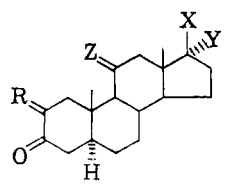
Communications TO THE EDITOR

Steroids. CCXVIII.[1] A Synthesis of α-Formyl-α,β-unsaturated Ketones. 2-Formyl-Δ¹- and Δ¹,⁴-3-keto Steroids

Sir:

The recent finding[2] that a series of 2-formyl-Δ²-androstene analogs had high anabolic activity with low androgenicity focussed our attention on approaches to 2-formyl-Δ¹- and Δ¹,⁴-3-keto steroids. No general method exists for the synthesis of α-formyl-α,β-unsaturated ketones although α-formyl ketones are readily obtained by the base-promoted condensation of a ketone with ethyl formate,[3] and they exist mainly in their enol form (α-hydroxymethylene ketones).

Initial attempts to prepare 2-formyl-Δ¹-androst-2-stene-17β-ol-3-one (IIa) *via* the bromination of hydroxymethyleneandrostane-17β-ol-3-one[3b,4] (Ia) followed by dehydrobromination were unsuccessful, and it was necessary to consider a new approach.



Ia. X = OH; Y = H; Z = H_2; R = CHOH
b. X = OH; Y = CH_3; Z = H_2; R = CHOH; with Δ⁴-double bond

c. X =  ; Y = H; Z = R = H_2

d. X =  ; Y = H; Z = H_2; R = CHOH

e. X =  ; Y = H; Z = H_2; R = CHOH; with Δ⁴-double bond

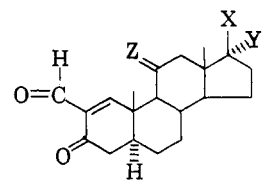
f. X =  ; Y = H; Z = H_2; R = CHOH; with Δ⁴-double bond

g. X,Y = bismethylenedioxy; Z =  ; R = H_2; with Δ⁴-double bond

h. X,Y = bismethylenedioxy; Z =  ; R = CHOH; with Δ⁴-double bond

The dehydrogenation of steroidal Δ⁴-3-ketones with quinones was originally studied by Agnello and Laubach and the reaction was postulated to proceed *via* the enol of the ketone.[5,6]

Since α-formyl ketones exist almost entirely in their enol form they should be extremely susceptible to dehydrogenation by a suitable quinone. Indeed, 2-hydroxymethyleneandrostane-17β-ol-3-one[3b,4] (Ia) upon treatment with 1.4 moles of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane solution for 2 minutes at 20° followed by dilution of the reaction mixture with methylene dichloride and rapid filtration through alumina afforded in 50% yield.[7] 2-formyl-Δ¹-androstene-17β-ol-3-one (IIa)

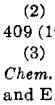


IIa. X = OH; Y = H; Z = H_2
b. X = OH; Y = CH_3; Z = H_2; with Δ⁴-double bond

c. X =  ; Y = H; Z = H_2

d. X =  ; Y = H; Z = H_2; with Δ⁴-double bond

e. X, Y = bismethylenedioxy; Z =  ; with Δ⁴-double bond

f. X =  ; Y = OH; Z =  ; with Δ⁴-double bond

(m.p. 215–217°; $[\alpha]D$ +23° (all rotations in chloroform); $\lambda_{max.}^{EtOH}$ 241 mμ, log ε 3.90; in the presence of

(1) Steroids CCXVII. A. Zaffaroni and A. Bowers, "*Proc. Intern. Congr. Steroid Hormones*, Milan, May, 1962.

(2) J. C. Orr, O. Halpern, and A. Bowers, *J. Med. Pharm. Chem.*, **5**, 409 (1962).

(3) (a) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954); (b) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *ibid.*, **81**, 427 (1959).

(4) J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959).

(5) E. J. Agnello and G. D. Laubach, *ibid.*, **82**, 4293 (1960).

(6) After the completion of this work H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962), reported on a detailed mechanistic study of the dehydrogenation of steroidal ketones with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and showed conclusively that these reactions proceed *via* the enol form of the ketone or unsaturated ketone.

(7) The 2-formyl-Δ¹-3-ketones described in this communication were all obtained in 40 to 60% yield from the corresponding α-hydroxymethylene ketones using 1.1-1.4 molar equivalents of D.D.Q. and a reaction period of 1–5 min. Extension of the reaction time led to reduced yields of the desired products.

alkali $\lambda_{max.}^{EtOH}$ 305 mμ, log ε 4.22; $\lambda_{max.}^{CHCl_3}$ 5.88, 5.95, and 6.23 μ. Found: C, 75.78, H, 8.96; O, 15.29).

Similarly 2-hydroxymethylene-17α-methyl-Δ⁴-androstene-17β-ol-3-one[3b] (Ib) gave 2-formyl-17α-methyl-Δ¹,⁴-androstadiene-17β-ol-3-one (IIb), (m.p. 107–110°; [α]D −66.5°; $\lambda_{max.}^{EtOH}$ 222 and 247 mμ, log ε 4.06 and 4.07; in the presence of alkali $\lambda_{max.}^{EtOH}$ 242 and 348 mμ, log ε 4.17 and 4.00; $\lambda_{max.}^{KBr}$ 5.85, 6.05, 6.18, and 6.25 μ. Found: C, 74.08; H, 8.55; acetone solvate).

In the pregnane series, chromium trioxide-pyridine oxidation of allopregnane-3β-ol 20-cycloethyleneketal (III) (m.p. 174–176°; [α]D +13°. Found: C, 75.50; H, 10.25; O, 13.45) afforded the 3-ketone Ic (m.p. 186–188°; [α]D +33°, $\lambda_{max.}^{KBr}$ 5.80 μ. Found: C, 76.36; H, 9.96; O, 13.25) which was converted into 2-hydroxymethylene-allopregnane-3-one 20-cycloethyleneketal (Id) (m.p. 176–178°; [α]D +68°; $\lambda_{max.}^{EtOH}$ 282 mμ, log ε 3.91; $\lambda_{max.}^{KBr}$ 6.46. Found: C, 73.94; H, 9.36; O, 16.63) by ethyl formate condensation with sodium methoxide. Reaction of Id with DDQ and subsequent hydrolytic cleavage of the 20-ketal group furnished 2-formyl-Δ¹-allopregnene-3,20-dione (IIc) (m.p. 194–196°, [α]D +109°; $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 3.89; in the presence of alkali $\lambda_{max.}^{EtOH}$ 304 mμ, log ε 4.23; $\lambda_{max.}^{KBr}$ 5.86, 5.96, 6.22 μ. Found: C, 76.70; H, 8.79; O, 14.36).

In addition, mild acid hydrolysis of 2-hydroxymethylene-Δ⁴-pregnene-3-one 20-cycloethyleneketal[8] (Ie) produced 2-hydroxymethyleneprogesterone (If) (m.p. 164–166°; [α]D +141°; $\lambda_{max.}^{EtOH}$ 253 and 307 mμ, log ε 4.08 and 3.80; $\lambda_{max.}^{KBr}$ 5.87, 6.10, and 6.38 μ. Found: C, 77.39; H, 8.92; O, 14.08) which readily underwent dehydrogenation with DDQ to yield 2-formyl-Δ¹-progesterone (IId) (m.p. 164–166°; [α]D +57°; $\lambda_{max.}^{EtOH}$ 221 and 247 mμ, log ε 4.08 and 4.14; in the presence of alkali, $\lambda_{max.}^{EtOH}$ 242 and 348 mμ, log ε 4.15 and 3.99; $\lambda_{max.}^{KBr}$ 5.86, 6.01, 6.13, and 6.21 μ. Found: C, 77.91; H, 7.94; O, 14.11).

In the corticoid series treatment of hydrocortisone bismethylenedioxy derivative (BMD)[9] (Ig) with ethyl formate in the presence of sodium methoxide readily afforded the corresponding 2-hydroxymethylene compound (Ih) (m.p. 257–259°; [α]D −44°; $\lambda_{max.}^{EtOH}$ 255 and 308 mμ, log ε 4.03 and 3.74; $\lambda_{max.}^{KBr}$ 6.12 and 6.30 μ. Found. C, 66.33; H, 7.79). Dehydrogenation of Ih with DDQ gave 2-formylprednisolone BMD (IIe) (m.p. 269–271°; [α]D −61°; $\lambda_{max.}^{EtOH}$ 221 and 245 mμ, log ε 4.16 and 4.07; in the presence of alkali, $\lambda_{max.}^{EtOH}$ 243 and 348 mμ, log ε 4.16 and 4.01; $\lambda_{max.}^{KBr}$ 5.85, 6.00, 6.15, and 6.21 μ. Found. C, 66.27, H, 7.42; O, 26.02).

Hydrolysis of the BMD protecting group followed by acetylation gave 2-formylprednisolone 21-acetate (IIf) (m.p. 253–255°; [α]D +76°; $\lambda_{max.}^{EtOH}$ 220 and 244 mμ, log ε 4.18 and 4.08; in the presence of alkali, $\lambda_{max.}^{EtOH}$ 244 and 347 mμ, log ε 4.14 and 4.01; $\lambda_{max.}^{KBr}$ 5.75, 5.90, 6.03, 6.17, and 6.25 μ. Found: C, 67.24; H, 7.17; O, 25.62).

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RECEIVED MAY 3, 1962

(8) H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

(9) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

Claisen Rearrangement to a *para* Side Chain

Sir:

The Claisen rearrangement maintains importance among organic reactions as an excellent prototype of a thermally induced, intramolecular isomerization.[1] Much of the research on this reaction in recent years has dealt with the nature of intermediates and transition states, with competitive pathways, and with "abnormal" products.[2] It has been established that the *para*-Claisen rearrangement involves two successive cyclic stages, each accompanied by a reversal of the allyl group.[3] This finding led us to consider that *multistage* rearrangements might be induced in which an allyl group migrates over more extensive distances if the intermediates along the way possess the proper structural features. We now report a successful "out-of-ring" migration of an allyl group to the β-carbon of a *para*-propenyl side chain.

Relevant compounds in this study are Ib, II, and III, which were prepared as follows. Treatment of 2,6-dimethyl-4-allylphenol with alkali gave 2,6-dimethyl-4-propenylphenol (Ia) which was converted to the corresponding allyl ether Ib with allyl bromide. Friedel–Crafts acylation of 2,6-dimethylphenol with 2-methylpentanoyl chloride gave 2,6-dimethyl-4-(2-methylpentanoyl)phenol, which was

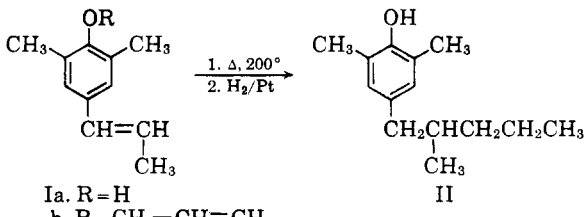
(1) D. S. Tarbell, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, Chap. 1.

(2) (a) For several papers by W. N. White and co-workers see *J. Org. Chem.*, **26**, 627 (1961); (b) A. W. Burgstahler, *J. Am. Chem. Soc.*, **82**, 4681 (1960); (c) H. L. Goering and R. R. Jacobson, *ibid.*, **80**, 3277 (1958); (d) L. D. Heustis and L. J. Andrews, *ibid.*, **83**, 1963 (1961); (e) K. R. Brower, *ibid.*, **83**, 4370 (1961); (f) E. N. Marvell and J. L. Stephenson, *J. Org. Chem.*, **25**, 676 (1960); (g) Y. Pocker, *Chem. Ind.* (London), 141 (1961); (h) S. Marcinkiewicz, J. Green, and P. Mamalis, *Tetrahedron*, **14**, 208 (1961); (i) K. Schmid and H. Schmid, *Helv. Chim. Acta*, **36**, 687 (1953); (j) E. N. Marvell, D. R. Anderson, and J. Ong., *J. Org. Chem.*, **27**, 1109 (1962).

(3) (a) C. D. Hurd and M. A. Pollack, *ibid.*, **3**, 550 (1939); D. Y. Curtin and R. J. Crawford, *J. Am. Chem. Soc.*, **79**, 3156 (1957); E. N. Marvell and R. Teranishi *ibid.*, **76**, 6165 (1954); J. P. Ryan and P. R. O'Connor, *ibid.*, **74**, 5866 (1952); H. Conroy and R. A. Firestone, *ibid.*, **78**, 2290 (1956); K. Schmid, W. Haegele, and H. Schmid, *Helv. Chim. Acta*, **37**, 1080 (1954); (b) Out-of-ring migrations to an *ortho* side chain appear to proceed principally through a two-cycle process [W. M. Lauer and D. W. Wujciak, *J. Am. Chem. Soc.*, **78**, 5601 (1956); E. N. Marvell, R. J. Dupzyk, J. L. Stephenson, and R. Anderson, *J. Org. Chem.* **25**, 608 (1960); K. Schmid, P. Fahrini, and H. Schmid, *Helv. Chim. Acta*, **39**, 708 (1956)].

readily hydrogenated to II with copper chromite. The known phenol III[4] was obtained similarly by acylation with propionyl chloride followed by hydrogenation. Phenols II and III show differences in infrared absorption and in gas chromatographic retention time.

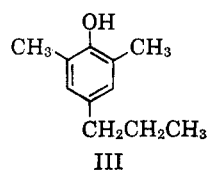
The allyl ether Ib was pyrolyzed in ethanol (8 hr. at 200°) and the product was directly hydrogenated (Pt). Chromatography on alumina gave, in the early fractions, phenol II identified by its infrared spectrum, by its retention time on gas chromatography, and by conversion to an α-naphthylurethan whose melting point was undepressed by an authentic sample. Later phenolic fractions from the chromatography consisted of II contaminated with III. Analysis of individual and pooled fractions by infrared absorption and gas chromatography showed that the total phenolic material eluted (41%) consisted of *ca.* 31% of II, 8% of III, and less than 2% of unidentified material showing carbonyl absorption. From current views on Claisen rearrangements a mechanism involving *three* consecutive "cycles" readily accounts for this out-of-ring migration to a *para* side chain.



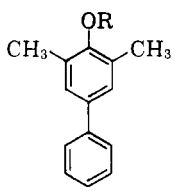
Ia. R = H
b. R = CH_2—CH=CH_2

II

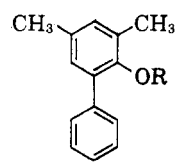
+



III



IVa. R = CH_3
b. R = H
c. R = CH_2CH=CH_2



Va. R = H
b. R = CH_2CH=CH_2

To examine if the olefinic unit serving as the acceptor in out-of-ring Claisen rearrangements could itself be part of a second phenyl ring we prepared IVc and Vb and studied their thermal behavior. Diazotized 2,6-dimethyl-4-aminoanisole was phenylated (Gomberg reaction[5]) to give 2,6-dimethyl-4-phenylanisole (IVa) which was cleaved (HI/HOAc) to the phenol IVb. This phenol was also obtained by ultraviolet irradiation of 2,6-dimethyl-4-iodophenol in benzene.[6] Allylation proceeded normally and gave IVc. Similarly, irradiation of 2,4-dimethyl-6-iodophenol in benzene solution produced Va, which was readily allylated to Vb.

Pyrolysis of IVc in decalin (8 hr. at 250°) and chromatography gave 75% of the parent phenol IVb, with no indication (infrared) of allylated products in the phenolic chromatography fractions. On milder treatment (*e.g.*, neat at 200° for 3 hr.) phenol IVb was accompanied by the starting ether IVc. Similarly, pyrolysis of Vb in decalin (8 hr. at 250°) or in the presence of sodium carbonate (5 hr. at 220°) followed by chromatography gave *ca.* 77% of the parent phenol Va; no C-allylated phenol was detected by infrared. We conclude that the unsubstituted phenyl ring in IVc and in Vb functions preferentially as a blocking group rather than as an allyl acceptor.

Constants[7] for the relevant compounds are: Ia m.p. 72–76°; ν 3620, 958 cm.$^{-1}$; λ (EtOH) 262 mμ (ϵ 16,600), 294 mμ (shoulder, ϵ 2700); α-naphthylurethan m.p. 192.5–195°. Ib b.p. 88–93° (0.2 mm.); n^{20}D 1.5406; ν (neat) 960, 920 cm.$^{-1}$. II b.p. 85–87° (0.1 mm.); n^{21}D 1.5114; m.p. 13–16°; ν (neat) 3500, 872 cm.$^{-1}$; α-naphthylurethan m.p. 154.5–155°. III m.p. 34.5–35.5°;[4] α-naphthylurethan m.p. 165–167.5°. IVa m.p. 31–31.5°; b.p. 126–130° (1.5 mm.); n^{21}D 1.5890. IVb m.p. 96.5–97°; ν (KBr) 3390 cm.$^{-1}$; α-naphthylurethan m.p. 220.5–221.5°. IVc m.p. 34.5–35°; ν 928 cm.$^{-1}$. Va b.p. 100–104° (0.1 mm.); n^{20}D 1.5955; ν (neat) 3509 cm.$^{-1}$; α-naphthylurethan m.p. 126–127.5°. Vb b.p. 100–106° (0.4 mm.); n^{22}D 1.5690; ν (neat) 926 cm.$^{-1}$.

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(4) K. von Auwers and E. Janssen, *Ann.*, **483**, 44 (1930).

(5) W. E. Bachmann and R. A. Hoffman, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. II, p. 224.

(6) W. Wolf and N. Kharasch, *J. Org. Chem.*, **26**, 283 (1961).

(7) All compounds gave satisfactory C and H analyses. Infrared spectra in carbon disulfide except where stated.

(8) This work was supported in part by the Alfred P. Sloan Foundation. A grant-in-aid from the Hynson, Westcott, and Dunning Fund is also gratefully acknowledged.

Total Synthesis of Alstoniline

Sir:

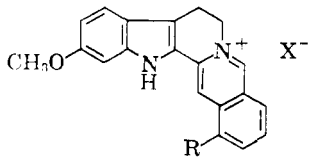
Alstoniline hydrochloride ($C_{22}H_{18}N_2O_3$·HCl·H_2O), a brilliant red alkaloid of *Alstonia constricta* F. Muell, was first isolated[1] and investigated by Elderfield and his co-workers, who established its structure (I. X = Cl) by degradation studies[2]

(1) W. L. Hawkins and R. C. Elderfield, *J. Org. Chem.*, **7**, 573 (1942).

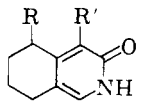
(2) (a) N. J. Leonard and R. C. Elderfield, *ibid.*, **7**, 556 (1942); (b) R. C. Elderfield and S. L. Wythe, *ibid.*, **19**, 683, 693 (1954); (c) R. C. Elderfield and O. L. McCurdy, *ibid.*, **21**, 295 (1956).

and then by an elegant synthesis of alstonilinol iodide (II. X = I).[3] This alkaloid has an unsaturated ring system containing no asymmetric carbon atom in which respect it constitutes one of two exceptions along with sempervirine[4] among the pentacyclic indolopyridocoline group of alkaloids. In view of this interesting feature and because of interest in the biogenetic pattern of these alkaloids,[5] attention was turned to the synthesis of alstoniline itself by an application of a new synthetic method for β-carboline derivatives which has been recently developed in this laboratory.[6] We now wish to announce the total synthesis of this alkaloid.

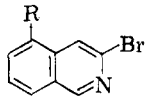
3-Keto-4-cyano-5-methyl-5,6,7,8-tetrahydro-2H-isoquinoline (III)[7] was hydrolyzed and decarboxylated by heating with 75% sulfuric acid under a stream of nitrogen at 175–180° for 15 hr. to give 3-keto-5-methyl-5,6,7,8-tetrahydro-2H-isoquinoline (IV), colorless needles, m.p. 126–127°, in 75% yield. Ultraviolet: λ_{max}^{EtOH} 308 mμ; λ_{min}^{EtOH} 254 mμ.



I. R = $COOCH_3$
II. R = CH_2OH



III. R = CH_3, R′ = CN
IV. R = CH_3, R′ = H



V. R = CH_2Br
VI. R = COOH
VII. R = $COOCH_3$

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.52; H, 8.32; N, 8.83. The keto base (IV) was heated with phosphorus oxybromide in a sealed tube at 160–170° for 20 hr. to furnish 3-bromo-5-bromomethylisoquinoline (V), pale yellow needles, m.p. 157–158°, in 32.8% yield. Ultraviolet λ_{max}^{EtOH} 333, 321, 294, and 282.5 mμ; λ_{min}^{EtOH} 325, 305, 289, and 263 mμ. *Anal.* Calcd. for $C_{10}H_7NBr_2$: Br, 53.15. Found: Br, 52.66. The dibromo base (V) was heated with selenium dioxide in nitrobenzene at 170–175° for 15 hr. to furnish the acid (VI), colorless needles, m.p. 251° in 63.5% yield. Ultraviolet: λ_{max}^{EtOH} 331, 322, 291, and 280 mμ; λ_{max}^{EtOH} 306, 303, 288, and 260 mμ. *Anal.* Calcd. for $C_{10}H_6NO_2Br$; C, 47.61; H, 2.38; N, 5.55; Br, 31.74. Found: C, 47.59; H, 2.48; N, 5.53; Br, 32.22. The acid (VI) was treated with thionyl bromide and then with methanol to give the corresponding ester (VII), colorless needles, m.p. 123°. *Anal.* Calcd. for $C_{11}H_8NO_2Br$: C, 49.62; H, 3.00; N, 5.26; Br, 30.07. Found: C, 49.63; H, 3.17; N, 5.41; Br, 30.71. When a mixture of 3-(2-bromoethyl)-6-methoxyindole and VII was heated in toluene at 90–95° in a current of nitrogen for 28 hr. a red-brown solid separated. This was washed with absolute ether, treated with silver chloride, and then recrystallized from methanol to give the hydrochloride, fine orange-red needles. The ultraviolet spectrum of this sample was identical with that of natural alstoniline sulfate (I. X = $\frac{1}{2}SO_4$) which was generously supplied by Professor Elderfield. The hydrochloride (I. X = Cl) is not suitable for identification since it decomposes over a wide range without melting. Therefore, the synthetic hydrochloride was converted to the picrate (I. X = picrate ion), red plates, m.p. 291° dec., which was directly compared with the picrate, red plates, m.p. 294° dec., derived from the natural alkaloid. The identity of both samples was established by mixed melting point determination and was further confirmed by their identical infrared spectra.

Acknowledgment.—We wish to express our deep gratitude to Professor R. C. Elderfield for his gracious gift of alstoniline sulfate, and to Dr. W. T. Sumerford, Mead Johnson Research Center, for kindly supplying 6-methoxyindole.

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(3) R. C. Elderfield and B. A. Fisher, *J. Org. Chem.*, **23**, 332, 949 (1958).

(4) R. B. Woodward and B. Witkop, *J. Am. Chem. Soc.*, **71**, 379 (1949).

(5) R. B. Woodward, *Nature*, **162**, 155 (1948); E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.*, **81**, 1474 (1959).

(6) Y. Ban and M. Seo, *Chem. Ind.*, 235 (1960); Y. Ban and M. Seo, *Tetrahedron*, **16**, 5, 11 (1961).

(7) U. Basu and B. Banerjee, *Ann.*, **516**, 243 (1935).

Reduction of 12-Keto Steroids

Sir:

It has been generally accepted that the reduction of cyclic ketones by either sodium in alcohol, or lithium–liquid ammonia–alcohol gives rise exclusively or almost exclusively to the alcohol containing the thermodynamically more stable equatorial hydroxyl group.[1]

Both of these methods of reduction have found wide use in steroid chemistry, and in fact the reduction of 11-keto steroids by lithium–liquid ammonia[2] or sodium in *n*-propyl alcohol[3] provides a major source of 11α-hydroxy steroids. Although a number of cases have been found where reduction of bridged ring ketones with sodium in alcohol

(1) (a) D. H. R. Barton, *Experientia*, **6**, 316 (1950); (b) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (c) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956); (d) W. Klyne, "Progress in Stereochemistry," Vol. I, Butterworths, London, 1954, pp. 57, 74; (e) W. G. Dauben and K. S. Pitzer in M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 47.

leads to a preponderance of the thermodynamically less stable alcohol,[4] and although the reduction of camphor with potassium, rubidium, or cesium in liquid ammonia with ethanol as a proton source gives principally the less stable *exo* alcohol,[4a] there seems to be little general doubt that reduction of cyclic ketones in general, and steroidal ketones in particular, with either of the above reagents gives principally the more stable equatorial alcohol.

In direct contrast to the above generalizations we have found that when either 12-ketocholanic acid,[5] or 12-cholanone, m.p. 115–117, α_D +89.4, prepared by the oxidation of 12α-cholanol,[6] are reduced by lithium–liquid ammonia–*n*-propyl alcohol in the usual manner[2] *the 12 α-(axial)ol was the only isolable product* (89 and 74% of the crude reaction mixture, respectively). When these same compounds were reduced with sodium in *n*-propyl alcohol.[3] the principal products were again the axial alcohols (67 ± 8 and 61%, respectively).[7] When the same methods of reduction were applied to hecogenin, lithium–ammonia gave the 12β-ol, rockogenin, as the only isolable product, and sodium–alcohol gave a maximum of 20% of the 12α-ol. Reduction of 3α-hydroxy-12-ketoetianic acid[8] gave 40 ± 5% of the α -ol when lithium–ammonia was used and 36 ± 5% with sodium–*n*-propyl alcohol. When 12-cholanone was stirred with lithium in ammonia, and *n*-propyl alcohol added after one hour,[2c] considerably different results were obtained. The crude reaction mixture consisted of 40% of a dimeric pinacol, m.p. 255–260°, 3% of the 12 α-ol and the balance was the 12β-ol, m.p. 91–92°, α_D +45. This method of reduction of hecogenin again gave only the equatorial isomer.

While it is difficult, on the basis of the above evidence, to give any definitive explanation of the exact factors governing the course of the above reductions it seems likely that *neither metal in ammonia nor sodium in alcohol reductions of ketones are thermodynamically controlled.*[9] A corollary to this is that it now appears that considerable caution must be exercised in making use of these reductive methods in the assignment of configuration to alcohols.

There appear to be two features in the steroid nucleus that are responsible for the peculiar behavior of the 12-keto compounds of reduction. The first is the presence of a *cis* A-B ring fusion in the 5β-steroids, studied and the second is some variety of shielding effect, probably by the C-21 methyl group in those compounds having a side chain.[10] This follows from our observation that those compounds (12-ketocholanic acid and 12-cholanone) having both a side chain and a *cis* A-B ring fusion give predominantly the axial alcohol on reduction, while the etianic acid gives a mixture of α- and β-ol. Hecogenin with a *trans* ring fusion and the side chain held in such a conformation as to be unable to shield the 12-position gives little if any axial alcohol.

We are currently carrying out experiments to help clarify the factors governing the course of these reductions.[11]

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(2) (a) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955); (b) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *ibid.*, **75**, 1282 (1953); (c) K. Heusler, H. Heusser, and R. Anliker, *Helv. Chim. Acta*, **36**, 652 (1953); (d) F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 2696 (1952).

(3) (a) H. L. Herzog, M. A. Jevnik, and E. B. Hershberg, *ibid.*, **75**, 269 (1953); (b) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957); (c) H. L. Heuser, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

(4) (a) G. Ourisson and A. Rassat, *Tetraheadron Letters*, **21**, 16 (1960) and references cited therein; (b) J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).

(5) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).

(6) R. T. Blickenstaff and F. C. Chang, *J. Am. Chem. Soc.*, **81**, 2835 (1959).

(7) Dr. F. C. Chang has also encountered various anomalies in the reductions of 12-keto steroids; F. C. Chang, private communication.

(8) E. Schwenk, B. Riegel, R. B. Moffett, and E. Stahl, *J. Am. Chem. Soc.*, **65**, 549 (1943).

(9) The alternate explanation, that the stereochemical assignments at C-12 in the steroid nucleus are incorrect seems remote. The proof of these assignments is discussed thoroughly by R. B. Turner in L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 1949, pp. 654–662. Since the 5β-compounds we have studied are all prepared from deoxycholic acid, by routes which go through the 12α-ol, and under conditions which preclude epimerization at C-12, the configuration of these compounds seems secure. The stereochemistry of rockogenin follows from its reactions which are discussed thoroughly by Hirschmann, *et al.*, *J. Am. Chem. Soc.*, **76**, 4013 (1954). An alternate explanation, that the axial alcohol is the more stable seems most unlikely in view of the overwhelming evidence to the contrary in other systems (see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, pp. 234–239).

(10) Interactions of the side chain in 12-hydroxy steroid acylations have been noted by Lardon (see L. F. Fieser and M. Fieser "Steroids," Reinhold, New York, 1959, p. 222) and in oxidations (ref. 8).

(11) All of the new compounds reported in this communication were characterized by elementary analysis and infrared spectroscopy. The analyses of the mixtures were carried out by chromatographic separation, polarimetry, infrared methods, and combinations thereof.

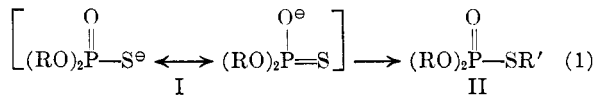
Preferential Alkylation of Nitrogen Rather Than Sulfur in Phosphoramidothioate Anions

Sir:

Several recent papers have discussed the alkylation of ambident anions, and several of the factors which determine whether an anion will be alkylated

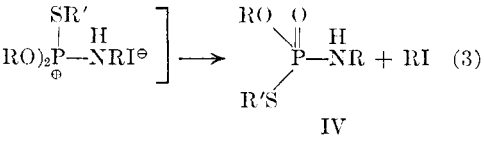
on carbon or oxygen or on nitrogen or oxygen have been elucidated.[1]

Anions which contain sulfur as a point of attack, however, have almost invariably been alkylated on the sulfur atom rather than on a first row element, as a consequence of the very high nucleophilicity of the thiol anion.[2] Thus, phosphorothioate anions (I) give only *S*-alkyl phosphorothioates (II) on alkylation (eq. 1),[3]



(1)

just as salts of thiocarboxylic acids give only *S*-alkyl esters.[4] Both thiocarboxylamides[5] and their anions react[6] with alkylating agents to give *S*-alkyl thioimides rather than the more stable *N*-alkyl thioamides (eq. 2). Similarly, phosphoramidothioates (III) give the *S*-alkylated products from reaction with alkyl iodides at elevated temperatures (eq. 3).[7]

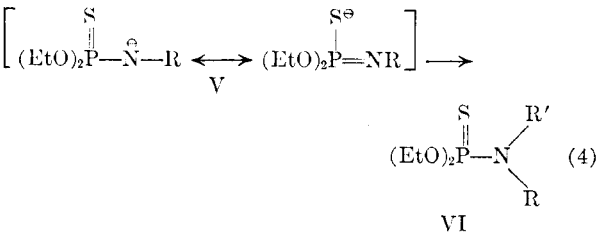


(2)

(3)

It would be expected, therefore, that anions of phosphoramidothioates would react with alkylating agents at the sulfur atom.

We have now found that the anions of *O,O*-diethyl phosphoramidothioates (V) react with alkylating agents exclusively on the nitrogen, rather than on the sulfur atom, to give *N*-alkylated phosphoramidothioates (VI). We could detect no indication of the formation of the expected *S*-alkylated products.



(4)

Anion V (R = Me) reacted with either methyl iodide or dimethyl sulfate to give VI (R = R′ = Me)[8] in 80–90% yield. The product was identical with a sample prepared from *O,O*-diethyl phosphorochloridothioate and dimethylamine. Similarly, V (R = C_6H_5) reacted with methyl iodide to give VI (R = C_6H_5, R′ = Me), identical with the product of the reaction of *N*-methylaniline with *O,O* - diethyl phosphorochloridothioate. (*Anal.* Found: C, 50.97; H, 17.17; N, 5.23; P, 11.69; S, 12.60.)

N-Alkylated phosphoramidothioates were similarly obtained when diethyl sulfate, methyl chloroacetate, and allyl bromide were used as the alkylating agents. The solvent and base employed did not seem to be critical, since the same products were obtained if potassium *tert*-butoxide in *tert*-butyl alcohol, *n*-butyllithium in diethyl ether, or sodium hydride in dimethoxyethane was used to form the anion.

In a typical reaction, *O,O*-diethyl *N*-methyl phosphoramidothioate (4.80 g., 0.032 mole) was dissolved in 100 ml. of *tert*-butyl alcohol containing 0.036 mole of potassium *tert*-butoxide. Methyl iodide (5.17 g., 0.036 mole) was added, the solution stirred for 15 min. at 25°, and worked up. Other alkylating agents required no more strenuous conditions.

VI cannot have been obtained *via* the rearrangement of an initially formed *S*-alkyl phosphorimidate, since dealkylation of an alkoxy group to give IV should occur much more readily than dealkylation of a thioalkyl group to give VI.[9]

Phosphoramidothioates were recovered unchanged from attempted alkylations in which sodium methoxide in methanol was employed as the base, although carboxylic thioamides react readily under these conditions.[6] Similarly, phosphoramidothioates and diazoacetic ester were recovered unchanged after 6-hr. heating in ethanol, while

(1) For valuable theoretical discussions and leading references see N. Kornblum, R. A. Smiley, R. K. Blackwood, and C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955); also, D. Y. Curtin, R. J. Crawford, and M. Wilhelm, *ibid.*, **80**, 1391 (1958); D. Y. Curtin and R. R. Fraser, *ibid.*, p. 6016.

(2) (a) C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953). (b) J. O. Edwards, *ibid.*, **76**, 1540 (1954).

(3) M. I. Kabachnik and T. A. Mastryukova, *Zh. Obsch. Khim.*, **25**, 1924 (1955).

(4) *E.g.*, H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **24**, 69 (1900); J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950).

(5) A. Bernthsen, *Ann.*, **197**, 341 (1879).

(6) O. Wallach, *Ber.*, **11**, 1590 (1878); E. Fromm and M. Bloch, *ibid.*, **32**, 2212 (1899); H. L. Wheeler and H. F. Merriam, *J. Am. Chem. Soc.*, **23**, 283 (1901).

(7) A. J. Burn and J. I. G. Cadogan, *J. Chem. Soc.*, 5532 (1961).

(8) A. Michaelis, *Ann.*, **326**, 210 (1903).

(9) Nucleophilic displacement of an alkyl group from an oxygen atom of a phosphate or thiophosphate occurs approximately 250 times as fast as displacement of an alkyl group from sulfur, B. Miller, *Proc. Chem. Soc.* in press. See also, S. DuBreuil and R. W. Young, Abstracts of the 137th Meeting of the American Chemical Society, Atlantic City, N. J., 1959, p. 101T.

carboxylic thioamides condense completely to thiazolones in 1 hr.[10]

These observations strongly suggest that thioamides of phosphoric acids are much weaker acids than thioamides of carboxylic acids. This is quite a surprising conclusion, in view of the great acidities of phosphoric and phosphorothioic acids relative to carboxylic acids.[11]

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(10) L. C. King and F. M. Miller, *J. Am. Chem. Soc.*, **71**, 367 (1949).
(11) M. I. Kabachnik, T. A. Mastryukova, A. E. Shipov, and T. A. Melent'eva, *Tetrahedron*, **9**, 10 (1960).