The Reaction of Amines with Isoflavones. I. Formation of Phenolic Pyrimidines

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The reaction of isoflavones with guanidine carbonate in xylene at reflux gave 2-aminophenolic pyrimidines.

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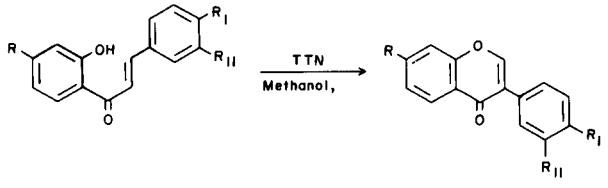
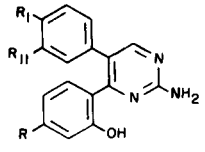
Aminopyrimidines have been found useful in medicine. The current work is aimed at finding a new route to active and inaccessible pyrimidines with potential antimicrobial value. Isoflavyliun salts (1) have been found to react with nucleophiles at either position 2 or 4 due to oxonium ion formation. Recently hydroxylamine and hydrazine have been reacted with isoflavone analogues to give isoxazoles and pyrazoles (2). When chalcones I-III were treated with thallium trinitrate trihydrate (TTN), (3-6), in methanol isoflavones IV-VI were obtained.



I, $R = R_{II} = H$, $R_I = OCH_3$
II, $R = H$, $R_I = R_{II} = OCH_3$
III, $R = R_I = OCH_3$, $R_{II} = H$

IV, $R = R_{II} = H$, $R_I = OCH_3$
V, $R = H$, $R_I = R_{II} = OCH_3$
VI, $R = R_I = OCH_3$, $R_{II} = H$

The isoflavones IV-VI were boiled at reflux in xylene with guanidine carbonate (7) to give 2-aminophenolic pyrimidines (VII-IX).



VII, $R = R_{II} = H$, $R_I = OCH_3$
VIII, $R = H$, $R_I = R_{II} = OCH_3$
IX, $R = R_I = OCH_3$, $R_{II} = H$

The structures of the pyrimidines were assigned by use of physical methods *viz*, uv, ir, pmr and elemental analysis.

The uv spectra of the phenolic pyrimidines gave four λ max in methanol as shown in the Experimental. Addition of 0.1*N* hydrochloric acid on these pyrimidines resulted in a bathochromic shift with concommittant hypochromic effect. No effect on λ max was observed when 0.1*N* sodium hydroxide was added but there was a marked hyperchromic effect.

The ir spectra of these phenolic pyrimidines showed absorptions at 3360-3365 cm^{-1} as doublets due to the presence of the primary amino stretching vibrations of the amino group on the pyrimidine ring. The hydroxyl stretching absorption appeared at 3140-3150 cm^{-1} as a broad band. There were also stretching vibrations due to -C=N- absorption band at 1650-1654 cm^{-1} (8). The -C=C- absorption of the phenyl ring appeared at 1600-1580 cm^{-1}.

The pmr data showed the presence of *O*-methyl protons at δ 3.80-3.85. The C-4 proton of the pyrimidine ring appeared at about δ 8.50 as singlet and the phenyl ring protons appeared as multiplets at about δ 7.40-6.20. There were three exchangeable protons at about δ 8.00 and at δ 3.00 to 2.00 for compounds VII-IX which were due to both the pyrimidine amino function and the phenyl hydroxyl protons.

EXPERIMENTAL

The melting points were determined with electrothermal melting point apparatus and are uncorrected. The ultraviolet spectra were taken on Pye Unicam SP8-400 uv/visible spectrophotometer while the infrared spectra were run on Pye Unicam Sp3-300 Infrared spectrometer. The pmr spectra were taken on Nicolet 360 MHz nmr instrument.

Synthesis of Isoflavones.

The chalcones I-III (0.01 mole) were dissolved in spectroscopic grade methanol (20 ml) respectively and thallium trinitrate trihydrate (TTN, 0.01 mole) was added. The mixture was refluxed with stirring at reflux for 2 hours and allowed to stand at room temperature overnight. Methanol was removed *in vacuo* and the residue dissolved in chloroform and consequently extracted with sodium hydroxide (10%, 50 × 4 ml). The chloroform layer was dried over sodium sulphate (anhydrous) and the solvent removed. The solid residue obtained crystallised from ethanol to give isoflavones IV-VI. 4'-Methoxyisoflavones, (IV), crystallised as colourless needles from ethanol, mp 137-138° (lit (5) mp 138-140°). 3',4'-Dimethoxyisoflavones, (V), crystallised as colourless needles from ethanol, mp 141-143° (lit (5), mp 145-146°). 4',7-Dimethoxyisoflavones, (VI), crystallised as light brown sandy prisms from ethanol, mp 158-159° (lit (4) mp 160°).

Synthesis of Phenolic Pyrimidines VII-IX.

The isoflavones IV-VI (0.0025 mole) were dissolved in boiling xylene (25 ml) respectively and guanidine carbonate (0.0025) was added. The mixture was then boiled for 6 hours at reflux and allowed to cool at room temperature. The solid precipitate collected was crystallised in xylene to give phenolic pyrimidines VII-IX.

2-Amino-5-(4-methoxyphenyl)-6-(2-hydroxyphenyl)pyrimidine (VII).

This compound crystallised from xylene as greenish yellow plates, mp 198-200° (0.62 g); ir (Nujol): 3360, 3310 (NH_2), 3150 (OH), 1650 (C=N), 1580, 1550 (C=C) cm^{-1}; uv (methanol): λ max nm (log ε) 202 (4.72), 232 (4.45), 260 (4.45), 340 (3.97); nmr (perdeuteriopyridine + TMS): δ 3.80 (s, 3H, OCH_3), 6.80-7.40 (m, 8H, benzene H), 8.55 (s, 1H, pyrimidine H4),

8.00 and 3.00 (br, 3H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33. Found: C, 69.56; H, 5.17; N, 14.40.

2-Amino-5-(3,4-dimethoxyphenyl)-6-(2-hydroxyphenyl)pyrimidine (VIII).

This compound crystallised from xylene as yellow sandy prisms, mp 188-190° (0.45 g); ir (Nujol): 3365, 3310 (NH_2), 3140 (OH), 1645 (C=N), 1575, 1555 (C=C) cm^{-1}; uv (methanol): λ max nm (log ε) 204 (4.89), 228 (4.73), 264 (4.55), 340 (4.09); nmr (perdeuteriopyridine + TMS): δ 3.85 and 3.95 (s, 6H, OCH_3), 6.70-7.40 (m, 7H, benzene H), 8.59 (s, 1H, pyrimidine H4), 8.00 and 2.00 (br, 3H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.87; H, 5.26; N, 13.00. Found: C, 66.80; H, 5.30; N, 13.10.

2-Amino-5-(4-methoxyphenyl)-6-(2-hydroxy-4-methoxyphenyl)pyrimidine (IX).

This compound was crystallized from xylene as greenish yellow needles, mp 196-198° (0.68 g); ir (Nujol): 3360, 3310 (NH_2), 3160 (OH), 1645 (C=N), 1600, 1575 (C=C) cm^{-1}; uv (methanol): λ max nm (log ε) 206 (4.59), 246 (4.44), 272 (4.32), 346 (4.18); nmr (perdeuteriopyridine + TMS): δ 3.85 and 3.95 (s, 6H OCH_3), 6.20-7.30 (m, 7H, benzene H), 8.55 (s, 1H, pyrimidine H4), 2.00 and 8.00 (br, 3H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.87; H, 5.26; N, 13.00. Found: C, 66.79; H, 5.25; N, 13.00.

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