Reactions of 4-Dicyanomethylenepyrans with Hindered Primary Amines

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The reaction of 2,6-dimethyl- and 2,6-diphenyl-4-dicyanomethylene-4*H*-pyran with hindered primary amines such as isopropylamine and cyclohexylamine gave 1-alkyl-2-amino-3-cyano-6-methyl(or phenyl)-4-acetonylidene (or phenacylidene)-1,4-dihydropyridine derivatives. The 6-methyl-4-acetonylidene examples underwent a facile thermal rearrangement to give 1-alkyl-2,6-dimethyl-4-dicyanomethylene-1,4-dihydropyridines. Several reactions of the acylidene derivatives are described.

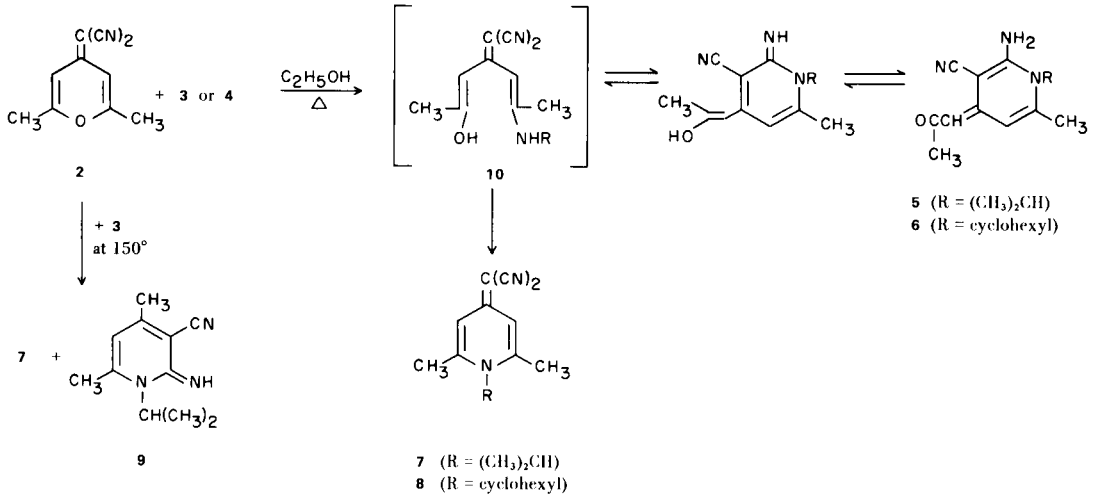
We have shown (1) that 4-dicyanomethylene-2,6-diphenyl-4*H*-pyran (**1**) reacts with *n*-alkylamines below 100° to give a mixture of 1-alkyl-4-dicyanomethylene-2,6-diphenyl-1,4-dihydropyridine and 1-alkyl-2-amino-3-cyano-4-phenacylidene-6-phenyl-1,4-dihydropyridine. Kato, *et al.*, have reported that 4-dicyanomethylene-2,6-dimethyl-4*H*-pyran (**2**) reacts with *n*-alkylamines to give dicyanomethylene dihydropyridine derivatives (2). The present paper describes the reactions of **1** and **2** with branched-chain primary amines such as iospropylamine (**3**) and cyclohexylamine (**4**).

The amines **3** and **4** reacted with **2** in refluxing alcohol to give high yields of the acetonylidene dihydropyridines **5** and **6** (Scheme I). Prolonged refluxing (2 hours or more) of **5** and **6** in acetonitrile, dimethylformamide or pyridine brought about a rearrangement with the formation of the compounds **7** and **8**. If **2** and **3** were heated at 150° in an autoclave, the products were **7** and **9**.

The results shown in Scheme I can be explained if it is assumed that **2** and the amines reacted to give the intermediate **10**, which then underwent a kinetically controlled cyclization to give **5** or **6**. Heating of **5** and **6** slowly provided the thermodynamically stable products **7** and **8**, respectively. The bulky nature of the R group therefore causes the formation of the less stable product. The products obtained from **2** and **3** at 150° were the result of the partial transformation of **5** to the more stable **7** along with a competing basic hydrolysis of the acetyl group of **5** to give **9**.

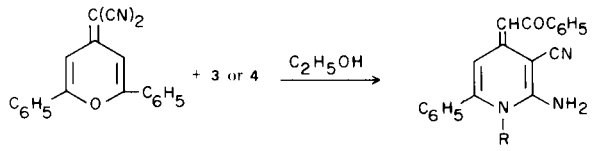
The pyran **1** reacted with the amines **3** and **4** to give exclusively the phenacylidene dihydropyridine derivatives **11** and **12**, which are evidently the thermodynamically

SCHEME I



stable isomers, since they were not changed on boiling in various solvents. Unsymmetrical dimethylhydrazine also gave the similar compound **13**.

SCHEME II

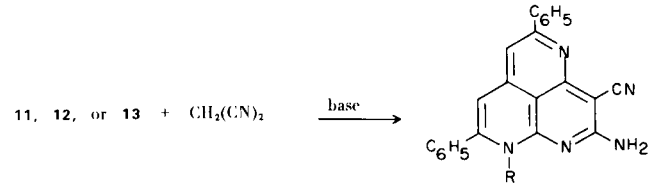


1

11 (R = $(CH_3)_2CH$)
12 (R = cyclohexyl)
13 (R = $(CH_3)_2N$)

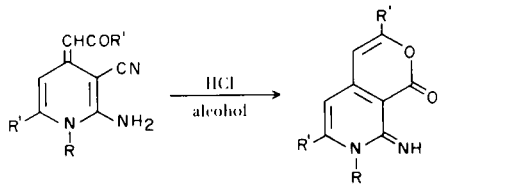
Compounds **11**, **12** and **13** reacted with malononitrile in basic media to give the polynuclear heterocyclic compounds **14**, **15** and **16** (Scheme III), as has been described for similar compounds (1). However, the reactions of **5** and **6** with malononitrile are more complex (see Scheme IV) since mixtures of products were obtained, and the reaction conditions affect the nature of the products. Under basic conditions, **5** reacted with malononitrile to give about 20% each of the isomers **17** and **18** and 45% of the rearranged product **7**. Under Knoevenagel conditions, the major product was **7** along with about 20% of **17**. Malononitrile reacted with **6** under basic conditions and Knoevenagel conditions to give **19** and the rearranged product **8**. The malonylidene derivatives **17** and **19** were heated with malononitrile and diisopropylethylamine in pyridine for 20 hours and gave the polycyclic compounds **18** and **20**. It is assumed that **17** and **19** add an additional mole of malononitrile to the nitrile group in the 3-position, followed by cyclization, with the elimination of malononitrile to give **18** or **20**.

SCHEME III



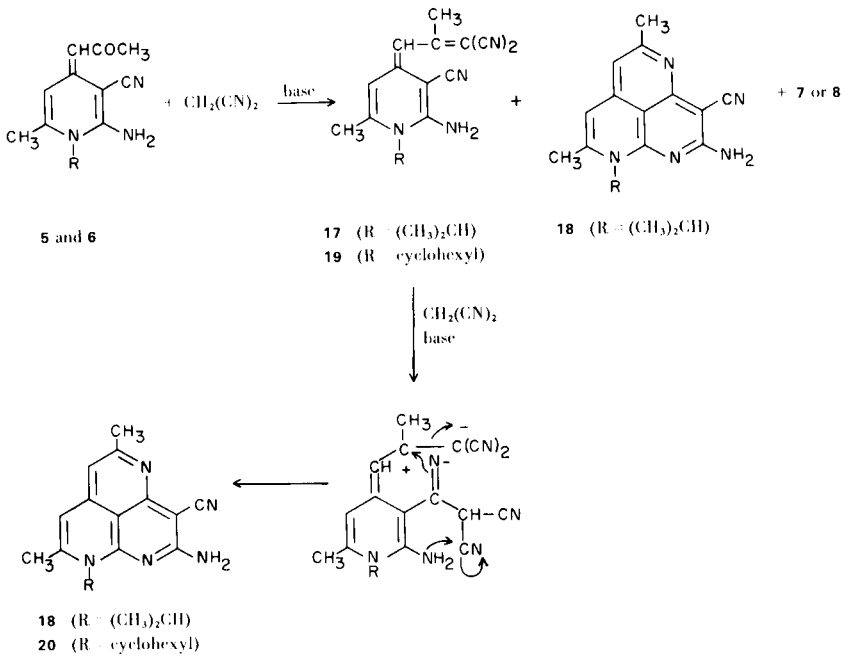
14 (R = $(CH_3)_2CH$)
15 (R = cyclohexyl)
16 (R = $(CH_3)_2N$)

SCHEME V



21 (R = cyclohexyl; R' = CH_3)
22 (R = $(CH_3)_2CH$; R' = C_6H_5)
23 (R = cyclohexyl; R' = C_6H_5)
24 (R = $(CH_3)_2N$; R' = C_6H_5)

SCHEME IV



18 (R = $(CH_3)_2CH$)
20 (R = cyclohexyl)

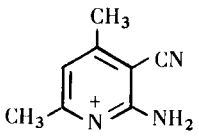
TABLE I

Physical Properties and Methods of Preparation

Cmpd. No.	Method of prep.	M.p., °C	Yield, %	Empirical formula	Anal. Calcd./found C	H	N	Solvent for crystallization	Absorption spectrum, λ max nm (ε x 10^{-3})	
5	A-4	200-201	92	$C_{13}H_{17}N_3O$	67.5 67.8	7.4 7.7	18.2 18.1	acetonitrile	238 (14.3) 274 (10.0)	363 (21.0)
6	A-4	217-219	81	$C_{16}H_{21}N_3O$	70.8 70.8	7.8 7.5	15.5 15.3	acetonitrile	240 (12.8) 273 (8.4)	365 (23.0)
7	A-3 B-1 C F	289-290	42 45 60 92	$C_{13}H_{15}N_3$	73.2 73.5	7.1 7.1	19.7 19.8	DMF	244 (8.7)	360 (43.0)
8	B-1 C F	339-340	49 32 95	$C_{16}H_{19}N_3$	75.8 75.7	7.6 7.8	16.6 16.8	DMF	248 (9.0)	360 (44.0)
9	A-3	68-69	31	$C_{11}H_{15}N_3$	69.8 70.2	8.0 8.1	22.2 22.4	ligroin (b.p. 63-75°)	261 (6.1)	390 (4.8)
11	A-1	197-198	83	$C_{23}H_{21}N_3O$	77.7 77.7	6.0 5.8	11.8 11.9	acetonitrile	245 (17.0) 275 (11.0)	355 (9.4) 405 (29.0)
12	A-1	254-256	75	$C_{26}H_{25}N_3O$	79.0 78.7	6.4 6.3	10.6 10.7	DMF	245 (23.2) 280 (14.4)	350 (11.9) 413 (35.0)
13	A-2	180-183	42	$C_{22}H_{20}N_4O$	74.1 74.2	5.7 5.5	15.7 15.5	acetonitrile	242 (20.2) 294 (12.0)	340 (9.2) 412 (32.0)
14	B-2 C	307-308	51 43	$C_{26}H_{21}N_5$	77.4 77.2	5.3 5.4	17.4 17.6	1,2,3-trichloropropane	240 (41.0) 270 (50.0) 352 (7.0)	405 (13.2) 425 (13.0)
15	B-2 C	360-361	74 49	$C_{29}H_{25}N_5$	78.5 78.4	5.7 5.8	15.8 15.7	pyridine		
16	B-2 C	235-236 (dec.)	70 47	$C_{25}H_{20}N_6$	74.2 74.2	5.0 4.8	20.8 20.7	alcohol		
17	B-1 C D	305-307	22 20 64	$C_{16}H_{17}N_5$	68.8 68.5	6.1 6.4	25.1 24.9	chloroform	238 (16.4) 311 (9.2) 360 (3.7)	~460 (49.0) 477 (67.3)
18	B-1 D	321-322	22 81	$C_{16}H_{17}N_5$	68.8 68.6	6.1 6.0	25.1 25.4	pyridine	217 (16.5) 288 (15.0)	321 (8.0) 398 (25.0)
19	B-1 C	305-306	15 55	$C_{19}H_{21}N_5$	71.4 71.4	6.6 6.5	21.9 21.8	DMF	238 (16.0) 310 (9.1) 360 (3.5)	~460 (48.7) 480 (67.0)
20	D	318-319	89	$C_{19}H_{21}N_5$	71.4 71.1	6.6 6.4	21.9 21.6	1,2,3-trichloropropane	220 (16.0) 288 (14.7)	322 (8.0) 402 (25.0)
21	E	149-150	67	$C_{16}H_{20}N_2O_2$	70.5 70.2	7.4 7.5	10.3 10.3	benzene		
22	E	207-208	78	$C_{23}H_{20}N_2O_2$	77.5 77.3	5.7 5.9	7.9 7.7	benzene	250 (22.4) 310 (23.6)	345 (26.0) 435 (7.2)
23	E	190-191	86	$C_{26}H_{24}N_2O_2$	78.8 79.1	6.1 6.1	7.1 7.4	pyridine + water	250 (24.0) 308 (25.0)	345 (29.0) 438 (7.4)
24	E	191-192	83	$C_{22}H_{19}N_3O_2$	74.0 73.8	5.4 5.6	11.8 11.7	toluene		

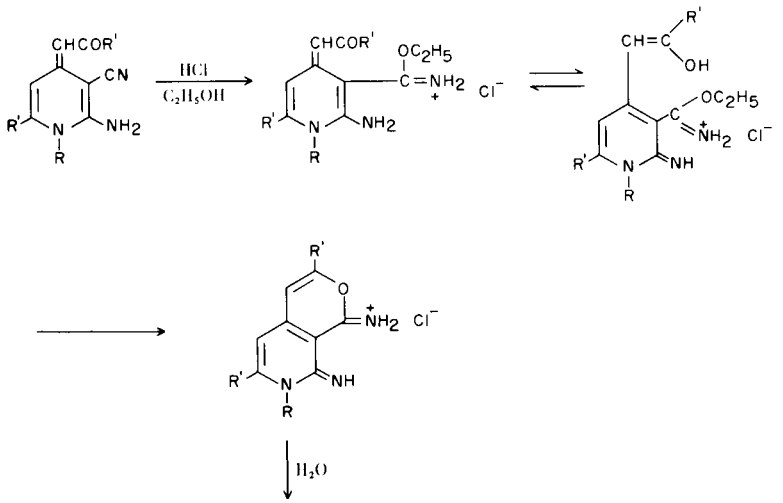
TABLE II

Important Mass Spectral Ions (a)

Compound number	Mass	Assignment	Relative intensity, %
6	271	M^+	16.0
	256	M-CH_3	5.0
	228	M-CH_3CO	4.3
	189	M-C_6H_{11}	64.0
	147	189-CH_2CO	100.0
11	355	M^+	6.7
	354	M-H	13.6
	313	M-C_3H_6	6.0
	105	C_6H_5CO	100.0
8	253	M^+	33.0
	171	M-C_6H_{10}	100.0
	83	C_6H_{11}	94.0
14	403	M^+	50.0
	361	M-C_3H_6	100.0
17	279	M^+	17.0
	264	M-CH_3	25.0
	237	M-C_3H_6	100.0
	147		70.0
23	396	M^+	5.0
	395	M-H	10.0
	314	M-C_6H_{10}	100.0

(a) Only one example of each class is shown, since the compounds followed a consistent pattern by class.

Compounds **6**, **11**, **12** and **13** undergo cyclization reactions on treatment with hydrochloric acid in alcohol to give the lactone derivatives **21**, **22**, **23** and **24** (Scheme V). This reaction seems to be general for acylidene groups that are adjacent to a cyano group (1). Compound **5** was an exception, since under these conditions it rearranged to the more stable isomer **7**. Lactone formation occurs under mild conditions, and it is a reasonable postulate that an intermediate imino ether was formed which underwent cyclization and hydrolysis to give the lactone as shown below.



No reaction took place when **1** and **2** were treated with *t*-butylamine, presumably because of the steric bulk of the amine, which prevented nucleophilic attack at the 2-position of the pyran.

EXPERIMENTAL (3)

The methods for the preparation of the compounds are described as general procedures and the data are collected in Table I. The mass spectral data are found in Table II.

General Procedures.

A-1. A mixture of 0.02 mole of the dicyanomethylene compounds **1** and **2**, 15 ml. of the amine and 70 ml. of alcohol was refluxed overnight. The mixture was chilled and the solid was collected.

A-2. The procedure was as described for A-1, but without the alcohol.

A-3. The mixture described in A-1 was heated in an autoclave at 150° for 7 hours.

A-4. The reaction was carried out as described in A-1 except the heating period was 45 minutes.

B-1. A mixture of 0.01 mole of the ketones **5** or **6**, 1 g. of malononitrile, 1 ml. of diisopropylethylamine and 25 ml. of pyridine was refluxed for 2 hours and chilled. The solid that separated was extracted three times with hot chloroform to remove **7** or **8**. The insoluble material (in the case of **5**) was **18**. The pyridine solution was diluted with water giving **17** or **19**.

B-2. A mixture of 0.01 mole of **11**, **12** or **13**, 1 g. of malononitrile, 1 ml. of diisopropylethylamine and 25 ml. of pyridine was refluxed overnight, diluted with water, and the solid was collected.

C. A mixture of 0.01 mole of **5**, **6**, **11**, **12** or **13**, 1 g. of malononitrile, 0.8 g. of ammonium acetate and 75 ml. of chloroform was refluxed for 4 hours using a water separator. The solution was chilled and the solid collected.

D. A mixture of 1 g. of **17** or **19**, 0.4 g. of malononitrile, 0.4 ml. of diisopropylethylamine and 20 ml. of pyridine was refluxed overnight, diluted with water, and the solid was collected.

E. A mixture of 0.01 mole of **5**, **6**, **11**, **12** or **13**, 30 ml. of alcohol and 12 ml. of concentrated hydrochloric acid was refluxed for 15 minutes and poured into water. The mixture was made basic with ammonium hydroxide and the solid was collected.

F. Compound **5** or **6** was refluxed in acetonitrile, dimethylformamide, or pyridine for 8 hours.

Acknowledgments.

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REFERENCES

(1) J. A. VanAllan, G. A. Reynolds, C. C. Petropoulos and D. P. Maier, *J. Heterocyclic Chem.*, 7, 495 (1970).

(2) H. Kato, T. Ogawa and M. Ohta, *Bull. Chem. Soc. Japan*, 33, 1468 (1960).

(3) The electronic spectra were determined in acetonitrile with a Cary Model 15 spectrophotometer. The mass spectra were measured using a Consolidated Electrodynamics Model 21-110B instrument. The nmr data are not reported since they are in complete agreement with the values reported for similar compounds (1).