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The Reaction of Nitrosyl Chloride and of Nitryl Chloride with 2-Cholestene[1]

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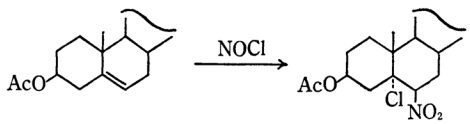
In connection with our studies on introduction of nitrogen functions into steroids we investigated the addition of nitrosyl chloride and of nitryl chloride to 2-chlestene. Addition of nitrosyl chloride to 2-cholestene followed by dehydrohalogenation with pyridine leads to 2-nitro-2-cholestene as the only isolable product. The formation of nitro addition products is not attributable to the reaction of the olefin with nitryl chloride since the latter reacts with 2-cholestene to give mainly 2β, 3α-dichlorocholestane and 3α-chloro-2β-cholestanyl nitrate.

Recently Hassner and Heathcock have reported the stereospecific introduction of nitrogen functions into steroids by addition of iodine isocyanate to 2-cholestene.[3,4] The *trans*-diaxial iodo isocyanate adduct could be converted into 2β, 3β-iminocholestane and these reactions were extended into a general synthesis of aziridines from olefins.[5] It has also been shown by these workers that the addition of nitrosyl chloride to Δ^5 steroid olefins (I) proceeds stereospecifically and in excellent yield to lead to 5α-chloro-6β-nitro adducts (II).[6]



I II

In fact this reaction, followed by zinc reduction, now represents the most convenient entry into 6-oxygenated steroids. The formation of *trans* chloro nitro compounds from the reaction of cholesteryl acetate (I) with nitrosyl chloride had been reported earlier by Tanabe and Hayashi[7] and has also been the subject of recent studies by Meakins *et al.*[8]

To explain the stereospecificity observed in the reaction of steroid-5-enes (I) with nitrosyl chloride one can postulate attack by NO^+ (followed by oxidation to nitro) or by $NO_2\cdot$ from the β-side on C-6. Although attack at C-6 is consistent with the formation of a stable tertiary ion or radical at C-5, approach of reagents in steroids is expected from the α-side. Addition of nitrosyl chloride to Δ^9-octalin[9] and to cyclohexene[10] was shown to proceed *trans* but to norbornene the reagent presumably adds *cis*[9] and no nitro compounds were formed in these reactions. It was therefore of interest to examine the addition of nitrosyl chloride and 2-cholestene from the point of view of synthetic utility and of stereochemical results of the reaction.

When a solution of 2-cholestene in dichloromethane is saturated with nitrosyl chloride under cooling, a greenish oil is obtained which does not crystallize. After dehydrochlorination with pyridine and chromatography a solid is obtained, the infrared spectrum of which indicates a nitro olefin structure. The product shows a marked melting point depression on admixture with 3-nitro-2-cholestene but is identical by infared and mixed melting point experiment to 2-nitro-2-cholestene.[11] The final proof for the position of the nitro group at C-2 comes from reductive hydrolysis of the nitro olefin with zinc in aqueous acetic acid to cholestan-2-one. This reaction proceeds by reduction of the olefinic nitro group to a vinyl amine which tautomerizes to an imine.[12] The position of the ketone resulting from hydrolysis of the imine then indicates the position of the nitro

1) a) Stereochemistry of Organic Nitrogen Compounds. XXVII. For paper XXVI see A. Hassner and P. Catsoulacos, *Chem. Commun.*, in press. b) Presented in part by A. Terada at the Meeting of the Chemical Society of Japan, Ōita City, December, 1965.

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3) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).

4) C. Heathcock and A. Hassner, *Angew. Chem.*, **75**, 344 (1963).

5) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

6) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

7) K. Tanabe and R. Hayashi, *Chem. Pharm. Bull.*, **10**, 1177 (1962).

8) W. A. Harrison, E. R. H. Jones, G. D. Meakins and P. A. Wilkinson, *J. Chem. Soc.*, **1964**, 3210.

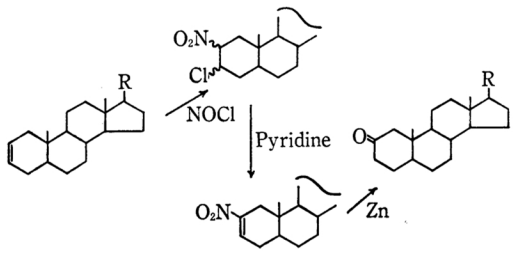
9) J. Meinwald, Y. C. Meinwald and T. N. Baker, *J. Am. Chem. Soc.*, **86**, 4074 (1964).

10) Z. Yoshida and K. Nakagawa, Abstracts of the Meeting on Olefins of the Chemical Society of Japan and the Society of Organic Synthetic Chemistry, Tokyo, Japan, November, 1964.

11) This compound was prepared independently by Dr. J. M. Larkin in this laboratory.

12) See for exampl L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishers, New York (1959), p. 44.

group. The yield of crude 2-nitro-2-cholestene is 46%. No other product was isolated and it appears that 2-nitro-3-chlorocholestane is the major product in the addition of nitrosyl chloride to 2-cholestene.



R: C_8H_{17}

Since a pure nitrochlorocholestane product could not be isolated, it is difficult to foretell the stereochemistry of the addition reaction. If the two functional groups were assumed to be axially oriented, as is the case in other examples of both ionic and free radical additions to steroid olefins[6,13] then the product would have the 3α-chloro-2β-nitro configuration and here again as in steroid-5-enes, the nitrogen function would appear to have entered from the more hindered β-side of the molecule.

As has been mentioned earlier, the nitro group resulting from nitrosyl chloride addition to some olefins could arise either from oxidation of a nitroso group by nitrosyl chloride or by direct introduction of an NO_2 species. It was therefore important to ascertain whether nitrosyl chloride was converted to nitryl chloride, which in turn was the reagent adding to the olefin. When nitryl chloride is added to 2-cholestene in dichloromethane, no chloronitrocholestane is found among the products. The major product, in 37%, is 2β, 3α-dichlorocholestane. Among the other products are two chloronitrate derivatives of cholestane, 2α, 3β-dichlorocholestane, cholestane-2-one and 2β, 3α-cholestanediol (see Table 1).

TABLE 1. PRODUCTS FROM THE REACTION OF NITRYL CHLORIDE WITH 2-CHOLESTENE

Product	Mp, °C	Yield, %
2α, 3β-Dichlorocholestane	145—147	6.4
2β, 3α-Dichlorocholestane	107—109	37.5
2, 3-Chlorocholestanyl nitrate	161—163	4.2
3α-Chloro-2β-cholestanyl nitrate	107—109	12.9
Cholestane-2-one	124—126	1.3
2β, 3α-Cholestanediol	207—209	3.7

13) Other examples of diaxial additions include the reaction a) of Br_2 (G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, **1959**, 4284), b) of HBr-free radical (C. W. Shoppee and R. Lack, *J. Chem. Soc.*, **1960**, 4864) and c) of NO_2I (A. Hassner and J. Kropp, unpublished results).

Several examples of nitryl chloride addition to olefins have been reported and the main products are usually a 1, 2-chloronitro adduct and a pseudonitrosite. In many cases the reaction is complicated by addition of the elements of chlorine, nitrogen sequioxide or nitrogen dioxide across the double bond, depending on the solvent used and the olefin studied.[14]

Since the total yield of crude products is 78% and that of pure products isolated as high as 65%, nitro chloro products, if produced at all, cannot account for a major pathway of the reaction of nitryl chloride with 2-cholestene. In our case the formation of addition products of chlorine and of chlorine nitrate suggests that disproportionation of nitryl chloride is taking place more readily than its direct addition to olefins. Seel and Nogradi[15] have postulated that nitryl chloride can disproportionate as follows:

$$2NO_2Cl \rightleftarrows N_2O_4 + Cl_2$$

$$N_2O_4 \rightarrow NO^+ + NO_3^-$$

$$N_2O_4 \rightarrow N_2O_3 + \text{oxidation}$$

To this should be added the reaction:

$$Cl_2 + N_2O_4 \rightarrow ClNO_3 + NOCl$$

Addition of chlorine to 2-cholestene is expected to lead mainly to the diaxial 2β, 3α-dichlorocholestane which, however, can rearrange to the more stable diequatorial 2α, 3β-dichloroisomer. The former is in fact the major product isolated from the nitryl chloride reaction. Similarly, attack of Cl^+ or of $Cl\cdot$ on 2-chlolestene can be followed by reaction of the intermediate ion or radical with nitrate ion or with N_2O_4 leading to chloro nitrates as products.

Both chlorocholestanyl nitrates show characteristic nitrate absorption[16] near 1640, 1270, 845 and 745 cm^{-1}. The major isomer shows axial chlorine absorption at 715 cm^{-1} and is assigned the 3α-chloro-2β-cholestanyl nitrate structure on the assumption of diaxial addition of $Cl^+NO_3^-$. This is consistent with the NMR spectrum of the compound that shows the 2- and 3-protons as peaks with half widths of 8—10 cps characteristic of equatorial hydrogens.[6] Attempted hydrolysis of this chloronitrate in dilute acetic acid containing sulfuric acid and ferrous sulfate lead to a small amount of a product which appears to be a chloroacetoxycholestane but the structure of which was

14) See for example: C. C. Price and C. A. Sears, *J. Am. Chem. Soc.*, **75**, 3275 (1953); H. Schechter, *Rec. Chem. Progr.*, **25**, 1 (1964).

15) F. Seel and J. Nogradi, *Z. Anorg. Allg. Chem.* **269**, 187 (1952); on the other hand see M. J. Collins, F. P. Gintz, D. R. Goddard, E. A. Hebdon and G. J. Muikoff, *J. Chem. Soc.*, **1958**, 438.

16) N. Yoda in "Infrared Spectra, Theories and Applications," Vol. 13, ed. by T. Shimanouchi, Y. Mashiko and K. Nakanishi, Nankodo, Tokyo (1961), p. 42.

not determined. The structure of the other chloronitrate isomer remains undetermined except that its infrared spectrum suggests the presence of an equatorial chlorine at 762 cm^{-1}, and its NMR spectrum indicates the presence of an equatorial substituent (the geminal proton is axial with a half width of 25 cps).

Of the four possible 2, 3-cholestanediol isomers, the 2α, 3α-, 2α, 3β-, and 2β, 3α-diols come into consideration for the diol isolated[17,23] on the basis of melting points. The infrared spectrum of the cholestanediol obtained above, mp 207—209°C, differs from the spectra of the 2α, 3α-, 2α, 3β- and also 2β, 3β-cholestanediols, but is identical with that of authentic 2β, 3α-cholestanediol, mp 205—205.5°C.[18,19] Possibly the diol arises from acid hydrolysis of the primarily formed 2α, 3α-oxidocholestane during work up.[24] The presence of cholestan-2-one can be explained as arising by hydrogen chloride elimination from one of the chlorocholestanyl nitrates.

Experimental

All melting points were taken on a Fisher-Johns melting point block and are uncorrected. All infrared spectra were taken as KBr disks on a Perkin Elmer Model 21 Spectrometer. Elemental analyses were performed by A. Bernhardt, Muelheim, Germany. NMR spectra were taken in D-chloroform on a Varian A60 instrument with tetramethylsilane as an internal standard.

Addition Reaction of Nitrosyl Chloride to 2-Cholestene. A sample of 3.706 g. (0.01 mol) of 2-cholestene was dissolved in 20 m*l* of dichloromethane. After saturation with nitrosyl chloride at 0°C the solution was allowed to stand at the same temperature for another half hour. On work up as usual, 4.785 g of a greenish very viscous oil was obtained, and this oil resisted crystallization from various solvents.

Treatment of the above oily product with pyridine under reflux for 3 hr gave 3.479 g of a brown resinoid solid. Recrystallization from acetone gave 1.073 g of crude crystals, mp 90—92°C. This sample was shown to be crude 2-nitro-2-cholestene by infrared comparison with an authentic sample. Repeated recrystallizations from acetone or ethylene dichloride - ethanol gave an analytical sample, mp 133—134°C.

Found: C, 78.01; H, 10.86; N, 3.52%. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.92; N, 3.37%.

ν_{max}^{KBr} 1671 (C=C); 1517, 1330 cm^{-1} (NO_2).

While the melting point was depressed greatly on admixture with an authentic sample of 3-nitro-2-cholestene, mp 129—130°C, it was not depressed on admixture with a sample of 2-nitro-2-cholestene, mp 130—131°C.[11]

A chromatographic separation of the mother liquor of the above crystals gave 53 mg (1.4%) of a crude 2-cholestene, and 0.848 g of a crude fraction of 2-nitro-2-cholestene (total yield of crude 2-nitro-2-cholestene was 46%).

Reductive Hydrolysis of 2-Nitro-2-Cholestene to Cholestane-2-one. A sample of 150 mg of the nitrocholestene (mp 133—134°C) was stirred in 9 m*l* of glacial acetic acid and 0.5 m*l* of water. To this, was added 480 mg of zinc dust in portions during a period of 2 min under stirring. The mixture was then stirred and refluxed for another 4 hr. After filtration the solution was poured into a large amount of water, taken up in benzene and in ether respectively. After usual work up, 70 mg of a crude sample of cholestane-2-one was obtained from the benzene extract. More cholestane-2-one 34 mg, total of 74%, was recovered from the ether extract. Recrystallization from ethanol gave an analytical sample melting at 127—128°C. This was identical with an authentic sample of cholestane-2-one (mp 127—130°C) by infrared spectrum comparison and by mixed melting point test.

Addition of Nitryl Chloride to 2-Cholestene. Nitryl chloride[27] was slowly distilled and introduced into a 50 m*l* three-necked flask containing 1.855 g (5 mmol) of 2-cholestene in 25 m*l* of dichloromethane during a period of 30 min under cooling in an ice bath. In the distillation of the nitryl chloride the initial run of the distillate containing chlorine or nitrogen oxides gas was purged out of the reaction system and only the fraction boiling at −17°C was used. The increase in weight of the reaction mixture was 2.396 g corresponding to the addition of 29.4 mmol of nitryl chloride. After standing for 30 min, the mixture was concentrated to dryness under vacuum at room temperature. The residual pale yellow oil (2.678 g) was taken up in ether, and the solution was washed with water until neutral and dried over anhydrous magnesium sulfate. On solvent removal, 2.44 g of a pale yellow oil was obtained.

On standing at room temperature, the oil partially solidified. After filtration and recrystallization of the solid from petroleum ether, bp 60—90°C, there was obtained 0.142 g (6.4%) of white needles, mp 131—136°C. Repeated recrystallizations furnished an analytical sample of 2α, 3β-dichlorcholestane, melting at 145—147°C (lit.,[13a] 150—152°C).

Found: C, 73.50; H, 10.12; Cl, 16.07%. Calcd for $C_{27}H_{46}Cl_2$: C, 73.45; H, 10.50; Cl, 16.05%.

17) R. Albrecht and C. Tamm, *Helv. Chim. Acta*, **40**, 2216 (1957).

18) Samples prepared in this laboratory by D. Davis.

19) The melting point has been reported as 159—161°C,[20] 195—197°C and 201°C,[21] 197—200°C[22] and 200—202°C.[23]

20) K. Hattori and T. Kawasaki, *J. Pharm. Soc. Japan*, **57**, 160 (1937).

21) R. E. Marker and L. Plambeck, Jr., *J. Am. Chem. Soc.*, **61**, 1332 (1939).

22) H. B. Henbest and M. Smith, *J. Chem. Soc.*, **1957**, 926.

23) C. W. Shoppee, D. N. Jones and C. H. R. Summers, *ibid.*, **1957**, 3100.

24) The 2, 3-oxide can be ring-opened under such a condition by dilute sulfuric acid[25] or by thiocyanic acid[26] at room temperature.

25) A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

26) K. Takeda, T. Komeno, J. Kawanami, S. Ishihara, H. Kadokawa, H. Tokura and H. Itani, *Tetrahedron*, **21**, 329 (1965).

27) R. Kaplan and H. Shechter "Inorganic Syntheses," Vol. 4, ed. by J. C. Bailar, Jr., McGraw Hill Co., N. Y. (1953), p. 52.

From the mother liquor of the above dichloro compound, 2.347 g of a pale yellow oil was recovered. This oil was dissolved in petroleum ether and fractionally separated by chromatography using 50 g of activated aluminum oxide (Merck, acid washed):

Fraction 3 (eluted with petroleum ether : benzene= 1 : 4) gave 0.826 g, 37.5% of 2β, 3α-dichlorocholestane, mp 107—109°C (lit.,[13a] 108—112°C).

Found: C, 73.55; H, 10.24; Cl, 16.15%. Calcd for $C_{27}H_{46}Cl_2$: C, 73.45; H, 10.50; Cl, 16.05%.

Fraction 5 (eluted with petroleum ether : benzene= 2 : 3) afforded 0.169 g of white crystals. Recrystallization from ethanol gave 99 mg of a chloronitrate adduct of 2-cholestene, mp 161—163°C.[28]

Found: C, 69.39; H, 10.09; N, 2.71%. Calcd for $C_{27}H_{46}ClNO_3$: C, 69.28; H, 9.91; N, 2.99%.

ν_{max}^{KBr}: 1645, 1270 (nitrate); 845 (NO); 745 (NO_2); 762 cm^{-1} (equatorial C-Cl).

From fraction 11 (eluted with benzene : ether=4 : 1), 96 mg of cholestane-2-one, mp 124—126°C, was obtained. It did not depress the melting point on admixture with an authentic sample of cholestane-2-one.

Fraction 17 (eluted with ether : methanol=3 : 2) gave 74 mg of a yellow powdery product. After recrystallization from methanol, 2β, 3α-cholestanediol was obtained, mp 207—208°C, identical by infrared with an authentic sample.[18]

ν_{max}^{KBr}: 3355 (OH); 1033, 1007, 957 cm^{-1} (axial alcohol).

From the chromatographic fraction 4 (eluted with petroleum ether : benzene=3 : 7), 735 mg of a transparent oil containing some crystals was obtained. This fraction was found to be still a mixture of the fractions 3 and 5, and hence was combined with the mother liquors of the fractions 3 and 5 (total, 0.784 g) and separated by renewed chromatography. Recrystallization of the second chromatographic fraction eluted with petroleum ether : benzene=9 : 1 (506 mg, mp 95—100°C) gave 302 mg of 3α-chloro-2β-cholestanyl nitrate, mp 107—108°C. Further recrystallizations did not change the melting point. The mixed melting point test with 2β, 3α-dichlorocholestane, mp 107—109°C, showed a marked depression. The protons at C-2 and C-3 appear at 4.8 and 5.7 with half widths of 10 and 8 cps.

Found: C, 69.37; H, 10.15; Cl, 7.71%. Calcd for $C_{27}H_{46}ClNO_3$: C, 69.28; H, 9.91; Cl, 7.57%.

ν_{max}^{KBr}: 1640, 1280 (nitrate); 845 (NO); 745 (NO_2); 715 cm^{-1} (axial C-Cl).

Attempts to hydrolyze 3α-chloro-2β-cholestanyl nitrate, mp 107—108°C by refluxing a mixture of 128 mg of the chloro nitrate, 1.0 g of ferrous sulfate heptahydrate and 4.0 m*l* of concentrated sulfuric acid in 15 m*l* of glacial acetic acid and 15 m*l* of water for 21 hr gave upon work up 107 mg of a brown oil. Recrystallization from ethanol gave 19 mg of crude crystals, mp 104—108°C. The melting point was markedly depressed on admixture with the starting material. The product gave a positive Beilstein test for chlorine, its infrared spectrum indicated the presence of an acetate function but it was not further characterized.

This investigation was supported by U. S. Public Health Service Grant CA-4474 from the National Cancer Institute.

28) This compound gives a positive diphenylamine test indicating the presence of nitrogen in a high oxidation state.