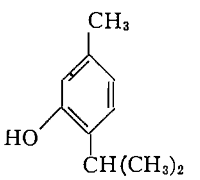
THE SYNTHESIS OF TWO ISOMERIC THYMOLS[1]

By R. A. B. Bannard and L. C. Leitch

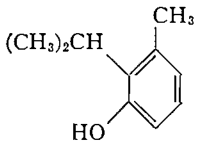
ABSTRACT

2-Isopropyl-3-methylphenol has been synthesized and found to be identical with the isopropyl-3-methylphenol of m.p. 69° C. obtained from the isopropylation of *m*-cresol. 6-Isopropyl-3-methoxytoluene has been synthesized and found to be identical with the methyl ether of the isopropyl-3-methylphenol of m.p. 112° C., also obtained from the isopropylation of *m*-cresol.

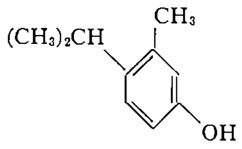
The alkylation of *m*-cresol with isopropyl alcohol in the presence of sulphuric acid reported by Chichibabine (4) and earlier workers gives, in addition to thymol (I), two isomers melting at 69° and 112° C. which were assigned the structures II and III respectively. On the basis of the orienting influences in *m*-cresol and melting points, these formulae were probably correct. It seemed desirable, however, to confirm these structures either by degradation to known compounds or by independent synthesis.



I



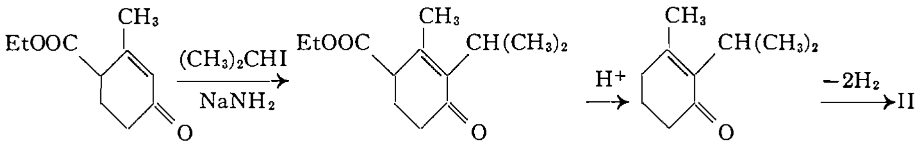
II



III

The first course was not successful. All attempts to determine the location of the isopropyl group in II and III by oxidation of the methyl ethers to methoxyphthalic acids failed. The compounds were apparently completely oxidized by potassium permanganate as copious amounts of carbon dioxide were evolved on acidifying the reaction mixture and no organic compound could be isolated.

Alternatively, 2-isopropyl-3-methylphenol (II) was synthesized by the following reactions:



IV V VI

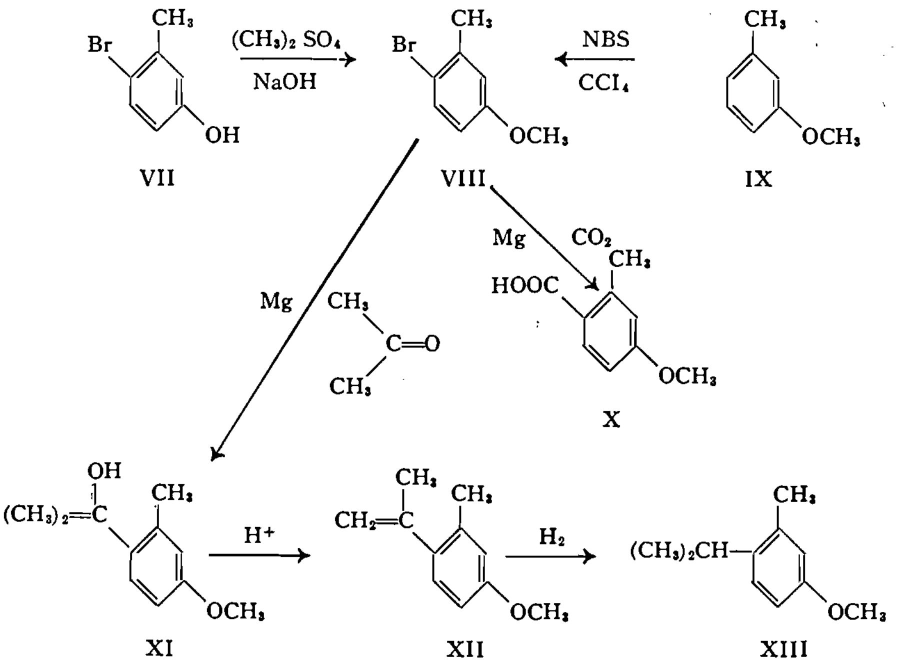
3-Methyl-4-carbethoxy-2-cyclohexene-1-one (IV), referred to as Hagemann's ester in the literature, was prepared from acetoacetic ester and trioxymethylene as described by Rouault and Smith (14). The sodio derivative of IV was

---

[1] *Manuscript received June 7, 1956.*
Contribution from the Division of Pure Chemistry, National Research Council, Ottawa, Canada, and Defence Research Chemical Laboratories, Ottawa, Canada. Issued as N.R.C. No. 4071 and D.R.C.L. Report No. 217.

prepared from sodamide in liquid ammonia and alkylated therein with isopropyl iodide to 2-isopropyl-3-methyl-4-carbethoxy-2-cyclohexene-1-one (V) by the procedure of Horning, Horning, and Platt (10). Hydrolysis and decarboxylation of V as described by Horning, Denekas, and Field (9) gave 2-isopropyl-3-methyl-2-cyclohexene-1-one (VI). The semicarbazone of the ketone melted at 165–6° C. as reported by Dieckmann (7). Dehydrogenation of the ketone in mesitylene with palladized carbon according to the directions of Horning, Horning, and Walker (11) gave a small yield of a phenol, m.p. 68.5 to 69.5° C. Admixture of this compound with the isomer, m.p. 69–70° C., isolated from the isopropylation of *m*-cresol caused no depression in melting point. The infrared spectra of the two compounds were likewise identical. The structure II assigned to this isomer of thymol is therefore correct.

6-Isopropyl-3-methoxytoluene was in turn synthesized by the following sequence of reactions:



6-Bromo-3-methoxytoluene (VIII) was prepared in two ways: (*a*) by methylation of 3-methyl-4-bromophenol (VII) as described by Darzens and Levy (5); (*b*) by bromination of 3-methoxytoluene (IX) with N-bromosuccinimide by the procedure of Bannard and Latremouille (1). The orientation of the bromine atom in VIII upon which rests subsequent proof of the structure III was proved by Darzens and Levy (5) by converting the halide to 2-methyl-4-methoxybenzoic acid (X) via the Grignard reagent. The compounds obtained by the two routes were identical as shown by a comparison of their boiling points and refractive indices. Buu-Hoi (3) and Quelet and Paty (13) assigned the same structure without proof to VIII prepared by bromination of 3-methoxytoluene (IX) with N-bromosuccinimide and bromine respectively.

The Grignard reagent prepared from 6-bromo-3-methoxytoluene (VIII) did not react with isopropyl bromide to give the expected 6-isopropyl-3-methoxytoluene. The result was surprising in view of the successful preparation of 6-*tert*-butyl-3-methoxytoluene from *tert*-butyl bromide and the same Grignard by Darzens and Levy (6). On treatment with acetone, however, the Grignard reagent gave a 45% yield of 2-(2-methyl-4-methoxyphenyl)-propanol-2 (XI) together with 38% of 6-isopropenyl-3-methoxytoluene (XII). The latter was undoubtedly formed by dehydration of the carbinol (XI) under the influence of iodine used to initiate the reaction. A similar instance has been reported recently by Edwards and Cashaw (8). 6-Isopropenyl-3-methoxytoluene was also obtained in 80% yield by dehydration of the carbinol (XI) with dilute sulphuric acid.

Hydrogenation of 6-isopropenyl-3-methoxytoluene (XII) with Adam's catalyst gave 92% of 6-isopropyl-3-methoxytoluene (XIII). Finally, methylation of the thymol isomer III yielded a product which has the same boiling point, refractive index, and infrared absorption spectrum as XIII. It must therefore be concluded that the isomer of m.p. 112° C. is 3-methyl-4-isopropylphenol.

EXPERIMENTAL*

A. Synthesis of 2-Isopropyl-3-methylphenol

3-Methyl-4-carbethoxy-2-cyclohexene-1-one (IV)

The ketoester was prepared in 40% yield by the directions of Rouault and Smith (14). After a small low-boiling fraction was collected, the pure ester distilled at 105–107° at 2 mm., n_D^{20} 1.4860.

2-Isopropyl-3-methyl-4-carbethoxy-2-cyclohexene-1-one (V)

For the alkylation of the ester IV the following modification of the method of Horning, Horning, and Platt (10) was used. The ketoester IV (25.7 gm., 0.14 mole) was added dropwise from a separatory funnel to sodamide prepared from 4.4 gm. of sodium and 125 ml. of liquid ammonia. The ammonia was allowed to evaporate during stirring and addition of 50 ml. of dry toluene. Isopropyl iodide (27.0 gm., 0.17 mole) was now added and the reaction mixture heated just below refluxing overnight. It was treated with a little ethanol and then poured into water. The toluene layer was washed with water and then dried over a small quantity of anhydrous calcium chloride. Most of the toluene was removed under 50 mm. pressure. The ester was then fractionated under 3 mm. in a small Vigreux column with total condensation – partial take-off still head. The main fraction of alkylated ketoester was collected between 115° and 119° C. at 3 mm. Yield: 15.0 gm. (60%), n_D^{20} 1.4868.

The semicarbazone separated from a solution of 1 gm. each of the ketoester, semicarbazide hydrochloride, and sodium acetate in dilute ethanol after it had been left to stand for a day. After one recrystallization from dilute ethanol–

**All melting points are uncorrected.*

water the semicarbazone melted at 203–204° C. Calc. for $C_{14}H_{23}N_3O_3$: C, 59.75%; H, 8.24%; N, 14.94%. Found: C, 60.21%; H, 8.36%; N, 15.13%.

2-Isopropyl-3-methyl-2-cyclohexene-1-one (*VI*)

The ketoester V (14.0 gm.) was hydrolyzed and decarboxylated by treating it successively with alcoholic sodium hydroxide and sulphuric acid as reported by Horning, Denekas, and Field (9). Fractional distillation of the ketone after it had been washed and dried in ether gave 6.7 gm. of product, b.p. 94–97° C. at 14 mm., n_D^{20} 1.4888. The semicarbazone prepared as described above melted at 165–166° C. after one recrystallization from ethanol–water. Dieckmann (7) gives 167–168° C. as the melting point of the semicarbazone.

2-Isopropyl-3-methylphenol (*II*)

The dehydrogenation of VI was carried out as described by Horning, Horning, and Walker (11) except that the palladium adsorbed on carbon was prepared from palladium chloride (1.0 gm.), carbon black (10.0 gm.), and formaldehyde (12). Five grams of 2-isopropyl-3-methyl-2-cyclohexene-1-one (VI) was heated under reflux for two hours with 1.5 gm. of the dehydrogenation catalyst in 20 ml. of mesitylene. The supernatant liquid was decanted and extracted with 5% aqueous sodium hydroxide. On acidification of the aqueous extract a small amount of oily material which crystallized on being cooled and stirred was precipitated. It was taken up in pentane and crystallized therefrom on slow evaporation. The crystals melted at 68–69.5° C. The melting point was unchanged by admixture with the isomer of m.p. 69° isolated from the isopropylation of *m*-cresol.

B. Synthesis of 6-Isopropyl-3-methoxytoluene

3-Methoxytoluene (*IX*)

3-Methoxytoluene (IX) was prepared by the method of Ullmann and Uzbachian (15). Yield 70.0%, b.p. 61–63° C. at 10 mm., n_D^{20} 1.5123. The infrared spectrum of this substance was identical with that reported by Barnes *et al.* (2).

3-Methyl-4-bromophenol (*VII*)

3-Methyl-4-bromophenol (VII) was obtained in approximately 50% yield by the method of von Walther and Zipper (16). It melted at 62.5–63.5° C.; von Walther and Zipper (16) report m.p. 62° C.; Darzens and Levy (5), 63° C.

6-Bromo-3-methoxytoluene (*VIII*)

(*a*) *From 3-methyl-4-bromophenol* (*VII*).—3-Methyl-4-bromophenol (VII) (32.8 gm., 0.175 mole) was dissolved in 15% sodium hydroxide (40 cc.) in a 150 cc. beaker equipped with a teflon-covered magnetic stirring bar, thermometer, and burette. The stirred solution was treated at 40° C. with dimethyl to sulphate (45.0 gm., 0.357 mole) in one portion. The temperature rose rapidly to 87° C., and the solution turned acidic, became turbid, and separated into two layers. The mixture was treated with small portions of 15% sodium hydroxide (approximately 3 cc. per addition) until no further acidic reaction was evident

(10 min., 36.5 cc.). Stirring was continued for a further 40 min. by which time the temperature had fallen to 35° C. The oily layer was taken up in ether (50 cc.), the aqueous phase extracted with ether (4×50 cc.), and the combined extracts dried over anhydrous magnesium sulphate (25 gm.). The ether solution was decanted, the ether removed by evaporation on the steam bath, and the residue distilled *in vacuo* yielding 18.1 gm. (51.4%) of 6-bromo-3-methoxytoluene (VIII) as a pale yellow oil, b.p. 104.5–106° C. at 10 mm., n_D^{20} 1.5609. (Quelet and Paty (13) report b.p. 111–112° C. at 15 mm., n_D^{20} 1.5593; Darzens and Levy (5) report b.p. 112° C. at 14 mm.) 4,6-Dibromo-3-methoxytoluene, 6.8 gm., m.p. 74–75° C., was obtained as by-product (Quelet and Paty (13) report m.p. 77° C.) together with 6.4 gm. of 3-methoxytoluene (IX).

(*b*) *From 3-methoxytoluene* (*IX*).—3-Methoxytoluene (IX) (61.0 gm., 0.500 mole) and carbon tetrachloride (80 cc.) were mixed in a 300-cc. round-bottomed flask and N-bromosuccinimide (89.0 gm., 0.500 mole) added in small portions. No evolution of heat occurred. The flask was fitted with a reflux condenser equipped with a calcium chloride guard-tube and the mixture heated by means of a "glascol" heating mantle. As soon as the solvent began to boil, a vigorous reaction occurred, making it necessary to replace the heating mantle by a cold water bath. After the initial vigorous reaction subsided, the mixture was heated under brisk reflux for six hours. The mixture was allowed to stand overnight and the precipitated succinimide removed by suction filtration and washed with carbon tetrachloride (3×20 cc.). The filtrate was concentrated by distillation at atmospheric pressure and the residue fractionated *in vacuo* yielding 89.0 gm. (88.1%) of 6-bromo-3-methoxytoluene (VIII) as a colorless oil, b.p. 104–105.5° C. at 10 mm., n_D^{20} 1.5610.

2-(2-Methyl-4-methoxyphenyl)-propanol-2 (*XI*)

A Grignard reagent was prepared in a conventional nitrogen-swept Grignard apparatus by addition of 6-bromo-3-methoxytoluene (VIII) (44.2 gm., 0.220 mole) in anhydrous ether (75 cc.) over a period of 3.5 hr. to magnesium turnings (4.86 gm., 0.200 gm-atom) covered with anhydrous ether (20 cc.) after the reaction had been initiated by addition of a small portion of the halide together with a crystal of iodine. The light brown reagent was heated under reflux for a further hour, then treated with a solution of acetone (11.6 gm., 0.200 mole) in anhydrous ether (15 cc.) over a period of 30 min. The reaction was exothermic and reflux was controlled by the rate of addition. Twenty minutes after the addition had been in progress the clear light brown solution deposited a pale yellow complex to form a very viscous mixture which became more fluid again by the time addition was complete. The mixture was heated under reflux for 15 min., allowed to stand overnight under nitrogen, and hydrolyzed by addition of saturated ammonium chloride solution (30 cc.) over a period of 30 min. The pale yellow solution was separated from the granular colorless solid by filtration and the latter washed with anhydrous ether (4×50 cc.). The combined filtrate and washings were dried over anhydrous magnesium sulphate (15 gm.). The ether solution was decanted and the drying agent washed with anhydrous ether (4×50 cc.). The ether was removed by heating on the steam bath and the residue was distilled *in vacuo* yielding 28.4 gm. of a mixture of oil and crystals, b.p. 100–130° C. at 10 mm. Separation of the crystals by filtration and further purification by recrystallization from 60–70° petroleum ether gave 16.2 gm. (45.0%) of 2-(2-methyl-4-methoxyphenyl)-propanol-2 (XI), m.p. 66–67° C. Calc. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%. Found: C, 73.73; H, 9.03%. The infrared spectrum of this substance showed strong hydroxyl absorption at 3.0 μ.

The residual oil, 12.2 gm. (38.0%), n_D^{25} 1.5237, b.p. 99–102° C. at 11 mm., was subsequently identified as 6-isopropenyl-3-methoxytoluene (XII).

6-Isopropenyl-3-methoxytoluene (*XII*)

2-(2-Methyl-4-methoxyphenyl)-propanol-2 (XI) (5.40 gm., 0.0300 mole) and 90% sulphuric acid (10 cc.) were placed in a 35-cc. round-bottomed flask equipped with a teflon-covered magnetic stirring bar and reflux condenser. The mixture was heated under reflux with stirring for six hours, cooled, and extracted with peroxide-free ether (4×10 cc.). The ether extract was washed with 5% sodium bicarbonate solution (10 cc.), then with water (2×10 cc.), and dried over anhydrous magnesium sulphate (5 gm.). The ether solution was decanted and the desiccant washed with anhydrous ether (4×10 cc.). The solutions were combined and concentrated by distillation on the steam bath. The residue was transferred to a 10-cc. pear-shaped modified Claisen flask and distilled *in vacuo* yielding 3.92 gm. (80.8%) of 6-isopropenyl-3-methoxytoluene (XII) as a colorless oil, b.p. 94.5° C. at 9 mm., n_D^{25} 1.5243. Calc. for $C_{11}H_{14}O$: C, 81.45; H, 8.70%. Found: C, 81.27; H, 8.83%. The infrared spectrum of this substance showed strong terminal methylene group absorption at 11.1 μ which disappeared on hydrogenation.

6-Isopropyl-3-methoxytoluene (*XIII*)

(*a*) *From 6-isopropenyl-3-methoxytoluene* (*XII*).—6-Isopropenyl-3-methoxytoluene (XII) (5.45 gm., 0.0336 mole) was placed in the reaction flask of a hydrogenator together with Adams' Catalyst (0.200 gm.) and absolute ethanol (100 cc.) and hydrogenated at atmospheric pressure. The reaction was complete in 13 min. The mixture was filtered to remove the catalyst, and the ethanol removed from the filtrate by distillation *in vacuo*. The residue was dissolved in anhydrous ether (50 cc.) and dried overnight over anhydrous magnesium sulphate (3 gm.). The orange solution was decanted and the desiccant washed with anhydrous ether (4×10 cc.). The combined ether solutions were evaporated on the steam bath, transferred to a 10-cc. pear-shaped modified Claisen flask, and distilled *in vacuo* yielding 5.09 gm. (92.3%) of colorless to amber colored oil, b.p. 98° C. at 9 mm., n_D^{25} 1.5081.

(*b*) *From 3-methyl-4-isopropylphenol* (*III*).—3-Methyl-4-isopropylphenol (III) (15.0 gm., 0.100 mole), m.p. 112–113° C., obtained from the isopropylation of *m*-cresol (4) was dissolved in 15% sodium hydroxide solution (25 cc.) in a 100-cc. beaker equipped with a teflon-covered magnetic stirring bar, burette, and thermometer. The stirred solution was treated at 40° C. with dimethyl sulphate (25.2 gm., 0.200 mole) added in one portion. The temperature rose rapidly to 82° C. and the solution became acidic and turbid and then separated into two layers. The mixture was treated with small portions (approximately 3 cc. per addition) of 15% sodium hydroxide until no further acidic reaction was evident (11 min., 18 cc.). The mixture was stirred for a further 30 min., transferred to a separatory funnel containing peroxide-free ether (25 cc.), and the ether layer separated. The aqueous phase was extracted with ether (3×25 cc.) and the combined ether solutions dried over magnesium sulphate (10 gm.). The ether solution was decanted, the desiccant washed with anhydrous ether (4×10 cc.), and the ether removed by evaporation on the steam bath. The residue was transferred to a 25-cc. pear-shaped modified Claisen flask and distilled *in vacuo* yielding 14.9 gm. (90.7%) of 6-isopropyl-3-methoxytoluene (XII) as a colorless oil, b.p. 98° C. at 9 mm., n_{D}^{25} 1.5083. Calc. for $C_{11}H_{16}O$: C, 80.46; H, 9.82%. Found: C, 80.56%; H, 9.90%. The infrared spectra of the 6-isopropyl-3-methoxytoluene (XIII) from 6-isopropenyl-3-methoxytoluene (XII) and from the isopropyl-3-methylphenol of m.p. 112–113° C. were measured as liquid films and found to be identical.

ACKNOWLEDGMENTS

The authors wish to thank Dr. S. F. MacDonald of the Division of Pure Chemistry for the use of his hydrogenation apparatus, and Dr. C. E. Hubley of Defence Research Chemical Laboratories for the infrared spectral analysis.

REFERENCES

1. Bannard, R. A. B. and Latremouille, G. Can. J. Chem. 31: 469. 1953.
2. Barnes, R. B., Gore, R. C., Liddel, V., and Williams, Van. Z. Infrared spectroscopy. Reinhold Publishing Corporation, New York. 1944. p. 67.
3. Buu-Hoi, Ng. Ph. Ann. 556: 1. 1944.
4. Chichibabine, A. E. and Barkovsky, C. Ann. chim. (Paris), 17: 316. 1942.
5. Darzens, G. and Levy, M. Compt. rend. 193: 292. 1931.
6. Darzens, G. and Levy, M. Compt. rend. 193: 321. 1931.
7. Dieckmann, W. Ber. 45: 2697. 1913.
8. Edwards, J. D. and Cashaw, J. L. J. Org. Chem. 20: 847. 1955.
9. Horning, E. C., Denekas, M. O., and Field, R. E. Org. Syntheses, 27: 24. 1947.
10. Horning, E. C., Horning, M. G., and Platt, E. J. J. Am. Chem. Soc. 71: 1773. 1949.
11. Horning, E. C., Horning, M. G., and Walker, G. N. J. Am. Chem. Soc. 71: 169. 1949.
12. Mozingo, R. Org. Syntheses 26: 77, Method B. 1946.
13. Quelet, R. and Paty, M. Procès-verbaux séances soc. sci. phys. et nat. Bordeaux, 19. 1944–45.
14. Rouault, G. F. and Smith, L. I. J. Am. Chem. Soc. 65: 631. 1943.
15. Ullmann, F. and Uzbachian, J. B. Ber. 36: 1804. 1903.
16. von Walther, R. F. and Zipper, W. J. prakt. Chem. [2], 91: 376. 1915.