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HYPOIODITE AND THE RELATED INTRAMOLECULAR RADICAL REACTIONS OF 3-O-ACETYL-12β-ETIOJERV-5-ENE-3β-20ξ-DIOL (1)

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In a previous communication (1), we have shown the successful introduction of an oxygen function at C-18 methyl of a C-nor-D-homosteroid with cis C/D ring junction by hypoiodite reaction. We now wish to report the results of hypoiodite and lead tetraacetate reactions of titled 20ξ-ol IIa of C-nor-D-homosteroid with trans C/D ring junction and α-substituent at C-17.

Sodium borohydride reduction of O-acetyletiojerv-5-ene-3β-ol-20-one (I) (2) yielded the corresponding 20-ol (IIa), m.p. 144-145°, as the sole product. Irradiation of IIa in cyclohexane in the presence of iodine and lead tetraacetate (3,4) gave, after column chromatography, two products, $C_{23}H_{32}O_4$ III, m.p. 215-216°, and $C_{21}H_{31}O_2I$ IV, m.p. 157-160°, in the yields of 2% and 27% respectively.

On the basis of the ir (γ-lactone, 1783 cm^{-1}; O-acetyl, 1736 cm^{-1}; no OH band), nmr (Table) and mass spectra (5) the former is formulated as a lactone (III) originated from intramolecular hydrogen abstraction.

The molecular formula of IV indicated the product stemmed from the β-scission of 20-alkoxyl radical followed by combination of the resultant C-17 carbon radical and iodine (6). The nmr spectrum of IV exhibited signals expected for the structure (IV) as shown in the Table (7). A signal for a proton attached to carbon bearing iodine appeared as a doublet with J=3.0 cps, which suggests the D-ring of this molecule may be a boat conformation.

Subsequent to these observations, we examined the Barton reaction of nitrite ester of IIa (8) and the similar and yet nonphotolytic intramolecular reaction, i.e., lead tetraacetate oxidation (9) which are of proven synthetic utility.

Irradiation of the nitrite IIb, m.p. 107-109°, prepared from IIa afforded largely I and IIa and only a small amount of the product from intramolecular hydrogen abstraction was formed.

Oxidation of IIa in benzene with lead tetraacetate has afforded beside recovered IIa (5%), five products, $C_{23}H_{34}O_4$ V, m.p. 184-185° (20%), $C_{23}H_{34}O_4$ VI, m.p. 176-178° (3%), $C_{27}H_{36}O_2$ VII, m.p. 190-191° (6%), $C_{23}H_{34}O_3$ VIII, m.p. 138-140° (2%) and the corresponding ketone I (2%), respectively.

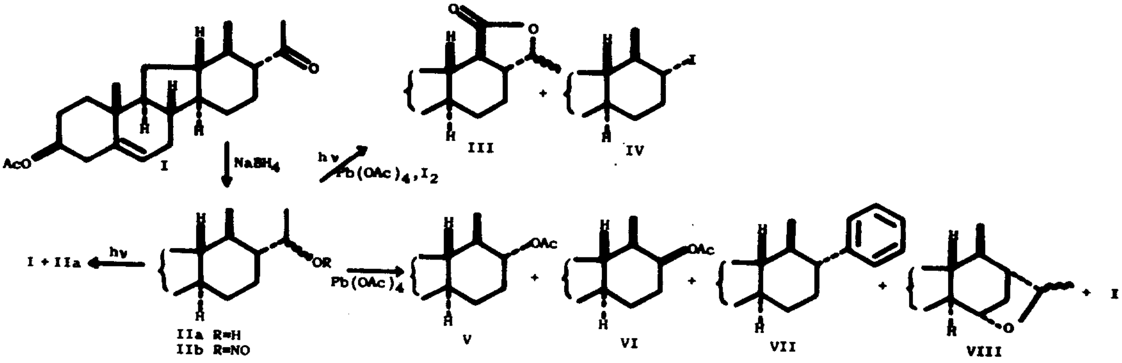
TABLE I (τ, 100MC, in $CDCl_3$)

Compounds	21 methyl	19 methyl	18 methyl	C-17 hydrogen (C-15 hydrogen)	acetyl
III*	8.59 d,J=6.0	8.99	None		7.98
IV	None	8.98	9.07 d,J=6.5	5.27 d,J=3.0	7.98
V	None	9.00	9.11 d,J=6.0	5.24~5.68 m	7.97 & 7.98
VI	None	8.99	9.15 d,J=5.2	5.08 WH=6.0	7.98 & 8.00
VII	None	8.98	9.34 d,J=6.0		7.98
VIII	8.77 d,J=6.0	9.01	9.00 d,J=6.3	5.68~6.40 m (6.33~6.83 m)	7.98

* Values taken by 60MC instrument

The nmr (Table), ir and mass spectra of V and VI suggested the structure to be etiojerv-5-ene-3β,17α-diol diacetate (V) and the C-17 epimer (VI) respectively which could arise via β-scission of 20-O-radical (10). The former has been identified by direct comparison of the saponified product of V with authentic etiojerv-5-ene-3β,17α-diol (11).

The nmr spectrum of VII has shown the presence of five aromatic protons of monosubstituted phenyl group as singlet at τ2.83 and the rest of the protons as shown in the Table. Since the protons of 18-methyl are considerably shielded, a phenyl group may be adjacent to this methyl. On the basis of this spectral evidence and the consideration of the possibility of β-scission, we conclude that the structure of VII is O-acetyl-17α-phenyletiojerv-5-ene-3β-ol (VII) (12).



The molecular formula and the ir spectrum of VIII suggested this is an ether arisen from intramolecular hydrogen abstraction. However, it was apparent from the nmr spectrum that all the three methyls were still intact in the product VIII and therefore the 20-alkoxyl radical of IIa must have abstracted hydrogen other than that of 18-methyl. The chair form of the D-ring of IIa having the equatorial 13β-methyl and C-17 substituent should be more stable than the boat form at room temperature. However, during thermal reaction, flipping from chair to boat may become more frequent. In a boat form of the D-ring in which C-17 substituent is axial and 12β-hydrogen and 16β-hydrogen are in bow-stern relationship, the 20-alkoxyl radical can abstract a hydrogen either on C-14 or C-15. The nmr spectrum of VIII proves that in actuality hydrogen was abstracted from C-15, and five-membered ring ether (VIII) with boat conformation of the D-ring is the correct formula for VIII, since a new multiplet (1H, τ6.33 to τ6.83) appeared in the low field of the nmr of VIII, which is attributable to a C-15-proton of ether VIII.

Thus, present investigations show an intriguing variation in the mode of the reactions in the photolytic and nonphotolytic procedures.

The formation of two epimers (e.g., V and VI) as the result of the β-scission has never previously been recorded in lead tetraacetate oxidation.

It is to be noted that in these reactions of IIa, β-scission of secondary alkoxyl radical overwhelmingly predominates over hydrogen abstraction.

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References and footnotes

(1) Photoinduced transformations XI. Paper X, H. Suginome, N. Sato and T. Masamune, Tetrahedron Letters, in press.

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(4) For review, see K. Heusler and J. Kalvoda, Angew. Chem., 76, 518 (1964).

(5) Mass spectrum of II showed no M^+ peak and exhibited the base peak at m/e 312 (M-60). All the 3-acetates in this communication (IIa, IV, V, VI, VII and VIII) revealed no M^+ peak and exhibited the corresponding M-60 peaks as were observed in the normal steroids. (H. Budzikiewicz, C. Djerassi and D. H. Williams, Structure Elucidation of Natural Products by Mass Spectrometry, II, Holden-Day, Inc., San Francisco, 1964, p. 98).

(6) Analogous examples in normal steroid series, see reference (3) and J. Kalvoda, Ch. Meystre and G. Anner, Helv. Chim. Acta., 49, 24 (1966).

(7) The possibility of β-configuration of iodine is not entirely excluded.

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(10) Analogous cases in normal steroids and non-rigid system, (a) G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailovic, D. Arigoni and O. Jeger, Helv. Chim. Acta., 44, 518 (1961). (b) M. Lj. Mihailovic, Z. Cekovic, Z. Maksimovic, D. Jeremic, Lj. Lorenc and R. I. Mamuzic, Tetrahedron, 21, 2799 (1965). (c) M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. Lj. Mihailovic, K. Schaffner, D. Arigoni and O. Jeger, Helv. Chim. Acta., 45, 2674 (1962).

(11) T. Masamune and K. Orito, Tetrahedron, in press.

(12) To our knowledge, this is the first example of incorporation of a solvent in the product due to β-scission during lead tetraacetate oxidation. The configuration of phenyl group is most probably α. See reference (10C).