concentrated. The crude product was purified by the silica gel chromato-strip method, using hexane in an ascending system. The major fraction, which fluoresced blue in ultraviolet light, was eluted from the strip with 25 ml. of methanol. The ultraviolet absorption spectrum of this solution was very similar to that of benzo[*e*]pyrene (Fig. 4).

Tetramethylnorcercosporin. A solution of tetramethylcercosporin (1.0 g. in 1 l. of methanol) was placed in a 2-l. flask and exposed to direct sunlight on a clear day with occasional shaking. After 6 hr. the solution, which had changed from orange to purple-red, was evaporated to dryness under reduced pressure. The residue was dissolved in benzene and chromatographed on 60 g. of calcium hydrogen phosphate, using benzene. Following a small amount of yellow colored impurity, the main fraction containing tetramethylnorcercosporin was eluted. This was concentrated by evaporation under reduced pressure and a small amount of benzene, ether, and petroleum ether added. Tetramethylnorcercosporin separated as dark red needles, which were recrystallized from methanol, mp. 241°. It was insoluble in aqueous sodium hydrogen carbonate, but in dilute aqueous-caustic alkali formed a clear blue solution. Alcoholic solutions gave a blue color with ferric chloride and purple color with magnesium acetate.

Anal. Calcd. for $C_{32}H_{32}O_{10}$: C, 66.66; H, 5.59; OCH_3, 21.60. Found: C, 66.41; H, 5.76; OCH_3, 21.30.

$\lambda_{max}^{CH_3OH}$ 226, 275, 330 infl. and 500 mμ (log ε 4.76, 4.63, 3.76, and 4.45). λ_{max} (in *N* sodium hydroxide containing 20% methanol), 240, 280 infl., 440, and 640 mμ ($E^{1\%}$ 850, 605, 155, 380). $\lambda_{max}^{coned.\ H_2SO_4}$ 238, 260 infl., 310, 400, 520, and 580 mμ ($E^{1\%}$ 830, 610, 250, 110, 380, and 390).

Diacetyltetramethylnorcercosporin. Tetramethylnorcercosporin (50 mg.) was treated with 2 ml. of pyridine and 2 ml. of acetic anhydride as described for the preparation of monoacetylpentamethylnorcercosporin. The crude product was purified by chromatography on calcium hydrogen phosphate using benzene. Diacetyltetramethylcercosporin was recrystallized from methanol as orange-red prisms, m.p. 225°.

Anal. Calcd. for $C_{36}H_{36}O_{12}$: C, 65.44; H, 5.49; CH_3CO, 13.0. Found: C, 65.50; H, 5.57; CH_3CO, 12.5.

Infrared: (potassium bromide) 1768, 1635 cm.$^{-1}$ (C=O).

Acknowledgment. The author gratefully acknowledges the continued advice and encouragement of Dr. T. Yabuta and Prof. Y. Sumiki of the University of Tokyo. The author is also indebted to Prof. T. Tamura, Prof. K. Munakata, and Prof. Y. Hirata of Nagoya Univeristy, and Prof. K. Nakanishi of the University of Education for their valuable advice and suggestion. Thanks are also due to Miss M. Miyata for performing the microanalyses.

ANJO, AICHI, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MUSLIM UNIVERSITY]

Studies on the C-Methyl-γ-benzopyrone System. Orientation in the Isoflavone Series

M. O. FAROOQ, W. RAHMAN, AND KH. TAKRIMULLAH NASIM

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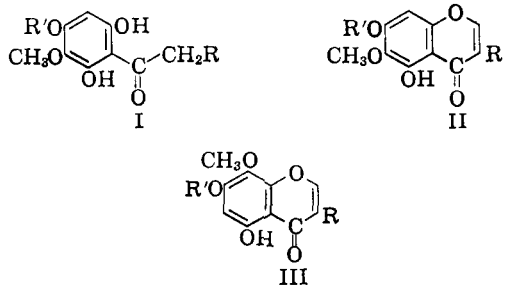
A tentative explanation of the different orientations of the isoflavones produced by ethoxalylation and by the ethyl formate-sodium synthesis has been advanced. The ethoxalylation of a C-methyl deoxybenzoin (2,4,6-trihydroxy-3-methyl-) (VII) has been studied. A mixture of two new isomeric isoflavones 5,7-dihydroxy-8-methyl-(IXa) and 5,7-dihydroxy-6-methyl-(IX-b), is obtained. The constitution of the two isoflavones has been proved by their synthesis through conventional methods. The difference in the behavior of the O-methyl deoxybenzoin of type I and C-methyl deoxybenzoin of type VII towards the same condensing agent, ethoxalyl chloride, has also been discussed.

It has been well established[1,2] that deoxybenzoins of type I(R = Ar) on treatment with ethyl formate and sodium yield the corresponding isoflavones of type II, which result from cyclization at the 6-hydroxyl group in I. However, when Baker, *et al.*[3] submitted the deoxybenzoin (I. R = *p*-HO-C_6H_4, R′ = H) to the ethoxalylation process, they obtained the product 5,7,4′-trihydroxy-8-methoxyisoflavone (III. R = *p*-HO−C_6H_4, R′ = H) resulting from cyclization involving the 2-hydroxyl group.



Baker *et al.* (*loc. cit.*) drew attention to this difference in the behavior of the two condensing agents and remarked that further cases of 5,7,8-orientation, and the reason causing the orientation in the ethoxalylation process to be different from the one in the ethyl formate–sodium method, would be

(1) R. L. Shriner and R. W. Stephenson, *J. Am. Chem. Soc.*, **64**, 2737 (1942).

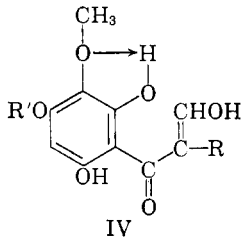
(2)(a) W. Baker and R. Robinson, *J. Chem. Soc.*, 152 (1929). (b) G. Bargellini, *Gazz. chim. ital.*, **45**, 69 (1915); **49**, 47 (1919). (c) E. Chapman, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 3015 (1927). (d) V. B. Mahesh, N. Narasimhachari, and T. R. Seshadri, *Proc. Indian, Acad. Sci.*, **39A**, 165 (1954). (e) S. A. Kagal, S. S. Karmarkar, and K. Venkataraman, *Proc. Indian, Acad. Sci.*, **44A**, 36 (1956).

(3) W. Baker, I. Dunstan, J. B. Harborne, W. D. Ollis, and R. Winter, *Chem. & Ind.*, 277 (1953).

explained later. However they have not published further work on this topic.

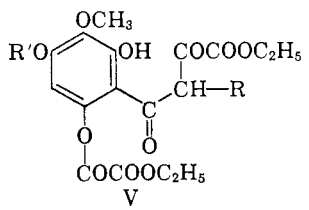
The present communication advances a tentative explanation of the different orientations with ethoxalyl chloride and ethyl formate–sodium.

The formation of isoflavones of type II from deoxybenzoins (I) by the ethyl formate–sodium method probably involves the intermediate (IV).[4] Intermediates of this type will cyclize to give 5,6,7- rather than 5,7,8-substituted flavonoids.[5] This preferential cyclization can probably be attributed to the fact that in IV the 2-hydroxyl group is hydrogen-bonded to the adjacent methoxyl and so is less reactive than the 6-hydroxyl (*cf.* ref. 5).

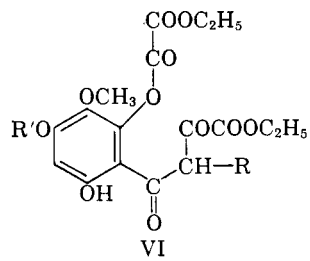


IV

In contrast, the ethoxalylation of I will lead to the intermediate V which then cyclizes to III.[6] The formation of intermediate V rather than VI is due to the fact that the 6-hydroxyl group in I is more reactive than the 2-hydroxyl. There are two reasons for this: Firstly the 2-hydroxyl is hydrogen-bonded to the adjacent methoxyl; secondly the 2-hydroxyl group is the more sterically hindered.



V



VI

As stated above Baker *et al.*[3] found that ethoxalylation of the *O*-methyldeoxybenzoin of type I gives an isoflavone of 5,7,8-orientation (III). The fact that the methyl group in C-methylphloroglucinol and C-methylphloroacetophenone derivatives is similar in behavior to the methoxyl or hydroxyl groups in methylation and chromone ring closure led us to investigate the ethoxalylation of C-methyldeoxybenzoin of type VII, with a view to obtaining an isoflavone of 5,7,8-orientation. A further advantage in this procedure was that it dispensed with the intermediate step of demethylation. The usual demethylating agents, hydriodic and hydrobromic acid, have been shown to bring about a partial change of orientation in such cases (methylgenistein and methylisogenistein)[7] from 5,7,8- to 5,6,7-positions, thus necessitating the cumbersome separation of the isomers. Even with a mild demethylating agent, aluminum chloride in dry benzene, the change of orientation in one case (8-methylisogenistein)[7] has been reported.

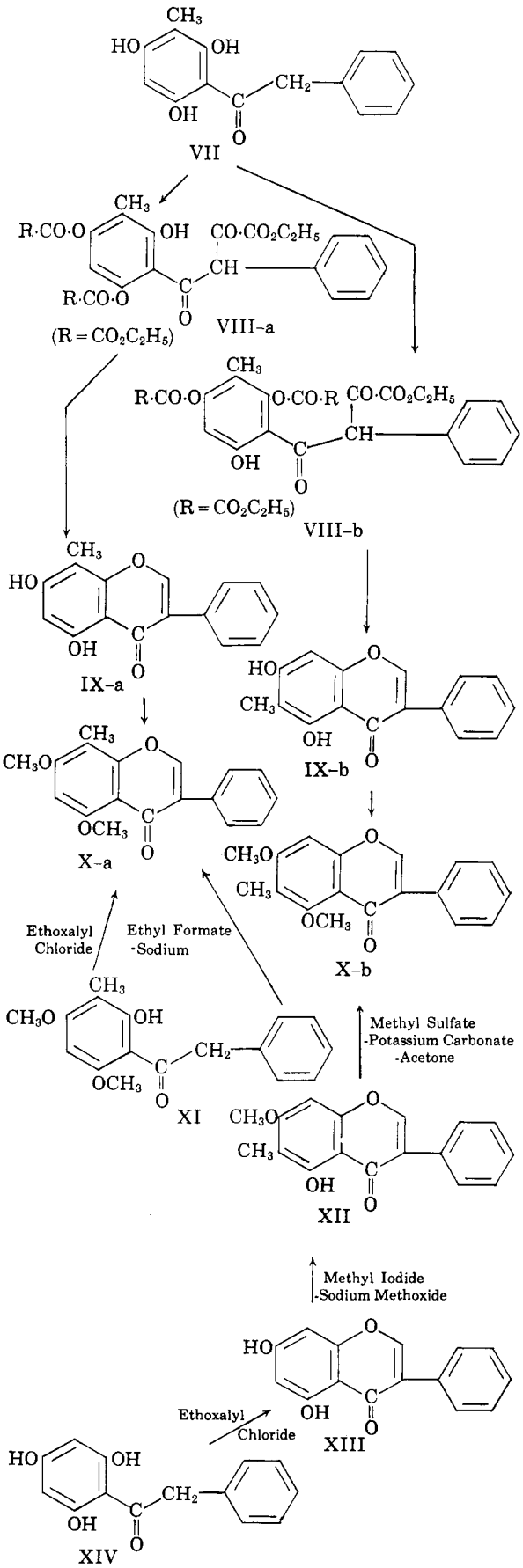
It was from these considerations that 2,4,6-trihydroxy-3-methyldeoxybenzoin (VII) was selected for the present study.

The deoxybenzoin (VII) was condensed with ethoxalyl chloride and the product on subsequent workup gave a gummy mass. The gummy mass on repeated crystallization from benzene and methyl alcohol separated into two definite carbethoxyisoflavones, one of which the more soluble had m.p. 179.5–180.5° and the other had m.p. 243–244°. The sodium amalgam tests with both the isoflavones were positive.

Carbethoxyisoflavone, m.p. 179.5–180.5° on hydrolysis gave the carboxyisoflavone m.p. 265° dec. which when decarboxylated by heating above its melting point produced the hydroxyisoflavone (IX a or IX b) m.p. 189–191°. The hydroxyisoflavone on methylation with methyl sulfate-potassium carbonate-acetone gave the methyl ether of the isoflavone m.p. 158–160°. This was identified as 5,7-dimethoxy-8-methylisoflavone (X a) by a mixed melting point determination with an authentic sample of the isoflavone prepared by two new unequivocal syntheses from 2-hydroxy-3-methyl-4,6-dimethoxydeoxybenzoin (XI), in one case through the ethyl formate-sodium synthesis, and in the other case by treatment with ethoxalyl chloride. In the latter case a thick oil was obtained, which even on repeated attempts could not be crystallized. The product was therefore treated with a mixture of glacial acetic and hydrochloric acids on a water bath for 0.5 hr. The crystalline product thus obtained gave on hydrolysis α-carboxyisoflavone m.p. 220–221° together with some unchanged deoxybenzoin. The acid on decarboxylation gave 5,7-dimethoxy-8-methyl isoflavone (X a) m.p. 158–160°.

It is suggested that the thick oil obtained by the ethoxalylation of the deoxybenzoin (XI) may be the 2-hydroxyisoflavanone derivative which on dehydration would give the easily crystallizable corresponding isoflavone derivative. This suggestion is in line with the findings of Baker *et al.*,[6] who have

(4) E. Spath and E. Lederer, *Ber.*, **63**, 743 (1930).
(5) T. S. Wheeler, *Bul. inst. politeh. Isasi*, **4**, 181 (1958).
(6) W. Baker, J. Chadderton, J. B. Harborne, and W. D. Ollis, *J. Chem. Soc.*, 1852 (1953).
(7)(a) W. B. Whalley, *Chem. & Ind.*, 277 (1953). (b) W. B. Whalley, *J. Chem. Soc.*, 3366 (1953).



reported that in the case of 2-hydroxy-4,6-dimethoxydeoxybenzoin the primary product of the reaction was 2-hydroxy-5,7-dimethoxyisoflavanone.

Carbethoxyisoflavone, m.p. 243–244° on hydrolysis gave a carboxyisoflavone, m.p. 281–282° dec., which yielded a hydroxyisoflavone, m.p. 225–227°. This isoflavone on partial methylation with methyl sulfate-potassium carbonate-acetone gave a product which separated from methanol as light yellow needles. These needles first changed into clusters of fine needles at 150° and finally melted at 170–172°. The product gave an intense green coloration with alcoholic ferric chloride, and was characterized as 5-hydroxy-7-methoxy-6-methylisoflavone (XII) by its melting and mixed melting points with an authentic sample. The authentic sample was prepared by methylation of 5,7-dihydroxyisoflavone (XIII) with methyl iodide in methanol containing sodium methoxide (Baker and Robinson[8]; Whalley[7]). Further the methylation of 5-hydroxy-7-methoxy-6-methylisoflavone (XII), obtained by either method, with methyl sulfate (large excess)–potassium carbonate for 60 hr. gave 5,7-dimethoxy-6-methylisoflavone (Xb), melting and mixed melting point 149–150°. It showed a negative ferric chloride reaction.

The melting points of the above 6- and 8-methylisoflavones and their intermediates are recorded in Table I, and except of the totally methylated isoflavone, lend further support to the observation that the 6-methyl derivatives melt higher than the corresponding 8-methyl derivatives.[9] This observation also holds good in the flavone and chromone series as is shown by Table II.

This dual course of ring closure in C-methyldeoxybenzoin finds an explanation on close examination of the mechanism[6] of the ethoxalylation process. The formation of the products of both 5,7,8- and 5,6,7-orientations suggests the intermediates (VIIIa and VIIIb). These intermediates can then cyclize to the corresponding isoflavones (IXa and IXb). It would be expected for steric reasons that the formation of VIIIa) should be favored, and hence IXa should, as we have observed experimentally, be formed in greater amount than IXb. The fact that the 3-methyldeoxybenzoin (VII) on ethoxalylation gives two isoflavones (IXa and IXb), while ethoxalylation of the 3-methoxydeoxybenzoin (I) gives only the 5,7,8-substituted isoflavone (III), is not surprising: the 2-hydroxyl group in I is hydrogen-bonded to the adjacent methoxyl and so should be less reactive than the 2-hydroxyl group in VII. Thus while the intermediates VIIIa and VIIIb are formed from VII, only the intermediate V and not VI is formed from I.

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

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

TABLE I

NEW 6- AND 8-METHYLISOFLAVONES

8-Methyl-	M.P.	6-Methyl-	M.P.
2-Carbethoxy-5,7-dihydroxy-8-methyl-	179.5°–180.5°	2-Carbethoxy-5,7-dihydroxy-6-methyl-	243–244°
2-Carboxy-5,7-dihydroxy-8-methyl-	265° dec.	2-Carboxy-5,7-dihydroxy-6-methyl-	281–282° dec.
5-7-Dihydroxy-8-methyl-	189–191°	5,7-Dihydroxy-6-methyl-	225–227°
5,7-Dimethoxy-8-methyl-	158–160°	5,7-Dimethoxy-6-methyl	149–150°

TABLE II

REPORTED 6- AND 8-METHYLFLAVONES, -CHROMONES AND -ISOFLAVONES

8-Methyl-	M.P.	6-Methyl-	M.P.
Flavones			
5,7-Dihydroxy-8-methyl- (8-Methylchrysin)	255–256°	5,7-Dihydroxy-6-methyl- (6-Methylchrysin)	308–310°
Chromones			
2,8-Dimethyl-5,7-dihydroxy- (Isoeugenitol)	235–237°	2,6-Dimethyl-5,7-dihydroxy (Eugenitol)	274–276°
2,8-Dimethyl-5-hydroxy-7-methoxy- (Isoeugenitin)	148–149°	2,6-Dimethyl-5-hydroxy-7-methoxy- (Eugenitin)	161–162°
Isoflavones			
5,7,2′-Trimethoxy-8-methyl-	180°	5,7,2′-Trimethoxy-6-methyl-	220°
5,7,4′-Trimethoxy-8-methyl-	181–183° and 180°	5,7,4′-Trimethoxy-6-methyl-	169[a]
5-Hydroxy-7,4′-dimethoxy-8-methyl	164–166° and 167°	5-Hydroxy-7,4′-dimethoxy-6-methyl-	200–202° and 169°
5,7,4′-Trihydroxy-8-methyl- (8-Methylgenistein).	231–232° and 252°	5,7,4′-Trihydroxy-6-methyl- (6-Methylgenistein).	276–278°

[a] The only exception noted is in the case of completely methylated methyl genistein.

EXPERIMENTAL[10]

Ethoxalylation of 2,4,6-trihydroxy-3-methyldeoxybenzoin (VII). To an ice cold solution of 2,4,6-trihydroxy-3-methyldoexybenzoin[11] (VII) (5.0 g.) in pyridine (50 cc.) was slowly added. Slowly with shaking redistilled ethoxalyl chloride (8.8 cc.). The mixture after standing for 24 hr. at room temperature was poured into water and extracted with chloroform. It was washed with 10% hydrochloric acid, dried (magnesium sulfate) and evaporated. The product on repeated crystallization from benzene and methanol gave two products. One of the products was less soluble and came in the form of yellow shining plates (1.2 g.), m.p. 243–244° giving a dirty green color with ferric chloride. The second product was obtained in yellow leaflets (1.6 g.), m.p. 179.5–180.5°, giving a reddish brown ferric chloride reaction. Both products gave a pink coloration with sodium amalgam followed by acidification with hydrochloric acid.

Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.06; H, 4.71. Found: for the product m.p. 243–244°, C, 67.32; H, 4.46 and for the product m.p. 179.5–180.5°, C, 66.84; H, 4.35.

5,7-Dihydroxy-8-methylisoflavone (IXa). The carbethoxyisoflavone, m.p. 179.5–180.5°, (1.5 g.) in acetone was warmed for 4 hr. with excess of 5% aqueous sodium carbonate. After evaporation of the acetone, the cooled solution on acidification precipitated the acid, which crystallized from dilute methanol as yellow prisms (1.2 g.) m.p. 265° dec.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.84. Found: C, 65.32; H, 3.74.

The acid was decarboxylated by heating rapidly in portions (*ca.* 50 mg.) to 275° till the evolution of carbon dioxide ceased. The crude melt was extracted with ethyl acetate, washed with aqueous sodium bicarbonate and then with water. The ethyl acetate extract was dried (magnesium sulfate) and the solvent recovered. The solid obtained on crystallization from ethyl acetate gave the isoflavone in cubical plates m.p. 189–191°. It gave a green color with ferric chloride and a positive test with sodium amalgam followed by acidification.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.26; H, 4.44.

It was characterized as 5,7-dihydroxy-8-methylisoflavone (IXa) by forming its methyl ether. The methylated product, m.p. 158–160°, showed no depression in the melting point on admixture with an authentic sample of 5,7-dimethoxy-8-methylisoflavone (X-a).

5,7-Dimethoxy-8-methylisoflavone (Xa). (a) *Methylation:* 5,7-Dihydroxy-8-methylisoflavone (IXa) (0.15 g.) was heated under reflux for 40 hr. in acetone (30 cc.) with freshly ignited potassium carbonate (2.0 g.) and methyl sulfate (0.20 cc.) yielding 5,7-dimethoxy-8-methylisoflavone (Xa) (0.12 g.) which crystallized from methanol as colorless shining needles m.p. 158–160°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.65; H, 5.39.

(b) *Ethyl formate-sodium synthesis:* A suspension of 2-hydroxy-3-methyl-4,6-dimethoxyphenyl benzyl ketone (XI)[11] (0.6 g.) in freshly distilled ethyl formate (15 cc.), cooled to 0°, was gradually added (over 30 min.) with stirring to pulverized sodium (0.5 g.). The stirring was continued for an hour and the reaction flask was left in the ice chest for 48 hr. Pieces of ice and hydrochloric acid (15 cc.) were then added and the unchanged ethyl formate was distilled under reduced pressure. The brown solid obtained on cooling was filtered and washed with water. On crystallization from methanol it separated in the form of colorless shining needles (0.37 g.) m.p. and mixed m.p. with 5,7-dimethoxy-8-methylisoflavone 158–159°.

(c) *Ethoxalylation:* Ethoxalyl chloride (0.9 cc.) was gradually added to an ice-cold solution of 2-hydroxy-3-methyl-4,6-dimethoxyphenyl benzyl ketone (XI) (1.0 g.). in pyridine (10 cc.). The mixture was left for 24 hr. at room

(10) All the melting points are uncorrected.

(11) R. Iengar, A. C. Mehta, T. R. Seshadri, and S. Varadarajan, *J. Sci. Ind. Res.* (*India*), **13B**, 166 (1954).

temperature and then poured into water. It was extracted with chloroform, washed with 10% hydrochloric acid and dried (magnesium sulfate). On evaporating the solvent a brown oily substance was left which could not be crystallized. It was heated for 0.5 hr. with a mixture of glacial acetic acid (10 cc.) and hydrochloric acid (1 cc.). The mixture was poured into a large volume of water which resulted in the separation of a faintly pink solid. On crystallization from ethanol it gave colorless needles, m.p. 153–154°. The ester (0.5 g.) in alcohol was refluxed for 4 hr. with excess of 5% aqueous sodium carbonate. After evaporation of alcohol the solution was cooled and acidified. The precipitate obtained was taken up in ether and thoroughly washed with an aqueous solution of sodium bicarbonate. The bicarbonate extract on acidification gave a solid product which on repeated crystallization from methanol separated into yellow shining needles, m.p. 220–221°. The ethereal layer on evaporation left a small quantity of unchanged XI. The carboxyisoflavone was decarboxylated in the usual manner by heating at 235°. On subsequent workup it gave a solid which on crystallization from methanol separated into colorless shining needles, m.p. 158–160°. It showed no depression in melting point with the 5,7-dimethoxy-8-methylisoflavone (X a) synthesized by either of the methods (a) and (b).

5,7-Dihydroxy-6-methyl isoflavone (IX b). The carbethoxyisoflavone, m.p. 243–244°, (1.2 g.) on hydrolysis in the usual manner gave a product which on crystallization from dilute methanol separated into light yellow aggregates of needles (0.5 g.) m.p. 281–282° dec. It gave a blackish green ferric chloride reaction.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.84. Found: C, 65.54; H, 3.91.

The carboxyisoflavone was decarboxylated in portions (*ca.* 50 mg.) at 295° exactly as described earlier. The product on crystallization from ethyl acetate gave rectangular plates m.p. 225–227°. It gave a positive test of isoflavone with sodium amalgam followed by acidification. It was characterized as 5,7-dihydroxy-6-methyl isoflavone (IX b).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.38; H, 4.61.

5-Hydroxy-7-methoxy-6-methylisoflavone (XII). 5,7-Dihydroxy-6-methylisoflavone (IX b) (0.3 g.) in dry acetone (50 cc.) was heated under reflux with methyl sulfate (1 mole) and anhydrous potassium carbonate (1 g.) for 8 hr. The product on the usual work up separated in quantitative yield from a large volume of methanol as light yellow needles changing into clusters of fine needles at 150° and finally melting at 170–172°. It gave a bluish green ferric chloride reaction in alcohol.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.29; H, 4.76.

5,7-Dimethoxy-6-methylisoflavone (X b). (a) The above isoflavone (XII) (0.2 g.) on further methylation with methyl sulfate (large excess)– potassium carbonate–acetone for 60 hr. gave a quantitative yield of 5,7-dimethoxy-6-methylisoflavone (X b) as colorless needles, m.p. 149–150°, (from dilute methanol.) It gave no color with alcoholic ferric chloride and a pink color with sodium amalgam.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 73.01; H, 5.29.

(b) Benzyl 2,4,6-trihydroxyphenyl ketone (XIV)[12] (2.6 g.) on ethoxalylation gave 2-carbethoxy-5,7-dihydroxyisoflavone (2.45 g. 70%; *cf.* 45% Baker *et al.*[10]) as light yellow needles, m.p. 230°. The carbethoxyisoflavone on work-up according to Baker *et al.*[10] gave 5,7-dihydroxyisoflavone (XIII) as plates, m.p. 195–196°.

5,7-Dihydroxyisoflavone (XIII), (0.45 g.) in methanol (25 cc.) containing dissolved sodium (0.7 g.) and methyl iodide (3.5 cc.) was refluxed for 15 hr. The product after removing the solvent under reduced pressure was treated with water and 2*N* hydrochloric acid. The precipitate on washing with water separated from a large volume of methanol in light yellow needles (80 mg.) changing into clusters of fine needles at 150° and finally melting at 170–172°. No depression in melting point was noted on admixture with 5-hydroxy-7-methoxy-6-methylisoflavone (XII) obtained earlier. It gave a bluish green ferric reaction in alcohol.

Further methylation for 60 hr. with methyl sulfate (large excess) potassium carbonate–acetone gave a quantitative yield of 5,7-dimethoxy-6-methylisoflavone (X b), m.p. and mixed m.p. with the compound obtained earlier 149–150°. It gave no coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.73; H, 5.52.

ALIGARH, INDIA

(12) G. G. Badcock, G. W. K. Cavill, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 2961 (1950).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XX.[1] Stevens Reaction in the Synthesis of 5-Ethyl-2′-hydroxy-2-methyl-(or phenethyl)-6,7-benzomorphan

SEIICHI SAITO[2] AND EVERETTE L. MAY

Received September 5, 1961

The Stevens reaction has been applied to the synthesis of 5-ethyl-2′-hydroxy-2-methyl (and -phenethyl)-6,7-benzomorphan (V). The 2-methyl compound (Va) was converted to the 2-phenethyl analog (Vb) and to 1-ethyl-7-methoxynaphthalene by standard reactions.

Previously we reported the synthesis and analgesic activity of 2′-hydroxy-2,5-dimethyl-6,7-benzomorphan (Xa)[3] and the 2-phenethyl analog (Xb).[4] Although the former was only a little more active than codeine, like other members of this class[1] it had no capacity for suppressing abstinence from morphine in an established addiction in the

(1) Paper XIX, J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962).

(2) Visiting Scientist from Osaka, Japan.

(3) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(4) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).