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THE SYNTHESIS OF 3-AMINOFLAVANONES

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Abstract—The stannous chloride–hydrochloric acid reduction of 3-oximinoflavanones, hitherto regarded as yielding 3-aminoflavanones,[2] is shown to give the corresponding 3-aminoflavones. 3-Aminoflavanones were readily obtained by application of the Neber reaction[7] to 4-oximinoflavan tosylates.[1,5b,8]

A projected synthesis of flavan-3,4-diols contemplated, as an intermediate stage, deamination of 3-aminoflavanones by nitrous acid. These compounds are reported[2] as available by stannous chloride–hydrochloric acid reduction of 3-oximinoflavanones. In fact, deamination of the so-called 3-aminoflavanone did not yield dihydroflavonol; further, the amine was stable towards ketonic and reducing agents and, though it formed a picrate, was a weak base. It was insoluble in dilute mineral acids and afforded an unstable hydrochloride. It had previously been noted[2] that the compound failed to undergo dimerization to dihydropyrazines by the Gutknecht[3] method and it could not be dehydrogenated to the corresponding flavone.[4]

The U.V. spectrum of the unsubstituted amino-compound in neutral medium was similar to that of flavonol, while in strong acid it resembled that given by flavone. It exhibited hypsochromic shifts, which indicated conjugation of the amino-group with a chromophore, and excluded a flavanone structure involving attachment of the amino-group to saturated carbon. The I.R. spectrum of the compound had a carbonyl absorption peak at a position which suggested α,β- and α',β'-unsaturation and chelation of amino-group with carbonyl. The amine is, therefore, 3-aminoflavone.

Following a preliminary communication[1] of these results, we were informed by Dr. Elstow[5a] that he had investigated the analogous compound reported as 3-amino-3′,4′-dimethoxyflavanone[2] as a route to the corresponding 3-hydroxyflavan and had concluded from the U.V. spectrum in ethanol that the compound was the 3-aminoflavone. Dr. Kidd[5b] also made a similar personal communication.

Elstow[5a] suggested that the stannic chloride formed in the reduction of the oximino-group oxidized the intermediate flavanone to the flavone, much as does phosphorous pentachloride.[6] However, as treatment with stannic chloride under the

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[1] R. Bognár, C. O'Brien, E. M. Philbin, S. Ushioda and T. S. Wheeler, *Chem. & Ind.* 1186 (1960) preliminary communication.

[2] T. Oyamada and T. Fukawa, *J. Chem. Soc. Japan* **64**, 1163 (1943).

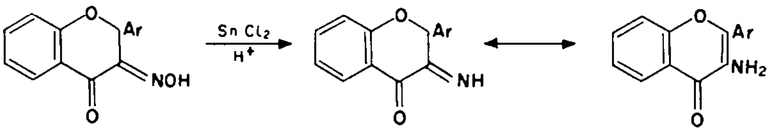
[3] For references see I. J. Krems and P. E. Spoerri, *Chem. Rev.* **40**, 290 (1947).

[4] M. Shimizu and S. Nakazawa, *J. Pharm. Soc. Japan* **73**, 522 (1953).

[5a] W. E. Elstow, Ph.D. Thesis, *Univ. of London* 26 (1954); [b] Dr. Kidd informs us that a group in the laboratories of T. H. Smith Ltd. (Edinburgh) had, in 1959, found that reduction of 7,4′-dimethoxy-3-oximinoflavanone ($SnCl_2$-HCl) gave the aminoflavone. The aminoflavanone was prepared by the Neber method.

[6] A. Löwenbein, *Ber. Dtsch. Chem. Ges.* **57**, 1515 (1924).

conditions of the stannous chloride reduction had no effect on authentic 3-aminoflavanone (see below) we believe the course of the reaction to be:



We eventually obtained the required 3-aminoflavanone in satisfactory yield by application of the Neber reaction[7] to 4-oximinoflavan tosylate. The U.V. spectrum of this amine hydrochloride was similar to that of dihydroflavonol, and the carbonyl absorption shown in the infrared also supported the flavanone structure. Further, nitrous acid deamination of the simplest amine afforded dihydroflavonol, and dehydrogenation by cinnamic acid and palladized charcoal gave 3-aminoflavone.

We also report the preparation of some substituted 3-aminoflavones, including those originally stated[2] to be 3-aminoflavanones. Tables 1 and 2 give, respectively, spectral results for 3-aminoflavones synthesized by stannous chloride–hydrochloric acid reduction of the corresponding 3-oximinoflavanones, and for authentic 3-aminoflavanones obtained by the Neber reaction.

A recent report[8] of the synthesis of 3-aminoflavanone through the Neber reaction considers this amine to be a stereoisomer of the product of the stannous chloride–hydrochloric acid reduction of 3-aminoflavanone. This conclusion is untenable in the light of our results.

We are currently studying the stereochemistry of the "Neber" 3-aminoflavanone and of some of its reduction products.

EXPERIMENTAL

U.V. spectra were determined in the region 214–400 mμ using a Beckman DU spectrophotometer. I.R. spectra were obtained with KBr discs and a Beckman IR5 I.R. machine.

3-*Oximinoflavanones* corresponding to the amines listed in Table 1 were prepared from flavanones using isoamyl nitrite and hydrochloric acid.[2,9] All but No. 6 are known.

6-*Chloro-3-oximinoflavanone* (from 6-chloroflavanone[10]) (Found: C, 63·1; H, 3·7; Cl, 11·9; N, 5·2. $C_{15}H_{10}ClNO_3$ requires: C, 62·6; H, 3·6; Cl, 12·4; N, 4·9%) separated from benzene in yellow needles, m.p. 155–158° (dec.).

3-*Aminoflavones.* Reduction (stannous chloride–hydrochloric acid) of the 3-oximinoflavanones afforded the corresponding pale yellow 3-aminoflavones:

3-*Aminoflavone.* (Found: C, 75·8; H, 4·9; N, 5·6; $C_{15}H_{11}NO_2$ requires: C, 75·9; H, 4·7; N, 5·9%), m.p. 137–138° (needles from ligroin) was also prepared by treatment of 3-aminoflavanone hydrochloride (below) with palladized charcoal. Shimizu and Nakazawa[4] carried out a similar experiment with the "3-aminoflavanone" (actually 3-aminoflavone) of Oyamada and Fukawa[2] with no useful result.

3-*Amino-4′-methoxyflavone.* (Found: C, 72·4; H, 5·0; N, 5·2; $C_{16}H_{13}NO_3$ requires: C, 71·9; H, 4·9; N, 5·2%), m.p. 152–153° (prisms from benzene); 3-*amino-3′,4′-dimethoxyflavone* (Found: C, 68·9; H, 5·3; N, 5·2. $C_{17}H_{15}NO_4$ requires: C, 68·7; H, 5·1; N, 4·7%), m.p. 125–126° (needles from aqueous methanol).

3-*Amino-3′,4′-methylenedioxyflavone.* (Found: C, 68·2; H, 4·0; N, 5·2; $C_{16}H_{11}NO_4$ requires: C, 68·3; H, 3·9; N, 5·0%), m.p. 183–184° (needles from ethanol). These compounds had the physical

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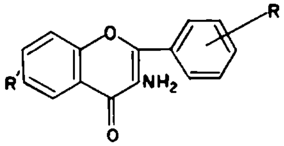
[7] For references see M. J. Hatch and D. J. Cram, *J. Amer. Chem. Soc.* **75**, 38 (1953).

[8] A. Kasahara, *J. Chem. Soc. Japan* **80**, 416 (1959).

[9] S. Kostanecki and V. Lampe, *Ber. Dtsch. Chem. Ges.* **37**, 773 (1904); A. Gutzeit and S. Kostanecki, *Ibid* **30**, 933 (1905).

[10] N. M. Shah and S. R. Parikh, *J. Indian Chem. Soc.* **36**, 72) (1959).

TABLE 1. 3-AMINOFLAVONES



No.	R	R′	λ_{max}^{MeOH}	log ε	$\lambda_{max}^{15\%\ HCl\text{-}MeOH}$	log ε	ν (CO) cm⁻¹
1	H	H	241	4·25	250	4·29	1637
			302	3·68	291	4·17	
			364	3·90			
2	3′-OMe	H	217	4·41			
			245	4·31	243	4·32	1637
			309	3·82	304	4·17	
			366	4·04			
			228	4·26			
3	4′-OMe	H	256	4·26	226	4·33	1626
			311	3·87	312	4·35	
			368	4·14			
4	3′,4′-di-OMe*	H	237	4·35	244	4·35	1622
			322	3·87	313	4·21	
			372	4·20			
			239	4·34	244	4·40	1634
5	3′,4′-CH_2O_2	H	324	3·85	311	4·20	
			372	4·16			
6	H	Cl	244	4·35	253	4·34	1639
			314	3·86	293	4·16	
			371	4·01			

* See also Reference 5*a* p. 31.

properties previously attributed[2] to the corresponding 3-aminoflavanones. 3-*Amino-6-chloroflavone* (Found: C, 66·6; H, 3·8; Cl, 13·2; N, 5·1; $C_{15}H_{10}ClNO_2$ requires: C, 66·3; H, 3·7; Cl, 13·1; N, 5·2%), m.p. 165–167° (needles from aqueous ethanol).

3-*Amino-3′-methoxyflavone* separated from methanol in yellow needles, m.p. 132°[11] (Found: C, 71·6; H, 4·8; N, 5·6; OMe, 11·3; $C_{16}H_{13}NO_3$ requires: C, 71·9; H, 4·9; N, 5·2; OMe, 11·6%).

4-*Oximinoflavans.* These compounds were prepared from the flavanone, hydroxylamine hydrochloride, and aqueous sodium hydroxide with sufficient ethanol to effect solution at the refluxing temperature. The 4-oximino-derivatives corresponding to amines Nos. 1,[8,12,13] 3,[12b] 6,[12b] in Table 2 had previously been prepared.

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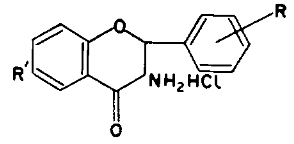
[11] C. Dempsey, Ph.D. Thesis, *National Univ. of Ireland* 237 (1961).

[12] [a] R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin and T. S. Wheeler, *Tetrahedron Letters* No. 19, 4 (1959); [b] R. Bognár, M. Rákosi, H. Fletcher, D. Kehoe, E. M. Philbin and T. S. Wheeler, *Tetrahedron* **18**, 135 (1962).

Some time after the work described in these references was completed, there was found in the archives of the Department of Chemistry, of University College, Dublin, a copy of a M.Sc. thesis, dated 1926, by Allan C. Rourke, B.Sc. This work was carried out under the supervision of the late Professor J. Algar. The thesis describes the preparation of flavanone oxime, 4-aminoflavan and flavan-4β-ol. These compounds were unwittingly given as new by Bognár *et al.*; there was then no knowledge in the department of the existence of this thesis.

[13] P. Venturella, A. Bellino and S. Cusmano, *Ann. Chim., Rome* **51**, 1074 (1961).

Table 2. 3-Aminoflavanone hydrochlorides



For R and R' see Table 1.

No.	λ_{max}^{MeOH}	log ε	γ (CO) cm^{-1}
1	215	4·45	1695
	255	4·05	1701
	325	3·60	
2	255	4·04	1712
	322	3·53	
3	215	4·45	1695
	254	4·08	
	323	3·57	
4	255	4·01	1701
	324	3·52	
5	253	4·07	
	289	3·73	1698
	322	3·54	
6	222	4·50	1703
	254	3·92	
	355	3·49	

3'-Methoxy-4-oximinoflavan (Found: C, 71·5; H, 5·7; N, 5·1; $C_{16}H_{15}NO_3$ requires: C, 71·4; H, 5·6; N, 5·2%), m.p. 150–151°.

3',4'-Dimethoxy-4-oximinoflavan (Found: C, 68·5; H, 5·7; N, 4·9; $C_{17}H_{17}NO_4$ requires: C, 68·2; H, 5·7; N, 4·7%), m.p. 152–153°.

3',4'-Methylenedioxy-4-oximinoflavan (Found: C, 67·7; H, 4·6; N, 4·9; $C_{16}H_{13}NO_4$ requires: C, 67·8; H, 4·6; N, 5·0%), m.p. 191–192° (dec.). These compounds separated from ethanol in needles.

4-(N-p-*Toluenesulphonyloxyimino*)flavans. The pyridine-acid chloride method was employed. 4-(N-*p*-toluenesulphonyloxyimino)flavan had the properties previously described;[8] *3'-methoxy-* (Found: C, 65·2; H, 5·0; N, 3·1; S, 7·2; $C_{23}H_{21}NO_5S$ requires: C, 65·2; H, 5·0; N, 3·3; S, 7·6%), m.p. 115–116° (from methanol); *4'-methoxy-* (Found: C, 65·3; H, 5·1; N, 3·8; S, 7·6. Required: as for the 3'-methoxy-isomer), m.p. 169–170° (from benzene–light petroleum, b.p. 60–80°); *3',4'-dimethoxy-* (Found: C, 63·9; H, 4·9; N, 3·3; S, 6·8, OMe, 13·7; $C_{24}H_{23}NO_6S$ requires: C, 63·6; H, 5·1; N, 3·1; S, 7·1%; OMe, 13·7%), m.p. 153–154° (from ethanol); *3',4'-methylenedioxy-* (Found: C, 62·8; H, 4·4; N, 3·0; S, 6·8; $C_{23}H_{19}NO_6$ requires: C, 63·2; H, 4·4; N, 3·2; S, 7·3%), m.p. 153–154° (from benzene–light petroleum, b.p. 60–80°); *6-chloro-* (Found: C, 61·2; H, 4·8; Cl, 8·4; N, 3·2; S, 7·2; $C_{22}H_{18}ClNO_4S$ requires: C, 61·7; H, 4·2; Cl, 8·3; N, 3·3; S, 7·5), m.p. 161–162° (from acetone).

The 3',4'-dimethoxy-derivative separated in prisms, the other compounds in needles.

Synthesis of 3-aminoflavanone hydrochlorides. The synthesis of 3-aminoflavanone hydrochloride illustrates the general procedure. A solution of the oximinoflavan tosylate (19·6 g, 0·05 mole) in dry benzene (100 ml) was treated with ethanolic potassium ethoxide (from K, 2 g, 0·05 mole; EtOH, 50 ml) at 0° and after 12 hr at room temp. the precipitate was removed. The filtrate was extracted with N-hydrochloric acid (100 ml; 75 ml; 75 ml; 75 ml). It is preferable to add the benzene solution to the acid in the separatory funnel.[14] The combined extracts were filtered hot (charcoal) and the filtrate when cold was treated with conc. hydrochloric acid (50 ml) and kept at 0° for 2 days. The amine hydrochloride which separated (7·4 g) crystallized in needles from dil. hydrochloric acid.

3-*Aminoflavanone hydrochloride* (Found: C, 65·0; H, 5·2; N, 5·3; Cl, 12·6; $C_{15}H_{14}ClNO_2$ requires: C, 65·3; H, 5·1; Cl, 12·9; N, 5·1%), m.p. 206° (dec.). A mixture of the hydrochloride (0·3 g), cinnamic acid (1 g) and palladized charcoal (0·1 g) was heated at 170° for 20 min. The cold mixture was triturated with aqueous sodium hydrogen carbonate. The residue yielded 3-aminoflavone (confirmation by I.R. spectrum) by extraction with ethanol.

3-*Amino*-3′-*methoxyflavanone hydrochloride* (Found: C, 62·8; H, 5·3; Cl, 11·6; N, 4·6; $C_{16}H_{16}ClNO_3$ requires: C, 62·8; H, 5·2; Cl, 11·6; N, 4·6%), m.p. 190° (dec.); 3-*amino*-4′-*methoxyflavanone hydrochloride* (Found: C, 63·3; H, 5·3; Cl, 12·3; N, 4·7. Required: as for the 3′-isomer), m.p. 185° (dec.); 3-*amino*-3′,4′-*dimethoxyflavanone hydrochloride* (Found: C, 60·9; H, 5·5; Cl, 10·2; N, 3·8. $C_{17}H_{18}ClNO_4$ requires: C, 60·8; H, 5·4; Cl, 10·6; N, 4·2%), m.p. 191° (dec.). The above 3 compounds separated in needles from dil. hydrochloric acid.

3-*Amino*-3′,4′-*methylenedioxyflavanone hydrochloride* separated from ethanol in needles with 1 mole solvent, m.p. 200° (dec.) (Found: C, 59·4; H, 5·2; Cl, 9·9; N, 4·1; $C_{16}H_{14}ClNO_4{\cdot}C_2H_5OH$ requires; C, 59·1; H, 5·5; Cl, 9·7; N, 3·8%). The *acetyl* derivative (pyridine–acetic anhydride) (Found: C, 66·0; H, 4·8; N, 4·3; $C_{18}H_{15}NO_5$ requires: C, 66·5; H, 4·7; N, 4·3%) had m.p. 216° (ethanol).

3-*Amino*-6-*chloroflavanone hydrochloride*. The acid extract was saturated with ammonium chloride to precipitate the amine hydrochloride. Attempted crystallization from methanol–ether gave an amorphous solid, m.p. 213° (dec.). (Found: N, 4·8; $C_{15}H_{13}Cl_2NO_2$ requires: N, 4·5%). The *acetyl* derivative (pyridine–acetic anhydride) separated from methanol as needles, m.p. 190–191° (Found: C, 64·2; H, 4·8; Cl, 11·3; N, 4·7; $C_{17}H_{14}ClNO_3$ requires: C, 64·7; H, 4·5; Cl, 11·2; N, 4·4%).

Deamination of 3-*aminoflavanone*. A solution of the amine hydrochloride (1·5 g) in 50% aqueous acetic acid (100 ml) was treated at 0° over 30 min with 2% aqueous sodium nitrite (25 ml). The mixture was stirred for 30 min at room temp. and was heated at 60° for 1 hr. The product was diluted with water, neutralized with potassium carbonate, and kept at 0°. Next day the precipitate was collected. After three crystallizations from methanol it formed needles (0·1 g), m.p. 181–183°. It was characterized as dihydroflavonol (mixed m.p. and I.R. spectrum).

Acknowledgements—are made by S. U. of the award of an Imperial Chemical Industries Fellowship and by C. O'B. for a Research Grant from the National Institutes of Health, Bethesda, Maryland.

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[14] H. E. Baumgarten and J. M. Petersen, *J. Amer. Chem. Soc.* **82**, 459 (1960).