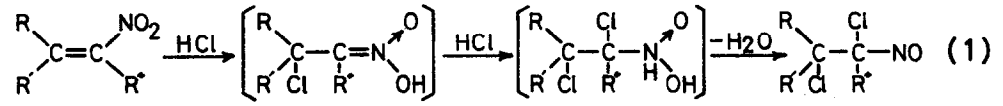
Tetrahedron Letters No.53, pp. 4677-4680, 1970. Pergamon Press. Printed in Great Britain.

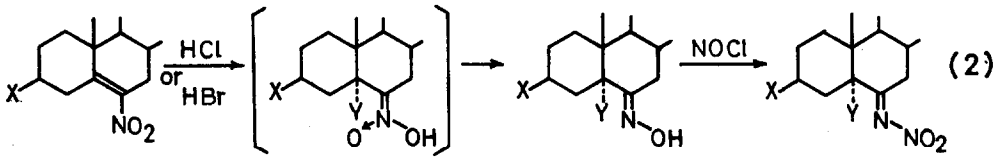
STEROID NITROGEN COMPOUNDS. II.[1] A NOVEL SYNTHESIS OF 5-CHLORO- AND 5-BROMO-6-OXIMINO-5α-CHOLESTANES AND ITS REACTION WITH NITROSYL CHLORIDE

Yoshihisa Komeichi, Shinji Tomioka, Tadaharu Iwasaki, and Katsuyuki Watanabe
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University
Setagaya, Tokyo, Japan

(Received in Japan 30 September 1970; received in UK for publication 19 October 1970)

During our studies on the chemistry of steroids having nitrogen functionality we have found that the treatment of 6-nitrocholest-5-enes with dry hydrogen chloride or bromide produces hitherto unaccessible 5-chloro- or 5-bromo-6-oximino-5α-cholestanes in high yields. While ordinary trisubstituted α,β-unsaturated nitro compounds are reported to give blue α,β-dichloronitroso compounds by addition of two moles of hydrogen chloride according to the following sequence of reactions (Eq. 1),[2] these unsaturated nitrosteroids are shown to add only one mole of hydrogen chloride or bromide with loss of oxygen atom (Eq. 2). We wish to report here this novel reaction of 6-nitro-5-enes and the stereochemistry of the resulting 5α-halo-6-oximes.





Ia X = OAc
Ib X = Cl
Ic X = H

β-Halonitronic Acid Intermediate
Y = Cl or Br

IIa X = OAc Y = Cl
IIb X = Cl Y = Cl
IIc X = H Y = Cl
IId X = OAc Y = Br
IIe X = OAc Y = OMe

IIIa X = OAc Y = Cl
IIIb X = H Y = Cl
IIIc X = OAc Y = OMe

The reaction can be illustrated with the following example: Into an ice cooled solution of 13.5 g of 6-nitrocholesteryl acetate (Ia) in 300 ml of absolute ether was passed a stream of dry hydrogen chloride for one and a half hour, and

the almost colorless reaction mixture was allowed to stand at about 2° overnight. The excess hydrogen chloride and the solvent were removed under reduced pressure and the faintly bluish residue was redissolved in ether, washed with water and dried. After evaporation of ether the resulting colorless solid was crystallized from acetone to give 12.8 g (93%) of 3β-acetoxy-5-chloro-6-oximino-5α-cholestane (IIa), mp 158-160° dec. Recrystallizations from acetone afforded analytical sample of IIa as colorless needles: mp 160-161° dec, $[\alpha]_D^{22}$ -53.5° (c 1, Chf); ν_{max}^{KBr} 3470 (N-OH), 1738, 1715 (acetate), 1648 (weak, C=N), 1242, 1040 (acetate), 950 (N-O) cm^{-1}. The nmr spectrum (60 MHz, $CDCl_3$) had peaks at δ 0.64 (s, C18-H), 0.97 (s, C19-H), 2.03 (s, acetate Me), 3.22 (d, 1H, C7β-H, J = 13 Hz), 5.32 (m, C3-H, W1/2 = ca. 21, axial), 8.93 (s, N-OH). On the basis of these spectral data, which show the acetoxy group is equatorial and thus indicate A/B junction trans, and elemental analyses, which establish the formula as $C_{29}H_{48}O_3NCl$*, structure IIa is assigned to the product. Further, the 5α-chloro-6-oxime (IIa), when dissolved in warm methanol, afforded 5α-methoxy-6-oxime (IIe), mp 221-222°, quantitatively, which was identical in every respect with the authentic sample.[3]

In like manner, 3β,5-dichloro-6-oximino-5α-cholestane (IIb)(72%), and 5-chloro-6-oximino-5α-cholestane (IIc)(73%) have been obtained from the unsaturated nitrosteroid, Ib, and Ic, respectively. Fine plates of dichlorooxime (IIb), mp 170° dec, $[\alpha]_D^{22}$ -50.9° (c 1, Chf), showed the following spectral data: ν_{max}^{KBr} 3350 (N-OH), 1655 (weak, C=N), 946 (N-O) cm^{-1}; nmr ($CDCl_3$) δ 0.64 (s, C18-H), 0.98 (s, C19-H), 3.21 (d, 1H, C7β-H, J = 13), 4.42 (m, C3-H, W1/2 = ca. 24, axial), 8.40 (s, N-OH). Colorless plates of chlorooxime (IIc), mp 150-151° dec, $[\alpha]_D^{22}$ -60.2° (c 2, Chf), showed the following spectral data: ν_{max}^{KBr} 3300 (N-OH), 1645 (weak, C=N), 949 (N-O) cm^{-1}; nmr ($CDCl_3$) δ 0.63 (s, C18-H), 0.92 (s, C19-H), 3.20 (d, 1H, C7β-H, J = 13), 8.78 (s, N-OH).

Similarly, on treatment with dry hydrogen bromide in methylene chloride the unsaturated nitrosteroid (Ia) afforded in 96% yield colorless needles of 5α-bromo-6-oxime (IId), mp 124-126° dec, $[\alpha]_D^{21}$ -52.0° (c 1, Chf); ν_{max}^{KBr} 3425 (N-OH), 1732, 1717 (acetate), 1637 (weak, C=N), 1240, 1040 (acetate), 959 (N-O) cm^{-1}; nmr ($CDCl_3$) δ 0.64 (s, C18-H), 0.98 (s, C19-H), 2.02 (s, acetate Me), 3.25 (d, 1H, C7β-H, J = 13), 5.41 (m, C3-H, W1/2 = ca. 24, axial).

As shown in the 60 MHz nmr data, these 5α-halo-6-oximes always showed one proton signal centered at about δ 3.2. The coupling pattern of IIa, IIc, and IId, which on measurement by a 100 MHz apparatus, appears as doublet (J = 12) of doublet (J = 3) caused by AMX-type coupling indicating the signal to be due to the C7β- equatorial hydrogen atom.[4] Thus these oximes obtained are assigned to be E-isomers.

As described above, the first step of hydrogen chloride or bromide addition to the unsaturated nitrosteroids was considered to give β-halonitronic acid intermediate resulting from 1,4-addition in ordinary way. In the present case, however, it seemed probable to assume that the initially formed β-halonitronic acid intermediate failed to react with more reagent, and stabilized with loss of oxygen atom to give α-halooximes. To account for this difference, one might postulate the steric hindrance towards C=N double bond of the intermediate exerted by the axial chlorine or bromine, and less effectively,[5] by angular methyl group both lying two atoms removed either from nitrogen or carbon of the C=N grouping.

The similar argument may also apply to the resulting halooximes, which have the same steric environment around the C=N double bond as above and fails to react normally with nitrosyl chloride but lead to anomalous products. In contrast to 6-oximino-5α-cholestane, for example, which on treatment with nitrosyl chloride in methylene chloride at 2° for several days, afforded blue gem-chloronitroso compound resulting from addition of the reagent to C=N double bond,[6] 5-chloro-6-oximino-5α-cholestanes, IIa, and IIc, when treated in a similar fashion, afforded less favorable substitution products, 5α-chloro-6-nitrimine IIIa [58%, mp 129-131°, $[\alpha]_D^{22}$ -68.4° (c 1, Chf)], and IIIb [41%, mp 80-81°, $[\alpha]_D^{22}$ -60.2° (c 2, Chf)], respectively, and normal addition product was not obtained. In the case of 5α-bromo-6-oxime (IId), the substitution reaction was accompanied by replacement of bromine with chlorine to give chloronitrimine (IIIa) in 69% yield. Similar nitrimine formation was expected with nitrosyl chloride from steroid 6-oximes having other bulky 5α-substituent. In agreement with our reasoning, 5α-methoxy-6-oxime (IIe),[3] for example, afforded 40% yield of the corresponding nitrimine (IIIc), mp 142.0-143.0°, $[\alpha]_D^{22}$ -76.7° (c 1, Chf).

In a recent paper, C. Shiue et al. reported briefly that α,β-disubstituted

cycloalkyl methyl ketoximes react with nitrosyl chloride to yield the corresponding nitrimines.[7] If the two substituents of the oximes were trans, then the steric environments are closely related to that of the steroid 5α-substituted 6-oximes, and the transformation might be explained by our scheme. The double γ-opposing effects are further considered to be operative in the reaction of several steroid olefins ($\Delta 4$,[5] $\Delta 5$,[5] $\Delta 9(11)$,[8] $\Delta 16$[5]), which are reported to give fluoronitrimine with the addition of nitrosyl fluoride.

Very similar results are obtained in the addition of hydrogen halides to 4-nitrocholest-4-ene and in the reactivity of resulting 5α-halo-4-oximes. The results and several nucleophilic substitution reactions of 5α-halogen of these oximes together with reactions yielding 5α-substituted 6-ones will be described in a later paper.

ACKNOWLEDGEMENTS

The authors are indebted to Prof. K. Hata, Drs. S. Mori and Y. Kamano for their helpful discussions, and to Mr. S. Kumon for nmr measurements.

REFERENCES

* Satisfactory analyses and spectra were obtained on all new compounds reported.

1. For paper I see Y. Komeichi, Y. Osawa, W. L. Duax, and A. Cooper, Steroids, 15, 619 (1970).
2. (a) V. V. Perekalin, Unsaturated Nitro Compounds, Israel Program for Scientific Translations Ltd., Jerusalem, 1964, p. 191.
   (b) P. A. S. Smith, The Chemistry of Open-Chain Organic Nitrogen Compounds, W. A. Benjamin, Inc., New York, 1966, Vol. 2, p. 411.
3. A. Hassner, and W. A. Heathcock, J. Org. Chem., 29, 1350 (1964).
4. K. Oka, and S. Hara, Chem. and Ind., 911 (1968).
5. G. A. Boswell, Jr., J. Org. Chem., 33, 3699 (1968).
6. E. Müller, H. Metzger, and D. Fries, Ber., 87, 1449 (1954).
   cf. Reference 2b, Vol. 2, p. 59.
7. C. Shiue, Y. P. Park, and L. B. Clapp, J. Org. Chem., 35, 2063 (1970).
8. J. P. Gratz, and D. Rosenthal, Steroids, 14, 729 (1969).