1,2-REARRANGEMENT OF N-CHLORO-N-ALKOXYAMINES IN REACTIONS WITH NUCLEOPHILES

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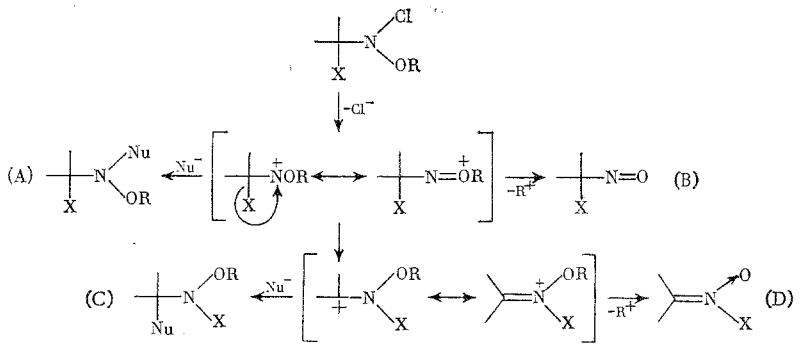
N-Chloro-N-alkoxy-tert-alkylamines react with alcohols in the presence of base to form N, N-dialkoxyamines [1-3]. This reaction (A) is apparently accomplished through a nitrenium–oxonium ion which gives fragmentation (B), a Wagner–Meerwein type of reaction (C), or rearrangement and fragmentation (D). Fragmentation (B) of the intermediate ion with the formation of nitrosoalkanes is seen in the reaction of N,N-dialkoxyamines with strong acids [3]. In the present work, the nucleophilic reactions of N-chloro-N-alkoxyamines accompanied by 1,2-rearrangements (C) and (D) were studied.

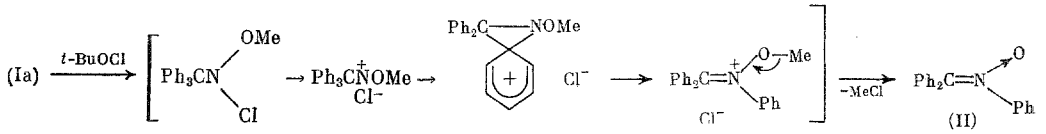


(1)

The synthesis of the unknown trialkoxyamines was planned from N,N-dialkoxytritylamines by hydrolysis to NH-dialkoxyamines with subsequent N-chlorination and alcoholysis. We planned to synthesize N,N-dialkoxytritylamines according to the synthetic scheme for N,N-dialkoxy-N-tert-alkylamines [1] from N-alkoxytritylamines (I)

$$Ph_3CCl + 2H_2NOR \rightarrow Ph_3CNHOR \quad (I) \qquad (2)$$
$$R = Me\ (a)\ [4],\ MeO_2CCMe_2\ (b).$$

However, the chlorination of (Ia) at −78°C with subsequent standing at 20°C yields triphenylnitrone (II) in high yield as a result of 1,2-rearrangement with fragmentation (D) by migration of a phenyl group from carbon to nitrogen and the elimination of MeCl



(3)

Product (II) was identified by comparison with a known sample [5] and by its mass spectrum in which we find $(M-1)^+$, $(M-16)^+$, and $(M-17)^+$ peaks diagnostic for aromatic nitrones [6]. The strong peaks for the $(M-CO)^+$, $PhCO^+$, PhN^+, and Ph^+ ions may be attributed, according to Kinstle [7] and Leyshon [8], to rearrangements of M^+ of the starting nitrone (II) upon electron impact into the corresponding amide and oxaziridine.

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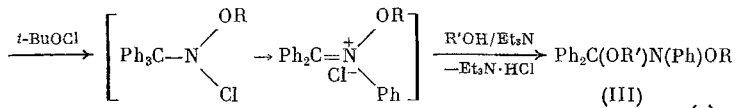
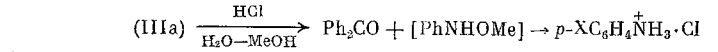
The chlorination of (I) at −78°C with subsequent treatment with alcohols in the presence of base under previous conditions [1-3] gave, in addition to the expected N,N-dialkoxytritylamines, the products of types (C) 1,2-rearrangement, namely, the N-alkoxy-N-phenylaminoketals of benzophenone (III)



(4)

R = R′ = Me (a), R = Me, R′ = Et (b), R = MeO_2CCMe_2, R′ = Me (c), R = MeO_2CCMe_2, R′ = Et (d).

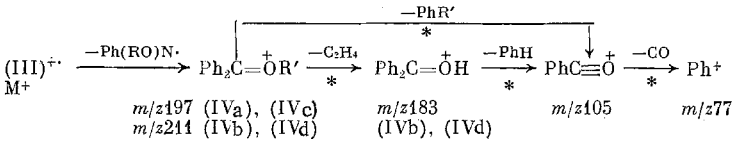
The structure of (III) was proved as follows. The PMR spectrum of (IIIa) shows a nonequivalence of the MeO groups, which excludes the alternative structure of the isomeric N,N-dialkoxyamine. Acid hydrolysis is (IIIa) yields benzophenone and a mixture of the hydrochloride salts of p-substituted anilines apparently formed from the intermediate O-methyl-N-phenylhydroxylamine according to Bamberger [9]. The mass spectra of all the products of (III) lack peaks for the Ph_3C^+ and $C_{13}H_9^+$ ions



(5)

X = Cl, MeO, HO.

characteristic for (Ia) and other trityl derivatives [10]. The dominant pathway for fragmentation with the formation of oxonium ions confirms the structure of (III)

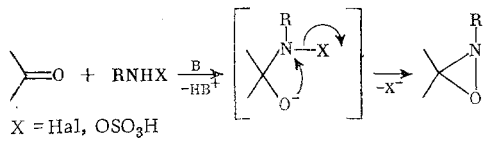


(6)

m/z197 (IVa), (IVc)
m/z211 (IVb), (IVd)
m/z183 (IVb), (IVd)
m/z105
m/z77

Reactions (3) and (4) are in many ways similar to the Stieglitz rearrangement of N-tritylhydroxylamines and N-halotritylamines to anilines through a nitrenium ion [11]. The lack of such rearrangements involving the MeO_2C, MeO_2CCH_2, and Me groups [1-3] may be attributed to their lower migratory capacity relative to Ph [12]. However, as shown below, the migration of these groups also occurs under certain conditions.

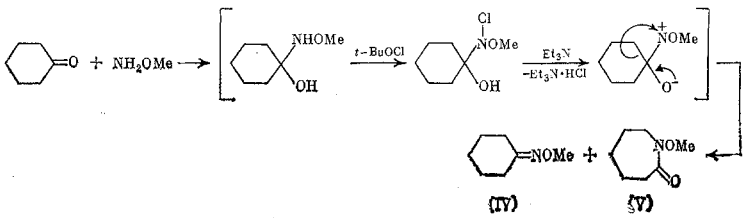
N-Chloro-N-alkoxyamines containing the OH groups in the γ position of the N-alkyl substituent are readily cyclized in the presence of base to form 2-alkoxyisoxazolidines [2]. In this regard, we become interested in the suitability of such a reaction for the synthesis of 2-alkoxyoxaziridines,* especially since the general method for the synthesis of 2-alkoxyoxaziridines consists in the iminization of carbonyl compounds [14]



(7)

X = Hal, OSO_3H

However, only the product of the dehydration of this adduct, O-methylcyclohexanone oxime (IV), and the product of the type (C) 1,2-rearrangement, N-methoxycaprolactam (V), were obtained from the adduct of methoxyamine with cyclohexanone upon chlorination and subsequent treatment with Et_3N. In this case, the migration of the alkyl group is facilitated by the action of the oxygen anionic center

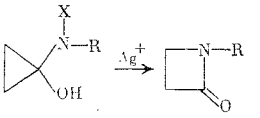


(8)

(IV) (V)

*There has been only one report on the preparation of 2-alkoxyoxaziridines by the thermolysis of nitrone ethers [13].

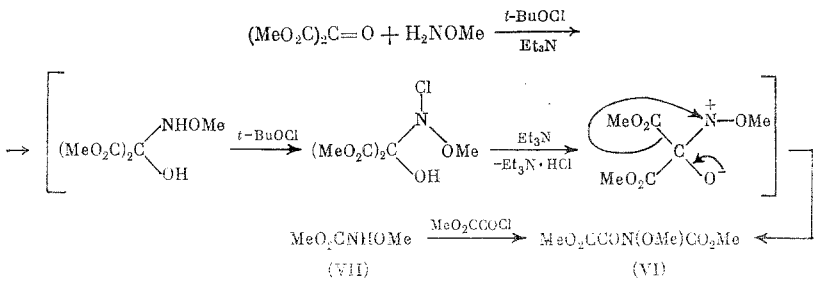
The difference in the directions of reactions (7) and (8) is apparently a result of the S_N2 intramolecular mechanism for the former and nitrenium ion mechanism of the latter. The generation of the nitrenium ion from N-chloroazabicyclic compounds is usually accompanied by the migration of alkyl groups to nitrogen [11]. A direct analogy for rearrangement (8) is the rearrangement studied by Wasserman [15]



(9)

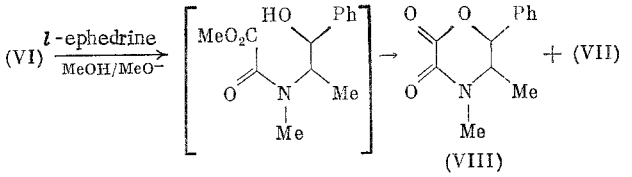
R = Alk, X = Cl, $PhCO_2$.

N-Chloro-N-methoxyamine obtained in the chlorination of the adduct of methoxyamine with dimethylmesoxalate undergoes type (C) 1,2-rearrangement upon treatment with Et_3N with migration of the carbomethoxy group and formation of N-methoxy-N-methyloxaloylurethylane (VI)



(10)

The structure of (VI) was proven by back synthesis and the conversion



(11)

The migration of the acyl group to the electron-deficient carbon atom has been well studied by Kagan [12] and Domagala [16], while the migration to the nitrogen atom has been seen in the thermolysis of substituted 3-benzoyloxaziridine [17].

We should especially note that all these type (C) 1,2-rearrangements with migration of acetyl, phenyl, and alkyl groups to nitrogen start with the generation of alkoxynitrenium ion by the action of BF_3 on substituted bicyclic N,N-dialkoxyamines which are derivatives of 2,9-dioxa-1-azabicyclo[4.3.0]nonane [18].

EXPERIMENTAL

The PMR spectra were taken on Tesla BS-487C (80 MHz) and JNN-C-6OHL (60 MHz) spectrometers in CCl_4 from HMDS (internal standard), δ, ppm. The mass spectra were taken on an MKh 1303 spectrometer with direct introduction of the sample into the ion source at 30-eV ionizing electron energy. Optical rotation was measured on a Polamat-A polarimeter.

The methyl ester of α-aminooxyisobutyric acid was obtained according to Kornawski et al. [19] on 66% yield, bp 82-84°C (38 mm).

N-Tritylmethoxyamine (Ia) was obtained according to Guthmann and Stieglitz [4] in 80.4% yield, mp 88-89°C, PMR spectrum (80 MHz): 3.36 (MeO), 6.04 (NH), 7.11 (Ph). Mass spectrum, m/z (rel. int., %): 244 (23), 243 Ph_3C^+ (100), 165 $C_{13}H_9^+$ (28), 132 (21), 91 $C_7H_7^+$ (25).

Methyl α-(N-Tritylaminooxy)isobutyrate (Ib). A mixture of 1.46 g (10 mmoles) methyl α-aminooxyisobutyrate, 2.07 g (15 mmoles) K_2CO_3, and 2.79 g (10 mmoles) trityl chloride in 20 ml abs. acetonitrile was stirred for 14 h at 20°C. The precipitate was filtered off, washed with acetonitrile, and stirred with a solution

of 2.02 g (20 mmoles) Et_3N in 20 methanol. The mixture obtained was stirred for 2 h and then the methanol was removed in vacuum. The residue was extracted into hot benzene. The benzene extracts were evaporated in vacuum and the residue was crystallized from hexane. A yield of 2.19 g (58.4%) (Ib) was obtained with mp 56°C. PMR spectrum: 1.04 (Me_2C), 3.61 (MeO_2C), 7.38 (Ph). Found: C 76.58; H 6.68; N 3.74%. Calculated for $C_{24}H_{25}NO_3$: C 76.78; H 6.71; N 3.73%.

Thermal Decomposition of N-Chloro-N-trityl-N-methoxyamine. A sample of 0.16 g (1.5 mmole) t-BuOCl in 0.5 ml abs. CH_2Cl_2 was added to 0.28 g (1 mmole) (Ia) in 2 ml abs. CH_2Cl_2 at −78°C and held for 6 h at −78°C and 24 h at 20°C. The solvent was removed in vacuum and the residue was crystallized from CCl_4. A yield of 0.21 g (76.9%) (II) was obtained with mp 219°C [5]. Mass spectrum, m/z (rel. int., %): M^+ 273 (44), 272 (14), 257 (18), 256 (8), 245 (8), 244 (12), 180 (38), 165 (28), 105 (56), 91 (100), 77 (41), 51 (3). Found: C 83.44; H 5.53; N 4.92%. Calculated for $C_{19}H_{15}NO$: C 83.49; H 5.53; N 5.12%.

General Method for the Synthesis of Benzophenone Aminoketals (III). An equimolar amount of t-BuOCl in CH_2Cl_2 is added to (I) in CH_2Cl_2 with stirring at −78°C. After 1 h, the solvent was removed in vacuum at ≤−40°C and an equimolar amount of Et_3N in the corresponding alcohol was added to the residue cooled to −78°C. The mixture was held for 1 h at this temperature and then the temperature was raised to 20°C over 19 h and the alcohol was removed in vacuum. The residue was extracted into abs. ether and the ethereal extract was evaporated in vacuum. The residue was crystallized from hexane. An 83.8% yield of (IIIa) was obtained with mp 98-99°C. PMR spectrum: 3.36, 3.38 (MeON and MeOC), 6.65-7.39 (Ph_2C and PhN). Mass spectrum, m/z (rel. int., %): M^+ − MeO 288 (1), M^+ − MeO − MeO 257 (3), 197 (100), 105 (37), 77 (21). Found: C 78.96; H 6.65; N 4.47%. Calculated for $C_{21}H_{21}NO_2$: C 78.97; H 6.63; N 4.39%. A 48% yield of (IIIb) was obtained with mp 75-76°C. PMR spectrum: 1.09, 3.65 (EtO, J = 7 Hz), 3.35 (MeO), 6.67-7.41 (Ph). Mass spectrum, m/z (rel. int., %): M^+ − MeO 302 (1), M^+ − EtO 288 (2), M^+ − MeO − C_2H_4 (1), M^+ − MeO − EtO 257 (3), 211 (100), 183 (34), 105 (60), 77 (12). Found: C 79.07; H 6.97; N 4.04%. Calculated for $C_{22}H_{23}NO_2$: C 79.25; H 6.95; N 4.20%. A 39% yield of (IIIc) was obtained with mp 68-69°C. PMR spectrum: 1.24 (Me_2C), 3.01 (MeON and MeOC), 6.58-7.88 (Ph). Mass spectrum, m/z (rel. int., %): M^+ − MeO 374 (1), M^+ − MeO_2CCMe_2 288 (3), M^+ − MeO − MeO_2CCMe_2 257 (1), 197 (100), 105 (23), 77 (8). Found: C 74.54; H 6.39; N 3.43%. Calculated for $C_{25}H_{27}NO_4$: C 74.05; H 6.71; N 3.45%. A yield of 31% (IIId) was obtained with 95-97°C. PMR spectrum: 1.28 (Me_2C), 1.28, 3.13 (EtO, J = 7 Hz), 2.99 (MeOC), 6.53-7.45 m (Ph). Mass spectrum, m/z (rel.int., %): M^+ − EtO 374 (1), M^+ − MeO_2CCMe_2 302 (2), M^+ − MeO_2CCMe_2 − C_2H_4 274 (1), M^+ − EtO − MeO_2 − $CCMe_2$ 257 (1), 211 (100), 183 (18), 105 (17), 77 (3).

Acid Hydrolysis of (IIIa). A sample of 1.24 g (3.89 mmoles) (IIIa) in a mixture of 20 ml methanol and 2 ml conc. HCl was stirred for 1 h. The solvent was removed in vacuum and the residue was extracted into ether. The insoluble portion was crystallized from acetonitrile. A yield of 0.26 g of a salt was obtained with mp 145-148°C. Ether was removed from the ethereal extract in vacuum and the residue was distilled. A yield of 0.91 g (74.9%) benzophenone with bp 121°C (3 mm) was obtained which was identified by its mass spectrum.

N-Methoxycaprolactam (V). A sample of 2.35 g (50 mmoles) $MeONH_2$ in 10 ml abs. ether was added to 4.9 g (50 mmoles) cyclohexanone in 20 ml abs. ether at −30°C with stirring. After 15 min, 5.4 g (50 mmoles) t-BuOCl in 20 ml abs. ether was added and after an additional 15 min, 5.05 g (50 mmoles) Et_3N in 10 ml abs. ether was added. The mixture was kept for 30 min at 0°C. The precipitate was filtered off and the ether was removed from the filtrate in vacuum. The residue was distilled to yield 0.64 g (10%) O-methylcyclohexanone oxime (IV) with bp 49°C (12 mm) [20] identified by PMR and mass spectroscopy and 2.1 g (29.2%) (V) with bp 72° (1 mm). PMR spectrum: 1.65 and 2.25 m (CH_2-ring), 3.63 (MeON). Found: C 58.64; H 9.08; N 9.70%. Calculated for $C_7H_{13}NO_2$: C 58.72; H 9.12; N 9.78.

N-Methoxy-N-methyloxaloylurethylane (VI). A sample of 1.46 g (30.2 mmoles) $MeONH_2$ in 10 ml abs. ether was added with stirring to 4.41 g (30.2 mmoles) dimethylmesoxalate in 20 ml abs. ether at 0°C. After 0.5 h, 3.37 g (30.2 mmoles) t-BuOCl in 10 ml abs. ether was added and after an additional 0.5 h, 3.14 g (30.2 mmoles) Et_3N in 10 ml abs. ether was added. The mixture was kept for 1 h at 20°C and after separation of a precipitate and removal of the ether in vacuum, the residue was distilled. A yield of 3.17 g (54.9%) (VI) was obtained with bp 83°C (0.5 mm). PMR spectrum: 3.22 (MeON), 3.42, 3.45 (MeOC). Found: C 37.93; H 4.81; N 7.51%. Calculated for $C_4H_9NO_6$: C 37.70; H 4.75; N 7.33%.

Back Synthesis of (VI). N-Methoxyurethylane (VII) was obtained from $MeONH_2$ and methyl chloroformate in abs. ether in 56% yield with bp 61°C (5 mm). PMR spectrum: 3.63 (MeON), 3.70 (MeOC), 8.23 (NH). Found: C 34.34; H 6.76; N 13.38%. Calculated for $C_3H_7NO_3$: C 34.29; H 6.71; N 13.33%.

b) A sample of 2.16 g (17.6 mmoles) MeO_2CCOCl was added dropwise with stirring to 1.68 g (16 mmoles) (VII) in 20 ml pyridine at −30°C. The mixture was kept for 14 h at 20°C and the solvent was then removed in vacuum. The residue was distilled to yield 0.8 g (26.6%) (VI).

The Reaction of (VI) with *l*-Ephedrine. A solution of 1.8 g (9.5 mmoles) (VI) and 0.78 g (4.7 mmoles) *l*-ephedrine in 10 ml abs. methanol with traces of NaOMe was maintained for 2 days at 20°C. The precipitate was separated and recrystallized from methanol to yield 0.87 g (82.9%) 2-phenyl-3,4-dimethyl-5,6-dioxomorpholine (VIII) with mp 183°C, $[\alpha]_{546}^{20}$ −178.5° (C 3.0, MeOH). PMR spectrum (CD_3OD): 0.9 (MeC, J_{MeCH} = 7.5 Hz), 3.05 (MeN), 4.0 m (CHN), 6.2 m (CHO), 7.48 (Ph). Mass spectrum at 70 eV, m/z (rel. int., %): M^+ − OC_2 − MeNCO 118 (91), 117 (55), 116 (10), 105 (11), 91 (19), 77 (14), 58 (48), 57 (100), 56 (22), 42 (56). Found: C 66.15; H 6.16; N 6.60%. Calculated for $C_{12}H_{13}NO_2$: C 65.74; H 5.98; N 6.39%. A yield of 0.9 g (90.6%) (VII) was obtained from the filtrate after separation of (VIII) and MeOH and distillation.

CONCLUSIONS

We discovered 1,2-rearrangements of N-chloro-N-alkoxyamines with migration of phenyl, alkyl, and carbomethoxy groups to the nitrogen atom.

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