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A SYNTHESIS OF ISOFLAVONES BY A MODIFIED VILSMEIER-HAACK REACTION

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THE modified Vilsmeier-Haack reaction, in which formylation is effected by dimethylformamide (DMF) and phosphorus oxychloride ($POCl_3$), has been widely used for the preparation of aldehydes of many types.[1] Buu-Hoi observed that in the DMF-$POCl_3$ reaction, unlike the Gattermann reaction, phenolic ethers were more reactive than the corresponding phenols; phenol at water-bath temperature gave a poor yield of p-hydroxybenzaldehyde, whereas anisole gave a high yield of anisaldehyde. However, resorcinol was formylated at room temperature in 46 per cent yield.[2d] Mangoni[3] obtained a higher yield (about 70 per cent) of β-resorcylaldehyde by treatment of resorcinol in DMF with $POCl_3$ at 50-60° and then for a few minutes at 100°; the dimethyl ether gave a slightly improved yield (74 per cent). Mangoni isolated a crystalline intermediate, $[Me_2N\text{-}CH\text{-}Ar]^+PO_2Cl_2^-$, which was hydrolysed quantitatively to ArCHO, $NHMe_2$, H_3PO_4 and HCl, and catalytically hydrogenated to $ArCH_2NMe_2$ (an unstable glass but chromatographically and analytically pure). Formylation normally takes place in the p-position, but if this is occupied, in the o-position.[2b] According to Buu-Hoi it is not possible to introduce

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[1] For recent reviews see [a] V.I. Minkin and G.N. Dorofeenko, Russian Chem. Rev. No. 11, 599 (1960); [b] H. Bredereck, R. Gompper, H.G. v. Schuh and G. Theilig, Angew. Chem. 71, 753 (1959).

[2a] N.P. Buu-Hoi, N.D. Xuong, M. Sy, G. Lejeune and N.B. Tien, Bull. Soc. Chim. Fr. 1594 (1955); [b] N.P. Buu-Hoi, G. Lejeune and M. Sy, C.R. Acad. Sci., Paris 240, 2241 (1955); [c] N.P. Buu-Hoi and D. Lavit, J. Chem. Soc. 1743 (1956); [d] M. Bisagni, N.P. Buu-Hoi and R. Royer, Ibid. 3693 (1955).

[3] L. Mangoni, Ann. Chim. 48, 930 (1958).

two formyl groups into the same aromatic nucleus, apparently as the result of the deactivating influence of the first formyl group; but he did not investigate phloroglucinol or its ethers. The action of DMF and $POCl_3$ on benzyl 2-hydroxyphenyl ketones derived from resorcinol and phloroglucinol has now been studied since formylation at the reactive methylene group should lead to an isoflavone directly.

Under the conditions used by Buu-Hoi[2] or Mangoni[3] for the formylation of resorcinol or its dimethyl ether or veratrole, no isoflavone could be isolated from benzyl 2,4-dihydroxyphenyl ketone (I), DMF and $POCl_3$; but the following conditions led to the isoflavone. $POCl_3$ (1 mole per mole of deoxybenzoin) was added dropwise to excess DMF cooled to 10°; the quantity of DMF was adequate for the deoxybenzoin to form a clear solution at room temperature. The mixture of DMF and $POCl_3$ was kept for 15 min at room temperature to complete complex formation. The deoxybenzoin (I) was then added to the pale pink solution of the DMF-$POCl_3$ complex in DMF, and allowed to dissolve. The solution was finally heated to gentle reflux for 18 hr, cooled to room temperature and poured into water. A single crystallization of the product gave 7-hydroxyisoflavone (III) in nearly quantitative yield. When the reaction mixture was worked up after heating for 1-3 hr, the isoflavone was also isolable, but in yields of 20-30 per cent. 4-Methoxybenzyl 2,4-dihydroxyphenyl ketone and benzyl 2,3,4-trihydroxyphenyl ketone similarly yielded formononetin and 7,8-dihydroxyisoflavone, protection of hydroxyl groups being unnecessary. 2-Phenylacetyl-1-naphthol gave 7,8-benzoisoflavone. The products agreed in m.p. and mixed m.p. with those prepared by the ethyl formate[4] and orthoformate methods.[5]

In the order of addition of the reagents our procedure follows the

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[4] H.S. Mahal, H.S. Rai and K. Venkataraman, J. Chem. Soc. 1120, 1769 (1934).
[5] V.R. Sathe and K. Venkataraman, Curr. Sci., India 18, 373 (1949).

formylation of dimethylaniline,[6] pyrrole,[7] and indole;[8] the latter required much lower temperatures and shorter periods, and hydrolysis of the reaction product ($ArCH<^{OPOCl_2}_{NMe_2}$) with aqueous sodium acetate or hydroxide was necessary for liberating the aldehyde.

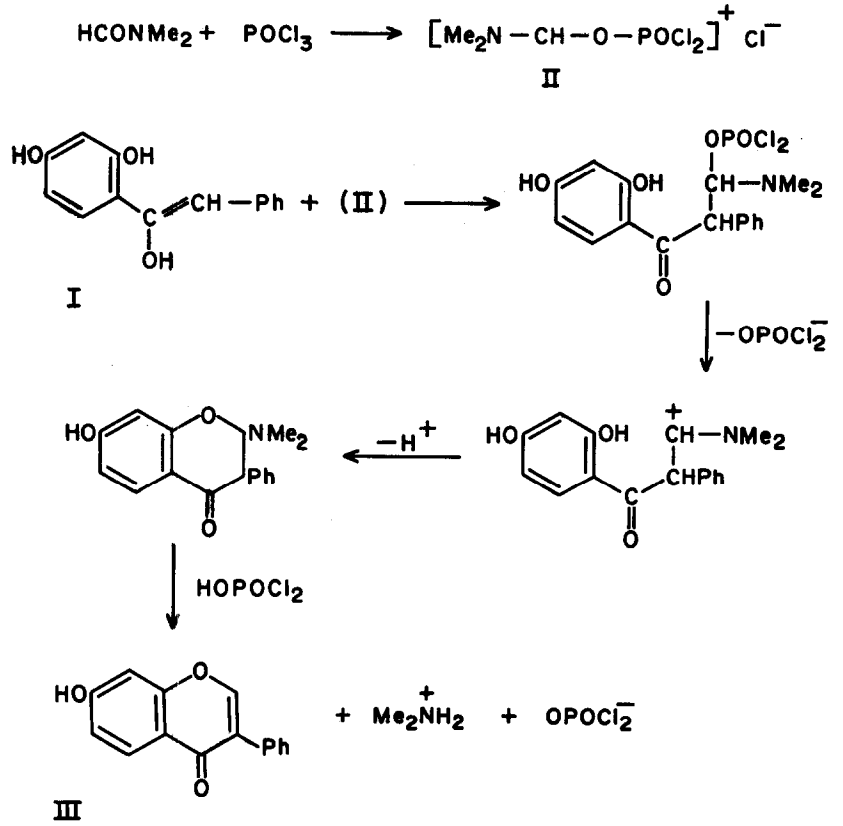
In view of the experimental conditions employed, as well as the earlier work of Smith who demonstrated the mechanism of the formylation of indole,[9] the probable path by which an isoflavone is formed when (I) is submitted to the action of DMF and $POCl_3$ is shown in Chart 1.

Benzyl 2-hydroxy-4,6-dimethoxyphenyl ketone failed to give 5,7-dimethoxyisoflavone by treatment with DMF and $POCl_3$ under a variety of conditions; at room temperature the deoxybenzoin was recovered, and at water-bath or higher temperatures, which enabled the methylene group to get formylated, the phloroglucinol nucleus reacted vigorously and led to a brown intractable material. These indicated that a single carbonyl group attached to the phloroglucinol nucleus did not deactivate it completely toward the DMF-$POCl_3$ reagent, and that nuclear formylation followed by polymerization preceded attack on the methylene group. Nuclear bromination of benzyl 2,4,6-trihydroxyphenyl ketone, reaction with DMF-$POCl_3$, and final debromination are now being studied. At the moment the DMF-$POCl_3$ method is limited in scope so far as naturally occurring isoflavones are concerned, because most of them have the phloroglucinol or 1,2,3,5-tetrahydroxybenzene pattern of substitution in the A-ring.[10]

The present isoflavone synthesis is similar in principle and scope to the Farkas method[11] in which a benzyl 2-hydroxyphenyl ketone is submitted

[6] E. Campaigne and W.L. Archer, Org. Synth. 33, 27 (1953).
[7] R.M. Silverstein, E.E. Ryskiewicz and C. Willard, Org. Synth. 36, 74 (1956).
[8] P.N. James and H.R. Snyder, Org. Synth. 39, 30 (1959).
[9] G.F. Smith, J. Chem. Soc. 3842 (1954).
[10] K. Venkataraman, Fortschr. Chem. Org. Naturstoffe 17, 1 (1959).
[11] L. Farkas, Chem. & Ind. 1212 (1957); Chem. Ber. 90, 2940 (1957).

Chart I



to a Gattermann-Adams formylation by zinc cyanide and hydrogen chloride; but it is distinct from the thermal reaction of benzyl o-hydroxyphenyl ketones with formamide (reflux temperature, 210°) or formanilide (250°) in an atmosphere of nitrogen reported by Wheeler.[12] Unlike the Vilsmeier reaction Wheeler's method did not require $POCl_3$. Wheeler noticed that all hydroxyl groups other than the hydroxyl providing the heterocyclic oxygen had to be protected by alkylation or esterification; the tosyl group promoted good yields, but was difficult to remove except by hydriodic acid

[12] T.S. Wheeler et al., J. Chem. Soc. 2495 (1958).

and acetic anhydride under demethylating conditions. Benzyl 2-hydroxy-4,6-dimethoxyphenyl ketone gave no isoflavone, but as in the ethyl orthoformate method,[13,14] the introduction of a p-nitro group in the benzyl moiety activated the methylene group and afforded 15 and 25 per cent yields of the isoflavone by treatment with formamide and formanilide respectively.

[13a] R.N. Iyer, K.H. Shah and K. Venkataraman, Proc. Indian Acad. Sci. 33A, 116 (1951); [b] S.A. Kagal, S.S. Karmarkar and K. Venkataraman, Ibid. 44A, 36 (1956).

[14] N.L. Dutta and J.L. Bose, J. Sci. Industr. Res. 11B, 413 (1952).