The Condensation Products of Acetamidophenol with Acetone1),*

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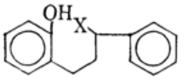
In a previous paper,2) the reaction of methylammonium 6-aminosalicylate with acetone at room temperature was found to afford the aminoflavan derivative. The process of the formation of this derivative was explained by a dimerization mechanism of the intermediate isopropenyl compound.

Though it is known that flavan derivatives are synthesized through the dehydration of phenyl-(*o*-hydroxyphenylethyl)-carbinol derivatives (Ia) or through the dehydrohalogenation of halogen compounds such as Ib, these methods are accompanied by too many side reactions and too many difficulties for purification to be possible. In 1905 Fabinyi and Szeky obtained the so-call "Dragon's blood" by reacting phenols with acetone in an acidic medium.3) Their structures were studied by Baker and explained as flavan derivatives.4) Both of these projects, however, reported methods of obtaining flavan derivatives which are not satisfactory for practical purposes.



Ia X=OH
Ib X=halogen

Fig. 1.

It has been found that aminoflavan derivatives are obtained easily by the acidic condensation of acetamidophenols with acetone. *m*-Acetamidophenol (II) was, therefore, dissolved in a large amount of acetone and heated at 50°C, and then dry hydrogen chloride gas was passed in. From the reaction mixture, a crystalline substance IV was obtained. Its ultraviolet absorption spectrum showed λ_{max} 250, 287 mμ. Compared with the absorption of II (λ_{max} 246, 284 mμ), no radical change was observed. Its infrared absorption spectrum showed absorptions at 1670 cm^{-1} (νC=O, acetamido), 3380 cm^{-1}, and 3240 cm^{-1} (νOH, νNH). As the ferric chloride test is positive, the existence of phenolic hydroxyl is evident. The position of each substituent can easily be estimated by the C–H out of plane deformation vibration band of the benzene ring (with one or two adjacent H atoms).5)

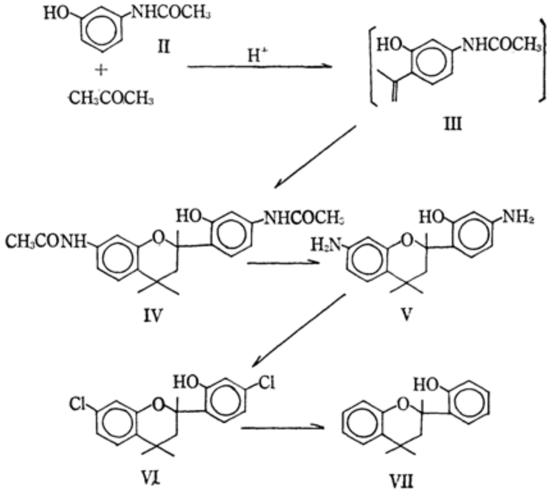


Fig. 2.

In order to determine the structure of IV, the following experiments were carried out. The refluxing of a suspension of IV in 10% hydrochloric acid for 5 hr. yielded a compound V. The ferric chloride test and Ehrlich-Herter test of V were positive, and its infrared absorption spectrum showed hydroxyl and amino groups. The ultraviolet absorption maximum of V coincided with that of 4′, 7-diamino-2′-hydroxy-2, 4, 4-trimethylflavan. V was not stable in the air, however, it turned black at room temperature.

V was deaminated to a stable derivative as follows. It was diazotized, and then chlorinated to VI by the Sandmeyer method.6) VI was then catalytically dechlorinated to VII at room temperature with palladium black, which did not show any melting point depression when mixed with authentic 2′-hydroxy-2, 4, 4-trimethylflavan.2) Moreover, its infrared sbsorption spectrum also coincided completely with that of this authentic sample. Therefore, the structure of IV was identified as 4′,7-diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan. Furthermore, the NMR spectrum of IV in carbon tetrachloride had a sharp singlet at 8.67τ (6: methyl protons of *gem*-dimethyl groups), a singlet at 8.54τ (3: methyl protons), singlet at 5.01τ (a hydroxyl proton), a doublet at 7.85τ (6: methyl protons of *N*-acetyl groups),7) a multiplet at 8.3—8.5τ (2:

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1) K. Yamada, Presented at the 16th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1963.

* Part IV in the series of Condensation of Aminosalicylic Acid Salts.

2) K. Yamada, This Bulletin, **38**, (1965).

3) I. Fabinyi and T. Széky, *Ber.*, **38**, 2307 (1905).

4) W. Baker and J. C. McGowan, *J. Chem. Soc.*, **1938**, 347.

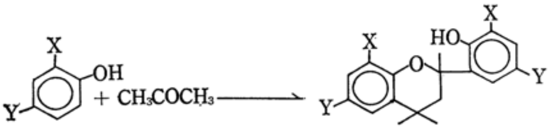
5) W. West, "Chemical Application of Spectroscopy," Interscience Publications, New York (1956).

6) T. Sandmeyer, *Ber.*, **17**, 1633 (1884).

7) L. D. Roberts, "Nuclear Magnetic Resonance," Applications to Organic Chemistry, McGrow-Hill, New York (1960).

aliphatic protons) and complex multiplets at 2.8—3.2τ(6: aromatic protons).[8] Thus, the NMR data also was consistent with the structure of 4′, 7-diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan.

A similar condensation reaction was applied to the *o*- and *p*-isomers of II. When *o*-acetamidophenol (VIII) and acetone were subjected to condensation by hydrogen chloride, a condensate (IX) was obtained. Its ultraviolet absorption maxima were at 248 and 286 mμ. Infrared absorptions were observed at 1668 cm⁻¹ (νC=O), 3389 cm⁻¹ (νOH), and 3300 cm⁻¹ (νNH) respectively. From these results, IX was identified as 3′, 8-diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan.

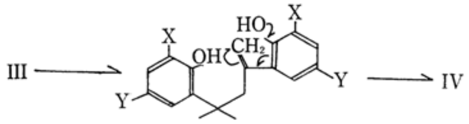


VIII X=NHCOCH$_3$ Y=H
IX X=NHCOCH$_3$ Y=H
X X=H Y=NHCOCH$_3$
XI X=H Y=NHCOCH$_3$

Fig. 3.

From *p*-acetamidophenol (X) and acetone 5′, 6-diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan (XI) was obtained. Its ultraviolet and infrared absorption were similar to those of IX.

As an intermediate product of the condensation reaction of II with acetone, III was considered. This process is supported by the formation of the flavan derivative from isopropenyl phenol in an acidic medium.[9] If Schnell's polymerization mechanism of vinyl compounds holds true, XII may be produced by the dimerization of III, and, further, will form a ring to yield IV. According to this mechanism, it is probable that isomeric acetamido-2-isopropenylphenol will be produced, however, due to the steric effect of the acetamido group, it is very difficult to produce it. The fact that the yields of the IX, IV, and XI condensates from *o*-, *m*- and *p*-acetamidophenol were 1.4, 5.2 and 4.7% respectively also supports the isopropenyl intermediate mechanism.



XII X=H or NHCOCH$_3$
Y=NHCOCH$_3$ or H

Fig. 4.

Experimental

4′, 7-Diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan (IV).—A mixture of *m*-acetamidophenol and 30 ml. of acetone was saturated with dry hydrogen chloride, and then kept at 50°C for 2 days. After the acetone had been removed, a dark red substance was obtained. After an excess of 20% sodium hydroxide solution had then been added to this substance, the mixture was stirred vigorously overnight. After filtration, the sodium hydroxide solution was acidified and next extracted with 250 ml. of ethyl acetate. The ethyl acetate solution was dried with sodium sulfate. After the distillation of ethyl acetate, the residue became a sodid. It was then purified by chromatography (alumina-acetone). After the acetone had been removed, the residual solid substance was recrystallized from ether-petroleum ether. Small rhombic crystals (IV), m. p. 165°C (decomp.), were obtained. Yield, 1.6 g.

Found: N, 6.01. Calcd. for $C_{22}H_{26}O_4N_2\cdot(C_2H_5)_2O$: N, 6.14%. This substance has 1 mol. of the ether of crystallization. It loses the ether of crystallization even upon standing in air, becoming opaque and sticky. UV: λ_{max}^{EtOH} 250, 287 mμ. IR: 3380, 3240, 1670, 870, 830 cm⁻¹.

4′, 7-Diamino-2′-hydroxy-2, 4, 4-trimethylflavan (V).—A suspension of 1 g. of IV in 20 ml. of 10% hydrochloric acid was refluxed for 5 hr. Neutralization with an aqueous sodium hydroxide solution produced percipitates. Recrystallization from petroleum ether-ether then gave pale yellow needles (V), m. p. 179.5°C (decomp.). Yield, 0.3 g.

Found: N, 7.23. Calcd. for $C_{18}H_{22}O_2N_2\cdot(C_2H_5)_2O$: N, 7.41%. The ferric chloride test and Ehrlich-Herter test were positive. UV: λ_{max}^{EtOH} 236, 325 mμ. IR: 3400, 3100, 880, 830 cm⁻¹.

2′-Hydroxy-2, 4, 4-trimethylflavan (VII).—Diaminoflavan (V) was converted into a dichloro compound according to the method described in a previous paper.[2] The dichloroflavan in methanol was dechlorinated with hydrogen at an atmospheric pressure of 5 in the presence of palladium black and powdered anhydrous sodium acetate for 10 hr. The dechlorinated substance (VII) was then recrystallized from petroleum ether-ether. M. p. 98°C.

Found: C, 80.3; H, 7.4. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5%. A mixed melting point determination with an authentic sample showed no depression (98°C), and its infrared and ultraviolet absorption spectra were identical with those of 2′-hydroxy-2, 4, 4-trimethylflavan.

3′, 8-Diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan (IX).—A mixture of 10 g. of *o*-acetamidophenol and 30 ml. of acetone was saturated with dry hydrogen chloride, and then kept at 50°C for a week, after which time the solution was treated in a manner similar to that described for IV. Yellow needles (IX), m. p. 146.5°C (decomp.), were obtained.

Found: N, 5.92. Calcd. for $C_{22}H_{26}O_4N_2\cdot(C_2H_5)_2O$: N, 6.14%. UV: λ_{max}^{EtOH} 248, 286 mμ. IR: 3340, 1668, 750 cm⁻¹. On standing in air, the crystals lost some of the ether of crystallization and became sticky. Yield, 0.4 g.

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[8] J. A. Pople W. G. Schneider and H. J. Bernstein "High-resolution Nuclear Magnetic Resonance," McGrow-Hill, New York (1959); E. J. Corey, E. M. Philbin and T. S. Wheeler, *Tetrahedron Letters*, **1961**, 429.

[9] N. Sugiyama, K. Taya, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 673 (1959); W. Baker and D. M. Besly, *J. Chem. Soc.*, **1940**, 1103; W. E. Noland, C. G. Richards, H. S. Desai and M. R. Venkiteswaran, *J. Org. Chem.*, **26**, 4254 (1961).

[10] UV, IR, NMR and pK_a' were measured with the same apparatus as the previous paper.[2]

5′, 6-Diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan (XI).—The reaction of 5 g. of *p*-acetamidophenol with acetone under the same conditions as above afforded 5′,6-diacetamido-2′-hydroxy-2, 4, 4-trimethylflavan (XI), m. p. 85°C (decomp.). Yield, 0.7 g.

Found: N, 6.02. Calcd. for $C_{22}H_{26}O_4N_2 \cdot (C_2H_5)_2O$: N, 6.14%. UV: λ_{max}^{EtOH} 250, 291 mμ. IR: 3390, 1664, 875 (w.), 825 cm^{-1}.

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