16897-54-4; XVa, 16897-55-5; XVa methanesulfonate, 16915-95-0; XVb, 16897-69-1; XVb hydrochloride, 16897-70-4; XVIa, 16897-71-5; XVIa hydrochloride, 16897-74-8; XVIb, 16897-75-9; XVIb hydrochloride, 16897-76-0; 4-ethynylpyridine, 2510-22-7.

Acknowledgments.—We thank Mr. D. F. Cortright and his associates for analytical data and for ir and uv spectral determinations and Dr. E. B. Whipple and associates for providing and aiding in the interpretation of nmr data.

The Reaction of Amino Heterocycles with Reactive Esters. I. 2-Aminopyridines

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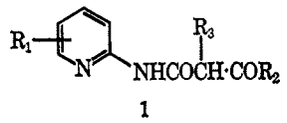
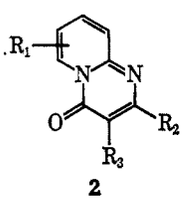
Very good yields of 4H-pyrido[1,2-*a*]pyrimidin-4-ones have been obtained in a one-stage synthesis by the condensation of 2-aminopyridines with β-keto esters or ethyl ethoxymethylenemalonate, and the corresponding 2,4-diones with diethyl malonate, in the presence of polyphosphoric acid (PPA). It is suggested that the cyclization of 2-acylacetamidopyridines with PPA to give pyrido[1,2-*a*]pyrimidin-4-ones involves the formation of N-(2-pyridyl)-β-(2′-pyridylamino)crotonamides since the latter on treatment with PPA give the same products.

It has recently been shown by Staskun and Israelstam[1] and Mallams and Israelstam[2] that hydroxyquinolines can be synthesized in one stage in good yields by heating arylamines with β-keto esters in the presence of PPA. This method avoids the necessity of following the two-stage method of Conrad and Limpach.[3-6] In an analogous way, we have now shown that pyrido[1,2-*a*]pyrimidin-4-ones can also easily be obtained in a one-stage process by condensing 2-aminopyridines with β-keto esters in the presence of PPA. The yields are much higher (in many cases 80% or more) than those obtained by other methods using a two-stage procedure involving the intermediate 2-acylacetamidopyridine (**1**) and its subsequent cyclization to the pyrido[1,2-*a*]pyrimidin-4-one (**2**).



1



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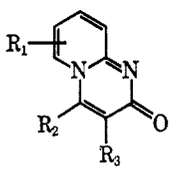
Optimum yields were obtained by heating 1 mol of the 2-aminopyridine with 1.5 mol of β-keto ester at 100° for about 1 hr together with a four- to sixfold quantity of PPA. Kato, *et al.*,[7] have obtained a 28% yield of 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one by treating 2-aminopyridine with diketene.

Table I gives some of the pyrido[1,2-*a*]pyrimidin-4-ones prepared, many of which are water soluble and pharmacologically active. 5-Nitro-2-aminopyridine failed to react.

Alkaline hydrolysis of these compounds yielded the 2-aminopyridines from which they were derived. This according to Lappin[8] proves that they were pyrido[1,2-*a*]pyrimidines and not 1,8-naphthyridines. Furthermore, oxidation yielded 4-hydroxypyrimidines.

Although some workers[9-14] considered that the base obtained from 2-aminopyridine and ethyl acetoacetate was 4-methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (**3**, $R_1 = R_3 = H$; $R_2 = CH_3$), Antaki and Petrow[15]



3

showed that the product was in fact the 2-methyl-4-keto isomer **2** ($R_1 = R_3 = H$; $R_2 = CH_3$) by virtue of its alternate synthesis from 2-bromopyridine and ethyl β-aminocrotonate.

The 4-keto structure was confirmed by Adams and Pachter[16] who converted 3-bromo-2-phenyl-4H-pyrido[1,2-*a*]pyrimidin-4-one into 2-phenylimidazo[1,2-*a*]pyridine.

However, further evidence has now been adduced not only in support of the 4-keto structure, but also of a possible mechanism for the reaction. Kucherov[13,14] has shown that, when N-(5-chloro-2-pyridyl)-β-(5′-chloro-2′-pyridylamino)crotonamide (**4**, $R_1 = R_4 =$ 5-Cl) is treated with sulfuric acid, a 7-chloropyrido[1,2-*a*]pyrimidinone was formed, which he incorrectly regarded as the 2-keto isomer.

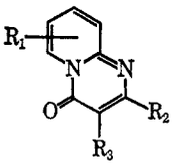
It was therefore decided to investigate the products obtained by cyclization of unsymmetrical crotonamides (**4**) since the nature of these products would provide evidence both of the structure of the pyrimidinone and of a possible mechanism.

The conversion of the crotonamide into the pyrimidinone probably occurs in two stages: first, hydrolytic fission could occur at either bonds a or b with

(1) B. Staskun and S. S. Israelstam, *J. Org. Chem.*, **26**, 3191 (1961).
(2) A. K. Mallams and S. S. Israelstam, *ibid.*, **29**, 3548 (1964).
(3) M. Conrad and L. Limpach, *Chem. Ber.*, **20**, 944 (1887).
(4) M. Conrad and L. Limpach, *ibid.*, **21**, 523 (1888).
(5) M. Conrad and L. Limpach, *ibid.*, **21**, 1649 (1888).
(6) M. Conrad and L. Limpach, *ibid.*, **24**, 2990 (1891).
(7) T. Kato, H. Yamanaka, T. Mitsuma, and M. Aizumi, *Chem. Pharm. Bull.*, **12** (8), 910 (1964).
(8) G. R. Lappin, *J. Amer. Chem. Soc.*, **70**, 3348 (1948).
(9) C. R. Hauser and M. J. Weiss, *J. Org. Chem.*, **14**, 453 (1949).
(10) F. Palazzo and A. Tamburini, *Atti Accad. Lincei*, **20** I, 37 (1911); *Chem. Abstr.*, **6**, 1586 (1911).
(11) Crippa and Scevola, *Gazz. Chim. Ital.*, **67**, 327 (1937); *Chem. Abstr.*, **32**, 166 (1938).
(12) S. N. Khitrik, *J. Gen. Chem. USSR*, **9**, 1109 (1939); *Chem. Abstr.* **33**, 8615 (1939).
(13) V. H. Kucherov, *J. Gen. Chem. USSR*, **20**, 1890 (1950); *Chem. Abstr.*, **45**, 2951 (1951).
(14) V. H. Kucherov, *J. Gen. Chem. USSR*, **21**, 1145 (1951); *Chem. Abstr.*, **46**, 5043 (1952).
(15) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).
(16) R. Adams and I. Pachter, *J. Amer. Chem. Soc.*, **74**, 5491 (1952).

TABLE I

4H-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES

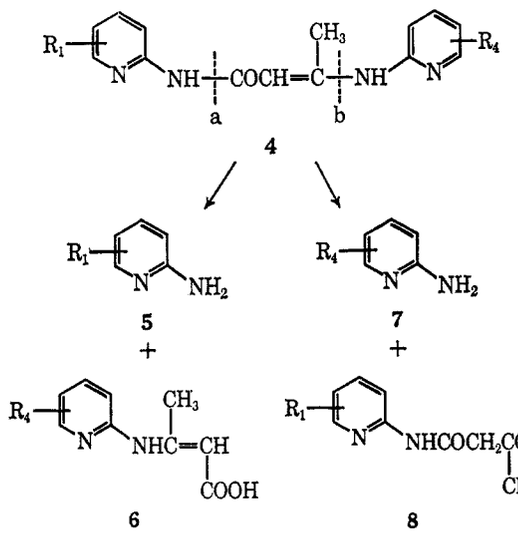


Substituent			Registry	Yield,	Mp,	Lit. yield,[a]	Lit. mp,		Anal, %					
									Calcd			Found		
R_1	R_2	R_3	no.	%	°C	%	°C	Formula	C	H	N	C	H	N
H	CH_3	H		96	123	NR	123–124[b]							
9-CH_3	CH_3	H		74	131–132	NR	130[c]							
6-CH_3	CH_3	H	16867-28-0	69	105	NR	NR	$C_{10}H_{10}N_2O$	68.98	5.75		68.99	5.91	
7-Cl	CH_3	H		98	169–170	22[d]	165–166[d]							
7,9-di-Br	CH_3	H	16878-10-7	86	167	NR	NR	$C_9H_6Br_2N_2O$	33.96	1.89		34.07	2.00	
H	CH_3	CH_3	16867-29-1	86	120–121	NR	NR	$C_{10}H_{10}N_2O$	68.98	5.75		68.91	5.68	
7-CH_3	CH_3	CH_3	16878-11-8	80	129–130	NR	NR	$C_{11}H_{12}N_2O$			14.89			14.80
7-Br	CH_3	C_2H_5	16867-30-4	82	138–139	NR	NR	$C_{11}H_{11}BrN_2O$	49.44	4.12		49.40	4.06	
H	CH_3	C_2H_5	16867-31-5	76	92–93	NR	NR	$C_{11}H_{12}N_2O$			14.89			14.90
6,8-di-CH_3	CH_3	C_2H_5	16867-32-6	88	128–129	NR	NR	$C_{13}H_{16}N_2O$	72.21	7.41		72.46	7.62	
H	CH_3	Cl	16867-33-7	51	186–187	NR	NR	$C_9H_7ClN_2O$	55.53	3.59		55.80	3.68	
7-Cl	C_6H_5	H	16867-34-8	54	170–171	NR	NR	$C_{14}H_9ClN_2O$			10.91			10.98
H	CH_2Cl	H	16867-35-9	44	169–170	NR	NR	$C_9H_7ClN_2O$	55.53	3.59		55.58	3.65	

[a] NR = not reported. [b] Reference 15. [c] Reference 7. [d] Reference 13.

the formation of either the aminopyridine (**5**) and the β-pyridylaminocrotonic acid (**6**) or the aminopyridine (**7**) and the 2-acetoacetamidopyridine (**8**) (Scheme I).

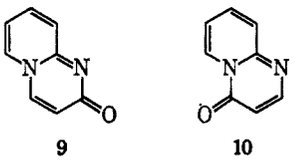
SCHEME I



The second stage would be the cyclization of either **6** to give the pyrimidin-4-one (**2**, $R_2 = CH_3$; $R_3 = H$) or of **8** which would be expected to give the pyrimidin-2-one (**3**, $R_2 = CH_3$; $R_3 = H$). It was found that the 2-aminopyridine formed was in fact **5** and that the pyrido[1,2-*a*]pyrimidinone formed contained the group R_4, and hence it may be concluded that the pyrimidinone is the 4-keto isomer **2** ($R_1 = R_4$; $R_2 = CH_3$; $R_3 = H$).

A number of symmetrical and unsymmetrical or "mixed" crotonamides were prepared. Symmetrical crotonamides were obtained by the interaction of 2-aminopyridines and the 2-acetoacetamidopyridine obtained from it and unsymmetrical crotonamides from 2-aminopyridines and a 2-acetoacetamidopyridine derived from a different 2-aminopyridine according to Khitrik[12] and Kucherov.[14] Attempts to prepare crotonamides from 6-methyl-2-aminopyridines led to the formation of symmetrical di(6-methyl-2-pyridyl)-ureas. It is interesting to note that, when 5-chloro-2-aminopyridine was heated with 4-methyl-2-acetoacetamidopyridine (**2**, R_1 = 4-CH_3; $R_2 = CH_3$; R_3 = H), only the symmetrical crotonamide, N-(5-chloro-2-pyridyl)-β-(5′-chloro-2′-pyridylamino)crotonamide (**4**, $R_1 = R_4$ = 5-Cl) was isolated. The conversion of the crotonamides (Table II) into the pyrido[1,2-*a*]-pyrimidin-4-ones was effected by heating them with PPA.

The ultraviolet spectra of a number of pyrido[1,2-*a*]-pyrimidin-4-ones obtained by the one-stage synthesis were determined and compared with those of **9** and **10**, obtained by Adams and Pachter.[16] The 4H-pyrido-[1,2-*a*]pyrimidin-4-ones show a characteristic two-band spectrum, one with maximum at about 350 mμ being ascribed[17,18] to the N-substituted pyridone-2-imine chromophore. The second band with maximum at about 245 mμ has been attributed[19] to the —C=C—C=O chromophore of the pyrimidine moiety. The ultraviolet absorption spectra of the pyrido[1,2-*a*]-pyrimidinones prepared were found to be very similar to that of 4H-pyrido[1,2-*a*]pyrimidin-4-one (**10**).



The 4H-pyrido[1,2-*a*]pyrimidin-4-ones obtained in the one-stage synthesis were also obtained by the cyclization of alkyl β-pyridylaminocrotonates (**11**) and

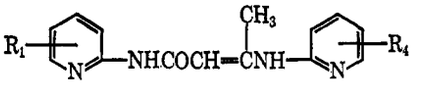
(17) H. Antaki, *ibid.*, **80**, 3066 (1958).

(18) L. C. Anderson and N. V. Seeger, *J. Amer. Chem. Soc.*, **71**, 340 (1949).

(19) H. Antaki, *J. Org. Chem.*, **27**, 1371 (1962).

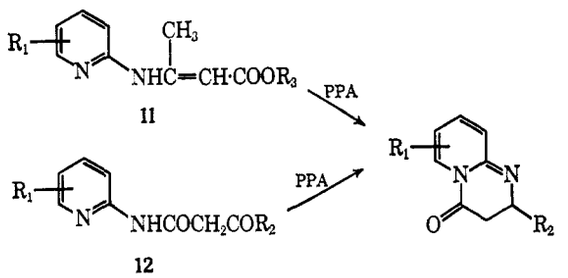
TABLE II

N-(2-PYRIDYL)-β-(2′-PYRIDYLAMINO)CROTONAMIDES



Substituents		Registry	Yield,			Anal, %			
						Calcd		Found	
R_1	R_4	no.	%	Mp, °C	Formula	C	H	C	H
4-CH_3	4-CH_3	16878-12-9	35	152–153	$C_{16}H_{18}N_4O$	68.10	6.38	68.08	6.49
5-CH_3	5-CH_3	16867-36-0	48	171–173	$C_{16}H_{18}N_4O$	68.10	6.38	68.29	6.65
H	5-Cl	16867-37-1	36	194–195	$C_{14}H_{13}ClN_4O$	58.20	4.51	58.11	4.58
H	4-CH_3	16867-38-2	41	127–128	$C_{15}H_{16}N_4O$	67.17	5.97	66.94	6.05
H	5-CH_3	16867-39-3	36	162–163	$C_{15}H_{16}N_4O$	67.17	5.97	67.29	6.00
H	5-Br	16867-40-6	32	184–185	$C_{14}H_{13}BrN_4O$	50.46	3.90	50.42	3.99
5-CH_3	5-Cl	16867-41-7	36	198–199	$C_{15}H_{15}ClN_4O$	59.55	4.96	59.66	5.02

2-acylacetamidopyridines (**12**) in the presence of PPA. This method was shorter and offered better yields than the sulfuric acid method used by other workers.[12–14]

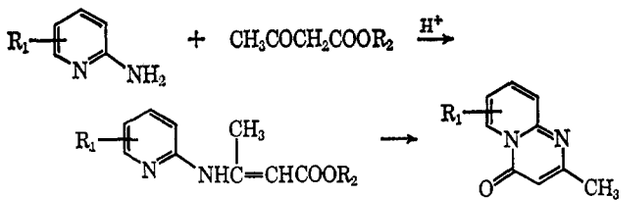


11 **12**

When preparing the acylacetamidopyridines it was found that the reaction between 6-methyl- and 4,6-dimethyl-2-aminopyridines and the α-methyl- and α-ethylacetoacetates did not yield any of the expected α-alkyl-2-acetoacetamidopyridines. As in the case of the preparation of the crotonamides mentioned above, dipyridylureas were formed instead, together with the corresponding methyl alkyl ketone. This is similar to the observation of Mallams and Israelstam[2] who obtained diarylureas by the interaction of certain arylamines and α-alkyl acetoacetates, instead of α-alkylacetoacetanilides.

It should be noted that Allen, *et al.*,[20] considered the compound obtained by the condensation of 3-methyl-2-aminopyridine and diketene to be 3-methyl-2-acetoacetamidopyridine (**12**, R_1 = 3-CH_3; R_2 = CH_3); we have shown that in fact this compound is 2,9-dimethyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (**2**, R_1 = 9-CH_3; R_2 = CH_3; R_3 = H).

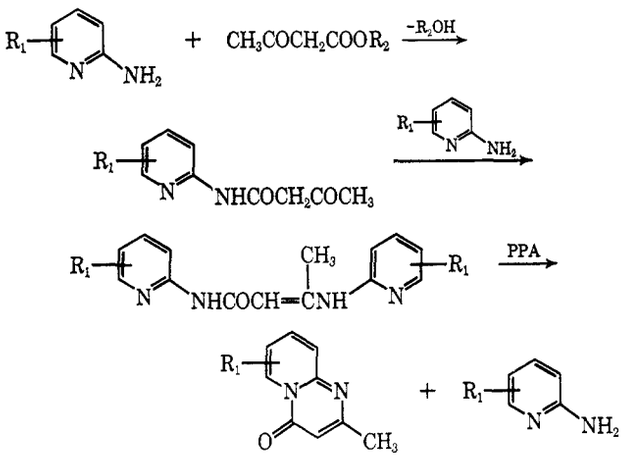
Since the crotonates have been shown to undergo cyclization to pyrimidin-4-ones when heated in PPA, it may be assumed that the mechanism of the direct synthesis in cases where the 2-aminopyridine is known to give a crotonate, is straightforward.



R_1 = 3-CH_3, 5-Cl, 5-Br, 3,5-diBr; R_2 = CH_3, C_2H_5

On the other hand, the mechanism for the formation of those pyrimidin-4-ones derived from 2-aminopyridines, which form 2-acylacetamidopyridines, is more complicated. It is suggested that in such cases a crotonamide is formed as an intermediate although no crotonamide was isolated in these reactions. However, Galasko and Israelstam[21] have isolated a crotonamide in the cyclization of 2-acetoacetamidothiazoles to thiazolo[3,2-*a*]pyrimidin-5-ones on heating with PPA. The mechanism shown in Scheme II is therefore proposed for the direct synthesis of 4H-pyrido[1,2-*a*]pyrimidin-4-ones from such 2-aminopyridines.

SCHEME II



R_1 = H, 4-CH_3, 5-CH_3, 6-CH_3, 5-Cl, 5-Br

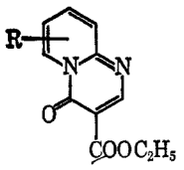
It is important to note that the yields of the pyrido[1,2-*a*]pyrimidin-4-ones obtained by the cyclization of 2-acylacetamidopyridines in the presence of PPA were generally less than 50%, whereas by cyclization of the alkyl β-(aminopyridyl)crotonates with the same reagent were almost quantitative. The lower yield in the former cyclization may be ascribed to the fact that only one-half of the aminopyridine used goes to form the pyridopyrimidin-4-one so that 2 mol of the aminopyridine are required to produce 1 mol of the pyridopyrimidin-4-one. In fact it was shown that, when an equimolecular quantity of 2-aminopyridine was added to the 2-acetoacetamidopyridine in the presence of PPA, the yield of 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one was raised from 56 to 81%.

(20) C. Allen, J. Van Allan, and C. Wilson, *J. Amer. Chem. Soc.*, **66**, 1805 (1944).

(21) G. Galasko and S. S. Israelstam, private communication.

TABLE III

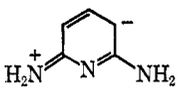
3-CARBETHOXY-4H-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES



Substituent R	Registry no.	Yield, %	Mp, °C	Lit. mp, °C	Formula	Anal, % Calcd C	Calcd H	Found C	Found H
9-CH_3[a]	16878-14-1	79	144–145	NR	$C_{12}H_{12}N_2O_3$	62.07	5.17	62.02	5.30
6-CH_3	16867-53-1	86	148–149	NR	$C_{12}H_{12}N_2O_3$	62.07	5.17	62.30	5.15
6,8-di-CH_3	16867-54-2	78	148–149	NR	$C_{13}H_{14}N_2O_3$	63.41	5.69	63.52	5.80
7-Cl	16867-55-3	76	147–148	132–133[b]	$C_{11}H_9ClN_2O_3$	52.28	3.56	52.21	3.60
7-Br	16867-56-4	81	155–156	134–135[b]	$C_{11}H_9BrN_2O_3$	44.44	3.03	44.65	3.41

[a] Obtained from ethyl (3-methyl-2-pyridylamino)methylenemalonate, mp 68–69°. *Anal.* Calcd for $C_{14}H_{18}O_4N_2$: C, 60.43; H, 6.47. Found: C, 60.47; H, 6.70. [b] Reference 8.

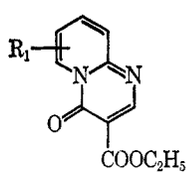
Although the various aminopyridines discussed above yielded pyrido[1,2-*a*]pyrimidin-4-ones when allowed to react with β-keto esters in the presence of PPA, it is interesting that in the case of 2,6-diaminopyridine the product obtained was 7-amino-2-hydroxy-1,8-naphthyridine. This is in accordance with the work of others.[8,22–24] It appears that the resonance structure (**13**) of 2,6-diaminopyridine makes the most important



13

contribution to the molecule, and, together with the steric effect of the 6-amino group, position 3 is more likely to be attacked than the ring nitrogen.

A similar investigation was carried out to study the reaction between 2-aminopyridines and ethyl ethoxymethylenemalonate (EMME) in the presence of PPA. A direct synthesis of 3-carbethoxy-4H-pyrido[1,2-*a*]-pyrimidin-4-ones (**14**) was thereby accomplished, the same compounds being obtained by the cyclization of the 2-pyridylaminomethylenemalonates (**15**) with PPA.



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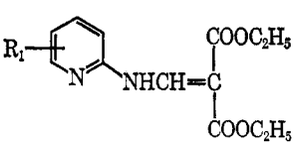
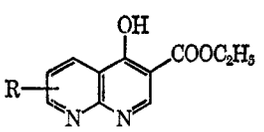


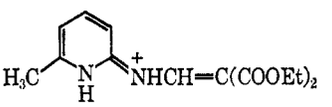
15

The malonates were made by using the method of Lappin,[8] who cyclized the malonates by boiling them in diphenyl ether and obtained either the pyrimidin-4-one (**14**) or the 3-carbethoxy-4-hydroxy-1,8-naphthyridine (**16**) depending on the nature and position of R.



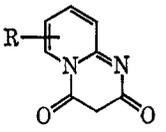
16

Lappin[8] found that pyrido[1,2-*a*]pyrimidin-4-ones (**13**) were formed except when the substituent in position 6 of the 2-aminopyridine was an electron-releasing group, when the naphthyridine (**15**) was obtained instead. The fact that ethyl (6-methyl-2-pyridylamino)methylenemalonate when cyclized with PPA gave a pyrimidin-4-one and not a naphthyridine may be accounted for on the supposition that the pyridylaminomethylenemalonate is protonated to give the cation



which is not possible when just heated alone. Cyclization would thus occur at the ring nitrogen rather than at position 3. We found that pyrido[1,2-*a*]pyrimidin-4-ones were obtained in all cases using PPA, except with 2,6-diaminopyridine when a tar was obtained. The 3-carbethoxy-4H-pyrido[1,2-*a*]pyrimidin-4-ones (**14**) prepared and cyclized are given in Table III.

When diethyl malonate was heated with 2-aminopyridines at 160° for 2 hr with PPA, good yields of 2,3-dihydro-4H-pyrido[1,2-*a*]pyrimidine-2,4-diones (**17**) were obtained. Chichibabin[23] reported the formation of 2,3-dihydro-4H-pyrido[1,2-*a*]pyrimidine-2,4-dione (**17**, R = H) in unspecified yield by heating 2-aminopyridine and diethyl malonate. When the latter compounds were heated with PPA at 130° during 1 hr, the malonamide (**18**, R = H) was obtained instead which was cyclized at 160° with PPA to the pyrimidine-2,4-dione (**17**, R = H).



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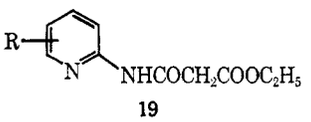
18



19

R = H, 4-CH_3, 5-CH_3

3-Methyl-2-aminopyridine was sufficiently reactive to give the pyrimidinedione (**17**, R = 9-CH_3) merely on heating in the absence of PPA, no malonamide being

(22) O. Seide, *Chem. Ber.*, **58**, 352 (1925).
(23) A. E. Chichibabin, *ibid.*, **57**, 1168 (1924).
(24) G. R. Lappin, Q. R. Peterson, and C. E. Wheeler, *J. Org. Chem.*, **15**, 377 (1950).

isolated. In certain cases a malonamate (**19**) was isolated along with a malonamide which was also obtained by heating the former with PPA.

It would therefore seem reasonable to suggest that the mechanism for the one-stage synthesis of the pyridopyrimidinedione is as shown in the following route.

2-aminopyridine + diethyl malonate ⟶ malonamate (**19**) $\xrightarrow{\text{2-aminopyridine}}$ malonamide (**18**) ⟶ pyridopyrimidine-2,4-dione (**17**)

This mechanism is more likely than that proposed by Khalifa[25] which postulates a rearrangement of the malonamate to a hypothetical 2-imino-N-carbethoxyacetopyridine as an intermediate.

When 6-methyl- and 5-halo-2-aminopyridines were heated with diethyl malonate up to 170° in PPA, only the malonamide was obtained; neither a 1,8-naphthyridine nor a pyridopyrimidinedione was isolated; *cf.* report by Lappin.[24]

Experimental Section

All melting points were determined on an electrically heated copper block and are uncorrected.

Alkyl β-(2-Pyridylamino)crotonates (11).—A mixture containing 0.03 mol of the 2-aminopyridine and 0.03 mol of ethyl β-aminocrotonate was heated at 140° for 1 hr. The reaction product was cooled and treated with dilute ethanol. The crude product (yields varying from 50 to 65%) was crystallized from ethanol to give colorless needles. The same products, in similar yields were obtained using Kucherov's method.[14] The following are new alkyl β-(2-pyridylamino)crotonates (**11**) obtained. R_1 and R_3 substituent, % yield, melting point, and analysis are given: 5-Cl, CH_3, 52%, 89–90° (Calcd for $C_{10}H_{11}ClN_2O_2$: C, 52.97; H, 4.86. Found: C, 53.03; H, 5.01); 3-CH_3, C_2H_5, 48% 63–64° (Calcd for $C_{12}H_{16}N_2O_2$: C, 65.46; H, 7.27. Found: C, 65.36; H, 7.12); 3-CH_3, CH_3, 45%, 83–84° (Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.79. Found: C, 64.05; H, 6.83), 3,5-di-Br, CH_3, 61%, 115–116° (Calcd for $C_{10}H_{10}Br_2N_2O_2$: C, 34.29; H, 2.86. Found: C, 34.35; H, 2.96).

Cyclization of Alkyl β-(2-Pyridylamino)crotonates.—About 1.0 g of the crotonate **11** and 8.0 g of PPA were heated for 30 min at 140° with frequent stirring. The reaction product was cooled and neutralized with 2 *N* NaOH to give the pyrido[1,2-*a*]-pyrimidin-4-one (crude yield 70–90%) crystallized from petroleum ether (bp 80–100°) or dilute ethanol as colorless needles.

2-Acylacetamidopyridines (12).—A mixture of 0.1 mol of the 2-aminopyridine and 0.2 mol of β-keto ester was heated for 1 hr at 150–160°. On cooling, the product solidified. The solid was triturated with 1% NaOH to remove unchanged reactants. The crude product (yields 75–95%) was crystallized from either water or dilute ethanol as colorless needles. The compound gave a purple color with an ethanolic solution of ferric chloride. New acylacetamidopyridines were obtained. Substituents, % yield, melting point, and analysis are given: group 1, R_1 = 4-CH_3, R_2 = CH_3, 75%, 122–123° (Calcd for $C_{10}H_{12}N_2O_2$; C, 62.50; H, 6.25. Found: C, 62.39; H, 6.34.); R_1 = 5-CH_3, R_2 = CH_3, 78%, 152–153° (Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25. Found: C, 62.54; H, 6.31); R_1 = 6-CH_3, R_2 = CH_3, 65%, 104° (Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25. Found: C, 62.51; H, 6.29); group 2, R_1 = 4-CH_3, R_2 = C_6H_5, 76%, 134° (Calcd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 11.20); R_1 = 5-CH_3, R_2 = C_6H_5, 74%, 162–163° (Calcd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.93); R_1 = 6-CH_3, R_2 = C_6H_5, 84%, 78–79° (Calcd for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.98); R_1 = 5-Cl, R_2 = C_6H_5, 98%, 161–162° (Calcd for $C_{14}H_{11}ClN_2O_2$: N, 10.20. Found: N, 10.39); R_1 = 5-Br, R_2 = C_6H_5, 89%, 159–160° (Calcd for $C_{14}H_{11}BrN_2O_2$: N, 8.77. Found: N, 8.65).

Cyclization of 2-Acylacetamidopyridines to Pyrido[1,2-*a*]-primidin-4-ones (2).—A mixture of 0.01 mol of the 2-acylacetamidopyridine and ten times the weight of PPA was heated at 140° with frequent stirring until the mixture became a dark red. It was then cooled and neutralized with 2 *N* NaOH and recooled in ice. The product was filtered, and the crude product was crystallized from petroleum ether (bp 60–80°) yielding colorless needles.

N-(2-Pyridyl)-β-(2′-pyridylamino)crotonamides (4). A. Symmetrical Crotonamides.—A mixture of 0.1 mol of 2-aminopyridine and 0.05 mol of β-keto ester was heated at 140° for 3 hr. The reaction, after solidifying, was triturated with hot water. The crude material was crystallized from ethanol yielding colorless needles. The hot washings gave a small quantity of the 2-acylacetamidopyridine on cooling.

B. Unsymmetrical Crotonamides.—A mixture of 0.02 mol of a 2-aminopyridine and 0.02 mol of an acetoacetamidopyridine derived from a different 2-aminopyridine was refluxed in alcohol containing 1 drop of concentrated H_2SO_4 for 3 hr. On cooling, the crotonamide separated and crystallized from ethanol as colorless needles.

Conversion of Crotonamides (4) into Pyrido[1,2-*a*]pyrimidin-4-ones (2).—A mixture of 0.005 mol of **4** and ten times that weight of PPA was heated at 150° with frequent stirring for 1 hr. After cooling and neutralizing with 2 *N* NaOH, the resulting solution was extracted with chloroform. The pyrimidin-4-one was obtained from the chloroform layer and crystallized from petroleum ether (bp 60–80°). Mixture melting points with pyrimidin-4-ones obtained by other methods were not depressed.

The aqueous layer on extraction with ether yielded a small quantity of the 2-aminopyridine (**5**).

Direct Synthesis of Pyrido[1,2-*a*]pyrimidin-4-ones (2) from 2-Aminopyridines and β-Keto Esters Using PPA.—A mixture of 0.1 mol of a 2-aminopyridine, 0.15 mol of β-keto ester, and six times the weight of the former of PPA was heated at 100° with frequent stirring (the 4- and 5-halo-2-aminopyridines required temperatures of up to 160°). After 1 hr the reaction mixture, which was a deep red color, was cooled and neutralized with 2 *N* NaOH to give, after cooling in ice, the pyrimidin-4-one. Crystallization from petroleum ether (bp 60–80°) or ethanol gave colorless needles. Uv spectra of the 2-methyl compounds showed maxima at 350 and 245 mμ, while the 2-phenyl analogs showed maxima at 350 and about 260 mμ.

Cyclization of Ethyl 2-Pyridylaminomethylenemalonates.—A mixture of 0.005 mol of ethyl 2-pyridylaminomethylenemalonate[26] as prepared by Lappin[8] and ten times its weight of PPA was heated for 4 hr at 110° with frequent stirring. The cooled reaction product was carefully neutralized with dilute ammonia. On cooling in ice for several hours a 3-carbethoxy-4H-pyrido-[1,2-*a*]pyrimidin-4-one separated in 70–90% yields. Crystallization from ethanol gave colorless needles.

Direct Synthesis of 3-Carbethoxy-4H-pyrido[1,2-*a*]pyrimidin-4-ones (14) Using PPA.—A mixture of 0.01 mol of the 2-aminopyridine, 0.01 mol of EMME, and eight times the weight of the 2-aminopyridine of PPA was heated at 110–120° for 2–3 hr with stirring. The cooled reaction product was neutralized with dilute ammonia to give **14**, crystallized from ethanol. A mixture melting point with the product obtained by the cyclization of the malonate was not depressed.

Direct Synthesis of 2,3-Dihydro-4H-pyrido[1,2-*a*]pyrimidine-2,4-diones (17).—A mixture of 0.02 mol of the 2-aminopyridine, 0.02 mol of diethyl malonate, and six times the weight of 2-aminopyridine of PPA was heated for 2 hr at 170° with stirring and the reaction product was neutralized with 2 *N* NaOH to give **17** in 60–70% yields. The melting point of two pyrimidine-2,4-diones were found to be different from those quoted in the literature, *viz.*, R = H, mp 305–308° (lit. mp 295–298°[24]), and R = 8-CH_3, mp 253–255° dec (lit. mp 270° dec[25]).

Di(2-pyridyl)malonamides (18).—A mixture of 0.02 mol of the 2-aminopyridine, 0.02 mol of diethyl malonate, and eight times the weight of the amine of PPA was heated at 130° with stirring. The cooled reaction product was neutralized with 2 *N* NaOH to give **18** in 30–40% yields. Crystallization from ethanol gave colorless needles. Three malonamides were found to have melting points different from those given by Lappin,[25] *viz.*, R = H, 226–227° dec (235°); R = 5-CH_3, 207–209° dec (200° dec); and R = 6-CH_3, 161–162° (145–146°).

(25) M. Khalifa, *Bull. Fac. Pharm.* (Cairo University), **1**, 149 (1961); *Chem. Abstr.*, **61**, 5643 (1964).

(26) The melting points given by Lappin[8] for ethyl (5-chloro-2-pyridylamino)methylenemalonate and the corresponding 5-bromo- were found to be incorrect. They should be, respectively, 131–132 and 135–136° (Calcd for $C_{15}H_{16}ClN_2O_4$: C, 52.26; H, 5.03. Found: C, 52.38; H, 5.24. Calcd for $C_{15}H_{16}BrN_2O_4$: C, 45.47; H, 4.38. Found: C, 45.71; H, 4.40).

Registry No.—**11** (R_1 = 5-Cl; R_3 = CH_3), 16867-42-8; **11** (R_1 = 3-CH_3; R_3 = C_2H_5), 16867-43-9; **11** (R_1 = 3-CH_3; R_3 = CH_3), 16878-13-0; **11** (R_1 = 3,5-di-Br; R_3 = CH_3), 16867-44-0; **12** (R_1 = 4-CH_3; R_2 = CH_3), 16867-45-1; **12** (R_1 = 5-CH_3; R_2 = CH_3), 16867-46-2; **12** (R_1 = 6-CH_3; R_2 = CH_3), 16867-47-3; **12** (R_1 = 4-CH_3; R_2 = C_6H_5), 16867-48-4; **12** (R_1 = 5-CH_3; (R_2 = C_6H_5), 16867-49-5; **12** (R_1 = 6-CH_3; R_2 = C_6H_5), 16867-50-8; **12** (R_1 = 5-Cl; R_2 = C_6H_5), 16867-51-9; **12** (R_1 = 5-Br; R_2 = C_6H_5), 16867-52-0; **15** (R = 3-CH_3), 16878-15-2; **15** (R = 5-Cl), 16867-57-5; **15** (R = 5-Br), 16867-58-6.

Acknowledgment.—One of us (S. S. I.) wishes to thank the South African Council for Scientific and Industrial Research for the award of an assistantship.

Unsaturated Heterocyclic Systems. XL. Evaluation of Spiro[9,10-ethanoanthracene-11,2′-thietane] S,S-Dioxides and 2-α-Dialkylaminoalkyl-3-dialkylaminothietane 1,1-Dioxides as Precursors of 2-Methylenethiete 1,1-Dioxide Derivatives[1,2]

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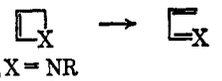
Three synthetic approaches to the highly strained 2-methylenethiete 1,1-dioxide ring system have been evaluated. The retro Diels–Alder route wherein the 9,10-ethanoanthracene moiety was employed as a blocking group for the exocyclic double bond met with failure when it was recognized that the temperatures required to liberate anthracene were well above those at which the desired tetravalent sulfur heterocycles decomposed. The Hofmann degradation approach suffered from the fact that 2α-dialkylaminoalkyl-3-dialkylaminothietane 1,1-dioxides such as **13** and **14** displayed a propensity for ring cleavage when treated with methyl iodide. Two intermediate methiodides, could, however, be isolated. When subjected in turn to the conditions of Hofmann elimination, these methiodides were found to be especially prone to demethylation. Alternatively, N-oxide degradation of 2α-dialkylaminoalkyl-3-dialkylaminothietane 1,1-dioxides, although not an entirely general procedure, was found to give rise to two methylenethiete dioxides. Pertinent mechanistic implications of the above reactions and the physical and spectral properties of the title sulfones are presented in some detail.

A common and fundamental property of unsaturated four-membered-ring heterocycles such as **1a–c** is the



1a, X = NR
b, X = O
c, X = S
d, X = SO_2

ease with which these molecules undergo electrocyclic bond reorganization with ring cleavage. Numerous past investigations have suggested the intermediacy of molecules such as **1** in a variety of chemical and photochemical transformations, but, in general, attempts at isolation have been unsuccessful and rearrangement products have resulted. Recently, however, the isolation of thiete (**1c**)[5a] and a bicyclic thiete derivative[5b] has been described; as expected, both substances have proven to be quite reactive at ambient temperatures.

It was recognized several years ago that the heterocyclic system in question, **1**, was uniquely stabilized when the hetero ring substituent was the sulfone group. Since the preparation of thiete 1,1-dioxide (**1d**) was first described and its chemical behavior examined in a preliminary fashion,[6] the chemistry of this ring system has received considerable attention[7] and a number of stable derivatives are now known.[7,8] It was our intent to investigate in some detail the synthesis and properties of exocyclic methylene derivatives of thiete dioxide, *e.g.*, **2**, in order to examine the effects which are produced by extension of the π-electron system in the indicated manner. That molecules such as **2** would be

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reactive and be subject to diverse types of reactions was anticipated on the basis of analogy to the chemical behavior of methylenecyclobutenes. For example, hydrocarbons **3–5** are known to polymerize readily and

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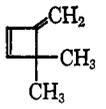

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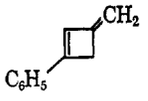

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(1) For paper XXXIX of this series, see L. A. Paquette and M. K. Scott, *J. Org. Chem.*, **33**, 2379 (1968).

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(3) Alfred P. Sloan Foundation Research Fellow.

(4) National Science Foundation Undergraduate Research Participant, summer 1966.

(5) (a) D. C. Dittmer, K. Takahashi, and F. A. Davis, *Tetrahedron Lett.*, 4061 (1967); (b) D. C. Dittmer and F. A. Davis, *J. Amer. Chem. Soc.*, **87**, 2064 (1965).

(6) (a) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961); (b) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962).

(7) (a) D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964); (b) L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); (c) L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965); (d) L. A. Paquette and M. Rosen, unpublished results; (e) D. C. Dittmer and F. A. Davis, *ibid.*, **32**, 3872 (1967).

(8) (a) W. E. Truce, J. R. Norell, J. E. Richman, and J. P. Walsh, *Tetrahedron Lett.*, 1677 (1963); (b) R. H. Hasek, P. G. Gott, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **28**, 2496 (1963); (c) G. Opitz and H. Schempp, *Z. Naturforsch.*, **19b**, 78 (1964); (d) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3236 (1963); (e) D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **29**, 3131 (1964); (f) G. Opitz and H. Schempp, *Ann.*, **684**, 103 (1965); (g) R. H. Hasek, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **30**, 1495 (1965); (h) J. N. Wells and F. S. Abbott, *J. Med. Chem.*, **9**, 489 (1966); (i) L. A. Paquette and M. Rosen, *J. Amer. Chem. Soc.*, **89**, 4102 (1967); (j) L. A. Paquette and M. Rosen, *J. Org. Chem.*, **33**, 2130 (1968).