Distances and Angles

Intramolecular bond lengths and angles not involving hydrogen atoms are listed in Fig. 3. The standard labelling of atoms is in the same figure. The H atom of the hydrobromide combines with N^3 of the phthalazine ring. Distances between N(1)-H(17), H(17)-Br and N(1)-Br are 1.17, 2.00 and 3.12 Å, respectively. The N(1)-H(17)----Br bond is a hydrogen bond, but no intermolecular hydrogen bonds are observed. The C(1)-N(3) bond length is shorter than the normal length (1.47 Å) by 0.12 Å. This fact indicates that the nitrogen atom (N(3)) would resonate with the phthalazine ring. The dihedral angle between the phthalazine ring and pyrazoline ring is 27.3°. The torsion angle C(2)-C(1)-N(3)-N(4), C(2)-C(1)-N(3)-C(11),N(2)-C(1)-N(3)-N(4) and N(2)-C(1)-N(3)-C(11) are 27.3°,—158.0°,—157.9° and 16.8°, respectively (Fig. 4).

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Synthetic Studies of Azaflavonoids. I. Studies on the Synthesis of 5-Azaflavone[1)]

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Azachalcones (IV) were synthesized from 2-cyano-3-hydroxy-pyridine (I) *via* three steps. Based on the ultraviolet spectroscopic data, the cyclization of IV to 5-azaflavanones (V) was assumed, but V could not be isolated. On the other hand, a 5-azaflavone (VIII) was prepared from I *via* five steps in a moderate yield.

Keywords——azaflavone; azaflavanone; azachalcone; pyridine derivative; Grignard reaction; acid catalyzed cyclization

In our laboratory, the synthetic studies of the heterocyclic compounds containing nitrogen atoms in the skeleton are in progress,[3)] and the several pyridoflavanones have already been synthesized.[4)]

Many years since the flavonoids as plant pigments have widely been studied. Rutin, hesperidin and myricitrin among them have some pharmacological activities against increased capillary fragility. The appropriate solubilizing and suspending agents were used in order to apply them to medicinal use because of their insolubility in water. Now azaflavonoids may be expected to have more activity than that of the flavonoids, because the solubility of azaflavonoids may be enhanced by salt formation. From the above point of view, the

1) A part of this work was presented at the 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, June 1975 (Kanazawa), and at the 96th Annual Meeting of Pharmaceutical Society of Japan, April 1976 (Nagoya).
2) Location: *Gofuku, Toyama.*
3) T. Yamazaki, K. Matoba, M. Yajima, M. Nagata, and R.N. Castle, *J. Heterocyclic Chem.*, **12**, 973 (1975), and references therein.
4) H. Matsumoto, M. Nagata, J. Kawahira, and T. Yamazaki, *Yakugaku Zasshi*, **88**, 1412 (1968).

synthetic studies of 5-azaflavanones and 5-azaflavone are described in this paper. On the other hand, 6-azaflavone had been synthesized by Lhommet, *et al.*[5]

As a starting material, 2-cyano-3-hydroxy-pyridine (I) was chosen. I was prepared from 3-hydroxy-pyridine *via* 3-hydroxy-2-iodo-pyridine by the known method.[6] The conversion of I to 2-acetyl-3-hydroxy-pyridine (III) was carried out by the Grignard reagent. I was at first derived to the corresponding acetate, 3-acetoxy-2-cyano-pyridine (II), which was successively subjected to the Grignard reaction to afford III. III exhibited a carbonyl band at 1655 cm^{-1} in the infrared (IR) spectrum and methyl signal at 2.73 ppm and phenolic proton at 11.70 ppm in the nuclear magnetic resonance (NMR) spectrum. III thus obtained was treated with three *p*-substituted aldehydes in the presence of sodium hydroxide to give 2-(4-substituted-benzylidene)acetyl-3-hydroxy-pyridine (aza-4′-substituted-chalcones)(IVa—c) in moderate yields. 4-Methoxy derivative (IVa), for example, was of green needles and exhibited a carbonyl band at 1640 cm^{-1} in IR spectrum, two absorption maxima at 236 and 376 nm in ultraviolet (UV) spectrum in ethanol, and two vinylic protons and phenolic proton at 7.30 and 12.50 ppm respectively in NMR spectrum.

Nextly the trials to cyclize IV to 5-aza-4′-substituted flavanone (V) were carried out. The reagents and conditions used were as follows: 1) at reflux or at room temperature in 50% acetic acid, 2) at 80—90° in 10% hydrochloric acid, 3) at reflux temperature in the presence of borontrifluoride etherate in ether, and 4) at 80—90° in 10% sodium carbonate.[7] In all the cases, the starting materials (IV) or its salt or unidentifiable purple pigments were obtained. However, when the NMR spectrum of IVa was measured in trifluoroacetic acid, the colour of the solution in the sample tube gradually faded. After 5 days, the signals due to IVa disappeared in the NMR chart, and those suggesting the formation of Va appeared, that is, the signals at 3.50—3.90 and 6.38 ppm were assigned to C-3 methylene protons and to C-2 methine proton respectively. This conversion was also supported by the UV spectrum measured in trifluoroacetic acid; an absorption maximum at 438 nm decreased in the

Table I. Temporal Change in the UV Absorption Maxima and Intensities of 4′-Substituted Azachalcones (IV) in CF_3COOH

hr	–OMe(IVa)		–Cl(IVb)		–NO_2(IVc)	
	nm	$\varepsilon \times 10^{-3}$	nm	$\varepsilon \times 10^{-3}$	nm	$\varepsilon \times 10^{-3}$
0	438	23.3	397	22.8	353	30
	313	19.2	328	5.0		
1	438	31.6	397	22.2	353	29.8
	313	17.9	328	4.9		
2	438	15.1	395	21.7	353	29.8
	313	9.1	328	4.5		
4	438	13.8	396	20.2	353	29.8
	313	9.2	325	4.6		
8	438	10.7	397	19.6	353	29.2
	313	5.4	325	4.2		
24	438	2.8	396	16.0	347	17.1
	313	5.2	323	4.0		
48	438	1.2	399	9.0	328	11.9
	313	5.1	318	6.3		
72	438	0.5	401	7.4	327	11.2
	313	4.8	318	6.3		
100	438	0	402	4.9	325	9.8
	313	3.8	315	5.7		

5) G. Lhommet, H. Sliwa, and P. Maitte, *J. Heterocyclic Chem.*, **8**, 517 (1971).
6) B. Blank, *J. Med. Chem.*, **17**, 1065 (1974).
7) F. Cramer and G.H. Elschnig, *Chem. Ber.*, **89**, 1 (1956).

intensity and became flat after 5 days (Table I). The isolation of Va from this solution of trifluoroacetic acid was unsuccessful, and there was obtained only a purple pigment, the structure of which was not determined from IR, UV, NMR, and mass spectra. For 4-chloro derivative (IVb) and 4-nitro derivative (IVc), it was suggested from these UV absorption maxima and intensities in Table I that they exsist in the equilibria of them Vb or Vc.

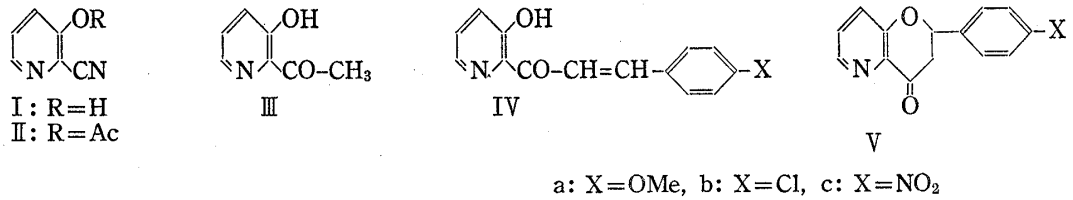

Chart 1

Nextly, the synthesis of 5-azaflavone (VIII) was studied. By the Allan-Robinson method the direct synthesis of VIII starting with III using benzoic anhydride and sodium benzoate was unsuccessful. In this case, only a black resinous material was obtained, and therefore the following stepwise synthesis[8] was adopted. III was converted to 2-acetyl-3-benzoyloxy-pyridine (VI) with benzoyl chloride in pyridine. VI exhibited carbonyl bands at 1735 and 1690 cm^{-1} in IR spectrum. Nextly the conversion of VI to benzoyl 3-hydroxy-2-pyridoyl methane(VII) was carried out using potassium carbonate in toluene or sodium hydride[9] in benzene. In the former case VII was obtained only in a poor yield, on the other hand, in the latter case in a moderate yield. The NMR spectrum of VII in deterochloroform revealed that it existed in enol form and keto form in about 5:1 ratio in this solvent, that is, methylene protons was observed at 4.80 ppm, phenolic proton at 11.08 ppm, and enolic proton at 15.03 ppm respectively. In the spectrum measured in pyridine the signals due to methylene protons disappeared because in this solvent VII should wholly exsist in enol form. Finally the conversion of VII to 5-azaflavone (VIII) was carried out in a usual manner, that is, it was performed with sodium acetate in glacial acetic acid. VIII thus obtained was white needles melting at 167—168° and positive toward the flavone-reaction. It exhibited a carbonyl band at 1645 cm^{-1} in the IR spectrum, an absorption maximum at 297 nm in the UV spectrum and a signal due to C-3 proton at 6.95 ppm in the NMR spectrum.

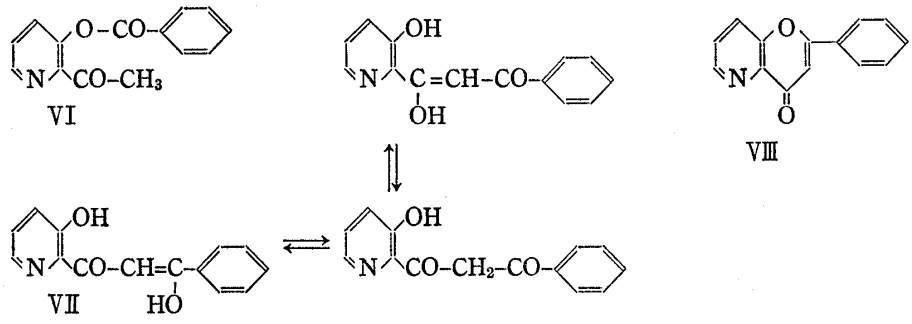

Chart 2

Experimental

All the melting points taken on a Kofler Block and the boiling points were uncorrected. The following equipments were used: IR spectra, Hitachi Grating Infra Red 215 Spectrometer; UV spectra, Hitachi 124 Spectrophotometer; NMR spectra, JEOL C-60H spectrometer with tetramethylsilane as an internal refer-

8) W. Baker, *J. Chem. Soc.*, **1933**, 1381.
9) T. Kurihara, T. Michida, and H. Hirano, *Chem. Pharm. Bull.* (Tokyo), **23**, 2451 (1975).

ence; Mass spectra, JEOL TMS-01SG (75 eV, direct inlet system). For column chromatography silica gel (Wako gel C-200) was used. The chemical shifts and coupling constants in NMR spectra were described in δ-value and Hz respectively. The abbreviations used to demonstrate coupling pattern are as follows; singlet-s, doublet-d, triplet-t, quartet-q, multiplet-m, broad-br. All the solvents were evaporated under reduced pressure.

3-Acetoxy-2-cyano-pyridine (II)——2-Cyano-3-hydroxy-pyridine (I) (10.1 g) was mixed with Ac_2O (9 g) and pyridine (30 ml). The mixture was warmed to dissolve I and stood overnight. The reaction mixture was concentrated *in vacuo* to give a colorless oil, which was dissolved in ether. The ether layer was dried over $MgSO_4$ after washing with bicarbonate solution and water. After the solvent was evaporated, the residue was distilled. bp 120° (7 mmHg). Yield: 12.6 g (92.4%). IR (film) cm^{-1}: $\nu_{C\equiv N}$ 2250, $\nu_{C=O}$ 1775. NMR (CCl_4): 2.37 (3H, s, $-CH_3$), 7.13—7.77 (2H, m, 4- and 5-H), 8.47 (1H, d.d, $J=4$ and 2, 6-H).

2-Acetyl-3-hydroxy-pyridine (III)——To the ice-cooled Grignard reagent prepared from Mg (9.45 g) and CH_3I (55.3 g) in ether (30 ml), II (12.6 g) in benzene (60 ml) was added during 1 hr. The mixture was refluxed for 5 hr on an oil bath followed by the decomposition of the complex with sat. NH_4Cl solution (30 ml). The aqueous layer was cautiously neutralized with dilute HCl solution and then extracted with ether. Both the benzene–ether and ether layers were combined, washed with sat. NaCl solution and dried over $MgSO_4$. After the solvent was distilled off, the residue was purified through a silica gel column. III was eluted with $CHCl_3$.

$FeCl_3$ reaction: positive, mp 58—60° (from *n*-hexane). Yield: 5.2 g (48.8%). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1655, $\nu_{C=C}$ 1580. NMR (CCl_4): 2.73 (3H, s, $-CH_3$), 7.26 (2H, m, 4- and 5-H), 8.13 (1H, q, $J=4$ and 2, 6-H), 11.70 (1H, s, –OH). *Anal.* Calcd. for $C_7H_7O_2N$: C, 61.31; H, 5.11; N, 10.22. Found: C, 61.26; H, 5.31; N, 9.88.

2-(4-Methoxy-benzylidene)acetyl-3-hydroxy-pyridine (IVa)——To an ethanolic solution of III (250 mg) and *p*-anisaldehyde (250 mg), 10% ethanolic NaOH (5 ml) was added under ice-cooling. The mixture was stirred overnight to give Na salt of IVa, which was dissolved in a large amount of water. The aqueous layer was washed with ether and neutralized with dilute AcOH to give IVa. Yield was 40.2%. mp 113—114° (green needles from EtOH). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1640, $\nu_{C=C}$ 1560, 1585, 1600. UV λ_{max}^{EtOH} nm (ε): 236 (10700), 376 (28600); $\lambda_{max}^{EtOH\text{-}OH^-}$: 233 (19200), 333 (16300), 400 (11300); $\lambda_{max}^{CF_3COOH}$: see Table I. NMR ($CDCl_3$): 3.78 (3H, s, $-OCH_3$), 6.84 and 7.61 (each 2H, A_2B_2, $J=9.5$, benzene aromatic H), 7.30 (2H, d.like, vinylic H), 7.85—8.53 (3H, m, pyridine aromatic H), 12.50 (1H, s, –OH). *Anal.* Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.54; H, 4.83; N, 5.41.

2-(4-Chloro-benzylidene)acetyl-3-hydroxy-pyridine (IVb)——From III (250 mg), *p*-chlorobenzaldehyde (250 mg) and 10% ethanolic NaOH (5 ml), IVb was obtained under the same conditions described in the preparation of IVa. mp 139—140.5°. Yield: 226 mg (49%). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1640, $\nu_{C=C}$ 1600. UV (in CF_3COOH): see Table I. NMR ($CDCl_3$): 6.90—8.80 (9H, m, aromatic and vinylic H), 12.33 (1H, s, –OH). Mass Spectrum *m/e*: 261 (M^++2, 45%), 259 (M^+, base peak), 232 (M^++2−CHO, 31%), 230 (M^+−CHO, 67%).

2-(4-Nitro-benzylidene)acetyl-3-hydroxy-pyridine (IVc)——From III (607 mg), *p*-nitrobenzaldehyde (552 mg), and 10% ethanolic NaOH (12—13 ml), IVc was obtained as in case of IVa. IVc: mp 178—179°. Yield: 480 mg (44%). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1640, ν_{NO} 1520, 1340. UV (in CF_3COOH): see Table I. NMR ($CDCl_3$): 12.13 (1H, s, –OH), 8.83—7.16 (9H, m, aromatic and vinylic H). Mass Spectrum *m/e*: 270 (M^+, base peak), 240 (M^+−NO, 67.9%).

5-Aza-4′-methoxy-flavanone (V)——IVa (20 mg) was dissolved in CF_3COOH (0.4 ml) in an NMR sample tube. IVa (in CF_3COOH): 4.03 (3H, s, $-OCH_3$), 7.15 and 8.23 (each 2H, A_2B_2, $J=9$, benzene aromatic H), 7.83 (2H, d.like, vinylic H). These signals and color (green) due to IVa gradually disappeared. After 5 days, this green color completely faded. The signals due to V in NMR spectrum were as follows: 3.50—3.90 (2H, m, $-CH_2$–CO–), 4.01 (3H, s, $-OCH_3$), 6.38 (1H, d.d, $J=8$, 6, >CH–O–), 7.16 and 7.43 (each 2H, A_2B_2, $J=9.5$, benzene aromatic H), 8.07—8.45 (3H, m, pyridine aromatic H). After CF_3COOH was evaporated, the residue dissolved in $CHCl_3$ was washed with sat. $NaHCO_3$ and sat. NaCl followed by dryness. $CHCl_3$ layer turned purple and the residue obtained from this layer was an unidentifiable purple pigment.

2-Acetyl-3-benzoyloxy-pyridine (VI)——A solution of III (5.2 g) and benzoyl chloride (7.3 g) in pyridine was warmed on a water bath for 15 min. After the solvent was evaporated, the residue dissolved in ether was washed several times with sat. $NaHCO_3$ and sat. NaCl solution followed by dryness over $MgSO_4$. A yellow oil solidified after the evaporation of the solvent. VI: mp 68.5—69.5° (yellow needles from *n*-hexane). Yield: 4.7 g (51.4%). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1735, 1690, $\nu_{C=C}$ 1580. NMR ($CDCl_3$): 2.63 (3H, s, $-CH_3$), 7.23——7.67 (5H, m, benzene aromatic H), 7.93—8.27 (2H, m, pyridine aromatic H), 8.37—8.57 (1H, m, pyridine aromatic H). *Anal.* Calcd. for $C_{14}H_{11}O_3N$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.70; H, 4.63; N, 6.03.

Benzoyl 3-Hydroxy-2-pyridoyl Methane (VII)——1) VI (1 g) and K_2CO_3 (4.5 g) were mixed in toluene (15 ml) and warmed at 100° for 4 hr with stirring. After freed from the solvent by filtration, the solid mass was dissolved in water. After the removal of the insoluble part, the aqueous layer was neutralized with AcOH to give a precipitate, which was dissolved in $CHCl_3$ and the solution was treated with activated charcoal. Yellow needles (0.1 g) were obtained after the removal of the solvent. VII: mp 145—145.5°. IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1730, 1605, $\nu_{C=C}$ 1575. NMR ($CDCl_3$): 4.80 (0.4H, s, $>CH_2$), 7.00—8.30 (8.8H, m, aromatic H and vinylic H), 11.80 (1H, br.s, phenolic OH), 15.03 (0.8H, enolic H). NMR (d_5-pyridine): 7.20—7.50

(5H, m, benzene aromatic H), 7.75 (1H, s, vinylic H), 7.78—8.33 (3H, m, pyridine aromatic H), 10.90 (2H, br.s, phenolic and enolic OH). *Anal.* Calcd. for $C_{14}H_{11}O_3N$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.73; H, 4.78; N, 5.97. Mass Spectrum *m/e*: 241 (M^+, 29%), 136 ($M^+-C_6H_5CO$, base peak), 122 ($M^+-C_6H_5COCH_2$, 18%).

2) VI (252 mg) in benzene (8 ml) was added to NaH (55% in oil, 273 mg) in benzene (8 ml) under N_2 atmosphere. After reflux for 1/2 hr, the reaction mixture was cooled and poured onto ice-water. The aqueous solution was separated and neutralized with 30% AcOH to give a brown precipitate. The precipitate was dissolved in $CHCl_3$ and purified through silica gel column to give yellow needles (VII). Yield: 122 mg (48.9%).

5-Azaflavone (VIII)——A solution of VII (123 mg) and AcONa (111 mg) in glacial AcOH (10 ml) was refluxed for 6 hr. After AcOH was evaporated, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with sat. $NaHCO_3$ solution and sat. NaCl solution followed by dryness. The black crystals obtained after the evaporation of the solvent were purified through column. From $CHCl_3$, white crystals (VIII, 100 mg, 81.3%) were eluted. mp 167—168° (from *n*-hexane). Mg–HCl reaction: positive (light pink). IR (Nujol) cm^{-1}: $\nu_{C=O}$ 1645. IR ($CHCl_3$) cm^{-1}: $\nu_{C=O}$ 1660, 1650. UV λ_{max}^{EtOH} nm (ε): 297 (24000). *Anal.* Calcd. for $C_{14}H_9O_2N$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.14; H, 3.87; N, 6.29. Mass Spectrum *m/e*: 223 (M^+, base peak), 222 (M^+-1, 71%), 195 (M^+-CO, 49%). NMR ($CDCl_3$): 6.95 (1H, s, 3-H), 7.10—7.63 (5H, m, benzene aromatic H), 7.63—8.20 (3H, m, pyridine aromatic H).

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