Synthesis of 1,3-Dialkyl-1,2-dihydro-2-oxopyrimidinium Salts by Direct Cyclization

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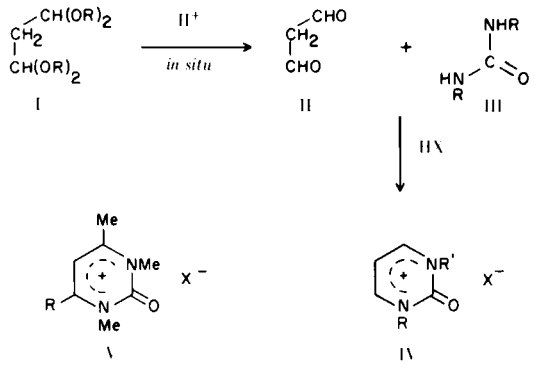
Quaternary heteroaromatic systems are normally made by alkylations of the parent base (1). The scope of this reaction as a synthetic method is, however, limited because of the relatively few alkylating agents which may be used (1). On the other hand, many pyrimidines are accessible by the condensation of β-dicarbonyl compounds with ureas, thiourea, guanidine, and amidines (2). For example, simple *N*-alkyl-2(1*H*)pyrimidinones have been made by the reaction of malondialdehyde (II) with *N*-alkylureas (III; R′ = H) (3). Since an acidic medium is required to generate the dialdehyde (II) from a tetralkylacetal (I; R = Me, Et) the *N*-alkyl-2-pyrimidone is isolated as a salt (IV; R′ = H) (3). This suggested that one might be able to prepare 1,3-dialkyl-2-oxopyrimidinium salts (IV; R,R′ ≠ H) in an analogous manner from 1,3-dialkylureas (III). Indeed, reaction of 1,1,3,3-tetraethoxypropane (I; R = Et) with 1,3-dimethylurea in ethanolic hydrochloric acid (or sulfuric acid) gave the desired chloride (or bisulphate) (IV; R = R′ = Me, X = Cl or HSO_4) in very good yield (4,5).



In connection with a study of pseudo-base formation we have now prepared several other such quaternary salts (see Table I). Most were obtained in good yield, notwithstanding certain difficulties in their isolation. For the larger alkyl and aryl substituents the rate of condensation is apparently slower, so that higher reaction temperatures and/or longer reaction times were required. Elevated temperatures, however, often resulted in tarry, coloured products which were more difficult to purify and to recrystallize. This is almost certainly the result of side reactions of malondialdehyde. So far we have not been able to cyclise a 1,3-diarylurea, presumably due to the much lower nucleophilicity of ArNH- groups. Attempts to cyclise 1,3-di-*t*-butyl urea using either hydrochloric acid, sulfuric acid, or hydriodic acid also failed.

Our earlier efforts involved the use of hydrochloric acid and sulfuric acid as acid catalysts, so that the salts formed were chlorides and bisulphates. Some of these, however, are hygroscopic and even deliquescent, a drawback we later overcame by using hydriodic acid and thus forming the iodides (see Table I). Moreover, with hydriodic acid side reactions seem to be less, and so this should, perhaps, be the reagent of choice (6).

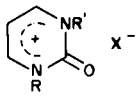
Cyclisation of 1,3-di*iso*propyl urea and 1,3-dicyclohexyl urea was carried out using sulfuric acid. However, from the analyses, nmr spectra, and chemical reactions of the products (IVq and IVu) it was apparent that the anion in these salts was $EtSO_4^-$ and not HSO_4^-. It appears, therefore, that in these two instances a better crystal lattice is formed with $EtSO_4^-$. This anion, of course, is derived from $EtOSO_3H$ formed from ethanol and sulfuric acid.

Analogous condensations have previously been carried out with acetylacetone and 3-ketobutyraldehyde (7), but the cited literature gives scant details and no physical properties of the salts produced. We have found that reaction of acetylacetone with 1,3-dimethylurea in ethanolic hydrochloric acid or sulfuric acid gives the appropriate salt V (R = Me, X = Cl or HSO_4) in 85% or 64% yield respectively. Similarly from 3-ketobutyraldehyde dimethyl acetal the salt V (R = H, X = HSO_4) was obtained in 99% yield.

The ureas (III) required for this work were either commerical samples, or were synthesized easily from appropriate amines and alkyl or aryl isocyanates (8).

TABLE I

Formation of the 2-Oxopyrimidinium Salts IV



IV	R	R′	X	Temp.	Time (hr.)	Yield (%)	M.p., °C	Remarks
a	Me	Me	Cl	60° C	1	85	245-250 dec.	ref. 4
b	Me	Me	HSO_4	50° C	0.5	95	204-206	ref. 5
c	Me	Et	Cl	reflux	4.5	74	217-219	hygroscopic
d	Me	Et	HSO_4	reflux	2	50		deliquescent
e	Me	Et	I	reflux	2	76	210-213	
f	Me	*i*-Pr	HSO_4	room	36	68	136-137	
g	Me	*t*-Bu	HSO_4	room	96	54	145-147	
h	Me	*c*-Hex	I	reflux	2	88	205-208	
i	Me	Ph	Cl	reflux	9	64	109-113	hygroscopic
j	Me	Ph	I	reflux	6	64	129-132	
k	Me	$PhCH_2$	HSO_4	reflux	18	96	250-255 dec.	
l	Et	Et	Cl	reflux	2	21		hygroscopic
m	Et	Et	HSO_4	reflux	2.8	40	87-94	hygroscopic
n	Et	Et	I	reflux	4	81	208-212	
o	Pr	Pr	Cl	reflux	1.5	85	138-141 (sealed tube)	hygroscopic
p	Pr	Pr	I	reflux	6.3	69	153-155	
q	*i*-Pr	*i*-Pr	$EtSO_4$	reflux	6	73	209-212	
r	*n*-Bu	*n*-Bu	Cl	reflux	3	91	122-125 (sealed tube)	hygroscopic
s	*n*-Bu	*n*-Bu	HSO_4	reflux	2	99	108-109	hygroscopic
t	$PhCH_2$	$PhCH_2$	HSO_4	reflux	4	70	175-177	
u	*c*-Hex	*c*-Hex	$EtSO_4$	reflux	52	94	177-179	

EXPERIMENTAL

The melting points in Table I are uncorrected. All new compounds showed satisfactory spectral properties, particularly in respect of their uv and nmr spectra. The salts IVd, IVl, IVo, and IVr which are highly hygroscopic were not submitted for elemental analysis. The remainder gave the analysis figures shown in Table II. Note that two salts (IVi, IVt) are hydrated. Also the analysis figures for IVi and IVu are barely acceptable. The former is quite hygroscopic and thus is difficult to purify. The latter (IVu) was recrystallized several times and analyzed three times with uniformly poor results even though its spectra were quite acceptable. Others have noted difficulty in obtaining good analyses for quaternary salts (10). Elemental analyses were performed by Galbraith Labs., Inc., Knoxville, Tenn.

General Method of Preparation of the Salts IV.

To a mixture of a dialkylurea III (25 mmoles) and 1,1,3,3-tetramethoxypropane I (25 mmoles) in 25 ml. of ethanol (or methanol) was added concentrated acid (30 mmoles of concentrated hydrochloric acid, concentrated sulfuric acid or 47% hydriodic acid). When the acid used was sulfuric acid, the mixture was precooled in ice-water. After addition of the acid, the mixture was stirred and heated at the temperature shown in Table I. After test aliquots of the reaction mixture showed acceptable spectra or readily crystallized, the solvent was removed under reduced pressure and the residue (sometimes solid, often tarry) was recrystallized from suitable solvents (ethanol-ether, ethanol-ethyl acetate, ethanol-acetone, *etc.*).

Preparation of Salts V.

These condensations were carried out in the manner described by Baumann *et al.* (7). 1,3-Dimethylurea and 3-ketobutyraldehyde dimethylacetal in the presence of concentrated sulfuric acid at room temperature for 22 hours gave the trimethyl salt V (R = H, X = HSO_4) in 99% yield. One recrystallization from ethanol/acetone gave colorless needles, m.p. 120-121°. Second recrystallization gave colorless plates, m.p. 106-107°.

Anal. Calcd. for $C_7H_{12}N_2O_5S \cdot H_2O$ (plates): C, 33.07; H, 5.55; N, 11.02. Found: C, 33.34; H, 5.73; N, 10.78.

Acetylacetone and 1,3-dimethylurea were reacted in the presence of concentrated hydrochloric acid for 5 hours at 70°

TABLE II

Elemental Analyses of the 2-Oxopyrimidinium Salts IV

IV	R	R′	X	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
c	Me	Et	Cl	$C_7H_{11}N_2OCl$	48.14	6.35	16.05	47.91	6.25	15.90
e	Me	Et	I	$C_7H_{11}N_2OI$	31.60	4.17	10.53	31.31	4.32	10.44
f	Me	*i*-Pr	HSO_4	$C_8H_{14}N_2O_5S$	38.39	5.64	11.20	38.54	5.56	11.22
g	Me	*i*-Bu	HSO_4	$C_9H_{16}N_2O_5S$	40.90	6.10	10.60	40.75	6.14	10.60
h	Me	*c*-Hex	I	$C_{11}H_{17}N_2OI$	41.27	5.35	8.75	41.43	5.32	8.78
i	Me	Ph	Cl	$C_{11}H_{11}N_2OCl\cdot H_2O$	54.89	5.44	11.64	54.23	5.56	11.37
j	Me	Ph	I	$C_{11}H_{11}N_2OI$	42.06	3.53	8.92	41.80	3.83	8.73
k	Me	$PhCH_2$	HSO_4	$C_{12}H_{14}N_2O_5S$	48.31	4.73	9.39	48.44	4.78	9.41
m	Et	Et	HSO_4	$C_8H_{14}N_2O_5S$	38.39	5.64	11.20	38.35	5.45	11.01
n	Et	Et	I	$C_8H_{13}N_2OI$	34.30	4.64	10.00	34.40	4.73	9.96
p	Pr	Pr	I	$C_{10}H_{17}N_2OI$	38.98	5.56	9.09	39.02	5.42	8.94
q	*i*-Pr	*i*-Pr	$EtSO_4$	$C_{12}H_{22}N_2O_5S$	47.04	7.24	9.14	47.24	7.39	9.22
s	*n*-Bu	*n*-Bu	HSO_4	$C_{12}H_{22}N_2O_5S$	47.04	7.24	9.14	46.98	7.22	9.07
t	$PhCH_2$	$PhCH_2$	HSO_4	$C_{18}H_{18}N_2O_5S\cdot 0.5H_2O$	56.38	5.00	7.31	56.35	5.46	6.96
u	*c*-Hex	*c*-Hex	$EtSO_4$	$C_{18}H_{32}N_2O_5S$	55.65	8.30	7.21	55.83	7.82	7.33

to give the tetramethyl salt V (R = Me, X = Cl) in 85% yield. Colorless needles from ethanol/acetone which upon heating became semiliquid at 80° and appeared to lose water. The material remaining melted with decomposition at 209-211°. Analysis of these needles approximately corresponded to a hydrate.

Anal. Calcd. for $C_8H_{13}N_2OCl\cdot 2.5H_2O$: C, 41.12; H, 7.77; N, 11.99. Found: C, 41.07; H, 7.08; N, 12.23.

A second recrystallization followed by drying *in vacuo* over silica gel gave needles which analyzed for a different hydrate, m.p. 210°.

Anal. Calcd. for $C_8H_{13}N_2OCl\cdot 0.5H_2O$: C, 48.61; H, 7.14; N, 14.17. Found: C, 48.72; H, 7.24; N, 14.07.

The corresponding tetramethyl pyrimidinium bisulphate V (R = Me, X = HSO_4) was obtained in 64% yield from reaction in the presence of concentrated sulfuric acid at room temperature for 21 hours. Colorless needles from ethanol/acetone, m.p. 144-145°. This material is slightly hygroscopic.

Anal. Calcd. for $C_8H_{14}N_2O_5S\cdot H_2O$: C, 35.82; H, 6.01; N, 10.44. Found: C, 35.75; H, 5.98; N, 10.39.

The pmr of these salts (V) in deuterium oxide shows C-Me at δ 2.7, N-Me at δ 3.7, 5-H at δ 6.9, and when R = H, 6-H at δ 8.66. The C-Me groups undergo facile H/D-exchange with the solvent (9).

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