CYCLIZATIONS WITH HYDRAZONES OF NITROGLYOXALIC ACID. SYNTHESIS AND STRUCTURE OF TETRAZOLO[5,1-b][1,2,4]TRIAZINES

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Condensation of tetrazolylhydrazone of ethyl nitroglyoxalate with aromatic amines gives rise to derivatives of 5-arylamino-6-oxo-6,7-dihydrotetrazolo-[5,1-b][1,2,4]triazine.

Condensation of diazopyrazole and diazo-1,2,4-triazole with nitroacetic ester in the presence of bases leads to derivatives of 6-nitro-7-oxo-4,7-dihydropyrazolo- or 1,2,4-triazol [5,1-c][1,2,4]triazine. When the reaction is carried out in an acidic medium, and when diazotetrazole is employed, the reaction stops at the stage of the corresponding azolylhydrazones of nitroglyoxalic acid [1, 2]. Treatment of hydrazones, having the pyrazole or triazol fragment, with alkalies and aliphatic amines, leads to cyclization of a 1,2,4-triazine ring with formation of nitro derivatives of azolo[5,1-c][1,2,4]triazine. Such hydrazones do not react with aromatic amines [2].

In order to determine the limits of applicability of this method, we studied the interaction of tetrazolylhydrazone of ethyl nitroglyoxalate with amines (I). It turned out that hydrazones of the tetrazole series behave in the reactions under consideration in a different way than the pyrazole and triazole derivatives. Reaction of aliphatic amines with hydrazone I yields no cyclic products. After abstraction of two protons by the base, a dianion is generated and the salt of II type is formed. Thus, for example, on heating of hydrazone I with diethylamine in alcohol, the bis(diethylammonium)salt was isolated. Acidification of the latter gives practically the quantitative amount of the regenerated starting hydrazine I.

Refluxing of hydrazone I in alcohol with aromatic amines gives rise to crystalline products whose IR spectra manifest the vibration bands of the NH and carbonyl groups; however they do not show the presence of the corresponding nitro- and azido groups; the latter can be formed as a result of the opening of the tetrazole rind [3]. The NMR data indicate the presence of aromatic protons in the molecule. This fact, and the elemental analysis of the products, indicate that the condensation is accompanied by the simultaneous departure of the ester and the nitro group in hydrazone I, while the cyclization and substitution can involve either one group.

The cyclization variant involving the nitro group and the triazole ring closure (compounc III), similar to the transformation of tetrazolylhydrazones of chloroformaldehyde [4, 5], was rejected after an attempt in the independent synthesis. The reaction of acid chloride of 3-azido-1,2,4-triazolocarboxylic acid with para-anisidine gives 3-azido-5-(4-methoxyphenylamido)-1,2,4-triazole whose characteristics are different from those of the investigated compound.

All the collected data lead to the conclusion that, analogously as in the reactions of triazolylhydrazones [1, 2], in this particular case, formation of 6-arylamino-7-oxo-4,7-dihydro[5,1-c][1,2,4]triazine (IV) occurs by cyclization of the hydrazone through the C_2H_5OCO fragment and $N_{(1)}$ of the tetrazole and as a result of replacement of the nitro group by arylamine.

However, the x-ray analysis of the condensation product of hydrazone I with para-anisidine showed that the reaction yields not compound IV but 5-(4-methoxyphenylamino)-6-oxo-6,7-dihydrotetrazolo[5,1-b][1,2,4]triazine (Vc, Fig. 1; Tables 1 and 2). The molecule is planar (Table 3), which is apparently due to the conjugation between the heterocyclic and aryl frag-

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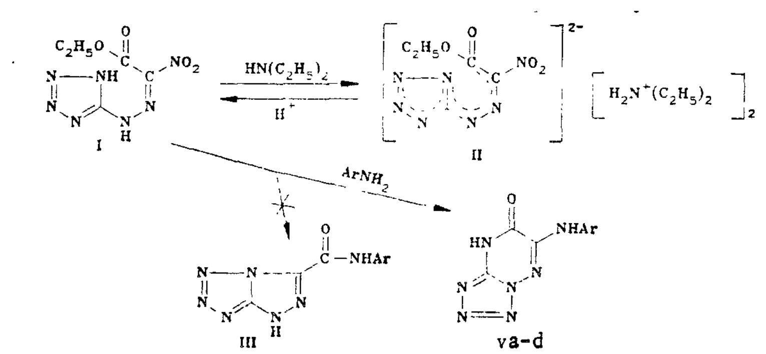

a Ar=C_6H_5, b Ar=p-$CH_3C_6H_4$, c Ar=p-$CH_3OC_6H_4$, d Ar=p-ClC_6H_4

ments of the molecule (the dihedral angle between the planes of these fragments constitutes only 4.9°). This leads to the intramolecular steric hindrance between $N_{(5)}$ and $H_{(9)}$ as well as to a significant deformation of the $N_{(5)}C_{(2)}N_{(7)}$ 122.3 (2)°, $C_{(2)}N_{(7)}C_{(4)}$ 129.2 (2)°, and $N_{(7)}C_{(4)}C_{(9)}$ 124.3 (2)° angles. In the heterocyclic parts of the molecules the lengths of the formally double C=N and N=N bonds are somewhat higher, and those of the formally single C–N and N–N bonds are somewhat lower than the standard values [6].

The crystal structure is formed from Vc and DMF molecules mutually connected with hydrogen $N_{(6)}$–H···$O_{(3)}$ bonds [N···O 2.677 (4), H···O 1.73 (4) Å, NHO 171 (2)°]. Moreover, the molecule of Vc has an additional active H($N_{(7)}$) proton, forming the intermolecular hydrogen $N_{(7)}$–H···$O_{(1)}$ bond (Vc^1, 1-x_1 2-y_1-z) and the $O_{(1)}$ atom of the initial molecule of Vc participates in the formation of a hydrogen bond with the H($N_{(7)}$) atom of the Vc molecule (1-x_1 2-y_1-z), i.e., the crystal contains associated DMF Vc···Vc^1 DMF^1 aggregates. The H($N_{(7)}$) atom also forms the hydrogen bond H($N_{(7)}$–H···$O_{(1)}$[N···O 2.659 (4), H···O 2.06 (4) Å, HNO 119° bond. Thus, the H($N_{(7)}$) proton participates in the formation of a forklike intra- and intermolecular hydrogen bond.

In the reactions of others than para-anisidine arylamines with hydrazone I, we also observed formation not of [5,1-c]-(Structure IV), but of [5,1-c]bicyclic systems. This is supported by the commonness of the UV and IR spectra of compounds Vc and Va, b, d. Formation of tetrazolo[5,1-b][1,2,4]triazines V apparently proceeds according to the sequence: a) cyclization to compound IV or VI; b) recyclization of tetrazole IV(VI) to compound V

TABLE 1. Atomic Coordinates (×10^4) and Their Anisotropic Temperature Factors in the Form of $T = \exp[-1/4(B_{11}h^2a^{*2} + \ldots + 2B_{23}k\ell b^*c^*)$

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
$O_{(1)}$	5999(1)	9851(3)	281(2)	3,9(1)	4,6(1)	7,1(1)	−0,1(1)	1,3(1)	1,7(1)
$O_{(2)}$	2651(1)	2543(3)	1482(2)	3,8(1)	5,0(1)	6,2(1)	−0,9(1)	1,9(1)	1,0(1)
$O_{(3)}$*	8289(1)	11026(3)	217(2)	4,4(1)	7,3(1)	6,2(1)	−1,7(1)	1,0(1)	1,3(1)
$N_{(1)}$	8668(2)	6774(4)	1500(2)	3,1(1)	6,7(1)	5,4(1)	0,0(1)	1,1(1)	1,0(1)
$N_{(2)}$	8757(2)	5165(4)	1974(2)	3,6(1)	7,8(1)	6,4(1)	0,7(1)	1,2(1)	1,3(1)
$N_{(3)}$	8007(2)	4578(4)	2060(2)	3,8(1)	5,2(1)	5,8(1)	0,9(1)	1,5(1)	1,3(1)
$N_{(4)}$	7411(1)	5848(4)	1634(2)	3,0(1)	4,7(2)	3,6(1)	0,2(1)	0,9(1)	0,6(1)
$N_{(5)}$	6531(1)	5693(3)	1543(2)	3,0(1)	4,4(1)	3,9(1)	−0,2(1)	1,2(1)	4,4(2)
$N_{(6)}$	7348(1)	8563(3)	835(2)	3,3(1)	4,7(2)	4,3(1)	−0,8(1)	1,1(1)	0,7(1)
$N_{(7)}$	5192(1)	7143(3)	860(2)	3,1(1)	3,6(1)	4,1(1)	−0,3(1)	1,1(2)	0,2(1)
$N_{(8)}$*	9673(2)	12092(3)	650(2)	3,5(1)	5,1(2)	5,8(2)	−0,4(1)	1,3(1)	1,3(1)
$C_{(1)}$	7820(2)	7146(4)	1309(2)	3,1(2)	4,9(2)	3,4(2)	−0,4(2)	0,7(2)	0,2(2)
$C_{(2)}$	6077(2)	7041(4)	1067(2)	3,2(2)	3,8(2)	3,1(2)	−0,5(2)	1,1(2)	−0,4(2)
$C_{(3)}$	6458(2)	8624(4)	690(2)	3,2(2)	4,2(2)	4,5(2)	−0,4(2)	0,9(2)	0,0(2)
$C_{(4)}$	4600(2)	5891(4)	1053(2)	3,2(2)	3,6(2)	3,1(2)	−0,4(2)	1,1(2)	−0,2(2)
$C_{(5)}$	3700(2)	6330(4)	725(2)	3,4(2)	3,7(2)	4,0(2)	−0,0(2)	1,3(2)	0,2(2)
$C_{(6)}$	3074(2)	5192(4)	887(2)	3,0(2)	4,5(2)	4,5(2)	0,1(2)	1,4(2)	0,2(2)
$C_{(7)}$	3325(2)	3588(4)	1368(2)	3,4(2)	4,2(2)	4,0(2)	−0,8(2)	1,5(2)	−0,2(2)
$C_{(8)}$	4209(2)	3131(3)	1701(2)	3,7(2)	4,1(2)	4,3(2)	−0,2(2)	1,2(2)	0,7(2)
$C_{(9)}$	4847(2)	4288(4)	1535(2)	3,1(2)	4,3(2)	4,2(2)	−0,1(2)	1,1(2)	0,1(2)
$C_{(10)}$	2879(2)	851(4)	1935(2)	4,9(2)	5,6(2)	5,9(2)	−1,4(2)	1,6(2)	1,3(2)
$C_{(11)}$*	9000(2)	11369(4)	856(2)	3,6(2)	6,8(2)	4,9(2)	−0,8(2)	1,0(2)	1,6(2)
$C_{(12)}$*	10470(2)	12524(4)	1428(2)	5,2(2)	10,1(2)	10,5(2)	−2,5(2)	−1,4(4)	4,7(3)
$C_{(13)}$*	9589(2)	12576(4)	−395(2)	7,6(2)	10,4(2)	6,8(2)	−3,1(2)	3,2(3)	1,5(3)

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*Atoms of the solvating DMF molecule [$O_{(3)}$–$C_{(11)}$ 1.235(4), $C_{(11)}$–$N_{(8)}$ 1.304(4), $N_{(8)}$–$C_{(12)}$ 1.433(5), $N_{(8)}$–$C_{(13)}$ 1.459(5) Å].

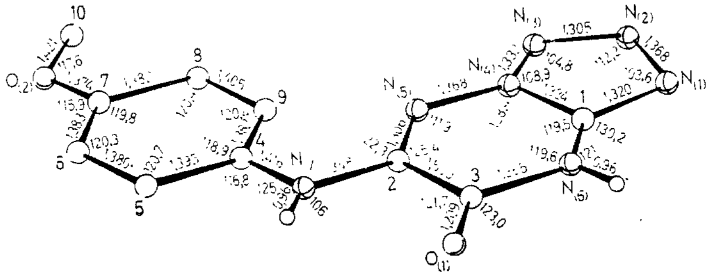

Fig. 1. Bond distances and valence angles of the molecule of Vc.

TABLE 2. Coordinates of H atoms (× 10^4) (numbers of H atoms coincide with the numbers of the carbon and nitrogen atoms linked to them)

Atom	x	y	z	Atom	x	y	z
$H_{(N6)}$	763(3)	952(5)	60(4)	$H_{(310)}$	322(3)	19(5)	156(4)
$H_{(N7)}$	502(3)	823(5)	49(4)	$H_{(11)}$	919(3)	1109(5)	155(4)
$H_{(5)}$	351(3)	745(5)	37(4)	$H_{(112)}$	1057(3)	1176(5)	181(4)
$H_{(6)}$	243(3)	552(5)	63(4)	$H_{(212)}$	1042(3)	1363(5)	153(4)
$H_{(8)}$	441(3)	208(5)	212(4)	$H_{(312)}$	1100(3)	1229(5)	120(4)
$H_{(9)}$	552(3)	390(5)	173(4)	$H_{(113)}$	1017(3)	1257(5)	−27(4)
$H_{(110)}$	234(3)	34(5)	185(4)	$H_{(213)}$	907(3)	1197(5)	−84(4)
$H_{(210)}$	334(3)	85(5)	264(4)	$H_{(313)}$	952(3)	1389(5)	−48(4)

TABLE 3. Coefficients of the Equations of the $A_x + B_y + C_x - D = 0$ Planes of Some Planar Fragments of the Molecule and DMF and Deviations of Atoms from These Planes in Å

Plane	Atoms	A	B	C	D
1	$N_{(1)}$ $N_{(2)}$ $N_{(3)}$ $N_{(4)}$ $N_{(5)}$ $N_{(6)}$ 0,019 0,016 −0,006 −0,026 −0,005 −0,010 $C_{(1)}$ $C_{(2)}$ $C_{(3)}$ $O_{(1)}$ −0,017 0,031 0,001 −0,002	0,1018	−0,4584	−0,8829	−2,778
2	$C_{(4)}$ $C_{(5)}$ $C_{(6)}$ $C_{(7)}$ $C_{(8)}$ $C_{(9)}$ 0,001 0,002 −0,005 −0,001 −0,006 0,004 $N_{(7)}$ $O_{(2)}$ 0,001 0,006	0,1836	−0,4365	−0,8808	−1,9111
3	$C_{(2)}$ $N_{(7)}$ $C_{(4)}$	0,1615	−0,4158	−0,8950	−1,9889
4	$C_{(7)}$ $O_{(2)}$ $C_{(10)}$	0,1620	−0,4007	−0,9018	−1,9549
5	$O_{(3)}$ $N_{(8)}$ $C_{(11)}$ $C_{(12)}$ $C_{(13)}$ −0,010 0,024 0,004 −0,014 −0,005	0,4132	−0,9015	−0,1286	−2,1409

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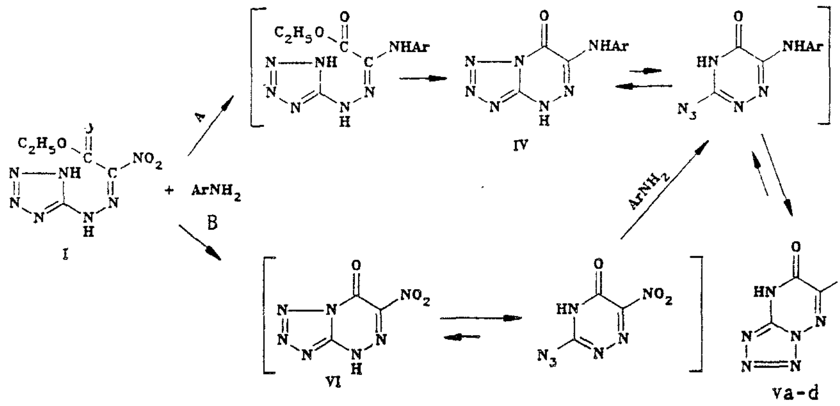
*The planes form the following dihedral angles: 1/2 = 4.9, 1/3 = 4.3, 1/5 = 55.3, 2/3 = 1.9, 2/4 = 1.7.

through the intermediate azide VII. The substitution of the nitro group by the arylamine moiety can proceed both during the triazine stage-route B, as well as during the hydrazone stage-route A.

The prevailing existence of [5,1-b] structures, apparently results from their transition to the more stable [7-9] form from the [5,1-c] isomer through the azidotetrazole equilibrium.

EXPERIMENTAL

The NMR spectra in DMSO-D_6 were taken on a Perkin—Elmer R-12B spectrometer (60 MHz) with TMS as an internal standard; the IR spectra were recorded in Nujol, ona UR-20 instrument and the UV spectra in ethanol on a Specord UV-vis spectrometer. The x-ray structure determination was carried out on a Sintax-P1 diffractometer using graphite-monochromatized Mo radiation, θ/2θ scanning, 3 ≤ 2θ ≤ 50°. The structure was solved by the direct method and



refined by the least-squares method in the full-matrix anisotropic (isotropic for the H atoms) approximation to R = 0.041, R_2 = 0.045 for 1703 reflections with $F^2 \geq 2$. The crystals of compound Vc in DMF are monoclinic: a) 15.843 (3), b) 7.584 (1), c) 13.852 (2) Å; β 107.28 (2)°, V = 1581.6 (5) Å^3, dcalc = 1.39, Z = 4, space group P2, In. The atomic coordinates and their temperature factors are listed in Tables 1 and 2.

Tetrazolylhydrazone of ethylnitroglyoxalate was obtained according to [1].

Bis(diethylammonium) Salt of Tetrazolylhydrazone of Ethyl Nitroglyoxalate (II). To a solution of 0.5 g (2.5 mmole) of compound I in 10 ml of ethanol was added 0.5 ml of diethyl amine. The solution was refluxed for 1 h and evaporated under vacuum. Yield 0.9 g (99%). MP 215-217°C. NMR spectrum: 1.15 (9H, t, CH_3); 1.25 (3H, t, CH_3); 2.95 (6H, q, NCH_2); 4.20 ppm (2H, 1, OCH_2). IR spectrum: 1330, 1465 (NO_2); 1724 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 260 (2.98), 400 nm (3.56). Found, %: C 41.6, H 7.7, N 33.7. $C_{13}H_{29}N_9O_4$. Calculated, %: C 41.6, H 7.7, N 33.6.

5-Phenylamino-6-oxo-6,7-dihydrotetrazolo[5,1-b][1,2,4]triazine (Va). A solution of 2.29 g (0.01 mole) of hydrazone I and 1.35 ml (0.015 mole) of aniline in 20 ml of ethanol was refluxed for 1 h, then evaporated under vacuum. The tarry precipitate was triturated in 10 ml of alcohol and precipitated again from DMF with water. Yield 0.69 g (30%). Mp 294-296°C (decomp.). NMR spectrum: 7.10-8.10 (5H, m, Ph); 9.8 ppm (1H, s, NH). IR spectrum 1720 (C=O); 3310 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 232 (3.21), 315 nm (3.26). Found, %: C 47.4, H 3.3, N 42.3. $C_9H_7N_7O$. Calculated, %: C 47.2, H 3.1, N 42.8.

Compounds Vb-d were obtained in an analogous way.

5-Tolylamino-6-oxo-6,7-dihydrotetrazolo[5,1-b][1,2,4]triazine (Vb). Yield 53%. Mp 273-275°C (decomp., from a 1:1 mixture of ethanol—acetic acid). NMR spectrum: 2.33 (3H, s, CH_3); 7.30 (2H, d, Ar); 7.92 (2H, d, Ar); 9.78 ppm (1H, s, NH). IR spectrum (1710 (C=O); 3350 cm^{-1} (NH). UV spectrum: λ_{max} (log ε): 234 (406), 323 nm (4.07). Found, %: C 49.6, H 3.9, N 40.9%. $C_{10}H_9N_7O$. Calculated, %: C 49.4, H 3.7, N 40.4.

5-(4-Methoxyphenylamino)-6-oxo-6,7-dihydrotetrazolo[5,1-b][1,2,4]triazine (Vc). Yield 60%. Mp 263-265°C (decomp., from alcohol). NMR spectrum: 3.76 (3H, s, OCH_3); 7.00 (2H, d, Ar); 7.83 (2H, d, Ar); 9.65 ppm (1H, s, NH). IR spectrum: 1692 (C=O); 3314 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 235 (4.00); 320 nm (4.05). Found, %: C 46.1, H 3.7, N 37.5. $C_{10}H_9N_7O_2$. Calculated, %: C 46.3, H 3.5, N 37.8.

5-(4-Chlorophenylamino)-6-oxo-6,7-dihydrotetrazolo[5,1-b][1,2,4]triazine (Vd). Yield 43%. Mp 253-255°C (decomp., from a 9:1 mixture of acetic acid and DMF). IR spectrum: 1720 (C=O); 3320 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 244 (4.03); 313 nm (3.98). Found, %: C 41.0, H 2.3, Cl 13.8, N 35.8. $C_9H_6ClN_7O$. Calculated, %: C 41.1, H 2.8, Cl 13.6, N 36.3.

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SYNTHESIS AND PROPERTIES OF 1,4,9-TRIAZASPIRO[5,5]UNDECANE AND 3,7,11-TRIAZASPIRO[5,6]DODECANE

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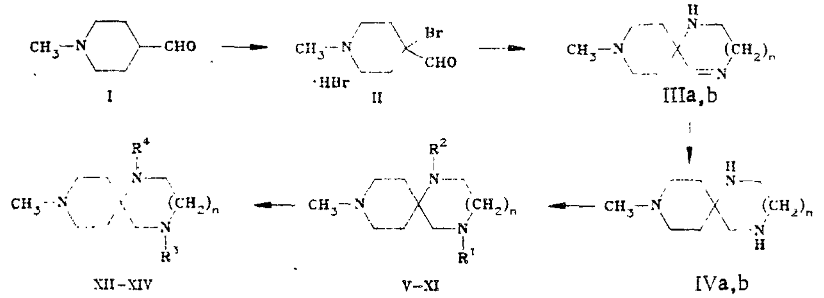
Bromination of 1-methylpiperidine-4-carboxaldehyde gave 4-bromo-1-methylpiperidine-4-carboxaldehyde hydrobromide which was used to synthesize 1,4,9-triazaspiro[5,5]undecane and 3,7,11-triazaspiro[5,6]dodecane. Cyanoethylation and alkylation with various alkyl halides gave their mono- and di-substituted derivatives. The side chain nitrile group was reduced and the hydrazide was obtained from the ester analog.

The synthesis has recently been reported of new spiroheterocycles combining different nitrogen-containing rings with tetrahydropyran and tetrahydrothiopyran systems [1-4]. Continuing this work, we have developed a synthetic method for new spiroheterocycles in which a piperidine ring is spiro joined to piperazines or perhydrodiazepines:



III, IV a n=1, b n=2; V, VII—XII, XIV n=1, VI, XIII n=2; R^1—R^4 see Table 1

Aldehyde I [5] was brominated in glacial acetic acid to give the α-bromoaldehyde hydrobromide (II) in almost quantitative yield. Treatment of II with ethylenediamine gave the spiroimine IIIa which was hydrogenated under pressure using Raney nickel to the spiro-amine IVa. A similar reaction of II with 1,3-diaminopropane led to IIIb, reduction of which with lithium aluminum hydride gave IVb. The nitrogen atom in IVa, b, situated α to the spiro carbon atom, was found to be relatively inert. Thus, treatment of IVa, b with excess acrylonitrile gave only the products of mono-addition V, VI occurring at the β position to the spiro carbon (in agreement with the inertness of the spiroimines IIIa, b under the same conditions). Mono-substituted derivatives of IVa were also obtained with excess of chloroacetonitrile (VII), chloroacetamide (VIII), ethyl acrylate (IX), and acrylamide (X). When ethyl bromoacetate was used to alkylate IVa, the production of di-substitution XI was obtained exclusively. Reduction of nitriles V, VI with lithium aluminum hydride gave the amines XII, XIII and the dihydrazide XIV was obtained from diester XI. The structures of the compounds obtained were proved by IR, PMR, and mass spectroscopic methods (Tables 1 and 2).

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