LACTAM ACETALS

X.* SYNTHESIS AND SOME PROPERTIES OF 1H,1-METHYL-6-OXO-2,3,4,5,6,11-HEXAHYDROAZEPINO[2,3-b]QUINOLINE AND ITS ANALOGS

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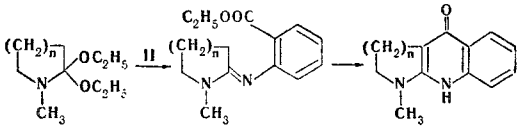
Derivatives of pyrrolo-, pyrido-, and azepino[2,3-b]quinolones were synthesized by condensation of N-methylbutyro-, N-methylvalero-, and N-methylcaprolactam diethyl acetals with ethyl anthranilate. The corresponding ethoxy derivatives were obtained by reaction of these compounds with triethyloxonium tetrafluoroborate, and condensed 4-chloroquinolines were synthesized with $POCl_3$.

It has been demonstrated [1] that the amidine grouping in various 2-arylimino derivatives of N-methyllactams activates the β position of the molecule to such an extent that the protons attached to the C_3 atom are exchanged by deuterium even under mild conditions. Although participation of the solvent is specified in the proposed [1] mechanism of deuterium exchange, one cannot exclude the possibility of thermal detachment of a proton from C_3. In this connection, 1-methyl-2-(o-carbethoxyphenylimino)hexahydroazepine (III) was synthesized by reaction of N-methylcaprolactam diethyl acetal (I) with ethyl anthranilate (II). Heating of III to 180-200°C is accompanied by intramolecular cyclization to give 1H,1-methyl-6-oxo-2,3,4,5,6-11-hexahydroazepino[2,3-b]quinoline (IVa).

In the cyclization of amidine III† in the presence of catalytic amounts of p-toluenesulfonic acid, the yield of IVa increases considerably (from 44 to 80%); this is in agreement with the concept of acid catalysis of cleavage of the C_3–H bond [1]. Derivatives IVb, c were similarly synthesized but without isolation of the intermediate amidines of the III type.



I a-c III IV a-c

I, IV a n=3; b n=2; c n=1; III n=3

Compounds IVa-c were subjected to alkylation with tertiary oxonium salts, which are usually more inclined to undergo O-alkylation reactions [2], although products of both O- and N-alkylation were isolated in the reaction of triethyloxonium tetrafluoroborate (V) with urea vinylogs [3].

Tetrafluoroborate salts (VIa and VIIa) were isolated from the reaction of IVa with tetrafluoroborate V in chloroform. The IR spectrum of salt VIa contains the absorption bands of an OH group at 3530 and

*See [1] for communication IX.

†It is not necessary to isolate intermediate amidine III (see the experimental section).

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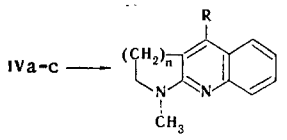
TABLE 1. PMR Spectra (ppm)

Compound	CH_2-2	CH_2-3	CH_2-4	CH_2-5	N-CH_3	H(Ar)	CH_3 (O=Et)	CH_2 (O=Et)	Solvent
IVa	3,40	1,75	1,75	2,75	3,08	7,05—8,00	—	—	d-DMSO
VIIa	3,81	1,96	1,96	2,98	3,36	7,40—8,00	1,51	4,26	d-DMSO
VIIIa	3,21	1,77	1,77	2,86	3,05	7,05—7,76	1,46	3,98	CCl_4
VIIIb	3,32	1,85	2,79	—	3,18	6,92—7,65	1,44	3,92	CCl_4
VIIIc	3,29	3,00	—	—	2,95	6,92—7,82	1,40	4,17	CCl_4

3590 cm^{-1}. Signals of a C_2H_5 group are not present in the PMR spectrum of VIa, and decomposition of it by both aqueous alkali and triethylamine in benzene gives starting IVa. Hence it is apparent that salt VIa is the tetrafluoroborate of IVa. The PMR spectrum of salt VIIa corresponds to the spectrum of the ethylation product (see Table 1). Treatment of this salt with alkali gives a compound which, according to the results of elementary analysis and the PMR spectrum, is 1H,1-methyl-6-ethoxy-2,3,4,5-tetrahydroazepino[2,3-b]-quinoline (VIIIa). An intense molecular ion peak with m/e 256 is observed in the mass spectrum of VIIIa. The characteristic path of disintegration of substances of the VIIIa type is elimination of an ethyl group from the molecular ion (to give a fragment with m/e 227) with subsequent ejection of CO, as a consequence of which a stable ion (m/e 199) with the azepino[2,3-b]indole structure [4] is formed. In addition to the metastable peaks corresponding to this scheme, the spectrum also contains characteristic (for fragmentation of the compounds with an ethoxy group) peaks of $[M-CH_3]^{\oplus}$, $[M-OC_2H_5]^{\oplus}$, and $[M-OC_2H_4]^{\oplus}$ ions.

Mixtures* of salts VIb, c and VIIb,c, which were subjected to alkaline treatment without separation, were obtained by alkylation of IVb,c. The structure of ethoxy derivatives VIIIb, c was proved by means of IR, PMR (see Tables 1 and 2), and mass spectra.



VIII, IX a-c

VIII a-c R = OC_2H_5; IXa-c R = Cl

The corresponding chloro derivatives (IXa-c) were then synthesized by reaction of oxo derivatives IVa-c with $POCl_3$. In the case of IVa, b, intermediate salts, to which the dichlorophosphate structure (IX-Xa, b) was assigned on the basis of modern concepts [5] of the structure of dimethylformamide/$POCl_3$ complexes, were isolated in this reaction.

The halogen atom in IXa-c proved to be inactive – the starting material was recovered completely even after chloro derivative IXa was heated with C_2H_5ONa in a bomb at 200-215° for 6 h. Negative results were also obtained on prolonged heating of IXa with amines at high temperatures. This deactivation of the halogen is associated with the strong-electron-donor effect of the N-methyl group in the 2 position of the quinoline ring.

All of the investigated compounds had a bacteristatic effect on microbacterium tuberculosis (15-125 μg/ml) in experiments in vitro. Substances of the azepine series (IVa and IXa) have the most pronounced antitubercular activity (15 μg/ml). Compounds Xa, b have a weak fungistatic effect with respect to Microsporom lanosum, Irichophyton gypseum, and Achorion schönleini (250-500 μg/ml), while IVa, b have a weak effect with respect to Candida albicans (250-500 μg/ml). All of the substances were inactive with respect to inducers of acute bacterial infections, except for IXa, which had a weak bacteriostatic effect with respect to gram-positive bacteria (500 μg/ml).

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil pastes were recorded with a Perkin-Elmer 457 recording spectrometer. The UV spectra of alcohol solutions (~10^{-4} M) were recorded with an EPS-3 spectrophotometer. The mass spectra were obtained with an MKh-1303 spectrometer, equipped with a direct inlet into the source, at an ionizing voltage of 50 eV.

*The formation of salts VIa-c is the result of reaction of tetrafluoroborate V with the alcohol present in the chloroform. The yield of ethoxy derivative VIIIa was 95% in the alkylation of IVa in CH_2Cl_2.

TABLE 2. Synthesized Compounds

Compound	Empirical formula	Found, %					Calculated, %					IR spectra, cm^{-1}	UV spectra	
		C	H	N	Cl	P	C	H	N	Cl	P		λ, nm	lg ε
IIIa	$C_{16}H_{22}N_2O_2$	70,0	7,9	10,0	—	—	70,1	8,0	10,2	—	—	1615 (C=N); 1710 (ester C=O, in chloroform)	310	3,5
IVa	$C_{14}H_{16}N_2O$	74,1	7,0	12,0	—	—	73,7	7,0	12,3	—	—	1580 (C=C), 1630 (amide C=O) 2500—2800 (associated NH)	228; 253; 322	4,4; 4,4; 4,2
IVa ·HCl	$C_{14}H_{16}N_2O \cdot HCl$	63,7	6,8	10,4	13,0	—	63,7	6,4	10,6	13,4	—	—	—	—
IVb	$C_{13}H_{14}N_2O$	73,2	6,7	13,0	—	—	72,9	6,5	13,1	—	—	1585 (C=C), 1630 (amide C=O) 2500—2700 (associated NH)	226; 247; 318	4,6; 4,5; 4,3
IVb ·HCl	$C_{13}H_{14}N_2O \cdot HCl$	—	—	—	13,8	—	—	—	—	14,2	—	—	—	—
IVc	$C_{12}H_{12}N_2O$	72,2	6,0	13,9	—	—	72,0	6,0	14,0	—	—	1580 (C=C), 1635 (amide C=O) 2500—2700 (associated NH)	223; 243; 320	4,5; 4,5; 4,2
VIa	$C_{14}H_{16}N_2O \cdot HBF_4$	50,2	6,0	8,1	—	—	50,3	5,7	8,4	—	—	1000—1140 ($BF_4^{\ominus}$), 1635 ($C=\overset{\oplus}{N}$), 3530 3590 (OH)	—	—
VIIa	$C_{16}H_{20}N_2O \cdot HBF_4$	55,8	6,0	8,1	—	—	55,8	6,0	8,1	—	—	1000—1140 ($BF_4^{\ominus}$), 1635 ($C=\overset{\oplus}{N}$)	—	—
VIIIa	$C_{16}H_{20}N_2O$	75,2	7,8	11,1	—	—	75,0	7,8	10,9	—	—	1615 (C=N)	255; 344	4,5; 3,7
VIIIa ·HCl	$C_{16}H_{20}N_2O \cdot HCl$	—	—	—	12,1	—	—	—	—	12,1	—	—	—	—
VIIIb	$C_{15}H_{18}N_2O$	73,9	7,4	11,6	—	—	74,4	7,4	11,6	—	—	1620 (C=N)	256; 279; 348; 360	4,6; 4,0; 3,9; 3,8
VIIIc	$C_{14}H_{16}N_2O$	73,8	7,2	12,7	—	—	73,7	7,0	12,3	—	—	1635 (C=N)	255; 276; 338	4,6; 4,0 3,8
Xb	$C_{13}H_{14}Cl_3N_2O_2P$	41,9	4,3	7,2	29,1	8,0	42,4	3,8	7,6	29,0	8,44	990 ($OPOCl_2^{\ominus}$), 1645 ($C=\overset{\oplus}{N}$)	—	—
Xa	$C_{14}H_{16}Cl_3N_2O_2P$	43,6	4,6	7,0	26,8	7,8	44,0	4,2	7,3	27,9	8,12	960 ($OPOCl_2^{\ominus}$), 1625 ($C=\overset{\oplus}{N}$)	—	—
IXa	$C_{14}H_{15}ClN_2$	68,5	5,9	11,3	14,7	—	68,2	6,1	11,3	14,4	—	1610 (C=N)	208; 258; 354	4,5; 4,9; 3,8
IXa·HCl	$C_{14}H_{15}ClN_2 \cdot HCl$	59,0	5,8	9,6	24,8	—	59,4	5,6	9,9	25,1	—	—	—	—
IXb	$C_{13}H_{13}ClN_2$	—	—	12,0	15,3	—	—	—	12,0	15,3	—	1612 (C=N)	257; 272; 282; 357;373	4,6; 4,1; 4,0; 3,9; 3,8
IXb ·HCl	$C_{13}H_{13}ClN_2 \cdot HCl$	57,9	5,2	10,5	26,5	—	58,0	5,2	10,3	26,5	—	—	—	—
IXc	$C_{12}H_{11}ClN_2$	66,3	5,1	12,8	16,2	—	66,1	5,0	12,7	16,3	—	1650 (C=N)	256; 278; 350; 366	4,5; 4,0; 3,9; 3,8

1-Methyl-2-(o-carbethoxyphenylimino)hexahydroazepine (IIa). A mixture of 12.1 g (60 mmole) of acetal Ia and 9.9 g (60 mmole) of II was heated at 50-55° for 3.5 h, after which it was evaporated and the residue was distilled to give 14.3 g (87%) of IIIc with bp 197-198° (3 mm).

1H,1-Methyl-6-oxo-2,3,4,5,6,11-hexahydroazepino[2,3-b]quinoline (IVa), 1H,1-Methyl-5-oxo-2,3,4,5,10-pentahydropyrido[2,3-b]quinoline (IVb), and 1H,1-Methyl-4-oxo-2,3,4,9-tetrahydropyrrolo[2,3-b]quinoline (IVc). A) A solution of 1.3 g (5 mmole) of IIIa in 15 ml of diethylene glycol and 0.05 g of p-toluenesulfonic acid (TsOH) was heated at 180-200° for 40 min, after which it was evaporated, and the solid was removed by filtration. Workup gave 0.95 g (83%) of IVa with mp 293-295° (from methanol).

B) A mixture of 5.2 g (25 mmole) of acetal Ia and 4.1 g (25 mmole) of ester II was heated at 50-55° for 3.5 h, after which 0.1 g of TsOH was added, and the mixture was heated at 180-200° for 40 min. It was then evaporated, and the residue was filtered to give 4.2 g (76%) of IVa. The same method was used to synthesize IVb, with mp > 300° (from methanol), in 71% yield and IVc, with mp > 300° (from methanol), in 43% yield from IIIb and IIIc, respectively.

C) Similarly, but without TsOH, IVa was obtained in 44% yield.

1H,1-Methyl-6-ethoxy-2,3,4,5-tetrahydroazepino[2,3-b]quinoline Tetrafluoroborate (VIa). A solution of 1.9 g (10 mmole) of triethyloxonium tetrafluoroborate (V) in 15 ml of dry chloroform was added to a suspension of 2.28 g (10 mmole) of IVa in 15 ml of dry chloroform, and the mixture was allowed to stand for 2 h, after which the precipitated VIa was removed by filtration to give 1.1 g (35%) of a product with mp 154-157°. The product had mp 178-179° (from alcohol) after it was washed three times with boiling chloroform. The chloroform solutions were evaporated to give 1.7 g (49%) of ethoxy derivative VIIa with mp 170-172°. The product was crystallized for analysis to give a sample with mp 195-197°.

1H,1-Methyl-6-ethoxy-2,3,4,5-tetrahydroazepino[2,3-b]quinoline (VIIIa), 1H,1-Methyl-5-ethoxy-2,3,4-trihydropyrido[2,3-b]quinoline (VIIIb), and 1H,1-Methyl-5-ethoxy-2,3-dihydropyrrolo[2,3-b]quinoline (VIIIc). Ethanol (150 ml) and a 20% aqueous NaOH solution were added to a mixture of salts VIa and VIIa, obtained from 30 g (0.13 mole) of IVa, until the pH was 9, after which the alcohol was evaporated. Chloroform (50 ml) was added, and the mixture was filtered to give 10.8 g of IVa with mp 270-272°. The layers were separated, and the aqueous layer was extracted with chloroform (three 20-ml portions). The extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was distilled to give 20.0 g (55%) of ethoxy derivative VIIIa with bp 177° (1 mm) and n_D^{20} 1.6171. Compounds VIIIb, with mp 71-72° (from hexane), and VIIIc, with mp 131-132° (from petroleum ether), were similarly synthesized in yields of 34% and 57%, respectively.

1H − 1 − Methyl-6-chloro-2,3,4,5,11-pentahydroazepino[2,3-b]quinoline Dichlorophosphate (Xa) and 1H,1-Methyl-5-chloro-2,3,4,10-tetrahydropyrido[2,3-b]quinoline Dichlorophosphate (Xb). A 3.2-g (15 mmole) sample of IVb was refluxed in 15 ml of $POCl_3$ for 3 h, after which the mixture was cooled, and the precipitate was removed by filtration and washed with ether. The yield of complex Xb, with mp 176-178° (dec.), was 4.45 g (82%). Compound Xa, with mp 131-133° was similarly obtained in 78% yield.

1H,1-Methyl-6-chloro-2,3,4,5-tetrahydroazepino[2,3-b]quinoline (IXa), 1H,1-Methyl-5-chloro-2,3,4-trihydropyrido[2,3-b]quinoline (IXb), and 1H,1-Methyl-4-chloro-2,3-dihydropyrrolo[2,3-b]quinoline (IXc). Water (20 ml) and 20 ml of chloroform were added to dichlorophosphate Xc, obtained from 4.5 g of oxo compound IVc, and the mixture was made alkaline to pH 9 with 20% aqueous NaOH. The layers were separated, and the aqueous layer was extracted with chloroform (two 20-ml portions). The extract was dried with Na_2SO_4 and filtered. The filtrate was evaporated to give 2.9 g (60%) of IXc with mp 137.5-138.5° (from acetone). A similar procedure was used to obtain IXb, with mp 73° (from hexane), in 83% yield. Compound IXa, with bp 173-175° (3 mm), was similarly synthesized in 79% yield, but the intermediate dichlorophosphate was not purified.

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