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STUDIES OF 1-AZABICYCLICS.

23.* NITRATION OF 1,2-DIHYDROPYRROLIZINE AND ITS HOMOLOGS

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Nitration of 1,2-dihydropyrrolizine and its homologs with a mixture of nitric acid and acetic anhydride has been shown to give a mixture of 5-, 6-, and 7-nitro-1,2-dihydropyrrolizines. The distribution of isomers with respect to the position of alkyl substituents in the nonaromatic portion of the bicyclic is discussed.

Within the pyrrole series, the nitration of pyrrole, its homologs, and various derivatives has been extensively studied [2-7]. 1,2-Dihydropyrrolizines are cyclic analogs of 1,2-dialkylpyrroles, and, in this regard, it would be interesting to study the behavior of compounds I-V in nitration reactions. We therefore decided, first of all, to determine the isomeric distribution of mononitro-substituted 1,2-dihydropyrrolizines and homologs among the nitration products; this knowledge is a prerequisite for a more general investigation of the effects of structural factors on the positional selectivity of the reaction.

*For Communication 22, see [1].

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TABLE 1. 5-Nitro-1,2-Dihydropyrrolizines

Compound	mp, °C (from petroleum ether)	UV spectrum λmax, nm	UV spectrum lg ε	Found, % C	Found, % H	Found, % N	Molecular formula	Calculated, % C	Calculated, % H	Calculated, % N
VI	83,0—84,5	352	4,06	55,5	5,6	19,0	$C_7H_8N_2O_2$	55,3	5,3	18,4
VII	47,0—47,5	353	4,20	57,9	6,0	17,8	$C_8H_{10}N_2O_2$	57,8	6,1	16,9
VIII	32,0—33,5	354	4,78	58,0	6,0	16,5	$C_8H_{10}N_2O_2$	57,8	6,1	16,9
X	64,0—65,5	355	4,29	63,9	8,1	13,6	$C_{11}H_{16}N_2O_2$	63,4	7,7	13,5

TABLE 2. ^{1}H-NMR Spectra of 5-, 6-, and 7-Nitro-1,2-dihydropyrrolizines*

Compound	δ, ppm† 5-H	δ, ppm† 6-H	δ, ppm† 7-H	J, Hz 5,6	J, Hz 5,7	J, Hz 6,7
VI	—	*7,02*	*5,88*	—	—	*4,3*
VII	—	*6,95*	*5,82*	—	—	*4,2* ‡
VIII	—	*7,02*	*5,83*	—	—	*4,5*
X	—	6,99	5,81	—	—	*4,1*
XI	7,13	—	6,09	—	1,2	—
XIII	7,28	—	6,19	—		—
XV	7,36	—	6,20	—	1,5	—
XVI	6,42	6,26	—	3,0	—	—
XVIII	6,53	6,35	—	3,1	—	—
XX	6,49	6,47	—	3,6	—	—

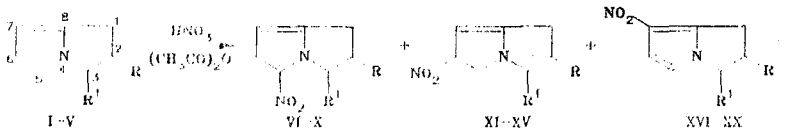
*Values obtained from the spectra of pure compounds are shown in italics; the remaining data was taken from the spectra of isomeric mixtures.

†Chemical shifts (in ppm) for assigned signals of other protons are as follows: VI (3-CH_2 4.43); VII (3-H_A 4.56, 3-H_B 3.89, 1-CH_2 3.00, 2-CH 2.54, 2-CH_3 1.28); VIII (3-CH 5.05, 3-CH_3 1.41); XIII (3-CH_3 1.47); XVIII (3-CH_3 1.47). Here and elsewhere the designation A refers to a proton located trans to a methyl group, and B refers to a proton in the cis position. In compounds XVI, XVIII, and XX the assignment of the 5-H and 6-H protons may be reversed.

‡Absolute values of other proton spin-spin coupling constants in compound VII: $^4J_{7\text{-H}, 1\text{-H}}$ 0.6, $^2J_{3\text{-H}A, 3\text{-H}B}$ 11.5, $^3J_{3\text{-H}A, 2\text{-H}}$ 7.5, $^3J_{3\text{-H}B, 2\text{-H}}$ 6.3 Hz.

TABLE 3. Isomeric Distribution Data for the Position of the Nitro Group in the Nitration Products of 1,2-Dihydropyrrolizines

Starting material	Isomeric position fraction for mixtures of 5-, 6-, and 7-nitro-1,2-dihydropyrrolizines, % 5	6	7
I	58±2	15±1	27±1
II	57±4	18±3	25±2
IV	59±3	15±2	25±1
III	43±1	23±1	34±2
V	44±1	27±1	29±1



I, VI, XI, XVI R=R¹=H; II, VII, XII, XVII R=CH₃, R¹=H; III, VIII, XIII, XVIII R=H, R¹=CH₃; IV, IX, XIV, XIX R=C₂H₅, R'=H; V, X, XV, XX R=H, R¹=C(CH₃)₃

The nitration of 1,2-dihydropyrrolizines was carried out in a manner analogous to that used for simple pyrroles [5], using a mixture of 94% nitric acid and acetic anhydride at temperatures between −50 and −60°C. In every case the reactions yielded a mixture of three compounds, which were identified as 5-, 6-, and 7-nitro-1,2-dihydropyrrolizine isomers, as well as a small amount of resinous material, which was not investigated.

The 5-nitro-1,2-dihydropyrrolizines VI-VIII and X were isolated by preparative column chromatography on aluminum oxide (Table 1) and were identified based on their UV and NMR spectra. Ethanolic solutions of compounds VI-VIII and X exhibit absorption maxima (λ_{max} 352-355 nm) whose position and intensity (log ε 4.20-4.96) are characteristic of pyrroles containing a nitro group in the α-carbon position of the ring [4, 5]. The δ and J values of the 6-H and 7-H proton signals and corresponding spin-spin couplings (Table 2) in the ^{1}H-NMR spectra of compounds VI-VIII and X are also characteristic of α-nitropyrroles [4, 5, 7].

The substitution pattern in the other isomers was interpreted on the basis of mixtures of the 6- and 7-nitro-1,2-dihydropyrrolizines (XI, XVI and XIII, XVIII), which were isolated from the nitration products of compounds I and III after preparative chromatography on aluminum oxide. The UV spectra of mixtures of XI, XVI and XIII, XVIII have diffuse bands in the absorption maxima region, which may be explained on the basis of overlap of the absorptions of two compounds in each case. The spectral parameters of a mixture of XI and XVI are λ_{max} 285 (log ε 3.97) and 327 nm (log ε 3.87), and of a mixture of XIII and XVIII, λ_{max} 285 (log ε 3.93) and 320-330 nm (log ε 3.90). A similar absorption pattern has been observed in the spectra of 3-nitropyrrole [4] and 2-methyl-3-nitropyrrole [5]. The ^{1}H-NMR spectra of these mixtures and, in particular, their comparison with the ^{1}H-NMR spectra of 3- or 4-nitropyrroles [4, 5, 7], provide unequivocal evidence for the assignment of the 6-position for the nitro group in compounds XI and XIII, and for the 7-position of the nitro group in compounds XVI and XVIII (Table 2).

In order to determine the ratio of the observed isomeric nitro-1,2-dihydropyrrolizines, we had to identify the peaks in the chromatograms of the reaction products after separation on immobile phases of polyethylene glycol 20,000, 1,4-butanediol dinitrate, and lucoprene. In all cases the first isomer to elute from the column was that with the nitro group in the 5-position; this was verified by comparison of the retention times of the components of the mixture with the retention times of reference compounds. The subsequent elution of the isomers with nitro groups in the 6- and 7- positions was determined by comparing the chromatograms and ^{1}H-NMR spectra of binary mixtures of XI and XVI and XIII and XVIII; it was found that the 7-nitro isomers eluted prior to the 6-nitro isomers. We are assuming that this observed elution order for the 7- and 6-nitro-1,2-dihydropyrrolizines is also applicable for other mixtures.

The isomeric distribution data for the nitro-1,2-dihydropyrrolizines was obtained from a series of experiments involving four nitration runs for each of the compounds I-V and four chromatographic measurements of the reaction products of each run of each experiment. The statistical results of these data are presented in Table 3. The error values were calculated based on 95% confidence.

As can be seen in Table 3, introduction of either a methyl or ethyl group in the second position of 1,2-dihydropyrrolizine does not significantly change the isomeric distribution ratio for the nitration products; this is due to the distance of these substituents from the reactive sites. Replacement of a hydrogen atom in position 3 with a methyl group decreases the fraction of isomer with a nitro group in the 5-position (compound III). This fact indicates that the methyl group results in partial blocking of the 5-position. The results obtained for the nitration of compound V with a tert-butyl group in the 3-position provide conclusive evidence for the large steric effect exerted by a substituent in the 3-position in deactivating position 5 of the dihydropyrrolizine system.

The larger amount of the 7-nitro-1,2-dihydropyrrolizines formed relative to the amount of the 6-nitro-1,2-dihydropyrrolizines is probably due to the influence of the aliphatic chain attached to $C_{(8)}$, which acts as a first order substituent.

We have previously described the hydroxyethylation [8] and carboethoxymethylation [9] of 1,2-dihydropyrrolizines, both of which also produce isomeric mixtures of substitution products. In both of these reactions, as in the nitration reaction, the isomer with the substituting group in the 5-position constitutes the largest product fraction. In contrast, the ratio between the 6- and 7-isomers depends on the nature of the reaction. In this regard, the nitration of 1,2-dihydropyrrolizines displays the least amount of positional selectivity.

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EXPERIMENTAL

PMR spectra (of solutions in CCl_4 at 0.18-0.3 mole/liter concentrations) were recorded on BS-477 (60 MHz), Perkin-Elmer R-12 (60 MHz), and Varian FT-80A spectrometers (resonance conditions were locked versus deuterium present in CD_3COCD_3 as solvent additive). HMDS was used as internal standard. Chemical shifts are reported on the δ scale relative to TMS. UV spectra were obtained on an SF-4 spectrophotometer.

Chromatographic analysis of the nitration products of compounds I, III-V was carried out on an LKhM-8MD chromatograph equipped with a flame ionization detector. The column was 1 m long and 3 mm in diameter and was filled with 6% polyethylene glycol 20,000 on silylated N-AW-HMDS chromaton (Chemapol, Czechoslavakia) (0.20-0.25 mm). The column temperature was 185°C; the rate of helium carrier gas flow was 70 ml/min. With the exception of compounds X, XV, and XX, this immobile phase was able to separate completely all of the isomers in the mixtures under investigation. 5-Nitro-1,2-dihydropyrrolizine (X) was completely separated from its isomers XV and XX, which overlapped partially. Use of lucoprene as the immobile phase on the same support material led to complete separation of all of the isomeric mixtures. The reaction products of compound II were analyzed on an LKhM-8MD chromatograph equipped with a thermal conductivity detector. Poly-1,4-butanediol dinitrate (10%) served as the immobile phase on the same support system described above. The column was 1.9 m long, 3 mm inner diameter, and its temperature was 223°C; the rate of hydrogen carrier gas flow was 110 ml/min.

The relative areas of the chromatographic peaks were used to calculate the weight concentrations of the individual components in the isomeric reaction mixtures.

Compounds I-V were prepared according to literature methods [10-13]. With regard to some discrepancy in the literature concerning the index of refraction of 1,2-dihydropyrrolizine (I) [10, 14-16], this value has been determined to be $n_D^{20} = 1.5293$ based on multiple syntheses and index of refraction measurements. The average yield of compound (I) was 44%.

Nitration of 1,2-Dihydropyrrolizine (I). A solution of 2 g (19 mmoles) of compound I in 9.5 ml of acetic anhydride was stirred vigorously at −50 to −60°C and an already cooled (about −40°C) solution of 1.5 g (24 mmoles) of HNO_3 (d 1.50) and 3.5 ml acetic anhydride was added dropwise over a 40 min period. The reaction mixture was stirred at −60°C an additional hour and cooling was discontinued. When the temperature of the reaction mixture reached 0°C, it was poured onto ice. The dark oil which separated was extracted with ether (5 × 50 ml). The combined ether extracts were washed with sodium hydroxide solution and dried over magnesium sulfate. The ether was evaporated and 15 g of product was obtained as a viscous dark brown oil, which crystallized upon cooling. The nitration experiment was repeated three times; each experiment was analyzed by GLC four times in order to determine the concentrations of isomers VI, XI, and XVI in the product mixtures.

Nitration of 1,2-Dihydropyrrolizines II-V. These experiments and analyses of the reaction products were carried out in an analogous manner. The total preparative yield of all of the isomeric nitrated 1,2-dihydropyrrolizine derivatives was about 50%.

5-Nitro-1,2-dihydropyrrolizine (VI). A 4-g mixture of isomers (VI) (58%), XI (15%) and XVI (27%) was subjected to column (2.5 × 70 cm) chromatography on aluminum oxide with benzene eluent. The separation was followed by TLC on an unmounted layer of activity II Al_2O_3.

Benzene was used as solvent and the separation was visualized using iodine and water vapor. Under the TLC conditions selected isomer VI was well separated (R_f 0.37) from the others, but isomers XI and XVI (Rf 0.23) could not be separated. Three fractions were obtained. The first fraction consists of isomer VI and yielded 0.25 g (6%) of compound VI, which was recrystallized from petroleum ether to give yellow crystals, readily soluble in ether, acetone, carbon tetrachloride, benzene, and ethyl acetate. The second fraction consisted of a mixture of three isomers, VI, XI, and XVI (0.9 g). The third fraction yielded 0.76 g of a mixture of isomers XI and XVI as yellow-green crystals, which were readily soluble in the same solvents as noted above for compound VI.

Compounds VII, VIII, and X were isolated in an analogous manner in yields of 11, 26. and 16%, respectively, from isomeric mixtures. In the last case the eluent used was 1:1 (by volume) benzene–hexane. We did not optimize the conditions for the preparative separation of the isomeric mixtures.

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