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SYNTHESIS AND CHARACTERIZATION OF 1,2-NITROMETHYLENE STEROIDS

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In an accompanying communication[2] we reported the preparation of steroidal 6β,7β-nitromethylene steroids, derived from the steroidal 6-chloro-4,6-diene-3-keto unit by treatment with nitromethane in DMF containing NaOMe. We now disclose application of this transformation to the 2-bromo-1-ene-3-keto system, to afford the 1,2-nitromethylene grouping. From our findings, and also those of Kocór and Kroszczynski[3], it would appear that this method is convenient in a general sense for the preparation of the nitromethylene unit conjugated with carbonyl functions.

Two representative examples have been prepared[4] and their structures and stereochemistries defined unequivocally by single-crystal X-ray analyses. Nitromethylene 1 was prepared in 44% overall yield from the 2-bromo-1,4,6-triene-17α-hydroxy 2[5] [nitromethane, NaOMe, DMF (0.1% water)] via the intermediate nitromethylene-17α-hydroxy 3, followed by esterification [AcOH, $(F_3CCO)_2O$, pTSA][6]. For the preparation of 4, NaOMe (270 mg) was added to a solution consisting of 5[7] (515 mg, 1 mmol), nitromethane (0.59 ml), DMF (6 ml), and water (0.2 ml). After allowing the solution to stand at room temperature for 16 hours, it was added to a saturated NaCl solution, and the precipitated solid isolated and crystallized from ether-hexane to yield 4 (69% yield). Chromatography [silica gel preparative plates, 1000μ, hexane-EtOAc (2:1)] separated a trace of more polar substance and afforded analytical material[8].

Orthorhombic crystals of 1 belong to space group $P2_12_12_1$, a = 11.14(1), b = 28.87(1), c = 6.92(1) Å, Z = 4. Crystals of 4 are monoclinic, space group $P2_1$, a = 12.52(1), b = 12.34(1), c = 7.64(1) Å, β = 90.8(1)°, Z = 2. Intensities for all unique reflections to θ 65°(1) and 67°(4) were measured on an Enraf-Nonius CAD 3 diffractometer (Ni-filtered Cu-K_α radiation, λ 1.5418 A) operating in the θ-2θ scanning mode. Both structures were solved by direct-phasing procedures by use of MULTAN[9]. Atomic positional and thermal (anisotropic C, N, O; isotropic H) parameters were refined by full-matrix least-squares calculations to R 0.065 for 1 (1196 reflections) and 0.050 for 4 (1768 reflections). Views of the structures

of 1 and 4 are shown in Figures 1 and 2, respectively. The results show that in 1 the 1,2-methylene unit is α-oriented whereas the corresponding unit in 4 is oriented β. In both compounds the nitro group is directed exo with respect to the steroid ring A, i.e. 1 is 1α,2α-methylene-(1'R)-nitro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate and 4 is 1β,2β-methylene-(1'S)-nitro-16α-methyl-9α-fluoro-11β,17α,21-trihydroxy-5β-pregnane-3,20-dione 21-acetate.

No other 1,2-nitromethylene isomer was isolated in addition to 1 or 4. The presumed intermediate in the reaction with 2 is an enol species 6 having the 1α-nitromethylene substituent whereas with 5 (cis A/B fusion) the corresponding intermediate is the 1β-nitromethylene 7, i.e. in each case the reaction proceeds to generate the axially oriented C-1 adduct.[10] Intermolecular protonation at C-2 followed by proton loss from C-1' or intramolecular proton transfer from C-1' to C-2 would generate the C-1' anion from both 6 and 7. Subsequent elimination of bromide ion would then accompany ring closure to yield the sterically favored exo nitro configuration.

Our stereochemical assignment of the nitromethylene grouping in 1 by X-ray analysis would also appear to apply to the 1,2-nitromethylene steroids reported in reference 3. For these latter compounds, which differ in C-17 substitution from our related compounds, the α-configuration of the 1,2-methylene unit was deduced principally on the basis of ^{1}H NMR analysis but the nitro group configuration was not established.

Acknowledgment. We thank Dr. R. Brambilla of the Physical Organic Research Department for helpful discussions with NMR interpretation.

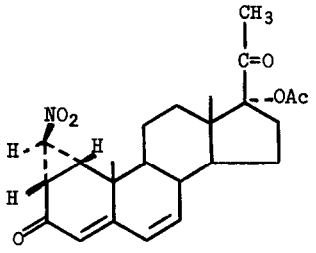
References and Footnotes

1. Schering Postdoctoral Fellow, 1970.
2. E.L. Shapiro, G. Page, L. Weber, M.J. Gentles, A.T. McPhail, and K.D. Onan, preceding communication.
3. While this manuscript was in preparation, M. Kocór and W. Kroszczynski, Synthesis, 813 (1976), reported on a somewhat similar process for the formation of the 1,2-nitromethylene grouping.
4. All new compounds have acceptable analyses.
5. Prepared from the 2-desbromo analog of 2 (Ger. 1,119,266, December 14, 1961, C.A. 56, 14373f, and U.S. Patent 2,962,510, November 29, 1960) by bromination in propionic acid, followed by exposure of the isolated crude product to pyridine at 60° for 2 hours (λ_{max} 222, 270, and 308 nm; ε 14,380, 11,180, and 9,440, respectively).
6. E.L. Shapiro, L. Finckenor, H. Pluchet, L. Weber, C.H. Robinson, E.P. Oliveto, H.L. Herzog, I.I.A. Tabachnick, and E. Collins, Steroids, 9, 143 (1967).
7. E.L. Shapiro, M.J. Gentles, A.T. McPhail, and K.D. Onan, J. Chem. Soc. Chem. Comm. , 961 (1976), m.p. 248-250° dec, $[\alpha]_D^{26}$ +61.5° (dioxane), λ_{max}^{MeOH} 252.5 nm (ε 7,600); NMR, δ (TMS as internal reference, DMSO-d_6), 0.73 and 0.82 (16-CH_3), 0.82 (13-CH_3), 1.49 (10-CH_3), 2.16 (21-$OCOCH_3$), 3.78-4.13 (11-H), 5.08 (17-OH), 5.26 (d, J = 5.5 Hz, 11-OH), 4.73 and 5.08 (doublets, J = 17.5 Hz, 21-CH_2), 7.56 (1-H).

8. For 1, m.p. 245-246°, $[\alpha]_D^{25}$+196° (dioxane), λ_{max}^{MeOH} 284 nm (ε 20,100); NMR, δ (TMS as internal reference, $CDCl_3$), 0.82 (13-CH_3), 1.3 (10-CH_3), 2.06 (17-$OCOCH_3$), 2.15 (20-CH_3), 2.7 (d of d, J = 3.5 and 10 Hz, 1-H), 3.10 (m, J = 4 and 10 Hz, 2-H), 4.42 (d of d, J = 2.5 and 3 Hz, 1'-H), 5.7 (d, J = 1 Hz, 4-H), and 6.13 (6- and 7-H). For 4, m.p. 212-216°, $[\alpha]_D^{25}$-16.5° (dioxane); NMR, δ (DMSO-d_6), 0.72 and 0.85 (16-CH_3), 0.85 (13-CH_3), 1.46 (10-CH_3), 2.09 (21-$OCOCH_3$), 2.84, 2.87 (1-H, 2-H), 4.78 and 4.98 (doublets, J = 17.5 Hz, 21-CH_2), 4.05-4.47 (11-H), 5.07 (17-OH), 5.17 (d, J = 5 Hz, 11-OH), 5.46 (smeared triplet, J = 2.5 Hz, 1'-H).

9. G. Germain, P. Main, and M.M. Woolfson, Acta Cryst, A27, 368 (1971).

10. In our accompanying paper (Reference 2), the nitromethylene unit is generated from a C-7β equatorially oriented adduct. We have no explanation at this time for this difference.



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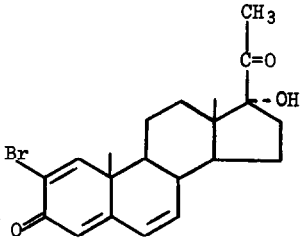

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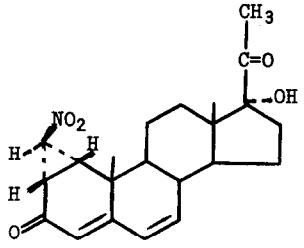

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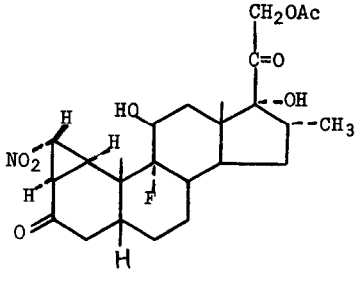

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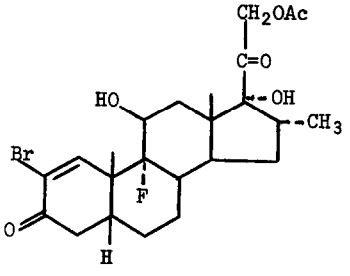

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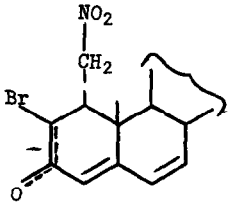

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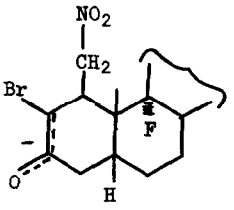

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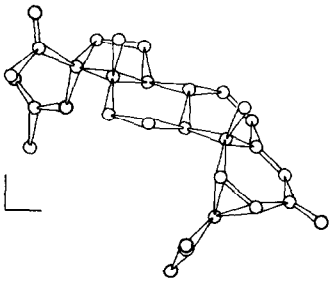

Fig. 1
Structure of 1

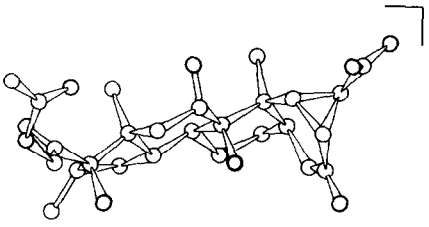

Fig. 2
Structure of 4