

C.S.I.R.O. Division of Plant Industry

The Reaction of Methyl Propiolate with 2-Aminopyridines

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The structure (III) reported by Lappin (2) for the diadducts formed by the reaction of methyl propiolate with 2-aminopyridines has been found to be incorrect. The correct structure (IV) has been proven by spectral studies and cyclisation to compound VII. In two cases new compounds having structures of the type (III) have been isolated. N.M.R. data are reported for all products.

Introduction.

A previous investigation (2) of the reaction of 2-aminopyridines with methyl propiolate resulted in the isolation of three types of products. 1. Bicyclo compounds whose structures were established as 2-*H*-pyrido[1,2-*a*]pyrimid-2-ones (I); 2. Monoadducts which were identified as 2-imino-1-2*H*-pyridineacrylic esters (II) by their alkaline hydrolysis to the corresponding 2-oxo-1-2*H*-pyridineacrylic acids (VI); and 3. Diadducts which were assigned the structures (III). These last were also formed by the addition of methyl propiolate to the monoadducts. The pyridopyrimidones (I) were obtained from all the 2-aminopyridines studied. Monoadducts were obtained from 3-methyl and 4-methyl-2-aminopyridines while diadducts were isolated from 2-aminopyridine itself as well as from 4-methyl and 5-methyl-2-aminopyridines.

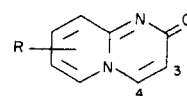
In the present study an examination of the nuclear magnetic resonance spectra of these products has confirmed the structures of the pyridopyrimidones and the monoadducts but has shown that the structure (III) of the diadducts is untenable. This structure (III) was however found to be that of the deep red compounds which were obtained in small yield from 2-aminopyridine and 5-methyl-2-aminopyridine.

The Pyridopyrimidones.

Each aminopyridine gave a pyridopyrimidone (I), this being the sole product in the case of 6-methyl-2-aminopyridine. Their N.M.R. spectra (Table I) are characterized by a pair of doublets at approximately 6.6 and 8.4 p.p.m. (variation within the series is small) with the coupling constant varying from 7.1 to 7.7 c.p.s., assignable to the 3 and 4 protons. Although no coupling was observed between these and the other ring protons, the methyl group on the pyridine ring was found to be coupled to a small extent ($J = 0.9 - 1.0$ c.p.s.) with the ortho protons.

TABLE I

Proton Chemical Shifts (ppm) and
Coupling Constants (cps) of Pyridopyrimidones

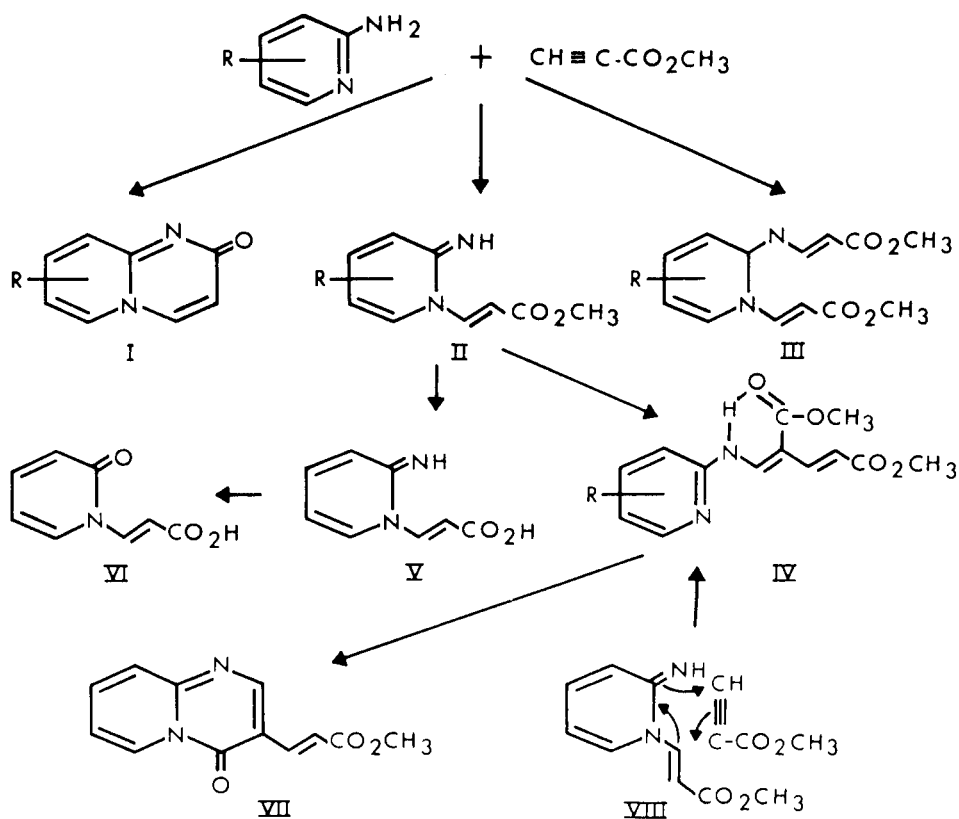


Compound	H ₃	H ₄	Me	J _{3,4}	J _{Ar-Me}
R = H	6.7	8.4	-	7.7	-
R = 5-Me	6.6	8.4	2.7	7.6	0.9
R = 6-Me	6.7	8.3	2.4	7.1	0.9
R = 7-Me	6.6	8.25	2.4	7.2	1.0
R = 8-Me	6.65	8.3	2.25	7.6	1.0

The Monoadducts.

3-Methyl- and 4-methyl-2-aminopyridine afforded non-cyclic monoadducts with methyl propiolate. The monoadduct from 2-aminopyridine could not be isolated but its formation was established by N.M.R. spectroscopic examination of the oily fraction remaining after removal of the crystalline products from the reaction mixture. Treatment of this fraction with water caused hydrolysis of the ester to 2-iminopyridine-1-acrylic acid (V) which was readily crystallized and found to be identical with the product from the reaction of 2-aminopyridine with propiolic acid (3). Alkaline hydrolysis converted it, with evolution of ammonia, into 2-oxo-1-2*H*-pyridineacrylic acid (VI), identical with that obtained by the reaction of 2-pyridone with propiolic acid.

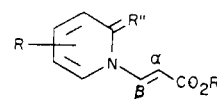
The N.M.R. spectra of the monoadducts which were



consistent with the structure (II) postulated by Lappin (2) (Table II) contained a pair of doublets centered around 6 and 8 p.p.m., the signals from the β-proton being broadened

TABLE II

Proton Chemical Shifts (p.p.m.) and Coupling Constants (c.p.s.) of Monoadducts and Related Compounds



Compound	Chemical Shift				J _{αβ}
	α	β	OMe	Ar-Me	
R = 3-Me, R' = Me R'' = NH	5.85	8.7	3.8	2.0	14.3
R = 4-Me, R' = Me R'' = NH	5.9	8.6	3.75	1.9	14.7
R = R' = H, R'' = NH (in D ₂ O at 100°)	6.55	7.5			14
R = R' = H, R'' = O (in DMSO-D ₆)	6.43	8.32			14.5

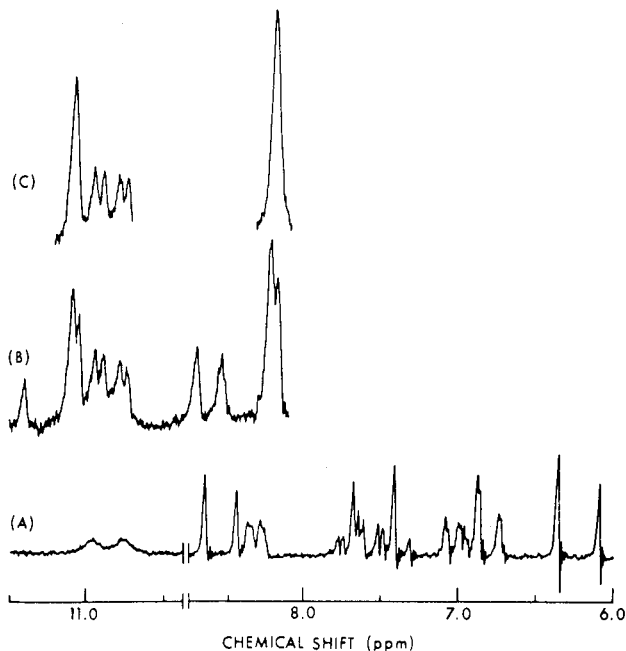


Figure 1. 60 Mc N.M.R. spectrum of diadduct from 2-aminopyridine and methyl propiolate (a) 500 c.p.s. sweep width, (b) 100 cps sweep width scan of doublet centered at 7.6 p.p.m. showing 0.6 c.p.s. splitting, (c) double irradiation experiment showing scan b repeated but with doublet centered at 8.5 p.p.m. irradiated with the H₂ field.

cm^{-1} in the infra-red spectrum confirmed the presence of the -NH- group. A second feature of the N.M.R. spectra which was inconsistent with the structure (III) became evident when the doublets at 7.60 and 8.50 p.p.m. were examined on an expanded scale. Each line of these two doublets exhibited a secondary splitting ($J = 0.6$ c.p.s.) and double irradiation experiments demonstrated that they were, in fact, coupled to one another (see Figure 1). Two double bonds were therefore conjugated with one another and the protons whose coupling gave rise to the 0.6 c.p.s. splitting were separated by at least four bonds (4).

The only structure in accordance with all the evidence is (IV) which is formed by the addition of two molecules of methyl propiolate to the amino substituent of the 2-aminopyridine. The two doublets at 6.25 and 7.60 p.p.m. are assigned to the *trans*-olefinic protons in the α and β positions of the $\alpha,\beta,\gamma,\delta$ unsaturated ester, while the remaining two doublets at 8.50 and 10.80 p.p.m. corresponding to the δ and N protons respectively. This type of coupling has been found to be characteristic of a series of substituted aminomethylenemalonic esters in which it is likewise eliminated by prolonged deuteration (5).

Hydrogen bonding between the NH and γ carbomethoxy group suggested by the low broad NH absorption in the infra-red spectrum favours the *cis* relationship between these two groups as shown in (IV) and the ester carbonyl absorption at 1667 cm^{-1} is also consistent with this interpretation.

The structure (IV) was further supported by the ready cyclization of the aminopyridine diadduct (IV, $R = H$) to the pyridopyrimidone (VII). The structure of the latter was supported by the N.M.R. spectrum (Table III) which exhibited long range couplings between the protons α and δ as well as β and δ to the ester group. Both couplings were confirmed by double irradiation experiments.

The formation of the diadduct obviously involved a rearrangement during addition of the second molecule of methyl propiolate to the monoadduct which is depicted (VIII) as proceeding through a six-centre cyclic mechanism. The final conformation of the product was presumably dictated by the stabilising influence of hydrogen bonding (IV).

From the reaction of 2-aminopyridine itself with methyl propiolate, it was possible to separate a second diadduct by means of its solubility in dilute acid. This compound was deep red in colour and examination of its N.M.R. spectrum (Table III) led to the conclusion that it was a diadduct having the structure (III) originally proposed by Lappin (2). The four vinyl protons all were sharp; and were arranged in two normal AB quartets with coupling constants ($J = 13$ and 15 c.p.s.) consistent with an all *trans* stereochemistry. The infra-red spectrum exhibited a broad ester carbonyl absorption at $1720\text{--}1685\text{ cm}^{-1}$ and a complete absence of absorption in the -NH- region.

EXPERIMENTAL

The N.M.R. spectra were obtained on a Varian A-60 spectrometer fitted with a V-6058a decoupler in deuteriochloroform solution, except where otherwise indicated. Melting points are uncorrected. Analyses were carried out by the Australian Analytical Service, Melbourne.

Reaction of 2-Aminopyridines with Methyl Propiolate.

Except as detailed below the conditions described by Lappin (2) were followed for the preparation of the pyridopyrimidones (1), the monoadducts (III) and the diadducts (IV).

Reaction of 2-Aminopyridine with Methyl Propiolate.

To a solution of 9.4 g. of 2-aminopyridine in 300 ml. of ether was added 8.6 g. of methyl propiolate in 50 ml. of ether. The mixture was allowed to stand overnight and the crystalline precipitate was collected and recrystallized from ethanol to yield the pyridopyrimidone (I, $R = H$) (0.5 g.). The ethanol filtrate was evaporated to dryness and the residue was taken up in carbon tetrachloride and filtered from a further amount (0.7 g.) of (I, $R = H$). The carbon tetrachloride solution was now evaporated to dryness. The residue was treated with water (150 ml.) and filtered ("Aqueous Filtrate") from undissolved material which was allowed to stand in the moist state for two days after which it was taken up in chloroform and filtered from a solid which crystallised from water in stout prisms (2.5 g.) of 2-imino-1-2*H*-pyridineacrylic acid monohydrate (V, $R = H$), m.p. 252° dec.

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 53.05; H, 5.64; N, 15.33.

Evaporation of the chloroform filtrate and treatment of the residue with N hydrochloric acid (30 ml.) left insoluble material which crystallised from methanol giving 3.3 g. of the diadduct (IV, $R = H$), m.p. $137\text{--}138^\circ$. Neutralisation of the filtrate with sodium bicarbonate gave a solid which separated from methanol as deep red prisms of the diadduct (III, $R = H$), m.p. $145\text{--}147^\circ$. Ultraviolet spectrum λ max, $m\mu$ (ϵ): (MeOH): 256 (12,260); 324 (17,100); 423 (13,060). Infra-red (CHCl_3): $1710, 1641\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.28; H, 5.50; N, 10.79.

Immediate chloroform extraction of the "Aqueous Filtrate" removed a deep red oily fraction which N.M.R. measurements indicated to be a mixture of 2-aminopyridine and methyl 2-imino-1-2*H*-pyridineacrylate (II, $R = H$), which resisted all attempts at isolation. However, when the mixture was allowed to stand overnight in water, crystals of the acrylic acid (V) m.p. 252° dec., were deposited.

Reaction of 5-Methyl-2-aminopyridine with Methyl Propiolate.

A solution of ester (8.4 g., 0.1 mole) and 5-methyl-2-aminopyridine (11.0 g., 0.1 mole) in 50 ml. of dry ether was kept at room temperature for 12 days. The crystalline deposit consisted of orange needles studded throughout with small clusters of red prisms. After washing of the collected product with cold ether, the red compound (0.7 g.) was separated by handpicking. Recrystallisation from methanol afforded 0.2 g. of the diadduct (III, $R = 5\text{-Me}$), m.p. $148\text{--}149^\circ$. On being cooled the methanol filtrate deposited an additional 50 mg.

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.77; H, 5.79; N, 10.41.

The bulk of the product was extracted with ether to give the diadduct (IV, $R = 5\text{-Me}$) (8.2 g.), m.p. $143\text{--}149^\circ$. Recrystallisation from ethanol gave the pure compound as orange-yellow needles, m.p. 150° .

Recrystallisation of the ether insoluble component (2.2 g., m.p. 220–225°) from chloroform-benzene afforded the pyridopyrimidone (I, R = 5-Me) as off-white plates, m.p. 225–226°. Sublimation (180°/0.2 mm) gave felted needles, m.p. 225–227°.

Cyclisation of Diadduct (IV, R = H).

Five-tenths g. of IV were heated in a metal bath at 250° for 5 minutes, cooled and the residue crystallised from methanol to yield hair-like crystals of VII, m.p. 158–159°. Ultra-violet spectrum λ max, $m\mu$ (ϵ), (MeOH): 261 (11,680); 310 (4,160). Infra-red spectrum, (CHCl₃): 1723, 1676 cm^{-1} .

Anal. Calcd. for C₁₂H₁₀N₂O₃: C, 62.60; H, 4.38; N, 12.17
Found: C, 62.45; H, 4.45; N, 12.42.

2-Oxo-1-2H-pyridineacrylic acid (VI).

A. Two g. of the corresponding imino acid were refluxed for 30 minutes in a solution of 1 g. of potassium hydroxide in 20 ml. of water. The solution turned red and ammonia was evolved. Acidification of the cooled solution precipitated a tannish solid which separated from ethanol (charcoal) in cream coloured needles (0.9 g.) m.p. 265° dec.

Anal. Calcd. for C₈H₇NO₃: C, 58.18; H, 4.27; N, 8.48.
Found: C, 57.92; H, 4.48; N, 8.48.

B. 2-Pyridone (9.5 g.) and propiolic acid (8.4 g.) were slowly heated in an oil-bath with careful stirring. At 135–140° a vigorous reaction began with evolution of gas and a rise in temperature to ca. 170°. Recrystallisation of the resulting solid from ethanol (charcoal) gave the pyridoneacrylic acid as needles (3.1 g.), m.p. 264–265° dec. Pachter (3) reports a m.p. of 220–225° dec. for the compound.

Anal. Calcd. for C₈H₇NO₃: C, 58.18; H, 4.27; N, 8.48.
Found: C, 57.99; H, 4.37; N, 8.49.

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