C-19 Functional Steroids. V.[1] Synthesis of Estrogen Biosynthesis Intermediates[2]

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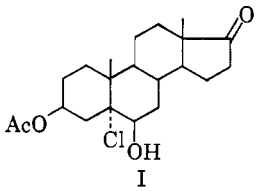
The synthesis of 19-hydroxyandrost-4-ene-3,17-dione, which has already been converted to a variety of C-19 oxygenated biosynthesis intermediates, is described. Treatment of androstenolone acetate with hypochlorous acid gave 5α-chloro-3β-hydroxyandrostan-17-one acetate. The nitrite ester derived from the foregoing chlorohydrin gave, on photolysis, the corresponding 19-oxime, which, on treatment with zinc in acetic acid, gave the corresponding Δ^5 compound, which furnished the 19-nitrile with acetic anhydride. Reduction of the 17-ketone with tri-*t*-butoxy lithium aluminum hydride, followed by partial reduction of the nitrile to the aldehyde with lithium aluminum hydride, gave 19-oxoandrost-5-ene-3β,17β-diol. The corresponding 19-alcohol was obtained with sodium borohydride, and Oppenauer oxidation gave the final product.

The determination of the biosynthetic pathway for the conversion of androgens to estrogens for some years has been an important problem. It has been demonstrated that 19-hydroxyandrost-4-ene-3,17-dione is an intermediate in the conversion of androst-4-ene-3,17-dione to estradiol.[3] More recent research[4] has been concerned with the nature of the intermediates following this 19-hydroxy steroid in the biosynthetic sequence. This work indicates that the Δ^1 derivative of either 19-hydroxyandrost-4-ene-3,17-dione or of the corresponding 19-aldehyde participates in the metabolic pathway.

Studies in the entire area have been hampered by poor availability of the C-19 oxygenated intermediates. Ehrenstein and co-workers[5] have developed methods for the preparation from strophanthidin of 19-hydroxyandrost-4-ene-3,17-dione. This substance is a key material in the chemical synthesis of estrogen biosynthesis intermediates, since methods exist for its conversion to the following compounds: 19-hydroxytestosterone[5] and its Δ^1 derivative,[5] 19-oxoandrost-4-ene-3,17-dione,[6] the corresponding C-19-carboxylic[6] acid, 19-norandrostenedione,[6] estrone,[7] and estradiol.[5]

A direct chemical synthesis of 19-hydroxyandrost-4-ene-3,17-dione from conventional steroids would be of value, therefore, since it would obviate the lengthy route from strophanthidin and also make possible the synthesis of C^{14}-labeled biosynthetic intermediates. The synthesis of this 19-hydroxy steroid starting from androstenolone acetate by means of intramolecular lead tetraacetate oxidation recently has been disclosed.[8] The present work deals with an alternate preparation of this substance utilizing partial reduction of steroidal 19-nitriles.

The preparation, in this laboratory, of the requisite 3β,17β-dihydroxyandrost-5-ene-19-nitrile VIII *via* the Barton reaction on steroidal 5,6-chlorohydrins has been described[9,10] and a modification of this method was used in the present study. Treatment of androstenolone acetate with calcium hypochlorite and acetic acid[11] gave the chlorohydrin I, which was allowed to react with nitrosyl chloride in pyridine solution to form the unstable 6-nitrite ester. Photolysis of the nitrite in toluene solution gave the colorless 19-nitroso dimer, which was rearranged in refluxing 2-propanol to afford the oxime II. Removal of the elements of hypochlorous acid from II by the action of zinc in acetic acid[9] gave the Δ^5 derivative III. It was possible to assign the *syn* oxime structure to III on chemical grounds. Acetylation of III gave the diacetate IV, which on melting readily formed VI. This facile



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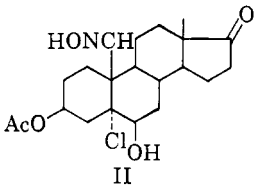

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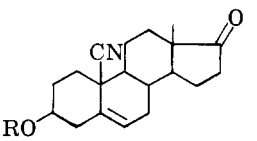
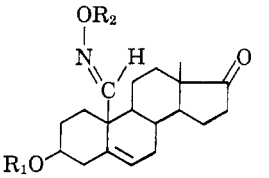
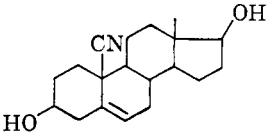


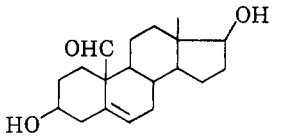
VI. R = Ac
VII. R = H



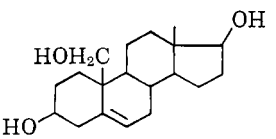
III. R_1 = Ac, R_2 = H
IV. R_1 = Ac, R_2 = Ac
V. R_1 = H, R_2 = H



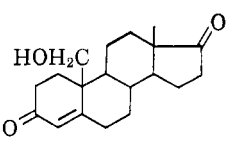
VIII



IX



X



XI

(1) Paper IV, N. Bhacca, M. E. Wolff, and R. Kwok, *J. Am. Chem. Soc.*, **84**, 4976 (1962).

(2) From the Ph.D. thesis of T. Jen, University of California, 1963. This investigation was supported by a PHS research grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. The n.m.r. spectrometer used in this study was provided by a grant (NSF-G 21268) from the National Science Foundation.

(3) J. E. Longchampt, C. Gual, M. Ehrenstein, and R. I. Dorfman, *Endocrinology*, **66**, 416 (1960).

(4) T. Morato, K. Raab, H. J. Brodie, M. Hayano, and R. I. Dorfman, *J. Am. Chem. Soc.*, **84**, 3764 (1962).

(5) M. Ehrenstein and K. Otto, *J. Org. Chem.*, **24**, 2006 (1959), and references cited therein.

(6) H. Hagiwara, *J. Pharm. Soc. Japan*, **80**, 1675 (1960).

(7) H. Hagiwara, *ibid.*, **80**, 1671 (1960).

(8) (a) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962); (b) K. Heusler, J. Kalvoda, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962); (c) also see K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1126 (1962).

(9) R. Kwok, T. Jen, and M. E. Wolff, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 43N; T. Jen and M. E. Wolff, *J. Med. Pharm. Chem.*, **5**, 876 (1962).

(10) R. Gardi and C. Pedrali, *Gazz. chim. ital.* **91**, 1120 (1961), have described an alternate synthesis of compound VIII *via* the Barton reaction.

(11) *Cf.* S. Mori, *J. Chem. Soc.* (Japan), **64**, 981 (1943).

pyrolysis is known[12] to proceed by *cis* elimination of acetic acid from *syn* oxime acetates. In preparative work, it was more convenient to prepare VI by heating III in acetic anhydride. Hydrolysis of VI gave VII,[9] which on reduction with lithium aluminum tri-*t*-butoxyhydride gave the diol VIII.[9,10]

The next stage in the synthesis called for the reduction of the nitrile function in VIII to an aldehyde. Although a number of methods exist which accomplish this conversion, a simple and convenient procedure was found in lithium aluminum hydride reduction. Whereas this reagent normally reduces nitriles to amines, in the present case the reduction was exceedingly slow, and even after 120 hours the major product was the imine. It is likely that this slow, partial reduction results from either poor solubility of the complexed reduction product in the reaction solvent, or the poor accessibility of the imine–metal complex to the hydride species. The 19-imine was not isolated, but was hydrolyzed in acid solution to the aldehyde IX, which was obtained in 60% yield from VIII. Reduction of IX with sodium borohydride in methanol, or lithium aluminum hydride in boiling tetrahydrofuran, gave the triol X.

Brief (ten-minute) Oppenauer oxidation of triol X gave XI in 26% yield, together with trace amounts of what were probably 19-hydroxytestosterone and 19-norandrostenedione. It is likely that the yield of XI could be raised if the reaction were run on a larger scale. The apparent formation of 19-norandrostenedione is probably due to elimination of formaldehyde from XI.

Experimental[13]

5α-Chloro-3β,6β-dihydroxyandrostan-17-one 3-Acetate (I).—A solution of 24.0 g. (0.0655 mole) of 3β-hydroxyandrost-5-en-17-one acetate in 600 ml. of ether was shaken with a suspension of 60.0 g. of calcium hypochlorite, 1800 ml. of water, and 45 ml. of glacial acetic acid for 20 min., during which the insoluble product precipitated. After separation of the aqueous layer, the ether suspension was washed with water and filtered to provide 12.0 g. of the crude chlorohydrin, m.p. 225–230°. Crystallization from ethanol–acetone–water afforded 10.5 g. (38%) of crystals, m.p. 235–238° (inserted at 230°). Evaporation of the ether filtrate and recrystallization of the residue gave an additional 0.5 g. of product, m.p. 233–237° (11.0 g., 40% total yield). The analytical sample, recrystallized from chloroform–methanol, had m.p. 242–244° (inserted at 235°), $[\alpha]^{25}D$ +11° (*c*, 0.4% in $CHCl_3$), μ_{max}^{KBr} 2.88, 5.77, 8.03.

Anal. Calcd. for $C_{21}H_{31}ClO_4$: C, 65.89; H, 8.16; Cl, 9.26. Found: C, 65.44; H, 8.26; Cl, 9.48.

5α-Chloro-3β,6β-dihydroxy-19-oximinoandrostan-17-one 3-Acetate (II).—A solution of 10.0 g. (0.0243 mole) of I in 100 ml. of pyridine was treated with excess nitrosyl chloride at 15–20° and poured into 1 l. of ice–water. The precipitate was filtered, washed with water, and triturated with a small amount of methanol to remove impurities. The residue was filtered and dried at room temperature under vacuum to afford 10.4 g. (97%) of the unstable nitrite ester, m.p. 212–214°, μ_{max}^{KBr} 5.76, 6.05, 8.05, 12.85, 13.00.

A solution of 5.0 g. (0.0121 mole) of the nitrite ester in 200 ml. of toluene was irradiated with an immersed 200-w. high pressure mercury arc equipped with a borosilicate filter. After the nitrite test[14] was negative, 3.0 g. (60%) of the precipitated 19-nitroso product was removed by filtration. One recrystallization from acetone–hexane at room temperature gave a product with double melting points: 145–146° (nitroso compound inserted at 140°) and 241–243° (oxime).

A solution of 6.0 g. (0.0145 mole) of the crude nitroso compound in 300 ml. of 2-propanol was refluxed for 2 hr. The solvent was evaporated and the residue was washed with ether and filtered. Crystallization from acetonitrile provided 5.5 g. (54% over-all) of the oxime, m.p. 242–244° (inserted a t230°). Further recrystallization gave the analytical sample, m.p. 243–245°, $[\alpha]^{25}D$ +18° (*c*, 1% in MeOH), μ_{max}^{KBr} 2.92, 2.98, 5.75, 5.85, 7.85.

Anal. Calcd. for $C_{21}H_{30}ClNO_5$: C, 61.23; H, 7.34. Found: C, 60.96; H, 7.26.

3β-Hydroxy-*syn*-19-oximinoandrost-5-en-17-one Acetate (III). A solution of 5.0 g. (0.0124 mole) of II in 60 ml. of glacial acetic acid (preheated to 85°) was stirred with 10.0 g. of zinc dust at 90–95° for 30 min., cooled to 25°, and filtered. The acetic acid filtrate was poured slowly into 600 ml. of water. After standing for 1 hr., the precipitate was filtered, washed with water, and dried to furnish 3.8 g. of crude product. Crystallization from aqueous ethanol yielded 3.3 g. (77%) of III, m.p. 176–182°. Further recrystallization gave the analytical sample, m.p. 182–185°, $[\alpha]^{25}D$ −89° (*c*, 1% in MeOH), μ_{max}^{KBr} 2.96, 5.80, 8.00.

Anal. Calcd. for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13. Found: C, 70.39; H, 8.05.

***syn*-19-Acetoxyimino-3β-hydroxyandrost-5-en-17-one Acetate (IV).**—A solution of 0.15 g. of the oxime (III), 2 ml. of glacial acetic acid, 1 ml. of acetic anhydride, and 0.02 g. of *p*-toluenesulfonic acid was kept at 27° for 5 hr. and poured into water to furnish 0.15 g. of the crude product, m.p. 136–139°. It was recrystallized from aqueous methanol to give the analytical sample, m.p. 140–141°, $[\alpha]^{25}D$ −142° (*c*, 1% in $CHCl_3$), μ_{max}^{KBr} 5.66, 5.78, 8.03, 8.24

Anal. Calcd. for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78. Found: C, 69.03; H, 7.91.

A sample of the diacetate was melted at a temperature of 142°, and allowed to cool. Recrystallization of the resulting solid from aqueous methanol gave VI, m.p. 189–190°.

3β-Hydroxy-*syn*-19-oximinoandrost-5-en-17-one (V).—A solution of 0.6 g. (0.00167 mole) of (III) in 20 ml. of 5% methanolic potassium hydroxide was kept at 27° for 18 hr. Addition of water, followed by acidification of the solution, furnished 0.5 g. (94%) of V, m.p. 243–245°. Recrystallization from aqueous ethanol gave the analytical sample, m.p. 245–246° (inserted at 235°), $[\alpha]^{25}D$ −95° (*c*, 1% in MeOH), μ_{max}^{KBr} 2.91, 3.00, 5.78.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57. Found: C, 71.69; H, 8.58.

3β-Hydroxy-17-oxoandrost-5-ene-19-nitrile Acetate (VI).—A solution of 1.0 g. (0.00278 mole) of III in 20 ml. of acetic anhydride was refluxed for 2 hr. and poured into 200 ml. of ice water. After 1 hr., the precipitate was filtered and washed with water to furnish 0.9 g. (95%), of the crude material, m.p. 183–186°. Several recrystallizations from aqueous methanol gave the analytical sample, m.p. 189–190°, $[\alpha]^{25}D$ −97° (*c*, 1% in MeOH), μ_{max}^{KBr} 4.50, 5.80, 7.96.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97. Found: C, 73.63; H, 7.80.

3β-Hydroxy-17-oxoandrost-5-ene-19-nitrile (VII).—A solution of 0.80 g. (0.00224 mole) of VI in 40 ml. of methanol was combined with a solution of 4.0 g. of potassium hydroxide in 8 ml. of water and kept at 27° for 18 hr. It was diluted with 100 ml. of water, and the resulting crystalline precipitate was filtered to furnish 0.6 g. of the crude material which was recrystallized from acetone–hexane to yield 0.55 g. (78%) of VII, m.p. 192–194°. The sample after further recrystallization had m.p. 193–195°, undepressed upon admixture with the sample obtained from selective oxidation of VIII.[9] Identical infrared spectra were obtained from both samples.

3β,17β-Dihydroxyandrost-5-ene-19-nitrile. (VIII).—A solution of 6.0 g. (0.02 mole) of VII and 9.0 g. of tri-*t*-butoxy lithium aluminum hydride in 60 ml. of tetrahydrofuran was kept at 0° for 1 hr. There was added 20% hydrochloric acid until a clear solution was obtained. The tetrahydrofuran was evaporated under reduced pressure during which the steroid crystallized from the aqueous solution. It was diluted with water and filtered to give 5.4 g. (90%) of II, m.p. 206–209°, lit. m.p. 209–210°,[10] 208–209°.[9]

(12) D. Ambrose and O. L. Brady, *J. Chem. Soc.*, 1243 (1950).

(13) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley. Optical rotations were obtained in a 0.5-dm. tube with a Rudolph photoelectric polarimeter. N.m.r. spectra were obtained at a field strength of 60 Mc. on samples in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Resonance positions are reported in δ (p.p.m.) values where possible; unresolved humps are described in c.p.s. units (60 Mc.).

(14) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, N. Y., 1960, p. 178.

19-Oxoandrost-5-ene-3β,17β-diol (IX).—A stirred suspension of 5.0 g. (0.0167 mole) of VIII and 2.5 g. of powdered lithium aluminum hydride in 750 ml. of anhydrous tetrahydrofuran was boiled under reflux for 120 hr., chilled in an ice bath, and the excess hydride was decomposed with ethyl acetate. After acidification with 20% hydrochloric acid, the mixture was refluxed for 3 hr. The solution was clarified, if necessary, by addition of acid and was evaporated under reduced pressure until heavy precipitation occurred. Water was added to effect further precipitation. The solid was filtered and washed with water, and, after recrystallization from aqueous ethanol, gave 2.95 g. (60%) of IX, m.p. 184–190°. The analytical sample recrystallized from acetone–hexane had m.p. 185–188°, μ_{max}^{KBr} 3.00 (strong), 3.73 (sh), 5.84 (strong), loss of −CN band at 4.5, $[\alpha]^{25}D$ −247° (*c*, 1% in MeOH).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.80; H, 9.13.

19-Oxoandrost-5-ene-3β,17β-diol Diacetate.—A solution of IX in pyridine and acetic anhydride was kept at 27° for 18 hr. and poured into ice–water. Filtration of the precipitate gave the crude product, which on recrystallization from aqueous ethanol, had m.p. 150–153°, μ_{max}^{KBr} 3.68 (sh), 5.80, 8.03, $[\alpha]^{25}D$ −252° (*c*, 1% in $CHCl_3$), n.m.r.: 0.75 (C(18)-H), 2.00, 2.03 (acetate methyls), 258–293 c.p.s. (broad hump) (3α-H, 17α-H), 345–363 c.p.s. (broad hump) (6–H), 9.75 (19–H).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.02; H, 8.27.

Androst-5-ene-3β,17β,19-triol (X).—A solution of 0.4 g. (0.00145 mole) of IX and 0.4 g. of sodium borohydride in 50 ml. of methanol was kept at 27° for 1 hr. and acidified with 10% hydrochloric acid to pH 1. The clear solution was concentrated under reduced pressure, diluted with water, and filtered to give 0.35 g. (87%) of X, m.p. 229–230°. The analytical sample, recrystallized from acetonitrile, had m.p. 232–233°, μ_{max}^{KBr} 3.03, 9.50, 9.70, $[\alpha]^{25}D$ −48° (*c*, 0.5% in MeOH).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.62; H, 9.81.

The product could also be prepared by reduction of IX with lithium aluminum hydride in boiling tetrahydrofuran solution for 1 hr.

19-Hydroxyandrost-4-ene-3,17-dione (XI).—A mixture of 10 ml. of cyclohexanone and 15 ml. of toluene was heated to boiling and 4 ml. of distillate was collected and discarded. Then 0.35 g. (0.00145 mole) of X was quickly dissolved in the hot anhydrous solution and 1.0 g. of powdered redistilled aluminum isopropoxide was added. The mixture quickly was brought to reflux and maintained there for 10 min. The mixed solvent was removed *in vacuo* at 70–75°, and the residue was taken up in 200 ml. of chloroform which was washed with 1 *N* sulfuric acid (100 ml.) and water and dried over sodium sulfate. Evaporation of the chloroform left a syrupy residue containing some cyclohexanone. The residue was chromatographed on 10.0 g. of neutral alumina; the following eluents were used: (4 × 5 ml.) ether; (4 × 5 ml.) methanol–ether (1%); (4 × 5 ml.) methanol–ether (2%); (4 × 5 ml.) methanol–ether (4%); (4 × 5 ml.) methanol–ether (8%); (4 × 5 ml.) methanol–ether (16%); (4 × 5 ml.) methanol–ether (32%). From the 2% methanol–ether fractions, a trace of what was apparently 19-norandrostenedione was isolated in crystalline form, m.p. 160–167 (reported[15] m.p. 171–172°), λ_{max}^{EtOH} 240 mμ, μ_{max}^{KBr} 5.75, 6.00, 6.18 (absence of —OH band). From the 8% methanol–ether fractions, 0.09 g. (26%) of colorless crystals of XI was isolated, which, after recrystallization from acetone–hexane had m.p. 168–170°, λ_{max}^{EtOH} 243 mμ, log *E* 4.18, $[\alpha]^{25}D$ +195° (*c*, 0.9% in chloroform), μ_{max}^{KBr} 2.95, 5.75, 6.04, 6.18, (reported[16] m.p. 168–170°, λ_{max}^{MeOH} 242 mμ, log *E* 4.18, $[\alpha]^{30}D$ +178 ± 4° (chloroform), $\mu_{max}^{solid\ film}$ 2.94, 5.80, 6.06, 6.17).[17]

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.05; H, 8.65.

From the 16% MeOH–ether fractions there was obtained 0.01 g. of what is probably 19-hydroxytestosterone, m.p. 199–201°, (reported[5] 201–203°), λ_{max}^{EtOH} 243 mμ, μ_{max}^{KBr} 3.05, 6.10, 6.19.

(15) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954).

(16) A. S. Meyer, *Experientia*, **11**, 99 (1955).

(17) Slightly differing physical constants for XI have been recorded in: M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, **21**, 774 (1956); M. Nishikawa and H. Hagiwara, *Chem. Pharm. Bull.*, **6**, 226 (1958); and in ref. 8. A double m.p., 169–172° and 180–182°, has been described in ref .5. We also sometimes have observed the double m.p. 169–172° and 180–182°. Since the double m.p. values are close together, resolidification of the melt probably is influenced very much by the rate of heating, presence of nuclei, etc., and frequently only the lower m.p. is seen.

Solvent Effects in the Menschutkin Reaction

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The rates of the reaction of pyridine with ethyl bromide and ethyl iodide have been determined in benzene, chlorobenzene, bromobenzene, and iodobenzene. The rate constant increase is proportional to the polarizability of the solvent, and is attributed to the interaction of the solvent with the leaving halide in the transition state.

The effect of the solvent upon the rate of the Menschutkin reaction had been shown to be important by many workers.[3–8] The reaction, in which ions are formed from electrically neutral reagents, proceeds more rapidly in solvents of high dielectric constant.

Attempts to correlate the solvent effect with physical properties of the solvent have been made by several authors. Eagle and Warner[8] correlated the reaction rate constant with the dielectric constant in the mixed solvent alcohol–water. Kosower[9] demonstrated that the rate constant for pure alcohol solvents correlate well with *Z*. A plot of log *k vs. Z* gave a linear relationship. Kerr[10] attempted to correlate the dipole moment with the reaction rate constant, but acknowledged that he had achieved only limited success. Grim, Ruf, and Wolf[11] showed that the rate constant varied with dielectric constant for solvents with a large range of *D* (dielectric constant), but could not demonstrate a quantitative relationship. A frequently used relationship between *D* and the rate constant is given in equation 1.[12]

(1) From the senior independent study theses of Wayne Meyers, 1961, and John Harley, 1962.

(2) Support of the URP program of the National Science Foundation is gratefully acknowledged.

(3) N. T. J. Pickles and C. N. Hinshelwood, *J. Chem. Soc.*, 1353 (1936).

(4) J. Norris and S. Prentiss, *J. Am. Chem. Soc.*, **50**, 3042 (1928).

(5) G. Poma and B. Tanzi, *Gazz. chim. ital.*, **42**, 425 (1912).

(6) H. McCombie, H. A. Scarborough, and F. F. Smith, *J. Chem. Soc.*, 102 (1927).

(7) K. J. Laidler, *ibid.*, 1786 (1938).

(8) S. Eagle and J. Warner, *J. Am. Chem. Soc.*, **61**, 488 (1939).

(9) E. M. Kosower, *ibid.*, **80**, 3267 (1958).

(10) R. N. Kerr, *J. Chem. Soc.*, 239 (1929).

(11) H. G. Grimm, H. Ruf, and H. Wolf, *Z. Phys. Chem.*, **13B**, 301 (1931).

(12) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Co., Inc., New York, N. Y., 1941, p. 419.