300. *Tautomeric Azines. Part II.*[1] *The Structure of "Malonyl-α-aminopyridine" and its Alkylation Products: Mesomeric Betaines with Six-membered Rings.*

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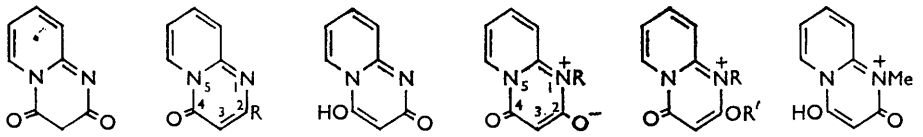
"Malonyl-α-aminopyridine" exists predominantly as the mesomeric betaine (IV; R = H). Alkylation in alkaline solution with methyl iodide gives the *N*-methyl derivative (IV; R = Me); alkylation with propargyl bromide gives the *O*- and the *N*-propargyl derivative; the single products previously obtained on alkylation and formulated [2] as *O*-derivatives (II; R = OAlk) are mesomeric betaines (IV; R = Alkyl). An unambiguous synthesis of 2-n-propylaminopyridine is described.

TSCHITSCHIBABIN [3] formulated the product he obtained from 2-aminopyridine and malonic ester in the dioxo-form (I); this structure was subsequently accepted (cf., *e.g.*, refs. 4

[1] Part I, preceding paper.
[2] Schulte and Witt, *Arch. Pharm.*, 1958, **291** (**63**), 298.
[3] Tschitschibabin, *Ber.*, 1924, **57**, 1168.
[4] Boeckelheide and Figueras, *J. Amer. Chem. Soc.*, 1949, **71**, 2587.

and 5) until Snyder and Robison [6] pointed out that the physical properties of the compound (high m. p., low solubility in non-polar solvents) were a contra-indication. These



(I) (II) (III) (IV) (V) (VI)

authors [6] considered structures (II; R = OH) and (III), favouring the former because phosphorus oxychloride gave a chloride (II; R = Cl); but they suggested that the hydroxy-compound might exist in a dimeric hydrogen-bonded form because its infrared spectrum does not show a hydroxyl stretching mode.

The alkylation of this compound, " malonyl-α-aminopyridine," has been studied by Schulte and Witt; [2] reaction of the potassium derivative with propargyl and but-2-ynyl bromide gave products which were formulated as *O*-derivatives (II; R = $HC{:}C{\cdot}CH_2{\cdot}O$ and $Me{\cdot}C{:}C{\cdot}CH_2{\cdot}O$). *C*-Alkylation was shown by independent synthesis not to have occurred.

It appeared to us that the high melting points (>200°) of the alkylation products could be better explained if they were *N*-derivatives (IV), and that " malonyl-α-aminopyridine " probably existed itself as the mesomeric betaine (IV; R = H) [anhydro-(2-hydroxy-4-oxopyrido[1,2-*a*]pyrimid-1-inium hydroxide)]. Structure (IV) is stabilised by resonance with a large number of other canonical forms, as are the more familiar 5-ring aromatic mesomeric betaines: [7] these compounds are often termed " mesoionic," but care is necessary in the use of this term.[8] The present paper records experiments which justify the above speculations.

Structure of Alkylation Products.—2-Chloropyrido[1,2-*a*]pyrimidin-4-one (II; R = Cl) with sodium methoxide or sodium propoxide gave the corresponding 2-methoxy- or 2-propoxy-derivatives (II; R = OMe or OPr^n): the latter product was different from the propyl derivative obtained by Schulte and Witt [2] by catalytic reduction of their propargyl derivative. Alkylation of " malonyl-α-aminopyridine " with methyl iodide by Schulte and Witt's method [2] gave 42% of the *N*-methyl derivative (IV; R = Me), as shown by hydrolysis to 2-methylaminopyridine. In our hands reaction of " malonyl-α-aminopyridine " with propargyl bromide in alkaline solution gave two products, of m. p. 156—157° (5%) and 264° (decomp.) (32%), which were separated because the latter was less soluble in the reaction mixture. These compounds were identified as the *O*- and the *N*-propargyl derivative, respectively, by reduction to the corresponding *O*- and *N*-propyl derivatives (m. p. 89·5—92° and 204—206°) and by spectral comparisons. Schulte and Witt's " *O*-propargyl " product of m. p. 245° was thus probably the somewhat impure *N*-propargyl derivative, and their " *O*-propyl " hydrogenation product of m. p. 202—203° was the pure *N*-propyl compound. Alkylation of " malonyl-α-aminopyridine " with propyl bromide gave a mixture from which some *O*-propyl derivative was isolated.

Hydrolysis of the *N*-propyl derivative gave an amine whose picrate (m. p. 148—150°) gave analyses correct for a propylaminopyridine picrate. The ultraviolet spectra of the free amine and the picrate were similar to those of 2-methylaminopyridine and its picrate, and the infrared spectrum of the free amine showed a single peak in the N–H stretching region. The preparations of " 2-n-propylaminopyridine " previously recorded had b.p. 145—160°/21 mm. (picrate m. p. 163°) [9] and b. p. 66°/1·5 mm. (picrate, m. p. 148·5—149·5°).[10] We prepared authentic 2-n-propylaminopyridine by the action of propylamine

[5] Lappin, Petersen, and Wheeler, *J. Org. Chem.*, 1950, **15**, 377.
[6] Snyder and Robison, *J. Amer. Chem. Soc.*, 1952, **74**, 4910.
[7] Baker and Ollis, *Quart. Rev.*, 1957, **11**, 15.
[8] Katritzky, *Chem. and Ind.*, 1955, 521.
[9] Slotta and Franke, *Ber.*, 1930, **63**, 678.
[10] Mihantef and Fedorof, *Zhur. obshchei Khim.*, 1960, **30**, 568.

on 2-bromopyridine, and found it to have b. p. 110—111°/15 mm. (picrate, m. p. 149—150·5°). This confirms Mihantef and Fedorof's results [10] and shows that the product obtained by Slotta and Franke [9] was not 2-n-propylaminopyridine.

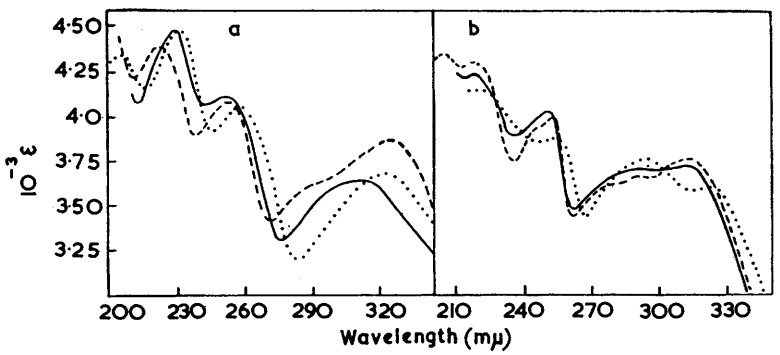
Ultraviolet spectra and pK_a values (at 24° ± 1°).

	Neutral species [a]		Conjugate acid					
Compound	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon_{max.}$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon_{max.}$	Solvent	pK_a	λ for determ. (mμ)	Gradient *
" Malonyl-α-amino-pyridine " [b]	230	30·4	217	17·65		0·07 ± 0·02	230	
			251	10·9	20N-H_2SO_4			1·0
	252	12·7	292	5·48				
	312	4·3	311	5·63		7·09 ± 0·02 †		
O-Methyl deriv.	222·5	23·8	217	22·0				
			247s	9·75	10N-H_2SO_4			
	254	12·0	252	11·2		1·36 ± 0·06	230	1·0
			293	5·24				
	325	7·23	313	6·67				
O-Propynyl deriv.	220	24·6						
	253	12·5	—	—	—	—	—	—
	326	7·85						
O-Propyl deriv.	224	25·8						
	254	11·9	—	—	—	—	—	—
	326	7·6						
N-Methyl deriv.	230	32·4	220	14·2 [c]				
			255	7·47	13·7N-H_2SO_4	0·18 ± 0·07	230	1·0
	257	12·0	293	5·89				
	322	4·75	325	4·09				
N-Propynyl deriv.	229	32·3						
	254	13·6	—	—	—	—	—	—
	317	4·92						
N-Propyl deriv.	231	32·9						
	256	11·4	—	—	—	—	—	—
	320	4·83						

[a] In phosphate buffer (pH 6·99) except " malonyl-α-aminopyridine " which was in 0·01N-H_2SO_4. [b] Slow hydrolysis occurs in both solvents. The values tabulated are for the first spectra run. The pK is calculated from values of ε extrapolated to zero time. [c] Values extrapolated to zero time.

* Gradient of graph of $\log_{10}\left(\frac{\varepsilon_{HA^+} - \varepsilon}{\varepsilon - \varepsilon_A}\right)$ against H_0. For a Hammett base the value should be 1·0.

† Titrimetric (removal of proton).



Ultraviolet spectra of (a) neutral forms and (b) protonated forms of (——) " malonyl-α-aminopyridine " and its (– – –) *O*-methyl and (. . .) *N*-methyl derivative.

Ultraviolet Spectra.—The spectrum of the neutral species of " malonyl-α-aminopyridine " resembles that of the *N*-methyl derivative (IV; R = Me) somewhat more than that of the *O*-methyl derivative (Fig. a and Table), if one takes into account the fact that alkylation usually results in a small bathochromic shift. This suggests that the

tautomeric compound exists predominantly as (IV; R = H), but all the spectra are too similar for conclusive deductions. In sulphuric acid the cations from " malonyl-α-aminopyridine " and its *O*-methyl derivatives have similar spectra (Fig. b), indicating that their structures are of type (V). The spectrum of the cation from the *N*-methyl derivative is somewhat different; this compound decomposes rapidly in sulphuric acid and the curve shown was obtained by extrapolation to zero time, which may have occasioned an error; alternatively, some cations of structure (VI) may be formed.

Basicity Measurements.—Since cations of similar structure are formed, basicities (see Table) give a value of *ca.* 20 for K_T between structures (II; R = OH) and (IV; R = H) in favour of the latter (betaine) structure. *N*-Alkylation raises the p*K* of compound (IV; R = H) by *ca.* 0·1 unit, a reasonable figure.

Infrared Spectra.—" Malonyl-α-aminopyridine " was insufficiently soluble for solution measurements: in Nujol the >NH group showed as a broad peak at *ca.* 2700 cm.$^{-1}$. In the 1500—1600 region absorption was:

" Malonyl-α-aminopyridine "	1690s	1651s	1615s	1593s	1523m
N-methyl deriv.	1704s	1653s	1633m	1565w	1522m
O-methyl deriv.	1712s		1635s	1575m	1537s
Deuterated " malonyl-α-aminopyridine " ...	1690s		1610s	1560m	1515m

It is difficult to draw reliable structural conclusions from these results. Full spectra of these compounds will be submitted to the D.M.S. collection.

Experimental

M. p.s were determined on a Kofler block.

" Malonyl-α-aminopyridine " [3] had m. p. 301—302° (decomp.) (lit.,[3] m. p. 295—298°).

2-Methoxypyrido[1,2-a]*pyrimidin-4-one* (II; R = OMe).—2-Chloropyrido[1,2-*a*]-pyrimidin-4-one [6] (6·5 g.) was refluxed with methanolic sodium methoxide [from sodium (0·83 g.) in methanol (30 c.c.)] for *ca.* 5 min. Sodium chloride was precipitated, followed by silky needles. After 3 hr. at 20°, methanol (100 c.c.) and ether (500 c.c.) were added, the whole was filtered, and the filtrate evaporated at 20 mm. to give the *methoxy-derivative* (4·93 g., 78%) which separated as off-white needles, m. p. 145—147°, from light petroleum (b. p. 100—120°)(Found: C, 61·3; H, 4·3; N, 16·2. $C_9H_8N_2O_2$ requires C, 61·3; H, 4·6; N, 15·9%).

The analogous *n-propoxy-compound* (3·2 g., 71%), prepared similarly, formed pale yellow crystals, m. p. 88—91°, from light petroleum (b. p. 60—80°) (Found: C, 64·7; H, 6·2; N, 13·9. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%).

Anhydro-(1-*methyl*-2-*hydroxy*-4-*oxopyrido*[1,2a]-*pyrimid*-1-*inium Hydroxide*).—" Malonyl-α-aminopyridine " (5 g.), methanolic potassium methoxide [from potassium (1·25 g.) and methanol (60 c.c.)], and methyl iodide (2·06 c.c.) were refluxed 7 hr. After cooling, the *betaine* separated as an amorphous yellow solid (3·35 g., 62%), m. p. 247—248° (from methanol), and when sublimed at 225°/10^{-4} mm. had m. p. 245—252° (decomp.) (Found: C, 61·0; H, 4·4; N, 15·8. $C_9H_8N_2O_2$ requires C, 61·3; H, 4·6; N, 15·9%).

This *N*-methyl-betaine (37·2 mg.) was refluxed for 18 hr. with 6N-hydrochloric acid (1·4 c.c.). After cooling, the solution was basified with 30% aqueous sodium hydroxide and extracted with ether. Evaporation of the ether gave an oil which was treated with picric acid in acetone. Two recrystallisations of the product from water afforded 2-methylaminopyridine picrate (34·6 mg., 50%), m. p. 186—189°; the mixed m. p. with an authentic specimen (of m. p. 187—190°) was 186·5—190° (lit.,[11] m. p. 190°; 2-aminopyridine picrate has m. p. 216—217° [12]). Infrared spectra (in Nujol) of the two specimens were identical.

Anhydro-(1-*prop*-2′-*ynyl*-2-*hydroxy*-4-*oxopyrido*[1,2-a]*pyrimid*-1-*inium Hydroxide*) *and* 2-*Prop*-2′-*ynyloxypyrido*[1,2-a]*pyrimidin*-4-*one*.—" Malonyl-α-aminopyridine " (5 g.), methanolic potassium methoxide [from potassium (1·25 g.) and methanol (60 c.c.)], and prop-2-ynyl bromide (4 g.) were refluxed for 4 hr. After cooling, the dark yellow N-*prop*-2′-*ynyl derivative* was filtered off, washed with water, and recrystallised from methanol as hexagonal prisms (1·98 g., 32%), m. p. 264—265° (rapid heating) (Found: C, 65·6; H, 3·7; N, 14·2. $C_{11}H_8N_2O_2$ requires C, 66·0; H, 4·0; N, 14·0%).

[11] Tschitschibabin, Konowalowa, and Konowalowa, *Ber.*, 1921, **54**, 814.
[12] Marckwald, *Ber.*, 1894, **27**, 1317.

Evaporation of the filtrate to half its volume gave the O-*prop*-2′-*ynyl derivative* which was filtered off, washed with cold water, and recrystallised from methanol as off-white needles (0·29 g., 5%), m. p. 156—157° (Found: C, 65·9; H, 4·3; N, 14·2%).

Reduction of the Propynyl Derivatives.—The *N*-propynyl derivative (0·204 g.) in methanol (40 c.c.), when shaken over palladium–calcium carbonate, absorbed 46 c.c. of hydrogen (calc., 47·7 c.c.). After filtration and evaporation the residue was sublimed at 180°/10^{-4} mm., giving the N-*propyl derivative*, m. p. 203·5—206·5° (Found: C, 65·2; H, 5·6; N, 13·8. $C_{11}H_{12}N_2O_2$ requires C, 64·8; H, 5·8; N, 13·7%).

The *N*-propyl derivative (50 mg.) was hydrolysed, etc., as described for the *N*-methyl derivative. The resulting 2-*propylaminopyridine picrate*, prepared in ethanol and recrystallised from acetone, formed yellow needles, m. p. 148—150° (Found: C, 46·1; H, 4·0; N, 19·2. $C_8H_{12}N_2,C_6H_3N_3O_7$ requires C, 46·0; H, 4·1; N, 19·2%).

Similarly, the *O*-propynyl derivative (73·2 mg.) in methanol absorbed 16·5 c.c. of hydrogen (calc., 17·5 c.c.), giving the *O*-propyl derivative, m. p. 89·5—92°, unchanged on admixture with the authentic propoxy-compound.

2-*Propoxypyrido*[1,2-a]*pyrimidin*-4-*one by Direct Alkylation.*—" Malonyl-α-aminopyridine " (5 g.), methanolic potassium methoxide [from potassium (1·25 g.) and methanol (60 c.c.)], and n-propyl bromide (8·1 g.) were refluxed for 8 hr. The solution was evaporated to 20 c.c. and the solid which separated was recrystallised from ethanol (0·66 g., 9·5%). Vacuum-sublimation gave the propoxy-derivative, m. p. 87—92°, with the correct infrared spectrum.

2-*n-Propylaminopyridine from* 2-*Bromopyridine.*—2-Bromopyridine [13] (5 g.), b. p. 84—86°/15 mm., and n-propylamine (25 c.c.) were heated for 10 hr. at 210° in a sealed tube. The remaining propylamine was distilled off, water (15 c.c.) added, and the whole extracted with ether (3 × 25 c.c.). After drying (KOH), the oil obtained from the extract was distilled, giving 2-*n-propylaminopyridine* (3·58 g., 83·6%), b. p. 110—111°/15 mm. (Found: C, 70·3; H, 9·4; N, 20·3. $C_8H_{12}N_2$ requires C, 70·6; H, 8·9; N, 20·6%). The picrate crystallised from ethanol as pale yellow needles, m. p. and mixed m. p. 149—150·5°

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[13] *Org. Synth.*, Coll. Vol. III, p. 136.