THE USE OF PHOTOCHEMICAL REACTIONS IN ORGANIC SYNTHESIS

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INTRODUCTION

In the last decade photochemistry has grown from a minor to a major activity in organic chemical laboratories. Many striking and (thermally) unusual processes can be observed and the mechanistic problems posed in their interpretation demand new dimensions in organic chemical thought. However, in spite of the large number of new photochemical reactions which have been discovered in recent years, rather few have yet found use in organic synthesis and fewer still have been of economic value in industry.

Some years ago[1] we adumbrated a new rearrangement reaction of alkoxyl radicals in general and of alkoxyl radical derived from the photolysis of nitrites in particular. This photochemical reaction has found a number of applications and it has value in the technical synthesis of aldosterone[2].

PHOTOLYSIS AND PYROLYSIS OF NITRITES

Mechanistic studies using ^{15}N have shown[3] that photolysis of a nitrite gives (step I) an alkoxyl radical and nitric oxide which are completely dissociated from each other. The alkoxyl radicals rearranges rapidly (step II) to a carbon radical which can be captured (step III) by deuterium atom
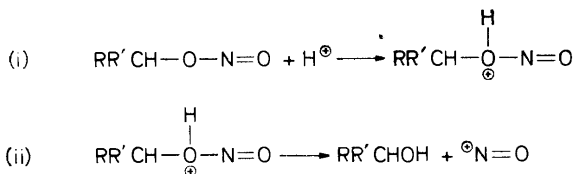

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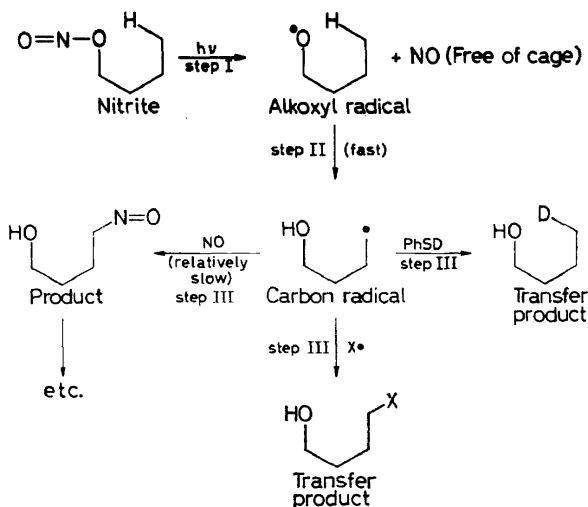
transfer (with deuterothiophenol) or by radical trapping reagents[4] to give 'transfer products'. The normal fate of the carbon radical, in the absence of trapping reagents, is, of course, to react (step III) relatively slowly with nitric oxide to afford the product, a nitroso-alcohol. The latter may be isolated as nitroso-dimer or, where the structure is permissive, rearranged to give oxime. As a particular example we may take 6β-hydroxycholestanol acetate nitrite (I) which on photolysis gives[1] in high yield the nitroso-dimer (II) and thence the oxime (III).
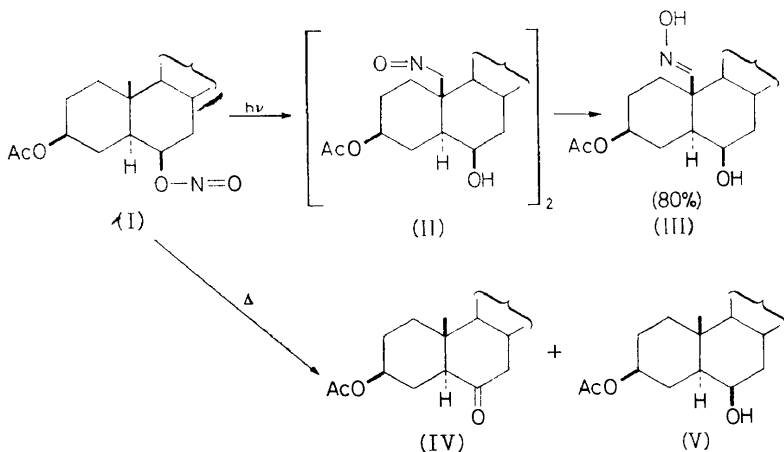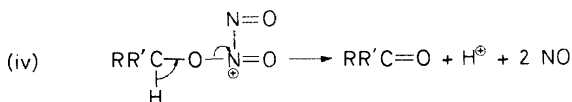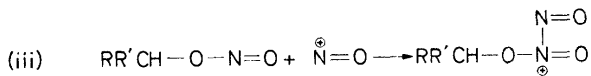

In the present account we give, firstly, some new information on the reactions of nitrites and then describe the use of photochemical reactions in the synthesis of two natural products.

The gas phase pyrolysis and photolysis of low molecular weight nitrites has been studied intensively by Steacie and other workers[5, 6]. It has been established that pyrolysis, like photolysis (see above), affords initially alkoxyl radicals and nitric oxide. Now, in our earlier work, we had studied the pyrolysis of the nitrite (I) and had shown that it afforded in high yield the ketone (IV) and the alcohol (V) in approximately equal amounts. There was no incorporation of nitrogen[7]. It was difficult to understand why photochemically and thermally generated alkoxyl radicals from nitrites should differ in chemical behaviour, especially as alkoxyl radicals generated thermally in other ways do show the expected rearrangement of hydrogen[8].

In solution or in the melt nitrites are sensitive to impurities, decomposing rapidly with traces of acid, but being stabilized by traces of pyridine. We consider that liquid phase pyrolysis does not involve radicals, but has an ionic mechanism such as the following[9]:

$$\text{(i)} \qquad RR'CH-O-N=O + H^\oplus \longrightarrow RR'CH-\underset{\oplus}{O}(H)-N=O$$

$$\text{(ii)} \qquad RR'CH-\underset{\oplus}{O}(H)-N=O \longrightarrow RR'CHOH + {}^\oplus N=O$$

2

(iii) $RR'CH-O-N=O + \overset{\oplus}{N}=O \longrightarrow RR'CH-O-\underset{\oplus}{\overset{\overset{\displaystyle N=O}{|}}{N}}=O$

(iv) $RR'\underset{\overset{\displaystyle |}{H}}{C}-O-\underset{\oplus}{\overset{\overset{\displaystyle N=O}{|}}{N}}=O \longrightarrow RR'C=O + H^{\oplus} + 2\ NO$

In order to demonstrate that nitrite pyrolysis would really furnish alkoxyl radicals which would rearrange intramolecularly we turned, therefore, to gas phase pyrolysis in the absence of solvent.

4-Phenylbutyl nitrite[10] (VI) was studied first. On photolysis under standard conditions[1, 10] this gave about 60 per cent of the expected nitroso-dimer

$$Ph-(CH_2)_3-CH_2-O-N=O \overset{h\nu}{\longrightarrow} \left[Ph-\overset{\overset{\displaystyle N=O}{|}}{CH}-(CH_2)_2-CH_2OH \right]_2$$

(VI)   (VII) (60%)

$\Big\downarrow \overset{300°/}{\underset{0·3\,mm}{}} \Delta$

$Ph-(CH_2)_3-CH_2-\overset{\bullet}{O} \longrightarrow Ph-\overset{\bullet}{C}H-(CH_2)_2-CH_2OH$

(VIII)   (IX)

$\Big\downarrow$

$\begin{array}{l} Ph-\underset{|}{CH}-CH_2-CO_2H \\ Ph-CH-CH_2-CO_2H \end{array} \longrightarrow \begin{array}{l} Ph-\underset{|}{CH}-(CH_2)_2-CH_2OH \\ Ph-CH-(CH_2)_2-CH_2OH \end{array}$

(X)   (XI)
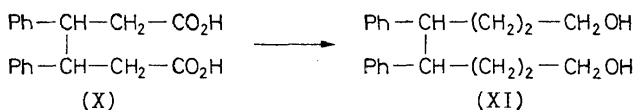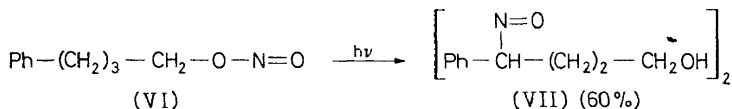
meso and (±)-   *meso* and (±)- (15 %)

(VII). On pyrolysis in the gas phase at 300° under 0·3 mm pressure a mixture of *meso*- and (±)-4,5-diphenyloctan-1,8-diols (XI) was obtained in about 15 per cent yield. The formation of these two diols suggests that the nitrite (VI) decomposes to the alkoxyl radical (VIII), which by rearrangement gives (IX), which on dimerization affords the two diols (XI). Authentic specimens of the latter were synthesized from the two known 3,4-diphenyl-adipic acids[11, 12].

The pyrolysis of *o*-tolylcarbinyl nitrite (XII) was also instructive. Under the above mentioned conditions this compound gave 2,2'-bishydroxymethyl-dibenzyl (XIII) in 52 per cent yield. This must arise by dimerization of radical (XIV, R=H). It is conceivable, however, that the carbon radical (XIV, R=H), as well as the radical (IX), are formed not by intramolecular rearrangement of an alkoxyl radical but by alkoxyl radical attack at the benzylic position of a molecule of undecomposed nitrite. The immediate products of coupling would then be the dinitrites of (XI) and (XIII), which would give the alcohols finally obtained by hydrolysis during work up. In order to distinguish between inter- and intra-molecular hydrogen transfer

processes *o*-tolylcarbinyl nitrite (XII) was pyrolysed in the presence of two-fold molar excess of *o*-tolylcarbinyl methyl ether (XV). An intermolecular hydrogen transfer process would have reduced the yield of (XIII) and have given some mixed product detectable by methoxyl signals in the nuclear magnetic resonance spectrum. In the event, the yield of (XIII) was reduced slightly (42 per cent), but the total crude dimer showed no methoxyl signal and, therefore, contained no cross-coupled product.
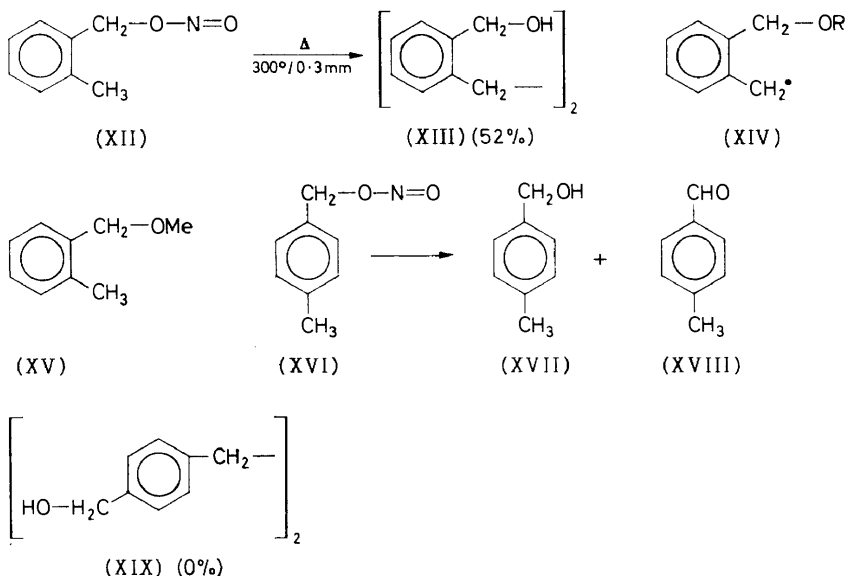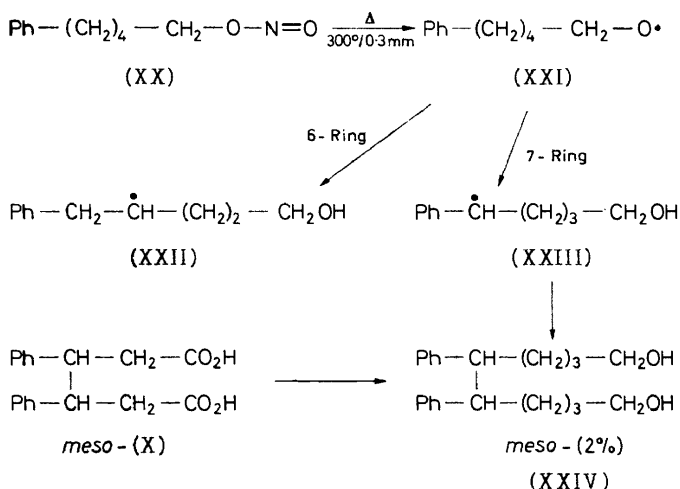

With similar intent the pyrolysis of *p*-tolylcarbinyl nitrite (XVI) was investigated. Here intramolecular hydrogen transfer would be impossible and, if dimer were formed, it could only result from the intermolecular radical transfer process. In fact, no dimer (XIX) could be detected and the products were *p*-tolylcarbinol (XVII) and *p*-tolualdehyde (XVIII). These correspond to the disproportionation normal[5, 6] in the gas phase pyrolysis of simple nitrites. Finally, an approximately equimolecular mixture of *o*- and *p*-tolylcarbinyl nitrites was pyrolysed. This gave the expected *o*-dimer (XIII) and no detectable amount of mixed or *p*-dimer. There seems, therefore, to be no reason to doubt that the alkoxyl radicals generated in our pyrolysis studies are rearranging by the anticipated intramolecular process where this is structurally permissive.

We have also examined briefly the pyrolysis of 5-phenylpentyl nitrite (XX). Here a desired alkoxyl radical has the choice of abstracting a benzylic hydrogen [see (XXI)→(XXIII)] or the 5-placed hydrogen [see (XXI)→ (XXII)]. The latter six-membered transition state is very common[13], although there are now several examples of the former[14]. In fact, pyrolysis of (XX) gave, as the only crystalline product, *meso*-5,6-diphenyldecan-1,10-diol (XXIV) in 2 per cent yield. An authentic specimen of the latter was synthesized from the *meso*-acid (X). Clearly, so far as identified products are

concerned, the process (XXI)→(XXIII) is preferred, no doubt because of the relatively low homolytic dissociation energy of a benzylic carbon–hydrogen bond.

$$Ph-(CH_2)_4-CH_2-O-N=O \xrightarrow[300°/0.3mm]{\Delta} Ph-(CH_2)_4-CH_2-O\bullet$$

(XX)   (XXI)

6-Ring   7-Ring

$$Ph-CH_2-\overset{\bullet}{C}H-(CH_2)_2-CH_2OH \qquad Ph-\overset{\bullet}{C}H-(CH_2)_3-CH_2OH$$

(XXII)   (XXIII)

$$\begin{array}{l} Ph-CH-CH_2-CO_2H \\ \quad | \\ Ph-CH-CH_2-CO_2H \end{array} \longrightarrow \begin{array}{l} Ph-CH-(CH_2)_3-CH_2OH \\ \quad | \\ Ph-CH-(CH_2)_3-CH_2OH \end{array}$$

meso - (X)   *meso* - (2%)

   (XXIV)

SYNTHESIS OF β-AMYRIN

We now describe the first synthesis of a naturally occurring member of the β-amyrin family of triterpenoids. More than a hundred members of this class of compound are known, all derivatives of β-amyrin itself (XXV, X=OH). In the literature three syntheses of δ-amyrene (XXVI) have already been recorded. The interconversion of δ-amyrene and 18a-β-amyrene
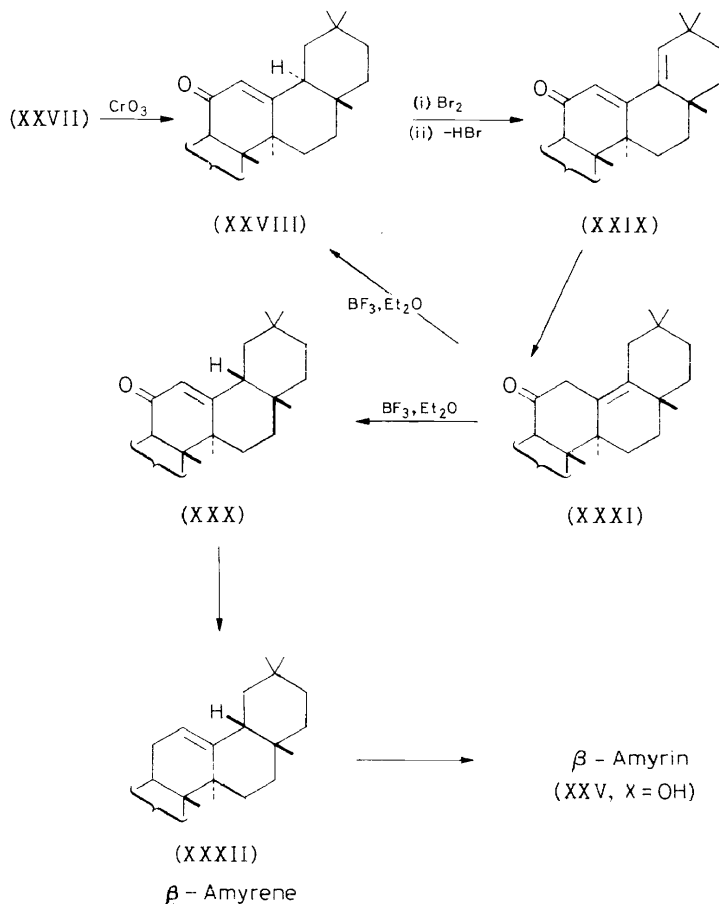

X = OH   β – Amyrin
X = H   β – Amyrene

(XXV)

(XXVI)   (XXVII)
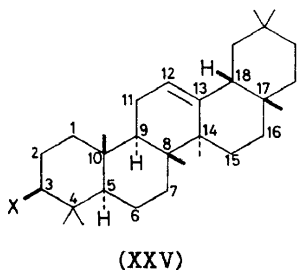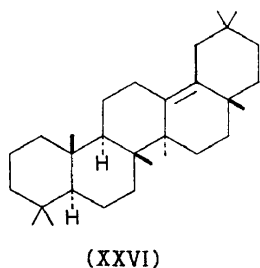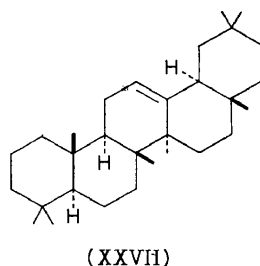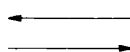
δ – Amyrene   18α – β – Amyrene

(XXVII) is also well known[16]. The synthesis of β-amyrin requires, therefore, the transformation of 18a-β-amyrene into β-amyrene (XXV, X=H) and the hydroxylation of the latter at C_3 in the β-configuration. 18a-β-Amyrene is considerably more stable than β-amyrene and we have not been able to demonstrate their mutual equilibration.

The following indirect method converted 18a-β-amyrene (XXVII) into β-amyrene (XXV, X=H). Chromic acid oxidation of the 18a-hydrocarbon (XXVII) gave the 11-ketone (XXVIII) which on bromination and dehydrobromination afforded the dienone (XXIX). Reduction of the latter with lithium in ammonia afforded a high yield of the β,γ-unsaturated ketone

(XXVII) $\xrightarrow{\text{CrO}_3}$

(XXVIII)

(i) Br$_2$
(ii) −HBr

(XXIX)

BF$_3$,Et$_2$O

BF$_3$,Et$_2$O

(XXX)

(XXXI)

(XXXII)

β − Amyrene

β − Amyrin
(XXV, X = OH)

(XXXI) which on treatment with boron trifluoride-etherate in benzene furnished approximately equal amounts of the starting ketone (XXVIII) and the desired 11-keto-β-amyrene[17] (XXX). The conversion of the latter into β-amyrene (XXXII) has already been reported[17].

The projected synthesis next involved the hydroxylation of β-amyrene to give 11α-hydroxy-β-amyrene (XXXIII, R=H). The published bromination method[18] using N-bromosuccinimide in a two phase system of carbon tetrachloride and water in which calcium carbonate was suspended did not, in our hands, give very reproducible results or good yields (0–20 per cent). We developed a new method which may have more general implications. β-Amyrene in benzene containing N-bromosuccinimide and lead tetra-acetate was heated under reflux for 30 min. Alkaline hydrolysis of the product gave 11α-hydroxy-β-amyrene (XXXIII, R=H) in reproducible (50 per cent) yield. This alcohol was treated with nitrosyl chloride in pyridine and the

(XXXII)   (XXXIII)   (XXXIV)

(XXXV)   (XXXVI)
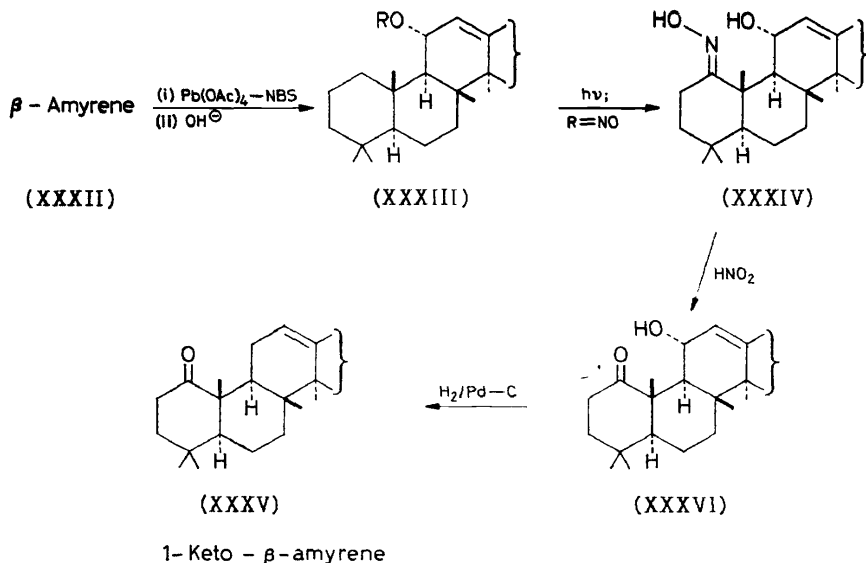
1- Keto – β – amyrene

crystalline nitrite (XXXIII, R=NO) thus obtained was photolysed in benzene solution to give 11α-hydroxy-1-oximino-β-amyrene (XXXIV) in reasonable (50 per cent) yield. With nitrous acid this oxime was converted smoothly into 11α-hydroxy-1-keto-β-amyrene (XXXVI) which existed solely in the 'open form' as written in the formula given. Hydrogenolysis of the keto-alcohol (XXXVI) gave 1-keto-β-amyrene (XXXV) without difficulty.

We also studied the corresponding series of reactions in the 11β-hydroxy series. Reduction of 11-keto-β-amyrene (XXX) with lithium aluminium hydride gave 11β-hydroxy-β-amyrene (XXXVII, R=H), which afforded the corresponding nitrite (XXXVII, R=NO) smoothly. Photolysis of the latter gave the aldoxime (XXXVIII) (in 50 per cent yield) as was proven by several separate reactions. Firstly, treatment with nitrous acid and oxidation with chromium trioxide in pyridine afforded the keto-aldehyde (XXXIX). On further oxidation with chromic acid in acetic acid this gave the keto-acid (XLII) existing in the solid state as the lactol (XLIII).

7

Secondly, on refluxing with acetic anhydride and sodium acetate the aldoxime (XXXVIII) furnished the nitrile-acetate (XL). Thirdly, on oxidation with Kiliani's chromic acid the aldoxime (XXXVIII) afforded the keto-nitrile (XLI) which with potassium *t*-butoxide in *t*-butanol gave the cross-conjugated dienone (XLIV) and cyanide ion.
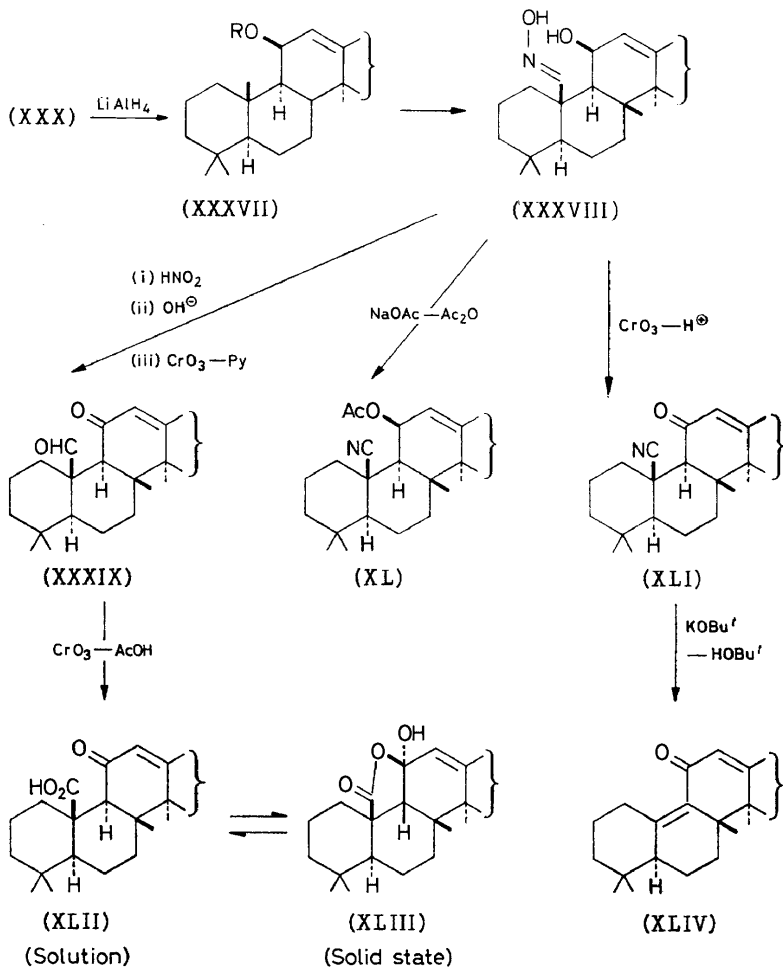

On bromination followed by dehydrobromination 1-keto-β-amyrene (XXXV) gave the unsaturated ketone (XLV) which readily added cyanide ion to furnish the cyano-ketone (XLVI). Bromination followed similarly by dehydrobromination then afforded the cyano-unsaturated ketone (XLIX). On treatment with sodium methoxide[19] the cyanide function was exchanged for methoxyl to furnish (XLVIII). Reduction of this compound with lithium

aluminium hydride followed by acid catalysed hydrolysis and elimination then afforded the known 1-dehydro-β-amyrenone[20] (XLVII). Hydrogenation of the latter gave β-amyrone. Reduction of this ketone with lithium aluminium hydride to give β-amyrin was already known[21] and completed the synthesis.

We also completed the following more original route to 1-dehydro-β-amyrone. The unsaturated cyano-ketone (XLIX) was treated with alkaline hydrogen peroxide to give the amide (LI). Oxidation of this with lead
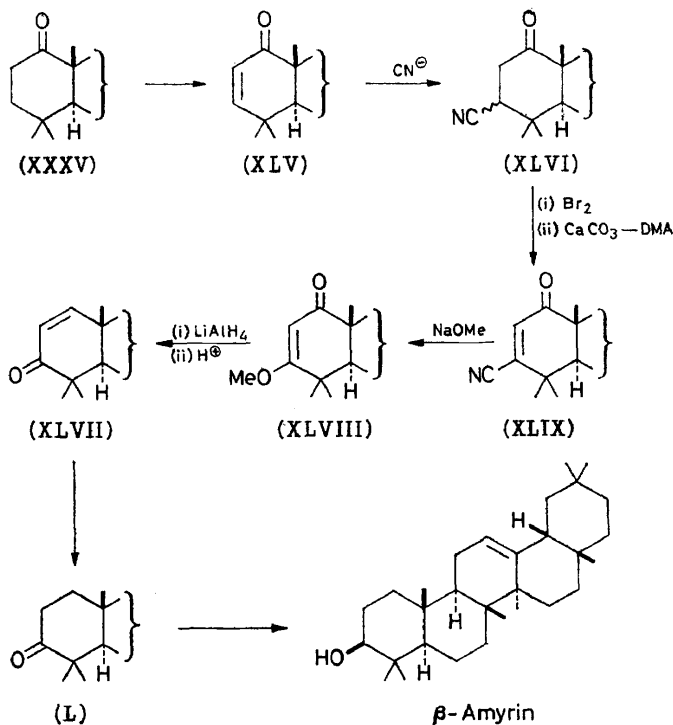
tetraacetate in benzene[22] gave the isocyanate (LII) which with methanol afforded the methyl carbamate (LIII). Alternatively, the latter was prepared directly by oxidation of the amide (LI) with lead tetraacetate in methanol[23]. Reduction of the methyl carbamate (LIII) with lithium alminium hydride and acid catalysed hydrolysis and dehydration gave the desired 1-dehydro-β-amyrone (XLVII). Alternatively the methyl carbamate was hydrolysed with alkali to the unusual β-amino-unsaturated ketone (LIV), which on lithium aluminium hydride reduction and treatment with acid also gave in good yield the desired 1-dehydro-β-amyrone (XLVII).
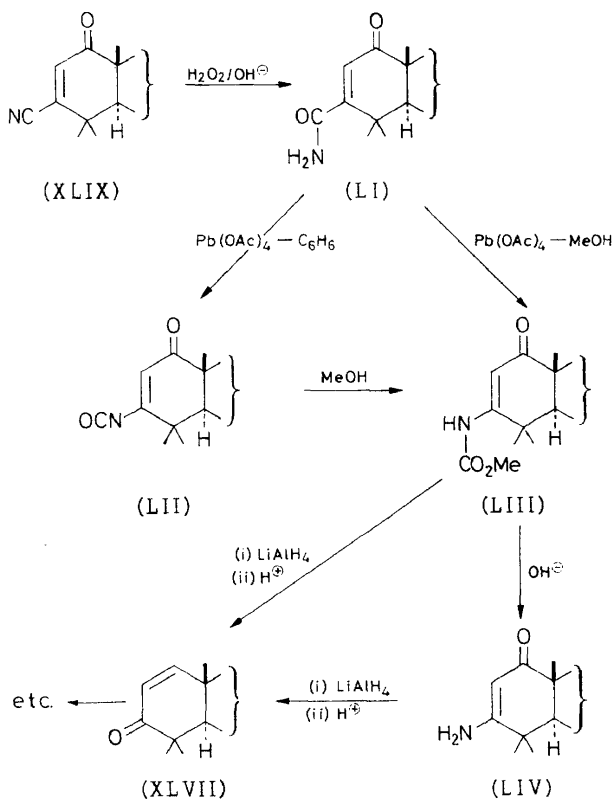
SYNTHESIS OF 18-HYDROXYOESTRONE

We now describe the first synthesis of 18-hydroxyoestrone (LV; R=H, R'=OH), a compound isolated by Marrian and his colleagues[24] from hydrolysed human pregnancy urine and which can also be obtained by hydroxylation of oestrone (LV; R=R'=H) with an adrenal homogenate from cattle[25]. This compound has never been available in anything but minute amounts and consequently a proper evaluation of its biological properties has not been possible.

The ready availability of oestrone (LV; R=R'=H) suggested this compound as starting material. We conceived that a suitable oestrone derivative [as (LVI)] might be transformed to a compound [as (LVII)], which by a radical exchange process with a six-membered ring transition state, might furnish an 18-substituted derivative [as (LVIII)]. Subsequent modification of X and Y would then afford the desired 18-hydroxyoestrone (LV; R=H, R'=OH). The first problem therefore was to select the nature of X and Y.

Now in recent years[26, 27] the formation of γ-lactones by the photolysis of halo-amides has received considerable attention. In our earlier work[26]

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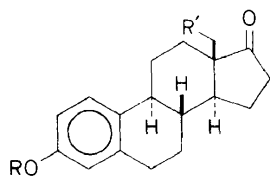
R = R′ = H ;   Oestrone
R = H, R′ = OH ; 18 – Hydroxyoestrone

(LV)

(LVI)   (LVII)   (LVIII)   (LV, R = H, R′ = OH)

(LIX)   (LX)   (LXI)   (LXII)
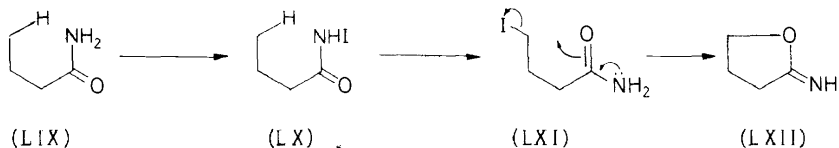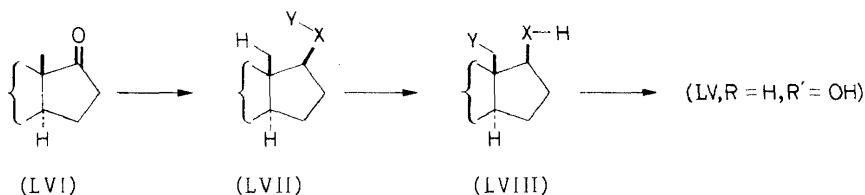
we showed that an amide [as (LIX)] could be transformed, suitably by the lead tetraacetate–iodine reagent, into an iodamide [as (LX)] which, on photolytic rearrangement, gave a γ-iodo-amide [as (LXI)]. The facile cyclization of γ-halo-amides to imino-lactones [as (LXII)] and the mild hydrolysis of the latter to γ-lactones was already well appreciated.

We considered that this γ-lactone synthesis might be adapted to the preparation of 18-hydroxyoestrone (LV; R=H, R′=OH) in the following way. Preliminary studies showed that the aromatic ring of oestrone and its ordinary derivatives like the methyl ether and the acetate was attacked readily by (electrophilic) iodinating agents. We had to select, therefore, a protecting group for the phenolic hydroxyl which would be strongly electron withdrawing and thus deactivate the aromatic ring. The mesylate ($CH_3 SO_2$—O—) showed the desired properties and was used in the synthesis. Oestrone mesylate was converted smoothly into a stereoisomeric mixture of cyanohydrins (LXIII). The mixture was dehydrated with phosphorous oxychloride in pyridine in high yield to the unsaturated nitrile (LXIV), which on hydrogenation afforded the 17β-cyano-derivative (LXV). Acid catalysed hydration of the latter gave the required amide (LXVIII) without difficulty. Oxidation of this amide with lead tetraacetate and iodine under irradiation was expected to furnish, after the appropriate working up, the γ-lactone (LXVII; X=H_2). In fact, the product was acidic and gave a crystalline anhydride (LXVII; X=O) on treatment with acetyl chloride. Although the formation of this anhydride was unexpected we argued that it could still be used in the synthesis in the following way. The anhydride,

11

treated with excess of phenyl lithium, gave, as a consequence of attack on the less hindered carbonyl group, the phenolic γ-lactone (LXVI). The excess of phenyl lithium removed the mesylate group as was expected. Reduction of the γ-lactone (LXVI) with lithium aluminium hydride, followed by mild acetylation with pyridine–acetic anhydride, afforded the diacetate (LIX).

At first we supposed that photolysis of the nitrite of the diacetate (LIX) would proceed with fragmentation to give a 17-oxime and benzophenone. Indeed, in a model experiment, we took isopropyldiphenylcarbinyl nitrite (LX; R=NO) and showed that on photolysis it gave a high yield of acetone oxime (LXI) and benzophenone (LXII). However, this reaction could

(LXIII) (LXIV) (LXV)

(LXVI) (LXVII) (LXVIII)

(LIX)
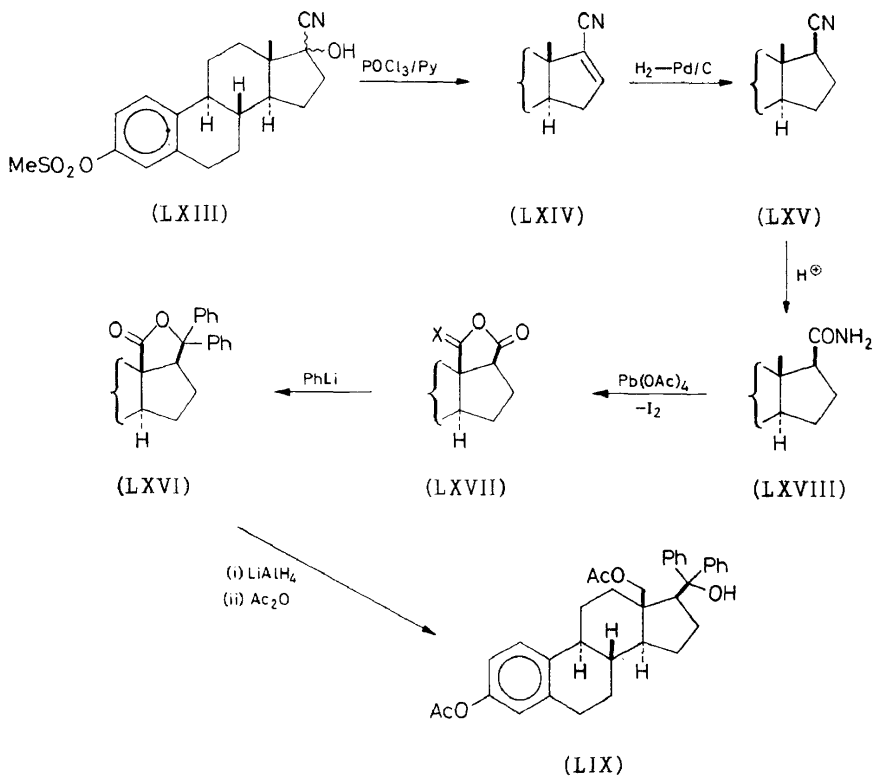
not be employed in the steroid case since attack at C_{18} proceeded more rapidly than fission of the C_{17}—C_{20} bond. We, therefore, used a more classical approach. The diacetate (LIX) was dehydrated smoothly with thionyl chloride–pyridine to the stilbene (LXIII) which on ozonolysis in chloroform at −20° followed by addition of triphenylphosphine gave a good yield of 18-hydroxyoestrone diacetate (LXIV). Very mild alkaline hydrolysis afforded finally 18-hydroxyoestrone (LV; R=H, R′=OH).

The formation of the anhydride (LXVII; X=O) rather than the expected lactone (LXVII; X=H_2) in the above reaction sequence is worthy of further comment. The double substitution of the C_{18} methyl group by attack of C_{20}-alkoxyl radicals in hypoiodite rearrangements has already been observed[28]

12

(LX)   (LXI)   (LXII)

(LIX)   (LXIII)   (LXIV)
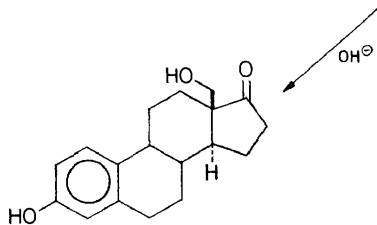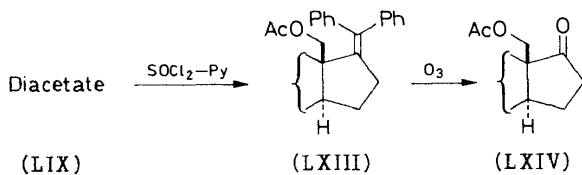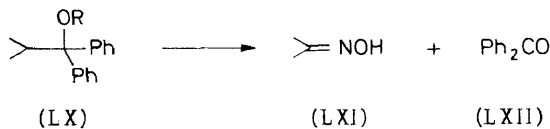
18 − Hydroxyoestrone

and reasonably attributed to the conformational preference of the C_{18}-iodomethyl group. This preference is such that the direction of the C_{18}-iodine bond in space does not favour the 'normal' process of tetrahydrofuran formation. The alternative process of further hydrogen abstraction from C_{18} is thus permitted[29]. Our earlier work[26] has shown that the amide→lactone reaction is analogous to the ether formation observed on photolysis or thermolysis of hypohalites as already discussed previously. It is, therefore, not really surprising that the oxidation of the amide (LXVIII) takes the course that it does. We envisage that the C_{18}-iodide (LXV) is indeed formed initially in our reaction. However, cyclization to the iminolactone

(LXV)   (LXVI)   (LXVII)   (LXVIII)

(LXIX)   (LXX)   (LXXI)   (LXXII)

13
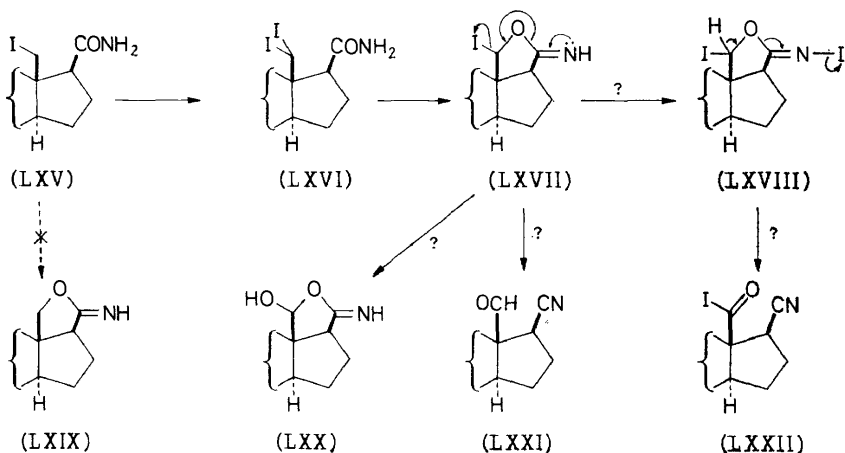
(LXIX) is relatively slow compared with further iodination and rearrangement of the amide function to give the diiodide (LXVI). The diiodomethyl group does, however, have the conformation needed for cyclization[28] so that the iodoiminolactone (LXVII) results. The latter may be hydrolysed to (LXX) and further oxidized during work up, or a fragmentation (LXVII, see arrows) to (LXXI) followed by further oxidation and hydrolysis may occur. Alternatively the iminolactone (LXVII) may be further iodinated[26] to an N-iodo-derivative (LXVIII) which by fragmentation (see arrows) could furnish the nitrile (LXXII) which, in turn, by hydrolysis alone, would give the oxidation level of the anhydride (LXVII; X=O). Clearly the final details of anhydride formation are not clear and need further study. The principle by which such a derivative arises does, however, seem established.

ACKNOWLEDGEMENT

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