ACETALS OF LACTAMS AND ACID AMIDES.

39.* SYNTHESIS OF THREE-RING DERIVATIVES OF PYRIDO[1,2-a]PYRIMIDINES ON THE BASIS OF THE REACTION OF DIMETHYLFORMAMIDE ACETAL WITH DICYANOMETHYLENECYCLOALKANES

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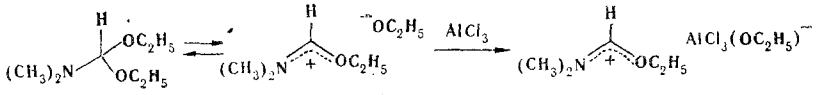
The reaction of dicyanomethylenecyclopentane and -cyclohexane with dimethylformamide diethylacetal was used to synthesize dieneamino nitriles, from which isoquinoline and 2-pyridine derivatives were obtained by treatment with ammonia. The reaction of 3-aminopyridine and 3-aminoisoquinoline derivatives with ethoxymethylenemalonic ester leads to pyrimido[1,2-b]isoquinoline and -2-pyrindene derivatives.

Enamino amides and enamino dinitriles are key compounds in the synthesis of condensed pyridine systems, including 2-aminopyridine derivatives [2]. Inasmuch as the latter can be used to obtain biologically active compounds, in the present research we studied new methods for the synthesis of 2-pyrindene and isoquinoline derivatives with oxo and amino groups in the α position of the pyridine ring. On the basis of the amino derivatives obtained we synthesized three-ring systems that contain a pyrido[1,2-a]pyrimidine fragment.

Dicyanomethylene- and cyanocarbamidomethylenecyclopentanes (Ia, IIa) and -cyclohexanes (Ib, IIb), which were obtained by reaction of the corresponding cyclic ketones with malonitrile and cyanoacetamide [3, 4], were selected as the starting compounds for the preparation of 2-pyrindene and isoquinoline derivatives. The condensation of dinitriles Ia, b does not proceed sufficiently smoothly, and the reactions (particularly for Ia) are accompanied by side processes, and the reaction products are markedly contaminated, which hinders their isolation in pure form. However, the use of aluminum chloride as a catalyst makes it possible to substantially increase the yields and quality of the final products. The use of Lewis acids for the activation of acetals of aldehydes and ketones has been described extensively [5], but, as far as we know, they have not been previously used in reactions of amide acetals. The catalytic effect evidently consists essentially in coordination of the Lewis acid with the alkoxide anion, thereby increasing the concentration of ambident cation A in the equilibrium mixture:



A

The dieneamino nitriles obtained (IVa, b) were treated with an alcohol solution of ammonia, as a result of which they underwent smooth transamination with subsequent cyclization at one of the cyano groups to give 3-amino-4-cyano-5,6-dihydro-7H-2-pyrindene (Va) and 3-amino-4-cyano-5,6,7,8-tetrahydroisoquinoline (Vb).†

The synthesized two-ring pyridines Va, b are good models for the examination of the dependence of the basicity on the size of the saturated ring (see [7]). It might be assumed

*See [1] for Communication 38.
†A similar scheme was previously [6] used for the synthesis of Vb, but orthoformic ester, rather than acetal III, was used.

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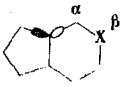
that, as in the case of simpler 2-aminopyridines [8], protonation of Va, b would take place at the ring nitrogen atom. We found that the pK_a values for Va, b in 50% alcohol are, respectively, 3.52 ± 0.04 and 3.19 ± 0.06, i.e., the pyrindene derivative is more basic than the isoquinoline derivative. These data are in agreement with the results in [9], in which the increased basicities of pyridines of this type, which are condensed with a five-membered ring, are ascribed to better stabilization of the positive charge on the pyridinium nitrogen atom in the protonated form in these compounds. Thummel and Kohli [9] assume that this stabilization is due to electron enrichment of the adjacent α-carbon atom of the pyridine ring. This point of view, however, disagrees with the concept in [10, 11], which is presently confirmed by voluminous experimental data [7]. According to this concept, the orbital directed from the aromatic ring to the condensed strained ring (blackened in the scheme) has increased p character. Consequently, the orbital directed to the α position of the aromatic ring has increased s character, which leads to an increase in its electron-acceptor properties and a decrease in the reactivity of the α position with respect to electrophilic reagents.



The results obtained in [9] and our results may be explained as follows: The orbital directed from the α position to the bridge carbon atom (when a condensed strained ring is present) also has increased s character (and increased p character relative to the β position), as a result of which, there is an increase in the electron density in the β position, and 2-pyrindene derivatives consequently have greater basicities than hydrogenated isoquinoline derivatives. If this is true, the Mills–Nixon effect [12] is due not only to a decrease in the reactivity of the α position of the aromatic ring annelated with a strained ring (with respect to electrophiles) but also to an increase in the reactivity of the β position. Condensation, which is not accompanied by pyrimidine cyclization, takes place when 2-aminopyridine derivatives Va, b are heated moderately with ethoxymethylenemalonic ester, and the corresponding N-hetaryleneamines VIa, b were isolated in high yields. Of the various methods for the cyclization of enamines of this type, heating in diphenyl oxide, which was also used for VIb, is the most widely employed method. In the case of VIa, however, this method did not give good results, and cyclization takes place to a better degree when VIa is heated in the presence of concentrated H_2SO_4. As a result, we synthesized pyrimido[1,2-b]-2-pyrindene (VIIa) and -isoquinoline (VIIb) derivatives.

In conclusion, we established that 2-pyrinden-3-one and isoquinol-3-one derivatives can also be obtained by a method similar to that used for the synthesis of Va, b. Thus 4-cyano-2,3,5,6-tetrahydro-7H-2-pyrinden-3-one (VIIIa) and 4-cyano-2,3,5,6,7,8-hexahydroisoquinolone (VIIIb) are formed from amides IIa, b and acetal III.

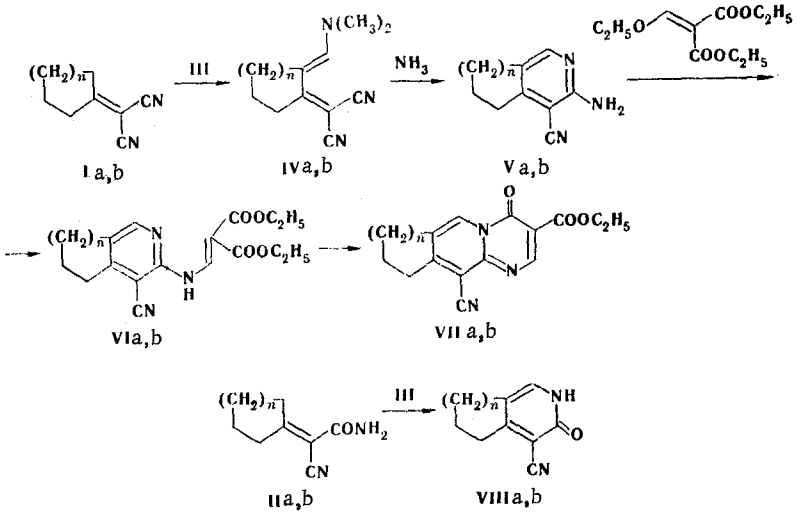


TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C (solvent)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IVa	136—137 (benzene – hexane)	70,8	6,6	22,5	$C_{11}H_{13}N_3$	70,6	7,0	22,4	55
IVb	126,5—127,5 (benzene – hexane)	71,9	7,9	20,7	$C_{12}H_{15}N_3$	71,6	7,5	20,9	75
Va	186—186,5 (sublimation)	68,2	5,7	26,7	$C_9H_9N_3$	67,9	5,7	26,4	60
Vb	152—154 (alcohol)	69,3	6,3	24,6	$C_{10}H_{11}N_3$	69,3	6,4	24,3	65
VIa	163—165 (alcohol)	62,1	5,8	13,0	$C_{17}H_{19}N_3O_4$	62,0	5,8	12,9	90
VIb	146—147 (alcohol)	63,0	6,0	12,3	$C_{18}H_{21}N_3O_4$	63,0	6,2	12,2	82
VIIa	183—185 (dec., pyridine – hexane)	63,5	4,5	14,4	$C_{15}H_{13}N_3O_3$	63,6	4,6	14,8	60
VIIb	159—161 (abs. alcohol)	64,2	5,0	14,3	$C_{16}H_{15}N_3O_3$	64,6	5,1	14,1	75
VIIIa	225—226 (sublimation)	67,7	5,0	17,8	$C_9H_8N_2O$	67,5	5,0	17,5	85
VIIIb	288—290 (dec., abs. alcohol)	68,9	5,8	16,1	$C_{10}H_{10}N_2O$	69,1	5,5	16,5	87

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Tesla BS-407 spectrometer (100 MHz) with hexamethyldisiloxane as the internal standard. The melting points were determined with a Boetius apparatus.

The individuality of all of the compounds obtained was confirmed chromatographically in a thin layer of Silufol UV-254.

1-Dicyanomethylene-2-N,N-dimethylaminomethylenecyclopentane (IVa) and 1-Dicyanomethylene-2-N,N-dimethylaminomethylenecyclohexane (IVb). A 25-ml sample of 80% acetal (0.15 mole) was added dropwise at 50°C to a mixture of 15 ml (0.1 mole) of Ia and 1.3 g (0.01 mole) of $AlCl_3$ in 50 ml of dry benzene, and the mixture was refluxed for 30 min. The benzene was removed by distillation, and the residue was recrystallized from benzene–hexane to give 10.3 g of IVa. PMR spectrum ($CDCl_3$): 1.64-1.90 (2H, m, 4-H), 2.62-2.86 (4H, q, 3- and 5-H), 3.18 (6H, s, NMe_2), and 8.15 ppm (1H, 2, =CH).

The constants, yields, and results of microanalysis of the synthesized compounds are presented in Table 1.

Compound IVb was synthesized by a similar method. PMR spectrum ($CDCl_3$): 1.5-1.68 (4H, m, 4- and 5-H), 2.36-2.6 (4H, m, 3- and 6-H), 3.14 (6H, s, NMe_2), and 7.3 ppm (1H, s, =CH).

3-Amino-4-cyano-5,6-dihydro-7H-2-pyrindene (Va) and 3-Amino-4-cyano-5,6,7,8-tetrahydroisoquinoline (Vb). A mixture of 3 g (0.015 mole) of dieneamine IVa and 10 ml of a 10% alcohol solution of ammonia was heated at 130°C for 1 h, after which it was cooled, and 1.5 g of Va was removed by filtration. PMR spectrum (CF_3COOH): 1.74-2.05 (2H, m, 6-H), 2.6 (2H, t, J = 8 Hz, 7-H), 2.84 (2H, t, J = 8 Hz, 5-H), and 7.5 ppm (1H, s, 1-H).

Compound Vb was similarly obtained. PMR spectrum (CF_3COOH): 1.38-1.64 (4H, m, 6- and 7-H), 2.28-2.4 (2H, m, 8-H), 2.6-2.72 (2H, m, 5-H), and 7.46 ppm (1H, s, 1-H).

3-(N-β-Dicarbethoxyvinyl)amino-4-cyano-5,6-dihydro-7H-2-pyrindene (VIa) and 3-(N-β-Dicarbethoxyvinyl)amino-4-cyano-5,6,7,8-tetrahydroisoquinoline (VIb). A mixture of 16 g (0.1 mole) of aminopyrindene Va and 30 ml of ethoxymethylenemalonic ester was heated at 150°C for 30 min, after which it was cooled to 50°C, and 30 ml of alcohol was added with stirring. The precipitated VIa was removed by filtration. IR spectrum: 1680 (C=O) and 2220 cm^{-1} (CN). PMR spectrum ($CDCl_3$): 1.12-1.43 (5H, m, 2-CH_3), 2.15-2.33 (2H, m, 6-H), 2.86-3.13 (4H, m, 5- and 7-H), 4.14-4.45 (4H, m, 2-OCH_2), 8.3 (1H, s, 1-H), 9.15 (1H, d, J = 12 Hz, vinyl CH), and 12.3 ppm (1H, d, J = 12 Hz, NH).

Compound VIb was similarly obtained. IR spectrum: 1700 (C=O) and 2220 cm^{-1} (CN). PMR spectrum ($CDCl_3$): 1.25-1.43 (6H, m, 2-CH_3), 1.83-1.86 (4H, m, 6- and 7-H), 2.71 and 2.89 (4H, d, J = 18 Hz, 5- and 8-H), 4.14-4.46 (4H, m, 2-OCH_2), 8.21 (1H, s, 1-H), 9.15 (1H, d, J = 12 Hz, vinyl CH), and 12.2 ppm (1H, d, J = 12 Hz, NH).

3-Carbethoxy-4-oxo-10-cyano-4,5,8,9-tetrahydropyrimido[1,2-b]-7H-2-pyrindene (VIIa). A 4-ml sample of concentrated H_2SO_4 was added at 20°C to a suspension of 3.29 g of enamine VIa in 10 g of acetic anhydride, after which the mixture was maintained at 90°C for 1 h. It was then cooled to 20°C and diluted with water (while cooling to 10-20°C), and the aqueous

mixture was made alkaline to pH 9 with NH_4OH. The mixture was filtered to give 1.7 g of VIIa. IR spectrum: 1720, 1745 (C=O); 2230 cm^{-1} (CN). PMR spectrum ($CDCl_3$): 1.26-1.40 (3H, t, J = 7 Hz, CH_3), 2.13-2.43 (2H, m, 8-H), 3.25-3.34 (4H, m, 7- and 9-H), 4.23-4.44 (2H, q, J = 7 Hz, OCH_2), 8.97 (1H, s, 2-H), and 9.11 ppm (1H, s, 6-H).

3-Carbethoxy-4-oxo-11-cyano-4,5,7,8,9,10-hexahydropyrimido[1,2-b]isoquinoline (VIIb). A 3.43-g (0.01 mole) sample of enamine VIb was added to diphenyl oxide heated to 180°C, and the mixture was maintained at 180°C for 3 h. It was then cooled rapidly and poured into cold hexane, and VIIb was removed by filtration. IR spectrum: 1720, 1750 (C=O); 2235 cm^{-1} (CN). PMR spectrum ($CDCl_3$): 1.30-1.44 (3H, t, J = 7 Hz, CH_3), 1.92-1.98 (4H, m, 8- and 9-H), 2.88-3.02 (2H, m, 10-H), 3.13-3.24 (2H, m, 7-H), 4.26-4.48 (2H, q, J = 7 Hz, OCH_2), 9.02 (1H, s, 2-H), and 9.11 ppm (1H, s, 6-H).

4-Cyano-2,3,5,6-tetrahydro-7H-2-pyrinden-3-one (VIIIa) and 4-Cyano-2,3,5,6,7,8-hexahydroisoquinol-3-one (VIIIb). A mixture of 15 g (0.1 mole) of amide IIa and 20 ml (0.12 mole) of 80% acetal III in 50 ml of benzene was refluxed for 3 h, after which the benzene was removed by distillation, and 20 ml of water was added to the residue. The mixture was filtered to give 12.8 g of VIIIa. IR spectrum: 1660 (C=O) and 2230 cm^{-1} (CN). PMR spectrum (d_5-pyridine): 1.56-1.86 (2H, m, 6-H), 2.40 (2H, t, J = 8 Hz, 7-H), 2.67 (2H, t, J = 8 Hz, 5-H), 7.36 (1H, s, 1-H), and 12.0 ppm (1H, broad s, NH).

Compound VIIIb was similarly obtained. IR spectrum: 1650 (C=O) and 2230 cm^{-1} (CN). PMR spectrum (d_5-pyridine): 1.33-1.54 (4H, m, 6- and 7-H), 2.24 (2H, t, J = 6 Hz, 5-H), 2.6 (2H, t, J = 6 Hz, 8-H), 7.41 (1H, s, 1-H), and 11.5 ppm (1H, broad s, NH).

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