with cold solution of ammonium hydroxide to about pH 8. The suspended yellowish amorphous precipitate was kept in a refrigerator for about 1 hr., filtered by suction, washed with alcohol, acetone, and ether, and dried at 110°/0.5 mm. The sample decomposed gradually when heated above 240°, but did not melt even at 330°.

Anal. Calcd. for $C_6H_7N_5$: N, 46.60. Found: N, 46.21.

No procedure could be developed to prepare a sample of higher purity by recrystallization or vacuum sublimation.

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Studies on the C-Methyl-γ-benzopyrone System. Orientation in the Isoflavone Series. II[1]

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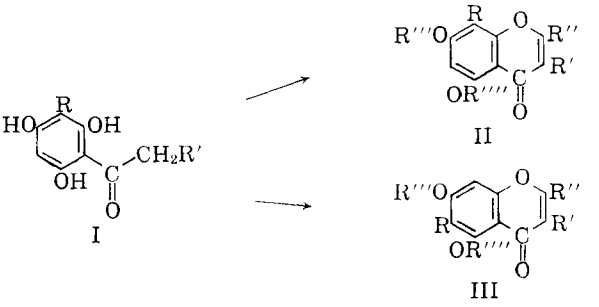
The ethoxalylation of 4′- and 2′-methyl ethers of 2,4,6-trihydroxy-3-methyldeoxybenzoin has resulted in the formation of an isomeric mixture of isoflavones of 5,6,7- and 5,7,8-orientations. The orientation of each isomer has been authenticated by comparison with synthetic standards. The investigation of the condensation of 2,4,6-trihydroxy-3-methyldeoxybenzoin with acetyl chloride and pyridine at 0° (followed by refluxing with aqueous sodium carbonate) and acetic anhydride and sodium acetate at high temperature has also given rise to an isomeric mixture of 2-methylisoflavones of the same orientations. The dual course of very facile Baker–Venkataraman transformation followed by isoflavone ring closure has been suggested for the formation of isomeric mixtures in some cases.

Mukerjee and Seshadri[2] have stated that in the synthesis of C-methyl isoflavones that "8-methyl compounds are generally formed if the temperature of the reaction is high[3a,b] (boiling acetic anhydride) whereas, if conducted at 0°,[3b] the 6-methyl compounds result." The present paper describes the reinvestigation of the work and reports our findings which do not agree with those of the previous workers.[3a,b]

Ethoxalyl Chloride–Pyridine.—Our earlier work[4] on the ethoxalylation of a C-methyl deoxybenzoin (I. R = Me, R′ = C_6H_5) established the formation of a mixture of isoflavones of 5,7,8- and 5,6,7-orientations. An explanation as to the dual course of cyclization involving 2- and 6-hydroxyl groups also was advanced. Mehta and Seshadri,[3b] however, using a deoxybenzoin of the similar type (I. R = Me, R′ = *p*-$MeOC_6H_4$) reported the exclusive formation of an isoflavone of 5,6,7-orientation. As their findings do not agree with our previous results and ideas the ethoxalylation of 2,4,6-trihydroxy-3-methyl-4′-methoxydeoxybenzoin was reinvestigated.

Mehta and Seshadri[3b] found that the deoxybenzoin (I. R = Me, R′ = *p*-$MeOC_6H_4$) on ethoxalylation gave a product, m.p. 176–178°, which was assigned the structure of ethyl 5,7-dihydroxy-4′-methoxy-6-methyl isoflavone-2-carboxylate (III. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = CO_2Et, R‴ = R⁗ = H). The carbethoxyisoflavone on hydrolysis yielded the corresponding carboxyisoflavone (melting point not reported) (III. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = CO_2H, R‴ = R⁗ = H). The crude carboxyisoflavone on decarboxylation at 275° gave an isoflavone, m.p. 210–212°. It was characterized by them as 5,7-dihydroxy-4′-methoxy-6-methylisoflavone (III. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = R‴ = R⁗ = H) by partial methylation to 5-hydroxy-7,4′-dimethoxy-6-methylisoflavone (III. R = R‴ = Me, R′ = *p*-$MeOC_6H_4$, R″ = R⁗ = H) and by comparing it with the nuclear methylation product of genistein.[5]



The present authors have now found the product, m.p. 176–178°, to be a mixture of the two isomers. It was, however, resolved by a careful fractional crystallization from benzene–methanol into two distinct products melting at 199–201° and 201–203°. The mixed melting point of the two isomers was found to be 172–173°.

The carbethoxyisoflavone, m.p. 199–201°, on usual hydrolysis gave the corresponding carboxyisoflavone m.p. 280–281°, which on subsequent de-

(1) Part I, *J. Org. Chem.*, **27**, 944 (1962).

(2) S. K. Mukerjee and T. R. Seshadri, *Chem. Ind.* (London), 271 (1955).

(3)(a) R. Ienger, A. C. Mehta, T. R. Seshadri, and S. Varadarajan, *J. Sci. Ind. Res.* (India), **13B**, 166 (1954). (b) A. C. Mehta and T. R. Seshadri, *J. Chem. Soc.*, 3823 (1954).

(4) M. O. Farooq, W. Rahman, and Kh. Takrimullah Nasim, *J. Org. Chem.*, **27**, 944 (1962).

(5) W. Baker and R. Robinson, *J. Chem. Soc.*, 2713 (1926).

carboxylation yielded an isoflavone m.p. 235–236°. The latter was characterized as 5,7-dihydroxy-4′-methoxy-8-methylisoflavone (II. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = R‴ = R⁗ = H) by its complete methylation to 5,7,4′-trimethoxy-8-methylisoflavone m.p. 180° (II. R = R‴ = R⁗ = Me, R′ = *p*-$MeOC_6H_4$, R″ = H) which did not depress the melting point on admixing with a synthetic standard prepared according to Whalley.[6]

The carbethoxyisoflavone, m.p. 201–203° (III. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = CO_2Et, R‴ = R⁗ = H), on similar treatment as above yielded the corresponding carboxyisoflavone, m.p. 288–291° (III. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = CO_2H, R‴ = R⁗ = H), and then an isoflavone, m.p. 260–263°. It was characterized as 5,7-dihydroxy-4′-methoxy-6-methylisoflavone (III. R = Me, R′ = *p*-$MeOC_6H_4$, R″ = R‴ = R⁗ = H) by the preparation of its complete methyl ether, m.p. 169°. It showed no depression in melting point on admixture with an authentic sample[6] of 5,7,4′-trimethoxy-6-methylisoflavone (III. R = R‴ = R⁗ = Me, R′ = *p*-$MeOC_6H_4$; R″ = H).

Thus, the ethoxalylation of I (R = Me, R′ = *p*-$MeOC_6H_4$) resulting in the formation of an isomeric mixture of isoflavones lends support to our work[4] and is not in agreement with the findings of Mehta and Seshadri.[3b] The fact that the melting points of 6-isomer and its intermediates (except the fully methylated isoflavone) are higher than the corresponding 8-methyl derivatives (Table I) is also in good agreement with the previous observations.[4,7]

TABLE I

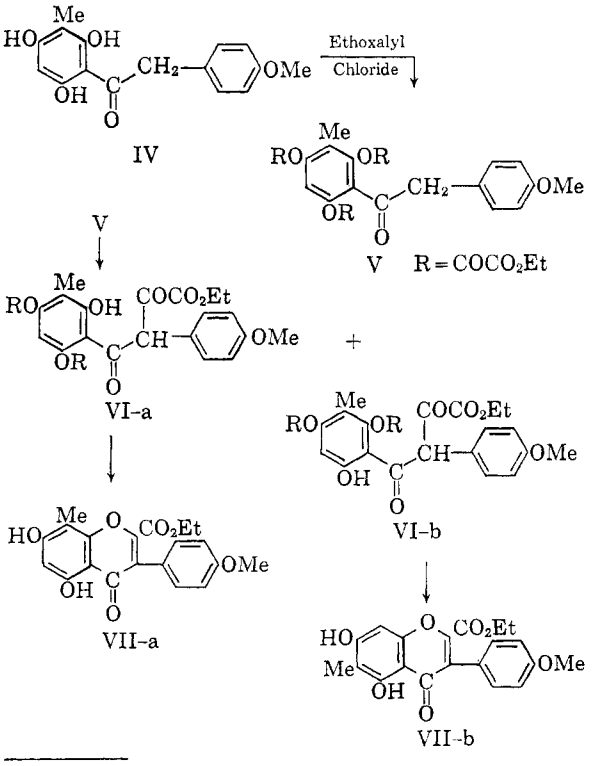
6-Methyl	M.p., °C.	8-Methyl	M.p., °C.
2-Carbethoxy-5,7-dihydroxy-4′-methoxy-	201–203	2-Carbethoxy-5,7-dihydroxy-4′-methoxy-	199–201
2-Carboxy-5,7-dihydroxy-4′-methoxy-	288–291	2-Carboxy-5,7-dihydroxy-4′-methoxy-	280–281
5,7-Dihydroxy-4′-methoxy-	260–263	5,7-Dihydroxy-4′-methoxy-	235–236
5,7,4′-Trimethoxy-	169	5,7,4′-Trimethoxy-	180

Our findings were further confirmed by the investigation of ethoxalylation of another deoxybenzoin of the similar type. 2,4,6-Trihydroxy-3-methyl-2′-methoxydeoxybenzoin[6] (I. R = Me, R′ = *o*-$MeOC_6H_4$) on ethoxalylation gave a gummy product which could not be obtained crystalline. The crude product was therefore subjected to methylation with methyl sulfate and potassium carbonate in acetone. On subsequent work-up and fractional crystallization using benzene–petrol followed by ethanol the methylated product separated into two crystalline products melting at 155–157° and 160–162°. The carbethoxymethoxyisoflavones melting at 155–157° and 160–162° gave on hydrolysis and decarboxylation methylated isoflavones m.p. 180–182 and 220°, respectively. The isoflavone melting at 180–182° has been characterized as the 5,7,2′-trimethoxy-8-methyl (II. R = R‴ = R⁗ = Me, R′ = *o*-$MeOC_6H_4$, R″ = H) and that melting at 220° as its 6-methyl isomer (III. R = R‴-R⁗ = Me, R′ = *o*-$MeOC_6H_4$, R″ = H) by melting and mixed melting points with synthetic standards.[6,17] All the intermediate compounds isolated have been shown with their melting points in Table II.

TABLE II

6-Methyl	M.p., °C.	8-Methyl	M.p., °C.
2-Carbethoxy-5,7,2′-trimethoxy-	160–162	2-Carbethoxy-5,7,2′-trimethoxy-	155–157
2-Carboxy-5,7,2′-trimethoxy-	222–224	2-Carboxy-5,7,2′-trimethoxy-	241–242
5,7,2′-Trimethoxy-	220	5,7,2′-Trimethoxy-	180–182

An explanation for the dual course of cyclization resulting in the formation of 6- and 8-isomers, the latter in greater amount has already been advanced.[4] It is based on the original mechanism of ethoxalylation process.[8] The formation of two isomers may also be explained by taking into consideration, as suggested by Gupta and Seshadri,[9] Baker–Venkataraman transformation during ethoxalylation.



(6) W. B. Whalley, *J. Am. Chem. Soc.*, **75**, 1059 (1953).

(7) T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.*, **37A**, 145 (1953).

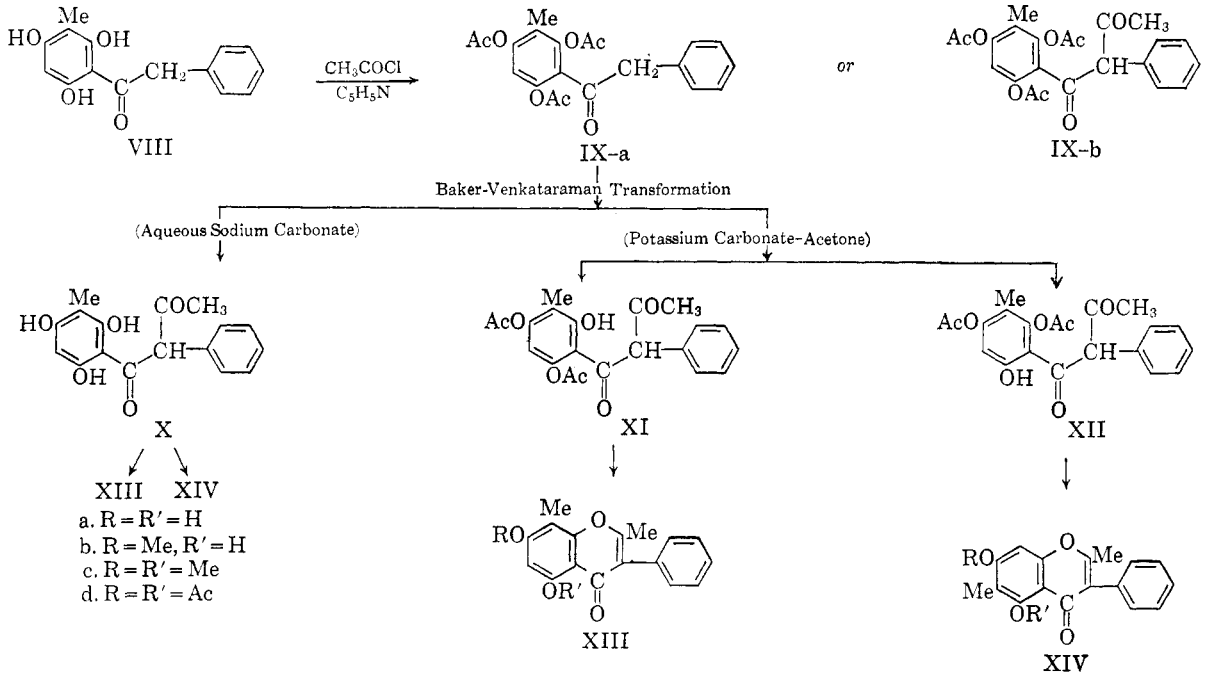
(8) W. Baker, J. Chadderton, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1852 (1953).

(9) V. N. Gupta and T. R. Seshadri, *J. Sci. Ind. Res.* (India), **16B**, 116 (1957).

With the type of deoxybenzoin used in these studies, two isomeric intermediates may presumably be formed by Baker–Venkataraman transformation of carbethoxalyl groups both *ortho* and *para* to the methyl group, thus making available both the alternative hydroxyl groups (2 and 6) for isoflavone ring closure. The steric acceleration by the methyl group which crowds the carbethoxalyl *ortho* to it may be responsible for the formation of 8-isomer in greater amount. The steps of this possible mechanism are shown on page 4216.

Acetyl Chloride–Pyridine.—Mehta and Seshadri[3b] reported the synthesis of 2,6-dimethyl-5,7-dihydroxyisoflavone and its 4′-methyl ether (exclusively 6-isomer) by the use of acetyl chloride and pyridine at 0° followed by refluxing the product with aqueous sodium carbonate. The later work of Gupta and Seshadri[9] indicated that the treatment of deoxybenzoin with acetyl chloride and pyridine at 0° furnished *O*-acetylated deoxybenzoin which undergo a very facile Baker–Venkataraman transformation and isoflavone ring closure with carbonate under either aqueous or nonaqueous conditions.

It appeared therefore that use of acetyl chloride–pyridine method with deoxybenzoins having a C-methyl phloroglucinol nucleus should lead to the formation of 6- and 8-methyl isomers. The course of the reaction may depend upon the reagent employed for bringing about Baker–Venkataraman transformation. In the case of anhydrous potassium carbonate acetone as the reagent for transformation, the mechanism may be quite similar to that postulated for the ethoxalylation process—*i.e.*, the formation of two isomeric intermediate diketones followed by ring closure to the corresponding isoflavones. Aqueous sodium carbonate, on the other hand, is expected to give rise to only one intermediate diketone having both the alternative hydroxyl groups available for cyclization. Consequently, the formation of the same isomeric isoflavones may take place either during the base treatment or during subsequent acidification. In this case the greater reactivity of 6-hydroxyl may be responsible for the formation of 6-isomer in greater amount, which has actually been found the case by the present authors. The greater reactivity of the 6-hydroxyl may be due to the steric hindrance that the methyl group exerts on the cyclization at C-2. The reason for the formation of only one intermediate may be assigned to Baker–Venkataraman transformation accompanied with simultaneous deacetylation of all the remaining groups which may not be the case with anhydrous potassium carbonate–acetone. The various possible steps involved in the mechanism are shown below.



The above arguments necessitated the reinvestigation of isoflavone formation with acetyl chloride–pyridine. The deoxybenzoin (I)[3a] on treatment with acetyl chloride–pyridine at 0° and subsequent work up as described by Mehta and Seshadri[3b] gave a product. The structure IXb was originally[3b] assigned but later[9] revised to IXa. The acetylated deoxybenzoin on refluxing with aqueous sodium carbonate followed by acidification gave a precipitate which crystallized from alcohol as colorless needles m.p. 220–225°. Mehta and Seshadri[3b] reported its m.p. 249–251° and characterized it as 5,7-dihydroxy-2,6-dimethylisoflavone (XIVa) by preparing its 7-methyl ether, m.p. 188–190°.

The product, m.p. 220–225°, suspected to be an isomeric mixture, separated on monomethylation into two products melting at 188–190° and 131–

(10) S. K. Mukerjee and T. R. Seshadri, *Proc. Indian Acad. Sci.* **38A**, 207 (1953).

132°. The former agrees with the melting point of the 6-isomer[3b] (XIVb) but for the latter (8-isomer) the reported melting point is 151–153°.[3a] Repeated attempts by crystallization to raise the m.p. of 131–132° to 151–153° proved fruitless. The expected mixture of the two hydroxyisoflavones on complete methylation separated into two fractions (methanol) melting at 176–177° and 184–186°. The latter agrees well with the melting point of 2,8-dimethyl-5,7-dimethoxyisoflavone[3a] (XIIIc). The melting point of the completely methylated product of the 6-isomer, which has already been characterized at the partial methylation stage, is however not reported in the literature.

Thus in the case of acetyl chloride also we have definite reasons not to agree with the statement[2] and the work[3b] because of the formation of both the isomers of 6- and 8-orientations (the 6-isomer in greater amount) and the fact that the essential step of the reaction is not conducted at 0°.

Acetic Anhydride–Sodium Acetate.—Ienger, *et al.*,[3a] in view of the greater reactivity of a hydroxyl *para* to a methyl group, attempted the synthesis of 2,6-dimethyl-5-hydroxy-7-methoxyisoflavone (XIVb) by the vigorous acetylation of VIII. Contrary to their expectations they got the isomer of 8-orientation. On the basis of the exclusive formation of the 8-isomer they stated that in the vigorous acetylation of the deoxybenzoin the hydroxyl *ortho* to the methyl had unexpectedly proved to be more reactive than the one *para* to it. The course of the reaction was considered to be VIII → X → XIII.

We do not agree with the above statement and believe that the *para* hydroxyl in VIII is as usual more reactive. The greater reactivity of the *para* hydroxyl (6-position) is evidenced by its preferential acetylation to 2-hydroxyl under regulated conditions of acetylation. The argument[3a] that the presence of an α-acetyl group in the intermediate diketone (X) seems to alter the relative reactivity of the hydroxyl groups also appears to be unsound.

The isoflavone formation with acetic anhydride-sodium acetate is an Allan–Robinson type of synthesis which probably involves a Baker–Venkataraman rearrangement. This should result in the formation of an isoflavone mixture of 6- and 8-orientations, the latter in greater amount. The reasoning used here is analogous to that used in the discussion of the ethoxalylation reaction above. Actually, both the isomers, that of 8-orientation in greater amount, have been isolated by the present authors. It is clear from the above discussion that the relative reactivities of the hydroxyl groups are not involved in the preferential formation of the 8-isomer and so the previous explanation[3a] can be rejected.

The deoxybenzoin (VIII) on treatment with acetic anhydride–sodium acetate exactly under the conditions as specified by Ienger *et al.*,[3a] gave a dark brown product. Fractional crystallization resulted in various crops of crystals melting from 176–207°. The separation into two distinct products could not be effected. Ienger, *et al.*,[3a] reported 188–190° as the melting point of the product and assigned to it the structure of 2,8-dimethyl-5,7-diacetoxyisoflavone (XIIId). The various crops of crystals obtained were combined and subjected to deacetylation. The product on crystallization from ethanol gave colorless needles, m.p. 220–240°. The separation, however, could not be effected even at this stage. The product m.p. 220–240° on monomethylation separated on fractional crystallization (methanol) into two distinct products melting at 188–190° and 131–132°. The former was characterized as 2,6-dimethyl-5-hydroxy-7-methoxy- (XIVb) and the latter as 2,8-dimethyl-5-hydroxy-7-methoxyisoflavone (XIIIb), by mixed melting points with the products obtained earlier by the acetyl chloride method. Further confirmation as to the orientation of the two isomers was furnished by complete methylation and separation of the completely methylated isomers (XIIIc and XIVc). The 8-isomer, as expected, was obtained in greater amount.

On the basis of our work using acetic anhydride–sodium acetate in isoflavone synthesis we neither agree with the statement[2] nor with the work and arguments[3a] advanced for its support. It may be of interest to point out here that the parallel examples of the formation of isomeric mixture of 6- and 8-orientations in flavone[10] and chromone[11] syntheses using Allan–Robinson method are already cited in the literature. The Allan–Robinson synthesis of flavones and chromones involves a Baker–Venkataraman transformation[12–14] and so the explanations suggested above for the formation of isomeric pairs in the isoflavone series probably also apply to the flavone and chromone cases.

Experimental[15,16]

Ethoxalylation of 2,4,6-Trihydroxy-3-methyl-4′-methoxydeoxybenzoin (I. R = Me, R′ = *p*-MeOC$_6$H$_4$).—The deoxybenzoin[6,7] (4.0 g.), pyridine (40 cc.), and redistilled ethoxalyl chloride (8 cc.) were used for the condensation. The ester (4.48 g.) on crystallization from benzene gave pale yellow needles m.p. 176–178°. This material (2.7 g.) on repeated crystallizations from benzene followed by dilute methanol separated into aggregates of light yellow needles m.p. 201–203° (0.85 g.) and another product in the form of stout bright yellow needles m.p. 199–201° (1.0 g.).

Further crystallizations from various solvents did not improve the melting point of either of the components.

(11) S. K. Mukerjee and T. R. Seshadri, *Chem. Ind.* (London), 1009 (1955).

(12) W. Baker, *J. Chem. Soc.*, 1381 (1933).

(13) A. T. M. Dunne, J. E. Gowan, John Keane, B. M. O'Kelly, Denis O'Sullivan, M. M. Roche, P. M. Ryan, and T. S. Wheeler, *ibid.*, 1252 (1952).

(14) W. D. Ollis and D. Weight, *ibid.*, 3826 (1952).

(15) All the melting points have been taken on a Kofler hot microscopical stage and are corrected.

(16) Microanalyses have been done by Drs. Weilers and Strauss, Oxford, London.

The mixed melting point of the two was found to be 172–173°.

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found for the product, m.p. 201–203°: C, 65.29; H, 4.71; for the product, m.p. 199–201°: C, 64.54; H, 4.62.

5,7-Dihydroxy-4′-methoxy-6-methylisoflavone (III. R = Me, R′ = *p*-MeOC$_6$H$_4$, R″ = R‴ = R⁗ = H).—The carbethoxyisoflavone, m.p. 201–203° (0.81 g.), in acetone was refluxed for 4 hr. with excess of 5% aqueous sodium carbonate. After evaporating acetone, the cooled solution on acidification precipitated the acid which crystallized from ethanol in light yellow needles (0.6 g.) m.p. 288–291° dec.

Anal. Calcd. for $C_{18}H_{14}O_7$: C, 63.16; H, 4.12; Found: C, 63.43; H, 4.40.

The acid (0.3 g.) was decarboxylated by heating rapidly in portions (*ca.* 50 mg.) at 300°. The crude melt was extracted with ethyl acetate, which was washed with aqueous sodium bicarbonate followed by water. The solid on recovery of the solvent gave on crystallization from ethyl acetate (charcoal) fine yellow shining needles (0.21 g.) m.p. 260–263°. Mehta and Seshadri[3b] have reported m.p. 210–212°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.23; H, 4.81.

5,7,4′-Trimethoxy-6-methylisoflavone (III. R = R‴ = R⁗ = Me, R′ = *p*-OMeC$_6$H$_4$, R″ = H).—The above dihydroxyisoflavone (100 mg.), dry acetone (60 cc.), methyl sulfate (0.7 cc.), and potassium carbonate (2 g.) were refluxed for 30 hr. The product crystallized from ethyl acetate in colorless needles (70 mg.), m.p. 169°. It showed no depression in melting point on admixture with an authentic sample obtained according to Whalley.[17]

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.64; H, 5.67.

5,7-Dihydroxy-4′-methoxy-8-methylisoflavone (II. R = Me, R′ = *p*-OMeC$_6$H$_4$, R″ = R‴ = R⁗ = H).—The carbethoxyisoflavone (0.95 g.), m.p. 199–201°, on hydrolysis in the usual manner gave a product which on crystallization from aqueous methanol separated into deep yellow needles (0.8 g.) m.p. 280–281° dec. The mixed melting point with the acid obtained earlier was found to be 264–265°.

Anal. Calcd. for $C_{18}H_{14}O_7$: C, 63.16; H, 4.12. Found: C, 62.84; H, 3.92.

The carboxyisoflavone (0.3 g.) on decarboxylation at 292° as described in the previous case yielded a product which crystallized from methanol (charcoal) into aggregates of pale yellow needles (0.2 g.) m.p. 235–236°. The mixed melting point with the 6-isomer obtained earlier was found to be 218–220°.

Anal. Calcd. for: $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.19; H, 4.38.

5,7,4′-Trimethoxy-8-methylisoflavone (II. R = R‴ = R⁗ = Me, R′ = *p*-OMeC$_6$H$_4$, R″ = H).—The hydroxy isoflavone (100 mg.) in dry acetone (60 cc.) was heated under reflux for 15 hr. with methyl sulfate (0.5 cc.) and potassium carbonate (2 g.) yielding the methylated isoflavone (75 mg.), m.p. 183.5–184° (*cf.* lit.[5,7] m.p. 180° and 181–183°). No depression in the melting point was observed on admixture with a sample prepared according to Whalley.[5]

Ethoxalylation of 2,4,6-Trihydroxy-3-methyl-2′-methoxydeoxybenzoin (I. R = Me, R′ = *o*-MeOC$_6$H$_4$).—The deoxybenzoin (3.0 g.) in pyridine (30 cc.) was treated with ethoxalyl chloride (6 cc.). On usual work up a reddish brown thick oily mass (4.0 g.) was obtained. Methylation of the oily mass by the methyl sulfate–potassium carbonate–acetone method followed by fractional crystallization from benzene–petrol and ethanol resulted in the separation of ethyl 5,7,2′-trimethoxy-8-methylisoflavone-2-carboxylate as colorless needles (1.2 g.), m.p. 155–157° (II. R = R‴ = R⁗ = Me, R′ = *o*-MeOC$_6$H$_4$, R″ = CO$_2$Et).

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.33; H, 5.52. Found: C, 65.98; H, 5.71.

(17) W. B. Whalley, *J. Chem. Soc.*, 3366 (1953).

The mother liquor on evaporation left an oil which was washed several times with petrol. The residue on crystallization from ethanol gave colorless shining needles (0.4 g.) of ethyl 5,7,2′-trimethoxy-6-methylisoflavone-2-carboxylate, m.p. 160–162° (III. R = R‴ = R⁗ = Me, R′ = *o*-MeOC$_6$H$_4$, R″ = CO$_2$Et).

Anal. Calcd. for $C_{22}H_{22}O_7$: C, 66.33; H, 5.52. Found: C, 66.49; H, 5.82.

5,7,2′-Trimethoxy-8-methylisoflavone (II. R = R‴ = R⁗ = Me. R′ = *o*-MeOC$_6$H$_4$, R″ = H).—The carbethoxyisoflavone (500 mg.), m.p. 155–157°, in acetone was refluxed for 4 hr. with excess of 5% aqueous sodium carbonate. After recovery of acetone, the cooled solution on acidification precipitated the carboxyisoflavone which crystallized from ethanol in colorless needles (350 mg.), m.p. 241–242° dec.

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.9. Found: C, 64.64; H, 5.12.

The acid (200 mg.) was decarboxylated by heating rapidly in portions (*ca.* 50 mg.) at 255° until effervescence ceased. The residue was then extracted with ethyl acetate which was washed with aqueous sodium bicarbonate and water, respectively. Evaporation of the solvent gave a product which crystallized from ethyl acetate as colorless needles (130 mg.), m.p. 180–182°. The product showed no depression in melting point on admixture with an authentic sample of 5,7,2′-trimethoxy-8-methylisoflavone.[5,17]

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.59; H, 5.37.

5,7,2′-Trimethoxy-6-methylisoflavone (III. R = R‴ = R⁗ = Me, R′ = *o*-MeOC$_6$H$_4$, R″ = H).—The carbethoxyisoflavone (300 mg.), m.p. 160–162°, on hydrolysis in the usual manner gave a product which crystallized from ethanol in colorless needles (120 mg.), m.p. 222–224° (dec.).

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.9. Found: C, 64.98; H, 4.73.

The above carboxyisoflavone (100 mg.) on decarboxylation at 240° as detailed earlier gave on crystallization from methanol colorless needles (45 mg.), m.p. 220°, identical with an authentic specimen of 5,7,2′-trimethoxy-6-methylisoflavone.[17]

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 70.13; H, 5.68.

Acetyl Chloride–Pyridine Method.—To 2,4,6-trihydroxy-3-methyldeoxybenzoin[3a] (VIII) (1.0 g.) in dry pyridine (20 cc.) at 0° was added freshly distilled acetyl chloride (1.4 cc.) with stirring. After leaving for 24 hr. at 0° crushed ice was added and the solution was extracted several times with ether. The combined extracts were washed with ice-cold hydrochloric acid, then with water, and dried. On distilling the ether a reddish brown semisolid mass (1.4 g.) was obtained. The structure IXb was originally[3b] assigned but later[9] revised to IXa.

The semisolid mass (1.4 g.) was refluxed with 10% aqueous sodium carbonate (60 cc.) for 2 hr., then cooled and acidified. The precipitate crystallized from alcohol as colorless needles (0.85 g.), m.p. 224–225°. Mehta and Seshadri[3b] recorded the m.p. 249–251° and gave it the structure of 5,7-dihydroxy-2,6-dimethylisoflavone (XIVa).

Methylation (Partial).—The product (0.3 g.) m.p. 224–225° was refluxed with methyl sulfate (0.1 cc., 1 mole) and potassium carbonate (1 g.) in acetone (30 cc.) for 3 hr. The solid mass obtained crystallized from methanol in colorless rectangular plates (0.24 g.), m.p. 150–176°; on repeated crystallizations from methanol a less soluble fraction separated in colorless needles (0.1 g.), m.p. 188–190°. It was assigned the probable structure of 5-hydroxy-7-methoxy-2,6-dimethylisoflavone (XIVb) (*cf.* lit.[3a,b] m.p. 188–190°). The more soluble fraction (probably 8-isomer) separated from the mother liquor as very light yellow needles (90 mg.) m.p. 131–132° (*cf.* lit.[3a] 151–153°).

Methylation (Total).—The product (0.2 g.) m.p. 224–225° in dry acetone (150 cc.) was heated under reflux with methyl sulfate (2 cc.) and potassium carbonate (5.0 g.) for 50 hr.

The product on repeated crystallizations from methanol separated into colorless shining needles (90 mg.), m.p. 176–177°. It showed no depression in melting point on admixture with an authentic sample of 2,6-dimethyl-5,7-dimethoxyisoflavone (XIVc) obtained by the complete methylation of the probable 2,6-dimethyl-5-hydroxy-7-methoxyisoflavone (XIVb). The second product which separated from methanol as colorless needles (60 mg.) melted at 184–186° and was characterized as 2,8-dimethyl-5,7-dimethoxyisoflavone (XIIIc) (*cf.* lit.,[3a] 184-186°).

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found for the product, m.p. 176–177°: C, 73.26; H, 5.55; and for the product, m.p. 184–186°: C, 73.84; H, 5.62.

Acetic Anhydride–Sodium Acetate Method.—2,4,6-Trihydroxy-3-methyldeoxybenzoin[3a] (VIII) (0.75 g.), acetic anhydride (12 cc.), and fused sodium acetate (2.0 g.) were refluxed at 170–180° for 12 hr. The contents were cooled to room temperature and then poured into crushed ice and the mixture left overnight. The brown solid on fractional crystallization from ethanol gave various crops of crystals melting in the range of 176–207°. Ienger, *et al.*,[3a] reported the m.p. 188–190° and gave it the structure of 2,8-dimethyl-5,7-diacetoxyisoflavone (XIIId).

Deacetylation.—All the crops of crystals obtained above were dissolved in alcohol (100 cc.) and concentrated sulfuric acid (4 cc.) added. The mixture after refluxing for 2 hr. was diluted with an equal amount of water and the alcohol distilled. The solid obtained on cooling was filtered, washed with water, and dried (0.6 g.) On crystallization from ethanol it separated into fine colorless needles, m.p. 220–240°. Ienger, *et al.*,[3a] reported the melting point as 256–257° and assigned it the structure of 2,8-dimethyl-5,7-dihydroxyisoflavone (XIIIa).

Methylation.—The product, m.p. 220–240° (150 mg.), on monomethylation using exactly 1 mole of methyl sulfate yielded a product which on repeated crystallizations from methanol separated into a less soluble fraction in the form of colorless needles (30 mg.), m.p. 188–190° (*cf.*[3a,b] m.p. 188–190°). The mixed melting point with the probable 2,6-dimethyl-5-hydroxy-7-methoxyisoflavone (XIVb) obtained by acetyl chloride method was undepressed. Repeated crystallizations of the solid obtained from mother liquor gave very light yellow needles (70 mg.), m.p. 131–132°.

The product showed no depression in melting point on admixture with a sample obtained earlier by acetyl chloride pyridine method. Complete methylation of the product, m.p. 220–240° (100 mg.), using a large excess of methyl sulfate resulted in the separation of 2,6-dimethyl-5,7-dimethoxyisoflavone (XIVc) (20 mg.), m.p. 176–177°, and 2,8-dimethyl-5,7-dimethoxyisoflavone (XIIIc) (64 mg.), m.p. 184–186°[3a].

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found for the product, m.p. 176–177°; C, 73.31; H, 5.72 and found for the product, m.p. 184–186°: C, 73.29; H, 5.56.

Alkylation of Pyridine Carboxaldoximes

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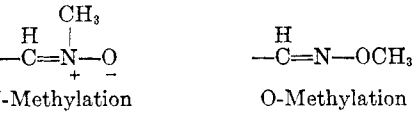
The reaction of methyl iodide with 6-methylpicolinaldehyde oxime was studied. It was found that the major reaction occurs at the nitrogen atom of the oxime function. A suitable synthesis of 1,6-dimethyl-2-formylpyridinium iodide oxime was accomplished by a route involving conversion of 6-methylpicolinaldehyde to its acetal, methylation, and hydrolysis to 1,6-dimethyl-2-formylpyridinium iodide followed by reaction with hydroxylamine.

Alkylation of the oximino group has been studied extensively.[2] Common reagents for this purpose are dimethyl sulfate and alkyl iodides either alone or in the presence of base. Methylation of an oxime usually gives a mixture of N- and O-alkylation products.[2]



N-Methylation

O-Methylation

These have been distinguished by hydrolysis to either N-methylhydroxylamine or hydroxylamine and methanol.

In the reaction of pyridine carboxaldoximes with alkylating agents one normally obtains the corresponding pyridinium carboxaldoximes in high yield.[3] When the ring nitrogen is hindered sterically, as in 6-methylpicolinaldehyde oxime (I), alkylation occurs instead on the oximino group. Thus Ginsburg and Wilson[3] report that "Methylation of 6-methylpyridine-2-aldoxime with methyl iodide yielded the hydroiodide of the methyl ether"; however, no experimental details for this reaction or further characterization of the product was made.

It was the dual purpose of this work to restudy the oxime alkylation reaction of I and to develop a suitable synthesis for hindered pyridinium carboxaldoximes.

Reaction of methyl iodide with I in alcohol or dimethylformamide afforded a single product in 72% yield. In order to establish the identity of the alkylation product, N-methyl-6-methylpicolinealdehyde oxime hydroiodide (II) and O-methyl-6-methylpicolinealdehyde oxime hydroiodide (III) were prepared *via* the reaction of 6-methylpicolin-

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(2) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, London, 1942, p. 173.

(3) (a) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958); (b) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).