NITROSOALKYLUREAS WITH A QUATERNARY NITROGEN ATOM.

COMMUNICATION 2. SELECTIVITY IN NITROSATION IN THE PREPARATION OF CHOLINELIKE NITROSOALKYLUREAS

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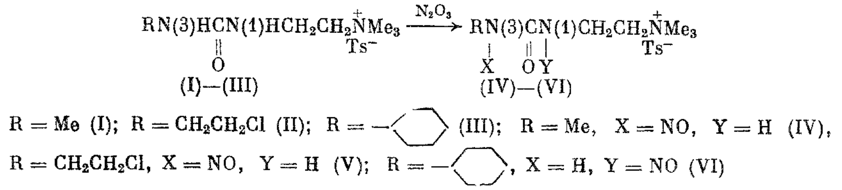
Cholinelike nitrosoalkylureas IV-VI [1] are of interest as potential anticancer agents. In principle, their preparation by means of nitrosation of alkylureidoethyltrimethylammonium salts I-III may lead to the formation of two isomers involving the position of the nitroso group. In the present research we made an attempt to explain the selectivity of nitrosation in terms of the theory of boundary orbitals with the aid of the results of quantum-chemical calculations.

Conclusions regarding the position of the nitroso group were drawn on the basis of a comparison of the PMR spectra of starting ureas I-III and their nitroso derivatives IV-VI (Table 1). The presence of signals of an ethyltrimethylammonium group and the NH protons of urea are common to the spectra of I-III. In the nitrosation of I the multiplet of the $\mathrm{NCH_2CH_2\overset{+}{N}}$ group (an A_2B_2 system) remains unchanged, whereas the doublet of the $\mathrm{CH_3N}$ protons undergoes the weak-field shift that is characteristic for $\mathrm{CH_3N(NO)}$ [2] and is converted to a singlet. In the nitrosation of III the multiplet of the $\mathrm{NCH_2CH_2\overset{+}{N}}$ group is split into two triplets (an A_2X_2 spin system, $\nu_{AX} = 86$, $J_{AX} = 6$ Hz); the position of the $\mathrm{CH_2N(NO)}$ methylene protons coincides with the data obtained for specifically deuterated compounds [3]. These results constitute evidence

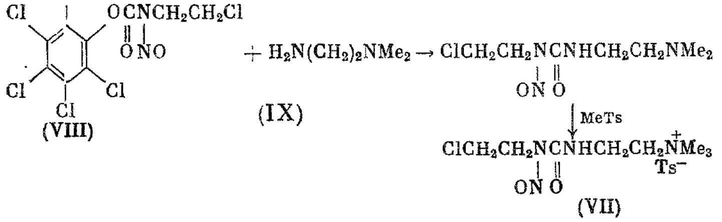


$$\underset{\text{(I)—(III)}}{\mathrm{RN(3)H\overset{O}{\overset{\|}{C}}N(1)HCH_2CH_2\overset{+}{N}Me_3\ Ts^-}} \xrightarrow{N_2O_3} \underset{\text{(IV)—(VI)}}{\mathrm{RN(3)(X)\overset{O}{\overset{\|}{C}}N(1)(Y)CH_2CH_2\overset{+}{N}Me_3\ Ts^-}}$$

R = Me (I); R = $\mathrm{CH_2CH_2Cl}$ (II); R = cyclohexyl (III); R = Me, X = NO, Y = H (IV), R = $\mathrm{CH_2CH_2Cl}$, X = NO, Y = H (V); R = cyclohexyl, X = H, Y = NO (VI)

that the nitroso group in IV is attached to the N^3 atom, whereas it is attached to the N^1 atom in VI. The presence of signals of one NH proton in the spectra also indicates the formation of one isomer.

In the nitrosation of II the appearance of one triplet in the region that is characteristic for the $\mathrm{CH_2N(NO)}$ protons [3] and the presence of one signal of NH protons constitute evidence for the formation of one of two possible isomers. In the spectrum of II the multiplet of the ethyltrimethylammonium group, and this makes it impossible to follow the changes in the signals of these groups and to establish the position of the nitroso group, although the spectrum of V makes it possible to assume the formation of an isomer with the nitroso group attached to the N^3 atom. To confirm this assumption we obtained isomer VII by a method that excludes the formation of the isomer with the nitroso group attached to the N^1 atom by means of pentachlorophenyl N-(2-chloroethyl)-N-nitrosocarbamate (VIII).



$$\underset{\text{(VIII)}}{\mathrm{C_6Cl_5OC(=O)N(NO)CH_2CH_2Cl}} + \underset{\text{(IX)}}{\mathrm{H_2N(CH_2)_2NMe_2}} \rightarrow \mathrm{ClCH_2CH_2N(NO)C(=O)NHCH_2CH_2NMe_2} \xrightarrow{MeTs} \underset{\text{(VII)}}{\mathrm{ClCH_2CH_2N(NO)C(=O)NHCH_2CH_2\overset{+}{N}Me_3\ Ts^-}}$$

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TABLE 1. Chemical Shifts of the Protons in I-VII (δ, ppm)

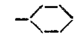
Compound	$\overset{+}{N}(CH_3)_3$	N^1H	N^3H	$NCH_2 \vdots CH_2\overset{+}{N}$	$ClCH_2 \vdots CH_2N$	CH_3N	
(I)	3,15 s	6,38 t	6,17 q	3,30–3,50 m	–	2,55 d	–
(II)	3,15 s	6,95 t	6,83 t	3,20–3,60 m		–	–
(III)	3,15 s	6,05–6,25 m		3,20–3,50 m	–	–	1,0–1,9 m
(IV)	3,15 s	8,00 t	–	3,25–3,60 m	–	3,05 s	–
(V)	3,15 s	9,08 t	–	3,50—3,80 m⋮4,12 t		–	–
(VI)	3,15 s	–	8,70 d	4,17 t ⋮3,30 t	—	–	1,1–2,0 m
(VII)	. 3,15 s	9,08 t	–	3,50—3,80 m: 4,12 t		–	–

TABLE 2. Partition Coefficients (c_i^{HOMO}) and Charges (q_i) on the N^1 and N^3 Atoms

Compound	q_{N^1}	q_{N^3}	$c_{N^1S}^{HOMO}$	$c_{N^1Px}^{HOMO}$	$c_{N^1Py}^{HOMO}$	$c_{N^1Pz}^{HOMO}$	$c_{N^3S}^{HOMO}$	$c_{N^3Px}^{HOMO}$	$c_{N^3Py}^{HOMO}$	$c_{N^3Pz}^{HOMO}$
(I)	−0,2315	−0,2199	−0,00499	−0,06517	0,00403	−0,12467	0,00635	−0,37305	−0,01081	−0,57351
(II)	−0,2315	−0,2315	−0,02804	0,03402	0,03553	−0,01353	−0,03042	0,36940	0,11109	0,43651
(III)	−0,2327	−0,2466	0,00027	0,01484	−0,00008	0,02362	−0,00049	−0,30835	0,02430	−0,48037

The good agreement in the PMR spectra of V and VII with respect to the position and form of the signals (see Table 1) and the complete coincidence of the IR spectra of these compounds [1] constitute evidence that an isomer with the nitroso group attached to the N^3 atom is formed in the nitrosation of II.

To explain the observed selectivity of the nitrosation we calculated the electronic structures of I-III by the CNDO/2 (complete neglect of differential overlap) method within the approximation of an isolated molecule. The results of the calculations showed that in the case of I and II the nitrosation reaction is orbitally controlled and takes place at the site of the highest partial electron density in the highest occupied molecular orbital (HOMO), viz., the N^3 atom; the charges (q_i) on the N^3 and N^1 atoms are virtually equal (Table 2). In the case of III steric conditions evidently direct the reaction to the N^1 atom, despite electronic factors. The electron densities in the HOMO for the N^3 and N^1 atoms were estimated by means of the calculated values of the c_i^{HOMO} coefficients for the AO of the given atoms (χ_i) in the HOMO expansion $\varphi_{HOMO} = \sum_i c_i^{HOMO} \chi_i$.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO [tetramethylsilane (TMS)] were recorded with a Tesla BS 467A spectrometer (100 MHz). The IR spectra of mineral oil films were obtained with a UR-20 spectrometer. The electronic structures were calculated by means of a system of Viking programs [4] with a BÉSM-6 computer. The geometries of the molecules were assigned on the basis of the data in [5-7]. Pentachlorophenyl N-(2-chloroethyl)-N-nitrosocarbamate (VIII) was obtained by the method in [8].

2-[3-(2-Chloroethyl)-3-nitrosoureido]ethyltrimethylammonium Tosylate (VII). A 0.20-g (0.0023 mole) sample of N,N-dimethylethylenediamine (IX) was added at −5°C to a solution of 1.0 g (0.0025 mole) of VIII in 5 ml of DMF. After 2 h, 0.64 g (0.0034 mole) of methyl tosylate was added, and the mixture was allowed to stand for 3 h. It was then diluted with 150 ml of absolute ether, and the mixture was allowed to stand overnight in a refrigerator. The precipitate was removed by filtration and recrystallized from absolute acetone to give 0.15 g (16%) of VII with mp 128°C (dec.). IR spectrum (ν, cm^{-1}): 1490 (N−NO); 1530 (N−H); 1720 (C=O); 3295, 3315 (N−H). Found: C 44.06; H 6.54; N 13.36%. $C_{15}H_{25}ClN_4O_5S$. Calculated: C 44.06; H 6.16; N 13.70%.

CONCLUSIONS

The selectivity of the nitrosation of cholinelike alkylureas is explained in terms of the theory of boundary orbitals.

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TELOMERIZATION OF ALKANE- AND ARENESULFONAMIDES WITH BUTADIENE CATALYZED BY PALLADIUM COMPLEXES

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In a continuation of our research [1-6] on the telomerization of 1,3-dienes with compounds that contain labile H atoms, for the first time we have investigated the reaction of butadiene with alkane- and arenesulfonamides under the influence of a catalyst of the Pd–Ln type, which is widely used in processes involving the telomerization of conjugated 1,3-dienes [7-9]. It might be assumed that the expected telomerization products, viz., N-substituted unsaturated sulfonamides, could be of interest for the synthesis of new effective antimicrobial preparations and complexing agents.

We have found that the reaction of N-methyl-p-toluenesulfonamide with 1,3-butadiene (BD) (in a ratio of 1:3) on a $Pd(acac)_2-PPh_3-AlEt_3$ catalyst (1:3:4) in toluene (100°C, 8 h) gives a mixture of unsaturated sulfonamides I and II, in which ~95% N-methyl-N-2,7-octadienyl-p-toluenesulfonamide (I) is present. The overall yield of I and II is no less than 99%. Under similar conditions N-methyl-n-butanesulfonamide reacts with BD to give unsaturated sulfonamides III and IV in a ratio of 9:1 in an overall yield of ~96%.

In contrast to N-substituted sulfonamides, unsubstituted toluene- and butanesulfonamides undergo reaction with BD under the conditions that we selected (100°C, 8 h) to give mixtures of mono- and dioctadienyl derivatives V, VI, and VII-X in high yields (90-98%).

According to data from the PMR and ^{13}C NMR spectra, dioctadienyl sulfonamides VII-X, in contrast to V and VI, are mixtures of 2,6- and 2,7-octadienyl sulfonamides in a ratio of 2:1. The chemical shift of the terminal Me group in VII (δ 17.90 ppm) constitutes evidence for the trans configuration of the C_6-C_7 double bond [10]. A comparison of the ^{13}C NMR spectra of individual amide VIII and the mixture of VII and VIII made it possible to sufficiently reliably establish the structures of VII and VIII. The amides in the mixture of IX and X were similarly identified.

In a study of the telomerization conditions on the compositions of the products of the reaction of butane- and toluenesulfonamides with BD we observed that exclusively di-2,7-octadienyl sulfonamides VIII and X are formed when the reaction time is increased to 20 h. These compounds are formed under the telomerization conditions, evidently as a result of a shift of the C_6-C_7 double bonds to the C_7-C_8 position under the influence

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