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Flavonoids: Part I. Synthesis and Spectral Study of 6-Chloro-8-Amino-4' (R) Flavonoids

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6-Chloro-8-amino-4' (OMe or H) flavonoids have been synthesised by the applications of the appropriate flavonoid syntheses to 2-hydroxy-3-amino 5-chloro acetophenone (I). The latter has been formed on Friedel-Crafts acetylation of 2-methoxy-5-chloro acetanilide. The ultraviolet spectra of these compounds have been studied.

For the work undertaken by us in connection with the study of the chemistry of pyranoquinolines, 6-chloro-8-amino flavonoids were required for a comparative study of the ultraviolet spectra and the colour reactions and as possible starting materials It was with this purpose that the work described in the present communication was undertaken. It may be interesting to note that the bz-chloro and bz-amino substituted flavonoids have been reported[1].

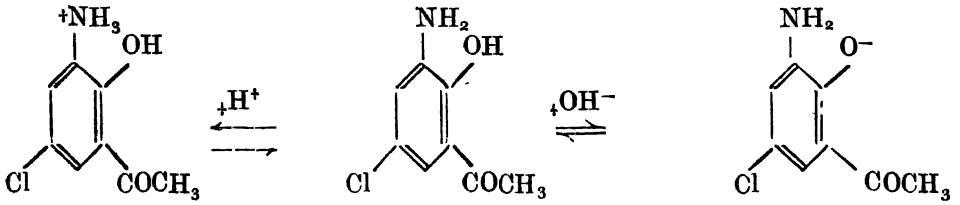
2-Methoxy-5-chloro acetanilide[2] was condensed with acetyl chloride in presence of anhydrous aluminium chloride at 100° affording 2-hydroxy-3-acetamido-5-chloro acetophenone(I) in 55% yield under the conditions described in the experimental. The compound (I) dissolved in dilute alkali solution and developed violet colour with Fe^{+3} in ethanol solution.

The compound (I) was condensed with benzaldehyde in presence of 40% alcoholic alkali solution at 0° to obtain 2'-hydroxy 3'-acetamido-5'-chloro chalcone (II). The same product was also formed when this condensation was effected at room temperature (30-40°). The chalcone(II) on treatment with 10% alcoholic hydrochloric acid solution afforded 6-chloro-8-amino flavanone(III), indicating that during the course of the reaction the acetamido group was hydrolysed. The chalcone(II) when refluxed with selenium dioxide in isoamyl alcohol solution, afforded 6-chloro-8-acetamido flavone (IV). The latter on treatment with hot hydrochloric acid solution was hydrolysed to 6-chloro 8-amino flavone (V). The chalcone (II) on treatment with cold alkaline hydrogen peroxide yielded 6-chloro-8-acetamido flavonol (VI).

Starting with (I) and anisaldehyde and following the methods described above, the corresponding flavonoid compounds, VII, VIII, IX, X, and XI listed in table-1 have been synthesised. These flavonoid compounds responded to characteristic colour reactions with concentrated sulphuric acid, alcoholic alkali solution and with magnesium and hydrochloric acid.

1. D. H. Marrian, P. B. Russell and A. R. Todd, *J. Chem. Soc.*, 1947, 1419; A. A. Raval and N. M. Shah, *J. Org. Chem.*, 1956, **21**, 1408; W. Feuerstein and St. V. Kostanecki, *Ber. Dtsch. Chem. Ges.*, 1818, **31**, 717; F. C. Chen and C. H. Yang, *Chem. Abstr.*, 1955, **49**, 2432; S. R. Parikh and N. M. Shah, *Jour. Indian Chem. Soc.*, 1959, **36**, 726, 729.
2. L. C. Raiford and J. C. Colbert, *J. Amer. Chem. Soc.*, 1926, **48**, 2657.

The ultraviolet spectra of 2-hydroxy-3-amino-5-chloro acetophenone (Ia) have been studied in aqueous alcoholic solution (10% H_2O) at three different *p*H's. These spectra have been shown in figure-1. The spectrum studied at *p*H=8.0 comprises three bands, a peak at 242 mμ (4.27), a broad shoulder at 270-80 mμ and a broad band at 375 mμ(3.48). The corresponding bands in the spectrum of the compound (Ia) at *p*H=11, have undergone bathochromic shifts; the longwavelength band, in particular, has undergone a bathochromic shift of 20 mμ and has suffered a hyperchromic change. The change in the nature of the spectrum seems to be due to the almost complete transformation of the ecmpound (Ia) into the corresponding phenoxide ion (XII) which would function as a compaiatively stronger chromophore. In an acidic medium, the compound (Ia) would be transformed into its conjugate acid(XIII) with the result that the lone pair of electrons on the nitrogen



(XIII) (Ia) (XII)

atom being used up in the bond formation with H^+ would not be available for interaction with the π-electron of benzene. The effect of this is discernible in the spectrum of the compound (Ia) studied in acidic medium (*p*H=1.1) which depicts a hypochromic change over the whole range of the spectrum and a hypsochromic effect of about 40 mμ for the longwavelength band. In an acidic medium, that the NH_2 group of the compound (Ia) is almost completely put of action in resonance interaction, is further indicated by the fact that the spectrum of the compound (Ia) in the acidic medium resembles very closely

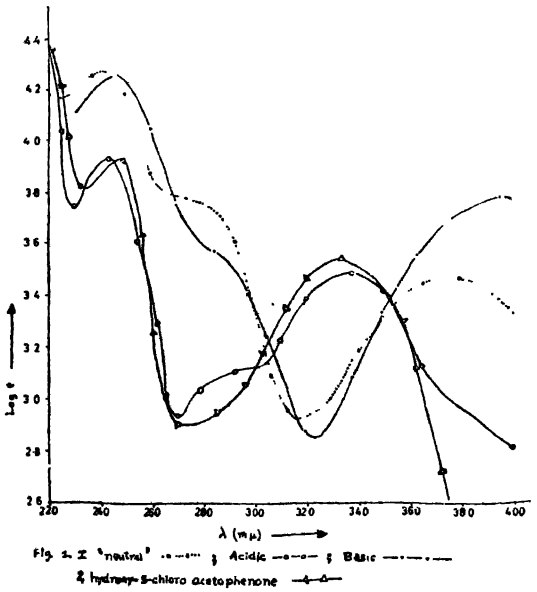


FIG. 1

the spectrum of 5-chloro-2-hydroxy acetophenone (vide fig. 1). It has been reported that the spectrum of anilinium ion is almost superimposable on that of benzene.[3]

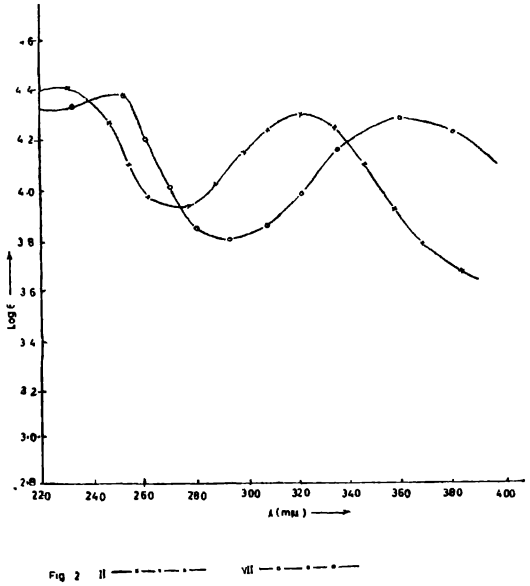


FIG. 2

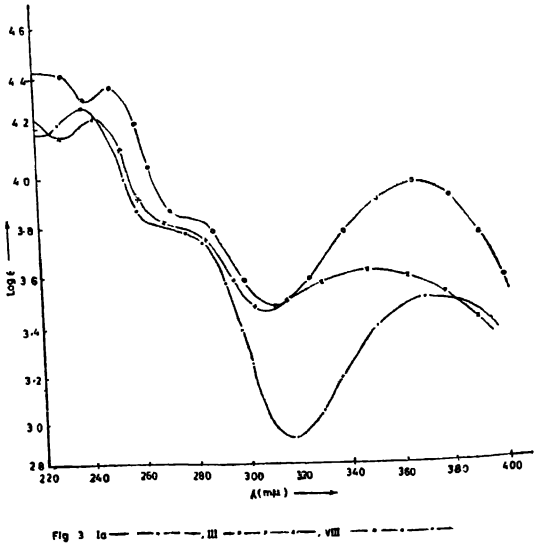


FIG. 3

TABLE I

No.	Compound	max (log ε)	max (log ε)
Ia	2-Hydroxy-3-amino-5-chloro acetophenone.		
	(*p*H=8.0)	241 (4.27) 280 (s) (3.76)	375 (3.48)
	(*p*H=11.0)	245 (4.25) 290 (s) (3.54)	393-94 (3.79)
	(*p*H=1.10)	244 (3.93) 285-290 (In) (3.08)	336 (b) (3.49)
II	2′-Hydroxy-3′-acetamido-5′-chloro chalcone.	228 (4.41)	320-330 (b) (3.27-3.29)
III	6-Chloro-8-amino flavanone	245 (4.22) 275-285 (3.71)	340-360 (b) (3.58)
V	6-Chloro-8-amino flavone	275-280 (b) (4.49)	350-60(s) (3.48-3.57)
VI	6-Chloro-8-acetamido flavonol	220-225 (4.49) 235-240 (s) (4.35-4.37)	320 (3.73) 345-350 (b) (3.70)
VII	2′-Hydroxy-3′-acetamido-5′-chloro-4-methoxy chalcone	245 (4.41)	355-365 (b) (4.33)
VIII	6-Chloro-8-amino-4′-methoxy flavonone	244 (4.38) 278 (s) (3.85)	360-370 (b) (3.99-4.00)
X	6-Chloro-8-amino-4′methoxy flavone	226 (4.44)	308-312 (b) (4.38-4.39)
XI	6-Chloro-8-acetamido-4′-methoxy flavonol	225 (s) (4.57) 255-265 (s) (4.28-4.29)	363-366 (b) (4.12)

b=broad, s=shoulder, In =Inflection.

3. Leonard Doub and J. M. Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714.

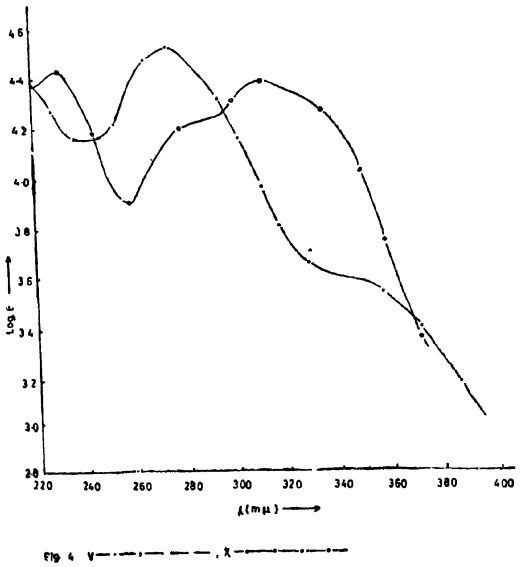
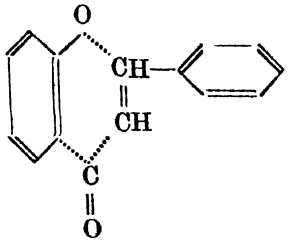


FIG. 4

The ultraviolet spectra of the flavonoids are shown in figures 2, 3 and 4. The spectra of flavonoid compounds have been studied by various workers[4]. The long and the short-wavelength bands in the spectrum of flavonoid compounds are designated as band-I and -II respectively[5]. The former has been considered to be due to the contribution of the cinnamoyl grouping and the latter (band-II) has been regarded as a contribution of the benzoyl grouping of the flavonoid system.[6]



Benzenoid grouping — Cinnamoyl grouping

The spectra of the chalcone derivatives (II) and (VII) comprise two intense bands. Both the bands and more particularly the band-I in the spectrum of compound (VII) appear at longer wavelengths than the corresponding bands in the spectrum of the compound (II). The bathochromic shift and the hyperchromic change that has been observed in the band-I in the spectrum of the chalcone (VII) seems to be due to additional 4'-methoxy group resulting in an increased conjugation of the cinnamoyl grouping.[6]

4. T. A. Geissman, E. C. Jorgensen, and J. B. Harborne, *Chem. Ind.* (London) 1953, 1389; T. Swain, *Chem. Ind.*, (Lond.) 1954, 1480; C. G. Nordstrom and T. Swain, *J. Chem. Soc.*, 1953, 2764.
5. T. A. Geissman, "Modern Methods of Plant Analysis", (Edited by K, Pacch and M. V. Tracey, Vol. III, p. 485, Julius Springer, Berlin (1955).
6. L. N. Ferguson and R. P., Barnes, *J. Amer. Chem. Soc.*, 1948, **70**, 3907; W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, 1954, **77**, 5134; H. H. Szmant, and A. Basso, *J. Amer. Chem. Soc.*, 1952, **74**, 4397.

The spectra of the flavanone type of compounds (III), (VIII) comprise two bands. The short wavelength band consists of an inflection and a shoulder at 244 and 278 mμ respectively. The long-wavelength band in the spectrum of each of these compounds is in the form of a broad band. In the spectrum of the compound (VIII), the shortwave length band is more intense and the long wavelength band appears at a longer wavelength than the corresponding band in the spectrum of the compound (III). These spectra appear to be very similar to that of 2-hydroxy-3-amino-5-chloro acetophenone (Ia) and the similarlity is somewhat striking in the short wavelength band of the spectra of these compounds. Since the spectra of flavanones are not due to differential resonance contributions of the benzoyl and cinnamoyl moieties because of the absence of the 2-3 double bond, it is hardly surprising that they should resemble the spectrum of an appropriately substituted acetophenones (plus benzene or anisole).

The spectrum of the flavone type of compound (V) consists of a broad peak at 277 mμ (4.49) and a shoulder at 355 mμ. The spectrum of the compound (X) comprises a small peak at 226 mμ (4.44) and an intense broad band with an inflection at 310 mμ (4.38). Much higher intensity of absorption exhibited by the band-I in the spectrum of the compound (X) is due to the presence of the 4′-methoxy group.

The spectrum of the flavonol type compound (VI) comprises two bands. The band-II is in the form of a broad shoulder (4.49-4.39). The band-I of the spectrum is a broad band running between 320-360 mμ with a slight depression at about 335 mμ. The spectrum of compound (XI) is similar to that of the compound (VI), but the constituent bands are more intense and appear at comparatively longer wavelengths.

EXPERIMENTAL

Friedel-Crafts acetylation of 2-methoxy-5-chloro acetanilide: *Formation of 2-hydroxy-3-acetamido-5-chloro acetophenone* (I): To a mixture of 2-methoxy-5-chloro acetanilide (15 g.) and finely powdered anhydrous aluminium chloride (45 g.), acetyl chloride (15 g.) was added dropwise at 0°C. The reaction mixture was left in an ice-bath for an hour, and was then heated on a boiling water-bath for 6 hr, cooled and decomposed with crushed ice and hydrochloric acid (5 ml.). The solid product was filtered, washed and air dried. It was crystallised from ethanol (charcoal) in a yellowish light powder, m.p. 139-40°, yield: 10 g. It developed a violet colour with neutral alcoholic ferric solution. (Found: N, 6.0; Cl, 15.3%; $C_{10}H_{10}O_3NCl$ requires N, 6.15; Cl, 15.6%).

2-Hydroxy-3-amino-5-chloro acetophenone (Ia): A suspension of 2-hydroxy-3-acetamido 5-chloro acetophenone (10 g.) in 75% hydrochloric acid solution (50 ml.) was heated on a water bath for 3 hr, cooled and neutralised by adding a required amount of solid sodium bicarbonate. The solid product which separated was collected, washed with water and crystallised from aqueous alcohol in yellow needles, m.p. 110-12°; yield: 8 g. (Found: N, 7.7%; $C_8H_8O_2NCl$ requires N, 7.5%).

2:4-Dinitrophenyl hydrazone of (Ia) was crystallised from alcohol in reddish yellow crystals, m.p. 263-65°. (Found: N, 18.9%; $C_{14}H_{12}O_5N_5Cl$ requires N=19.1%).

2′-Hydroxy-3′-acetamido-5′-chloro chalcone (II): A solution of (I) (2.3 g.) and benzaldehyde (1.0 g.) in ethanol (20 ml.) was added in small lots to sodium hydroxide solution

(15 ml., 40%) and left for 12 hr at room temperature, mixed with ice (50 g.) and acidified by adding required amount of acetic acid. The solid product was collected, washed successively with water, dilute solution of sodium bicarbonate and water. The air-dried product was crystallised from ethanol (charcoal) in yellow needles, m.p. 180-82°; yield: 1.5g. It developed an orange yellow and a deep red colour with 20% alkali and concentrated sulphuric acid respectively. (Found: N, 4.8; Cl, 11.1%; $C_{17}H_{14}O_3NCl$ requires N, 4.4; Cl. 11.1%).

2′-Hydroxy-3′ -acetamido-5′ -chloro-4-methoxy chalcone (VII): It was formed as described above from (I) and anisaldehyde. It was crystallised from benzene in yellow needles, m.p. 203-4°. It developed deep orange yellow and deep violet colour with 20% alkali and concentrated sulphuric acid respectively. (Found: N, 4.3; Cl, 10.1%; $C_{18}H_{16}O_4NCl$ requires N, 4.0; Cl, 10.3%).

6-Chloro-8-amino flavanone (III): A solution of the chalcone (II) (0.5 g.) in ethanol (20 ml.) was mixed with hydrochloric acid solution (10 ml, 20%) and extra amount of ethanol (10 ml) was then added to clear up the solution. The solution was then refluxed on a water-bath for 45 hr and distilled to remove major part of alcohol. The residual solution was diluted with water to 50 ml. and neutralised by adding a required amount of ammonia. The solid product was collected, washed and dried. It was crystallised from hot ethanol in small brownish yellow needles, m.p. 140-42°, yield: 0.12 g. It developed pale yellow, orange and yellow colour with 20% alkali, concentrated sulphuric acid and magnesium hydrochloric acid respectively. (Found: N, 4.9, Cl, 12.8%; $C_{15}H_{12}O_2NCl$ requires N, 5.1, Cl, 13.0%).

6-Chloro-8-amino-4′-methoxy flavanone: (VIII): It was prepared as described above from the chalcone (VII). It was crystallised from ethanol in reddish brown needles, m.p. 148-50°. It developed reddish brown violet and yellow colour with 20% alkali, concentrated sulphuric acid and magnesium hydrochloric acid respectively. (Found: N, 4.8, Cl, 11.4%; $C_{16}H_{14}O_3NCl$ requires N, 4.6, Cl, 11.1%).

6-Choloro-8-acetamido flavone (IV): A suspension of 2′-hydroxy-3′ -acetamido-5′ -chloro chalcone (II) (0.5 g.) and selenium dioxide (0.5 g.) in isoamyl alcohol (20 ml.) was refluxed at 140-50° for 18 hr. The cooled reaction mixture was filtered twice to remove the residual selenium metal. The residue was washed with chloroform. The mixed chloroformisoamyl alcohol filtrate after treatment with charcoal was diluted with excess petroleum ether to precipitate the product which was collected and crystallised from chloroform in yellowish white needles, m.p. 280-82°, yield: 0.2 g. (Found: N 4.1, Cl, 11.1%; $C_{17}H_{12}O_3NCl$ requires N, 4.4, Cl, 11.3%).

6-Chloro-8-amino flavone (V) formed on hydrolysis of (IV) with boiling alcoholic hydrochloric acid solution (1:1) was crystallised from ethanol (charcoal) in fine yellow needles, m.p. 248-49°. It developed red, deep yellow and light yellow colour with 20% alkali, contentrated sulphuric acid and magnesium hydrochloric acid respectively. (Found: N 4.9, Cl, 13.2%; $C_{15}H_{10}O_2NCl$ requires N, 5.1, Cl, 13.1%).

6-Chloro-8-acetamido-4′ -methoxy flavone (IX): It was obtained on cyclo-dehydrogenation of the chalcone (VII) with selenium dioxide by the method described above. It was crystallised from glacial acetic acid in bright yellow needles, m.p. 286-87°. (Found: N. 4.3, Cl, 10.5%; $C_{18}H_{14}O_4NCl$ requires N, 4.1, Cl, 10.3%).

6-Chloro-8-amino-4′ -methoxy flavone (X) was obtained on hydrolysis of above compound with boiling alcoholic hydrochloric acid. It was crystallised from acetic acid in greenish yellow small needles, m.p. 236-37°. It developed yellow, red brown and yellow colours with 20% alkali concentrated sulphuric acid and magnesium hydrochloric acid respectively. (Found: N, 4.6, Cl, 11.9%; $C_{16}H_{12}O_3NCl$ requires N, 4.6, Cl, 11.7%).

6-*Chloro*-8-*acetamido flavonol* (VI): An ice-cooled solution containing 2′-hydroxy-3′ -acetamido 5′-chloro chalcone (II) (0.5 g.), a solution of sodium hydroxide (15 ml, 15%) and methyl alcohol (15 ml.) was mixed with ice-cold hydrogen peroxide (6 ml, 18%), left in refrigerator for 3 hr and then at room temperature for 24 hr. The reaction mixture was mixed with crushed ice (100 g.) just acidified with acetic acid. The solid product was collected, washed and dried in air. It was crystallised from glacial acetic acid in yellow needles, m.p. 304-6°, yield; 0.2 g. It developed yellow colour with 20% alkali and concentrated sulphuric acid. (Found: N, 4.4, Cl, 10.9%; $C_{17}H_{12}O_4NCl$ requires N, 4.2, Cl, 10.7 %).

6-*Chloro*-8-*acetamido*-4′ -*methoxy flavonol* (XI): It was prepared as described above from 2′-hydroxy-3′-acetamido-5′-chloro-4-methoxy chalcone (VII). It was crystallised from glacial acetic acid, m.p. 322-24°. It developed yellow colour with 20% alkali and concentrated sulphuric acid. (Found: N, 4.05, Cl, 10.1%; $C_{18}H_{14}O_5$ NCl requires N, 3.9, Cl, 9.9%).

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