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THE REACTIONS OF FLAVONOIDS WITH *p*-TOSYLHYDRAZINE

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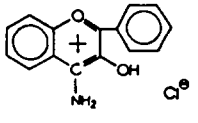
Abstract—Flavanone and flavone react with *p*-tosylhydrazine in acid medium to give the *p*-tosylhydrazones; 3-hydroxyflavanones yield a 3-hydroxy-4-aminoflavylium salt which is hydrolysed by alkali to the corresponding flavonol. Flavanonol has been converted in this way into 3-hydroxy-4-aminoflavylium chloride and then to flavonol; taxifolin 5,7,3′,4′-tetramethyl ether afforded 4-amino-5,7,3′,4′-tetra-O-methylcyanidin chloride and subsequently 5,7,3′,4′-tetra-O-methylquercetin.

IN A previous paper[1] we reported that both flavanone and flavone react with toluene-*p*-sulphonylhydrazine in acid medium to yield the corresponding tosylhydrazones. However, flavanonol has been found to give under similar conditions an entirely different product, 3-hydroxy-4-aminoflavylium chloride.

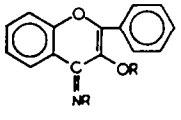
Such flavylium salts may be of considerable interest as synthetic intermediates in the interconversions of natural flavonoids, therefore this reaction has been investigated in greater detail.

The literature contains few references to 4-aminoflavylium salts. 4-Amino-5,6,7,4′-tetramethoxyflavylium picrate was synthesized and isolated in the course of a research proving the structure of scutellarein.[2] Recently, N-substituted 4-aminoflavylium perchlorates have been synthesized[3] from flavylium perchlorate. Both these examples have been obtained by entirely different synthetic routes and contain no hydroxyl group at C_3.

The structure of 3-hydroxy-4-aminoflavylium chloride (I) is proved by its analysis, IR spectrum (phenolic or enolic C—O stretching at 1210 cm^{-1}; C=N at 1665; N—H bending at 1555, and $-\overset{+}{N}H_2$ at about 3000 cm^{-1}; the C=O and C—O stretching vibrations of flavanonol at 1695 and 1010 cm^{-1}, resp., are absent) and some chemical reactions.



I.



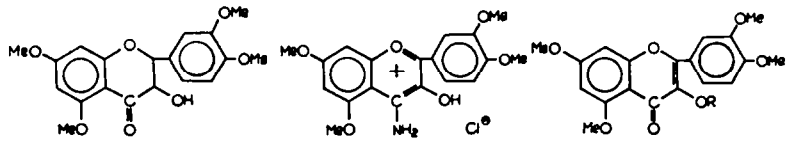
II.

The free base (II; R = H) cannot be liberated, owing to its expected[2] lack of stability. A diacetyl derivative (II; R = Ac) of rather poor stability may be obtained on acetylation at room temperature. (The IR spectrum showed the presence of a C=O vibration at 1770 cm^{-1} (in enolic ester); C=O at 1640 cm^{-1} (Amide I band); C=N at 1682 cm^{-1}.) This derivative is hydrolysed by hydrochloric acid to yield

[1] G. Janzsó, F. Kállay and I. Koczor, *Tetrahedron Letters* 2269 (1965).
[2] R. Robinson and G. Schwarzenbach, *J. Chem. Soc.* 822 (1930).
[3] R. L. Shriner and R. Sutton, *J. Amer. Chem. Soc.* **85**, 3988 (1963).

flavonol. Likewise, the flavylium salt (I) is hydrolysed by alkali to give flavonol and ammonia.

In order to illustrate this new method, using a natural flavonoid, optically active taxifolin has been converted into the 5,7,3′,4′-tetramethyl ether[4] (III) and reacted with *p*-tosylhydrazine in the presence of hydrochloric acid. This reaction gives 4-amino-5,7,3′,4′-tetra-O-methylcyanidin chloride (IV) which was hydrolysed by alkali to 5,7,3′,4′-tetra-O-methylquercetin (V; R = H) and identified as its 3-acetyl derivative[4] (V; R = Ac).



III. IV. V.

The rotational dispersion curve of IV reveals its complete optical inactivity, in accordance with the flavylium salt structure. This, cannot be the consequence of racemization[5] during conversion of taxifolin into the flavylium salt. Though $[\alpha]_D \sim 0$ is found for III, its optical activity is clearly shown by the negative optical rotational dispersion curve (Fig. 1). This activity is not due to the presence of an impurity of taxifolin, since the latter has a positive plain curve. Finally, the racemization of III prior to conversion to the flavylium salt is excluded since the rotational dispersion

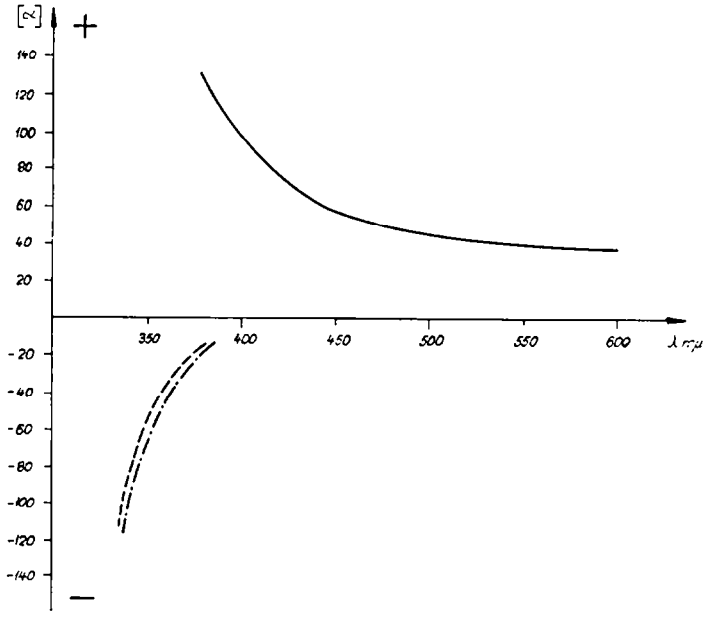


Fig. 1. ——taxifolin; – – –5,7,3′,4′-tetra-O-methyltaxifolin (III); -·-·- III after boiling with HCl.

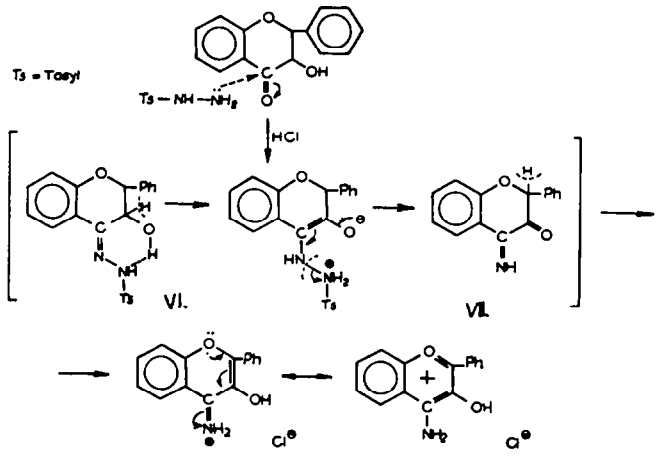
[4] H. L. Hergert, P. Coad and A. V. Logan, *J. Org. Chem.* **21**, 304 (1956).

[5] M. Shimokoriyama, *The Chemistry of Flavonoid Compounds* (Edited by T. A. Geissman) p. 294. Pergamon Press, Oxford (1962).

curve of taxifolin tetramethylether remains unchanged even after boiling for 6 hr with hydrochloric acid in ethanol.

Consequently, the inactivity of the flavylium salt is due to the elimination of the asymmetric centres at C_2 and C_3.

On the basis of the experimental evidence, the mechanism of formation of a 3-hydroxy-4-aminoflavylium salt is as follows:



The tosylhydrazone (VI), formed initially, may immediately undergo an intramolecular reaction involving the enolized C_3 hydroxyl group; toluene-*p*-sulphonamide is eliminated, and the resulting keto-imine (VII) becomes stabilised by rearrangement into the flavylium salt.

The reaction with *p*-tosylhydrazine appears to be generally applicable to flavanones containing a C_3 hydroxyl substituent, affording, by the alkaline hydrolysis of the 4-aminoanthocyanidin salt, a new method of indirect oxidation of flavanonols to flavonols. The decreased reactivity of the carbonyl group in compounds containing a free C_5 hydroxyl may be overcome by temporary blocking of this hydroxyl group.

Further synthetic interest is attached to the 3-hydroxy-4-aminoflavylium salts by the possibility of reducing them to 3-hydroxy-4-aminoflavans.

EXPERIMENTAL

All m.ps were determined on a Kofler block, and are uncorrected. All products were examined by TLC on Kieselgel HF_{254} using the system toluene–ethyl formate–formic acid (5:4:1), unless stated otherwise.

Flavanone p-*tosylhydrazone.* Flavanone (10 g; 0·0446 mole) and toluene-*p*-sulphonylhydrazine (13·4 g; 0·072 mole) were refluxed in EtOH (180 ml) in the presence of conc. HCl (1 ml) for 4 hr. The pale green reaction mixture was kept in a refrigerator for 24 hr, when light yellow crystals separated (14·5 g; 83%), m.p. 177–177·5°. The product was pure by TLC (benzene–AcOEt 95:5), and showed negative $FeCl_3$ test. (Found: C, 67·30; H, 5·05; O (direct) 12·70; N, 7·50; S, 8·08. $C_{28}H_{30}O_3N_2S$ (392·46) requires: C, 67·32; H, 5·14; O, 12·24; N, 7·14; S, 8·17%.)

Hydrolysis of the product with 10% HClaq gave flavanone.

Flavone p-*tosylhydrazone*

Flavone (1·5 g; 0·00675 mole) in EtOH (30 ml) was refluxed with *p*-tosylhydrazine (2 g; 0·0107 mole) and conc. HCl (0·2 ml) for 8 hr. Cooling to 0° gave yellow crystals (1·31 g; 50%), m.p. 205–206°, with negative $FeCl_3$ test (absence of pyrazole derivative), TLC in benzene–AcOEt 95:5.

(Found: C, 67·36; H, 5·05; O (direct) 12·89; N, 7·67; S, 8·28%. $C_{22}H_{18}O_3N_2S$ (390·44) requires: C, 67·69; H, 4·64; O, 12·27; N, 7·18; S, 8·20%.)

Flavone *p*-tosylhydrazone was hydrolysed by boiling 10% HCl to flavone.

3-*Hydroxy*-4-*aminoflavylium chloride* (I)

3-Hydroxyflavanone (1 g; 0·00416 mole) in EtOH (100 ml) was refluxed with *p*-tosylhydrazine (780 mg; 0·0042 mole) and conc. HCl (1 ml) for 6 hr. The solution was cooled, mixed with *n*-hexane (50 ml) and allowed to stand in a refrigerator overnight. Yellow crystals (764 mg; 67%) separated, m.p. 258–260°. The product was chromatographically pure (R_f 0·24) and gave a positive $FeCl_3$ colour reaction. It is sparingly soluble in water, and the presence of chloride ion was shown by $AgNO_3$. (Found: C, 66·22, H, 4·74; O (direct) 11·59; N, 5·22; Cl (ionic) 13·15; Cl (total) 13·25. $C_{15}H_{12}O_2NCl$ (273·71) requires: C, 65·99; H, 4·43; O, 11·70; N, 5·12; Cl, 12·99%.)

No product of osazone character was formed even when the experiment was repeated using excess (3·5 mole) of *p*-tosylhydrazine.

Evaporation of the mother liquor and extraction of the residue with hot water gave toluene-*p*-sulphonamide (197 mg), m.p. 135–137°, mixed m.p. with an authentic sample 137–138°.

3-*Acetoxy*-4-*acetiminoflavan* (II; R = Ac)

The salt (I; 400 mg) was allowed to stand in pyridine (20 ml) and Ac_2O (20 ml) at room temp for 2·5 hr. The solution was poured into ice-water (100 ml) to give a pale yellow microcrystalline precipitate (356 mg; 52%), m.p. 127–129°.

The compound is slowly decomposed on standing at room temp with the loss of acetic acid.

3-*Hydroxyflavone*

(a) *From* 3-*hydroxy*-4-*aminoflavylium chloride*. 3-Hydroxy-4-aminoflavylium chloride (300 mg) suspended in 10% NaOHaq (20 ml) was stirred and refluxed for 4 hr. The orange-red suspension became yellow and NH_3 was evolved. Acidification with dil. HCl to pH = 2 gave 3-hydroxyflavone; the recrystallized product (180 mg; 70·2%) had m.p. 171–172°, and mixed m.p. with an authentic sample[6] 171–172°. The product was also identified by comparison of the IR spectrum with that of flavonol.

(b) *From* 3-*acetoxy*-4-*acetaminoflavan*. Compound II; R = Ac; 100 mg) was refluxed in EtOH (30 ml) and 5% HClaq (10 ml) for 1 hr. Cooling to 0° gave colourless needles of 3-hydroxyflavone (495 mg; 67·5%), m.p. 170–172°, mixed m.p. with an authentic sample 170–172°.

The flavylium chloride resisted the action of 10% HCl; after refluxing for 6 hr, 93% of the starting material was recovered unchanged.

4-*Amino*-5,7,3′,4′-*tetra*-O-*methylcyanidin chloride* (IV)

(+)-Taxifolin was converted[4] into III, m.p. 171–172°. This product (III; 500 mg; 0·00139 mole) was refluxed in EtOH (35 ml) with *p*-tosylhydrazine (260 mg; 0·00139 mole) and conc. HCl (0·5 ml) for 5 hr. After the second hr of boiling, fine, bright yellow needles were observed. The product (504 mg; 92·5%), m.p. 220–221°, was soluble in water. (Found: C, 57·82; H, 5·57; O (direct) 24·15; N, 3·58; Cl, 8·64. $C_{19}H_{20}O_6NCl$ (393·81) requires; C, 57·98; H, 5·13; O, 24·39; N, 3·56; Cl, 9·02%.)

5,7,3′,4′-*Tetra*-O-*methylquercetin* (V; R = H)

Compound IV (500 mg; 0·00127 mole) was hydrolysed in 10% NaOH (20 ml) as described for 3-hydroxy-4-aminoflavylium chloride. The yellow crystalline needles (322 mg; 71%) melted after recrystallization from EtOH–acetone (1:1) at 200·5° (lit.[4] m.p.: 196°). (Found: C, 63·25; H, 5·13; O (direct) 31·77. Calc. for $C_{19}H_{18}O_7$: C, 63·51; H, 5·05; O, 31·26%.)

Acetylation in Ac_2O–pyridine gave V (R = Ac), m.p. 162°, (lit.[4] m.p. 162°).

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[6] R. Bognár and M. Rákosi, *Chem. & Ind.* 773 (1955).