DIAZIRIDINE-3,3-DICARBOXYLIC ACID DERIVATIVES

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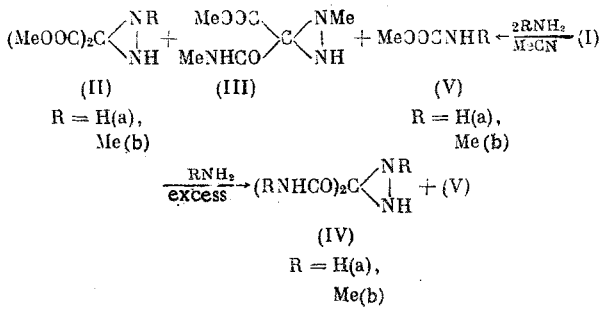
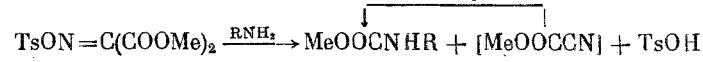
The high pyramidal stability of the nitrogen in diaziridines [1] made it possible to effect a partial kinetic separation of the enantiomers with an asymmetric nitrogen [2]. It was postulated to accomplish a complete separation on the basis of the functional derivatives of diaziridine by inserting an auxiliary asymmetric substituent, separation of the diastereomers, and subsequent removal of the auxiliary substituent. For this purpose we studied the preparation of diaziridine-3,3-dicarboxylic acid derivatives by the reaction of dimethyl mesoxalate O-tosyloxime (I) with NH_3 and CH_3NH_2.

The synthesis of diaziridines via the O-sulfonyloximes of ketones is complicated by the facile Beckmann rearrangement [3]. The communication on the synthesis of pentamethylenediaziridines via cyclohexanone oxime O-sulfonate (with a reference to unpublished data [4]) evokes doubt, since the latter easily undergoes rearrangement [5].

The Beckmann rearrangement is hindered if an electronegative substituent is inserted in the migrating phenyl group of acetophenone O-benzenesulfonyloxime [6]. In general, the presence of electronegative substituents in the O-tosyloximes of fluoroketones excludes the rearrangement and makes it possible to obtain the diaziridines in high yields [7]. Judging by the acid properties of diethyl mesoxalate oxime (pK_a 5.48 [8]) and hexafluoroacetone oxime (pK_a 6.0 [7]) the COOR and CF_3 groups are close in their electron-acceptor capacity. Consequently, we attempted to synthesize the diaziridines from (I).



Diaziridine (II) and its partial aminolysis product (III) were obtained when we used a 2:1 mole ratio of amine: O-tosyloxime (I) in CH_3CN at −40°. Only the complete aminolysis products (IV) are obtained under the conditions of excess amine. The easy aminolysis of the diaziridine-3,3-dicarboxylic acid esters was shown by an independent experiment on the example of (III), which is quantitatively converted to (VI) under the influence of excess CH_3NH_2 (20°, 4 h). In both cases, the urethylans (V) are formed in addition to the diaziridines.



The quite high yield of (V) can be explained by the indicated successive reactions [9]. A similar fragmentation of the tosyloxime was postulated in [10].

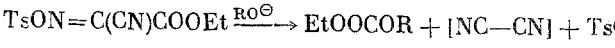


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TABLE 1

Compound	Formula	Yield, %	Yield of (V), %	Mp, °C	ν, cm⁻¹ (KBr) C=O	ν, cm⁻¹ (KBr) NH	NMR spectra, δ, ppm	Solvent
(IIa)	$(MeOOC)_2C$ with NH* and NH	47	5	49—52	1760	3270	2,89(NH), 3,77(MeO)	$CDCl_3$
(IIb)	$(MeOOC)_2C$ with NMe and NH	41	19	66—67	1775	3240	2,36(MeN), 3,16(NH), 3,28 and 3,42 Δν 8,4 Hz MeO)	Ph_2O
(IIc)	$(MeOOC)_2C$ with NCONHPh and NCONHPh	97	—	171	1690 1740	3260	3,67(MeO), 7,25 (Ph, multiplet), 10,40 (NH)	$(CD_3)_2SO$
(IId)	$(MeOOC)_2C$ with NCH_2OH and NH	48	—	Oil	—	—	2,42(NH), 3,26(OH), 3,84 and 3,96Δν 7,5Hz, (MeO), 4,68(H_B), 4,88(H_A) J_{AB} 7,8 Hz	C_6F_6
(III)	MeOOC, MeNHCO, C, NMe, NH	13	19	103—104	1675 1755	3220 3360	2,36(MeN), 2,64 (MeNH), 3,75(MeO)	CD_3OD
(IVa)	$(H_2NCO)_2C$ with NH and NH	36	55	180—184 (decomp.)	1695	3160 3220 3320	Singlet	D_2O
(IVb)	$(MeNHCO)_2C$ with NMe and NH	56	25	160—161	1690	3190 3330 3410	2,40(MeN), 2,80d (MeNH)J3Hz,3,61(NH), 6,90(HNCO)	$CDCl_3$

*Isomeric hydrazone [11]: mp 134-135°; δ, ppm (in $CDCl_3$):3.9, Δν 1.4 Hz (MeO), 9.58 (NH_2).

Compounds (II)-(IV) have the oxidation properties characteristic for diaziridines [4], namely the liberation of I_2 from KI. Diaziridine (IIa) differs from the isomeric hydrazone [11] and gives the dicarbamoyl (IIc) and monomethylol (IId) derivatives (Table 1).

The structure of products (II)-(IV) was confirmed by the NMR, IR, and mass spectra. A nonequivalence of the MeO groups, Δν 4.87 Hz at 160° (in Ph_2O), is observed on the basis of the NMR spectrum of (IIb), which testifies to the pyramidal stability of the chiral nitrogen. The hindered inversion of the nitrogen in (IId) follows both from the nonequivalence of the MeO groups and from the geminal nonequivalence of the methylene protons of the substituent (Fig. 1).

EXPERIMENTAL METHOD

The NMR spectra were measured on a Jeol JNM-C-60HL spectrometer (internal standard = HMDS), the IR spectra were taken on a UR-10 spectrophotometer as KBr pellets, while the mass spectra were taken on MX-1303 and LKB-9000 spectrometers, respectively at 30 eV and 70 eV.

Dimethyl mesoxalate O-tosyloxime (I) was obtained in 61% yield from dimethyl malonate by nitrosation and subsequent tosylation as described in [12], mp 93-94° (from MeOH); NMR spectrum ($CDCl_3$, δ, ppm): 2.38 (MeC), 3.77 and 3.84 (MeO), 7.60 (Ph). Mass spectrum (70 eV, m/e, relative intensity in %): M^+ 315 (4), 155 (100) 91 (93), 65 (18), 59 (16).

Dimethyl Ester of Diaziridine-3,3-dicarboxylic Acid (IIa). With stirring and cooling (—40°), to a solution of 1.70 g (0.1 mole) of NH_3 in 50 ml of CH_3CN was added in drops a solution of 15.75 g (0.05 mole) of O-tosyloxime (I) in 50 ml of CH_3CN and the stirring was continued for 1.5 h. After removal of the precipitate the solvent was evaporated in vacuo and the products were extracted from the residue with absolute ether. After removal of the ether the residue was sublimed into a trap (—70°) to give: 0.39 g (5%) of urethylan (Va), sublimes at 21° (1 mm), mp 53-54° (from benzene), cf. [13]; NMR spectrum (CD_3OD, δ, ppm): 3.65 (CH_3O), 4.88 (NH); 3.75 g (47%) of product (IIa), sublimes at 100° (1 mm), mp 49-52° (from ether). Found: C 37.99; H 5.12; N 17.17%. $C_5H_8O_4N_2$. Calculated: C 37.51; H 5.04; N 17.49%. Mass spectrum (70 eV, m/e, relative intensity in %): $(M-31)^+$, 129 (10), 101 (30), 70 (63), 69 (100), 59 (70), 42 (38), 15 (74).

Dimethyl Ester of 1-Methyldiaziridine-3,3-dicarboxylic Acid (IIb) and Methyl Ester of Methylamide of 1-Methyldiaziridine-3,3-dicarboxylic Acid (III). The reaction of (I) (15.75 g; 0.05 mole) with CH_3NH_2 (3.11 g; 0.1 mole) in CH_3CN and the workup of the mixture were run the same as in the preceding experiment. A crystalline precipitate deposits from the ether extract on standing, which was separated and

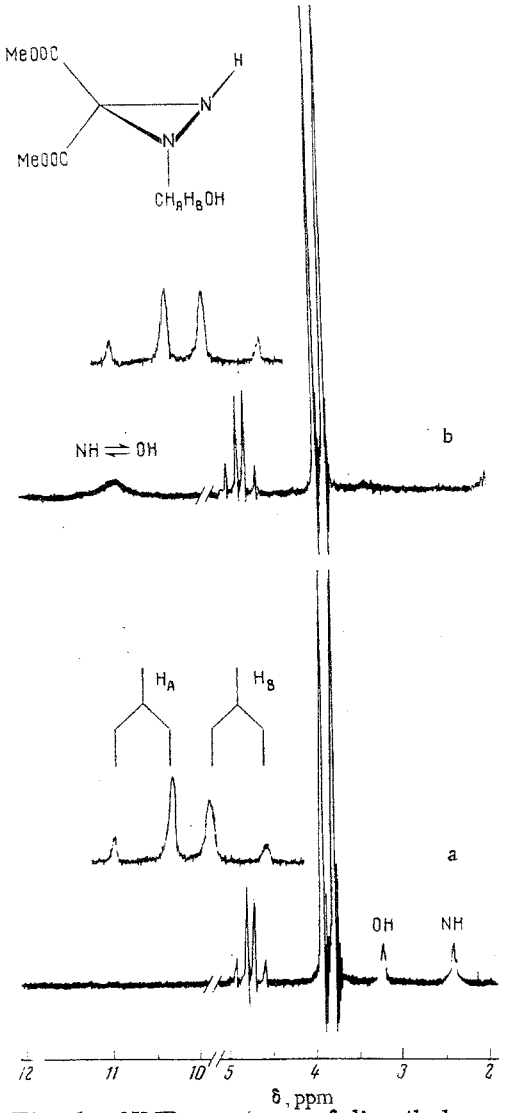

Fig. 1. NMR spectrum of dimethyl ester of 1-hydroxymethyldiaziridine-3, 3-dicarboxylic acid (IId) in C_6F_6 (a), and with added deuteroacetic acid (b).

recrystallized from i-PrOH. We obtained 1.1 g (13%) of (III), mp 103-104°. Found %: C 41.65, H 6.49; N 24.30%. $C_6H_{11}N_3O_3$. Calculated: C 41.62; H 6.40; N 24.26%. Mass spectrum (30 eV, m/e, relative intensity in %): M^+ 173 (3), 158(25), 59(21), 58(50), 57(85), 56 (44), 44(42), 42(58), 28(100). After removal of the ether the residual mother liquor was distilled to give 1.7 g (19%) of methylurethylan (Vb), bp 56.5-57° (9 mm), n_D^{20} 1.4150 (cf. [13]); NMR spectrum (CCl_4, δ, ppm): 2.7 d (MeNH, J 5.4 Hz), 3.6 (MeO), 5.8 (NH). The residue crystallized after 3 days at 0°. We obtained 5.6 g (69%) of crude product (IIb). Recrystallization from ethanol gave 3.5 g (41%) of pure (IIb), mp 66-67°. Found: C 41.56; H 6.01; N 16.02%. $C_6H_{10}N_2O_4$. Calculated: C 41.37; H 5.73; N 16.02%. Mass spectrum (70 eV, m/e, relative intensity in %): M^+ 174(1), 159(75), 127(81), 99(25), 69(28), 59(67), 55(44), 43(43), 42(37), 30(30), 28(40), 15(100).

Dimethyl Ester of 1,2-bis(Phenylcarbamoyl)diaziridine-3,3-dicarboxylic Acid (IIc). The reaction of 0.48 g (0.003 mole) of (IIa) and 0.72 g (0.006 mole) of phenyl isocyanate in 20 ml of ether for 10 days gave 1.13 g (97%) of (IIc), mp 171° (from CH_3CN). Found: C 57.32; H 4.55; N 14.15%. $C_{19}H_{18}N_4O_6$. Calculated: C 57.29; H 4.55; N 14.06%. Mass spectrum (70 eV, m/e, relative intensity in %): $(M-120)^+$, 278(32), 220(30), 119(100), 101(40), 91(36), 77(40), 69(28), 65(25), 15(30).

Dimethyl Ester of 1-Hydroxymethyldiaziridine-3,3-dicarboxylic Acid (IId). A mixture of 0.68 g (0.004 mole) of (IIa) and 0.28 g (0.009 mole) of CH_2O in 15 ml of absolute methanol was refluxed for 1 h. After removal of the solvent and azeotropic drying of the residue with benzene the product was extracted with ether. We obtained 0.38 g (47.5%) of (IId) as a yellowish oil. The product was characterized by the NMR spectrum (see Table 1 and Fig. 1).

Diamide of Diaziridine-3,3-dicarboxylic Acid (IVa). To 15.75 g (0.05 mole) of (I) was added 50 ml of liquid NH_3, the mixture was stirred at −60° for 0.5 h, and the NH_3 was evaporated in 2 h. Extraction with ether gave 4.1 g (55%) of urethylan (Va), mp 54-55° (from benzene). The residue was washed with absolute methanol to remove the ammonium tosylate; the yield of (IVa) was 2.33 g (36%), mp 180-184° (decomposition) (from 60% aqueous MeOH). Found: C 27.81; H 4.70; N 42.98%. $C_3H_6N_4O_2$. Calculated: C 27.70; H 4.65; N 43.06%. Mass spectrum (70 eV, m/e, relative intensity in %): $(M-28)^+$, 102(2), 85(84), 69(20), 44(100), 43(78), 42(57), 18(27).

N,N'-Dimethyldiamide of 1-Methyldiaziridine-3,3-dicarboxylic Acid (IVb). To 15.75 g (0.05 mole) of (I) was added 47.5 g of absolute CH_3NH_2, the mixture was stirred at −50° for 4 h, and the amine was evaporated. Extraction with ether gave 2.26 g (25%) of methylurethylan (Vb), bp 56-60° (11-12 mm). Sublimation of the residue at 125-130° (0.2 mm) gave 4.78 g (56%) of (IVb), mp 160-161.5° (from i-PrOH). Found: C 41.86; H 7.24; N 32.50%. $C_6H_{12}N_4O_2$. Calculated: C 41.85; H 7.00; N 32.54%. Mass spectrum (70 eV, m/e, relative intensity in %): M^+ 172(3), 157(100), 144(21), 100(42), 83(24), 58(92), 57(70), 44(42), 42(72), 30(50), 28(98), 15(48). Compound (IVb) was also obtained by treating 0.091 g (0.0005 mole) of (III) with methylamine (1 ml) (in a sealed ampul at 20° for 4 h); yield 0.09 g (~100%); it was identified by the mixed melting point and the NMR spectrum.

CONCLUSIONS

The first functional diaziridines, and specifically the diaziridine-3,3-dicarboxylic acid derivatives, were synthesized, which are suitable for separating into the enantiomers by inserting the moiety of an

optically active alcohol and separation of the diastereomers, with subsequent removal of the asymmetric substituent by aminolysis, the possibility of which was shown.

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