

THE SYNTHESIS OF EUPARIN AND DEHYDROTREMETONE

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The boron trifluoride catalyzed acetylation of methyl 6-methoxycoumarilate, with concomitant cleavage of the methoxyl group, enabled the separation of the isomeric methyl 5- and 7-acetyl-6-hydroxycoumarilates¹.

We have now converted methyl 5-acetyl-6-hydroxycoumarilate (I) to 5-acetyl-6-hydroxy-2-isopropenylbenzofuran, euparin, a compound isolated from Eupatorium purpureum², E. cannabinum³ and E. japonica⁴. The O-acetate of I was submitted to ketalization with ethylene glycol, with the loss of the O-acetyl group. Excess methylmagnesium iodide gave an adduct which, on chromatography on acid washed alumina gave euparin m.p. 121-122° (Found: C, 72.08; H, 5.93. Calcd. for C₁₃H₁₂O₃: C, 72.21; H, 5.60). $\lambda_{\text{max}}^{\text{EtOH}}$ 263,

¹ P. K. Ramachandran, A. T. Tefteller, G. O. Paulson, T. Cheng, C. T. Lin and W. J. Horton, J. Org. Chem. **28**, 398 (1963).

² B. Kamthong and A. Robertson, J. Chem. Soc. 925 (1939).

³ F. v. Gizycki, Süddeut. Apoth.-Ztg. **90**, 503 (1950). Z. I. Jerzmanowska, Polska Akad. Umiej., Prace Kom. Farm. Dissertationes Pharm. **3**, 165 (1951). J. Sykulski, Acta Polon. Pharm. **15**, 361 (1958).

⁴ T. Nakaoki, N. Morita and S. Nishino, Yakugaku Zasshi **78**, 557 (1958). Chem. Abstr. **52**, 13190 (1958).

358 μ (ϵ , 34400, 5900). $\lambda_{\text{max}}^{\text{CCl}_4}$ 6.10, 6.95, 7.20, 7.35, 7.55, 8.60, 8.80, 9.60, 11.18 μ . Its melting point and the melting points of its semicarbazone, 254-255°, dinitrophenylhydrazone, 254-255°, and maleic anhydride adduct, 244-245° agreed with those reported^{2,3}. The green color with ferric chloride and the orange to red, brown and then green color with concentrated sulfuric acid agreed with the original report².

The aluminum chloride catalyzed acetylation of methyl coumarilate gave methyl 5-acetylcoumarilate (II). Attack at the 5-position is consistent with that of other electrophilic reagents⁵ and confirmed by the Beckmann rearrangement of the oxime of II to give the 5-amino compound which was converted to methyl 5-chlorocoumarilate m.p. 94-96°; reported 96-97°⁶. In further support of this structure assignment, II was catalytically reduced to methyl 5-ethylcoumarilate which was identical to material prepared from 5-ethyl-2-hydroxybenzaldehyde according to Tanaka's method⁷.

Formation of the ethylene glycol ketal of II followed by the addition of methylmagnesium iodide gave the ketal of a tertiary alcohol which was dehydrated and cleaved by acid to dehydrotremetone m.p. 84.0-85.5° $\lambda_{\text{max}}^{\text{EtOH}}$ 253, 280.5, 292.5 μ (ϵ , 39100, 19150, 14900); oxime m.p. 131.5-133.5°; reported m.p. 87.5-88.5°⁸ $\lambda_{\text{max}}^{\text{EtOH}}$ 252, 280, 292 μ (ϵ , 39000, 19000, 15500)⁸;

⁵ A. L. Mndzhoyan and A. A. Aroyan, Izvest. Akad. Nauk Armyan. S.S.R., Khim. Nauki 11, 45 (1958); E. L. Martin, U. S. 2,754,286; Chem. Abstr. 51, 920 (1957); E. I. du Pont de Nemours and Co., Brit. 705,950; Chem. Abstr. 49, 2233 (1955). S. Tanaka, J. Chem. Soc. Japan 73, 872 (1951).

⁶ Q. Andrisano and F. Duro, Gazz. chim. ital. 85, 381 (1955).

⁷ S. Tanaka, J. Am. Chem. Soc. 73, 872 (1951).

⁸ W. A. Bonner, J. I. Degraw, D. M. Bowen and V. R. Shah, Tetrahedron Letters 12, 417 (1961); Tetrahedron 18, 1295 (1962); J. Org. Chem. 27, 3917 (1962).

oxime m.p. 131-132°⁸. The maleic anhydride adduct melted at 205-210° (dec.) (Found: C, 68.72; H, 4.23. Calcd. for C₁₇H₁₄O₅: C, 68.45; H, 4.73).

Dehydrotremetone has been isolated from Eupatorium urticaefolium⁸ and from Aploppus heterophyllus⁹. A mixture of synthetic material m.p. 84.0-85.5° with dehydrotremetone from A. heterophyllus m.p. 80-82° (cor.) gave no depression on melting and the infrared curves were identical in all details. The chief bands were at 5.98, 7.00, 7.41, 7.74, 8.68 and 11.14 μ (all in carbon tetrachloride) which confirms the values previously reported⁸. A sample of dehydrotremetone from E. urticaefolium⁸ melted at 83.5-85.5° and was unchanged in melting point on mixing with our synthetic sample. This sample in carbon tetrachloride exhibited absorption bands in the infrared region identical in all details to the other samples above. A mixture of the oxime of dehydrotremetone m.p. 131-132°⁸ and the oxime of synthetic dehydrotremetone melted at 132-133°.

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⁹ L. H. Zalkow, N. Burke, G. Cabat and E. A. Grula, J. Med. Pharm. Chem. 5, 1342 (1962).