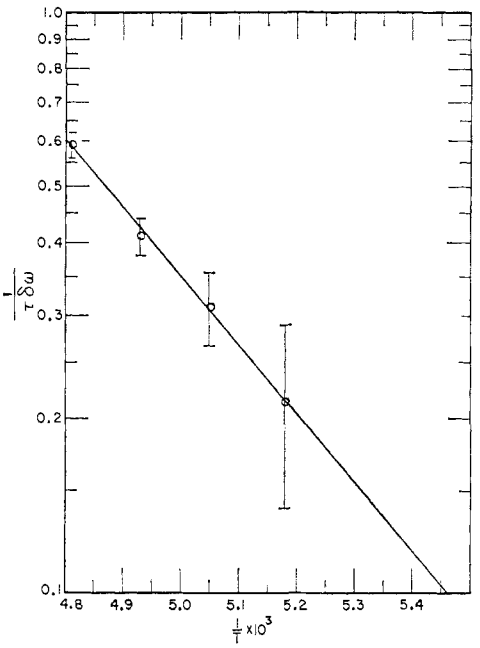

Figure 2. Temperature dependence of the reorientation rate of the methylene protons of II.

group are nonequivalent; models show that with a reasonable orientation of the side chain one C–H bond is more nearly perpendicular to the aromatic ring, and thus should couple more strongly (the two endor lines represent a factor of four difference in coupling). Rotation to the mirror image conformation interconverts these proton environments. Furthermore, such a change has also been seen[6] in 2,2′-bis(methylenethiomethyl)-4′′-dimethylaminotriphenylmethyl cation, a carbonium ion related to II, in which the room-temperature methylene nmr singlet goes to an AB quartet at low temperature. In such a process for II, two different pairs of *ortho* protons also interchange environments, accounting for the other endor changes.

The usual nmr approaches[1,7] to the study of chemical rate processes make the assumption that radiofrequency power saturation is not occurring—an invalid assumption for the endor experiment. We have, nevertheless, attempted to use the method of Gutowsky and Holm[7] to obtain an activation energy E_a and a frequency factor ν_0. One may rewrite the Arrhenius equation as

$$\log 1/\tau\delta\omega = \log 2\nu_0/\delta\omega - E_a/(2.3RT)$$

where $\delta\omega$ is the separation of the lines in the limit of slow exchange and τ is the lifetime of a proton in a particular site. If $1/T_2 < \delta\omega$, where T_2 determines the observed line width, then values for τ as a function of temperature may be determined from the equation

$$1/\tau\delta\omega = 2^{-1/2}[1 - (\delta\omega_e/\delta\omega)^2]^{1/2}$$

where $\delta\omega_e$ is the experimentally observed separation. For IIb, the value of $\delta\omega$ at $-85°$ was assumed to be at the limit 890 kHz. The data are plotted in Figure 2. The slope yields an activation energy of 5.5 kcal/mole, and the frequency factor determined from the intercept is about 10^{11} cps.

The original interest in radical II was the possibility that the sulfur might solvate the radical appreciably. Kinetic evidence for solvation of radicals is well known,[8] and cations related to II (*e.g.*, I) show strong interaction.[5] However, the relatively low spin density at the methyl of II (which is, however, 40% of that at the methylene) and the high spin density in the aromatic rings suggest no major coordination of the sulfur with the methine carbon.

(6) D. LaFollette, unpublished observations. The rate of equilibration is $\sim10^5$ slower in this cation than in II. Since in the nmr experiment the nonequivalent protons are seen to be coupled, other types of conformational isomerism are excluded. A somewhat different equilibration in some trityl cations has been studied by Kurland, *et al.*, *J. Am. Chem. Soc.*, 87, 2278, 2279 (1965).

(7) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 25, 1228 (1956).

(8) A particularly relevant study is that by W. G. Bentrude and J. C. Martin, *J. Am. Chem. Soc.*, 84, 1561 (1962).

(9) National Institutes of Health Postdoctoral Fellow.

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Received August 26, 1966

Steroids. CCCIII.[1] Angular Methylation and a "Wittig" Reaction with a Zinc–Methylene Iodide Reagent

Sir:

We wish to report an unusual example of methylenation with a modified Simmons–Smith reagent.[2] Reaction of 17β-acetoxy-11β-hydroxyestr-5(10)-en-3-one (I) with a reagent obtained by refluxing a large excess of zinc–copper couple[3] with methylene iodide for 4–6 hr in ether solution affords the product of replacement of the 3-ketone function by methylene [II, mp 146–148°; infrared (Nujol) 3475, 3070, 1727, 1653, and 877 cm^{-1}; nmr (60 Mcps) 63 (18-H), 122 (OAc), 160 (4-H), 259 (11α-H), ~280 (17α-H), and 283 (methylene) cps. *Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.09].[4] In addition, the noncrystalline 3-spirocyclopropane [IIIa, infrared 3500, 3080, and 1735 cm^{-1}; nmr 16 (cyclopropyl-H), 64 (18-H), 121 (OAc), 259 (11α-H), and 280 (17α-H) cps; characterized after base hydrolysis as the 17-carbinol, IIIb, mp 74–78°; infrared (KBr) 3450, 3075 cm^{-1}; nmr 16 (cyclopropyl-H), 61 (18-H), 218 (17α-H), and 260 (11α-H) cps. *Anal.* Calcd for $C_{20}H_{30}O_2 \cdot 0.5H_2O$: C, 77.12; H, 10.03. Found: C, 77.24; H, 9.92] was obtained in experiments where the preparation of the reagent had been interrupted after 2–3 hr reflux. The observation of a Wittig reaction with a zinc reagent is unprecedented.[5] The importance of the 11β-hydroxy group is suggested by the lack of reaction of either saturated 3- or 17-keto steroids or the 11-desoxy analog of I.

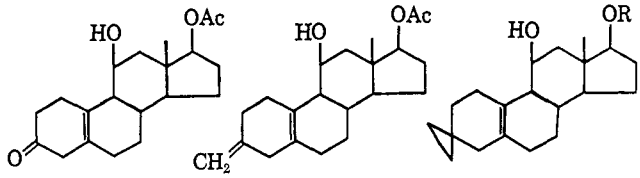
(1) Steroids. CCCII: P. Hodge, J. A. Edwards, and J. H. Fried, *Tetrahedron Letters* (publication pending).

(2) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 80, 5323 (1958); 81, 4256 (1959); H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, 86, 1347 (1964); G. Wittig and F. Wengler, *Chem. Ber.*, 97, 2146 (1964).

(3) E. LeGoff, *J. Org. Chem.*, 29, 2048 (1964).

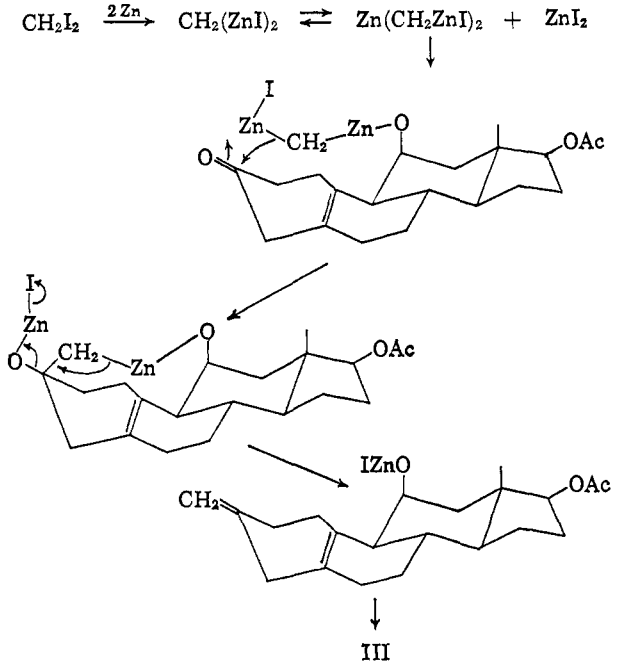
(4) In a typical experiment, 2 ml of methylene iodide, 2.5 g of zinc–copper couple, and 8 ml of ether were refluxed under nitrogen for 4 hr. After adding 200 mg of I, reflux was continued an additional hour followed by standard work-up.

(5) *Cf.* S. Trippett, *Quart. Rev.* (London), 17, 406 (1963).



I II IIIa, R=$COCH_3$ b, R=H

The stoichiometry of the zinc–methylene iodide reagent suggests the intermediacy of bis(iodozinc)methylene which, by analogy with allylic and homoallylic hydroxyl-assisted Simmons–Smith reactions,[6] undergoes the following equilibrium and further reactions

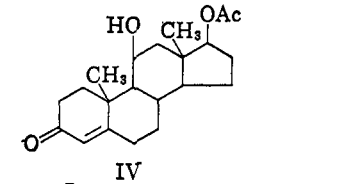


III

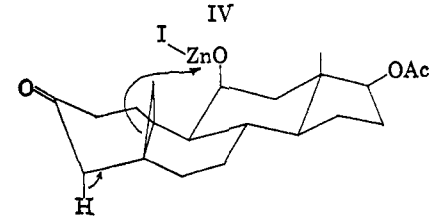
This transformation is undoubtedly made possible by the very high flexibility and the unhindered β face of ring A in the $\Delta^{5(10)}$ steroid. With the aid of molecular models it can readily be shown that the C-11 bound methylene reagent comes within normal bonding distance of the C-3 ketone.

The formation of the C-3 spirocyclopropane can be attributed to the presence of a small amount of bis(iodomethylene)zinc which undergoes the usual Simmons–Smith reaction with the 3-*exo*-methylene group.

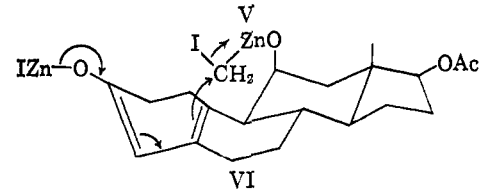
In contrast to these results the reaction of I with a reagent prepared *in situ* with an approximately 1:1 molar ratio of zinc and methylene iodide affords the product of angular methylation at C-10.[7,8] This product can be explained by either the normal homoallylic hydroxyl-assisted Simmons–Smith reaction followed by ring opening with proton loss at C-4 catalyzed by the C-11 iodozinc alkoxide (*cf.* V), or one-step reaction proceeding with the $\Delta^{3,5(10)}$-dienol formed by Lewis acids present in solution (*cf.* VI).[9,10] The latter mechanism is favored in view of the considerable stability of a related 11-desoxy-5β,19-cycloandrostan-3-one.[11]



IV



V



VI

Compound I was prepared from $\Delta^{9,11}$-estrone 3-methyl ether[13] by a six-step sequence. Hydroboration followed by peroxide oxidation[14] affords estra-1,3,5(10)-triene-3,11α,17β-triol 3-methyl ether[15] which on Moffatt[16] oxidation gives 3-methoxyestra-1,3,5(10)-triene-11,17-dione.[15] Reduction of this diketone with lithium tri-*t*-butoxyaluminum hydride affords estra-1,3,5(10)-triene-3,11β,17β-triol 3-methyl ether [mp 153–154°. *Anal.* Calcd for $C_{19}H_{26}O_3 \cdot CH_3OH$: C, 71.82; H, 9.04. Found: C, 72.44; H, 8.65] which on Birch reduction and oxalic acid hydrolysis yields 11β,17β-dihydroxyestr-5(10)-en-3-one [mp 193–196° dec. *Anal.* Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.52; H, 9.01]. Selective pyridine–acetic anhydride acetylation of this diol gives I [mp 180–182°. *Anal.* Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.45].

(6) S. Winstein, J. Sonnenberg, and L. DeVries, *J. Am. Chem. Soc.*, **81**, 6523 (1959); S. Winstein and J. Sonnenberg, *ibid.*, **83**, 3235 (1961); W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); E. P. Blanchard and H. E. Simmons, *ibid.*, **86**, 1337 (1964).

(7) Established by melting point and mixture melting point with an authentic sample of 11β,17β-dihydroxyandrost-4-en-3-one acetate (mp 150–151°) and comparison of infrared spectra in KBr disks.

(8) This experiment was carried out by suspending the zinc–copper couple in ether followed by addition of a small amount of methylene iodide and a crystal of iodine and adding a solution of the steroid in methylene iodide to the refluxing reaction mixture over a period of 1 hr. Constant volume was maintained by the slow distillation of ether. Reflux was continued for 4 hr followed by standard work-up.

(9) Simmons–Smith reaction under the usual conditions[2,6] with estr-5(10)-ene-3α,11β,17β-triol 3,17-diacetate [mp 194–196°. *Anal.* Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.28; H, 8.45] prepared from I (17β-OH) by sodium borohydride reduction and acetylation affords the expected 5β,19-cycloandrostane-3α,11β,17β-triol 3,17-diacetate [mp 137–138°; nmr 36 (19-H) and 61 (18-H) cps. *Anal.* Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.98; H, 8.81].

(10) α-Side methylenation of the 5(10) double bond directed by a 3α-hydroxy group has been reported by R. Ginsig and A. D. Cross, *J. Am. Chem. Soc.*, **87**, 4629 (1965).

(11) This compound was stable in a refluxing solution of zinc acetate and 1:1 water–acetic acid for 100 min and in 90% aqueous formic acid for 10 min at reflux.[12]

(12) Personal communication from Dr. I. Harrison. However, *cf.* G. Stork and J. Tsuji, *J. Am. Chem. Soc.*, **83**, 2783 (1961).

(13) D. Banes and J. Carol, *J. Biol. Chem.*, **204**, 509 (1953); B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2220 (1958).

(14) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

(15) H. Hasegawa, S. Nozoe, and K. Tsuda, *Chem. Pharm. Bull. Japan*, **11**, 1037 (1963).

(16) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963); **87**, 5661 (1965). The use of dichloroacetic acid as the acid catalyst was found to be essential for obtaining a high yield (80%) in this reaction.

Since $\Delta^{9,11}$-estrone 3-methyl ether is available by a highly practical and efficient four-step total synthesis from simple bicyclic precursors,[17] the transformations here described afford a totally synthetic entry to 11β-hydroxyandrostanes which in turn have been converted by well-established methods of side-chain synthesis to cortisone and the therapeutically important 16-substituted corticoids.[18]

(17) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963). For recent reviews *cf.* I. V. Torgov, *Pure Appl. Chem.*, **6**, 525 (1963); T. B. Windholz and M. Windholz, *Angew. Chem. Intern. Ed. Engl.*, 3, 353 (1964).

(18) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1959; L. Velluz, G. Nominé and J. Mathieu, *Angew. Chem.*, 72, 725 (1960).

(19) Syntex Postdoctoral Fellow, 1964–1965.

(20) Syntex Postdoctoral Fellow, 1965–1966.

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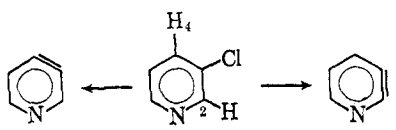
Hydrogen–Deuterium Exchange in Some Halopyridines and the Mechanism of Pyridyne Formation

Sir:

Halopyridines may undergo dehydrohalogenation in the presence of strong base to form pyridyne,[1] a heterocyclic counterpart of benzyne. With 3-chloropyridine (I) this elimination may in principle proceed by the formation of 2,3-pyridyne (II) and 3,4-pyridyne (III). Although there is solid evidence for III, no proof exists for the formation of II from I.



III I II

Dehydrochlorination of I by lithium piperidide in ether–piperidine is said to proceed by a two-step mechanism involving the formation of a lithiopyridine by removal of hydrogen adjacent to the halogen. 2-Lithio-3-chloropyridine is expected to be more stable than 4-lithio-3-chloropyridine.[1a,2] Competition experiments indicate pyridyne III is more selective and hence more stable than benzyne,[1a] and molecular orbital calculations suggest II should be more stable than III because of the added electron delocalization involving the nitrogen electron pair.[3] In light of these suggestions why does II not form from I?

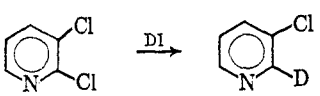
In this communication we demonstrate that the rate of hydrogen exchange at the 2 position of I is immeasurably slow relative to the exchange rate at the 4 position. Two different solvent systems were employed, methanol and ammonia.

In methanol, methoxide ion brings about deprotonation of I and also of 3,5-dichloropyridine (IV) under relatively mild conditions. Both incorporation of deuterium from CH_3OD into unlabeled chloropyridine and removal of deuterium from substrate into CH_3OH were examined in each of the following experiments. Samples under nitrogen were sealed in nmr tubes and incubated in a thermostated bath. The cooled mixture was examined periodically for hydrogen content in substrate. Nonexchanging sites of substrate served as internal standards in calculating per cent deprotonation from nmr peak areas. From reactions on a larger scale, chloropyridine was recovered and the neat material was analyzed directly. The data in Table I indicate, the surprising results. With both I and IV it is H-4 which exchanges most rapidly.[4,5] There is no evidence for deprotonation at the 2 position of I.[6] Only traces of chloride ion were detected under conditions of hydrogen exchange. To further demonstrate the authenticity of 3-chloropyridine-4-*d* (V), obtained by exchange in CH_3OD, 3-chloropyridine-2-*d* (VI) was prepared for comparison by the following method. Deuteriodechlorination of 2,3-dichloropyridine (VII)[7] by refluxing with constant-boiling DI[8] for 18 hr gave 53% VI having 61% D.[9,10] That the nmr spectra of deuterated V and VI were significantly different substantiated the assignment of the position of the label.

Table I. Equilibrium Deuteration of Chloropyridines in CH_3OD at 74°

Pyridine	Position of exchange[a]	CH_3ONa, *M*	Time, hr[b]
3-Chloro	4	3.2	21
3,5-Dichloro	4	1.6	24[c]
3,5-Dichloro	2,6	2.6	48[d]

[a] Retention time by glpc analysis for deuterium product is identical with that for hydrogen reactant. [b] To achieve equilibrium deuteration which is no less than 75% D at the position indicated. [c] At 23°. [d] Only 39% D under these conditions.



VII VI

In ammonia, amide ion brings about both hydrogen exchange and dehydrochlorination. Deuterated chloropyridines V and VI were examined separately.[11] Reactions were interrupted before complete chloride ion loss, and recovered substrate was analyzed for deuterium content. The data in Table II indicate a large reduction

(1) For review articles see (a) T. Kauffmann, *Angew. Chem. Intern. Ed. Engl.*, 4, 543 (1965); (b) H. J. den Hertog and H. C. van der Plas, *Advan. Heterocyclic Chem.*, 4, (1965).

(2) T. Kauffmann and F. P. Boettcher, *Chem. Ber.*, 95, 1528 (1962).

(3) H. L. Jones and D. L. Beveridge, *Tetrahedron Letters*, 1577 (1964).

(4) 3-Substituted pyridines exhibit in ABCD nmr spectrum. For a thorough analysis see (a) V. J. Kowaleski and D. G. de Kowaleski, *J. Chem. Phys.*, 36, 266 (1962); (b) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 112.

(5) Deuteration of I leads to a large diminution in the intensity of the H-4 multiplet and simplification of the over-all coupling pattern. The most dramatic spin decoupling occurs with H-5 which changes from a quartet to a doublet with the introduction of D-4.

(6) A similar observation was made on 3-bromopyridine.

(7) H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. Trav. Chim.*, 69, 673 (1950).

(8) Prepared by repeated exchange of constant boiling HI with >99.5% D_2O.

(9) This reaction frequently has been used for proteodechlorinations. See H. E. Mertel, "Pyridine and Its Derivatives," Part II, E. Klingsberk, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, pp 339–344.

(10) Acid-catalyzed H–D exchange in pyridines is a slow process. See (a) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), 12, 1384 (1964); (b) A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.*, 3753 (1963).

(11) Reaction conditions and work-up are essentially those employed in ref 12 except that nmr was used to analyze for deuterium.

(12) J. A. Zoltewicz and J. F. Bunnett, *J. Am. Chem. Soc.*, 87, 2640 (1965).