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PERFLUOROACYLHYDRAZONES OF AROMATIC ALDEHYDES. SYNTHESIS AND PROPERTIES

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The available published information on high tubercular-static (both in vitro and in vivo), antimalarial, hypotensive, etc. activity of some phtalazine derivatives (benzo[d]pyridazine) stimulated us to start studies on synthesis and properties of their fluorinated analogues.

One of the common methods for phtalazine derivatives preparation is that of cyclodehydration of aromatic aldehyde acylhydrazones [1]. The latter are easily produced through the condensation of hydrazides with appropriate aldehydes. It is of both scientific and practical interest to carry out the said conversion with hydrazides of fluorine-containing acids.

Our studies resulted in the conclusion that under action of dehydrating agents the aromatic aldehyde acylhydrazones "A" give either acyclic ("B") or heterocyclic ("C" and "D") products, both having potential as biologically active substances (see Diagram 1).

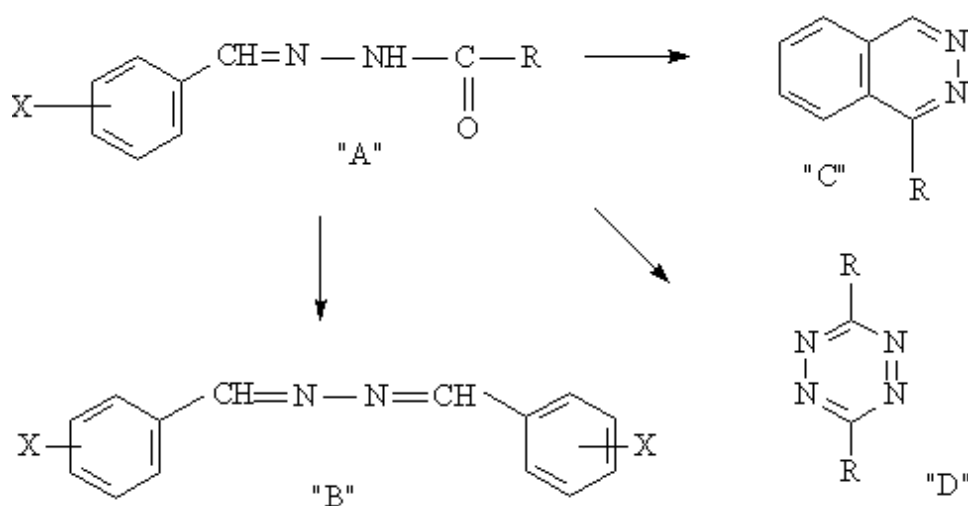


DIAGRAM 1

Acylhydrazones with perfluorinated substituents in the molecule acyl-group were studied as precursors of heteroaromatics in relation to diverse biological activity of fluorine-substituted heterocycle substances.

We have synthesized a number of perfluoroacylhydrazones "A" ($\text{R}=\text{CF}_3$, C_4F_9 , C_6F_{13} ; $\text{X}=\text{H}$, 2-HO-, 4-HO-, 4-Cl-, 4- NO_2 -, 4-(CH_3)₂N-) (see Diagram 2).

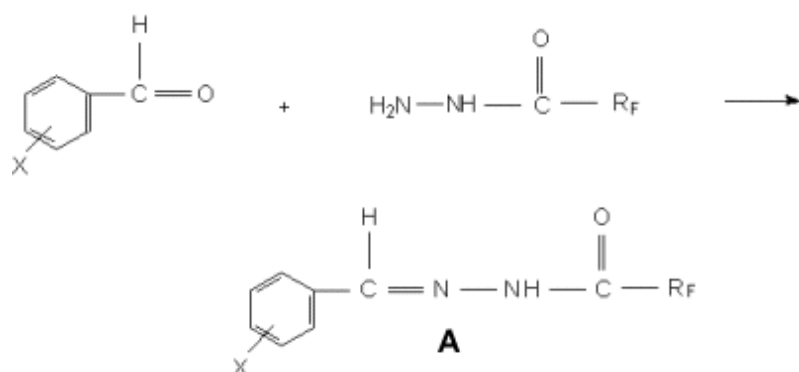


DIAGRAM 2

Perfluoroacylhydrazones "A" are formed through interaction of equimolar amount of aromatic aldehyde with perfluoro-acyl-hydrazine in alcohol at moderate heating (3-4 hours, 40-50°C). Their isolation procedure implies partial evaporation of the solvent and dissolving of the reaction mass in water. The product yield achieves 80-90%.

The completeness of the reaction and the product purity were controlled with the help of thin-layer chromatography. The structures of the synthesized compounds were confirmed by IR-spectroscopy, NMR-spectrometry and chromat-mass-spectrometry. Some properties of the synthesized acylhydrazones are presented in Table 1.

Conversion of perfluoroacylhydrazones under the action of some dehydration agents ($\text{PCl}_5/\text{POCl}_3$, POCl_3 in CCl_4 , HCl in pentanole at heating) was investigated. Perfluoroacylhydrazones with electron-seeking substituents in their aromatic fragments were found to be chemically inert to the action of phosphorus oxychloride: boiling for 5-8 hours in tetrachloromethane in the presence of phosphorus oxychloride has not produced any change in the substance structure. The IR spectra of the substances after 6 hours of boiling were found to be identical with those of initial acylhydrazones, the same about their RF values.

Benzaldehyde perfluoroacylhydrazones and also perfluoroacylhydrazones with electron-donating substituent in aromatic fragment form acyclic products "B" under the action of the above mentioned agents. The structure of benzylidene-azines "B-1" and "B-5" was confirmed by their IR-spectra, NMR ^1H and ^{13}C and by mass-spectrometry: intensive peaks corresponding to molecular ions 208 and 294 are present in those substances mass-spectra.

The characteristics of the products of the cyclization process are shown in Table 2.

TABLE 1
CHARACTERISTICS OF TRIFLUOROACYLHYDRAZONES

R _f	X	R	T melt °C	IR spectra cm ⁻¹
CF ₃ "À-1"	H	H	103-105	3400; 3220; 3080-2900; 1710; 1630; 1610; 1605; 1580; 1335; 1315; 1230; 1205; 1170; 1155; 1060; 1030; 1000; 975; 965; 930; 850; 760; 740; 695; 660; 640; 530
CF ₃ "À-2"	p-Cl-	H	227 (decomp.)	1680; 1630; 1600; 1595; 1580; 1480; 1320; 1210; 1180; 1095; 1020; 975; 940; 870; 835; 830; 730; 560; 505
CF ₃ "À-3"	p-NO ₂	H	254 (decomp.)	1685; 1635; 1600; 1530; 1295; 1215; 1110; 1025; 985; 980; 960; 860; 840; 750; 695; 560 495
CF ₃ "À-4"	p-HO-	H	198 (decomp.)	3490; 1680;5; 1675; 1625; 1610; 1600; 1565; 1515; 1505; 1300; 1285; 1260; 1235; 1205; 1165; 1130; 1025; 970; 960; 945; 890; 840; 820; 785; 720; 555; 510; 490
CF ₃ "À-5"	p-(CH ₃) ₂ -N-	H	79-82	1730; 1675; 1665; 1605; 1590; 1550; 1530; 1360; 1320; 1250; 1235; 1205; 1190; 1180; 1130; 1070; 950; 825; 730; 525
C ₄ F ₉ "À-6"	H	CF ₃	78-80	3434; 3040-2920; 1970; 1670; 1605; 1566; 1493; 1444; 1363; 1311; 1286; 1178; 1163; 1075; 1023; 915; 760; 690; 652; 565

TABLE 2
CHARACTERISTICS OF PRODUCTS OF DEHYDRATION OF PERFLUOROACYLHYDRAZONES

Initial substance	Product	T melt., °C	IR spectra, cm ⁻¹	Spectra ^1H , md DMCO-d ⁶	Spectra ^{13}C , md
"À-1"	"B-1"	67-69	3200, 1710, 1670, 1625, 1575, 1305, 1210, 1170, 1150, 1070, 1020	7,50; 7,51; 7,88; 7,89; 8,72	127,62; 128,29; 128,83; 131,29; 161,43
"À-2"	"A-2"	-	1680; 1630; 1600; 1595; 1580; 1480; 1320; 1210; 1180; 1095; 1020; 975; 940; 870; 835; 830; 730; 560; 505	-	-
"À-3"	"A-3"	-	1685; 1635; 1600; 1530; 1295; 1215; 1110; 1025;	-	-

			985; 980; 960; 860; 840; 750; 695; 560 495		
"À-5"	"B-5"	208-211	3200; 1700; 1605; 1550; 1520; 1300; 1230; 1185; 1170; 1065; 960; 950; 820; 750; 730; 530	6,7; 6,72; 7,25; 7,68; 7,70; 8,57	111,72; 122,30; 129,81; 152; 10; 160;67

EXPERIMENT

NMR spectra ^1H and ^{13}C of the substance solutions in DMSO- d_6 were recorded with the help of Bruker AM 500 NMR spectrometer (work frequencies were 500MHz and 75MHz respectively), the chemical shifts are shown relative to TMS. IR spectra of the samples suspension in vaseline oil were recorded with the help of IR-spectrophotometer Specord IR 75.

Hydrazide of trifluoroacetic acid was prepared from ethyl ester of trifluoroacetic acid [2] in line with the published methods [3, 4].

***N,N*-Trifluoroacetylbenzalhydrazone ("A-1").** The solution prepared of 2,2 g (0,02 mole) of benzaldehyde in 5 ml of alcohol was added to 2,56 g (0,02 mole) of trifluoroacetylhydrazine in 45 ml of alcohol. The blend was mixed for 2 hours at room temperature. The blend was allowed to stand for a night till the sediment disappeared. The solvent was removed until dry under vacuum of a water-jet pump. The obtained product was 4,1 g (95%) benzalhydrazide (4 á), yellowish-brown powder. R_f 0,10 (toluene).

***Cyclocondensation of N,N*-Trifluoroacetylbenzalhydrazone.** To the suspension of 2,16 g (0,01 mole) benzalhydrazide of trifluoroacetic acid in 25 ml of chloroform we added the solution prepared of 1,1 ml of phosphorus oxychloride in 5 ml of chloroform under continuous blending during 30 min. The resulted blend was heated to 70 $^{\circ}\text{C}$ and allowed to stand for 5 hours. Then the solvent was distilled, and the residue was dried under vacuum, treated with 70 ml of water, and neutralized with sodium bicarbonate. The product was filtered, washed with water in the filter (2*20 ml), and dried in the air. The obtained product was "B-1" 0,9 g (46 %), yellow powder. R_f 0,50 (toluene).

Calculated: C 54,55; H 1,86; F 28,79. $\text{C}_9\text{H}_5\text{F}_3\text{N}_2$.

Obtained: C 54,67; H 2,03; F 28,7.

IR spectrum, vaseline oil (cm^{-1}): 3200, 1710, 1670, 1625, 1575, 1305, 1210, 1170, 1150, 1070, 1020.

NMR ^1H , DMSO - d_6 (md): 7,50; 7,51; 7,88; 7,89; 8,72.

NMR ^{13}C , DMSO- d_6 (md): 127,62; 128,29; 128,83; 131,29; 161,43.

Mass spectrum: m/z 208 [M^+].

***N,N*-Trifluoroacetyl(δ - δ benzal)hydrazone ("A-2").** The solution of 3,5 g (0,025 mole) of δ -chlorobenzaldehyde in 20 ml of alcohol was added to the solution of 3,2 g (0,025 mole) of trifluoroacetylhydrazine in 10 ml of water under continuous mixing at room temperature. The blend was mixed for 2 hours and allowed to stay for a night. The drained light-lemon sediment was dried in the air. The yield was 3,6 g (57,4%). R_f 0,66 (toluene); 0,80 (toluene/chloroform = 4:1).

***N,N*-Trifluoroacetyl(δ -nitrobenzal)hydrazone ("A-3").** Under similar conditions (see "A-2") from 4,35 g (0,03 mole) of δ -nitrobenzaldehyde and 3,48 g (0,03 mole) of trifluoroacetylhydrazine we obtained 4,7 g (60%) of light-yellow crystal powder.

***N,N*-Trifluoroacetyl(δ -oxybenzal)hydrazone ("A-4").** Prepared at the same manner as ("A-3") from 4,20 g (0,034 mole) of δ -oxybenzaldehyde and 4,9 g (0,039 mole) of trifluoroacetylhydrazine. The yield was 4,6g (65,7%).

***N,N*-Trifluoroacetyl(δ -dimethylaminebenzal)hydrazone ("A-5").** The solution of 4,2 g (0,03 mole) of trifluoroacetylhydrazine in 25 of alcohol was added to the solution of 4,5 g (0,03 mole) of δ -dimethylaminebenzaldehyde in 50 ml of alcohol under continuous mixing during 30 min. The blend was allowed to stay for 24 hours at room temperature, after that 50 ml of water was added. The sediment was drained and dried. The yield was 6,0 g (77 %), O.melt. 79-82 $^{\circ}\text{C}$.

***Cyclocondensation of N,N*-trifluoroacetyl(δ - dimethylaminebenzal)hydrazone.** The solution prepared of 3 g (0,02 mole) of phosphorus oxychloride in 5 ml of carbon tetrachloride was added to the suspension prepared of 1,56 g (0,006 mole) of *N,N*-trifluoroacetyl-(δ -dimethylaminebenzal)hydrazone ("A-5") in 25 ml of carbon tetrachloride under continuous mixing during 30 min. The reaction blend was boiled for 14 hours under stirring. The solvent was distilled, the residue was treated with 30 ml of alcohol and then with 20% solution of sodium carbonate until $\text{d}\bar{\text{I}}=8$. The sediment was drained and dissolved in 30 ml of chloroform. The solvent was evaporated. The product was re-crystallized from alcohol. The yield was 0,7 g (47%); light brown powder, O.melt. was 208-211 $^{\circ}\text{C}$. NMR ^1H , CDCl_3 (md.): 7,24; 7,44; 7,45; 7,94; 7,95; 7,96. NMR ^{13}C , CDCl_3 (md): 126,63; 128,35; 129,60; 138,50; 157,74. Mass-spectrum: m/z 294 [M^+].

***N,N*-Tridecafluoroheptanoyl-(δ -dimethylaminobenzal)hydrazone.** The solution prepared of 2,0 g (0,0053 mole) of hydrazide of perfluoroenanthoil acid (T melt. 85⁰C) in 25 ml of alcohol was added to the suspension prepared of 0,75 g (0,005 mole) of δ -dimethylaminobenzaldehyde in 15 ml of alcohol under stirring at room temperature, then heated to 45-50⁰C and allowed to stay for 4 hours under continuous stirring, and for a night at room temperature. Crystal sediment was formed. We added 50 ml of water under stirring. The formed sediment was drained and dried. The yield was 2,2 g (85%); \bar{O} melt. 96-98⁰C. C₁₆H₁₂F₁₃N₃O.

***N,N*-Nonafluoropentanoyl-(δ -dimethylaminobenzal)-hydrazone.** Prepared at the same manner from 0,005 mole of δ -dimethylaminobenzaldehyde and hydrazide of perfluoropentane acid.

***N,N*-Nonafluoropentanoyl -(2,4-dimethoxybenzal)-hydrazone**

Acetophenone trifluoroacetylhydrazone ("A-6"). Prepared at the same manner as ("A-4") from 3,6 g (0,03 mole) of acetophenone and 4,2 g (0,03 mole) of trifluoroacetylhydrazine with the yield 3,1 g (44 %).

CONCLUSIONS

1. A number of perfluoroacylhydrazones of aromatic aldehydes is synthesized.
2. It is determined that perfluoroacylhydrazones with electron-seeking substituents in aromatic fragment are chemically stable under the experiment conditions.
3. It is shown that dehydration of perfluoroacylhydrazones with electron-donating substituents occurs with splitting-off of perfluoroacyl fragment and results in formation of benzylidene-azine derivatives.

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