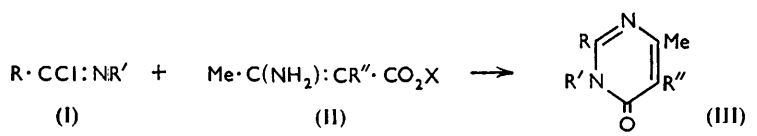
920. *A New Synthesis of 2 : 3 : 5 : 6-Substituted 4-Pyrimidones.*

By BENJAMIN STASKUN and HENRY STEPHEN.

2 : 3 : 5 : 6-Substituted 4-pyrimidones are readily synthesised by condensation of imidoyl chlorides with methyl or ethyl α-alkyl-β-aminocrotonates.

THE present synthesis involves condensation of imidoyl chlorides (I) with the amino-group of methyl or ethyl α-alkyl-β-aminocrotonates (II), followed by ring closure to 2 : 3 : 5 : 6-substituted 4-pyrimidones (III), the reaction being analogous to the synthesis of quin-



azolones from imidoyl chlorides and methyl anthranilate.[1] The methyl and the ethyl ester of the same α-alkyl-β-aminocrotonic acid give, of course, the same pyrimidone.

The synthesis was modified by preparing imidoyl chlorides by rearranging ketoximes with phosphorus pentachloride,[2] which has the advantage that certain imidoyl chlorides, *e.g.*, Me·CCl:NPh, which are difficult to prepare from the amides, can be obtained and used *in situ*, and it is unnecessary to remove the phosphorus oxychloride produced during the rearrangement since it has no action on α-alkyl-β-aminocrotonic esters under the experimental conditions. Since hydrogen chloride and methanol or ethanol produced during the condensations react with imidoyl chlorides and α-alkyl-β-aminocrotonic esters the yields of pyrimidones were 50—65% when equimolecular proportions of the reactants were used. Improved yields (70—80%) were obtained by using an excess of either imidoyl chloride or ester.

EXPERIMENTAL

α-Alkyl-β-aminocrotonic esters were prepared by Conrad and Epstein's method,[3] and stored over phosphoric oxide.

General Procedures (cf. Table 1).—(*a*) The imidoyl chloride (0·01 mol.) and α-alkyl-β-aminocrotonic ester (0·005, 0·01, or 0·02 mol.) were refluxed in dry chloroform (40 c.c.) for 3—4 hr. (method A) or allowed to remain at room temperature for 2—3 days (method B). These methods furnish pyrimidones in poor yields from relatively unreactive imidoyl chlorides. In such cases the imidoyl chloride and ester were heated (paraffin-bath) in the absence of a solvent (method C), hydrogen chloride and alcohol being evolved. The products (any of the methods) were acidified with dilute hydrochloric acid and steam-distilled; this hydrolysed unchanged ester to give steam-volatile or water-soluble products, and converted unchanged imidoyl chloride

[1] Levy and Stephen, *J.*, 1956, 985.
[2] Stephen and Staskun, *J.*, 1956, 980.
[3] Conrad and Epstein, *Ber.*, 1887, **20**, 3055.

TABLE 1. 2 : 3 : 5 : 6-*Substituted pyrimidones.*

R·CCl:NR′		Me·C(NH$_2$):CR″·CO$_2$X		Molar ratio		Product				
R	R′	R″	X	(I) : (II)	Method	Formula	Yield (%)	M. p.	Found, N (%)	Reqd., N (%)
Ph	Ph	Me	Me	1 : 1	C, 140°, ½ hr.	—	—	—	—	—
		Me	Et	1 : 1	C, 140°, ½ hr.	$C_{18}H_{16}ON_2$	45	157°	10·35	10·15
		Et	Et	1 : 2	A, 4 hr.	$C_{19}H_{18}ON_2$	79	159	9·6	9·65
Ph	*o*-C$_6$H$_4$Me	Me	Me	1 : 1	A, 3 hr.	$C_{19}H_{18}ON_2$	53	114	9·6	9·65
		Et	Et	1 : 2	A, 4 hr.	$C_{20}H_{20}ON_2$	80	152	9·2	9·3
Ph	*m*-C$_6$H$_4$Me	Me	Me	1 : 1	C, 100°, ½ hr.	$C_{19}H_{18}ON_2$	31	129	9·95	9·65
		Me	Et	1 : 1	C, 100°, ½ hr.	—	28	—	—	—
		Et	Me	1 : 1	C, 100°, ½ hr.	$C_{20}H_{20}ON_2$	77	136	9·4	9·2
		Et	Et	1 : 2	A, 3 hr.					
Ph	*p*-C$_6$H$_4$Me	Me	Me	1 : 2	A, 3 hr.	$C_{19}H_{18}ON_2$	77	146	9·7	9·65
		Et	Et	1 : 2	B, 3 hr.	$C_{20}H_{20}ON_2$	75	152	9·2	9·2
Ph	2 : 4 : 1-Me$_2$C$_6$H$_3$	Me	Me	2 : 1	A, 3 hr.	$C_{20}H_{20}ON_2$	83	152	9·1	9·2
		Me	Et	2 : 1	A, 3 hr.	—	—	—	—	—
		Et	Et	2 : 1	A, 3 hr.	$C_{21}H_{22}ON_2$	83	146	8·6	8·8
Ph	*p*-MeO·C$_6$H$_4$	Et	Et	1 : 2	B, 3 hr.	$C_{20}H_{20}O_2N_2$	81	161	8·75	8·75
		Pr^n	Me	1 : 2	C, 155°, ½ hr.	$C_{21}H_{22}O_2N_2$	55	163	8·3	8·4
Ph	*m*-NO$_2$·C$_6$H$_4$	Me	Me	1 : 2	C, 140°, ½ hr.	$C_{18}H_{15}O_3N_3$	62	159	13·3	13·1
		Me	Et	1 : 2	C, 140°, ½ hr.	—	34	—	—	—
		Et	Me	1 : 2	C, 140°, ½ hr.	$C_{19}H_{17}O_3N_3$	24	160	12·35	12·5
		Et	Et	1 : 2	C, 140°, ½ hr.	—	38	—	—	—
Ph	1-C$_{10}$H$_7$	Me	Et	1 : 2	A, 3 hr.	$C_{22}H_{18}ON_2$	64	174	8·2	8·6
Ph	2-C$_{10}$H$_7$	Me	Et	1 : 2	A, 3 hr.	$C_{22}H_{18}ON_2$	50	189	8·4	8·6
		Et	Et	1 : 2	A, 3 hr.	$C_{23}H_{20}ON_2$	40	184	8·5	8·2
Ph	*o*-C$_6$H$_4$Cl	Me	Et	2 : 1	A, 3 hr.	$C_{18}H_{15}ON_2Cl$	13	151	9·2	9·0
		Et	Et	2 : 1	C, 170°, ½ hr.	$C_{19}H_{17}ON_2Cl$	32	192	8·4	8·6
Ph	*m*-C$_6$H$_4$Cl	Me	Me	1 : 1	C, 150°, ½ hr.	$C_{18}H_{15}ON_2Cl$	35	152	9·0	9·0
Ph	*p*-C$_6$H$_4$Cl	Et	Et	1 : 2	C, 185°, ½ hr.	$C_{19}H_{17}ON_2Cl$	59	148	8·4	8·6
		Pr^n	Me	1 : 2	C, 185°, ½ hr.	$C_{20}H_{19}ON_2Cl$	37	154	8·05	8·2
Ph	Et	Et	Et	1 : 2	B, 3 hr.	$C_{14}H_{16}ON_2$	73	82	12·5	12·3
		Me	Et	1 : 2	B, 3 hr.	$C_{15}H_{18}ON_2$	51	118	11·25	11·5
o-C$_6$H$_4$Me	Ph	Me	Me	2 : 1	A, 3 hr.	$C_{19}H_{18}ON_2$	80	112	9·45	9·65
		Et	Et	2 : 1	A, 3 hr.	$C_{20}H_{20}ON_2$	74	137	9·1	9·2
p-C$_6$H$_4$Cl	Ph	Et	Et	1 : 2	C, 155°, ½ hr.	$C_{19}H_{17}ON_2Cl$	67	146	8·8	8·6
		Pr^n	Me	1 : 2	C, 155°, ½ hr.	$C_{20}H_{19}ON_2Cl$	21	151	8·3	8·3
3 : 4 : 5-(MeO)$_3$C$_6$H$_2$	Ph	Me	Me	1 : 2	A, 3 hr.	$C_{21}H_{22}O_4N_2$	20	181	8·0	7·65
		Et	Et	1 : 2	A, 3 hr.	$C_{22}H_{24}O_4N_2$	37	129	7·2	7·4

into the amide. After cooling, the latter was filtered off, and the filtrate, on treatment with charcoal and ammonia, deposited the crude pyrimidone which crystallised from dilute methanol or ethanol in colourless needles.

(*b*) To a solution of the ketoxime (0·01 mol.) in chloroform (50 c.c.) at 0° finely powdered phosphorus pentachloride (0·01 mol.) was rapidly added and the whole shaken for 1—2 min. to dissolve the pentachloride. The solution was removed from the ice-bath and treated according to one of the following procedures. The solution was refluxed for 15 min. to complete the rearrangement of the ketoxime, the α-alkyl-β-aminocrotonic ester (0·02—0·03 mol.) in chloroform (10 c.c.) was added, and refluxing continued for 2—3 hr. (method D). Alternatively, the solution after remaining at room temperature for 2 hr. was cooled (10°), the ester (0·02—0·03 mol.) in chloroform (10 c.c.; 10°) was added, and the mixture allowed to remain for 1—2 days at room temperature (method E).

TABLE 2.

			Pyrimidone				
Ketoxime	R in $Me{\cdot}C(NH_2){:}CR{\cdot}CO_2X$	Method	Formula	Yield (%)	M. p.	Found, N (%)	Reqd., N (%)
PhMeC:N·OH	Et	E	$C_{14}H_{16}ON_2$	65	126°	12·5	12·3
(*p*-C_6H_4Me)MeC:N·OH	Et	E	$C_{15}H_{18}ON_2$	65	82	11·6	11·6
,,	Me	D	$C_{14}H_{16}ON_2$	65	146	12·2	12·3
2-$C_{10}H_7$·CMe:N·OH ...	Et	F	$C_{18}H_{18}ON_2$,HCl	65	130	8·4	8·9
PhPr^{n}C:N·OH	Et	E	$C_{15}H_{18}ON_2$	72	106	11·3	11·6
,, ...	Me	E	$C_{14}H_{16}ON_2$	35	73	12·1	12·3
(*p*-C_6H_4Me)$_2$C:N·OH...	Me	F	$C_{20}H_{20}ON_2$	73	128	9·5	9·2
... ,,	Et	F	$C_{21}H_{22}ON_2$	60	140	9·0	8·8
Ph_2C:N·OH	Et	D	Table 1	55	157	—	—

The following method (F) gave good yields of pyrimidones. The rearranged solution of the ketoxime, after remaining for 2 hr. at room temperature, was distilled at 40—45°/30 mm. to remove solvent (30 c.c.) and some phosphorus oxychloride. The α-alkyl-β-aminocrotonic ester (0·02—0·03 mol.) in chloroform (30 c.c.) was added and the mixture stored for 1—2 days at room temperature. The products were treated as described previously. Results are recorded in Table 2. The pyrimidones crystallised in colourless needles from methanol or ethanol.

UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG, SOUTH AFRICA.

[*Received, June 5th*, 1956.]