ELECTROPHILIC SUBSTITUTION IN A NUMBER OF N-EXO-CARBAMOYL DERIVATIVES OF SYDNONEIMINES

Z. A. Olovyanishnikova, B.I. Bryantsev, I. S. Slyusarenko, and V. G. Yashunskii

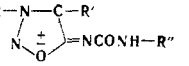
UDC 547.793.1:542.944.1'958.1

Depending on the character of the substituents and the reaction conditions, the bromination of N-exo-carbamoyl derivatives of sydnoneimines may proceed in the heterocyclic ring and (or) in the phenyl ring of the exocyclic substituent. Nitration proceeds only in the phenyl rings of the substituents.

Physiologically active and medicinal substances are found among N-exo-cyclic derivatives of sydnoneimines [1-3], but insufficient study has been devoted to the chemistry of these compounds. In particular, electrophilic substitution reactions at the quaternary carbon atom of the heterocyclic ring have received little study. These reactions take on special interest when substituents containing a phenyl group are present in the 3 position of the ring and the exocyclic nitrogen atom, inasmuch as the phenyl ring may also undergo electrophilic attack.

We have studied the bromination and nitration of N-phenylcarbamoyl-3-phenylisopropylsydnoneimine (I) – the new medicinal preparation "sidnokarb" [1] – and of its analogs – N-exo-methylcarbamoyl-3-phenylisopropyl- (II) and N-exo-phenylcarbomoyl-3-methylsydnoneimine (III) [4, 5].

The bromination of some N-exo-carbamoyl derivatives of sydnoneimines was previously described in [6], but the structures of the compounds obtained in this case were not established sufficiently clearly.



I-XV, XVIII, XIX

I $R=C_6H_5CH_2(CH_3)CH$, $R'=H$, $R''=C_6H_5$; II $R=C_6H_5CH_2(CH_3)CH$, $R'=H$, $R''=CH_3$; III $R=CH_3$, $R'=H$, $R''=C_6H_5$; IV $R=C_6H_5CH_2(CH_3)CH$, $R'=Br$, $R''=CH_3$; V $R=C_6H_5CH_2(CH_3)CH$, $R'=H$, $R''=4\text{-}BrC_6H_4$; VI $R=CH_3$, $R'=H$, $R''=4\text{-}BrC_6H_4$; VII $R=C_6H_5CH_2(CH_3)CH$, $R'=Br$, $R''=4\text{-}BrC_6H_4$; VIII $R=CH_3$, $R''=4\text{-}BrC_6H_4$, $R'=Br$; IX $R=C_6H_5CH_2(CH_3)CH$, $R'=Br$, $R''=2,4\text{-}Br_2C_6H_3$; X $R=C_6H_5CH_2CH_2$, $R'=H$, $R''=C_6H_5$; XI $R=3,4\text{-}(CH_3O)_2C_6H_3CH_2CH_2$, $R'=H$, $R''=C_6H_5$; XII $R=4\text{-}NO_2C_6H_4CH_2(CH_3)CH$, $R'=H$, $R''=2,4\text{-}(NO_2)_2C_6H_3$; XIII $R=4\text{-}NO_2C_6H_4CH_2(CH_3)CH$, $R'=H$, $R''=CH_3$; XIV $R=CH_3$, $R'=H$, $R''=2,4\text{-}(NO_2)_2C_6H_3$; XV $R=4\text{-}NO_2C_6H_4CH_2(CH_3)CH$, $R'=H$, $R''=C_6H_5$; XVIII $R=4\text{-}NO_2C_6H_4CH_2H_4CH_2CH_2$, $R'=H$, $R''=C_6H_5$; XIX $R=4\text{-}NH_2C_6H_4CH_2CH_2$, $R'=H$, $R''=C_6H_5$

The action of bromine on N-exo-methylcarbamoyl derivative II in glacial acetic acid gave monobromo derivative IV, which was isolated as the hydrobromide. The absence of the signal of a proton attached to C_4 in the PMR spectrum and of the absorption band of a C_4-H bond in the IR spectrum of the product, as well as the identical character of the singlets of the protons of the benzene ring in the PMR spectra of IV and II, indicate that the bromine atom in monobromo derivative IV is in the 4 position of the heterocyclic ring.

Monobromo derivatives V and VI were also isolated in the form of the hydrobromides in the bromination, under the same conditions, of I and III, which contain a phenylcarbamoyl substituent, but the bromine atom in them was found to be in the para position of the benzene ring of the exocyclic group. This was established unambiguously by means of the PMR spectra: the PMR spectra of bromo derivative V and

Institute of Biophysics of the Ministry of Public Health of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1198-1203, September, 1975. Original article submitted September 9, 1974.

TABLE 1. Properties of N-exo-Carbamoyl Derivatives of Sydnoneimines

Compound	mp, °C	Empirical formula	Found, %				Calc., %				ν_{C_4-H} cm^{-1}	PMR spectra, δ, ppm (J, Hz)†			Yield, %
			C	H	Br	N	C	H	Br	N		4-H	protons	NH-protons	
II	120—121	$C_{13}H_{16}N_4O_2$	60,4	6,4	—	21,2	60,4	6,2		21,5	3178	8,00	7,16		58
III	175—176	$C_{10}H_{10}N_4O_2$	55,0	4,6	—	25,3	54,9	4,6		25,5	3165	8,03	—	6,72—7,78 m	44
IV·HBr	121—122	$C_{13}H_{15}BrN_4O_2 \cdot HBr$	37,8	3,8	37,9	13,0	37,2	3,8	37,8	13,3	—	—	7,20	—	55
V	138—140	$C_{18}H_{17}BrN_4O_2$	53,9	4,5	19,8	13,8	53,8	4,3	19,9	13,9	3165	8,30	7,22	7,38 d (8,8), 7,64 d (8,8)	40
V·HBr	160—161	$C_{18}H_{17}BrN_4O_2 \cdot HBr$	44,8	3,8	32,8	11,7	44,9	3,8	33,1	11,6					65
VI·HBr	194—195	$C_{10}H_9BrN_4O_2 \cdot HBr$	32,6	2,9	—	15,1	31,9	3,1		14,8	3200	8,70	—	7,36 d (9,0), 7,52 d (9,0)	49
VII	128—129	$C_{18}H_{16}Br_2N_4O_2$	44,8	3,5	33,1	11,5	45,6	3,5	35,3	11,7	—	—	7,16	7,38d (9,0), 7,62d (9,0)	76
VIII	163—164*	$C_{10}H_8Br_2N_4O_2$	31,9	2,1	—	14,6	31,9	2,1		14,9	—	—	—	7,28 d (9,0), 7,58 d (9,0)	48
IX	125—126	$C_{18}H_{15}Br_3N_4O_2$	38,2	2,7	42,2	9,6	38,6	2,7	42,7	10,0	—	—	7,16	7,43 d (8,8 and 2,3)	46
XII	190—192	$C_{18}H_{15}N_7O_8$	47,2	3,3		20,6	47,4	3,3		21,4	3180	8,35	7,47 d (8,5) 8,12 d (8,5)	8,70d (2,5), 8,58d (9,2) 8,38d, 8,34d (2,5 and 9,2)	58
XIII	176—178*	$C_{13}H_{15}N_5O_4$	51,5	5,1		22,8	51,4	5,0		22,9	3160	7,96	7,47 d (8,5) 8,12 d (8,5)		64
XIV	201—202*	$C_{10}H_8N_6O_4$	38,3	2,5		26,9	38,8	2,6		27,2	3205	8,13	—	8,72d (2,5), 8,57d (9,2) 8,38 d 8,30d (2,5 and 9,2)	70
XV	148—150	$C_{18}H_{17}N_5O_4$	58,5	4,7			58,8	4,6			3140	8,16	7,46 d (8,5) 8,08 d (8,5)	6,68—7,66 m	37
XVIII	166—167*	$C_{17}H_{15}N_5O_4$	57,7	4,5		19,7	58,0	4,3		19,8	3180	8,12	7,48 d (8,5) 8,08 d (8,5)	6,70—7,60 m	49
XIX·2HCl	163—165	$C_{17}H_{17}N_5O_2 \cdot 2HCl$	51,7	5,1		17,6	51,5	4,8		17,8	3176	8,87	7,20 d (8,5) 7,52 d (8,5)	6,90—7,60 m	13

*Recrystallized from alcohol.

†The numbers without abbreviations pertain to singlets, and d is doublet and m is multiplet.

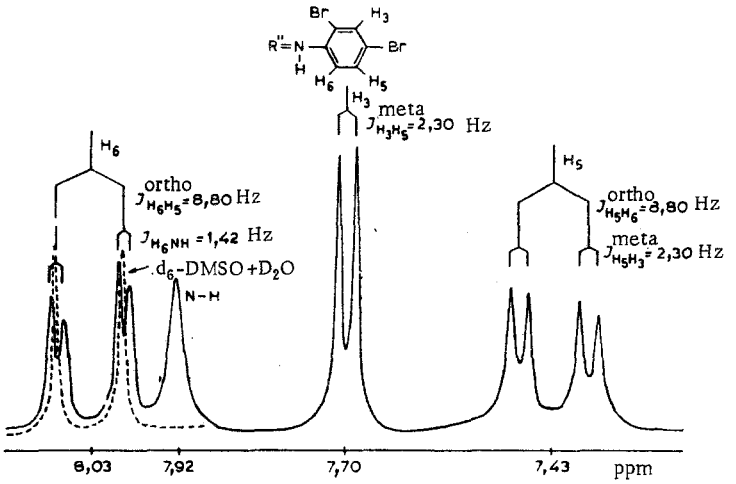


Fig. 1. PMR spectrum of IX.

starting I contained a singlet of protons of the benzene ring of the phenylisopropyl grouping, whereas the protons of the phenylcarbamoyl group give a spectrum of the AB type with the spin–spin coupling constants (SSCC) characteristic for p-substituted benzenes (Table 1). Compound V was also obtained by bromination of phenylcarbamoyl derivative I in ether in the presence of sodium bicarbonate. Dibromo derivative VII was isolated when the amount of bromine was increased to 2 g-equivalent. On the basis of the results of elementary analysis and the IR and PMR spectra, in which, in contrast to the spectrum of monosubstituted derivative V, the absorption band of the C_4–H bond and the signal of the proton attached to C_4 are absent, the N-exo-4-bromophenylcarbamoyl-3-phenylisopropyl-4-bromosydnoneimine structure (VII) was assigned to this compound. A dibromo derivative (VIII) of similar structure was obtained by bromination of exo-carbamoyl derivative III under the same conditions.

The action of a large excess of bromine on I in ether in the presence of $NaHCO_3$ gives a tribromo derivative (IX). As in the spectra of VII and VIII, the signal of a proton attached to C_4 is absent in the PMR spectrum of this compound, whereas the signal of protons of a phenylisopropyl grouping appears as a singlet, and this indicates the absence of substituents in this ring (Table 1). The resonance signals of the aromatic protons of the exocyclic group are situated at weaker field and couple with one another with characteristic SSCC, which make it possible to conclude that the bromine atoms are in the ortho and para positions of the benzene ring (Fig. 1). An interesting feature of the PMR spectrum of IX is the long-range spin–spin coupling of hydrogen atom 6 of the phenylcarbamoyl group with the NH proton (J = 1.42 Hz). When a sample of this compound (solution in d_6-DMSO) is shaken with a small amount of heavy water, the signal from this proton vanishes as a result of rapid exchange of the proton of the NH group by deuterium, and the signal of the 6-H proton is converted to a doublet ($J_{H_6H_5}$ = 8.80 Hz). All of this provides a basis for the assertion that the tribromo derivative is N-exo-2,4-dibromophenylcarbamoyl-3-phenylisopropyl-4-bromosydnoneimine (IX).

Thus the nucleophilic activity of the C_4 atom of the sydnoneimine ring is lower in this reaction than that of the phenyl group of the exocyclic grouping. This shows up most distinctly when bromination is carried out in acetic acid, in which the formation of a cationic form of the molecule is possible.

In contrast to bromination, we were never able to obtain substitution products involving the carbon atom of the sydnoneimine ring in the nitration of sydnoneimine I and its analogs.

Substitution did not occur when I was treated with a mixture of nitric and acetic acids at room temperature, i.e., under the conditions of nitration of sydnones containing a carbonyl group in place of the carbamoyl group. Only the nitrate of exo-carbamoyl derivative I was isolated. Similar results were obtained in the nitration of N-exo-phenylcarbomyl derivatives of 3-phenylethyl- (X) [4] and 3-(3',4'-dimethoxyphenyl)ethylsydnoneimine (XI) [5] under these conditions. The nitration of I under more severe conditions with a mixture of nitric and sulfuric acids gave a bright-yellow substance (XII), which, according to the results of elementary analysis, contains three nitro groups. The PMR spectrum of nitro compound XII contains a complex multiplet of eight protons at 7.4-8.8 ppm. A detailed analysis of this portion of the spectrum enabled us to establish that one of the nitro groups is in the para position of the phenylisopropyl grouping (the aromatic 2-H, 3-H, 5-H, and 6-H protons form an AB system with the SSCC characteristic

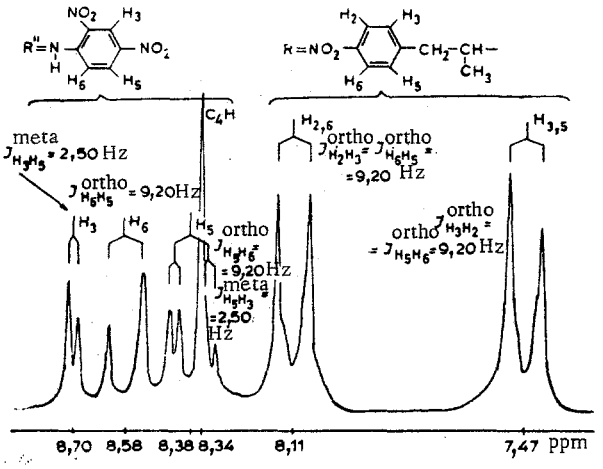


Fig. 2. PMR spectrum of nitro compound XII.

for this system), whereas the other two nitro groups are in the ortho and para positions of the carbamoyl group (Fig. 2). In this case we did not observe splitting of the signal of the 6-H proton as a result of coupling with the NH proton, and this is evidently associated with the nature of the substituent attached to the benzene ring.

The data from the IR spectra and the results of nitration of analogs of sidnokarb serve as a confirmation of the proposed structure of nitration product XII. Mononitro derivative XIII, for which, according to the PMR spectra, the presence of a nitro group in the para position of the benzene ring was unambiguously demonstrated, was isolated from the reaction of nitrosylsulfuric acid with II. Nitration of sydnoneimine III under these conditions gave dinitro derivative XIV, which, according to the PMR spectral data, contains nitro groups in the ortho and para positions of the phenyl substituent of the exocyclic group.

Thus we did not detect products of nitration of the sydnoneimine ring in a single case, and this is probably due to the sharp reduction of the nucleophilic activity of the entire molecule and, first and foremost, of the carbon atom of the heterocyclic ring in strongly acidic media due to protonation of the exocyclic nitrogen atom of the heteroring.

In order to introduce a single nitro group in the sidnokarb molecule we accomplished the direct synthesis of XV with a nitro group in the para position of the phenyl ring of the phenylisopropyl substituent starting from p-nitrophenylisopropylamine via the generally accepted scheme. Similarly, the N-exophenylcarbamoyl derivative of 3-(p-nitrophenylethyl)sydnoneimine (XVIII) was synthesized through the appropriate p-nitrophenylethylsydnoneimine hydrochloride (XVII). The data from the PMR spectra of mononitro derivatives XV and XVIII once again confirmed the correctness of the proposed structure of the products of nitration of I and its analogs. Compound XVIII was converted to the corresponding amino derivative (XIX) by reduction with iron in alcohol.

EXPERIMENTAL

The PMR spectra of d_6-DMSO solutions of the compounds were recorded with a Varian HA-100D spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer.

3-(p-Nitrophenylisopropyl)sydnoneimine Hydrochloride (XVI). A solution of 5.0 g (0.023 mole) of p-nitrophenylisopropylamine hydrochloride in 25 ml of water was treated with 1.54 g (0.023 mole) of KCN and 2.16 g (0.023 mole) of formalin at 5°, after which the mixture was stirred for 3 h and extracted with ethyl acetate. The solvent was removed from the extract by distillation, and the residue was diluted with 15 ml of water and acidified to pH 2-3 with concentrated HCl. A solution of 1.62 g (0.023 mole) of $NaNO_2$ in 5 ml of water was added to the resulting acidic solution at 5°, after which the mixture was stirred for 2 h and extracted with ethyl acetate. The extract was dried and treated with an alcohol solution of HCl to give 0.7 g of hydrochloride XVI with mp 158-159° (from alcohol–ether). Found: C 46.7; H 5.0; Cl 12.2; N 19.5%. $C_{11}H_{12}N_4O_3 \cdot HCl$. Calculated: C 46.4; H 4.6; Cl 12.1; N 19.7%.

3-(p-Nitrophenylethyl)sydnoneimine Hydrochloride (XVII). A solution of 2.35 g (0.013 mole) of p-nitrophenylethylamine hydrochloride in 5 ml of water was treated with 0.86 g of KCN and 1.2 g of formalin

at 5° and pH 3. After 3 h, the liberated oil was extracted with ether, and the extract was dried and treated with an ether solution of HCl to give 0.6 g of p-nitrophenylethylaminoacetonitrile hydrochloride with mp 182-185° (from alcohol). Found: Cl 14.1%. $C_{10}H_{11}N_3O_2 \cdot HCl$. Calculated %: Cl 14.7%. A solution of 0.23 g of $NaNO_2$ in 5 ml of water was added at 2-3° to a solution of the hydrochloride in 50 ml of aqueous HCl solution; after 2 h, the mixture was extracted with ether to give 0.25 g of N-nitroso(p-nitrophenylethylamino)-acetonitrile with mp 72-74° (from alcohol). Found: N 23.8%. $C_{10}N_{10}N_4O_3$. Calculated %: N 23.9%. A 0.25 g sample of the latter was treated with 15 ml of an alcohol solution of HCl to give 0.2 g of hydrochloride XVII with mp 177-179° (from methanol–ether). Found: C 44.7; H 4.1; Cl 13.5; N 20.8%. $C_{10}H_{10}N_4O_3 \cdot HCl$. Calculated %: C 44.6; H 4.1; Cl 13.2; N 20.7%.

N-exo-Carbamoyl Derivatives of Sydnoneimines (II, III) (Table 1). A solution of 0.1 mole of sydnoneimine hydrochloride in 500 ml of dry pyridine was treated with 0.1 mole of isocyanate (methyl isocyanate was used in the form of a solution in CCl_4). The next day, the mixture was poured into water, and the precipitated product was recrystallized from alcohol. Compound II was obtained in isopropyl alcohol in the presence of anhydrous sodium acetate and was purified by recrystallization from water.

Bromination of N-exo-Carbamoylsydnoneimines I-III (Table 1). A) In acetic acid. A solution of 0.2 ml (5 mmole) of bromine in 5 ml of CH_3COOH was added at 20° to a solution of 1 g (4 mmole) of I in 15 ml of glacial acetic acid at 20°. The next day, the mixture was vacuum evaporated to give hydrobromide VI, which was crystallized from alcohol. Compounds I and III were similarly brominated. The bases were isolated by the action of $NaHCO_3$ on the hydrobromides.

B) In ether. A 1.47 ml (0.03 mole) sample of bromine was added at 2-3° to a mixture of 7.5 g (0.024 mole) of I and 9 g of $NaHCO_3$ in 45 ml of ether. After 2 h, the mixture was filtered, and monobromo derivative was isolated from the filtrate. Tribromo derivative IX was similarly obtained by the action of 7.5 ml (0.15 mole) of bromine. The products were purified by recrystallization from alcohol.

A suspension of 6.44 g (0.02 mole) of sydnoneimine I and 8.2 g (0.1 mole) of fused sodium acetate in 200 ml of ether was heated to the boiling point and treated with a solution of 2.6 ml (0.053 mole) of bromine in 8 ml of chloroform. The mixture was then refluxed for 3 h, and precipitated dibromoderivative VII was removed by filtration, washed with water and alcohol, and crystallized from alcohol.

Nitration of N-exo-Carbamoylsydnoneimines. A) With a mixture of nitric and acetic acids. A solution of 0.23 ml of HNO_3 (sp. gr. 1.5) in 3 ml of glacial acetic acid was added at ~20° to a solution of 2 g of I in 5 ml of glacial acetic acid. After 2 h, the precipitate was removed by filtration to give 1.7 g of the nitrate of sidnokarb I with mp 149-150° (from alcohol). Found: C 55.8; H 5.0; N 18.3%. $C_{18}H_{18}N_4O_2 \cdot HNO_3$. Calculated: C 56.2; H 4.9; N 18.2%. Nitrate X · HNO_3, with mp 154-155° (from alcohol), was similarly obtained. Found: C 55.0; H 4.7; N 18.7%. $C_{17}H_{16}N_4O_2 \cdot HNO_3$. Calculated: C 55.1; H 4.6; N 18.9%. Nitrate XI · HNO_3, with mp 188-189° (from alcohol), was also similarly obtained. Found: C 53.2; H 4.5%. $C_{19}H_{10}N_4O_4 \cdot HNO_3$. Calculated: C 52.8; H 4.9%.

B) With a mixture of nitric and sulfuric acids. A 1.5-ml sample of HNO_3 (sp. gr. 1.5) was added dropwise at −15° to a suspension of 6 g of I in 15 ml of concentrated H_2SO_4. After 3 h, the mixture was poured into 500 ml of ice water, and the resulting precipitate was removed by filtration and washed successively with water, 5% ammonium hydroxide, and water. The nitro compound obtained (XII, Table 1) was crystallized from glacial acetic acid. Compounds II and III were nitrated under similar conditions.

N-exo-Phenylcarbamoyl-3-(p-aminophenylisopropyl)sydnoneimine Dihydrochloride (XIX). Iron filings (2.2 g) were added to a solution of 2 g (6 mmole) of XVIII, 0.1 g of NH_4Cl, and one drop of concentrated HCl in 15 ml of 90% ethanol. At the end of the vigorous reaction, the mixture was refluxed for 1.5 h and filtered. The filtrate was evaporated to dryness, and the residue was dissolved in 20 ml of 50% alcohol. The alcohol solution was treated with concentrated NaOH and extracted with $CHCl_3$. The solvent was evaporated, and 15% HCl was added to the residue to give dihydrochloride XIX, which was reprecipitated from alcohol solution by the addition of ether.

LITERATURE CITED

1. M. D. Mashkovskii, Medicinals [in Russian], Vol. 1, Meditsina, Moscow (1972), p. 133.
2. L. E. Kholodov, V. G. Yashunskii, R. A. Al'tshuler, M. D. Mashkovskii, L. F. Roshchina, S. I. Shershneva, F. Ya. Leibel'man, O. N. Volzhina, and N. A. Petrova, Khim.-Farmats. Zh., No. 1, 50 (1973).
3. A. Tanayama, Japanese J. Pharmac., 20, 413 (1970).

4. L. E. Kholodov, I. F. Tishchenkova, Z. A. Pankina, and V. G. Yashunskii, Zh. Organ. Khim., 3, 1513 (1967).
5. Z. A. Olovyanishnikova, V. V. Ogorodnikova, V. I. Mamonov, V. G. Yashunskii, R. A. Al'tshuler, and M. D. Mashkovskii, Khim.-Farmats. Zh., No. 6, 20 (1972).
6. H. V. Dainiker and T. Druey, Helv. Chim. Acta, 45, 2441 (1962).