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CYCLIZATION OF FLUOROALKYL-CONTAINING 1,3-DICARBONYL COMPOUNDS WITH ETHYLENEDIAMINE HYDROPERCHLORATE TO 1,4-DIAZEPINES

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2,3-Dihydro-1H-1,4-diazepines and 1,2,3,4-tetrahydro-1,4-diazepin-5-ones were obtained by direct condensation of fluorine-containing 1,3-diketones and 1,3-keto ethers, respectively, with ethylenediamine monohydroperchlorate. The structure of the compounds was confirmed by ^{1}H NMR, mass spectrometry and molecular weight determination.

It is known that symmetric 1,3-diketones with bulky substituents (t-Bu, i-Pr) do not react with ethylenediamine (EDA) [1]. Acetylacetone (AA) and hexafluoroacetylacetone (HFAA) form with EDA 2,3- dihydro-1H-1,4-diazepines and N,N'-ethylenebis(aminovinyl ketones) [2-4], but the latter obtained from HFAA are not stable and convert to 1,4-diazepine upon standing [4]. The reaction of nonsymmetric 1,3-diketones with EDA [4-6] is limited to formation of the corresponding N,N'-ethylenebis(aminovinyl ketones), with the exception of 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione, for which 1,4-diazepine was also found [4]. Other 7-fluoroalkyl-1,4-diazepines were obtained only by the reaction of EDA with 1,3-aminovinyl ketones that contain an amino group on the carbon bonded to the fluoroalkyl radical (yield 71-82%) [7].

Esters of aceto- and difluoroacetoacetic acids form as the only product of the reaction with EDA ethyl- (or methyl-) 3,3'-(N,N'-diaminoethylene)-bis(2-butenoate) [8, 9]. The reaction of trifluoroacetoacetic ester (TFAAE) with EDA in xylene leads to a mixture of ethyl-2-(trifluoromethyl)imidazolidine acetate (yield 25%) and 1,2,3,4-tetrahydro-1,4-diazepin-5-one (16%) [10]. When the inner salt of TFAAE aminoethylamide is heated to 170°C the yield of 1,4-diazepinone increases to 47% [10], while the inner salts of TFAAE aminoethylamides and other fluorinated 1,3-keto ethers cannot be closed in a proton-donor solvent [9].

The formation of cyclic products in the direction of the reactions of fluorinated 1,3-dicarbonyl compounds with EDA is episodic in character. Cyclization with EDA to 1,4-diazepines and 14-member macrocyclic compounds is easily accomplished for acetone or α,β-unsaturated ketones in the presence of strong acids [11, p. 66]. Such reactions are not known for fluorinated 1,3-dicarbonyl compounds.

We have investigated the reaction of AA (Ia), acetoacetic ether (AAE), fluorinated 1,3-diketones (Ib-g), and 1,3-keto ethers (IIb, c) with EDA monohydroperchlorate.

By analogy with α,β-unsaturated ketones [11, p. 66] one can expect, in the reactions of 1,3-diketones with EDA·$HClO_4$, the formation of the dihydroperchlorate of the tetraazomacrocyclic compound (III) and a protonated salt of 1,4-diazepine (IV).

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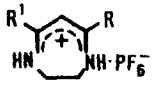
TABLE 1. Characteristics of Monohydrohexafluorophosphates of 2,3-Dihydro-1,4-diazepines (Va, c-f)



Compound	R¹	R	Yield, %	Mp, °C	Found/Calculated, %				Empirical formula	IR spectrum, ν, cm⁻¹ †	
					C	H	F	N		NH	C=N+, C=C
(Va)	Me	Me	64	119–121	31,70 / 31,12	4,87 / 4,85	–	10.46 / 10,37	$C_7H_{12}N_2 \cdot HPF_6$	3400 3300 1560	1620
(Vc)	$H(CF_2)_2$	Me	75	185–187	27,34 / 26,97	3,12 / 3,11	–	7,53 / 7,87	$C_8H_{10}F_4N_2 \cdot HPF_6$	3380 1560	1645, 1595, 1510
(Vd)	CF_3	Ph	75	151–153	37,44 / 37,32	3,18 / 3,13	44,23 / 44,27	7,87 / 7,25	$C_{12}H_{11}F_3N_2 \cdot HPF_6$	3370 1560	1635, 1610, 1580, 1500
(Ve)	$H(CF_2)_2$	Ph	95	152–153	37,66 / 37,34	3,12 / 3,13	45,80 / 45,43	7,04 / 6,76	$C_{13}H_{12}F_4N_2 \cdot HPF_6$	3390 3350 1560	1620, 1600, 1580, 1500
(Vf) *	$H(CF_2)_2$	$C(Me)_3$	65	154–155	33,62 / 33,18	4,35 / 4,30	47,78 / 47,71	7,46 / 7,04	$C_{11}H_{16}F_4N_2 \cdot HPF_6$	3380 3350 1560	1620, 1600, 1580, 1500

*PMR spectrum (δ, ppm, acetone-d_6): 5.62 s (1H, CH), 4.01 br.s (4H, CH_2CH_2), 1.43 s (9H, $C(Me)_3$), 6.65 t.t (1H, $H(CF_2)_2$), J_{HCF_2} = 52.3, $J_{HCF_2CF_2}$ = 4.5 Hz.

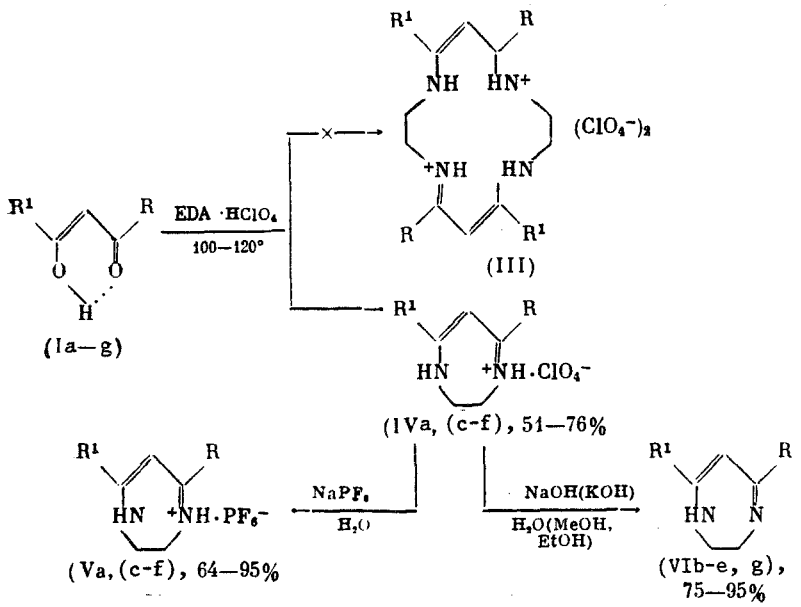
†$\nu_{PF_6^-}$ = 850.550 cm^{-1}.

TABLE 2. Description of Monohydroperchlorates of 2,3-Dihydro-1H-1,4-diazepines (IVa, c-f)

Compound	R'	R	Yield, %	Mp, °C	Found/Calculated, %					Empirical formula	IR spectrum, ν, cm⁻¹ †		PMR spectrum (δ, ppm, acetone-d₆)				
					C	H	F	Cl	N		NH	C=N+ C=C	CH	CH_2CH_2	R	H(CF_2)₂ (J, Hz)	NH
(IVa)	Me	Me	76	139–141 (cf. [2])	37,37 / 37,42	5,51 / 5,83		16,41 / 15,78	12,18 / 12,47	$C_7H_{12}N_2 \cdot HClO_4$	3100 3320 1530	1610 1595 sh	5,12 s	3,77 m	2,29 s	–	8,86 br.s
(IVc)	H(CF_2)₂	Me	59	188–190	30,48 / 30,93	3,69 / 3,57	24,12 / 24,46	12,41 / 11,41	8,77 / 9,02	$C_8H_{10}F_4N_2 \cdot HClO_4$	3300 1575	1650 1590 sh	5,52 s	3,97 br.s	2,52 s	6,60 t.t (52,3 4,7)	10,05 br.s
(IVd)*	CF_3	Ph	68	151–153	42,83 / 42,31	3,42 / 3,55	16,45 / 16,73	10,73 / 10,41	8,48 / 8,22	$C_{12}H_{11}F_3N_2 \cdot HClO_4$	3280 1560	1630 1615 1600 1580 sh	5,90 s	4,18 m	7,70 m	–	10,00 br.s
(IVe)	H(CF_2)₂	Ph	51	145–146	42,07 / 41,89	3,31 / 3,52	20,44 / 20,39	9,02 / 9,51	7,34 / 7,52	$C_{13}H_{12}F_4N_2 \cdot HClO_4$	3280 1550	1630 1600 1580 sh	5,80 s	4,15 br.s	7,70 m	6,75 t.t (52,3 4,7)	10,15 br.s
(IVf)	H(CF_2)₂	C(Me)₃	71	154–156	37,78 / 37,46	5,10 / 4,86	21,46 / 21,55	10,47 / 10,05	8,08 / 7,94	$C_{11}H_{16}F_4N_2 \cdot HClO_4$	3320 1565	1630 1620 sh	5,60 s	3,99 br.s	1,43 s	6,60 t.t (52,3 4,7)	10,05 br.s

*^{19}F NMR spectrum (δ, ppm, HFB): 95.32 s (CF_3).

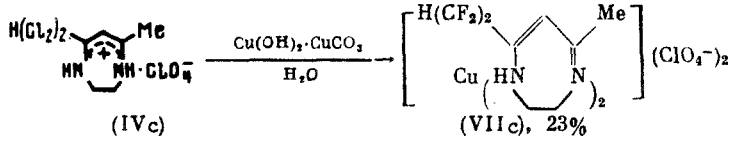
†ν_{ClO_4} = 1050.620 cm^{-1}.



R = Me, R¹ = Me (Ia, IVa, Va), CF_3 (Ib, VIb), H $(CF_2)_2$ (Ic, IVc, Vc, VIc).
R = Ph, R¹ = CF_3 (Id, IVd, Vd, VId), H $(CF_2)_2$ (Ie, IVe, Ve, VIe).
R = *t*-Bu, R¹ = H $(CF_2)_2$ (If, IVf, Vf).
F = R¹ = CF_3 (Ig, VIg).

It turned out that 1,3-diketones (Ia, c-f) upon reaction with EDA·$HClO_4$ undergo only condensation with the formation of the monohydroperchlorates of 1,4-diazepines (IVa, c-f) (Table 2). The hexafluorophosphates (Va, c-f) (Table 1) were obtained by the exchange reaction with $NaPF_6$ from (IVa, c-f), while the free bases (VIc-e) were obtained by the exchange reaction with alkali (Table 3). The salts (IVb, g) could not be recovered for TFAA (Ib) and HFAA (Ig). In this case only (VIb, g) were obtained, which is evidence of the reduced basicity of 1,4-diazepines that have electron-acceptor CF_3 substituents and their high thermodynamic stability with respect to the corresponding conjugated acids (in contrast to unsubstituted 2,3-dihydro-1H-1,4-diazepines [12]). The negative polar effect of the HCF_2—CF_2 group in (VIc) is smaller than that of CF_3 [13], which evidently governs the possibility of isolating the protonated salts (IVc) and (Vc). The t-Bu and Ph substituents make a significant contribution to stabilizing the monoprotonated base, by assuring the stability of the salts (IVd-f) and (Vd-f) so much that for (IVf) one cannot recover the base (VIf).

The structure of the compounds that were obtained was confirmed by elemental analysis and IR and PMR spectroscopy (see Tables 1-3). However, these methods do not permit an unambiguous choice between the structure of the diazepine (IV) and the tetraene tetraazamacrocycle compound (III). Moreover, (IVc) forms the coordination compound (VIIc) with copper-(II) carbonate (by the technique of [11, p. 74])

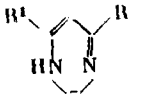


Mass spectrometry was used to make a final structure attribution for (IVc) and (Vc, e, f) (the mass spectra of the salts of the amines with inorganic acids are identical to the spectra of the starting amines [14]).

The mass spectra of (IVc) and (Vc, e, f) contains a peak $[M^+]$ that corresponds to the molecular weight of 1,4-diazepine, and not the macrocyclic compound (III).

Thus, in contrast to the reaction of α,β-unsaturated ketones with EDA perchlorate, in which salts of 1,4-diazepines are by-products in the formation of diene tetraazamacrocycles [11], for 1,3-diketones this direction becomes the main one, regardless of the nature of the dicarbonyl fragment.

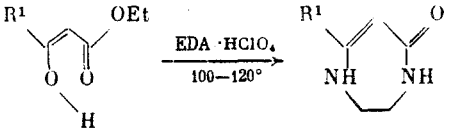
TABLE 3. Characteristics of 2,3-Dihydro-1H-1,4-diazepines (VIb-e, g)



Compound	R¹	R	Yield, %	Mp, °C (solvent)	Found/Calculated, % C	H	F	N	Empirical formula	Compound	IR spectrum, cm^{-1} NH	PMR spectrum (δ, ppm, acetone-d_6) C=N, C=C	CH	$CH_2N=C$	CH_2N-C	R	$H(CF_2)_2$ (J, Hz)	NH
(VIb)	CF_3	Me	76	116–117 (hexane) (see [7])	47,50 / 47,19	5.11 / 5,09	31,80 / 31,99	16,00 / 15,73	$C_7H_8F_3N_2$	(VI·b)	3200, 3100, 1530	1630, 1600	4,80 s	3,97 m	3.37 m	2,96 s	–	6,70 br.s
(VIc) *	$H(CF_2)_2$	Me	75	–	45,74 / 45,72	4,82 / 4,80	35,98 / 36,16	12,86 / 13,33	$C_8H_{10}F_4N_2$	(VIc) †	3100, 3240, 1535	1610, 1570	5,08 s	3,88 m	3,38 m	2,06 s	6.59 t.t (53,29 5,86)	5,04 br.s
(VId) *	CF_3	Ph	95	147–148 (water) (see [7])	60,10 / 60,00	4,89 / 4,62	23,54 / 23,72	11,57 / 11,66	$C_{12}H_{11}F_3N_2$	(VId)	3200, 1530	1610, 1575	5,19 s	4,02 m	3,51 m	7,05 m	–	7,25 br.s
(VIe) *	$H(CF_2)_2$	Ph	95	118–119 (water) (see [7])	56,61 / 57,35	4,46 / 4,44	28,10 / 27,92	10,27 / 10,29	$C_{13}H_{12}F_4N_2$	(VIe)	3200, 1525	1600, 1565	5,30 s	4,03 m	3,53 m	7,05 m	6,56 t.t (53,30 6,00)	7,10 br.s
(VIg)	CF_3	CF_3	85	109–110 (hexane)	36,09 / 36,22	2.82 / 2,60	49,04 / 49,11	12,47 / 12,07	$C_7H_6F_6N_2$	(VIg)	3200, 3100, 1570	1640	5,35 s	3,80 m		–	–	6,70 br.s

*Yields given with respect to salts.
†IR spectrum in a thin layer.

The reaction of (IIb, c) with EDA·$HClO_4$ leads to 1,2,3,4-tetrahydro-1,4-diazepin-5-ones (VIIIb, c) similar to the reaction of TFAAE with EDA or to heating of the inner salt of TFAAE aminoethylamide [10], although for AAE a mixture of products that is difficult to interpret is formed under these conditions.



(IIb, c) (VIIIb, c), 58—78%

$R^1 = CF_3$ (IIb, VIIIb), $H(CF_2)_4$ (IIc, VIIIc).

The presence of $HClO_4$ provides cyclization with EDA to 1,4-diazepinone for (IIc), while according to the data of [10] the 1,3-keto ether with C_2F_5 substituents does not form 1,4-diazepinone in the reaction with EDA.

EXPERIMENTAL

The IR spectra of the compounds were recorded on a Specord 75 IR spectrometer in the 400-4000 cm^{-1} interval in a mineral oil suspension. PMR spectra were recorded on a Tesla BS-567 A instrument (^1H, 100 MHz, acetone-d_6, relative to TMS). Mass spectra were acquired on a Varian MAT 311a instrument in standard regime. The molecular weight was measured by the ITEK method in DMF on a Hitachi Perkin-Elmer 115 instrument. Column chromatography was done on silica gel L 100/250 using MeOH as eluent.

Monohydroperchlorates of 2,3-Dihydro-1H-7-fluoroalkyl-1,4-diazepines (IVa, c-f). A mixture of 2.6 g (10 mmoles) EDA·$2HClO_4$, 0.6 g (10 mmoles) anhydrous EDA, and 25 mmoles (Ia, c-f) was carefully heated for 8-10 h at 100-120°C. The reaction mixture was dissolved in 20 ml alcohol, precipitated with ether, and (IVa, c-f) was obtained. The yields and physicochemical constants are given in Table 2. Mass spectrum of (IVc), (m/z): 210 $[M - HClO_4]^+$.

Monohydrohexafluorophosphates of 2,3-Dihydro-1H-7-fluoroalkyl-1,4-diazepines (Va, c-f). Solutions of 2.52 g (1.5 mmoles) $NaPF_6$ in 30 ml water and 1.5 mmoles (IVa, c-f) in 20 ml water were mixed, the mixture was cooled on an ice bath for 2 h, filtered, recrystallized from water, and dried in vacuum. The yields and constants of the substances are given in Table 2. Mass spectra of (V) (m/z): (Vc), 210 $[M - HPF_6]^+$; (Ve), 272 $[M - HPF_6]^+$; (Vf), 252 $(M - HPF_6]^+$.

2,3-Dihydro-1H-7-fluoroalkyl-1,4-diazepines (VIb-Vg). (VIc-e) were obtained from the corresponding (IVc-e). To 1 mmole (IVd, e) in 10 ml water was added an aqueous NaOH solution to pH 10-11, the crystalline product was filtered off, and crystallized from a mixture of alcohol and water. The result was 0.95 mmole (VId, e). (VId): Found M = 244 a.u. Calculated M = 240 a.u. (VIe): Found M = 273 a.u. Calculated M = 272 a.u.

To 2 g (6 mmoles) (IVc) in 10 ml alcohol was added an alcoholic solution of KOH to pH 10-11, $KClO_4$ was filtered off, and the solvent was evaporated. Column chromatography produced 1.0 g (75%) resinous (VIc).

Synthesis of (VIb, g). A mixture of 2.6 g (10 mmoles) EDA·$2HClO_4$, 0.6 g (10 mmoles) anhydrous EDA, and 25 mmoles (Ib, g) was heated for 8-10 h at 100-120°C. The reaction mixture was dissolved in 20 ml alcohol, an alcoholic solution in KOH was added to pH 10-11, $KClO_4$ was filtered off, and the solvent was evaporated. Extraction of the residue with hot hexane followed by recrystallization from hexane produced (VIb, g). The yields and constants of the substances are given in Table 3.

Bis(1,4-diazepine) copper(II) perchlorate (VIIc) was obtained by the technique of [11, p. 74] from 1.6 g (5.2 mmoles) (IVc) and 0.7 g (3.1 mmoles) $CuCO_3 \cdot Cu(OH)_2$. The yield of (VIIc) was 0.4 g (23%), mp 181-182°C. Found, %: C 28.66, H 3.45, F 22.22, Cl 10.40, N 7.99. $C_{16}H_{20}F_8Cl_2N_4O_8Cu$. Calculated, %: C 28.14, H 2.95, F 22.26, Cl 10.38, N 8.21. IR spectrum (ν, cm^{-1}): 3300, 1565 (NH), 1645, 1590 (C=N, C=C).

1,2,3,4-Tetrahydro-7-trifluoromethyl-1,4-diazepin-5-one (VIIIb). The following mixture was heated: 2.6 g (10 mmoles) EDA·$2HClO_4$, 0.6 g (10 mmoles) anhydrous EDA, and 4.6 g (25 mmoles) TFAAE (IIb). Treatment of the reaction mixture with KOH to pH 10-11, filtration to remove $KClO_4$, and removal of solvent produced (VIIIb) in the form of pale yellow crystals.

Recrystallization from MeOH produced 2.1 g (58%) (VIIIb), mp 191-192°C/methanol (see [10]). Found, %: C 40.61, H 3.90, F 31.67, N 15.28. $C_6H_7F_3N_2O$. Calculated, %: C 40.09, H 3.92, F 31.64, N 15.52. IR spectrum (ν, cm^{-1}): 3280, 3170, 1560 (NH), 1650 (C=O), 1620 (C=C). PMR data correspond to those given in [10].

7-Octafluorobutyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one (VIIIc) was obtained analogously from 7.1 g (25 mmoles) (IIc), 2.6 g (10 mmoles) EDA·$2HClO_4$, and 0.6 g (10 mmoles) EDA; (VIIIc) was purified by precipitation from MeOH with water. The yield of (VIIIc) was 4.9 g (78%), mp 165-166°C (methanol–water). Found, %: C 34.52, H 2.49, F 48.60, N 8.73. $C_9H_8F_8 \cdot N_2O$. Calculated, %: C 34.63, H 2.58, F 48.69, N 8.97. IR spectrum (ν, cm^{-1}): 3250, 3180, 1560 (NH), 1640 (C=O), 1620 sh (C=C). PMR spectrum (δ, ppm, J, Hz): 4.89 s (1H, CH), 3.51 m (2H, CH_2), 3.58 m (2H, CH_2), 6.77 t.t (1H, $H(CF_2)_4$, J = 51.18, 5.63), 6.90 br.s (1H, NH), 7.50 br.s (1H, NH).

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