studied. It remains to be shown whether the postulated hydride form of vitamin $B_{12s}$ has any existence at all, even at low concentration as a component of an equilibrium.

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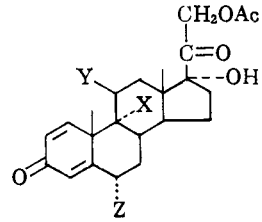
## A Novel Steroid Aromatization Reaction

*Sir:*

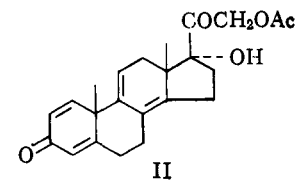
Apart from total synthetic methods,[1] ring AB aromatic steroids have been prepared by (a) palladium–carbon-catalyzed dehydrogenation of a ring A[2,3] or B[3] aromatic precursor, (b) acid elimination of an allylic hydroxyl group in a ring A aromatic compound with subsequent rearrangement of double bonds,[4] and (c) pyrolysis of a $\Delta^{1,4,6}$-triene followed by selenium dioxide dehydrogenation.[5] We now wish to report the partial synthesis of ring AB aromatic steroids from nonaromatic intermediates by a new ionic method[6] with elimination of the C-19 methyl group. This method, moreover, provides a means of preparing ring AB aromatic steroids with a variety of C-17 substituents, such as the dihydroxyacetone moiety.

When 21-acetoxy-9$\alpha$,11$\beta$-dichloro-17$\alpha$-hydroxypregna-1,4-diene-3,20-dione (Ia)[7] was refluxed in dimethylformamide for 0.5 hr., or in pyridine for at least 6 hr., two major products resulted, each in 20–25% yield. One product was assigned the structure 21-acetoxy-17$\alpha$-hydroxypregna-1,4,8(14),9(11)-tetraene-3,20-dione (II),[8] m.p. 249–252°; $\lambda_{max}^{MeOH}$ 241 m$\mu$ ($\epsilon$ 18,900); n.m.r. ($SiMe_4$): 5.72 p.p.m. (C-11 vinyl H); maleic anhydride adduct, m.p. 230–237°. The other product was assigned the structure 21-acetoxy-3,17$\alpha$-dihydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIa), $\lambda_{max}^{MeOH}$ 230, 270, 280, 292, 327, and 341 m$\mu$ ($\epsilon$ 66,000, 4780, 5520, 3980, 2280, and 2650, respectively). The n.m.r. spectrum of the corresponding 3,17-diacetate IIIb showed signals for methyl groups at 0.58 p.p.m. (C-18 methyl) and at 2.22 and 2.39 p.p.m. (acetate methyl).

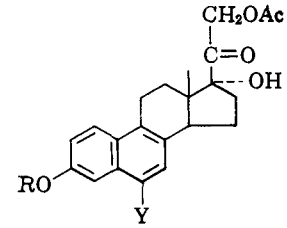
Similarly, 21-acetoxy-9$\alpha$,11$\beta$-dichloro-6$\alpha$-fluoro-17$\alpha$-hydroxypregna-1,4-diene-3,20-dione (Ib)[9] in dimethylformamide was refluxed for 0.5 hr., and the crude product was acetylated to give 3,21-diacetoxy-6-fluoro-17$\alpha$-hydroxy-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIIc). In addition, 21-acetoxy-9$\alpha$,11$\beta$-dichloro-17$\alpha$-hydroxy-6$\alpha$-methylpregna-1,4-diene-3,20-dione (Ic)[11] was converted into 3,21-diacetoxy-17$\alpha$-hydroxy-6-methyl-19-norpregna-1,3,5(10),6,8-pentaen-20-one (IIId), characterized as the 3,17$\alpha$,21-triol IIIe.



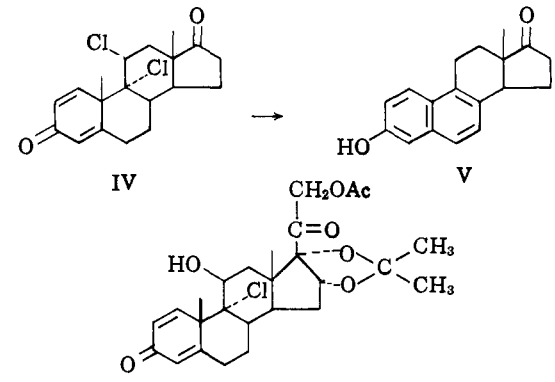
Ia, X = Y = Cl; Z = H
Ib, X = Y = Cl; Z = F
Ic, X = Y = Cl; Z = $CH_3$
Id, X = Br; Y = OH; Z = H



II



IIIa, R = Y = H
IIIb, R = Ac; Y = H
IIIc, R = Ac; Y = F
IIId, R = Ac; Y = $CH_3$



IV V VI

Definitive proof of the aromatic system generated by this rearrangement was provided by treatment of 9$\alpha$,11$\beta$-dichloroandrosta-1,4-diene-3,17-dione (IV)[7] in refluxing dimethylformamide which gave equilenin (V).[12]

A further investigation revealed that 21-acetoxy-9$\alpha$-bromo-11$\beta$,17$\alpha$-dihydroxypregna-1,4-diene-3,20-dione (Id)[13] with dimethylformamide gave IIIa. Also, 21-acetoxy-9$\alpha$-chloro-11$\beta$-hydroxy-16$\alpha$,17$\alpha$-isopropylidenedioxypregna-1.4-diene-3,20-dione (VI) yielded the corresponding 19-norpregna-1,3,5(10),6,8-pentaene.

The fate of the C-19 methyl group was established by gas chromatographic analysis which showed that methyl chloride was evolved during the aromatization of the 9$\alpha$,11$\beta$-dichloro-1,4-diene Ia. Methyl bromide was obtained from the bromohydrin Id. These ob-

(1) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 481.

(2) A. Butenandt, A. Wolff, and P. Karlson, *Chem. Ber.*, **74**, 1308 (1941).

(3) W. E. Bachmann and A. S. Dreiding, *J. Am. Chem. Soc.*, **72**, 1323 (1950).

(4) R. P. A. Sneeden and R. B. Turner, *ibid.*, **77**, 130 (1955); Ch. Tamm, G. Volpp, and G. Baumgartner, *Helv. Chim. Acta*, **40**, 1469 (1957).

(5) St. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531 (1950).

(6) (a) K. Tsuda, E. Ohki, S. Nozoe, and N. Ikekawa, *J. Org. Chem.*, **26**, 2614 (1961); K. Tsuda, E. Ohki, and S. Nozoe, *ibid.*, **28**, 783 (1963); **28**, 786 (1963), have prepared ring A aromatic steroids from nonaromatic precursors with elimination of the C-19 methyl group by means of zinc in pyridine. (b) H. L. Dryden, Jr., G. M. Webber, and J. J. Wieczorek, *J. Am. Chem. Soc.*, **86**, 742 (1964), have recently announced a method for the reductive aromatization of steroidal dienones with elimination of the C-19 methyl group as methyllithium.

(7) C. H. Robinson, L. Finckenor, E. P. Oliveto, and D. Gould, *ibid.*, **81**, 2191 (1959).

(8) Satisfactory analytical data were obtained for all new compounds prepared. The assigned structures were also supported by infrared spectral data and, in the case of the tetraene II, by mass spectrometric analysis.

(9) Compound Ib was prepared by N-chlorosuccinimide–lithium chloride–acetic acid treatment[7] of 21-acetoxy-6$\alpha$-fluoro-17$\alpha$-hydroxypregna-1,4,9(11)-triene-3,20-dione.[10]

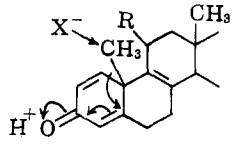
(10) G. B. Spero, B. J. Magerlein, W. P. Schneider, and J. A. Hogg, U. S. Patent 2,838,499 (1958).

(11) D. Gould, H. Reimann, and L. E. Finckenor, U. S. Patent 2,894,963 (1959).

(12) We wish to thank Dr. T. F. Gallagher for providing us with an authentic sample of equilenin for infrared spectral comparison.

(13) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman, and F. M. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

servations, in addition to others to be elaborated on in a more detailed report, suggest that the halide ion initially generated by elimination of the 9α-halogen attacks the C-19 methyl group facilitated by protonation of the C-3 oxygen. Prior to this, or perhaps concurrently, an allylic shift, elimination, and isomerization provide the double bonds required for the aromatization of ring B



X = Cl⁻ or Br⁻
R = Cl or OH

Further work is in progress on the nature of the structural features in rings B and C necessary for the aromatization reaction to take place.

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## The Rapid Oxidation of Iron(II) Porphyrins by Alkyl Halides. A Possible Mode of Intoxication of Organisms by Alkyl Halides

*Sir:*

Low-valent iron porphyrin complexes are manifest in all aerobic organisms and are essential to life.[1] Yet, the chemistry of these substances has remained obscure because of their difficult preparation and ready air oxidation.[2a,b] Knowledge of the kinds of molecules that are capable of undergoing oxidation–reduction reactions with iron porphyrin complexes should be helpful to an understanding of the detailed mechanism of "electron transport" in biological systems.

The author wishes to report that dilute solutions of $Fe^{II}$ porphyrins are rapidly oxidized by alkyl halides at room temperature to the corresponding $Fe^{III}$ halide complexes (hemins).

Thus, solutions of $Fe^{II}$ deuterioporphyrin ($Fe^{II}D$) ($\lambda_{max}$ 550, 522 mμ) in 1:1 isopropyl alcohol–acetic acid,[3] under nitrogen, saturated with KCl, are rapidly oxidized to deuteriohemin ($Fe^{III}DCl$) ($\lambda_{max}$ 620, 524, 498 mμ) by the following halides: allyl chloride, phenacyl chloride, α-phenethyl chloride, 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT), 1,2-dibromo-3-chloropropane, hexachloroethane, and *cis*-1,3-dichloropropene. Both *n*-propyl chloride and β-phenethyl chloride were innocuous. Very dilute solutions of $Fe^{II}$ protoporphyrin were oxidized in similar fashion.

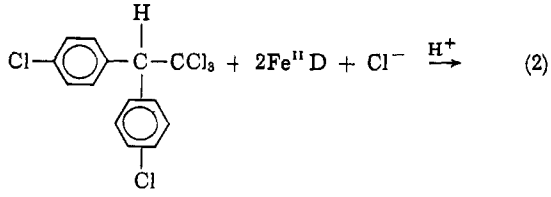
The rate of oxidation of $Fe^{II}D$ by *cis*-1,3-dichloropropene was determined spectrophotometrically by following the $Fe^{III}$ band at 620 mμ. The third-order rate expression (1) was obtained from pseudo-second-order plots at varying high initial concentrations of halide. The rate constants[4] are presented in Table I.

$$\text{rate} = k_3[Fe^{II}D]^2[RCl] \quad (1)$$

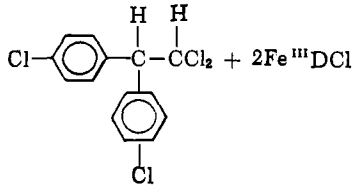
TABLE I

| $[Fe^{II}D]_0$, *M* | $[RCl]_0$, *M* | $k_3$, l.²/mole²/min. |
|---|---|---|
| $2.08 \times 10^{-4}$ | 0.0275 | $4.4 \times 10^4$ |
| $2.08 \times 10^{-4}$ | 0.0550 | $4.0 \times 10^4$ |
| $2.08 \times 10^{-4}$ | 0.0550 | $4.1 \times 10^4$ |
| $2.08 \times 10^{-4}$ | 0.110 | $4.1 \times 10^4$ |

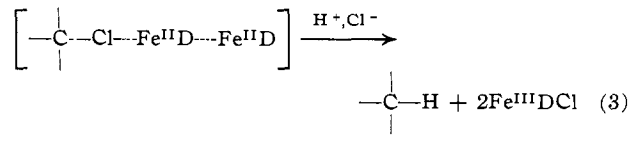
Under similar conditions, allyl chloride, α-phenethyl chloride, and DDT were extremely reactive. The rate of oxidation of $Fe^{II}D$ by DDT was estimated from the slopes of concentration *vs.* time plots at various initial concentrations of reactants. The rate expression (1) was obeyed with $k_3 \sim 3 \times 10^7$ l.²/mole²/min. This reaction proceeds quantitatively to the hydrogenolysis product[5,6] (2)—a transformation of DDT recently reported to occur with yeast cells.[6a]



(2)



A plausible transition state for these oxidations might be (3) in which chlorine is transferred from carbon to iron.[7]



(3)

The rapidity of these reactions suggests that if a haloorganic biocide survives the nucleophilic sites[8] of a cell wall,[9] it may readily interact with an iron center in the respiratory chain.[10] This interaction should be an attractive alternate to "alkylation"[11] as a mode of intoxication.

(1) For a recent survey, "Haematin Enzymes," J. E. Falk, R. Lemberg and R. K. Morton, Ed., Pergamon Press, London, 1961.

(2) (a) H. Fischer, A. Treibs, and K. Zeile, *Z. Physiol. Chem.*, **195**, 1 (1931); (b) D. G. Whitten, E. W. Baker, and A. H. Corwin, *J. Org. Chem.*, **28**, 2363 (1963).

(3) The preparation of these solutions by the iron powder reduction of deuteriohemin was patterned after the recent description of ferrous mesoporphyrin IX dimethyl ester; ref. 2b.

(4) Good pseudo-second-order plots were obtained in some cases through 90% completion.

(5) Gas and thin layer chromatographic properties of the product as well as a mixture melting point (111°) were identical with those of authentic material.

(6) (a) B. J. Kallman and A. K. Andrews, *Science*, **141**, 1051 (1963). A series of unusual metabolic dehalogenations have been observed; (b) T. C. Butler, *J. Pharmacol.*, **134**, 311 (1961), $CCl_4 \rightarrow CHCl_3$ (dogs); (c) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 31, $Cl_3C{-}CCl_3 \rightarrow Cl_3C{=}CCl_2 + Cl_2CHCHCl_2$ (rabbits). These conversions are not unlike those effected by low-valent metal ions [C. E. Castro and W. C. Kray, Jr., *J. Am. Chem. Soc.*, **85**, 2768 (1963)] and might be explained by a process analogous to (2).

(7) Whether or not a bridging ligand (Cl) should be present between the iron atoms remains open.

(8) S. Bartnicki-Garcia and W. J. Nickerson, *Biochem. Biophys. Acta*, **58**, 102 (1962).

(9) This is reasonable since rates of nucleophilic displacement are by comparison slow. Thus, the basic hydrolysis of *cis*-1,3-dichloropropene and related allylic chlorides proceeds with $k_2 \sim 0.1$–0.3 l./mole/hr. at room temperature [L. J. Andrews and R. E. Kepner, *J. Am. Chem. Soc.*, **70**, 3458 (1948)].

(10) Moreover, the fact that alkyl halides can affect the respiratory system has been noted [R. L. Metcalf, Symposia Genetica et Biologica Italia Celebrazione Spallanzaniana VIII, 1961, p. 431].

(11) Reference 6b, p. 25, S. E. Lewis, *Nature*, **161**, 692 (1948); W. Moje, J. P. Martin, and R. C. Baines, *J. Agr. Food Chem.*, **5**, 32 (1957).