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The Preparation, Structure and Reactions of Some "Malonyl-α-aminopyridines"

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The reaction of several substituted 2-aminopyridines with diethyl malonate was studied. The "methylmalonyl-α-aminopyridines" were shown to exist in the same tautomeric form as "malonyl-α-aminopyridine". Formylation of these compounds takes place in the 3-position and has led to the formation of a new tricyclic compound.

In 1924 Tschitschibabin (1) carried out the condensation of 2-aminopyridine and malonic ester to yield a bicyclic compound for which structures such as I, II, III, and IV as well as an enol dimer structure have at various times been proposed. In 1962 Katritzky and Waring (2) demonstrated that the "malonyl-α-aminopyridine" existed predominantly as anhydro(2-hydroxy-4-oxopyrido[1,2-*a*]-pyrimid-1-inium hydroxide) (IV).

Several groups have investigated this reaction with substituted 2-aminopyridines. Kucherova and co-workers (3) reported that 5-nitro-2-aminopyridine and 3,5-dihalo-2-aminopyridines failed to react and that 5-halo-2-aminopyridines led to the formation of only noncyclic products of types V and VI. Lappin and co-workers (4), however, found that the 5-chloro and 5-bromo compounds gave products of the type I-IV. A number of 6-substituted-2-aminopyridines gave 1,8-naphthyridines and noncyclic products but no compounds of the type I-IV were isolated (4). It was further reported (4) that 4- and 5-methyl-2-aminopyridine gave products of the type I-IV together with noncyclic products. These workers (4) gave no yields and in fact indicated that the yields varied widely.

In regard to the chemistry of IV the oxygen in the 2-position can readily be replaced by a chlorine atom (5,6) which is reactive towards nucleophilic reagents (6). The 3-position of IV was found to be involved in coupling reactions with diazonium salts (5) and alkylation takes place at the 1-position (2).

With the above background available it was decided to look further into the chemistry of IV and also to determine whether the pyridine ring substituted analogues also were predominantly in structure IV.

Reaction of 2-aminopyridine, 2-amino-3-picoline, 2-amino-4-picoline, and 2-amino-5-picoline with diethyl malonate gave bicyclic products. The 3-picoline had not previously been subjected to this reaction. In several cases noncyclic products of the type V and VI were also isolated. In agreement with the Russians (3) but in conflict with Lappin (4) we could only isolate V and VI from the reaction of 5-chloro- and 5-bromo-2-aminopyridine. Although 5-nitro-2-aminopyridine had been reported not to react (3) we obtained a product of the type V from this pyridine. 4,6-Dimethyl-2-aminopyridine gave V and VI and 2-aminoquinoline gave a product analogous to V which is consistent with the report (4) that 6-substituted-2-aminopyridines do not give pyridopyrimidines. Numerous attempts under a variety of conditions were made, without success, to cyclize the product of the type V from 2-amino-6-picoline.

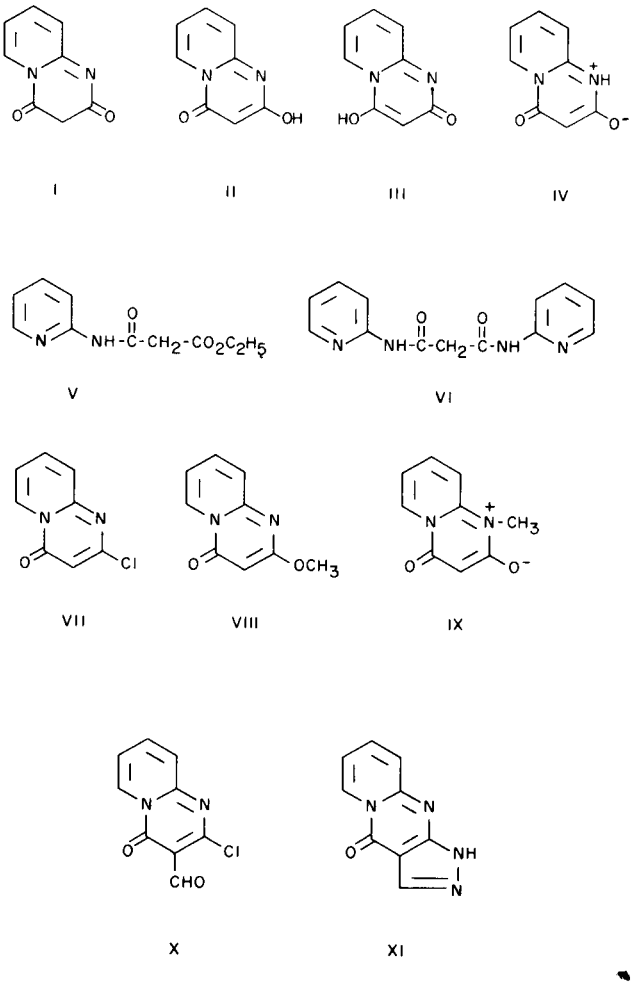
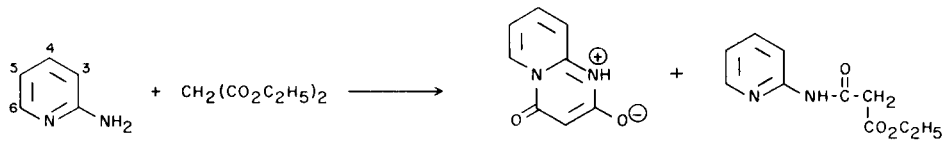
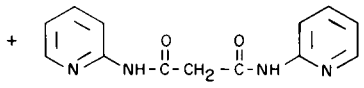


TABLE I

Reaction of Diethyl Malonate and 2-Aminopyridines (a)



IV V



VI

2-Aminopyridine	Product (b)	M.p.	Yield (c)	Analyses Calculated C	H	N	Found C	H	N
3-methyl	IV	287-291 (d)	96	61.35	4.58	15.90	61.42	4.72	15.87
4-methyl	IV	251-253 (e,f)	94	61.35	4.58	15.90	61.18	4.50	15.96
6-methyl	V	88-90 (d,g)	58	59.42	6.35	12.60	59.39	6.38	12.62
4,6-dimethyl	V	133-135	21	60.99	6.83	11.86	61.21	6.94	11.72
	VI	224-226 (d)	79	65.36	6.45	17.94	65.08	6.59	17.96
5-chloro	VI	247-250 (d,h)	11	48.02	3.10	17.23	47.75	3.26	17.31
5-bromo	VI	245-246 (i)	3	37.71	2.43	13.53	37.67	2.70	13.46
5-nitro	V	125-125 (d)	53	47.43	4.38	16.59	47.35	4.39	16.70
5,6-benzo (j)	V	150-152 (d)	61	65.10	5.46	10.85	65.25	5.46	10.83

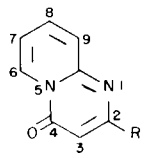
(a) Only new compounds and those whose melting point does not correspond with reported values are included. (b) Refers to Roman numeral in text. (c) Refers to yield of product reported, in some reactions additional quantities of previously reported (3,4) compounds were obtained. (d) Recrystallized from ethanol. (e) Reported (4) m.p. 270°. (f) Recrystallized from ethanol-ethyl acetate. (g) Reported (4) m.p. 72-73°. (h) Reported (3) m.p. 236-237°. (i) Reported (3) m.p. 238-239°. (j) 2-Aminoquinoline.

3-Nitro-2-aminopyridine gave only recovery of starting material. Attempts to prepare a seven membered ring through use of 2-aminomethylpyridine led only to the isolation of compounds of the type V and VI. Table I includes new compounds prepared from 2-aminopyridines and diethyl malonate as well as some compounds previously reported in which our melting points differ from the reported value. Except for the lack of formation of IV from 6-substituted-2-aminopyridines little can be said about the factors which influence cyclization to IV except that it appears that electron withdrawing groups on the 2-aminopyridine may inhibit this cyclization (7).

The methylpyridopyrimidines derived from 2-amino-3-, -4-, and -5-picolines all were converted to the chloro compounds VII and the chlorine was readily displaced by sodium methoxide to give the *O*-methyl analogues VIII. Methylation of the methylpyridopyrimidines gave the *N*-methyl products IX from the 7- and 8-methyl compounds. These structures are based on analogy with the work on the unsubstituted compounds (2,5). Attempts to methylate the 9-methyl compound failed under a variety of conditions. This may be caused by the proximity of the 9-methyl group to the 1-nitrogen. Products of the type VII and VIII are shown in Table II.

Examination of the infrared and ultraviolet spectra of the 9-methyl, 8-methyl, and 7-methylpyridopyrimidines and the corresponding *O*-methyl (VIII) and *N*-methyl (IX) analogues indicated a marked similarity with the spectra of

TABLE II



Substituent	R	M.p.	Yield	Analyses Calculated C	H	N	Cl	Found C	H	N	Cl
7-methyl	Cl	197-198	74	55.54	3.63	14.40	18.22	55.55	3.69	14.43	18.30
7-methyl	OCH_3	150-151	93	63.14	5.30	14.73		63.01	5.17	14.84	
8-methyl	Cl	201-203	75	55.54	3.63	14.40	18.22	55.48	3.68	14.38	18.20
8-methyl	OCH_3	123-125	93	63.14	5.30	14.73		63.05	5.37	14.74	
9-methyl	Cl	124-125	84	55.54	3.63	14.40	18.22	55.67	3.78	14.42	18.21
9-methyl	OCH_3	138-139	62	63.14	5.30	14.73		62.79	5.41	14.65	

the parent compound and its *O*-methyl and *N*-methyl analogues respectively. Both the position of the peaks and in the case of the ultraviolet spectra, the general shape of the curves correspond closely with those reported (2) for IV and its *O*-methyl and *N*-methyl analogues. Based on these spectral comparisons it was concluded that the methyl analogues exist in the same predominant tautomeric structure (IV) (2) as the parent compound.

As a further study of the reactivity of IV the compound was subjected to the conditions of the Vilsmeier-Haack reaction. The reaction led to introduction of both a chlorine atom and a formyl group to give X. The position of the formyl group was demonstrated by the hydrolysis of X to 2-aminopyridine. Formylation with phosgene gave a mixture containing a small amount of X and a larger amount of the 3-formyl derivative of IV. Formylation of the 9-methyl analogue of IV under Vilsmeier-Haack conditions gave the 9-methyl analogues of X. Formylation of VIII under these same Vilsmeier-Haack conditions gave X but use of a milder temperature led to the 3-formyl derivative of VIII. The 3-formyl derivative of IV was converted to the trimethylhydrazinium iodide but treatment of this iodide with base failed to yield the 3-cyano compound.

Reaction of X with hydrazine gave the tricyclic compound XI. This is consistent with the observation that reaction of VII with hydrazine gave the 2-hydrazino analogue (6) which could then be condensed with benzaldehyde. The 2-morpholine derivative of VII was also prepared by nucleophilic displacement.

EXPERIMENTAL (8)

Reaction of Diethyl Malonate and 2-Aminopyridine.

In a typical experiment 0.05 mole of the 2-aminopyridine and 12 g. (0.075 mole) of diethyl malonate were placed in a flask set for distillation. The mixture was heated at 200° for 1 hour during which time ethanol distilled. The residue was separated and purified by treatment with ethanol or by chromatography on Merck neutral alumina. Products of the types IV, V, and VI were obtained. New products or products having different melting points than those reported (3,4) are included in Table I. Other products had melting points as recorded in the literature.

Reaction of Diethyl Malonate and 2-Aminomethylpyridine.

Following the same procedure as above a brown oil was obtained which was chromatographed on alumina. Elution with benzene gave a yellow oil (compound of the type V) (20% yield based on picrate) which formed a picrate, m.p. 141-143° from ethanol.

Anal. Calcd. for $C_{17}H_{17}N_5O_{10}$: C, 45.74; H, 3.80; N, 15.52. Found: C, 45.92; H, 3.97; N, 15.68.

Elution with chloroform gave an oil which on trituration with benzene yielded a white solid (compound of the type VI), m.p. 94-95.5°, in 26% yield.

Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.47; H, 5.65; N, 19.80.

Preparation of 2-Chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (VII).

A mixture of 10.9 g. (0.062 mole) of the 7-, 8-, and 9-methyl analogues of IV and 15 ml. of phosphorus oxychloride was refluxed for 4 hours. The solution was cooled, poured into water and extracted with chloroform. Concentration of the chloroform gave a solid which was recrystallized from ethanol to give the solids in Table II.

Preparation of 2-Methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones(VIII).

A mixture of 0.54 g. (0.0028 mole) of the above 2-chloro compounds (VII) and 0.33 g. (0.0028 mole) of sodium methoxide in 30 ml. of methanol was refluxed for 3 hours. The solution was poured into water and extracted with chloroform. The chloroform was evaporated and the solid recrystallized from ethanol to give the compounds in Table II. The 9-methyl-2-methoxy compound was also obtained in 65% yield by use of diazomethane on the 9 methyl analogue of IV.

7- and 8-Methyl Analogues of IX.

A mixture of 1 g. (0.0056 mole) of the 7- and 8-methyl analogue of IV, 0.66 g. (0.0056 mole) of sodium methoxide and 2 ml. of methyl iodide in 30 ml. of methanol was refluxed for 4

hours. The mixture was poured into water and extracted with chloroform. In the case of the 7-methyl compound evaporation of the chloroform gave a solid, m.p. 187-190° from ethanol-ethyl acetate, in 96% yield.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.92; H, 5.29; N, 14.61.

In the case of the 8 methyl compound a solid, m.p. 253-255° from ethanol was obtained in 53% yield.

Anal. Found: C, 62.91; H, 5.19; N, 14.66.

Attempts to prepare the 9-methyl analogue by this and a variety of other methods failed.

Formylation of Anhydro(2-hydroxy-4-oxopyrido[1,2-*a*]pyrimid-1-inium Hydroxide (IV).

(a) To 22 ml. of dimethylformamide in an ice bath was slowly added 14 ml. of phosphorus oxychloride. Then 7.62 g. (0.047 mole) of IV in 200 ml. of dimethylformamide was added slowly with stirring, the mixture was heated on a steam bath for 1 hour and poured into 500 g. of ice to yield 5.13 g. (39%) of a solid (X), m.p. 223-225° from ethanol.

Anal. Calcd. for $C_9H_5ClN_2O_2$: C, 51.82; H, 2.42; N, 13.43; Cl, 17.00. Found: C, 51.71; H, 2.43; N, 13.44; Cl, 16.81.

A mixture of the above aldehyde (X) and potassium hydroxide in aqueous ethanol was refluxed for 2 hours, poured into water, and extracted with chloroform. Concentration of the chloroform gave an oil whose infrared spectrum was identical to that of 2-aminopyridine. This oil gave a picrate identical in all respects to 2-aminopyridine picrate.

(b) To 21.9 g. of dimethylformamide in an ice-bath was added 15 g. of phosgene in chloroform. To this solution was added 4.8 g. (0.0294 mole) of IV in chloroform and the mixture was heated on a steam bath for 1 hour. Sodium acetate was added and the solution poured into water. Chloroform extraction gave 0.5 g. (8.3%) of X identical with that obtained above. A second solid precipitated from the aqueous layer and was the 3-formyl derivative of IV. Recrystallization from ethanol gave 1.3 g. (23%), m.p. 268-270°.

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.70; H, 3.26; N, 14.70.

A mixture of 0.5 g. (0.0026 mole) of this aldehyde and 0.15 g. (0.0026 mole) of *N,N*-dimethylhydrazine in 25 ml. of benzene was refluxed for 30 minutes. The solution was concentrated to ½ volume and 2 ml. of methyl iodide was added. After standing for 5 hours, 0.20 g. (21%) of a solid, m.p. 206.5-208.5° from ethanol, was obtained.

Anal. Calcd. for $C_{12}H_{15}IN_4O_2$: C, 38.51; H, 4.04; N, 14.98. Found: C, 38.21; H, 4.17; N, 14.79.

Formylation of the 9-Methyl Analogue of IV.

This reaction was carried out in the same manner as the above procedure (a) to give a quantitative yield of solid, m.p. 185.5-186.5° from ethanol.

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.73; H, 3.05; N, 12.53.

The semicarbazone, m.p. 210-212°, was prepared.

Anal. Calcd. for $C_{11}H_{10}ClN_5O_2$: C, 47.24; H, 3.60. Found: C, 47.37; H, 3.68.

The thiosemicarbazone, m.p. 232-234°, was also prepared.

Anal. Calcd. for $C_{11}H_{10}ClN_5OS$: C, 44.67; H, 3.41; N, 23.68. Found: C, 44.74; H, 3.54; N, 23.62.

Formylation of VIII.

(a) Using procedure (a) shown above VIII gave the chloro aldehyde X.

(b) To 5 ml. of dimethylformamide in an ice bath was added 5 ml. of phosphorus oxychloride. To the cooled solution was then added 0.38 g. (0.00214 mole) of VIII and the solution was heated to 45° for 30 minutes and was poured onto ice. Extraction with chloroform gave after evaporation of the chloroform 0.285 g. (65%) of solid, m.p. 178-179° from ethanol. This procedure gave the methoxy aldehyde.

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.94; N, 13.72. Found: C, 58.63; H, 3.97; N, 13.71.

Preparation of Tricyclic Compound XI.

A mixture of 0.5 g. (0.0024 mole) of X and 1 ml. (0.024 mole) of hydrazine in 25 ml. of ethanol was heated under reflux for 2 hours, and a yellow precipitate, m.p. 320-321° from ethanol, was obtained in 82% yield.

Anal. Calcd. for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.10. Found: C, 58.16; H, 3.18; N, 30.16.

Reaction of VII with Nucleophiles.

A mixture of 0.5 g. (0.00277 mole) of VII and 2.40 g. (0.0277 mole) of morpholine in 25 ml. of ethanol was refluxed for 2 hours. poured into water, and extracted with chloroform. Evaporation of the chloroform gave a quantitative yield of solid, m.p. 187° from ethanol.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 62.33; H, 5.66; N, 18.17. Found: C, 62.40; H, 5.63; N, 18.27.

Reaction of VII with hydrazine as described above for the chloro aldehyde gave the 2-hydrazino compound (6). Treatment of this compound with an equimolar amount of benzaldehyde in refluxing ethanol gave a solid, m.p. 264-266° from ethanol, in 80% yield.

Anal. Calcd. for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58. Found: C, 68.25; H, 4.62.

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(7) This is supported by the fact that 3-hydroxy-2-aminopyridine appears to undergo cyclization to I-IV. This compound, however, could not be adequately purified.

(8) Analyses by Spang Microanalytical Lab. Melting points are corrected.

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