A New Type of Intramolecular Group-transfer in Steroid Photochemistry. A Contribution to the Mechanism of the Oxidative Cyanohydrin-Cyano-ketone Rearrangement[1,2]

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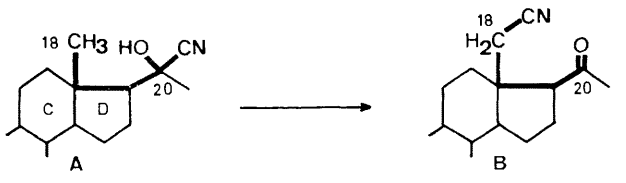
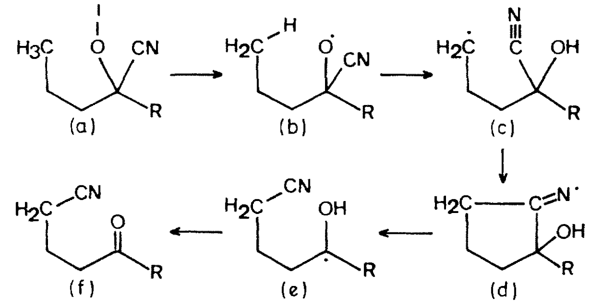
Summary A radical-induced intramolecular transfer of a cyano-group is initiated by photolysis of a nitrite function situated in the ϵ-position with respect to the migrating group.

DURING the last 12 years a number of new intramolecular radical processes[3] corresponding to the general formulation of the Barton reaction[4,5] have been described.† The hypoiodite reaction[3c,6] can be considered as one of the most versatile of these new methods. A specially interesting aspect of the hypoiodite reaction is represented by the oxidative cyanohydrin–cyano-ketone rearrangement.[6,7] The overall result of this process applied to a cyanohydrin of type (A) (*e.g.* to a 20-hydroxy-20-cyano-steroid) consists in a 1,4-shift of the nitrile group accompanied by the loss of two atoms of hydrogen and the formation of the corresponding γ-cyano-ketone (B). The reaction takes place under the usual conditions of the hypoiodite reaction, *e.g.* by treating the alcohol (A) in the presence of iodine with lead(IV) acetate, or *N*-iodosuccinimide.



The migration of the cyano-group in the conversion of (A) into (B) could be shown to be a strictly intramolecular reaction.[7b] All the known facts concerning this peculiar transformation can be most plausibly rationalized by the following reaction scheme:[3c,7b]



The crucial step in this sequence is the addition of the preformed *C*-radical (c) to the nitrile triple bond. In other words, the alcoholic function of the cyanohydrin does not take part directly in the transfer step, but is serving merely as an auxiliary group to form the first carbon radical (c) and to stabilize the second one (e). On the basis of the suggested mechanism any other suitable auxiliary group W, favourably situated in any other part of

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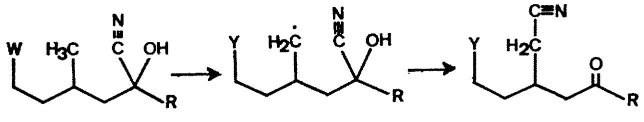
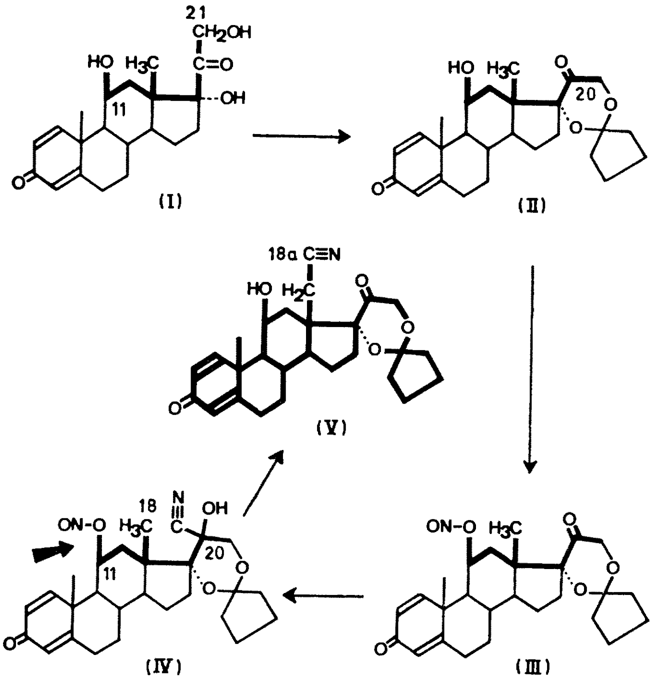
† The lead(IV) acetate oxidation of monohydric alcohols which belongs formally to this group of reactions, differs in some important points from the general scheme.[3c]

the molecule [*e.g.* in (g)], could play the role of the hydroxyl, generating the necessary radical (h), which could then follow the same reaction path as before, and form the cyano-ketone (k). To test this hypothesis, the following experiments have been performed: prednisolone (I) was transformed to the acetal (II),[8] thus fixing the spatial arrangement of the 20-oxo-group and blocking both the 17α- and 21-hydroxy-groups. Treatment of (II) with nitrosyl chloride in pyridine at —10° gave the corresponding 11-nitrite (III) m.p. 202–204° dec.; $[\alpha]_D^{20}$ +128° *c* 0·624 (CHCl$_3$) in almost quantitative yield. By subsequent reaction of (III) with KCN in acetic acid (r.t.) a mixture‡ of the epimeric cyanohydrins (IV) m.p. 166° dec.; $[\alpha]_D^{20}$ +20°, *c* 0·216 (CHCl$_3$) was formed. In these compounds the 11β-nitrite function represents the desired auxiliary group and depending on the conformation of the spiro-ring the nitrile group in both epimeric cyanohydrins can adopt a favourable position with respect to the angular methyl at C-13. An 11β-oxy-radical generated by photolysis of the nitrite should, at least partly§ attack C-18, forming the corresponding *C*-radical. As it is known[10] that the NO fragment formed during irradiation of a nitrite is a rather poor radical scavenger we thought that there might be a possibility for the C-18 radical centre to react intramolecularly with the adjacent nitrile group, before being trapped by NO. In fact, after the irradiation of a 0·2% toluene solution of (IV) by a Hanau high-pressure u.v. lamp (Q-81) a mixture of products was obtained from which the desired 18-cyano-compound (V), m.p. 213—214°; $[\alpha]_D^{20}$ +70°, *c* 0·328 (CHCl$_3$), was isolated by chromatography on silica gel and subsequent crystallization in a yield of 20—25%.¶



(g) (h) (k)

This result can be considered as strong evidence in favour of the suggested mechanism for the oxidative cyanohydrin–cyano-ketone rearrangement. At the same time, it shows that in rigid systems, such as steroids and terpenoids, a sterically favourably situated group can initiate a reaction which finally takes place on a fairly distant centre in the molecule. Two other similar cases were reported by Barton and his co-workers in the nitrite photolysis[11,12] and by Wenkert[13] in his so-called "billiard reaction." The special feature of the present reaction is a new type of an intramolecular transfer of an entire functional group.



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‡ No attempt has been made to separate the two epimers showing very similar R_F values in the t.l.c.

§ One competing reaction is the attack on the second angular methyl group (C-19).[4b] In a compound containing a 1,2-double bond however, a preferential hydrogen abstraction at carbon C-18 can be expected.

¶ The same reaction sequence has been applied to other different derivatives of 11β-hydroxyprogesterone, leading to the corresponding 18-cyano-compounds in comparable yields. The full account of the experiments performed will be published in *Helv. Chim. Acta*.

[1] Presented in part at the VIth International Symposium on the Chemistry of Natural Products in Mexico City, April 1969.

[2] Previous publication in the series: P. Wieland, *Helv. Chim. Acta*, 1970, **53**, 171.

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