylbenzamide* was obtained

as needles, m. p. 97—98° (Found: C, 75·2; H, 6·4; N, 5·2. $C_{16}H_{17}O_2N$ requires C, 75·4; H, 6·7; N, 5·5%), in 94% and 78% yield, respectively.

Tetra-(3-phenylsalicylide) (IV; R = Ph, R′ = H).—Technical 3-phenylsalicylic acid (I; R = Ph, R′ = H) (20 g.), distilled phosphorus oxychloride (40 c.c.), and toluene (200 c.c.) were heated on the steam-bath for 40 hr., during which large crystals slowly separated. These were washed with benzene, then with water, and dried (6·1 g., 33%). *Tetra-(3-phenylsalicylide)* (IV; R = Ph, R′ = H) separates from benzene, or from chloroform–light petroleum (b. p. 60—80°) in plates, m. p. 360° [Found: C, 80·0; H, 4·1%; *M* (ebullioscopic in benzene), 731; *M* (ebullioscopic in chloroform), 802. $C_{52}H_{32}O_8$ requires C, 79·6; H, 4·1%; *M*, 784]. The toluene solution contained 3-phenylsalicylic acid and polymeric material.

2-tert.-*Butyl-5-methylphenol* (tert.-*Butyl*-m-*cresol*).—*From* m-*cresol*, tert.-*butyl alcohol, and ferric chloride* (cf. Nazarova and Tsukervanick, *loc. cit.*). Anhydrous ferric chloride (150 g.) was slowly added to *tert.*-butyl alcohol (125 g.) with stirring and cooling, followed by *m*-cresol (110 g.). After 4 days at room temperature, the mixture was poured into water and steam-distilled. A first portion of the distillate (500 c.c.) gave *m*-cresol (24 g.), and the organic layer from the later distillate (3 l.) was separated, dried in ethereal solution ($MgSO_4$), and fractionated in a lagged column, giving *m*-cresol (6 g.; b. p. 105—107°/35 mm.) and 2-*tert.*-butyl-5-methylphenol (60 g.; b. p. 130—135°/35 mm.) (later portions of the steam-distillate contained only material of higher b. p.). The 2-*tert.*-butyl-5-methylphenol was added to stirred, cooled water, giving needles of the hydrate which were dried in a current of air. This product was now dried ($MgSO_4$) in ethereal solution and distilled, giving the free 2-*tert.*-butyl-5-methylphenol, b. p. 130°/13 mm., which solidified on cooling as needles, m. p. 23° (Found: C, 80·7; H, 9·9. Calc. for $C_{11}H_{16}O$: C, 80·5; H, 9·8%). The *hydrate*, prepared from the purified compound, had m. p. 37° [Found: C, 77·6; H, 9·8. $(C_{11}H_{16}O)_3,H_2O$ requires C, 77·6; H, 9·8%. $(C_{11}H_{16}O)_4,H_2O$ requires C, 78·3; H, 9·8%].

2-tert.-*Butyl-6-hydroxy-5-methylbenzoic acid* (3-tert.-*Butyl-6-methylsalicylic Acid*) (I; R = Bu^t, R′ = Me) (cf. Lespagnol and Bar, *loc. cit.*).—To 2-*tert.*-butyl-5-methylphenol (100 g.) in xylene (2 l.) was added sodium (30 g.) in portions with stirring, and the resulting solution heated to boiling (oil-bath) while a vigorous current of carbon dioxide was passed in through two tubes, so as to cause maximum turbulence of the rapidly stirred mixture. This was continued without stoppage for 5 days, xylene (1 l.) removed by distillation, and ethanol (100 c.c.) added to react with any sodium, followed after several hours by shaking with water (1 l.). The aqueous layer and aqueous washings of the xylene layer were acidified, and the solid was collected, dried, and crystallised from light petroleum (b. p. 80—100°) (charcoal), giving finally 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid as colourless needles (110 g., 85%), m. p. 180° (Found: C, 68·9; H, 7·7%; equiv., 203. Calc. for $C_{11}H_{15}O{\cdot}CO_2H$: C, 69·2; H, 7·7%; equiv., 208). This acid gives with alcoholic ferric chloride a deep green colour which changes to blue on addition of water. 6-Acetoxy-2-*tert.*-butyl-5-methylbenzoic acid was obtained by boiling the acid with excess of acetic anhydride and a trace of pyridine for 2 hr., then shaking with much water, and the product which finally solidified was dissolved in cold carbon tetrachloride, and light petroleum (b. p. 40—60°) added till a slight turbidity was produced. After several days, the solid was collected and recrystallised in the same manner, giving the acetyl derivative as needles, m. p. 112° (Lespagnol and Bar gave m. p. 108°).

Di-(3-tert.-butyl-6-methylsalicylide) (II; R = Bu^t, R′ = Me).—The thermal decomposition of 6-acetoxy-2-*tert.*-butyl-5-methylbenzoic acid was carried out in the apparatus described in Part II (*loc. cit.*, p. 206).

The acid (20 g.) was distilled at 15 mm., the temperature being gradually raised to 350°. Acetic acid was evolved at 120—160°, and a yellowish oil solidifying to a glass was collected mainly at 240—260°. This was dissolved in chloroform, the solution washed with aqueous sodium carbonate, and dried, the chloroform removed, and the residue crystallised from alcohol (yield 5 g., 28%; m. p. 238°), and then from benzene, giving *di-(3-tert.-butyl-6-methylsalicylide)* as needles, m. p. 238° (Found: C, 75·6; H, 7·1%; *M*, 388. $C_{24}H_{28}O_4$ requires C, 75·8; H, 7·4%; *M*, 380). This compound was also obtained as the only anhydro-derivative by dehydration of the acid with either phosphorus oxychloride in xylene (cf. dehydration of 2-hydroxy-3 : 6-dimethylbenzoic acid, p. 2044) (yield 16%) or phosphoric anhydride in xylene (cf. dehydration of *o*-thymotic acid, Baker, Gilbert, and Ollis, Part VI, *J.*, 1952, 1444) (yield, 20%). Hydrolysis by boiling with 50% ethanolic potassium hydroxide for 20 hr. gave 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid, m. p. 180°, in 94% yield.

2-*Hydroxy*-3-*methyl*-6-iso*propylbenzoic Acid* (o-*Carvacrotic Acid*) (3-*Methyl*-6-iso*propylsalicylic Acid*) (I; R = Me, R′ = Pr^i).—This acid had been prepared by Kolbe's method in un-

stated yield (Kekulé and Fleischer, *Ber.*, 1873, **6**, 1089; Lustig, *Ber.*, 1886, **19**, 18). It has now been prepared from carvacrol (100 g.) exactly as described above in the case of 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid, the crude product being treated with charcoal in boiling alcohol, and then crystallised from light petroleum (b. p. 80—100°), giving the pure acid as needles, m. p. 140° (103 g., 80%). This acid yielded 2-*acetoxy*-3-*methyl*-6-iso*propylbenzoic acid* when boiled for 2 hr. with acetic anhydride and a little pyridine; it separated from ethanol on cautious addition of water at room temperature as needles, m. p. 131° (Found: C, 66·4; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

Action of Heat on 2-*Acetoxy*-3-*methyl*-6-iso*propylbenzoic Acid: Di-*(3-*methyl*-6-iso*propylsalicylide*) (II; R = Me, R′ = Pr^i).—The acetoxy-derivative (1·4 g.) was distilled at 15 mm. as described above for 6-acetoxy-2-*tert.*-butyl-5-methylbenzoic acid. Acetic acid was evolved at 120—140°, and a thick oil at 300—320° which solidified to a glass. This product was shaken in chloroform solution with aqueous sodium carbonate, the solution dried and evaporated, and the residue crystallised from ethanol, giving *di*-(3-*methyl*-6-iso*propylsalicylide*) (0·4 g., 32%) as needles, m. p. 174° (Found: C, 75·1; H, 6·8%; *M*, 340. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·8%; *M*, 352).

Action of Phosphorus Oxychloride on 2-*Hydroxy*-3-*methyl*-6-iso*propylbenzoic Acid: Di- and Tri-*(3-*methyl*-6-iso*propylsalicylide*) (II and III; R = Me, R′ = Pr^i).—Phosphorus oxychloride (10 c.c.) was added to a solution of the acid (17 g.) in xylene (100 c.c.), and the mixture boiled for 24 hr., cooled, poured into ice, and well shaken. The xylene layer was shaken with aqueous sodium carbonate, dried, and distilled under reduced pressure, and the residue crystallised from alcohol, giving octagonal plates (3·5 g., 23%) and needles (1·5 g., 10%) which were separated by hand. The needles, m. p. 174°, were di-(3-methyl-6-*iso*propylsalicylide). The octagonal plates, m. p. 247°, were *tri*-(3-*methyl*-6-iso*propylsalicylide*) (Found: C, 74·8; H, 6·8%; *M*, 534. $C_{33}H_{36}O_6$ requires C, 75·0; H, 6·8%; *M*, 528).

Action of Phosphoric Anhydride on 2-*Hydroxy*-3-*methyl*-6-iso*propylbenzoic Acid: Di-, Tri-, and Tetra-*(3-*methyl*-6-iso*propylsalicylide*) (II, III, and IV; R = Me, R′ = Pr^i).—The acid (15 g.) was boiled for 72 hr. in xylene (115 c.c.) with phosphoric anhydride (15 g.), and the products were isolated and recrystallised as in the preceding paragraph. There were isolated the di- (4·5 g., 33%) and tri- (1·5 g., 11%) anhydro-compounds, and also microscopic needles of the *tetra*-(3-*methyl*-6-iso*propylsalicylide*) (0·15 g., 1%), m. p. 323° (Found: C, 74·9; H, 6·8%; *M*, 656. $C_{44}H_{48}O_8$ requires C, 75·0; H, 6·8%; *M*, 704).

The di-, tri-, and tetra-anhydro-compounds were each hydrolysed with boiling 50% ethanolic potassium hydroxide for 24 hr. The first two gave 2-hydroxy-3-methyl-6-*iso*propylbenzoic acid in 98% yield; the last, owing to its insolubility was partly unchanged, but also gave the same acid.

2-*Hydroxy*-6-*methyl*-4-iso*propylbenzoic Acid* (6-*Methyl*-4-iso*propylsalicylic Acid*) (V).—This acid was prepared from 3-methyl-5-*iso*propylphenol (purified technical material) (100 g.) in the same way as 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid was prepared from 2-*tert.*-butyl-5-methylphenol. The *acid* separates from light petroleum (b. p. 80—100°) or very dilute ethanol in needles (110 g., 85%), m. p. 136° (Found: C, 68·4; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%). With alcoholic ferric chloride it gives an intense purple-blue colour.

Di-(6-*methyl*-4-iso*propylsalicylide*).—The acid (V) was acetylated with acetic anhydride and pyridine, and the oily acetyl derivative (10 g.) distilled at 15 mm. as described in previous cases. Acetic acid was evolved at a bath temperature of 120—140°, and a thick yellowish oil collected between 300° and 330°. This product was worked up as in the case of the 3-methyl-6-*iso*propyl derivative, and gave *di*-(6-*methyl*-4-iso*propylsalicylide*) (2·9 g., 27%) as needles, m. p. 136° (Found: C, 75·0; H, 6·8%; *M*, 360. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·8%; *M*, 352).

Tri-(6-*methyl*-4-iso*propylsalicylide*).—Dehydration of the acid (V) with either phosphorus oxychloride or phosphoric anhydride in xylene at the b. p. as in previous cases gave from each experiment a 7% yield of *tri*-(6-*methyl*-4-iso*propylsalicylide*), which separated from ethanol as needles, m. p. 191° (Found: C, 75·1; H, 6·8%; *M*, 547. $C_{33}H_{36}O_6$ requires C, 75·0; H, 6·8%; *M*, 528).

Hydrolysis of di- and tri-(6-methyl-4-*iso*propylsalicylide) with 50% ethanolic potassium hydroxide for 24 hr. gave 96% and 90% yields, respectively, of 6-methyl-4-*iso*propylsalicylic acid (V), m. p. 136°.

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