REACTION OF 2,3-DIOXO-4-(N,N-DIMETHYLAMINOMETHYLENE)HEXAHYDROAZEPINE WITH HYDROXYLAMINE*

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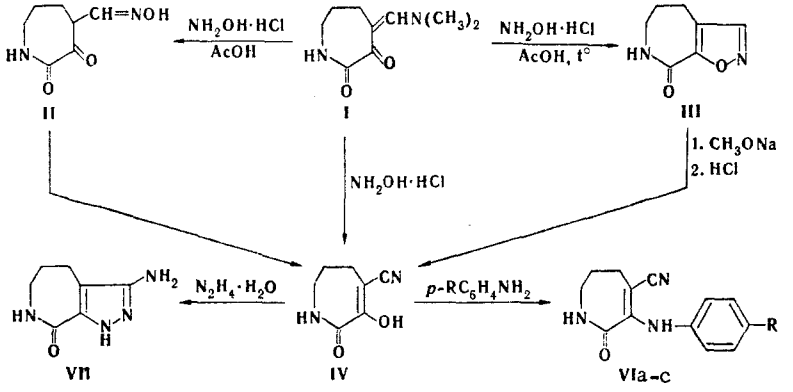
Depending on the conditions selected, the reaction of 2,3-dioxo-4-(N,N-dimethylaminomethylene)hexahydroazepine with hydroxylamine gives 2,3-dioxo-4-formylhexahydroazepine 4-oxime, 8-oxo-8H-4,5,6,7-tetrahydroisoxazolo[5,4-c]azepine, or 2-oxo-3-hydroxy-4-cyano-2H-1,5,6,7-tetrahydroazepine. The reaction of the latter with aromatic amines and hydrazine hydrate was used to synthesize 3-arylamino-2-oxo-4-cyano-2H-1,5,6,7-tetrahydroazepines and 3-amino-8-oxo-8H-4,5,6,7-tetrahydropyrazolo[5,4-c]azepine, respectively. The structures of the compounds obtained were confirmed by the IR, UV, and PMR spectra.

Considering the ability of 2,3-dioxo-4-(N,N-dimethylaminomethylene)hexahydroazepine (I) to undergo transamination under the influence of hydrazine and its derivatives [1], we studied the reaction of enamino ketone I with hydroxylamine.



VI a R=H; b R=OCH_3; c R=Cl

Oxime II was obtained by reaction of enamino ketone I with $NH_2OH \cdot HCl$ in glacial acetic acid in the presence of a catalytic amount of concentrated H_2SO_4 at 20°C; however, isoxazoloazepine III was synthesized when the mixture was refluxed and salt Va, from which hydroxy nitrile IV, which has rather strong acid properties (pK_a 5.15), was obtained by the action of mineral acid, was isolated when I was heated with $NH_2OH \cdot HCl$ in alcohol in the presence of triethylamine. The conversion of enamino ketone I to hydroxy nitrile IV proceeds via transamination of I with hydroxylamine and subsequent dehydration of intermediate oxime II; this was confirmed by conversion of the latter to hydroxy nitrile IV by heating oxime II in alcohol in the presence of triethylamine and subsequent decomposition of salt Vb with hydrochloric acid. On the basis of the data in [2, 3], which indicate the ability of isoxazole derivatives in alkaline media to undergo ring opening to give substituted nitriles, we accomplished the similar isomerization of isoxazoloazepine III to hydroxy nitrile IV by heating in methanol in the presence of sodium methoxide with subsequent acidification of the sodium salt of hydroxy nitrile IV with hydrochloric acid.

Hydroxy nitrile IV reacts with aromatic amines to give 3-arylamino-2-oxo-4-cyano-2H-1,5,6,7-tetrahydroazepines (VIa-c) and with hydrazine to give 3-amino-8-oxo-8H-4,5,6,7-

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TABLE 1. Properties of II-VII

Compound	mp, °C (solvent)	IR spectra, cm^{-1}			λ_{max}, nm (lg ε)	Found, %			Empirical formula	Calc., %			Yield, %
		C=O	C≡N	NH, OH		C	H	N		C	H	N	
II	185–186 (dec. water)	1665	—	3320 3220		49,2	6,1	16,2	$C_7H_{10}N_2O_3$	49,4	5,9	16,5	88
III	189–193 (MeOH)	1665	—	3280	238 (4,02)	54,9	5,2	18,4	$C_7H_8N_2O_2$	55,2	5,3	18,4	58
IV	200–203 (EtOH)	1660	2230	3270	258 (3,80)	54,7	5,3	18,4	$C_7H_8N_2O_2$	55,2	5,3	18,4	75 33 77
Va	172–174,5 (dec., MeOH)	1670	2190	3210		54,6	7,7	21,7	$C_9H_{15}N_3O_2$	54,8	7,7	21,3	78
VIb	109–113 (ethyl acetate)	1650	2160	3260 3160		61,3	8,4	16,8	$C_{13}H_{23}N_3O_2$	61,6	9,1	16,6	77
VIa	240–243 ($MeOCH_2CH_2OH$)	1670	2200	3320 3280	246 (4,07) 336 (4,03)	68,2	5,9	18,3	$C_{13}H_{13}N_3O$	68,7	5,8	18,5	93
VIb	173–177 (ethyl acetate)	1670	2190	3280 3180	247 (4,05) 336 (3,90)	65,4	5,8	16,5	$C_{14}H_{15}N_3O_2$	65,4	5,9	16,3	90
VIc*	189–194 (iso-PrOH)	1670	2210	3290 3190	253 (4,13) 336 (4,10)	59,9	4,7	16,0	$C_{13}H_{12}ClN_3O$	59,7	4,6	16,0	95
VII	230–234° (MeOH)	1640	—	3390 3310 3240 3180	233 (4,08) shoulder 280 (3,01)	50,5	6,0	33,7	$C_7H_{10}N_4O$	50,6	6,1	33,7	84

*Found: Cl 13.2%. Calculated: Cl 13.5%.

tetrahydropyrazolo[5,4-c]azepine (VII). A comparison of the PMR spectra of the synthesized compounds shows that the chemical shift and character of the splitting of the signals of th protons of the hexahydroazepine ring in the spectra of all of these compounds are of the same type and are similar to the characteristics observed in the spectrum of enamino ketone I [4]. The structure of IV was proved by the IR spectrum from the absence of an absorption band at 1700-1720 cm^{-1} and by the PMR spectrum, in which, according to the integration data, only signals of the protons of the CH_2 group in the 7 position are found at 3.0-3.2 ppm, and the signal of a CH proton in the 4 position of the azepine fragment is absent. It follows from a comparison of the PMR spectra of isoxazoloazepine III and 1-phenyl-8-oxo-8H-4,5,6,7-tetrahydropyrazolo[5,4-c]azepine (IX) [1] that the signal of the CH proton in the 3 position of III, in contrast to the spectrum of pyrazoloazepine IX, is shifted 1 ppm to weak field, evidently due to the acceptor effect of the oxygen atom of the isoxazole ring.

EXPERIMENTAL

The UV spectra of the compounds were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with Perkin—Elmer 457 and UR-10 spectrometers. The PMR spectra of solutions of the compounds in $(CD_3)_2SO-CCl_4$ (for I-IV) and d_7-DMF (for VII) were recorded with a JMH-4H-100 spectrometer with tetramethylsilane as the internal standard. The melting points of the compounds were determined with an MP-1 apparatus (Gamato Scientific Co., Ltd.). The purity of the compounds was monitored by chromatography on Silufol UV-254 plates.

2,3-Dioxo-4-formylhexahydroazepine 4-Oxime (II). One drop of concentrated H_2SO_4 was added to a solution of 1.8 g (0.01 mole) of enamino ketone I and 0.8 g (0.011 mole) of hydroxylamine hydrochloride in 6 ml of glacial acetic acid, and the mixture was stirred at 20°C for 2 h. The precipitate was removed by filtration, washed with ether, and dried to give oxime II (Table 1). PMR spectrum: 1.61 (4H, m, 5-CH_2, 6-CH_2), 3.10 (3H, m, 4-CH, 7-CH_2), 7.14 (1H, s, OH), 7.42 (1H, d, =CH), and 7.87 ppm (1H, t, NH).

8-Oxo-8H-4,5,6,7-tetrahydroisoxazolo[5,4-c]azepine (III). One to two drops of concentrated H_2SO_4 were added to a solution of 7.3 g (40 mmole) of enamino ketone I and 3.05 g (44 mmole) of hydroxylamine hydrochloride in 24 ml of glacial acetic acid, and the mixture was refluxed for 4 h. At the end of the reaction, the mixture was evaporated in vacuo, and the oily residue was dissolved in 20 ml of water. The aqueous solution was extracted with chloroform, and the extract was dried with calcined sodium sulfate and evaporated in vacuo. The residue was triturated with ethyl acetate, the mixture was filtered, and the solid was dried to give isoxazoloazepine III (Table 1). PMR spectrum: 1.98 (2H, m, 5-CH_2), 2.75 (2H, t, 4-CH_2), 3.25 (2H, q, 6-CH_2), 8.34 (1H, t, NH), and 8.53 ppm (1H, s, 3-CH).

2-Oxo-3-hydroxy-4-cyano-2H-1,5,6,7-tetrahydroazepine (IV). A) From Enamino Ketone I. A mixture of 14.7 g (80 mmole) of enamino ketone I, 6.1 g (88 mmole) of hydroxylamine hydrochloride, 11.1 g (0.11 mole) of triethylamine, and 160 ml of absolute alcohol was refluxed for 4 h, after which it was cooled, and the precipitate was removed by filtration to give salt Va (Table 1). The latter was dissolved in the minimum amount of warm water, and the solution was acidified to pH 4 with 2 N HCl, cooled, and filtered to give hydroxy nitrile IV in 75% yield (Table 1). PMR spectrum: 1.83 (2H, quintet, 6-CH_2), 2.28 (2H, t, 5-CH_2), 3.11 (2H, q, 7-CH_2), and 8.43 ppm (1H, t, NH).

B) From Isoxazoloazepine III. Sodium methoxide (from 0.28 g of Na and 7 ml of absolute MeOH) was added to a suspension of 0.6 g (4 mmole) of isoxazoloazepine III in 30 ml of MeOH, and the mixture was refluxed for 1 h. It was then evaporated in vacuo, and the residue was dissolved in water. The aqueous solution was acidified to pH 4 with 2 N HCl, and the resulting solution was extracted with ethyl acetate. Hydroxy nitrile IV was isolated in 33% yield (Table 1).

C) From Oxime II. A mixture of 1 g (6 mmole) of oxime II, 0.65 g (6.5 mmole) of triethylamine, and 10 ml of absolute alcohol was refluxed for 3 h, after which it was subjected to evaporation, and the residue was triturated with ethyl acetate to give salt Vb, which was dissolved in 1.5 ml of water. The solution was acidified to pH 4 with 2 N HCl, and the precipitated hydroxy nitrile IV (77%) was removed by filtration (Table 1).

2-Oxo-3-(p-anisidino)-4-cyano-2H-1,5,6,7-tetrahydroazepine (VIb). A mixture of 15.2 g (0.1 mole) of hydroxy nitrile IV, 13.6 g (0.11 mole) of p-anisidine, and 500 ml of benzene was refluxed for 5.5 h in the presence of a catalytic amount of p-TsOH to give VIb (Table 1).

PMR spectrum: 1.83 (2H, quintet, 6-CH_2), 2.27 (2H, t, 5-CH_2), 3.29 (2H, q, 7-CH_2), 3.7 (3H, s, OCH_3), 6.73 and 6.80 (4H, d, aromatic CH=), 8.34 (1H, t, 1-NH), and 8.58 ppm (1H, s, NH).

2-Oxo-3-phenylamino-4-cyano-2H-1,5,6,7-tetrahydroazepine (VIa). This compound was similarly obtained (Table 1). PMR spectrum: 1.85 (2H, quintet, 6-CH_2), 2.33 (2H, t, 5-CH_2), 3.61 (2H, q, 7-CH_2), 6.87-7.18 (m, aromatic CH=), and 8.45 ppm (1H, t, 1-NH).

2-Oxo-3-(p-chlorophenyl)amino-4-cyano-2H-1,5,6,7-tetrahydroazepine (VIc). This compound was similarly obtained (Table 1). PMR spectrum: 1.85 (2H, quintet, 6-CH_2), 2.31 (2H, t, 5-CH_2), 3.30 (2H, q, 7-CH_2), 6.83 and 7.29 (4H, d, aromatic CH=), and 8.48 ppm (1H, t, 1-NH).

3-Amino-8-oxo-8H-4,5,6,7-tetrahydropyrazolo[5,4-c]azepine (VII). A mixture of 1.5 g (10 mmole) of hydroxy nitrile IV, 0.55 g (11 mmole) of hydrazine hydrate, and 20 ml of absolute alcohol was refluxed for 1.5 h, after which it was worked up to give VII (Table 1). PMR spectrum: 1.96 (2H, m, 5-CH_2), 2.61 (2H, t, 4-CH_2), 3.35 (2H, q, 6-CH_2), and 7.91 ppm (1H, t, NH).

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REACTION OF METHYLPYRIMIDINES WITH TRICHLORO- AND TRIFLUOROACETYL CHLORIDES

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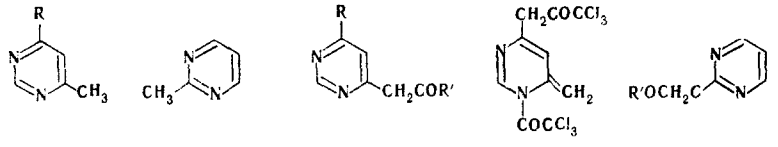
The corresponding trichloro- and trifluoroacetonylpyrimidines were obtained by reaction of 2- and 4-methylpyrimidines with trichloro- and trifluoroacetyl chlorides.

It is known [1, 2] that phenacylpyrimidines are formed in the reaction of 4,6-dimethylpyrimidine with aromatic acid chlorides in the presence of triethylamine. In the present research we studied the reaction of methylpyrimidines with trichloro- and trifluoroacetyl chlorides; this reaction leads to α-halo ketones of the pyrimidine series.



I-III IV V-IX X XI, XII

I R=CH_3; II R=OCH_3; III R=H; V R=CH_3, R′=CCl_3; VI R=OCH_3, R′=CCl_3; VII R=H, R′=CCl_3; VIII R=CH_3, R′=CF_3; IX R=H, R′=CF_3; XI R′=CCl_3; XII R′=CF_3

The reaction of methylpyrimidines I-IV with the acid chlorides in the presence of triethylamine proceeds vigorously as the mixtures are cooled. The amino alkenone, which is readily formed by the action of tertiary amines on the perhalo acid chlorides, was therefore obtained in only 1% yield in our case.

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