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ELECTROPHILIC SUBSTITUTION IN THE 1-PHENYL-2-ACYLPYRAZOLIDINE SERIES

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Bromination, nitration, and sulfonation reactions in the acylphenylpyrazolidine series were investigated. 1-(p-Bromophenyl)-2-acylpyrazolidines are formed in good yields in the bromination of these compounds over a wide range of temperatures in various solvents. Removal of the acyl group takes place simultaneously with sulfonation in the para position of the phenyl ring in the sulfonation of phenylacylpyrazolidines with concentrated sulfuric acid at room temperature; the p-sulfophenylpyrazolidines formed in this case exist in the form of betain structures. The nitration of acylphenylpyrazolidines with concentrated nitric acid (sp. gr. 1.52) leads to 1-(2,4-dinitrophenyl)-2-acylpyrazolidines. However, the nitration of these compounds with dilute nitric acid (sp. gr. 1.35) is accompanied by pronounced resinification; both 2,4-dinitrophenyl and p-nitrophenyl-2-acylpyrazolidines, as well as dimers of the latter, were detected among the reaction products.

Five-membered cyclic arylhydrazines — 1-arylpyrazolidines — are key compounds in the synthesis of pyrimidoindole derivatives [1]. Reduction [2, 3] with lithium aluminum hydride (LAH) of the corresponding readily available aryl-3-pyrazolidones or aryl-5-pyrazolidones serves as the principal method for their synthesis. However, compounds containing groups that are sensitive to the action of LAH in the phenyl ring cannot be obtained by this method. The electrophilic substitution reactions in cyclic arylhydrazine derivatives have not been adequately studied [4]. In our research we investigated the electrophilic substitution reactions (bromination, sulfonation, and nitration) of 1-phenyl-2-acylpyrazolidines (I). The action of bromine in various solvents (CCl_4, $CHCl_3$, and CH_3COOH) on these pyrazolidines (I) over a wide range of temperatures (from −10 to +20°C) leads to 1-(p-bromophenyl)-2-acylpyrazolidines (II) in 60-80% yields. Substitution in the para position is confirmed by the PMR spectra of these compounds, which contain two doublets of an A_2B_2 system in the aromatic proton region, and by the IR spectra, in which an absorption band of p-substituted phenyl ring appears at 840 cm^{-1}. In contrast to 1-phenyl-3-pyrazolidone, the bromination of which is accompanied by simultaneous oxidation of the five-membered ring to the corresponding pyrazolone [5], products of oxidation of the pyrazolidine ring were not detected in the case of bromination of I. Moreover, isomers that are possible in the bromination reaction also were not found, i.e., the process is regiospecific.

The nitration of I proceeds less unambiguously. Thus nitration with dilute nitric acid (sp. gr. 1.35) in acetic anhydride at −10 to −30°C leads to a mixture of mononitro derivatives IVa-d in low yield containing their dimerization products (V). Nitration with concen-

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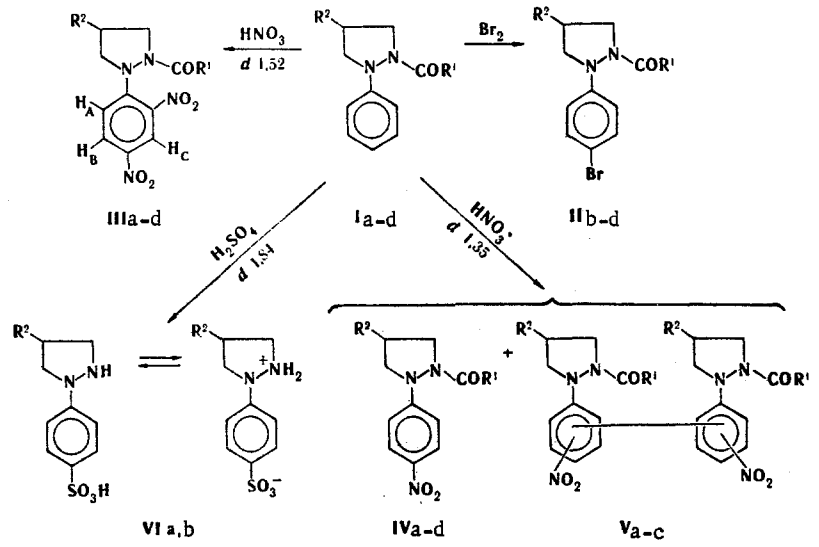
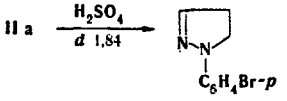


I–VI a $R^1=CH_3$, $R^2=H$; b $R^1=R^2=CH_3$; c $R^1=C_2H_5$, $R^2=H$; d $R^1=C_2H_5$, $R^2=CH_3$

trated nitric acid (sp. gr. 1.52), for which only dinitro derivatives III are obtained in high yields in some cases, proceeds more unambiguously. Their structures were confirmed by the PMR spectra, in which an H_A doublet with J_{AB} = 8.9 Hz, and H_B multiplet with J_{BA} = 8.9 Hz and J_{BC} = 1.8 Hz, and an H_C doublet with J_{CB} = 1.8 Hz are observed in the aromatic region. However, a mixture of IIIb, IVb, and Vb was obtained in the nitration of Ib (at −35°C). It should be noted that the nitration of I is accompanied by pronounced resinification and evidently cannot serve as a preparative method for the synthesis of nitrophenylpyrazolidines.

High-melting substances that are insoluble in all organic solvents but quite soluble in alkalis are formed by the action of concentrated sulfuric acid (sp. gr. 1.84) on 1-phenyl-2-acylpyrazolidines at 20°C. A study of the PMR spectra and the results of elementary analysis made it possible to establish that in this case detachment of an acyl group takes place at the same time as sulfonation. Regardless of the structure of R^1, the same compound (VI) is formed in the sulfonation. Intense absorption bands at 1140 ($\nu^{s}_{SO_2}$) and 1040 cm^{-1} ($\nu^{as}_{SO_2}$) and a broad absorption band at 2500-3100 cm^{-1}, which is characteristic for 1-arylpyrazolidine hydrochlorides, are observed in the IR spectra of compounds of the VI type; this indicates the existence of VI in the betain form. The aliphatic portion of the PMR spectrum of VIa resembles the aliphatic portion of the PMR spectrum of 1-phenylpyrazolidine hydrochloride, and two doublets of an A_2X_2 system of aromatic protons are observed in the aromatic proton region; this confirms substitution in the 4 position of the phenyl ring. When there is a substituent (for example, a methyl group or a chlorine atom) in the para position of the phenyl ring of the starting acylpyrazolidine, sulfonation does not occur under the described conditions, but the acyl group is removed. However, in contrast to sulfophenylpyrazolidines, which, like the hydrochlorides, are resistant to oxidation, only the corresponding Δ^2-pyrazoline VII can be isolated in this case.



VII

Signals of acyl group protons and signals of protons in the 3 position of the pyrazolidine ring are absent in the PMR spectrum of VII. A multiplet of an AA'BB' system of protons, which is characteristic for pyrazolines, is observed in the aliphatic portion of the spectrum, and the aromatic portion of the spectrum contains, in addition to the A_2B_2 system of a p-substituted phenyl ring, a singlet of the proton in the 3 position; this is also characteristic for Δ^2-pyrazolines, since it is known that $J_{3,4}$ does not exceed 1 Hz in the spectra of most of these compounds.

EXPERIMENTAL

The IR spectra of mineral oil and hexachlorobutadiene suspensions and CCl_4 solutions of the compounds were recorded with IKS-22 and UR-20 spectrometers. The PMR spectra of the compounds were recorded with Varian T-60 and RS-60 spectrometers with tetramethylsilane as the internal standard. The individuality of the compounds obtained was monitored by chromatography on activity II Al_2O_3 in a benzene–methanol system (9:1).

1-(p-Bromophenyl)-4-methyl-2-acetylpyrazolidine (IIb). A solution of 14 g (0.069 mole) of Ib in 100 ml of chloroform was cooled to −5°C, and a solution of 3.5 g (0.069 mole) of bromine in 10 ml of chloroform was added dropwise with stirring. After the mixture became colorless, it was washed successively with a saturated solution of sodium carbonate and water and dried with potassium carbonate. The chloroform was removed by distillation, and the resulting precipitate was recrystallized from benzene to give 12.9 g (66%) of IIb with mp 82-83°C. IR spectrum (CCl_4): 840 and 1660 cm^{-1} (amide C=O). PMR spectrum (CCl_4): 1.1 (d, 3H, 4-CH_3), 1.9 (s, 3H, CH_3CO), 2.1-3.9 (m, 5H, 3-, 5-, and 4-H), 6.8 (d, 2H, aromatic), and 7.2 ppm (d, 2H, aromatic). Found: C 50.7; H 5.2%. $C_{12}H_{15}BrN_2O$. Calculated: C 50.8; H 5.3%.

1-(p-Bromophenyl)-2-propionylpyrazolidine (IIc). A solution of 2.04 ml (0.04 mole) of bromine in 50 ml of CCl_4 was added slowly to a solution of 7.64 g (0.04 mole) of I in 50 ml of CCl_4, and the mixture was worked up as described above to give 11.6 g (75%) of bromo derivative IIc with mp 91-92°C (from hexane). IR spectrum: 840 and 1660 cm^{-1} (amide CO). Found: C 51.2; H 5.2%. $C_{12}H_{15}BrN_2O$. Calculated: C 50.9; H 5.3%.

1-(p-Bromophenyl)-4-methyl-2-propionylpyrazolidine (IId). A solution of 1.55 ml (0.03 mole) of bromine in 25 ml of acetic acid was added dropwise with cooling to −10°C to a solution of 6.6 g (0.03 mole) of Id in 50 ml of acetic acid, after which the mixture was made alkaline to pH ∿9. It was then extracted with ether, and the extract was dried with potassium carbonate. The ether was removed by distillation, and the residual oil was purified by low-temperature crystallization from hexane to give 5.75 g (64%) of IId with mp 41-42°C. Found: C 52.7; H 6.0%. $C_{13}H_{17}BrN_2O$. Calculated: C 52.5; H 5.7%.

1-(p-Sulfophenyl)pyrazolidine (VIa). A solution of 3.5 g (0.015 mole) of Ic in 50 ml of concentrated H_2SO_4 was allowed to stand at room temperature for 50 h, after which it was poured into a fivefold volume of water. The aqueous mixture was cooled, and the resulting precipitate was recrystallized from water to give 1.9 g (56%) of sulfonic acid VIa with mp 254-255°C. IR spectrum (hexachlorobutadiene suspension): 1040 ($\nu^{as}_{SO_2}$), 1140 ($\nu^{s}_{SO_2}$), and 2500-3000 cm^{-1} ($\overset{+}{N}H_2$). PMR spectrum (D_2O): 1.9-2.3 (m, 2H, 4-H), 2.8-3.3 (m, 4H, 3- and 5-H), 6.7-7.0 (d, 2H, C_6H_4), and 7.8-8.0 ppm (d, 2H, C_6H_4). Found: C 47.4; H 5.4%. $C_9H_{12}N_2O_3S$. Calculated: C 47.4; H 5.2%.

1-(p-Sulfophenyl)-4-methylpyrazolidine (VIb). This compound [1.34 g (60%)], with mp 235-237°C (from water), was similarly obtained from 2.65 g (0.012 mole) of pyrazolidine Id. IR spectrum: 1040 ($\nu^{as}_{SO_2}$), 1140 ($\nu^{s}_{SO_2}$), and 2500-3000 cm^{-1} ($\overset{+}{N}H_2$). PMR spectrum (in NaOH solution): 1.35 (d, 3H, 4-CH_3), 2.65-3.90 (m, 5H, 3-, 5-, and 4-H), 7.18 (d, 2H, C_6H_4), and 8.05 ppm (d, 2H, C_6H_4). Found: C 49.5; H 5.8; N 11.5%. $C_{10}H_{14}N_2O_3S$. Calculated: C 49.6; H 5.8; N 11.8%. Compound VIb was also obtained under the conditions described above by reaction of concentrated H_2SO_4 with 2-acetyl-, 2-butyryl-, and 2-isobutyryl-1-phenyl-4-methylpyrazolidines.

1-(p-Bromophenyl)-Δ^2-pyrazoline (VII). A 2.5-g (8.8 mmole) sample of IIc was dissolved in excess concentrated H_2SO_4, and the solution was allowed to stand at room temperature for 72 h. It was then poured over ice, and the aqueous mixture was treated with alkali (to pH ∿7) and extracted with ether. The ether was then removed by evaporation to give 1.3 g (65%) of VII with mp 80-81°C (from heptane). PMR spectrum (C_2Cl_4): 3.1-4.4 (m, 4H, 4- and 5-H), 7.1 (s, 1H, 3-H), 7.2-7.4 (d, 2H, C_6H_4), and 7.9-8.1 ppm (d, 2H, C_6H_4). Found: C 47.7; H 4.1%. $C_9H_9BrN_2$. Calculated: C 48.0; H 4.0%.

Nitration of 1-Phenyl-2-acetylpyrazolidine (Ia). A) A solution of 1 ml of nitric acid (sp. gr. 1.52) in 25 ml of acetic anhydride was added dropwise with stirring and cooling to −10°C to a solution of 2 g (0.01 mole) of Ia in 20 ml of acetic anhydride, and the mixture was poured into water. The aqueous mixture was made alkaline successively with potassium carbonate and NaOH solution to pH ∿11, and the mixture was extracted with chloroform. The

solvent was removed by distillation, and the residual oil was crystallized by the addition of ether to give 0.39 g (17%) of dinitro derivative IIIa with mp 120-121°C (from alcohol) and R_f 0.67. Found: C 47.0; H 4.3; M 280 (by mass spectrometry). $C_{11}H_{12}N_4O_5$. Calculated: C 47.2; H 4.3%; M 280.

B) A solution of 0.42 ml of nitric acid (sp. gr. 1.35) in 5 ml of acetic anhydride was added with cooling to −30°C to a solution of 1 g (0.005 mole) of Ia in 20 ml of acetic anhydride, after which the mixture was worked up as described above to give 0.8 g of crystals containing two substances with R_f 0.30 and 0.55. Recrystallization from alcohol gave 0.27 g of mononitro derivative IVa (R_f 0.55) with mp 133-135°C. Found: C 56.3; H 5.6%; M 235 (by mass spectrometry). $C_{11}H_{13}N_3O_3$. Calculated: C 56.1; H 5.5%; M 235. The alcohol-insoluble crystals (0.095 g) were identified as dimerization product Va with R_f 0.3 and mp 284-285°C (dec.). Found: C 56.4; H 5.5%. $C_{22}H_{24}N_6O_6$. Calculated: C 56.4; H 5.6%.

Nitration of Ic. A) Nitration of 2.04 g (0.01 mole) of Ic under conditions similar to those used for Ia (method A) gave 1.7 g (59%) of dinitro derivative IIIc (R_f 0.75) with mp 113°C (from alcohol). Found: C 49.0; H 4.9%, M 294 (by mass spectrometry). $C_{12}H_{14}N_4O_5$. Calculated: C 49.0; H 4.9%, M 294.

B) Nitration of 3.45 g of Ic by method B (under conditions similar to those used for Ia) gave 1.9 g of a mixture of two substances with R_f 0.38 and 0.65. Repeated recrystallization from alcohol gave 0.1 g of mononitro derivative IVc (R_f 0.65) with mp 91-92°C. Found: C 58.0; H 5.8%. $C_{12}H_{15}N_3O_3$. Calculated: C 57.8; H 6.0%. Also isolated was 0.26 g of dimer Vc with mp 245-246°C (R_f 0.38). Found: C 57.3; H 5.6%. $C_{24}H_{28}N_6O_6$. Calculated: C 57.7; H 5.6%.

Nitration of 4-Methyl-1-phenyl-2-acetylpyrazolidine (Ib). A) Nitration of 3.6 g (0.018 mole) of Ib at −35°C with nitric acid (sp. gr. 1.52) under the conditions described above gave 4.5 g of a crude substance containing three products with R_f 0.1, 0.41, and 0.67. The ether-insoluble crystals were separated and recrystallized several times from alcohol to give 0.66 g of dimer Vb with R_f 0.1 and mp 226-228°C. Found: C 57.8; H 5.6%. $C_{24}H_{28}N_6O_6$. Calculated: C 58.0; H 5.6%. Evaporation of the ether solution and crystallization of the residue from alcohol gave 1.2 g of mononitro derivative IVb with mp 98°C and R_f 0.41. Found: C 58.0; H 6.2%. $C_{12}H_{15}N_3O_3$. Calculated: C 57.8; H 6.4%. Workup of the residual alcohol solution yielded 0.83 g of dinitro derivative IIIb with mp 102°C and R_f 0.67. Found: C 48.3; H 4.8%. $C_{12}H_{14}N_4O_5$. Calculated: C 48.7; H 4.7%.

Nitration of 4-Methyl-1-phenyl-2-propionylpyrazolidine (Id). A) Nitration of 5 g (0.023 mole) of Id under conditions similar to those used in the preparation of Ic (method A) with nitric acid (sp. gr. 1.51) gave 5.2 g (87%) of dinitro derivative IIId with mp 128°C (from alcohol) and R_f 0.78. Found: C 50.6; H 5.3%. $C_{13}H_{16}N_4O_5$. Calculated: C 50.6; H 5.2%.

B) Nitration of 4.8 g (0.022 mole) of Id with nitric acid (sp. gr. 1.35) under the conditions described above gave an extremely contaminated mixture, from which 0.58 (10%) of mononitro derivative IVd, with mp 172-173°C, was isolated in the individual state after several recrystallizations. Found: C 59.2; H 6.3%. $C_{13}N_{17}N_3O_3$. Calculated: C 59.3; H 6.4%.

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