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REACTIONS OF α-CHLORONITRONES WITH UNSATURATED ETHERS

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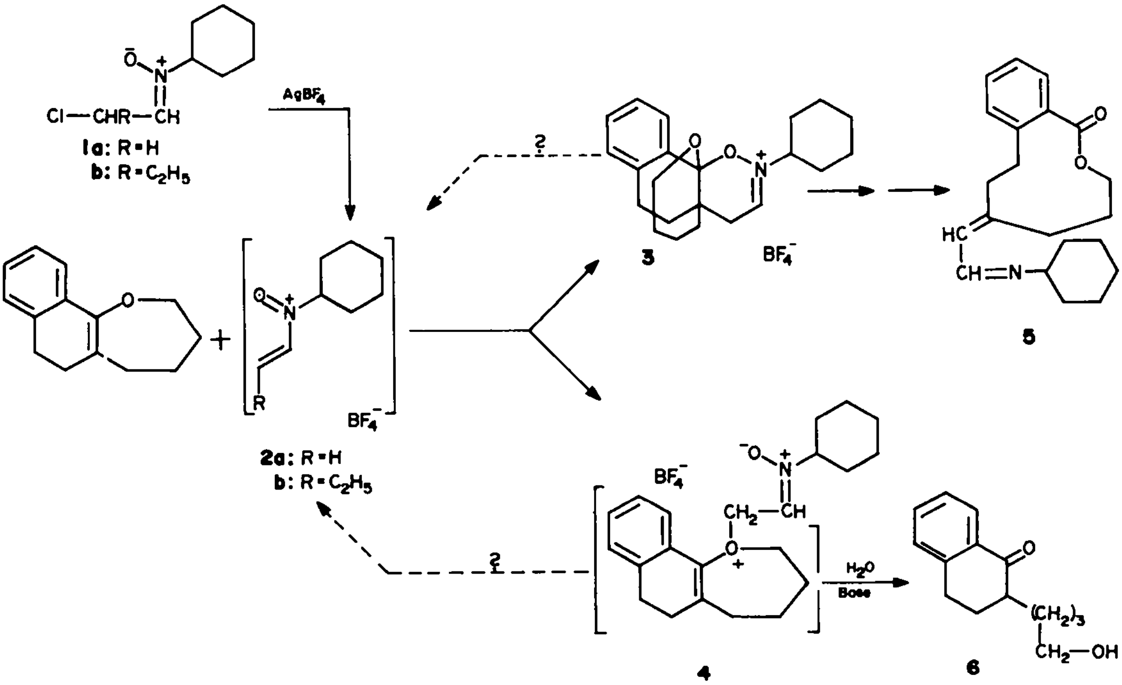
Abstract—The Ag^+ induced reaction of α-chloronitrones with unsaturated ethers goes in two parallel competitive directions. On the one hand cycloadducts like 3 are formed and on the other hand oxonium ions like 4. Formation of analogous oxonium compounds occurs also when α-alkoxynitrones are treated with $Et_3O^+BF_4^-$ in 1,2-dichloroethane. Formation of oxonium compounds with the enol-ethers is practically irreversible and leads to enol-ether fragmentation. With the saturated ethers compounds like 25 were formed and were used as a potential source of N-alkyl-N-vinyl-nitrosonium ions.

The Ag^+ induced cycloaddition of α-chloronitrones to polycyclic enol-ethers was applied for the construction of propellanes like 3 (Scheme 1). These were key intermediates in a synthesis of medium ring lactones 5.[1] The main reaction products in the Ag^+ induced reaction with the enol ethers were the hydroxy-ketones like 6. It was assumed that the latter were formed in a parallel process involving the reaction intermediate 2a and the enol-ether which gave oxonium compound 4. This intermediate was assumed to hydrolyse under the reaction work-up treatment (20% KCN–water) to the keto alcohol. We felt it was necessary to study the influence of the basic ether-O-atom on the Ag^+ induced reaction of α-chloronitrones. This involved: (a) Looking if the structure of the unsaturated ether affects this undesired process e.g. comparing the behaviour of 9, 13, 16, 18 and 20 in the Ag^+ induced reaction with α-chloronitrones. (b) Checking if oxonium compounds analogous to 4 could be prepared independently as potential sources of the elusive N-alkyl-N-vinyl-nitrosonium ion.

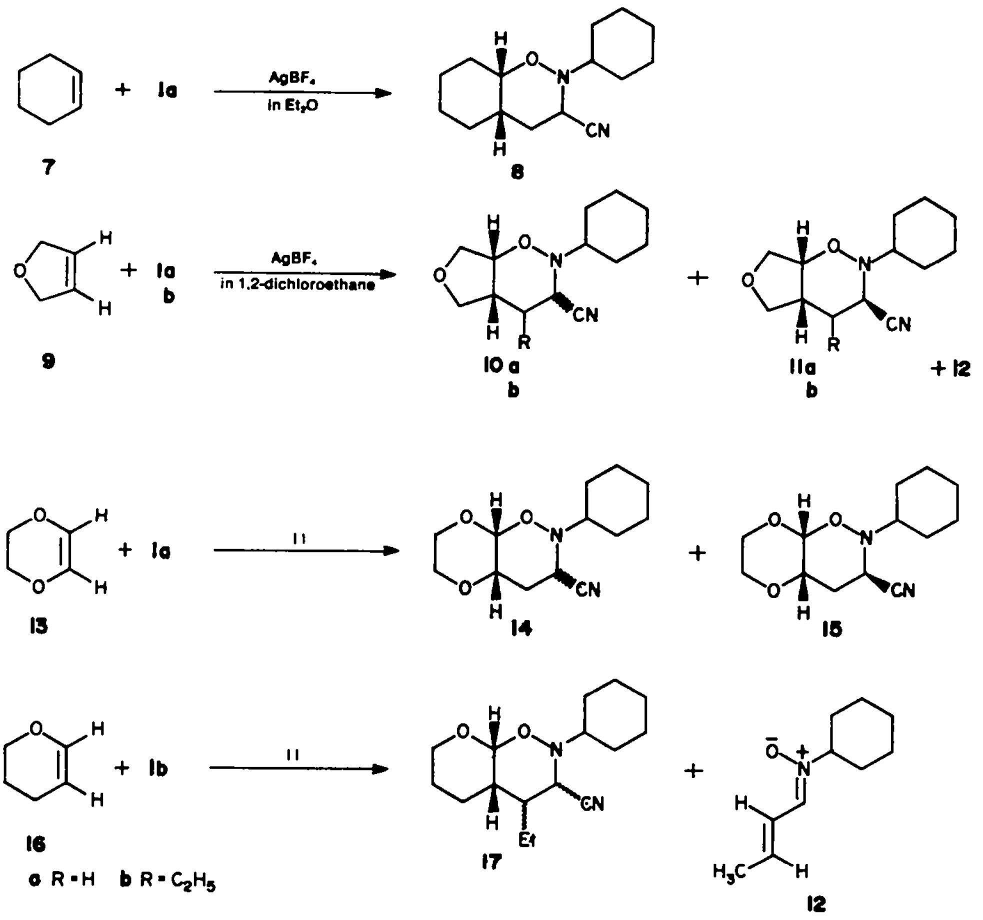
RESULTS AND DISCUSSION

It was noted before that ester groups compete with the double-bonds in the Ag^+ induced reaction of α-chloronitrones with unsaturated esters.[2] This difficulty could partially be solved by changing the reaction conditions. With the aromatic ethers, e.g. 1,4-dimethoxy benzene, no difficulty in the electrophyllic substitution reaction was observed and ether cleavage did not play an important role in that reaction.[3] With the enol-ethers, basic O-atom did not only serve as an activating factor in the nature of the 1,4-dipolarophyl, but also forced a parallel process which could not be suppressed by changing the reaction conditions.[1] We therefore, compared the reactions of various unsaturated ether systems with α-chloronitrones in the presence of $AgBF_4$ (Scheme 2).

2,5-Dihydrofuran 9 gave CN isomers in a highly stereoselective cycloaddition reaction. The total cycloaddition yields were 36% in 1,2-dichloroethane and 42% in liquid SO_2.[4] When the reaction was carried out with



Scheme 1.



Scheme 2.

1b, a pollar by-product **12** was isolated in low yield.[5]† Cycloaddition yield was comparable to that found with cyclohexene using 1,2-dichloroethane as a reaction solvent.[6] It was also found that diethyl ether could be used as a reaction solvent for the cycloaddition of **1a** to cyclohexene in the presence of $AgBF_4$ yielding the usual reaction product in 47% yield (in 1,2-dichloroethane this was 56%[6]‡). It was therefore concluded that the presence of the basic ether O-atom did not have a major practical influence on the preparative usefulness of the Ag^+ induced reaction in the cases of simple ethers. A similar picture was obtained with the unpolarized electron-rich double bond in 1,4-dioxene **13**. Reactions in liquid SO_2 (Ref. 4) and in 1,2-dichloroethane gave cycloaddition of 36% and 32% yield respectively. The picture changed when enol-ethers were used as substrates. The Ag^+ induced reaction of **1a** and **1b** with the polarized electron rich bond of 5,6-4H-dihydropyrane **16**. When SO_2 was used as a reaction solvent, practically no cycloaddition products were obtained. In 1,2-dichloroethane 3% were isolated with **1a** and 12% yield of cycloaddition was determined with **1b**. In the latter experiment **12** was isolated in 10% yield as one component of the more polar reaction product mixture.[5] It seemed that with the enol-ethers there is a drastic change of the nature of the reaction's intermediate **2**. Experiments with the open-chain enol-ethers (Scheme 3) did not give practically any products that could be identified

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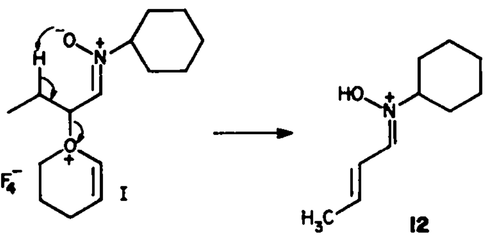
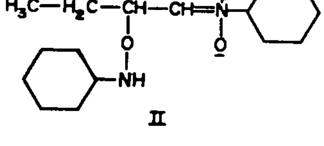
†N-cyclohexyl *trans* crotonaldehydenitrone was isolated in 56% yield when **1b** was put to reaction with **16** in nitromethane. An intermediate I could give the protonated form of 12

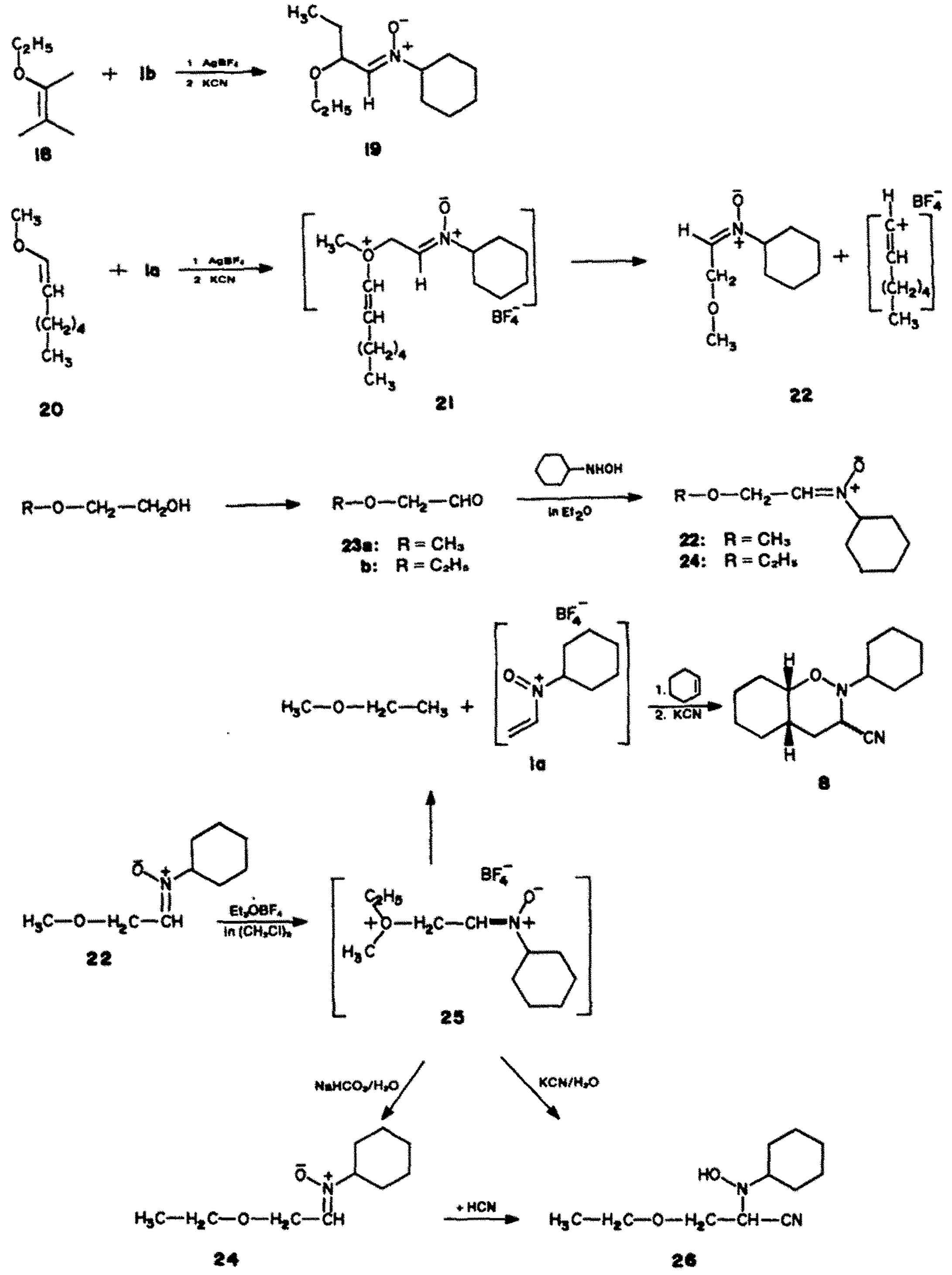


‡A blank experiment done with diethyl ether and N-cyclohexyl-2-chloro-n-butyraldehydenitrone **16** did not yield products in which ether was incorporated to the α-chloronitrone. Only N-cyclohexyl-α-(N-cyclohexylaminoxy)-n-butyraldehydenitrone II could be isolated. The formation of an analogous material was observed by Lindner and Eschenmoser under other reaction conditions involving no ether.



II

as cycloaddition products. Instead, α-alkoxy nitrones **19** and **22** were isolated in 49% and 30% yield when doing a Ag^+ induced reaction with the enol-ethers **18** and **20**. The compounds **22** and **24** were obtained independently by reacting the corresponding α-alkoxy aldehydes **23a** and **23b** with N-cyclohexyl-hydroxylamine. The isolation of these α-alkoxy nitrones as reaction products proposed the existence of an intermediate like **21** as the major reaction product with the open chain enol-ethers. The mechanism of the decomposition process is not yet established. However, it could be understood if vinyl cations were formed in the fragmentation of **21** to the α-alkoxy nitrones. This observation indicated that the oxonium ion **21** is indeed formed in the reaction with the enol-ethers. From reaction yields, it is concluded that formation of such oxonium ions is the major process. It was suggested that cycloadducts like **3** could be used as potential sources to the reactive reaction intermediate **2a**



Scheme 3.

if a cycloreversion of **3** was possible. Experiments done by us were until now abortive. It looked as if oxonium compounds **4** and **21** could not serve for this purpose. We therefore turned to the oxonium compound **25** since it looked, from the reaction with 2,5-dihydrofuran **9** and from the reaction with cyclohexene in diethyl-ether, that compounds like **25** might decompose more easily to their components. The formation of **25** was done by reacting **22** with $Et_3O^+BF_4^-$ in 1,2-dichloroethane. This was left for one hour at room temperature and **24** was isolated when the reaction mixture was worked up with aq. $NaHCO_3$. When it was treated with KCN/H_2O solution, only **26** was isolated. The fact that **24** and its CN^- addition products were isolated in this process indicated the existence of oxonium compound **25**. The next experiment was done in order to examine a possible way of generating the reactive intermediate **2a** not in a Ag^+ induced reaction with α-chloronitrones. Cyclohexene was added to the solution of **25** in 1,2-dichloroethane and left for 30 min. After work up with 20% KCN/H_2O main reaction product was still **26**. However **8** was also isolated in 4% yield as one of the reaction products. This result manifests that oxonium ions of type **25** are rather stable and that the process of loosing the ether moiety is difficult under the tested reaction conditions. However, the use of other leaving group than Cl^- and particularly avoiding Ag^+ ions in the use of N-alkyl-N-vinyl nitrosonium ions may be of importance in the higher scale uses of this 1–4 dipolar cycloaddition reaction for synthesis.

CONCLUSIONS

Formation of oxonium compounds like **4** is the major reaction product in the Ag^+ induced reaction of α-chloronitrones with enol-ethers. These can undergo either elimination or fragmentation reactions. The reversed process in the case of enol ether is very slow and practically does not affect the preparative way of propellanes like **3**. Oxonium compounds like **25** could be prepared by alkylation of the α-alkoxy nitrones with Meerwein salt. These intermediates decompose also to give the reactive intermediate **2a**. Under the conditions tested, this is unfortunately not a fast process. However, this observation opens new possibilities for the preparation of **2a**. Work in this direction is now carried out in our laboratory.

EXPERIMENTAL†

Reaction of N-*cyclohexyl-α-chloroacetaldehydnitrone* **1a** *with cyclohexene in ether*

A soln of 700 mg (3.44 mmol) **1a** in 40 ml Et_2O was added dropwise at 0° to a stirred soln of 700 mg (3.60 mmol) $AgBF_4$, 1.0 g (11.9 mmol) cyclohexene in 60 ml ether over 30 min. The reaction was stirred for another 30 min and worked up with 20 ml of 4M KCN. The aqueous phase was extracted twice with 20 ml ether and dried over Na_2SO_4. The crude material was chromatographed over Al_2O_3 using ligroin-benzene mixtures. 240 mg **8** m.p. 85–86°[4] (from hexene CH_2Cl_2) together with 240 mg oil ($^-$CN isomers mixture) together 46% yield of **8** was obtained.

General procedure for Ag^+ *induced reaction of α-chloronitrones in* 1,2-*dichloroethane*. A soln of α-chloronitrone in dry 1,2-dichloroethane (20 ml) was added under dry N_2 to a stirred soln of $AgBF_4$ in dry 1,2-dichloroethane (40 ml) and the olefin at −15° during 2 hr. After a further 1 hr at 0° the mixture was shaken with a 20% KCN-water (20 ml) during 5 min. The aqueous soln was then extracted twice with dichloroethane and the combined organic layers were dried over Na_2SO_4. The residue obtained after removal of the solvents *in vacuo* was chromatographed over Al_2O_3 (Ref. 7) (using ligroin-benzene mixtures). The following were obtained after reaction with:

(i) 2,5-*Dihydrofurane* 9 *and* N-*cyclohexyl-2-chloroacetaldehydenitrone* **1a**. The unsaturated ether **9** 1.4 gr (20 mmol), 800 mg $AgBF_4$ (4.12 mmol) and 700 mg **1a** (3.98 mmol) gave 890 mg crude product. After chromatography the following were obtained:

(a) 176 mg solid R_f[4] 0.6 crystallization from hexane gave 167 mg white powder m.p. 70–71° 17% yield; IR 2250 cm^{-1}; ^{1}HMR 4.58 (tripl. doublet Jt = 5.1 Ht, Jd = 4 Hz, 1H), 4.1–3.5 (m, 5H); 2.8 (m, 1H); 2.4–2.0 (m, 3H) and 2.0–1.0 (m, 10H); MS (236.316), 236 (3%), 209 (3%), 193 (27%), 156 (18%), 150 (17%), 136 (12%), 110 (14%), 83 (87%), 55 (100%). (Found for $C_{13}H_{20}N_2O_2$: C, 66.20; H, 8.46; N, 11.68%). This was identified as **10a**.

(b) 187 mg solid, R_f value[4] = 0.5. Crystallization from hexane gave white needles m.p. 77–78°, 178 mg, 19% yield: IR 2240 cm^{-1}; ^{1}HMR 4.43 (tripl. doublet, Jt = 3.2 Hz, Jd = 1.5 Hz, 1H); 4.2–3.8 (m, 5H); 2.8 (m, 1H); 2.4–2.0 (m, 3H) and 2.0–1.0 (m, 10H); MS (236.316), 236 (2%), 209 (3%), 193 (27%), 166 (11%), 150 (10%), 136 (8%), 110 (10%), 193 (12%), 183 (47%). (Found for $C_{13}H_{20}N_2O_2$: C, 65.91; H, 8.51; N, 11.70%). This was identified as **11a**.[4]

(ii) 1,4-*Dioxene and* N-*cyclohexyl-2-chloroacetaldehyde nitrone* **1a**. The unsaturated ether **13** 1.0 gr (11.6 mmol), 800 mg $AgBF_4$ (4.12 mmol) and 700 mg **1a** (3.98 mmol) gave 917 mg crude product. After chromatography the following were obtained:

(a) 181 mg solid recrystallization from hexene–CH_2Cl_2 gave 172 mg, m.p. 90–91°, 17% yield; IR 2240 cm^{-1}; ^{1}HMR 4.78 (d, 0.5 Hz, 1H); 4.2–3.4 (m, 6H); 2.87 (m, 1H); 2.3–2.1 (m, 2H) and 2.0–1.0 (m, 10H); MS (252, 314) 252 (12%), 225 (2%), 153 (15%), 152 (37%), 148 (40%), 136 (7%), 100 (92%), 99 (90%), 83 (100%). (Found for $C_{13}H_{20}N_2O_3$: C, 62.00; H, 8.12; N, 10.95%). This was identified as **14**.[4]

(b) 169 mg solid recrystallization from hexene/CH_2Cl_2 gave 157 mg m.p. 68–69°, 15% yield; IR 2260 cm^{-1}: ^{1}HMR 4.85 (d, 1.8 Hz, 1H), 4.2–3.4 (m, 6H), 2.98 (m, 1H), 2.3–2.1 (m, 2H) and 1.8–1.1 (m, 10H); MS (252, 314) 252 (12%), 225 (2%), 190 (2%), 153 (17%), 152 (30%), 148 (43%), 100 (100%), 99 (98%), 83 (90%). (Found for $C_{13}H_{20}N_2O_3$: C, 61.70; H, 8.10; N, 11.20%). This was identified as **15**.[4]

(iii) *Reaction of 2,5-dihydrofurane* **9** *with α-chlorobutyraldehyde*-N-*cyclohexylnitrone* **1b**. The unsaturated ether 2 gr (28.5 mmol), 800 mg $AgBF_4$ (4.12 mmol) 800 mg **1b** (4.12 mmol) gave 1.2 gr crude product. After chromatography the following were obtained:

(a) 123 mg of a mixture of isomers of **10b** and **11b** which was not further worked: IR 2240 cm^{-1}; ^{1}HMR 0.9 (t, 8 Hz, 3H), 1.0–2.3 (m, 14H), 2.8 (m, 1H), 3.8–4.2 (m, 5H) and 4.7 (m, 1H), (11% yield).

(b) 267 mg solid recrystallized from ether, m.p. 103–105° (245 mg; 21.3%) identical in its spectral data with **12** obtained from reaction with 5,6-dihy-4H-pyrane.

(iv) 2H 3,4-*dihydropyrane* **16** *and* N-*cyclohexyl-2-chlorobutyraldehyde-nitrone* **1b**. The unsaturated ether 2.0 g (23.8 mmol), 1.92 g $AgBF_4$ (9.9 mmol) and 2.0 g **1b** (9.80 mmol) gave 4.05 g crude product. After chromatography the following were obtained:

(a) 316 mg solid from which 240 mg (8.8%) were obtained as white crystals m.p. 105°; IR 2225 and 1160 cm^{-1}; ^{1}HMR 1.06 (t, 7 Hz, 3H), 0.9–2.2 (m, 18H), 2.90 (m, 1H), 3.80 (m, 2H) and 4.90 (d, 1 Hz, 1H). MS 278 (278, 396). (Found for $C_{16}H_{26}N_2O_2$: C,

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†Melting points are uncorrected. UV spectra were taken on a Cary 14 instrument. IR spectra were taken in KBr pellets on a Perkin Elmer 251. ^{1}HMR spectra were taken in CCl_4 and are in δ values. Olefines and ethers were dried on distillation over Na. Merck Al_2O_3 Art 1097 activity II–III was used for the column chromatography. Dry solvents were obtained by distillation over P_2O_5 and filtration over a 100 fold amount of basic Al_2O_3 (activity 1, Merck).

69.04; H, 9.20; N, 9.74%). This was identified as **17**. From the mother liquid 86 mg of a mixture containing **17** and isomers (together 11.9% yield) were isolated.

(b) On eluting with a benzene–ether 1:1 mixture 237 mg solid were isolated. Crystallization from diethyl ether (at −40°) gave 174 mg crystals m.p. 110–111°; IR 2460, 1630 and 1550 cm^{-1}; ^{1}HMR 7.08 (d, 8.5 Hz, 1H), 6.79 (ddq. J, 15, 5 Hz, Jz 8.5 Hz, J3 1 Hz, 1H), 6.22 (dq J, 1.5 Hz, Jz 7 Hz, 1H), 3.6 (m, 1H), 1.92 (d, 7 Hz, 3H) and 2.2–1.1 (m, 10H), λ_{max}EtOH 285 (ϵ = 10,000) and 230 (ϵ = 5700). (Found for $C_{10}H_{17}NO$: C, 71.60; H. 10.35; N, 8.05%). This was identified as the nitrone of *trans* crotonaldehyde **12**[9] obtained in 10.56% yield.

(v) *With ethyl vinyl ether and 2-chlorobutynaldehyde*-N-*cyclohexyl nitrone*. The enol ether 1.0 g (13.8 mmol), 850 mg $AgBF_4$ (4.38 mmol) and 1.0 g **1b** (4.90 mmol) gave 1.6 g crude material. After chromatography the following were isolated:

(a) 40 mg oil. TLC analysis indicated a mixture of various compounds.

(b) 520 mg m.p. 82° (49%); IR 3060, 2530, 1580 and 1120 cm^{-1}; ^{1}HMR 0.98 (t, 7 Hz, 3H), 1.18 (t, 6.5 Hz), 0.8–2.2 (m, 14H), 3.50 (q, 7.3, 2H), 3.6 (m, 1H), 4.50 (q, 6.3 Hz, 1H), 6.68 (d, 6.3 Hz, 1H); MS 213 (213, 320). (Found for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.86; N, 6.56%). This was identified as **19**.

(vi) *With 1-methoxy 1-heptene and α-chloracetaldehyde* N-*cyclohexyl nitrone* **1a**. The enol ether (E + Z 1:1) **20**, 1.2 g 600 mg $AgBF_4$ (3.1 mmol) and 600 mg **1a** (3.42 mmol) gave 430 mg crude product. After chromatography the following were obtained:

(a) 62 mg mixture of various compounds.

(b) 217 mg solid crystallization from pentone at −20° gave 172 mg white solid m.p. 52° identical in its spectral data obtained for the same material **22** which was synthesized from α-methoxy acetaldehyde (30% yield).

General procedure for Ag$^+$ *induced reaction of chloronitrones in liquid* SO_2. Onto a suspension of $AgBF_4$ and the olefin, dry SO_2 was condensed (*ca* 50 ml), the suspension was heated to reflux temp (−10°) under dry N_2. A soln of the nitrone in 20 ml dry CH_2Cl_2 was added with stirring during 2 hr. After a further 30 min reflux, SO_2 was removed in a slow stream of dry N_2 and finally *in vacuo*. 20 ml dry dichloromethane were added to the remaining material and the soln was shaken with 5 g KCN in 20 ml water during 5 min. The aqueous soln was then extracted twice with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The residue obtained after removal of the solvents *in vacuo* was chromatographed over Al_2O_3 (Ref. 8) (using ligroin-benzene mixtures). The following were obtained after reaction with:

(i) *2,5-Dihydrofuran and α-chloroacetaldehyde* N-*cyclohexyl nitrone*. (a) **10a** was obtained, m.p. 70–71° in 22% yield. (b) **11b** was obtained in 20% yield m.p. 78° identical with material obtained in 1,2-dichloroethene.

(ii) *With 1,4-dioxene and* N-*cyclohexyl α-chloroacetoacetoldehyde nitrone*. (a) **14** was obtained in 18% yield, m.p. 90–91°. (b) **15** was obtained in 20% yield, m.p. 67–68° both identical in their spectral data with the materials obtained in 1,2-dichloroethane.

Preparation of α-alkoxyl nitrones

α-Methoxyaldehydes were prepared by oxidation with $K_2Cr_2O_7$ of the corresponding β-alkoxy-ethanols. The azeotopic mixtures were dried over $MgSO_4$, filtered and the solns obtained (80% aldehyde in water) were used for further work. 6 g of that aldehyde soln were added to 50 ml diethyl ether and 5 g N-cyclohexylhydroxylamine. The mixture was stirred at 0° under N_2 over 1 hr. The resulting soln was left overnight at 0° over a mixture of anhyd Na_2SO_4 and $CaSO_4$. After filtration, the ether was removed *in vacuo* and the residue was dissolved in 100 ml hexane and dried once more over $MgSO_4$, filtered and the resulting solid obtained after removal of the solvent *in vacuo* was recrystallized from pentane at −10°. The following were obtained:

(i) *From α-methoxyacetaldehyde*. 6.5 g of the nitrone **22** m.p. 52–53°; IR 2540, 1580 and 1100 cm^{-1}; ^{1}HMR 1.0–2.1 (m, 10H), 3.40 (s, 3H), 3.60 (m, 1H), 4.38 (d, 4.5 Hz, 2H) and 6.9 (t, 4.5 Hz, 1H); MS (171, 239) 171 (6%). (Found for $C_9H_7NO_2$: C, 62.93; H, 10.37; N, 8.37%).

(ii) *From α-ethoxyacetaldehyde*. 5.8 g nitrone **24** m.p. 75°; IR 2540, 1070 and 1100 cm^{-1}; ^{1}HMR 1.2 (t, 6 Hz, 3H), 1.0–2.1 (m, 10H), 3.70 (m, 1H), 3.60 (q, 6 Hz, 2H); 4.45 (d, 4.5 Hz, 2H); 6.90 (t, 4.5 Hz, 1H). (Found for $C_{10}H_{19}NO_2$: C, 65.06; H, 10.47; N, 7.89%).

Reactions of α-methoxyacetaldehyde nitrone with $Et_3O^+BF_4^-$ *in dichloroethane*

(i) 2 g $Et_3O^+BF_4^-$ (9.95 mmol) and 1.0 g (5.8 mmol) α-methoxynitrone were dissolved in 30 ml dry dichloroethane and left at room temp for 30 min. The mixture was poured into 30 ml ice water containing 4 g $NaHCO_3$, extracted with three portions of 20 ml CH_2Cl_2, dried and the residue was chromatographed using ligroin as eluent. 873 mg solid were isolated (81% yield) and recrystallized from pentane m.p. 67° identical with material obtained from **24**.

(ii) When the reaction was worked up by shaking with 30 ml of a 20% KCN–H_2O soln, a liquid b.p. 70° at 0.5 mm Hg 670 mg (58.9% yield) of the HCN adduct **27** were isolated; IR (neat) 3500 (braced) 2240(W) and 1100 cm^{-1}; ^{1}HMR 1.07 (t, 6.5 Hz, 3H), 1.7 Hz (d, 8 Hz, 2H), 1.0–2.1 (m, 10H), 2.8 (m, H), 3.70 (q, 6.5 Hz, 2H) and 3.8 (t, 8 Hz, 1H), 4.90 (m, 1H) disappears on adding H_2O. MS (196, 282) 196. (Found for $C_{11}H_{20}N_2O$: C, 67.71; H, 10.02; N, 14.67%). Cyclohexene was added to the reaction and left at room temp during 30 min. The reaction was worked up with 5 g KCN in 20 ml H_2O. After chromatography the following were obtained: (a) **27** 770 mg (62.4%), identical with the material described above. (b) 64 mg **8** m.p. 85–86° (Ref. 6) (4.4% yield), identical with the material obtained from α-chloroacetaldehyde nitrone in the Ag$^+$ induced cycloaddition in 1,2-dichloroethane.

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