Reactions of 4-Pyrones with Primary Amines. A New Class of Ionic Associates.

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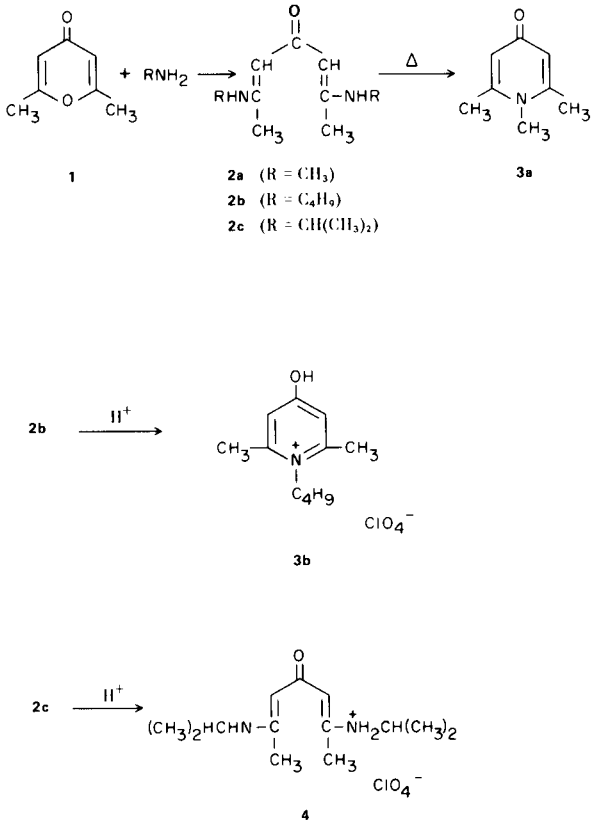
Primary aliphatic amines react with 2,6-dimethyl-4-pyrone to give 2,6-dialkylamino-2,5-heptadien-4-one derivatives. When the alkyl group was methyl, the diamino derivative cyclized on warming to give 1,2,6-trimethyl-4-pyridone. The corresponding butylamino derivative did not thermally cyclize, but did give a pyridone on treatment with acid. The isopropylaminoketone did not cyclize. Several examples of 1,2,6-trisubstituted-4-pyridones formed "ionic associates" consisting of two parts of the pyridone and one part of perchloric acid. These associates are useful primary standards for nonaqueous titrations.

A well known method for preparing pyridones involves reaction of a pyrone with a primary amine (1). For example the reaction of 2,6-dimethyl-4-pyrone (**1**) in a refluxing solution of methylamine in alcohol has been shown to give 1,2,6-trimethyl-4-pyridone (**3a**) (2). Our attempts to extend this method to the reaction between **1** and butylamine have led us to examine the reactions of **1** with primary aliphatic amines in more detail.

We have found that **1** and butylamine react under a variety of conditions to give a product derived from two moles of the amine and one of **1** and to which we have assigned the structure **2b**. A similar compound has been obtained from 4-pyrone and aniline (3). Attempts to thermally cyclize **2b** were unsuccessful; vacuum distillation and refluxing in 1,2,4-trichlorobenzene gave unchanged **2b**. Methylamine and **1** gave **3a** by the published procedure (1), but the diamino compound **2a** was obtained when the reaction was carried out at room temperature. Compound **2a** cyclized readily on warming to give **3a**. Isopropylamine and **1** gave the diamino compound **2c** under all conditions that were tried, but **2c** could not be thermally cyclized to a pyridone. The butylamine adduct, **2b**, was cyclized to the pyridone **3b** (isolated as the perchlorate salt) in hot, concentrated sulfuric acid, but the isopropylamine adduct **2c** did not cyclize under these conditions but gave **4**, which is the salt of **2c** (isolated as the perchlorate). Evidently, steric effects are important in the conversion of 4-pyrones to pyridones. These reactions are summarized in Scheme I.

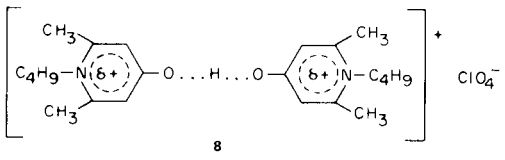
SCHEME I



Our attempts to prepare 1-butyl-2,6-dimethyl-4-pyridone (**5**) from the salt **3b** by treatment of **3b** with aqueous sodium carbonate gave a highly crystalline compound containing **5** and perchloric acid in the ratio of 2:1. Salts of this type have been reported previously; as for example with antipyrine (4), and 2-pyridones (5). The Russian authors refer to these salts as ionic associates (4), and we will use this term. The pyridone **5** was prepared by treatment of the salt **3b** with either aqueous potassium carbonate or methanolic potassium hydroxide. The pyridone ionic associate could be prepared from **5**, either by gradual addition of perchloric acid to a cold aqueous solution of **5**, or by the addition of acetic acid to an aqueous solution of **5** and sodium perchlorate. The insolubility of potassium perchlorate in water serves to explain the different results obtained when **3b** was treated with sodium or potassium carbonate.

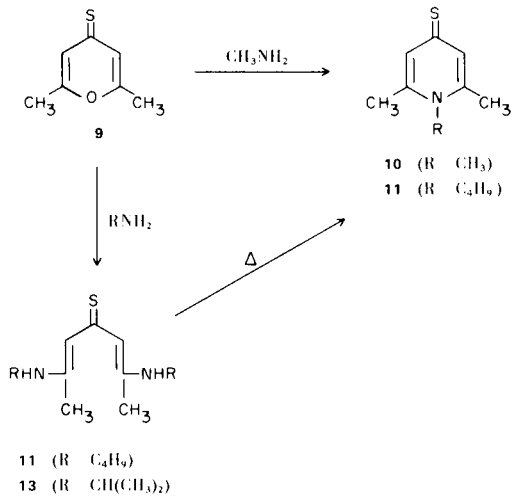
We were unable to prepare an ionic associate from 1,2,6-trimethyl-4-pyridone, but ionic associates (compounds **14** and **15**) were made from 1-methyl-2,6-diphenyl-4-pyridone (**6**) and 2,6-dimethyl-1-phenyl-4-pyridone (**7**).

On the basis of the previous work (4,5), the ionic associate of 1-butyl-2,6-dimethyl-4-pyridone could be assigned structure **8** and the physical properties were in agreement with those reported for the similar salts. We feel, however, that structures such as **8** have not been definitely established.



8

SCHEME II



Elkaschef and Nosseir (2) have allowed 2,6-dimethylpyran-4-thione (**9**) to react with methanolic methylamine and have obtained the thionopyridone **10**. We found that butylamine and **9** gave the diamine (**11**) at room temperature, but if the reaction mixture was refluxed for 4 hours, the thionopyridone **12** was obtained. Isopropylamine reacted with **9** to give **13**, which did not cyclize on prolonged heating. The thionopyridone **12** did not form an ionic associate with perchloric acid.

Some pyridone derivatives have been titrated to see if there is any correlation between basicity and the ability to form ionic associates. The data are collected in Table I, and it is seen that changing the substituent on the nitrogen atom has little effect on the basicity. Antipyrine, which is a very weak base, readily forms ionic associates, and we must conclude that there is no correlation between basicity and associate formation. The two values for the HNP (half neutralization potential) of certain of the compounds in Table I correspond to the formation of the ionic associate and the full salt. It is seen that an associate is formed with **3a**, even though we could not isolate such a compound.

TABLE I

Base Strength of Pyridones

Compound	Substituent on nitrogen	HNP m. V. (CH_3CN)	pK_b (H_2O)
2,6-dimethyl-4-pyridone	H	------	9.9
3a	CH_3	+50; +260	9.9
5	C_4H_9	+50; +270	9.9
7	C_6H_5	+150; +305	10.3
12	---	+280	---
antipyrine	---	+365	11.9

The titration results of the ionic associates are collected in Table II. These compounds act as fairly strong acids toward base and as fairly strong bases toward acids. On the basis of these data, the ionic associates are proposed as useful primary standards for the titration of both nonaqueous acids and bases, since they have sharp inflection points on titration, are soluble in common organic solvents, are nonhygroscopic, and have high equivalent weights.

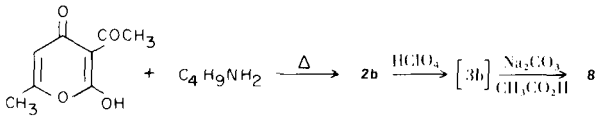
TABLE II

Titration Results for Ionic Associates in Acetonitrile

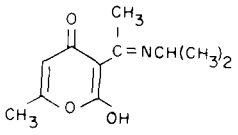
Compound	HNP (m. V.) on titration with Base	Acid
8	50	270
14	180	350
15	145	340

The fact that the ionic associate of 1-butyl-2,6-dimethyl-4-pyridone is a particularly useful titration standard prompted us to investigate a simple synthesis for this compound. This was achieved by the procedure outlined in Scheme III.

SCHEME III



It is interesting to note that dehydroacetic acid reacted with isopropylamine to give the Schiff's base **16**, rather than **2c**, as shown by the hydrolysis of **16** with acids or bases to regenerate dehydroacetic acid.



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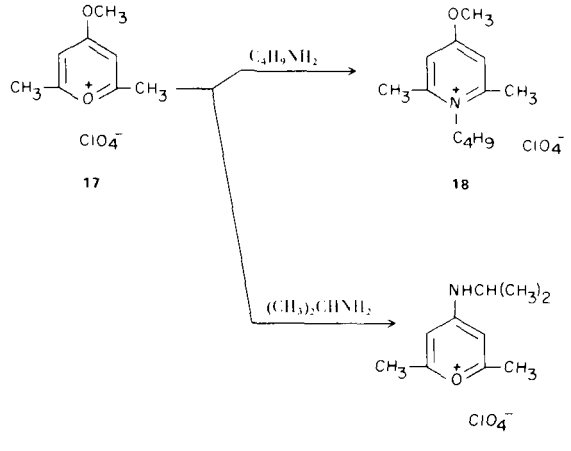
The obvious steric effects that were noted with isopropylamine (*cf.* **2c**, **13** and **16**) led us to compare the reaction of 2,6-dimethyl-4-methoxypyrylium perchlorate, **17**, with butylamine and with isopropylamine. The reaction with butylamine proceeded in the usual fashion (**6**) to give the pyridinium salt **18**, while with isopropylamine the pyrylium salt **19** was formed. It is clear that the steric bulk of the amine completely alters the reaction path with **17**.

SCHEME IV



17 18 19

EXPERIMENTAL

The methods used for the preparation of the compounds are described as general procedures when possible, and the physical data are collected in Table III.

General Procedures.

(A) A solution of 0.02 mole of the pyrone, thionopyrone, or dehydroacetic acid in 5 ml. of water and 4 ml. of the amine (40% aqueous methylamine was used for the preparation of **2a**) was allowed to stand for 24 hours, and the solid was collected and crystallized.

(B) The reaction was carried out as described in procedure A, except that the mixture was refluxed for 4 hours.

(C) A solution of 0.1 mole of the perchlorate salt of the pyridone in 25 ml. of warm methyl alcohol was made basic by the addition of methanolic potassium hydroxide. The solid was separated by filtration. The filtrate was evaporated to dryness and the residue crystallized.

(D) A solution of 0.25 mole of the bis-amino adduct of the pyrone in 50 ml. of sulfuric acid was heated on a steam bath for ½ hour and poured onto approximately 100 g. of ice. The solution was mixed with 40 ml. of 70% perchloric acid, and the solid was collected and crystallized.

(E) A mixture of 0.03 mole of the pyridone, 60 ml. of acetic acid, and 16 ml. of 70% perchloric acid was heated until complete solution resulted; the solution was cooled and the solid that formed was collected.

(F) The ionic associate was crystallized twice from 10% aqueous perchloric acid.

(G) A suspension of 0.07 g. of the perchlorate salt of the pyridone in 75 ml. of water and 15 ml. of saturated sodium carbonate solution was heated until the solid dissolved. After cooling, the solution was diluted with 15 ml. of acetic acid and the solid was collected.

(H) A mixture of 0.01 mole of the perchlorate salt of pyridone, 2 g. of potassium carbonate and 25 ml. of water was stirred for ½ hour. The solid was collected and extracted with hot methyl alcohol. The extract was evaporated to dryness and the residue crystallized.

(I) A mixture of 5 g. of **17**, 1.5 ml. of the amine and 75 ml. of methyl alcohol was stirred for 1 hour. The solution was diluted with 100 ml. of ether, chilled, and the solid was collected and crystallized.

Synthesis of the Ionic Associate **8**.

A mixture of 100 g. of dehydroacetic acid and 233 ml. of *n*-butylamine was heated on a steam bath for 3 hours, the solution was evaporated to dryness *in vacuo* and the residue was crystallized from ligroin (b.p. 100-115°). The bis-amine adduct (125 g.) was stirred for ½ hour with 600 ml. of water and 186 ml. of 70% perchloric acid. To this solution was added 115 g. of sodium carbonate in 300 ml. of water; then 100 ml. of acetic acid was added. The solid was collected and crystallized from water (Norit) to give 90 g. of **8**.

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TABLE III

Physical Constants of Compounds

Cmpd. No.	M.p., °C	Method of preparation	Empirical formula	Anal. Calcd./Found C	H	N or Cl	Solvent for recrystn. (a)	Absorption spectra (b)
2a	167-168	A	$C_9H_{16}N_2O$	64.2 64.1	9.6 9.6	16.7 17.0	L	240 (7.0) 275 (3.5) 373 (53.0)
2b	67- 68	A, B	$C_{15}H_{28}N_2O$	71.4 71.5	11.2 11.3	11.1 11.3	L	235 (7.2) 280 (3.6) 375 (53.6)
2c	117-118	A	$C_{13}H_{24}N_2O$	69.6 69.5	10.8 10.9	12.5 12.6	C	-------
3a	244-245	B	$C_8H_{11}NO$	70.0 69.8	8.1 8.1	10.2 10.2	W	217 (17.8) 267 (14.0)
3b	109-110	D, E, F	$C_{11}H_{18}ClNO_5$	47.2 47.6	6.5 (Cl) 6.4	12.7 12.6	W	245 (9.8)
4	173-175	D	$C_{13}H_{25}ClN_2O_5$	48.1 47.9	7.8 7.6	8.6 8.8	A+E	-------
5	85- 86	C, H	$C_{11}H_{17}NO$	73.7 73.9	9.6 9.6	7.8 7.5	T	212 (13.5)
6	192-193	Reference 2						241 (24.0) 270 (16.7)
7	197-198 (c)							263 (20.0)
8	161-162	G	$C_{22}H_{35}ClN_2O_6$	57.6 57.3	7.7 7.6	6.1 (Cl) 7.8 6.1 8.0	W	262 (42.4)
10	279-280	B	Reference 1					
11	117-118	A	$C_{15}H_{28}N_2S$	67.1 67.3	10.5 10.5	10.5 10.1	A	222 (12.6) 355 (14.6) 430 (40.6)
12	193-195	B	$C_{11}H_{17}NS$	67.6 68.0	8.8 8.7	7.2 7.1	A	241 (10.4) 353 (30.4)
13	84- 85	B	$C_{13}H_{24}N_2S$	64.9 64.5	10.1 9.9	11.7 11.3	C	
14 (d)	239-240	G	$C_{36}H_{31}ClN_2O_6$	69.4 68.9	5.0 (Cl) 5.1	5.7 6.0	Ac	235 (51.8) 266 (38.4)
15 (e)	284-285	G	$C_{26}H_{27}ClN_2O_6$	62.6 62.4	5.5 (Cl) 5.6	7.1 6.8	A	263 (40.3)
16	59- 60	B	$C_{11}H_{15}NO_3$	63.1 63.1	7.2 7.1	6.7 6.6	W	
18	100-101	I	$C_{12}H_{20}ClNO_5$	49.1 49.4	6.9 6.6	4.8 5.1	A	242 (14.6)
19	118-119	I	$C_{10}H_{16}ClNO_5$	45.2 45.3	6.1 5.8	5.3 5.6	A	228 (7.9) 271 (22.1)

(a) The solvents are designated as follows: L is ligroin (b.p. 63-75°); C is cyclohexane; W is water; Ac is acetic acid; A is alcohol; E is ether; T is toluene. (b) The spectra of **2a**, **2b**, **12**, **13**, **16** and **20** were determined in acetonitrile and those of the other compounds in methyl alcohol. (c) S. Hünig and G. Köbrich, *Ann. Chem.*, 617, 194 (1958). (d) This is the ionic associate from 1-methyl-2,6-diphenyl-4-pyridone. (e) This is the ionic associate from 2,6-dimethyl-1-phenyl-4-pyridone.

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(2) M. A. Elkaschef and M. H. Nosseir, *J. Am. Chem. Soc.*, 82, 4344 (1960).

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