Wagner–Meerwein Rearrangements. IV. Some Reassignments of Structure

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In 1959, H. L. H. and L. M. assigned Δ^{12} structures to certain of the products of the illustrated Wagner–Meerwein rearrangements of I[1] and II[2] (Schemes I and II).

The location of the double bond at C-12 in IIIa and IVa was derived entirely from an nmr argument. Tortorella and Romeo[3] repeated the synthesis from I and measurement of the nmr spectrum,[4] from which they concluded that the Δ^{13} structure (IIIb) is the correct formulation of the product. Similar studies with the 5,6-dihydro derivative of I were used to confirm the assignment.[3] In order to resolve further the difference in interpretation of identical spectra,[4] we have now transformed IIIb into the 3-keto-Δ^4 analog VI (*via* IIIc[5]), with which the presence or absence of a vinyl hydrogen at C-12 could be determined without quantitation. The fact that the product of the Oppenauer oxidation showed a resonance at 5.72 ppm (one vinyl proton α to a carbonyl) and no other resonances in the vinyl region is taken to confirm further the assignment IIIb of Tortorella and Romeo.

Since the assignment of structure to IVa was based on the same kind of nmr evidence as that for IIIa, we have now reexamined that assignment using a 60 Mc nmr spectrum of the 3,16-diacetate of IVa. The resonance between 4.4 and 4.9 ppm (1 proton) is due to the axial C-3 proton. The multiplet with peaks at 5.4, 5.6, and 5.7 ppm (two protons), ascribed in our earlier work to two vinyl protons,[2] is now reassigned to the superposition of the C-6 vinyl proton and C-16 proton (on carbon bearing acetoxy).[6] This assignment is based on the observation that the C-16 proton of a number of 16-acetoxypregnane compounds[6] appears in the range 5.3–5.8 ppm. For instance, 17β-azido-3β,16β-dihydroxy-5α,17α-pregnane-11,20-dione 3,16-diacetate shows the C-16 proton resonance at 5.59 ppm; 3β,16β-dihydroxy-5α-pregnan-20-one 3,16-diacetate and its 16α isomer show the C-16 proton resonance at 5.3–5.8 and 5.4–5.7 ppm, respectively. From this interpretation we conclude that there is but one vinyl proton in the structure.

If we review all the evidence concerning the previously assigned structures[2] of the rearrangement products IVa and Va illustrated in Scheme II, we reach the conclusion that IVb and Vb are the correct structures and that the latter structures differ only in the configuration at C-16. The 16α,17α-oxide VII is rearranged into the 16α-ol VIII by hydrogen fluoride.[1] The 16β,17β-oxide IX is rearranged into the 16β-ol X by hydrogen fluoride.[1] That VIII and X differ only in configuration at C-16 we have now proved by oxidizing them to the same 16-ketone XI using the Jones reagent. Since IVb is converted into X by the action of *Flavobacterium dehydrogenans*,[1] this is interpreted to support the assignment of configuration of the hydroxyl group at C-16 in IVb as β. Since Vb is converted into VIII under the same conditions,[1] this is interpreted to support the assignment of the configuration of the hydroxyl group at C-16 in Vb as α. The explanation for the formation of the 16β-ol IVb from the 16α,17α-epoxide II is the same as that given by us previously,[1,2] namely, that there is an acid- (and base-) catalyzed, reverse-aldol equilibrium between IVb and Vb which exists under the Wagner–Meerwein conditions and the first product of Wagner–Meerwein rearrangement (Vb) undergoes further transformation by the reverse-aldol mechanism to IVb. The existence of this equilibrium, starting from IVb or Vb, with acid or base, has been proved by us already.[2]

Experimental Section[7]

18-Nor-17β-methyl-17-iso-4,13-pregnadiene-3,20-dione (VI).—3β-Hydroxy-18-nor-17β-methyl-17-iso-5,13-pregnadien-20-one (IIIc, 200 mg), dissolved in toluene (20 ml) and distilled cyclohexanone (5 ml), was heated at reflux and 5 ml of distillate was collected. Aluminum isopropoxide (500 mg) in dry toluene (10 ml) was then added dropwise. The reaction mixture was heated at reflux for 5 hr, during which time 15 ml of distillate was collected. Water was then added and the organic solvents were removed by steam distillation. The resulting aqueous suspension was extracted with methylene chloride and the extracts were washed with water, dried over anhydrous sodium sulfate, concentrated to a small volume, and chromatographed over Florisil (15 g). The major product (70 mg) was eluted with 30% ether-in-hexane. Recrystallization from acetone–hexane afforded 45 mg of 18-nor-17β-methyl-17-iso-4,13-pregnadiene-3,20-dione (VI): mp 119–122°; $[\alpha]^{25}D$ +255° ($CHCl_3$); λ_{max}^{MeOH} 238 mμ (ϵ 17,000); λ_{max}^{Nujol} 5.81 and 5.87 μ (20-carbonyl), 5.97 μ (3-carbonyl), 6.18 μ (Δ^4), 11.57 μ (C-4 vinyl CH).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.43; H, 9.07.

18-Nor-17β-methyl-17-iso-4,13-pregnadiene-3,16,20-trione (XI).

A. From 16α-Hydroxy-18-nor-17β-methyl-17-iso-4,13-pregnadiene-3,20-dione (VIII).—To a solution of 200 mg of 16α-hydroxy-18-nor-17β-methyl-17-iso-4,13-pregnadiene-3,20-dione (VIII) in 10 ml of reagent acetone at 0° under nitrogen was added dropwise, with good agitation, Jones reagent (prepared from 66.8 g of chromic acid and 57.5 ml of sulfuric acid diluted to 250 ml with water) until an orange color persisted in the mixture. Excess methanol was then added to destroy the excess Jones reagent and the resulting green mixture was poured into

(1) E. L. Shapiro, M. Steinberg, D. Gould, M. J. Gentles, H. L. Herzog, M. Gilmore, W. Charney, E. B. Hershberg, and L. Mandell, *J. Am. Chem. Soc.*, **81**, 6483 (1959).

(2) H. L. Herzog, M. J. Gentles, A. Mitchell, E. B. Hershberg, and L. Mandell, *ibid.*, **81**, 6478 (1959).

(3) V. Fortorella and A. Romeo, *Gazz. Chim. Ital.*, **92**, 1118 (1962).

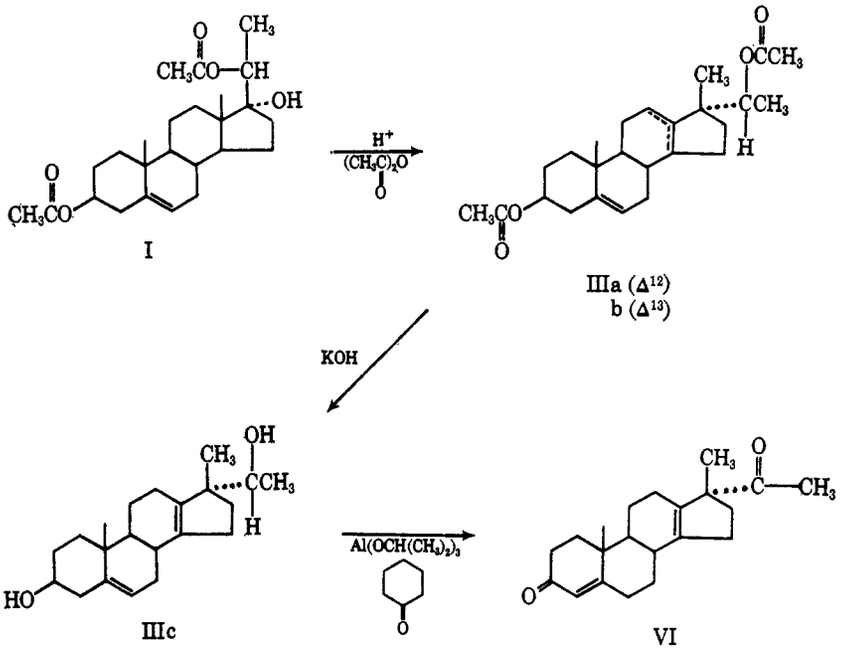
(4) The spectrum obtained by Tortorella[3] was identical with that measured by us.

(5) H. L. Herzog, C. C. Joyner, M. J. Gentles, M. J. Hughes, E. P. Oliveto, E. B. Hershberg, and D. H. R. Barton, *J. Org. Chem.*, **22**, 1413 (1957).

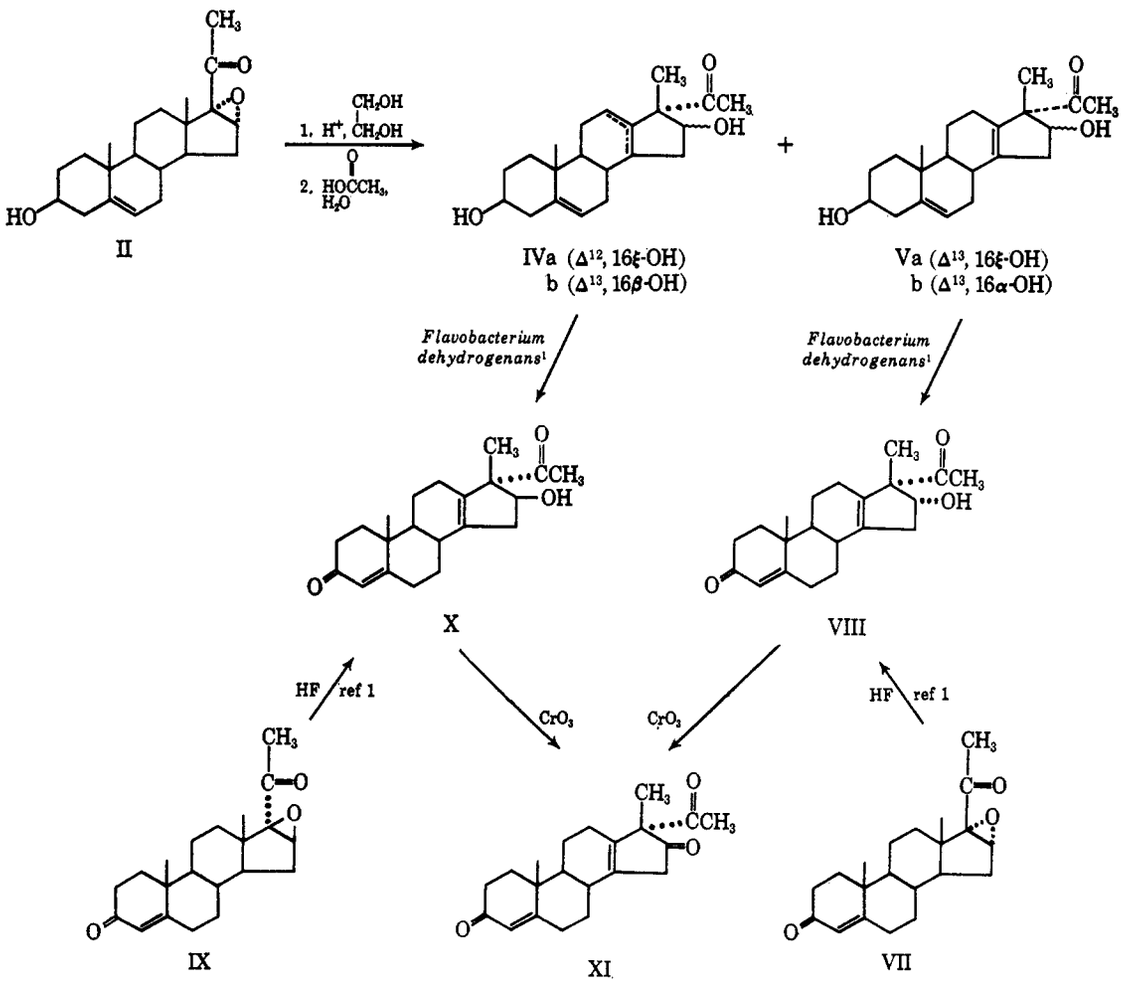
(6) G. Nathansohn, G. Winters, and A. Vigevani, *Gazz. Chim. Ital.*, **95**, 1338 (1965).

(7) Melting points were observed with a Kofler micro hot stage. All physical measurements and analyses other than nmr measurements were made by members of the Physical Organic Chemistry Department, Schering Corp. Nmr spectra were measured with a Varian A-60 instrument at Emory University and Lepetit, as well as with a Varian A-60-A at Schering Corp. All spectra were measured in deuteriochloroform with tetramethylsilane as an internal reference. Resonances are reported in parts per million relative to tetramethylsilane.

SCHEME I



SCHEME II



water. The resulting mixture was extracted with methylene chloride and the extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to an oily residue. The oil was taken up in ether, from which crystallization occurred, affording 70 mg of 18-nor-17β-methyl-17-iso-4,13-pregnadiene-3,16,20-trione (XI): mp 145–151° dec; λ_{max}^{MeOH} 239 mμ (ϵ 17,290); $[\alpha]^{25}D$ +179° (dioxane); λ_{max}^{Nujol} 5.72 μ (16-carbonyl) 5.82 and 5.85 (20-carbonyl), 6.01 (3-carbonyl), 6.20 (Δ^4), and 11.60 (C-4 vinyl CH).

Anal. Calcd for $C_{21}H_{26}O_3 \cdot {}^1/_2H_2O$: C, 75.19; H, 8.11. Found: C, 75.03, 75.09; H, 7.98, 7.99.

B. From 16β-Hydroxy-18-nor-17β-methyl-17-iso-4,13-pregnadiene-3,20-dione (X).—From 50 mg of 16β-hydroxy-18-nor-17β-methyl-17-iso-4,13-pregnadiene-3,20-dione (X) oxidized with

Jones reagent by the method given in part A of this section, there resulted 20 mg of XI, mp 140–147° dec, of identical mobility with the same product obtained by the oxidation of VIII as measured in the thin layer chromatographic system $CHCl_3$–ethyl acetate (3:1) over silica gel GF (Analchem, Wilmington, Del.). The infrared and nmr spectra of the 16-ketone XI from this experiment were indistinguishable from the same spectra obtained with product from part A of this section, using VIII as the starting material.

Registry No.—VI, 13341-84-9; XI, 13341-85-0.

Nitric Oxide Induced Free-Radical Reactions

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The reaction of *t*-butyl hydroperoxide with nitric oxide was first reported by Blum[2] who succeeded in isolating *t*-butyl alcohol, *t*-butyl nitrate, and water as reaction products. Our reinvestigation of the reaction in benzene solution at 25° revealed the presence of additional products. Observation of the progress of the reaction by vapor phase chromatographic analysis at 35° made possible separation and identification of components which decompose under conditions of conventional distillation procedures employed by Blum. Changes in the relative amounts of products observed as the reaction progressed gave evidence of an initial rapid reaction and a subsequent process which consumed some of the initial products.

A rapid reaction was observed between nitric oxide at 1-atm. pressure and a 0.5 *M* solution of *t*-butyl hydroperoxide which formed, as first products, equimolar quantities of *t*-butyl alcohol and *t*-butyl nitrate. Product concentrations as a function of reaction time are shown in Figure 1. The simultaneous formation of nitrous acid was indicated by the slow disappearance of the alcohol and its replacement by an equimolar amount of *t*-butyl nitrite.

The detection of *t*-butyl nitrite only during the latter part of the reaction is not consistent with a simple thermal homolysis of the hydroperoxide and subsequent coupling of nitric oxide with *t*-butoxy radicals. A reaction sequence which is consistent with the experimental observations presented in Figure 1 involves a free-radical reaction sequence (eq 1–4) induced by nitric oxide.

$$t\text{-BuOOH} + \text{NO} \longrightarrow t\text{-BuO}\cdot + \text{HONO} \quad (1)$$

$$t\text{-BuO}\cdot + t\text{-BuOOH} \longrightarrow t\text{-BuOH} + t\text{-BuOO}\cdot \quad (2)$$

$$t\text{-BuOO}\cdot + \text{NO} \longrightarrow [t\text{-BuOONO}] \longrightarrow t\text{-BuONO}_2 \quad (3)$$

$$t\text{-BuOH} + \text{HONO} \longrightarrow t\text{-BuONO} + \text{HOH} \quad (4)$$

A nitric oxide induced decomposition of the hydroperoxide (eq 1) could form nitrous acid and *t*-butoxy radical. The *t*-butoxy radical could either fragment

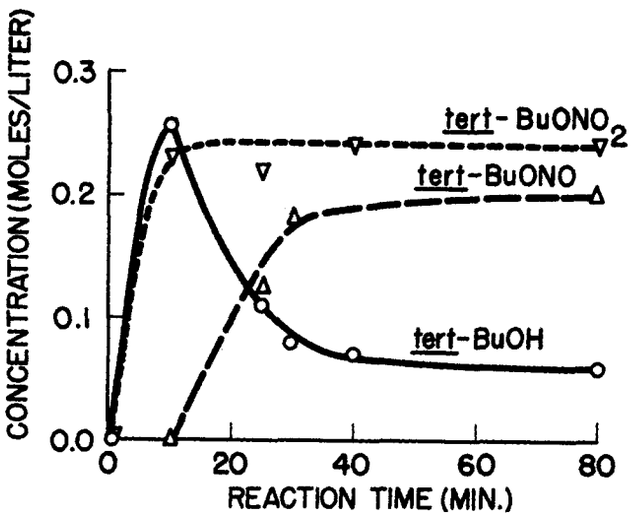

Figure 1.—Concentration of reaction products *vs.* reaction time of *t*-butyl hydroperoxide plus nitric oxide.

to the methyl radical and acetone, couple with nitric oxide to form *t*-butyl nitrite, or abstract a hydrogen atom from an available hydrogen donor in the reaction medium (eq 2). Neither acetone nor nitrite appears as an initial product, but *t*-butyl alcohol is formed rapidly. The only reactive hydrogen donor present is the hydroperoxide; hence, the *t*-butylperoxy radical is inferred as an intermediate. (Hydrogen abstraction by the peroxy radical would be an identity reaction and would go undetected.) The coupling product of *t*-butylperoxy radical with nitric oxide would be peroxynitrite which would be expected to undergo a facile rearrangement to a nitrate[3,4] (eq 3).

Reaction of *t*-butyl alcohol with nitrous acid would account for the observed decrease in alcohol concentration after the initial reaction subsides, with formation of an equivalent quantity of *t*-butyl nitrite (eq 4).

The presence of a species capable of hydrogen abstraction was confirmed by conducting the reaction in chloroform. Chloroform acts as a hydrogen donor with formation of trichloromethyl radical (eq 5). Coupling of nitric oxide with the trichloromethyl radical (eq 6) produced the observed nitrosotrichloromethane.

$$t\text{-BuO}\cdot + \text{HCCl}_3 \longrightarrow t\text{-BuOH} + \cdot\text{CCl}_3 \quad (5)$$

$$\cdot\text{CCl}_3 + \longrightarrow \text{ONCCl}_3 \quad (6)$$

At the concentrations of hydroperoxide employed in this investigation the hydroperoxide would be present mainly as a hydrogen-bonded dimer.[5] Nitric oxide might react with dimer to yield alcohol, nitrous acid, and *t*-butyl hydroperoxy radical directly (eq 7). This could account for the absence of acetone which normally accompanies the formation of *t*-butoxy radical; however, the presence of a readily abstractable hydrogen is frequently sufficient to minimize acetone formation.[6]

$$(t\text{-BuOOH})_2 + \text{NO} \longrightarrow t\text{-BuOH} + \text{HONO} + t\text{-BuOO}\cdot \quad (7)$$

Another possible reaction route is the abstraction of hydrogen from hydroperoxide by nitric oxide with formation of $(\text{HON})_2$. The decomposition of hypo-

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(2) J. Blum, *Compt. Rend.*, **248**, 2769 (1959).

(3) A. Baeyer and V. Villiger, *Ber.*, **34**, 755 (1901).

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