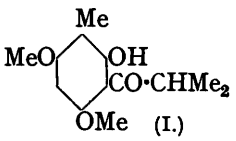
NOTES.

The Synthesis of Baeckeol. By B. A. HEMS and A. R. TODD.

RAMAGE and STOWE (this vol., p. 425) reported that they had synthesised methylphlor*iso*butyrophenone dimethyl ether (I) and shown it to be identical with baeckeol, a phenolic constituent of essential oils from certain species of *Myrtaceæ* (Penfold and Morrison, *J. Proc. Roy. Soc. New South Wales*, 1922, **56**, 87). In the course of some unpublished synthetic work on constituents of the anthelminthic drug kousso (cf. Hems and Todd, J., 1937, 562), carried out in the University of Edinburgh some years ago, we had occasion to synthesise (I). The method employed was direct methylation of phlor*iso*butyrophenone in acetone solution with methyl iodide and potassium carbonate and the synthesis is worthy of record, since it is preferable to that of Ramage and Stowe should (I) be required in any quantity. The orientation of our material as 2-hydroxy-4 : 6-dimethoxy-3-methyl*iso*butyrophenone (I) follows from the fact that it gives a reddish-violet colour with ferric chloride and a blue colour with 2 : 6-dichloroquinonechloroimide, the latter reaction indicating that the *p*-position to the free hydroxyl is unsubstituted.



(I.)

There appeared to be one serious discrepancy between our results and those of Ramage and Stowe; the acetate of our product crystallised from aqueous methanol in needles, m. p. 79—80°, whereas the synthetic baeckeol of these authors gave an acetate crystallising from the same solvent in prisms, m. p. 73°, undepressed on admixture with natural baeckeol acetate (prisms, m. p. 71—72°. Penfold and Simonsen, *J. Proc. Roy. Soc. New South Wales*, 1938, **71**, 291). Through the kindness of Professor Simonsen and Dr. Ramage we have been able to compare the natural and the synthetic product and clear up the discrepancy, which is due to dimorphism (see below). If the prism form is melted and maintained at 75° for a minute or so, it resolidifies at that temperature and on further heating melts at 79—80°.

*2-Hydroxy-4 : 6-dimethoxy-3-methyl*iso*butyrophenone* (*Baeckeol*) (I).—A mixture of phlor*iso*butyrophenone (2 g.) (Karrer, *Helv. Chim. Acta*, 1919, **2**, 466), methyl iodide (4 c.c.), acetone (20 c.c.), and anhydrous potassium carbonate (6 g.) was refluxed for 2 hours and cooled, and the liquid filtered and evaporated to dryness. The residue on recrystallisation from methanol gave (I) in pale yellow needles (0·7 g.), m. p. 103—104° (Found : C, 65·3; H, 7·6. Calc. for $C_{13}H_{18}O_4$: C, 65·5; H, 7·6%). The mixed m. p. with natural or synthetic (R. and S.) baeckeol showed no depression.

*2-Acetoxy-4 : 6-dimethoxy-3-methyl*iso*butyrophenone*—The synthetic phenol was refluxed for 1½ hours in pyridine solution with acetic anhydride. On crystallisation from warm aqueous methanol the acetate separated in colourless needles, m. p. 79—80° (Found : C, 64·2; H, 7·4. Calc. for $C_{15}H_{20}O_5$: C, 64·3; H, 7·1%). When the acetate was dissolved in warm aqueous methanol of such a concentration that no crystallisation occurred before the solution reached room temperature, and the solution was left in the ice-chest for several hours, colourless prisms were obtained, m. p. 73° (Found : C, 63·9; H, 7·2%). A mixed m. p. with a specimen of synthetic baeckeol acetate (R. and S., m. p. 73°) showed no depression, and a mixture of the prism and the needle form melted at 79—80°.

Baeckeol Acetate from Natural Material.—Prepared from natural baeckeol by the above

methods, the acetate was obtained in needles, m. p. 79°, and in prisms, m. p. 73°, undepressed on admixture with the corresponding forms prepared from the synthetic product.

The authors are indebted to the Carnegie Trustees for a Research Scholarship held by one of them (B. A. H.).—THE UNIVERSITY, MANCHESTER. [*Received, July 17th*, 1940.]

An Attempted Synthesis of Papaverine. By J. F. KEFFORD.

AN attempt was made to apply a new general synthesis of 1-*iso*quinoline derivatives (Davies, Kefford, and Osborne, J., 1939, 360) to the synthesis of papaverine by condensing ω-bromo-6-cyano-3 : 4-dimethoxystyrene with the Grignard compound of veratryl bromide. However, attempts to prepare the latter Grignard compound were unsuccessful. Certain intermediates which have not previously been recorded are here described.

6-Nitro-3 : 4-dimethoxycinnamic acid, prepared from 6-nitroveratraldehyde by malonic acid condensation, formed yellow needles, m. p. 286° (decomp.), from glacial acetic acid. Kanevska *et al.* (*Arch. Pharm.*, 1934, **272**, 770) record m. p. 281—282° (decomp.).

The acid (25 g.) was dissolved in 200 ml. of concentrated aqueous ammonia, added to a hot ferrous sulphate solution (250 g. in 400 ml.), and boiled for 10 minutes with shaking. After cooling and filtration, neutralisation of the filtrate with sulphuric acid precipitated brown plates (16 g.), m. p. 175—177°, of 6-amino-3 : 4-dimethoxycinnamic acid. The amino-acid was not further purified; but treatment with concentrated hydrochloric acid, decoloration with charcoal, and precipitation with sodium acetate solution yielded white needles of 6 : 7-*dimethoxycarbostyril*, m. p. 229° after recrystallisation from alcohol (Found : N, 6·8. $C_{11}H_{11}O_2N$ requires N, 6·8%).

6-*Cyano*-3 : 4-*dimethoxycinnamic Acid*.—A solution of the 6-amino-acid (20 g.) in 200 ml. of ice-cold N-sulphuric acid was diazotised, and the diazo-solution run slowly with stirring into a hot solution of copper sulphate (24·6 g.) and sodium cyanide (16·8 g.) in 160 ml. of water. The mixture was heated on the water-bath for 10 minutes, acidified, cooled, and filtered. The product was best purified by drying and extraction with hot alcohol. After evaporation of the alcohol, the residue was dissolved in aqueous ammonia, decolorised with charcoal, and acidified to give a gelatinous precipitate, which crystallised from glacial acetic acid in white plates (9 g.), m. p. 273—274° (Found : equiv., 232·3. $C_{12}H_{11}O_4N$ requires equiv., 233·2).

ω-*Bromo*-6-*cyano*-3 : 4-*dimethoxystyrene*.—The cyano-acid (2·5 g.) was kept for 3 days over bromine (1·72 g.) in a desiccator. The buff powder was refluxed for 1 hour with sodium acetate solution (5 g. in 50 ml.), cooled, and extracted with ether. The aqueous layer, on acidification, gave an acid, which crystallised from glacial acetic acid in white plates, m. p. 282°, and contained bromine but no nitrogen. It is evidently αβ-*dibromo*-6-*carboxy*-3 : 4-*dimethoxyphenylpropionic acid* (Found : equiv., 206·0. $C_{12}H_{12}O_6Br_2$ requires equiv., 206·0). The ethereal layer yielded colourless, silky needles (1·5 g.), m. p. 155° after recrystallisation from methyl alcohol (Found : Br, 29·75. $C_{11}H_{10}O_2NBr$ requires Br, 29·8%). On the analogy of the ω-bromo-*o*-cyanostyrenes (Davies, Holmes, and Kefford, J., 1939, 357), this is cis-ω-*bromo*-6-*cyano*-3 : 4-*dimethoxystyrene*, since, presumably, it is *trans*-6-cyano-3 : 4-dimethoxycinnamic acid which is prepared by the above procedure.—THE UNIVERSITY OF MELBOURNE. [*Received, February 12th*, 1940.]
