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SYNTHESIS OF 6β,7β-NITROMETHYLENE STEROIDS

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We report the formation of novel 6,7-nitromethylene[2] steroids by the reaction of the steroidal 3-keto-6-chloro-4,6-diene moiety with nitromethane. For example, exposure of 6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione acetate (1)[3] at room temperature to nitromethane in DMF containing NaOMe gave a product (2, m/e 441, 55% purified yield) for which analysis revealed the absence of chlorine, ir showed the presence of a nitro grouping (ν_{max} 1530 cm^{-1}), uv exhibited absorption at λ_{max} 258 nm (ε 15,100) with an inflexion at 238 nm, and the ^1H NMR spectrum revealed an apparent triplet at δ 4.50 (J=2.5 and 0.75 Hz) which was assigned to the hydrogen geminal to the nitro grouping on the cyclopropyl unit.

Definitive assignment for 2 as 6β,7β-methylene-(6'S)-nitro-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-acetate[4,5] was achieved by single-crystal X-ray analysis which established not only the β-orientation of the 6,7-methylene unit but also showed that the nitro group was directed exo with respect to the steroid plane and thus the configuration at C-6' was S. Crystals of 2 are orthorhombic, space group $P2_12_12_1$, a = 13.84(1), b = 22.86(1), c = 7.07(1) Å, Z = 4. Intensities for all unique reflections with θ < 27° were measured on an Enraf-Nonius CAD 3 diffractometer (Zr-filtered Mo-K_α radiation, λ = 0.7107 A; 3° take-off angle) by the θ -2θ scanning procedure. The structure was solved by direct-phasing methods by use of MULTAN[6], and the positional and thermal parameters (anisotropic C, N, O) refined by full-matrix least-squares calculations to R 0.077 over 1269 statistically significant [$I > 2\sigma(I)$] reflections. A view of 2 is shown in the Figure.

Extension of this reaction to the 6-chloro- compounds 3[7] and 4[8] which possess the same A,B ring system gave 6β,7β-methylene-(6'S)-nitro-17β-hydroxy-4-pregnene-3-one 21-carboxylic acid lactone (5, 58% yield)[5] and 6β,7β-methylene-(6'S)-nitro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione 21-acetate (6, 63% yield)[5], respectively. The preparation of 5 illustrates the process. To a solution of 3 (188 mg, 0.5 mmol), 0.3 ml of nitromethane, 3.1 ml of DMF, and 0.1 ml of water, was added NaOMe (135 mg). After the mixture had been allowed to stand at room tempera-

ture for 4 hours, addition to water and the usual workup gave a residue which was chromatographed [1000μ silica gel preparative plates, EtOAc-C_6H_{14} (1:1)] to afford 5 (crystallized from ether-hexane). The structural assignments for 5 and 6 followed by analogy with 2 and were supported by comparisons of optical rotation data for these compounds[9].

In the three examples described, no 6α,7α-nitromethylene product was definitively observed. These findings are in contrast to the 6,7-methylene formation from dimethyloxosulfonium methylide[9] with which reagent the α:β ratio was found to vary depending upon the steroidal substrate used, and only with an 11β-hydroxy-bearing substrate was no α-methylene product obtained.

The process for the formation of the 6β,7β-nitromethylene unit may be considered as proceeding through the sterically hindered C-7β equatorially oriented adduct (7). Either intermolecular protonation at C-6 followed by proton loss from the nitromethylene group or intramolecular transfer of a nitromethylene hydrogen to C-6 would produce a carbanion geminal to the nitro grouping; ring closure accompanied by extrusion of chloride ion would then follow.

This report delineates the transformation of a γ,δ-unit to the substituted methylene grouping. In our accompanying communication, we show the extension of this reaction to the α,β system (1-ene-3-one). It would appear (cf. ref. 2) that this method of preparing the nitrocyclomethylene unit has general applicability in steroids, and may, we believe, prove to be a useful alternative procedure from those previously described[10] for non-steroidal systems. We point out, however, the limitation of this reaction with the 4,6-diene system. In our hands, attempted extension with 1 to prepare alkyl analogs failed--use of reagent nitroethane did not give the methylnitromethylene unit. The failure to effect this transformation may have been due to steric factors, a restriction which may not apply in some other steroid systems or in non-steroidal situations.

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. While this manuscript was in preparation, M. Kocór and W. Kroszczynski, Synthesis, 813 (1976), reported the formation of 1,2-nitromethylene steroids by a somewhat similar process.
3. E.L. Shapiro, L. Weber, H. Harris, C. Miskowicz, R. Neri, and H.L. Herzog, J. Med. Chem., 15, 1716 (1972), and references cited therein.
4. All new compounds have acceptable analyses.
5. Compound 2, m.p. 204-205°; NMR, δ (internal reference TMS, $CDCl_3$), 0.75 (13-CH_3), 1.11 (10-CH_3), 2.14 (20-CH_3), 2.05 (17-$OCOCH_3$), 5.48 and 5.60 (16=CH_2), 6.06 (4-H). Compound 5, m.p. 145° (dec.), sintering 136-138°, α_D^{25} -70.2° (dioxane) (M_D-429); λ_{max}^{MeOH} 258 nm (ε 15,200), inflexion 237 nm, NMR, δ ($CDCl_3$), 0.98 (13-CH_3), 1.11 (10-CH_3), 4.49 (t, J = 3 Hz, 6'H), 6.12 (4-H). Compound 6, m.p. 180-185° (dec.), α_D^{25} +51.8° (dioxane) (M_D +239), λ_{max}^{MeOH} 259 nm (ε 14,384), inflexion 232 nm; NMR, δ ($CDCl_3$), 0.95 (13-CH_3), 1.35 (10-CH_3), 2.20 (21-$OCOCH_3$), 4.67 (unresolved d of d, J = 3.4 Hz, 6'-H), 3.6 (17- and 11-OH), 4.45 (11-H), 4.96 (21-OH), 6.01 (4-H).

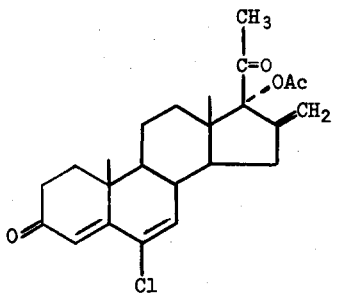
6. G. Germain, P. Main, and M.M. Woolfson, Acta Cryst., A27, 368 (1971).

7. Prepared from the 6-deschloro analog of 3 [J.A. Cella and R.C. Tweit, J. Org. Chem., 24, 1109 (1959)] by peracid epoxidation, then 6,7-chlorohydrin formation and dehydration in the manner described in ref. 3.

8. British Patent 951,460 (March 4, 1964), Chem. Abst., 61, 5733g (1964).

9. See, G.E. Arth, G.F. Reynolds, G.H. Rasmusson, A. Chen, and A.A. Patchett, Tet. Lett., 291 (1974), and references cited therein. The large negative molecular rotation shift of 2 vis a vis the 6,7-dihydro-6-deschloro analog of 1 [-471°], 5 vs 6,7-dihydro-6-deschloro of 3 [-686°], and 6 vs 6,7-dihydro-deschloro of 4 [-431°], is consistent with findings for the 6,7-methylene adducts cited.

10. E.P. Kohler and H.F. Engelbrecht, J. Amer. Chem. Soc., 41, 1379 (1919); L.I. Smith and J.S. Showell, J. Org. Chem., 17, 827 (1952).



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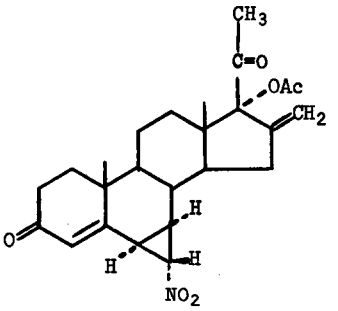

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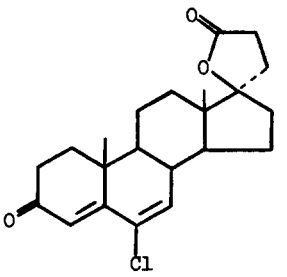

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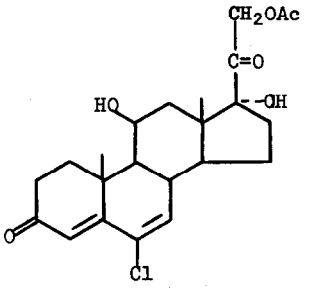

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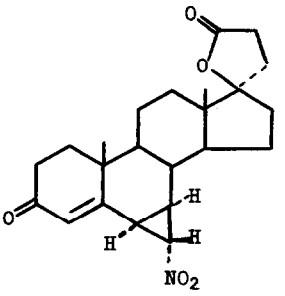

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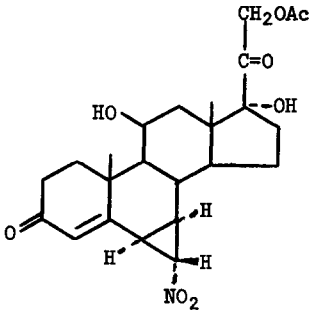

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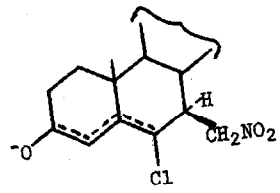

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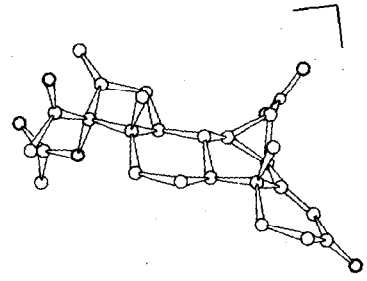

Fig. Structure of 2