Oxidation of Hydrazones with Lead Tetra-acetate

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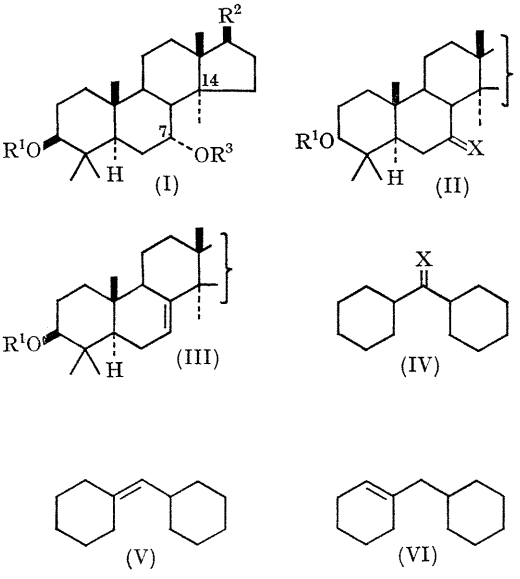
DERIVATIVES of lanosterol with the 14-methyl group in various states of oxidation are widely accepted as intermediates in cholesterol biosynthesis. Such 14-substituted compounds have recently been made available by partial synthesis.[1,2] All these syntheses depend upon the generation of 7α-alkoxy-radicals and therefore require 7α-hydroxy-derivatives of lanosterol. Since the best method[3] for obtaining the axially substituted 7α-hydroxylanostanyl



acetate (I; R^1 = Ac, R^2 = C_8H_{17}, R^3 = H) is the acid-catalysed catalytic hydrogenation of the corresponding 7-ketone (II; R^1 = Ac, R^2 = C_8H_{17}, X = O), it cannot be applied without modification to the true lanosterol series with the unsaturated side-chain. By analogy with recent work on the oxidation of substituted hydrazones with lead tetra-acetate,[4] we conceived that a corresponding oxidation of the hydrazone of a 7-ketone would afford a 7α-acetoxy-derivative. We now report that this reaction is indeed a convenient synthesis of 7α-acetoxy-derivatives and should have general implications.

3β-Hydroxylanost-24-en-7-one† (II; R^1 = H, R^2 = C_8H_{15}, X = O), m.p. 163—164°, $[\alpha]_D$ +29° (all $[\alpha]_D$ in $CHCl_3$, $c \simeq 1$ unless stated otherwise) gave with hydrazine hydrate in refluxing ethylene glycol the corresponding hydrazone (II, R^1 = H, R^2 = C_8H_{15}, X = N·NH_2) {*N*-acetyl derivative m.p. 187—189°, $[\alpha]_D$ +43° (in tetrahydrofuran)}. Oxidation in CH_2Cl_2 at 0—5° with lead tetra-acetate (2 mols.) for up to 5 min. gave, after chromatography, 3β-hydroxylanosta-7,24-diene (III; R^1 = H, R^2 = C_8H_{15}) (20%), m.p. 150—151°, $[\alpha]_D$ + 9° and 3β-hydroxy-7α-acetoxylanost-24-ene (I; R^1 = H, R^2 = C_8H_{15}, R^3 = Ac) (68%), m.p. 188—189°, $[\alpha]_D$ −14°. Chromic acid oxidation afforded 7α-acetoxylanost-24-en-3-one, m.p. 135—136°, $[\alpha]_D$ −40°.

Similarly 3β-hydroxylanostan-7-one[3] (II; R^1 = H, R^2 = C_8H_{17}, X = O) was converted into the hydrazone (*N*-acetyl derivative m.p. 219—220°, $[\alpha]_D$ +50° (in tetrahydrofuran) and oxidised to give, after acetylation, 3β-acetoxylanost-7-ene (III; R^1 = Ac, R^2 = C_8H_{17}) (18%) and 3β,7α-diacetoxylanostane[3] (I; R^1 = R^3 = Ac, R^2 = C_8H_{17}) (70%), both identical with authentic specimens.

The hydrazone (II; R^1 = H, R^2 = C_8H_{17}, X = N·NH_2) has also been oxidised at 20° in a similar manner in various solvents. We list the solvents and (in parentheses) the yields (%) of 7(8)-olefin and 7α-acetate, respectively: CH_2Cl_2 (17, 72), C_6H_6 (15, 74), dimethylacetamide (15, 63), MeOH (18, 45), and light petroleum (b.p. 40—60°) (14, 75).

We have also compared at 20° (see Table) the oxidation of the hydrazone (II; R^1 = H, R^2 = C_8H_{17}, X = N·NH_2) and the hydrazone of benzophenone using, except where otherwise specified, CH_2Cl_2 as solvent. The oxidation of benzophenone hydrazone immediately produces the red colour of diphenyldiazomethane. Oxidation of diphenyldiazomethane with 2 mol. of $Pb(OAc)_4$ followed by alkaline hydrolysis gave 85% Ph_2CO and 7% benzhydrol. Addition of 2 mol. of AcOH changed these percentages to 43 and 50, respectively. All the data in the benzophenone series (above, and see Table) are consistent with the rapid oxidation of the hydrazone to diphenyldiazomethane and the partition of this between the normal reaction with acetic

TABLE

Addenda (mol.)	(II; R^1 = H, R^2 = C_8H_{17}, X = N·NH_2) Yields, % (after acetylation) (III; R^1 = Ac, R^2 = C_8H_{17})	(I; R^1 = R^3 = Ac, R^2 = C_8H_{17})	Ph_2C:N·NH_2 Yields, % Ph_2CO	Ph_2CHOH
2 $Pb(OAc)_4$	17	72	36	52
2 $Pb(OAc)_4$: 2 AcOH	—	—	25	60
2 $Pb(OAc)_4$: 5 AcOH	14	73	16	68
2 $Pb(OAc)_4$: 10 AcOH	17	70	14	75
2 $Pb(OAc)_4$: pure AcOH	17	70	10	85
2 $Pb(OAc)_4$: 10 Me_4N^+ OAc^-	11	63	53	28

acid to give benzhydryl acetate and further oxidation to diacetoxydiphenylmethane. Indeed, the formation of the latter in the oxidation of diphenyldiazomethane is already well established.[5]

Oxidation of dicyclohexyl ketone hydrazone (IV; X = N·NH_2) m.p. 46—47°, *N*-acetyl derivative m.p. 167—168°) with lead tetra-acetate (2 mols.) at 20° in CH_2Cl_2 gave dicyclohexyl ketone (2%), dicyclohexylcarbinyl acetate (IV; R = H,OAc) (43%), the olefin (V) (46%), and the olefin (VI) (8%). The mixture was analysed by g.l.c. and authentic specimens of all compounds were synthesised. The olefins (V) and (VI) are not interconverted under the reaction conditions and (VI) must be formed by concerted hydride migration. Increased proportions of lead tetra-acetate, or the addition of acetic acid or of acetate ion, had negligible effects on the product composition.

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[1] (a) J. Fried, J. W. Brown, and M. Applebaum, *Tetrahedron Letters*, 1965, 849; (b) J. Fried, J. W. Brown, and L. Borkenhagen, *ibid.*, p. 2499; (c) C. W. Shoppee, J. C. Coll, N. W. Hughes, and R. E. Lack, *ibid.*, p. 3249; (d) J. Fried and J. W. Brown, *ibid.*, 1966, 1677; (e) C. W. Shoppee, N. W. Hughes and R. E. Lack, *J. Chem. Soc.* (*C*), 1966, 2359.

[2] (a) T. J. Bentley, J. F. McGhie, and D. H. R. Barton, *Tetrahedron Letters*, 1965, 2497; (b) D. H. R. Barton, A. Hameed, and J. F. McGhie, *ibid.*, p. 4343.

[3] D. H. R. Barton and R. B. Thomas, *J. Chem. Soc.*, 1953, 1842.

[4] D. C. Iffland and E. Cerda, *J. Amer. Chem. Soc.*, 1961, **83**, 747; *J. Org. Chem.*, 1963, **28**, 2769; W. A. F. Gladstone, *Chem. Comm.*, 1969, 179; J. B. Aylward and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1968, 2399, and preceding papers by Norman and his colleagues.

† All new compounds were adequately characterised. New, or improved, methods of preparation will, in appropriate cases, be described in our full paper.

[5] R. H. Hensel, *Chem. Ber.*, 1955, **88**, 257.