ACETALS OF LACTAMS AND ACID AMIDES. XV*. REACTION OF ACETALS OF N,N-DIMETHYL- AND N-METHYL-N-(β-CARBETHOXYETHYL)ACETAMIDES WITH ETHYL ANTHRANILATE AND SYNTHESIS OF 4-QUINOLONE AND 4-QUINAZOLONE DERIVATIVES

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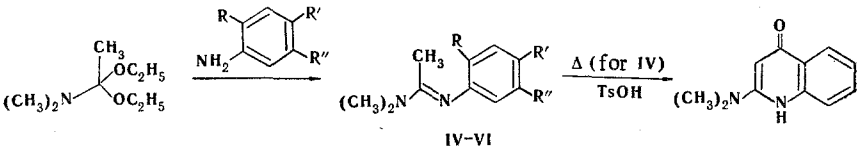
N,N-Dimethyl- and N-methyl-N-(β-carbethoxyethyl)-N^1-(o-carbethoxyphenyl)acetamidines were synthesized by reaction of diethylacetals of N,N-dimethyl- and N-methyl-N-(β-carbethoxyethyl)acetamides with ethyl anthranilate. The thermal cyclization of these amidines proceeds in different ways — 2-dimethylamino-4-quinolone is formed in the first case, and 2,3-dimethyl-4-quinazolone is formed in the second.

Amidines synthesized from acetals of lactams and ethyl anthranilate (I) are readily converted to pyrrolo-, pyrido-, and azepino [2,3-b]quinoline derivatives on heating [2]. Considering this fact, as well as the fact that, in contrast to dimethylformamide acetal, very little study [3] has been devoted to the reaction of its homologs with amines, we investigated the possibility of the synthesis of amidines based on ester I and the diethylacetals of N,N-dimethylacetamide (II) [4] and N-methyl-N-(β-carbethoxyethyl)acetamide (III). As in the case of p- and m-nitroanilines, the reaction of acetal II with ester I proceeds smoothly and gives N,N-dimethyl-N-arylacetamidines (IV-VI) in satisfactory yields. The PMR spectrum of amidine IV contains proton signals at 1.31 (Me in the COOEt group), 1.78 (C=Me), 3.03 ($N-Me_2$), 4.25 (OCH_2), and 6.75, 6.99, 7.40, and 7.74 ppm (phenyl ring). It was found that, just as in the case of N-arylimino derivatives of lactams, the $C-CH_3$ group of IV undergoes deuteration when it is allowed to stand in CD_3OD solutions, and the deuterium-exchange rate constant under first-order reaction conditions is $(9.46 \pm 1.077)\cdot 10^{-5}$ at 40°C.

Heating amidine IV in the presence of catalytic amounts of p-toluenesulfonic acid gives 2-(N,N-dimethylamino)-4-quinolone (VII) in satisfactory yield. The structure of VII was confirmed by its PMR spectrum in CF_3COOH [signals at 3.41 ($N-Me_2$), 6.48 (C_3-H), and 7.45-8.25 ppm (Ph)].



IV-VI

IV $R=COOC_2H_5$, $R'=R''=H$; V $R=R'=H$, $R''=NO_2$; VI $R=R''=H$, $R'=NO_2$

Alkylation of N-acetyl-β-alanine ethyl ester (VIII) with dimethyl sulfate gave the corresponding amino ether IX, which was converted to acetal III* by a method developed previously for lactim ethers [6]. The structure of III was confirmed by reaction with nitrometh-

*See [1] for communication XIV.

†Acetal III was previously used, without isolation, for the synthesis of 1-methyl-2-ethoxy-4-oxo-1,4,5,6-tetrahydropyridine [7].

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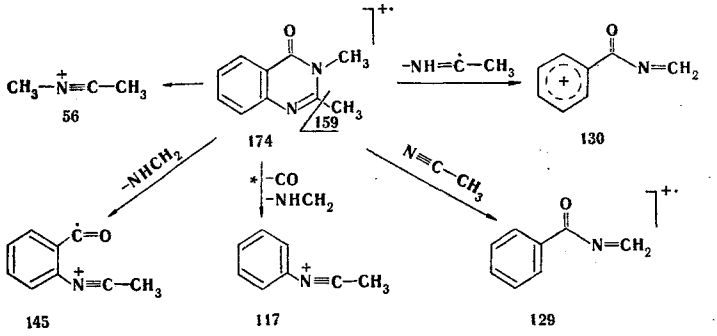
ane, which gave 1- nitro-2-methyl-2-[N-methyl-N-(β-carbethoxyethylamino)]ethylene (X). N-Methyl-N-(β-carbethoxyethyl)-N¹-(o-carbethoxyphenyl)acetamidine (XI) was synthesized by reaction of acetal III with ester I. A low-intensity molecular ion peak with a mass of 320 au is observed in the mass spectrum of this compound. Its initial fragmentation occurs with elimination of carbethoxy groups, as a consequence of which $[M - OC_2H_5\cdot]^+$ (275), $[M - COOC_2H_5\cdot]^+$ (247), and $[M - 2COOC_2H_5\cdot]^+$ (174) ion peaks are observed in the spectrum; the latter peak is the maximum-intensity peak in the spectrum. The subsequent fragmentation of this ion proceeds with the loss of methyl and ethylene fragments to give ions with m/e 159 and 146. A very intense peak with a mass of 56, to which the $CH_3\overset{+}{N}\equiv C-CH_3$ structure can be assigned, is also observed in the spectrum.

An attempt to cyclize XI in analogy with amidine IV led to unexpected results. The PMR spectra of the reaction product did not correspond either to the spectrum of the expected 2-[N-methyl-N-(β-carbethoxyethyl)amino]-4-quinolone or to the spectra of compounds that might have been formed from it by cyclization with participation of the carbethoxy group at nitrogen or the C-3 position of the quinoline ring. The PMR spectrum of XII contained singlets of C-methyl protons at 2.54 ppm (3H), of protons of a N-methyl group at 3.55 ppm (3H), and of aromatic protons at 7.24-8.17 ppm (4H). An intense molecular ion peak (m/e 174) and ion peaks with m/e 159, 145, 130, 117, and 56 are observed in the mass spectrum of this compound. All of this information made it possible to assign the 2,3-dimethyl-4-quinazolone (XIV) structure to the product; its fragmentation under the influence of electron impact can be represented by the following scheme:



The data obtained in this study show that in the case of amidine XII, cyclization is evidently accompanied by elimination of an ethyl acrylate molecule.

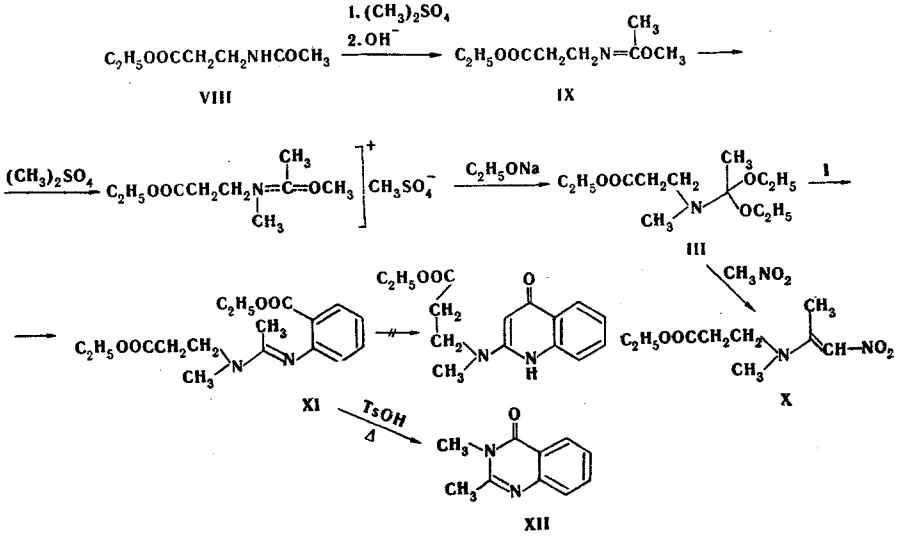


TABLE 1. Yields and Physical Constants of the Compounds Obtained

Compound	mp, °C, or bp °C (mm)	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
IV	137—145 (1—2)	$C_{13}H_{18}N_2O_2$	66,3	7,8	12,1	66,7	7,7	12,0	74,5
VI	94—95 (hexane)	$C_{10}H_{13}N_3O_2$	58,4	6,7	20,3	58,0	6,3	20,3	92,5
V	145—146 (1)	$C_{10}H_{13}N_3O_2$	58,4	6,4	19,8	58,0	6,3	20,3	86
VII	>300 (methanol)	$C_{11}H_{12}N_2O$	70,0	6,6	14,7	70,2	6,4	14,9	60
IX	63—65 (2)	$C_8H_{15}NO_3$	—	—	7,8	—	—	8,1	66
III	80—93 (3)	$C_{12}H_{25}NO_4$	58,3	9,6	—	58,3	10,1		63
X	69—70 (heptane)	$C_9H_{16}N_2O_4$	50,0	7,5	12,8	50,0	7,4	12,9	
XI	135—175 (1)								44
XII	108—110 (heptane) 108—109[8]	$C_{10}H_{10}N_2O$	68,7	5,7	15,9	69,0	5,8	16,1	

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz and tetramethylsilane as the standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the source at an ionizing voltage energy of 50 eV.

N,N-Dimethyl-N^1-(o-carbethoxyphenyl)acetamidine (IV). A mixture of 8 g (0.05 mole) of acetal II and 8.25 g (0.05 mole) of ester I was refluxed for 3 h, after which the liberated alcohol was evaporated, and the residue was fractionated.

N,N-Dimethyl-N^1-(o-nitrophenyl)acetamidine (VI). A mixture of 5 g (0.03 mole) of acetal II and 3 g (0.022 mole) of p-nitroaniline was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration.

N,N-Dimethyl-N^1-(m-nitrophenyl)acetamidine (V). A mixture of 5 g (0.03 mole) of acetal II and 3 g (0.022 mole) of m-nitroaniline in 10 ml of anhydrous benzene was refluxed for 7 h, after which the benzene and liberated alcohol were evaporated, and the residual mass was fractionated.

2-(N,N-Dimethyl)amino-4-quinolone (VII). A 40.68-g sample of amidine IV was heated at 225° in the presence of a catalytic amount of p-toluenesulfonic acid for 10 min, after which it was cooled (upon which it began to crystallize) and filtered.

Methyl N-(β-carbethoxyethyl)ethanimidate (IX). A mixture of 15.9 g (82.5 mmole) of ester VIII and 13.0 g of dimethyl sulfate was heated at 60-70° for 3 h, and the resulting complex was washed ether. Chloroform was added, and the mixture was made alkaline to pH 10 with 50% K_2CO_3 solution. The aqueous layer was extracted with chloroform, and the chloroform extract was dried with Na_2SO_4. The chloroform was evaporated, and the residue was fractionated.

N-Methyl-N-(β-carbethoxyethyl)acetamide Diethylacetal (III). A 9.4-g (74 mmole) sample of dimethyl sulfate was added to 13.8 g (74 mmole) of imino ester IX, and the mixture was heated at 40-50° for 3 h. The resulting complex was washed with anhydrous ether and added slowly to a solution of sodium ethoxide (from 1.8 g of sodium and 30 ml of absolute alcohol). The precipitate was removed by filtration, the mother liquor was vacuum evaporated, and the residue was fractionated. Addition of nitromethane to acetal III gave X.

N-Methyl-N-(β-carbethoxyethyl)-N^1-(o-carbethoxyphenyl)acetamidine (XI). A 3-g (18.2 mmole) sample of ester I was added to 4.5 g (18.2 mmole) of acetal III, and the mixture was refluxed for 3 h. The alcohol was evaporated, and the residue was fractionated.

2.3-Dimethyl-4-quinazolone (XII). A 2.5-g (7.8 mmole) sample of amidine XI was heated at 230° in the presence of a catalytic amount of p-toluenesulfonic acid for 2 h. The low-boiling products were vacuum evaporated, and the residue began to crystallize.

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SYNTHESIS OF A NEW FOURTEEN-MEMBERED MACROHETEROCYCLIC SYSTEM BY MEANS OF A SUBSTITUTED 5-CHLOROPYRAZOLE

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A new fourteen-membered macrocyclic system was obtained by template cyclization of 4-(2-bromophenylazo)-5-chloro-3-methyl-1-phenylpyrazole with 2,2'-diaminoazobenzene in an aprotic solvent in the presence of nickel acetate and potassium carbonate.

5-Chloropyrazoles containing an azo group in the 4 position have increased reactivity in nucleophilic substitution reaction [1]. It is also known that a halogen atom in the ortho position relative to the azo group in aromatic azo compounds is readily replaced by substituted amino groups when the metal template method is used [2,3]. We used these facts in the the synthesis of a new 14-membered macroheterocyclic system containing a 5,12-dihydro-1,2,3,8,9,12-hexaazatetradecyne ring starting from 4-(2-bromophenylazo)-5-chloropyrazole (I). 2,2'-Diaminoazobenzene was used as the nucleophilic reagent, and the reaction was carried out in polar aprotic solvents in the presence of nickel (II) acetate and potassium carbonate. It was established that [10,21-dihydro-3-methyl-1-phenylpyrazole[4,5-c]tribenzo[f,j,m][1,2,5,8,9,12]hexaazacyclotetradecynato(2−)N^4,N^{10},N^{15},N^{21}]nickel (II) and 5-{[2-(2-aminophenylazo)phenyl]amino-4-(2-bromophenylazo)-3-methyl-1-phenylpyrazolato}(2−)nickel (III) are formed at the very start of the reaction (III is present in relatively large amounts) in the course of the synthesis in Hexametapol (hexamethylphosphoric triamide). The amount of III subsequently gradually decreases. A somewhat different pattern is observed when the reaction is carried out in dimethylformamide (DMF): the amounts of II and III increase with time, but the amount of III does not subsequently decrease. It was established by special experiments that III is cyclized to complex III when it is heated in Hexametapol in the presence of nickel(II) acetate and potassium carbonate. This sort of process does not occur in DMF. It may be assumed that the successive replacement of chlorine and bromine and double (synchronous) nucleophilic substitution of these halogens proceed simultaneously and that double nucleophilic substitution is the only source of the macroheterocyclic system when the synthesis is carried out in DMF.

Macrocyclic chelate II is characterized by high stability, and the nickel ion is not freed under the influence of concentrated acids. Chelate III is demetallized to give free ligand IV even in dilute mineral acid.

The IR spectra of II do not contain characteristic bands in the region of the stretching vibrations of NH bonds. The IR spectrum of III has a characteristic band of NH-bond vibra-

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