LACTAMS OF ACETALS AND ACID AMIDES.

45.* SYNTHESIS OF CONDENSED 2-PYRIDONES FROM ACTIVATED AMIDES, LACTAMS, AND LACTONES

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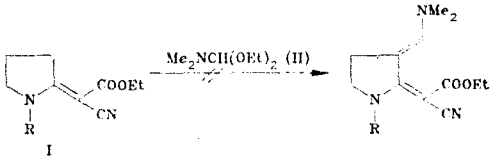
By reaction of lactim ethers with N-substituted cyanoacetamides, the corresponding enaminoamides were obtained, cyclization of which by dimethylformamide acetal gave derivatives of pyrrolo[3,2-c]pyridine, 1,6-naphthyridine, and pyrido[4,3-b]azepine, having a substituent at the nitrogen atom of the pyridone ring. N-substituted furo[3,2-c]pyridines were synthesized from the diethyl acetals of butyrolactone and 3-(dimethylaminomethylene)butyrolactone and dimethylformamide acetal.

It is known that secondary and tertiary enaminoamides can be readily converted into condensed 2-pyridones, unsubstituted at the nitrogen atom of the pyridone ring [1, 2]. The problem of obtaining N-substituted pyridones is more complicated. The difficulties arising in this case are due to the fact that the corresponding starting compounds cannot always be obtained, for example the enaminoester I cannot be reacted with dimethylformamide diethyl acetal (II), while a direct alkylation (in the case of N-aryl derivatives) of condensed 2-pyridones often leads to the preparation of O- and not N-derivatives [3, 4].



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Therefore, in the present work, we made an attempt to carry out an unequivocal synthesis of N-alkyl(aryl)derivatives of 2-pyridone, condensed with pyrrolidine, piperidine, and hexahydroazepine rings. By reaction of O-methylbutyro- (IIIa), valero- (IIIb), and caprolactams (IIIc) with N-phenyl- (IVa) and N-benzylcyanoacetamides (IVb), N-substituted enaminoamides Va-f were obtained, which were further condensed with acetal II. Under the same conditions — on boiling in xylene — a distinct difference is observed between enaminoamides with five (Va,b) and six-membered rings (Vc,d): In the case of the former it is possible to isolate substituted diene-diamines VIa,b, while in the case of the latter a further cyclization is observed with the formation of 1,6-naphthyridine derivatives VIIa,b. Hexahydroazepine derivatives occupy an intermediate position and in order to prepare the individual compounds, the condensation with acetal II was carried out at a higher temperature with the intermediate formation of pyridoazepines VIIc,d. Heating of diene-diamide VIb in DMFA gives 5-benzyl-7-cyano-2,3-dihydropyrrolo[3,2-c]pyrid-6-one (VIII).

Synthesis of compounds having sterically converging enamine and carbamide functions (as in VIa,b), can be carried out not only from activated lactams, but also by using activated lactones as starting compounds [5]. We therefore synthesized the N-substituted furo[3,2-c]-pyridones (IXa,b) in the present work, and carried out a comparison of the two possible paths of their preparation from butyrolactone (X).

3-Dimethylaminomethylenebutyrolactone diethyl acetal (XI), obtained from enaminolactone XII [6, 7] by the method in [6], reacts smoothly with amides IVa,b with the formation of diene-aminoamides XIIIa,b. Cyclization of the latter with heating in acetic acid leads to N-benzyl- and N-phenylfuro[3,2-c]pyridones (IXa,b). For comparison, N-phenylamide XIV was

*For communication 44, see [1].

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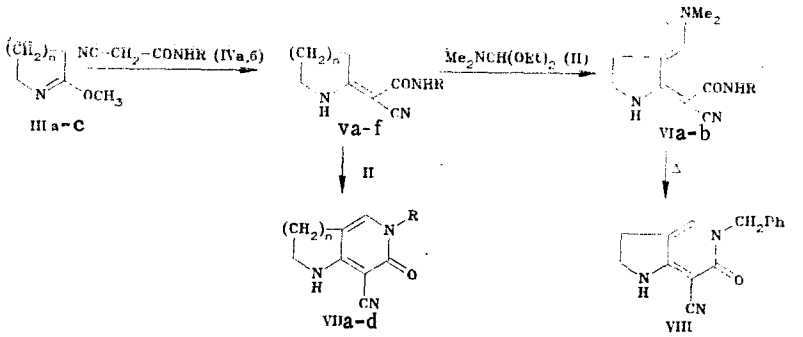
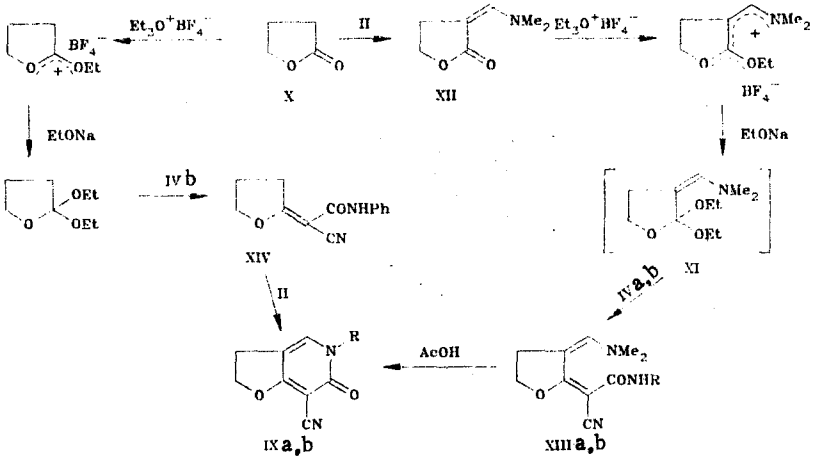


IV—VI a R=Ph, n=1; b R=CH_2Ph, n=1; Vc, VIIa R=Ph, n=2; Vd, VIIb R=CH_2Ph, n=2; Ve, VIIc R=Ph, n=3; Vf, VIId R=CH_2Ph, n=3

prepared from butyrolactone diethyl acetal [5] and N-phenylcyanoacetamide (IVa). On heating, compound IVa condenses with acetal II and a cyclization with the formation of compound IXa is immediately observed; however, in this case, the yield is much lower than when enaminolactone XII is used as the starting compound.



IX, XIII a R=Ph; b R=CH_2Ph

Thus, by a combined use of lactim ethers or lactone acetals with amide acetals (exemplified by the use of dimethylformamide diethyl acetal) it was possible to develop preparatively suitable methods of synthesis of different condensed 2-pyridones having substituents attached to the pyridone nitrogen atom.

EXPERIMENTAL

The mass spectra were obtained on a Varian MAT-112 spectrometer with direct introduction of the sample into the ion source. The temperature of the ionization chamber was 180°C and the energy of the ionizing electrons 70 eV. The melting points were determined on a Boetius-type heating block.

The characteristics of the compounds synthesized are given in Table 1.

2-(2-N-Phenylcarbamido-2-cyano)methylenepyrrolidine (Va). A mixture of 3.5 g (22 mmoles) of N-phenylcyanoacetamide IVa and 7 ml of O-methylbutyrolactim in 40 ml of DMFA is boiled for 3 h. It is then evaporated, the residue is ground with ether, and 3.3 g of compound Va are filtered off.

Derivatives of tetrahydropyrrolidine, hexahydropyridine, and hexahydroazepine Vb-f were obtained in a similar way.

2-(2-N-Phenylcarbamido-2-cyano)methylene-3-N',N'-dimethylaminomethylenepyrrolidine (VIa). A mixture of 4.1 g (18 mmoles) of compound Va, 20 ml of 70% acetal II, and 25 ml of dry xylene is boiled for 7 h, then evaporated, the residue is ground with ethyl acetate, and 3 g of compound VIa are filtered off.

TABLE 1. Characteristics of Compounds V-IX, XIII, XIV

Compound	Mp,* °C	M+	Found, %			Empirical formula	Calculated, %			Yield, % (method)
			C	H	N		C	H	N	
Va	164—166	227	68,8	5,8	18,6	$C_{13}H_{13}N_3O$	68,7	5,7	18,5	67
Vb	170—172	241	69,7	6,3	17,4	$C_{14}H_{15}N_3O$	69,7	6,2	17,4	70
Vc	174—176	241	69,9	6,1	17,6	$C_{14}H_{15}N_3O$	69,7	6,2	17,4	66
Vd	141—143	255	70,6	6,7	16,4	$C_{15}H_{17}N_3O$	70,6	6,7	16,5	75
Ve	162—164	255	70,8	6,5	16,5	$C_{15}H_{17}N_3O$	70,6	6,7	16,5	63
Vf	138—140	269	71,1	7,0	15,4	$C_{16}H_{19}N_3O$	71,4	7,1	15,6	97
VIa	211—213	282	68,2	6,3	19,9	$C_{16}H_{18}N_4O$	68,1	6,4	19,9	59
VIb	135—140	296	68,7	6,7	18,7	$C_{17}H_{20}N_4O$	68,9	6,8	18,9	59
VIIa	217—219	251	71,5	5,3	16,6	$C_{15}H_{13}N_3O$	71,7	5,2	16,7	67
VIIb	218—220	265	72,3	5,8	15,9	$C_{16}H_{15}N_3O$	72,5	5,7	15,9	14
VIIc	207—209	265	72,3	5,8	15,9	$C_{16}H_{15}N_3O$	72,5	5,7	15,9	88
VIId	188—190	279	73,2	6,1	15,0	$C_{17}H_{17}N_3O$	73,1	6,1	15,1	68
VIII	264—266	251	71,6	5,2	17,0	$C_{15}H_{13}N_3O$	71,7	5,2	16,7	83
IXa	240—242	238	70,7	4,2	11,9	$C_{14}H_{10}N_2O_2$	70,6	4,2	11,8	60 (A); 19 (B)
IXb	148—150	252	71,4	4,8	10,9	$C_{15}H_{12}N_2O_2$	71,4	4,8	11,1	24
XIIIa	252—254	283	67,8	6,2	14,9	$C_{16}H_{17}N_3O_2$	67,8	6,0	14,8	98
XIV	153—155	228	68,5	5,3	12,4	$C_{13}H_{12}N_2O_2$	68,4	5,3	12,3	70

*Compounds Va,b,e,f, VIa,b, VIIa-d were crystallized from isopropanol; Vc,d and VIII from ethanol; IXa,b and XIV from ethyl acetate; XIIIa from DMFA.

Diene-diamine VIb is obtained in a similar way.

5-Benzyl-6-oxo-7-cyano-2,3,5,6-tetrahydropyrrolo[3,2-c]pyridine (VIII). A solution of 1 g (3.3 mmoles) of compound VIb in 10 ml of DMFA is boiled for 7 h, is then evaporated, the residue is ground with ether, and 0.7 g of compound VIII is filtered off.

6-Phenyl-7-oxo-9-cyano-1,2,3,4,6,7-hexahydrol-1,6-naphthyridine (VIII). A mixture of 1 g (4.1 mmoles) of compound Vc, 5 ml of 70% acetal II, and 10 ml of dry xylene is boiled for 7 h, then cooled, and the precipitate is filtered and washed with ether to yield 0.7 g of compound VIIa.

Naphthyridone VIIb is obtained in a similar way, but on longer boiling (14 h).

7-Phenyl-8-oxo-9-cyano-1,2,3,4,7,8-hexahydropyrido[4,3-b]azepine (VIIc). A mixture of 1.2 g (4.7 mmoles) of compound Ve, 5 ml of 70% acetal II and 10 ml of DMFA is boiled for 14 h, then is evaporated, the residue is ground with ether, and 1.1 g of compound VIIc is filtered off.

Hexahydroazepinopyridine VIId is prepared in a similar way.

2-(2-N-Phenylcarbamido-2-cyanomethylene)-3-N',N'-dimethylaminomethylenetetrahydrofuran (XIIIa). A 4.2 g portion (15.5 mmoles) of a borofluoride complex is added to a solution of sodium ethylate (prepared from 0.5 g of Na and 20 ml of absolute alcohol). The reaction mixture is allowed to stand for 20 min, cooled to 15°C, and filtered. A 2.5 g portion (15.6 mmoles) of compound IVa is added to the filtrate, the mixture is left to stand for 30 min, then filtered, and the precipitate is washed with water. Yield, 4.3 g of compound XIIIa.

Tetrahydrofuran XIIIb is obtained in a similar way. Because of high solubility in water, the compound cannot be purified from the sodium salt. M^+ 297.

5-Phenyl-6-oxo-7-cyano-2,3,5,6-tetrahydrofuro[3,2-c]pyridine (IXa). A. A mixture of 1 g (4.2 mmoles) of compound XIIIa and 10 ml of glacial acetic acid is boiled for 7 h, then evaporated, the residue is washed with water, the water is decanted, the residue is ground in ether, and 0.5 g of compound IXa is filtered off.

B. A mixture of 1 g (4.4 mmoles) of compound XIV and 8 ml of 70% acetal II is boiled for 1.5 h, is then evaporated, and the residue is dissolved at the boiling point in 5 ml of DMFA, cooled, and precipitated by 10 ml of water, and the precipitate is filtered. Yield, 0.2 g of compound IXa.

Tetrahydrofuropyridine IXb is obtained in a similar way by method A.

2-(2-N-Phenylcarbamido-2-cyano)methylenetetrahydrofuran (XIV). A mixture of 1.7 g (9 mmoles) of compound IVb and 4 ml of butyrolactone acetal is boiled for 1 h, then cooled, and the precipitate is filtered and washed with alcohol. Yield, 1.3 g of compound XIV. The mother liquor is evaporated, and the residue is ground with ether. Yield, 0.4 g of compound XIV. Overall yield 1.7 g.

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STUDY OF REACTION OF 2,3,3-TRIMETHYL-3H-INDOLE WITH HALOACETIC ACID AMIDES. SYNTHESIS OF 1,2,3,9a-TETRAHYDRO-9H-IMIDAZO[1,2-a]INDOL-2-ONES

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In the reaction of 2,3,3-trimethyl-3H-indole with α-chloro- and α-iodoacetamides, 1-carbamoylmethyl-2,3,3-trimethyl-3H-indolium salts are formed, which by the action of bases convert into imidazo[1,2-a]indol-2-one and 1-carbamoyl-2-methylene-2,3-dihydroindole. The latter compound can by cyclized into imidazo[1,2-a]indol-2-one by the action of acetic acid.

The products of the reaction of 3H indoles with haloacetic acids and their derivatives have not been extensively described. Thus, the reactions of 2,3,3-trimethyl-3H-indole with α-bromoacetic acid and its ethyl ester are described in [1, 2]. In the view of the authors of [3], the cyclization products of 1-carboxymethyl derivatives of 3H-indoles are oxazolo-[3,2-a]indol-2-ones. There is a report [4] on the use of the 1-carbamoylmethyl derivatives of 3H-indoles for the synthesis of dyes, but there are no data on the preparation and structure of these compounds.

To carry out the synthesis of the new heterocyclic compounds belonging to the practically unexplored series of imidazo[1,2-a]indole derivatives, we studied the reaction of 3H-indoles Ia-c with haloacetic acid amides. The reaction of 2,3,3-trimethyl-3H-indole (Ia) with α-chloroacetamide proceeds at 100-150°C in aromatic hydrocarbons, nitrobenzene, or in the absence of solvent. The best results were obtained on heating indole Ia with an amide, at a molar ratio of 1:1.1, in the presence of a small amount of xylene at 140°C. Under these conditions, the main reaction product was 1-carbamoylmethyl-2,3,3-trimethyl-3H-indolium chloride (IIa).

The structure of chloride IIa is confirmed mostly by the presence of a singlet of the 2-CH_3 group protons at 2.45 ppm in the PMR spectrum (in CF_3COOH), which is absent on recording the spectrum in D_2O because of deutero-exchange, characteristic of 2-methyl-3-H-indolium salts [5].

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