NITROSOALKYLUREAS CONTAINING QUATERNARY NITROGEN ATOMS.

COMMUNICATION 4. SYNTHESIS OF NEW NITROSOALKYLUREAS FROM BISQUATERNARY ETHYLENEDIAMMONIUM SALTS

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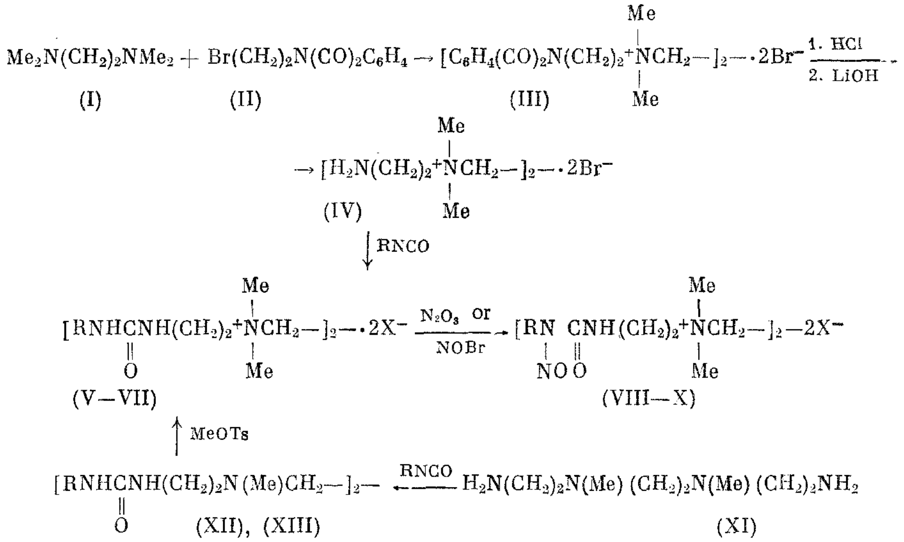
As part of our continuing research into the synthesis of new compounds with potential antitumor activity, we have been investigating nitrosoalkylurea (NAU) derivatives containing a quaternary N atom [1] and have recently synthesized disubstituted NAU from bisquaternary ethylenediammonium salts (VIII)-(X). Bisquaternary ammonium cations are capable of selectively accumulating in connective and other organ tissue, apparently as a result of ionic bonding with sulfate and phosphate anions present in chondroitin sulfate and cellular DNA, which gives rise to bridged structures [2]. Based on these observations, one might expect a heightened affinity of bisquaternary NAU derivatives for connective tissue tumors.

The methyl and chloroethyl R substituted derivatives (VIII)-(X) were selected for study since the corresponding NAU compounds exhibit high antitumor activity [3].



$$\underset{(I)}{Me_2N(CH_2)_2NMe_2} + \underset{(II)}{Br(CH_2)_2N(CO)_2C_6H_4} \rightarrow \underset{(III)}{[C_6H_4(CO)_2N(CH_2)_2{}^+\overset{Me}{\underset{Me}{N}}CH_2-]_2-\cdot 2Br^-} \xrightarrow[2.\ LiOH]{1.\ HCl}$$

$$\rightarrow \underset{(IV)}{[H_2N(CH_2)_2{}^+\overset{Me}{\underset{Me}{N}}CH_2-]_2-\cdot 2Br^-} \xrightarrow{RNCO}$$

$$\underset{(V-VII)}{[RNH\underset{O}{C}NH(CH_2)_2{}^+\overset{Me}{\underset{Me}{N}}CH_2-]_2-\cdot 2X^-} \xrightarrow[NOBr]{N_2O_3\ or} \underset{(VIII-X)}{[R\underset{NO}{N}\underset{O}{C}NH(CH_2)_2{}^+\overset{Me}{\underset{Me}{N}}CH_2-]_2-2X^-}$$

$$\underset{(XII),\ (XIII)}{[RNH\underset{O}{C}NH(CH_2)_2N(Me)CH_2-]_2-} \xleftarrow{RNCO} \underset{(XI)}{H_2N(CH_2)_2N(Me)(CH_2)_2N(Me)(CH_2)_2NH_2}$$

$$(XII),(XIII) \xrightarrow{MeOTs} (V-VII)$$

$R = CH_2CH_2Cl$, $X = Br$ (V), (VIII); $R = Me$, $X = Br$ (VI), (IX); $R = Me$, $X = TsO$ (VII), (X); $R = CH_2CH_2Cl$ (XII); $R = Me$ (XIII).

We examined the possibility of preparing bisquaternary NAU derivatives (VIII)-(X) in a manner analogous to that used for cholinelike NAU [1], namely, via carbamoylation of the primary-tertiary 4,7-dimethyltriethylenetetramine (XI), followed by quaternization of the resulting ureas (XII) and (XIII) with methyl tosylate and nitrosation of the quaternary salts with N_2O_3 in an organic solvent. In the case of the synthesis of quaternary ethylenediamine salts, it is known that quaternization of the amino groups proceeds in a sequential fashion, i.e., formation of the first quaternary N atom occurs very readily, and quaternization of the second N atom requires much more vigorous reaction conditions [4]. We have also observed in our studies that the easily synthesized ureas (XII) and (XIII) undergo facile monoquaternization with methyl tosylate even at 20°C (based on TLC data), but that formation of the bisquaternary derivatives requires extended heating with excess alkylating agent. For instance, starting with (XIII) followed by nitrosation with N_2O_3 in an organic solvent, the methyl derivative (X) was obtained; in the case of the thermally labile urea (XII) TLC analysis revealed that quaternization was accompanied by a significant amount of side-product formation.

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TABLE 1

Compound	mp, °C (solvent)	Molecular formula	Found/Calculated, %			UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
			C	H	N			
(III)	225 (EtOH–H_2O)	$C_{16}H_{32}Br_2N_4O_4 \cdot 2H_2O$	47,40 47,29	5,68 5,50	8,32 8,48	–	–	–
(IV)	173 (MeOH)	$C_{10}H_{28}Br_2N_2$	33,20 32,98	8,13 7,75	15,37 15,39	–	–	–
(V)	124 (EtOH)	$C_{16}H_{36}Br_2Cl_3N_6O_2$	33,09 33,41	6,40 6,31	14,24 14,61	–	3460, 3280, 1570(NH), 1660(C=O), 1620(CON)	4,07 s ($\overset{+}{N}CH_2CH_2N$), 3,56 m ($ClCH_2CH_2N$ and $NCH_2CH_2\overset{+}{N}$), 3,32 s ($\overset{+}{N}(CH_3)_2$)
(VI)	217 (EtOH)	$C_{14}H_{34}Br_2N_6O_2$	35,57 35,15	7,48 7,18	17,84 17,57		3350, 3260, 1560(NH), 1660(C=O), 1280(CON)	4,09 s ($\overset{+}{N}CH_2CH_2\overset{+}{N}$), 3,65 m ($NCH_2CH_2\overset{+}{N}$), 3,34s ($\overset{+}{N}(CH_3)_2$), 2,70 s ($CH_3N$)
(VIII)	143 (dec.)	$C_{16}H_{34}Br_2Cl_2N_8O_4$	30,11 30,35	5,54 5,42	17,37 17,70	198 (4,30) 235 (3,96) 398 (2,20)	3240, 1530(NH), 1725(C=O), 1485(NNO)	4,23s ($\overset{+}{N}CH_2CH_2\overset{+}{N}$), 4,22 t ($N(NO)CH_2$), 3,93m ($\overset{+}{N}CH_2CH_2N$), 3,42 s ($\overset{+}{N}(CH_3)_2$), 3,64 t ($ClCH_2$)
(IX)	155 (dec.)	$C_{14}H_{32}Br_2N_8O_4$	31,70 31,35	6,31 6,03	21,05 20,90	198 (4,30) 235 (4,04) 395 (2,23)	3230, 1530(NH), 1725(C=O), 1495(NNO)	4,24 s ($\overset{+}{N}CH_2CH_2\overset{+}{N}$), 3,93m ($NCH_2CH_2\overset{+}{N}$), 3,43s ($\overset{+}{N}(CH_3)_2$), 3,18 s ($CH_3N(NO)$)
(X)	167 (dec.)	$C_{28}H_{46}N_8O_{10}S_2$	46,80 46,78	6,40 6,45	15,15 15,59	197 (4,60) 223 (4,48) 395 (2,20)	3340, 1520(NH), 1725(C=O), 1475(NNO)	8,98t (NH), 4,03s ($\overset{+}{N}CH_2CH_2\overset{+}{N}$), 3,70m ($NCH_2CH_2\overset{+}{N}$), 3,24 s ($\overset{+}{N}(CH_3)_2$), 3,10 s ($NCH_3$)
(XII)	105 (MeCN)	$C_{14}H_{30}Cl_2N_6O_2$	43,48 43,64	8,07 7,85	22,05 21,81	–	3330, 3300, 1580(NH), 2800(NCH_3), 1620(C=O)	–

We have thus developed an alternative method for the synthesis of bisquaternary NAU derivatives based on the use of N,N'-bis-2-aminoethyl-N,N,N',N'-tetramethylethylenediammonium dibromide (IV), which is carbamoylated with alkyl isocyanates. This method avoided heating the compounds which already contained a chloroethyl group. Diamine (IV) was prepared from tetramethylethylenediamine (I) and N-2-bromoethylphthalimide (II) followed by acidic hydrolysis of the phthalimide functional group; the free base was obtained by treatment of the chlorohydrate (IV) with a solution of LiOH in methanol. Nitrosation of the bisquaternary ureas (V) and (VI) with nitrosyl bromide in DMF gave the NAU derivatives (VIII)-(X), which exist as light-yellow crystalline compounds and are readily soluble in water.

The composition and structure of the newly prepared compounds were verified based on their elemental analyses and IR, UV, and PMR spectra, which are summarized in Table 1.

The IR spectra of the NAU derivatives contain two characteristic bands, one at 1490-1480 (NO) and another at 1730-1710 cm^{-1} (CON). The latter bands are shifted ~50 cm^{-1} toward higher frequency in comparison with the urea precursors (V) and (VI) [3].

The main absorption maximum is found at 230 nm in the UV spectra of the NAU derivatives (VIII) and (IX); in the case of (X) this band is obscured by the tosylate ion band at 223 nm. A second absorption maximum is found at 395 nm [3]. In addition, the spectra of (VIII) and (IX) also contain absorption due to the bromide ion at 198 nm.

Two isomers, differing in the position of the nitroso group, should be possible for the nitrosation of ureas (V)-(VII). Based on PMR spectral data of the starting urea derivatives and of the NAU derivatives (VIII)-(X), we conclude, in analogy with [5], that the NO group is found on the NR group nitrogen atom in all cases.

EXPERIMENTAL

TLC on Al_2O_3 was used to monitor the course of the reactions as well as product purity [1].

UV spectra were recorded on a Specord UV-VIS spectrophotometer for aqueous solutions. IR spectra were obtained on a UR-20 spectrophotometer using thin films of Vaseline mulls. PMR spectra were recorded on a Tesla BS-467A spectrometer using either DMSO-d_6 vs TMS or D_2O vs. 2,2-dimethyl-2-silapentane-5-sulfonic acid as reference compounds. 4,7-Dimethyltriethylenetetramine was prepared according to [6].

N,N'-Bis(2-phthalimidoethyl)-N,N,N',N'-tetramethylethylenediammonium Dibromide (III). Compound (I) (5.8 g, 50 mmoles) was added at 20°C to 30 g (120 mmoles) of (II), and the mixture was heated at 100°C for 3 h, followed by 10 h at 120°C. After cooling, the resulting fused material was pulverized and recrystallized from 100 ml of boiling absolute ethanol; the solution was filtered hot, and the product was washed with boiling ethanol. Yield, 18.2 g (58%).

N,N'-Bis(2-aminoethyl)-N,N,N',N'-tetramethylethylenediammonium Dibromide (IV). Compound (III) (22.5 g, 36 mmoles) was refluxed for 6 h in 145 ml of 12 N hydrochloric acid, then allowed to stand overnight in a refrigerator. The resulting precipitate of phthalic acid was removed by filtration; the filtrate was concentrated to dryness under vacuum, and the residue was suspended in boiling methanol and then filtered after cooling. Yield, 11.1 g (70%) of chlorohydrate (IV), which was refluxed in a solution of 2.14 g (25 mmoles) of $LiOH \cdot H_2O$ in 60 ml of dry methanol until it dissolved, then filtered; the precipitate which formed upon cooling was collected by filtration. Yield, 5.93 g (64%).

N,N'-Bis{2-[3-(2-chloroethyl)ureido]ethyl}-N,N,N',N'-tetramethylethylenediammonium Dibromide (VIII) and N,N'-Bis[2-(3-methylureido)ethyl-N,N,N',N'-tetramethylethylenediammonium Dibromide (VI). A solution of 1.0 g (2.7 mmoles) of (IV) in a mixture of 15 ml methanol and 2 ml water was treated with 8.1 mmoles of alkyl isocyanate at 10-15°C. After 2 h the bis(2-chloroethyl)urea was removed by filtration, the filtrate was concentrated under vacuum, and the remaining oil was triturated with dry acetone. Yield of ureas (V) and (VI), 90-95%.

N,N'-Bis{2-[3-(2-chloroethyl)-3-nitrosoureido]ethyl}-N,N,N',N'-tetramethylethylenediammonium Dibromide (VIII) and N,N'-Bis[2(3-methyl-3-nitrosoureido)ethyl]-n,N',N'-tetramethylethylenediammonium Dibromide (IX). A suspension of 1.2 mmoles of (V) or (VI) in 4 ml of DMFA was cooled to −5°C, and a twofold excess of 50% NOBr in acetonitrile was added with stirring; the mixture was maintained for 2 h and then warmed to 20°C. The product was precipitated with ether and recrystallized from 2:1 ethanol—acetone. Yield of NAU (VII) or (IX), 62-75%.

N,N'-Bis[2-(3-methyl-3-nitrosoureido)ethyl]-N,N,N',N'-tetramethylethylenediammonium Ditosylate (X). A solution of 0.86 g (15 mmoles) of methyl isocyanate in 8 ml of dry MeCN was cooled to 0°C and 0.88 g (5 mmoles) of (XI) in 8 ml MeCN was added with stirring. After 1 h 5.6 g (30 mmoles) of methyl tosylate was added and the mixture was refluxed for 8 h. The reaction mixture was diluted with ether and the resulting oil was dissolved in 30 ml MeCN and 10 ml DMFA. The resulting solution was treated at −10°C with gaseous N_2O_3; a precipitate formed. When the reaction mixture had turned blue, the nitrogen oxides were evaporated under vacuum and the resulting precipitate was filtered and washed with MeCN. Yield, 2.1 g (57%).

N,N'-Bis{2-[3-(2-chloroethyl)ureido]ethyl}-N,N'-dimethylethylenediamine (XII). A solution of 0.8 g (7.6 mmoles) of chloroethyl isocyanate in 4 ml of dry MeCN was treated with 0.44 g (2.5 mmoles) of (XI) in 4 ml of dry MeCN at −5°C with stirring. After 1 h the resulting precipitate was filtered and washed with MeCN. Yield 0.7 g (72%).

CONCLUSIONS

A method has been developed for the synthesis of new nitrosoalkylureas based on bisquaternary ethylenediammonium salts.

LITERATURE CITED

1. A. A. Belyaev, V. F. Gopko, and L. B. Radina, Izv. Akad. Nauk SSSR, Ser.Khim., 365 (1985).
2. H. Shindo, E. Nakajima, and E. Shigehara, Chem. Pharm. Bull., 24, 2327 (1976).
3. N. M. Emanuel', D. B. Korman, L. A. Ostrovskaya, L. B. Gorbacheva, and N. P. Dement'eva, Nitrosoalkylureas, A New Class of Antitumor Drugs [in Russian], Nauka, Moscow (L978). p. 20.
4. R. Rometsch, A. Marxer, and K. Miescher, Helv. Chim. Acta, 34,1611 (1951).
5. A. A. Belyaev, V. F. Gopko, and L. B. Radina, Izv. Akad. Nauk SSSR, Ser. Khim., 369 (1985).
6. G. H. Searle, M. Petkovic, and F. R. Keene, Aust. J. Chem., 25, 2045 (1972).

OXIDATION OF HOMOALLYL ALCOHOLS

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The oxidation of diallylcarbinol (II) is the most convenient method for the synthesis of diallyl ketone (I). However, there is no information at all on the oxidation of bis(homoallyl)-type alcohols, and in some examples of oxidation of homoallyl alcohols unsatisfactory results were obtained.

We studied the oxidation of homoallyl alcohols both by standard methods usually used for oxidation of unsaturated alcohols and by some new original modifications of known methods.

The specific effect of two β,γ double bonds on the oxidation process of the alcohol was shown.

Thus, in the oxidation of (II) and allylpropenylcarbonol (III) by chromic acid under standard conditions [1] to ~100% conversion (GLC), there were significant overconsumption of the reagent (3-4 equivalents) and large losses of the product. Under these same conditions, propargylpropenylcarbinol (IV) was oxidized with degradation. With aqueous chromic acid, satisfactory yields of ketone (I) were obtained by two-phase oxidation in a medium of methylene chloride or ether (Table 1, No. 1a). Other standard methods for oxidation of alcohols based on Cr^{6+}, with pyridinium chloride chromate (PCC) and pyridinium dichromate (PDC), also gave unsatisfactory results for alcohols (II)-(IV) (see Table 1, Nos. 4a and 6a and b). In addition, a polymeric by-product was always obtained which was apparently formed via radical intermediates of oxidation by intermediate-valence chromium (Cr^{4+}) compounds (cf. [1]). Examples are known for suppression of the undesirable participation of such active oxidizing agents by a radical path with the addition of catalysts of the disproportionation $Cr^{4+} \rightarrow Cr^{3+} + Cr^{+}$ of

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