TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA

Protons[a]	Type	Etioporphyrin II	N-Methyletioporphyrin II	N-Ethyletioporphyrin II
N—Et—CH_3				12.37
N—Et—CH_2				15.16
N—CH_3			14.89	
N—H		13.79	13.12 (broad)	Not observed
R—Et—CH_3	A		8.58	8.61[b]
	B	8.13	8.15	8.14
R—CH_3	A		6.80	6.78
	B		6.50	6.48
	C	6.38	6.34	6.35
R—Et—CH_2	A		6.04	6.06
	B	5.89	5.86	5.88
Methine—H	A		0.03	0.04
	B	−.11	−.01	−.08

[a] See footnote 7. [b] This triplet is distorted somewhat by a weak broad band on the high field side. Although the origin of this band is uncertain, it is probably due, at least in part, to water which has often been observed in this region. This is an extremely low field position for N–H which, to be sure, was not observed elsewhere in the spectrum.

III, respectively. Integration data show a proton ratio of 3:6:3 for types A, B, and C, respectively. In the R—Et—CH_3 spectra integration shows three protons for type A and nine protons for type B. Here the type A triplet can be assigned to ring I and the R—Et—CH_3 groups of the other rings, being essentially equivalent, appear as type B. Assignments of the number of protons to each type of R—Et—CH_2 are not completely clear but the overlapping quartets are roughly equivalent in area. Slight non-equivalence is also found in the methine proton spectra. The α and δ protons can be expected to be essentially equivalent and different from the β and γ protons, which are also equivalent; a pair of peaks, each representing two protons, is indeed observed. These spectra might be compared with those of etioporphyrin II and thereby assign type A to the α and δ protons and type B to the β and γ protons. More likely, however, the nonplanar substituents in ring I result in less effective shielding of the α and δ protons than is the case with the β and γ protons and thereby make an opposite assignment the correct one. Thus for each of the N-alkyl compounds the n.m.r. data are consistent with and provide experimental evidence for a conformation with reasonable deviations from planarity. It should be added, however, that an evaluation of the effect of N-alkylation in the absence of conformational changes has not been attempted.

The ring current field strength appears to be only slightly less in the N-alkyl compounds than in etioporphyrin II. This can be concluded from the similarity in the spectra for protons remaining inplane (the methine protons and R—CH_3 and R—Et protons assigned to ring III) in the N-alkyl compounds compared with etioporphyrin II spectra.[4] If a single large ring current field is considered to be present and the strength of this field to be a measure of the degree of π-electron delocalization and consequently a measure of aromaticity, as has been done with six π-electron systems,[8] annulenes,[9] and porphyrins,[4] it is apparent that the deviations from planarity encountered here do not markedly affect the aromaticity of these compounds. (Metal ions complexed with the central nitrogen atoms and electron-withdrawing peripheral substituents do affect ring current field strengths.[4]) Furthermore these data suggest that appreciable deviations from over-all ring planarity can occur at the expense of little energy. Therefore the possibility of such nonplanarity must be given careful consideration in porphyrins and metalloporphyrins. The possibility of nonplanarity in palladium (II) complexes was suggested previously.[4]

(8) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(9) R. A. Raphael, *Proc. Chem. Soc.*, 97 (1962).

Experimental

The n.m.r. spectra were obtained with a Varian A-60 spectrometer in ~ 0.09 *M* deuteriochloroform solutions with tetramethylsilane as an internal standard. Concentrations were varied without significant effect on the spectra. The data are reported as τ values.

Materials.—Etioporphyrin II was prepared as described previously.[4] N-methyletioporphyrin II and N-ethyletioporphyrin II were kindly supplied by Professor A. H. Corwin.

Acknowledgment.—This work was supported by grants from the U.S. Public Health Service (H-6079 and RG-7274).

Synthesis of 2β-Hydroxy Steroids. II[1,2]

P. NARASIMHA RAO, HAROLD R. GOLLBERG,[3] AND LEONARD R. AXELROD

Department of Biochemistry, Southwest Foundation for Research and Education, San Antonio, Texas

Received August 27, 1962

We have previously described a method for the synthesis of 2β-hydroxylated steroids which resulted in the synthesis of 2β-hydroxytestosterone.[1] The chemistry of the 2β-hydroxyl group is interesting since, from a thermodynamic standpoint, the 2β-configuration (axial) would be expected to be less stable when compared with the 2α-configuration (equatorial) and thus would tend to isomerize to the more stable 2α-form. In agreement with this, synthetic studies have shown that prolonged treatment of 2β-hydroxylated-Δ^4-3-keto steroids with potassium acetate in acetic acid does isomerize the 2β-function to the stable 2α-form.[4] However, since our communication[1] still other 2β-hydroxylated steroids have been obtained from microbiological incubations.[5] In view of this increased interest in

(1) P. N. Rao and L. R. Axelrod, *J. Am. Chem. Soc.*, **82**, 2830 (1960), should be considered as Part I of the series.

(2) This work was supported by a grant (A-3270) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

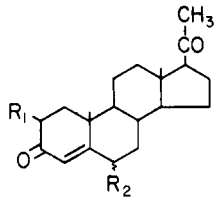
(3) This paper represents part of a thesis submitted by H. R. Gollberg to the Graduate School of St. Mary's University, San Antonio, Tex., in partial fulfillment of the requirements for the degree of Master of Science.

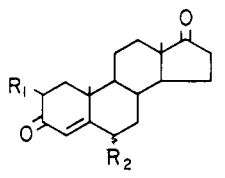
(4) (a) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953); (b) R. L. Clark, K. Dobriner, A. Mooradian, and C. M. Martini, *ibid.*, **77**, 661 (1955).

(5) (a) M. Shirasaka, M. Tsuruta, and M. Nakamura, *Bull. Agr. Chem. Soc. Japan*, **22**, 273 (1958); (b) M. Shirasaka, R. Takasaki, R. Hayashi, and M. Tsuruta, *ibid.*, **23**, 245 (1959); (c) K. Tanabe, R. Takasaki, R. Hayashi, and M. Shirasaka, *Chem. Pharm. Bull.* (Tokyo), **1**, 804 (1959); (d) M. Shirasaka and M. Tsuruta, *Arch. Biochem. Biophys.*, **87**, 338 (1960); (e) L. L. Smith, H. Mendelsohn, T. Foell, and J. J. Goodman, *J. Org. Chem.*, **26**, 2859 (1961).

2β-hydroxy steroids we have now extended our earlier method to synthesize 2β-hydroxyprogesterone (IV) and 2β-hydroxy-4-androstene-3,17-dione (IX). This appears to be a general synthetic route to the preparation of 2β-hydroxy steroids.

Progesterone and 4-androstene-3,17-dione were brominated with N-bromosuccinamide in carbon tetrachloride essentially as described in the literature to give respectively 6-bromoprogesterone (I)[4a] and 6-bromo-4-androstene-3,17-dione (VI).[6] Rearrangement of the 6-bromo-Δ^4-3-ketones by refluxing with potassium acetate in glacial acetic acid for twelve minutes gave a mixture of 2α- and 2β-acetates. These conditions have been shown to produce optimum yields of the 2β-isomer.[1]





I R_1 = H; R_2 = Br
II R_1 = α -OAc; R_2 = H
III R_1 = β -OAc; R_2 = H
IV R_1 = β -OH; R_2 = H
V R_1 = α -OH; R_2 = H

VI R_1 = H; R_2 = Br
VII R_1 = α -OAc; R_2 = H
VIII R_1 = β -OAc; R_2 = H
IX R_1 = β -OH; R_2 = H
X R_1 = α -OH; R_2 = H

In the progesterone series, the mixture of 2-acetates was fractionally crystallized to yield the known 2α-acetoxyprogesterone (II)[4a] and 2β-acetoxyprogesterone (III), both in 20–25% yield. Similar fractionation of the 2-acetates of 4-androstene-3,17-dione gave the known 2α-acetoxy-4-androstene-3,17-dione (VII)[7] in 15–20% yield and 2β-acetoxy-4-androstene-3,17-dione (VII) in 25–30% yield.

The 2β-acetates II and VIII were separately hydrolyzed under controlled conditions with one equivalent of 1 *N* methanolic potassium hydroxide at room temperature to give respectively 2β-hydroxyprogesterone (IV) and 2β-hydroxy-4-androstene-3,17-dione (IX) *without isomerization to the 2α-form*. Similar hydrolysis of the 2α-acetates II and VII afforded the known 2α-hydroxyprogesterone (V)[4a] and 2α-hydroxy-4-androstene-3,17-dione (X). The structures of the 2β-esters III and VIII as well as the 2β-hydroxy compounds IV and IX are based on their elemental analyses, infrared and ultraviolet spectral data, and the following evidences. It has been shown that 2β-hydroxy-Δ^4-3-keto steroids exhibit strong negative molecular rotatory differences (ΔMD), with the values varying from −519 to −768.[1,5e] In keeping with this, the ΔMD values observed for IV and IX are −748 and −648, respectively. Refluxing either the 2β-acetate (III) or the 2β-hydroxy compound (IV) for four hours with potassium acetate in glacial acetic acid resulted exclusively in the corresponding 2α-compounds. Their identities were established by mixture melting point determinations and by a comparison of their infrared spectra with authentic samples. Further, acetylation of IV with pyridine–acetic anhydride gave the back the 2β-acetate (III) thus proving that no inversion of the 2β-configuration occurred during the hydrolysis.

It has been noted that in mild alkaline solutions 2β- and 2α-hydroxyls attain equilibrium with one another; therefore, the same alkaline ultraviolet spectrum must result for both configurations of a given pair of 2-hydroxy-Δ^4-3-keto steroids.[8] Accordingly, treatment of IV, V, IX, and X with alkaline ethanol solution resulted in ultraviolet curves identical to those obtained by Meyer.[9] Consequently, IV and IX must contain the 2β-configuration. We have also observed that 2β-hydroxy steroids absorb at slightly higher wave lengths (bathochromic shift) in the ultraviolet region when compared with the 2α-hydroxy compound. Thus the ultraviolet absorption for the 2β-hydroxy compounds IV and SX is 242 mμ whereas for the 2α-hydroxy compounds V and X it is 240 mμ. Ultraviolet curves were also taken of the 2-hydroxy compounds in concentrated sulfuric acid according to Zaffaroni.[10] The 2α-hydroxy compounds V and X[11] had absorptions at 298 and 346 mμ, of which the peak at 298 mμ was stronger. Similar curves taken of the 2β-hydroxy compounds IV and IX also showed absorptions at 298 and 347 mμ. However, in this case, the absorption intensities were reversed with the 347-mμ peak having the stronger absorption.

Experimental[12]

6-Bromoprogesterone (I).—Progesterone (10 g.) reacted as described in the literature[4a] to yield 6-bromoprogesterone (I, 6.85 g., 48%), m.p. 137–138° dec. One further crystallization raised the melting point to 138.5–141° dec. (lit.,[4a] anal. sample m.p. 143–145° dec.). This product was used without further purification for the next reaction.

6-Bromo-4-androstene-3,17-dione (VI).—4-Androstene-3,17-dione (4.072 g.) was brominated also as described in the literature[6] to give 6-bromo-4-androstene-3,17-dione (VI, 3.694 g., 58%), m.p. 170° dec. which was used without further purification for the next reaction (lit.,[6] analytical sample m.p. 175–177° dec.).

2α-Acetoxyprogesterone (II).—A mixture of 6-bromoprogesterone (I, 8.38 g.), anhydrous potassium acetate (21 g.), and glacial acetic acid (110 ml.) was stirred and boiled under reflux for 12 min., cooled, and poured into ice–water. The precipitated material was filtered, washed thoroughly with cold water, collected, and crystallized from ethyl acetate–petroleum ether to give 2α-acetoxyprogesterone (II, 1.24 g., 22%) which melted at 182–190°. Further crystallization from the same solvent afforded the analytical product, m.p. 196.5–197.5°, $[\alpha]_D$ +165° (*c* 1.03), λ_{max} 240 mμ (ε 17,383), ν_{max} 1737 cm.$^{-1}$ (acetate carbonyl), 1682 cm.$^{-1}$ (20-ketone), 1673 cm.$^{-1}$ (conjugated carbonyl), 1605 cm.$^{-1}$ (C=C of the conjugated ketone), 1213 and 1232 cm.$^{-1}$ (acetoxy) (lit.,[4a] m.p. 197–198°, $[\alpha]_D$ +164°).

Anal. Calcd. for $C_{23}H_{32}O_4$ (372.5): C, 74.16; H, 8.66. Found: C, 73.87; H, 8.65.

2β-Acetoxyprogesterone (III).—The first two mother liquors from the above crystallization were combined and further fractionated from acetone–petroleum ether to give 2β-acetoxyprogesterone (III, 1.21 g., 22%), m.p. 120–125°. Three additional crystallizations from ethyl acetate–petroleum ether gave the

(6) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(7) G. Rosenkranz, O. Mancera, and F. Sondheimer, *ibid.*, **77**, 145 (1955).

(8) H. L. Herzog, M. J. Gentles, E. B. Hershberg, F. Carvajal, D. Sutter, W. Charney, and C. P. Schaffner, *ibid.*, **79**, 3921 (1957).

(9) A. S. Meyer, *J. Org. Chem.*, **20**, 1240 (1955).

(10) A. Zaffaroni, *J. Am. Chem. Soc.*, **72**, 3828 (1950).

(11) J. S. Baran, *ibid.*, **80**, 1687 (1958).

(12) All melting points were determined on samples dried under high vacuum at 60° for 24 hr. and are uncorrected. The ultraviolet absorption spectra were determined in methanol with a Cary recording spectrophotometer (Model 11 MS). The infrared absorption spectra were determined in a KBr disk on a Perkin-Elmer (Model 21) spectrophotometer. All optical rotations were measured in chloroform solution at 25 ± 3° on a Zeiss-Winkel polarimeter. All microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

analytical sample, m.p. 126–127°, $[\alpha]_D$ 32° (*c* 0.86), λ_{max} 242 mμ (ε 16,092), ν_{max} 1740 cm.$^{-1}$ (acetate carbonyl), 1693 cm.$^{-1}$ (20-ketone), 1673 cm.$^{-1}$ (conjugated carbonyl), 1615 cm.$^{-1}$ (C=C of the conjugated carbonyl), and 1210 cm.$^{-1}$ (acetoxy).

Anal. Calcd. for $C_{23}H_{32}O_4$ (372.5): C, 74.16; H, 8.66. Found: C, 73.68; H, 8.83.

2α-Acetoxy-4-androstene-3,17-dione (VII).—The mixed acetates obtained by similar acetolysis of 6-bromo-4-androstene-3,17-dione (IV, 4.652 g.) were fractionally crystallized from methanol to yield 2α-acetoxy-4-androstene-3,17-dione (VII, 450 mg., 15%), m.p. 210–211.5°, $(\alpha)_D$ +138° (*c* 0.66), λ_{max} 240 mμ (ε 15,262), ν_{max} 1733 cm.$^{-1}$ (fused five-membered ring ketone and acetate carbonyl), 1680 cm.$^{-1}$ (conjugated carbonyl), 1605 cm.$^{-1}$ (C=C of the conjugated carbonyl), 1217 and 1233 cm.$^{-1}$ (acetoxy) (lit.,[8] m.p. 209–210°, $[\alpha]_D$ +146).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.4): C, 73.23; H, 8.19. Found: C, 73.20; H, 8.19.

2β-Acetoxy-4-androstene-3,17-dione (VIII).—Further fractionation of the above mother liquors from dilute methanol gave 2β-acetoxy-4-androstene-3,17-dione (VIII, 865 mg., 25%), m.p. 156–158°, $[\alpha]_D$ −8.9° (*c* 1.03), λ_{max} 242 mμ (ε 14,472), ν_{max} 1756 and 1745 cm.$^{-1}$ (acetate carbonyl and 17-ketone), 1688 cm.$^{-1}$ (conjugated carbonyl), 1620 cm.$^{-1}$. (C=C of the conjugated carbonyl), and 1225 cm.$^{-1}$ (acetoxy) (lit.,[13] m.p. 157–158°, $[\alpha]_D$ −5.9°).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.4): C, 73.23; H, 8.19. Found: C, 73.12; H, 8.11.

Saponification of 2-Acetoxy Compounds. 2α-Hydroxyprogesterone (V).—2α-Acetoxyprogesterone (II, 600 mg.) was dissolved in methanol (18.3 ml.) and dry nitrogen was bubbled through the solution. Then exactly one equivalent of methanolic potassium hydroxide (1.4 ml. of a 1 *N* solution) was added and the solution was stirred at 30° for *4 min.* Then methanol (10 ml.) containing 2 drops of water was added and stirring continued for an additional *4 min.* (total time 8 min. at 30°). The solution was then acidified with 1 *N* acetic acid (2 ml.), concentrated to one-third volume, diluted with water, chilled in an icebox, and filtered to give 2α-hydroxyprogesterone (V) which was crystallized from acetone–petroleum ether, m.p. 184–187°, $[\alpha]_D$ +188° *c* 1.09), λ_{max} 240 mμ (ε 15,474), ν_{max} 3560 cm.$^{-1}$ (hydroxyl), 1695 and 1675 cm.$^{-1}$ (20- and 3-ketones), and 1615 cm.$^{-1}$ (C=C of the conjugated carbonyl) (lit.,[4a] m.p. 182–183° $[\alpha]_D$ +199°).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.5): C, 76.32; H, 9.15. Found: C, 76.16; H, 9.52.

2β-Hydroxyprogesterone (IV).—Saponification of the 2β-acetate (III, 607 mg.) exactly as described above furnished 2α-hydroxyprogesterone (IV) in quantitative yield, m.p. 191–193°, $(\alpha)_D$ −51° (*c* 1.02), λ_{max} 242 mμ (ε 15,728), ν_{max} 3565 cm.$^{-1}$ (hydroxyl), 1695 and 1675 cm.$^{-1}$ (20- and 3-ketones), and 1625 cm.$^{-1}$ (C=C of the conjugated carbonyl).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.5): C, 76.32; H, 9.15. Found: C, 76.46; H, 9.25.

2α-Hydroxy-4-androstene-3,17-dione (X).—Controlled hydrolysis of the 2α-acetate (VII, 285 mg.) by the above-described procedure gave 2α-hydroxy-4-androstene-3,17-dione (X), crystallized from acetone–petroleum ether, m.p. 160–161°, $[\alpha]_D$ +204° (*c* 1.01), λ_{max} 240 mμ (ε 15,266), ν_{max} 3430 cm.$^{-1}$ (hydroxyl), 1738 cm.$^{-1}$ (five-membered ring ketone), 1665 cm.$^{-1}$ (conjugated carbonyl), and 1600 cm.$^{-1}$ (C=C of the conjugated carbonyl).[14]

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.4): C, 75.46; H, 8.67. Found: C, 74.77; H, 8.33.

2β-Hydroxy-4-androstene-3,17-dione (IX).—Similar hydrolysis of the 2β-acetate (VIII, 533 mg.) afforded 2β-hydroxy-4-androstene-3,17-dione (IX), which crystallized from acetone–petroleum ether, m.p. 144–147°, $[\alpha]_D$ −32° (*c* 0.99), λ_{max} 242 mμ (ε 14,830), ν_{max} 3480 cm.$^{-1}$ (hydroxyl), 1735 cm.$^{-1}$ (five-membered ring ketone), 1675 cm.$^{-1}$ (conjugated carbonyl), and 1610 cm.$^{-1}$ (C=C of the conjugated carbonyl) (lit.,[13] m.p. 143–145°, $[\alpha]_D$ −36.8°).

Anal. Calcd. for $C_{19}H_{26}O_3$ (302.4): C, 75.46; H, 8.67. Found: C, 74.75; H, 8.60.

(13) R. M. Dodson, A. H. Goldkamp, and R. O. Muir, *J. Am. Chem. Soc.*, **79**, 3921 (1957); **82**, 4026 (1960).

(14) Compound X has been described as "known" by several authors.[8,11] However, a thorough search of the literature indicated that the physical constants of this compound have never been described. Therefore, this note appears to be the first to list the physical constants for 2α-hydroxy-4-androstene-3,17-dione (X).

The Synthesis of Some Quaternary Aminophosphonium Salts Containing Siloxyl, Alkenyl, and Arylalkyl Groups

NATHAN L. SMITH AND HARRY H. SISLER

Department of Chemistry, University of Florida, Gainesville, Florida

Received September 7, 1961

We have previously reported that *t*-butylaminodiphenylphosphine reacts with benzyl chloride and with bis(chloroethyl) ether to produce quaternary aminophosphonium chlorides.[1] We now have extended this procedure to include the reactions of 1,4-dibromobutene-2, bis(bromomethyl)tetramethyldisiloxane, *p*-fluorobenzyl chloride, and 9,10-bis(chloromethyl)anthracene with *t*-butylaminodiphenylphosphine to produce the corresponding *t*-butylaminophosphonium salts. Further, we have converted *P*-(9,10-anthracenedimethyl)-bis[*t*-butylaminodiphenylphosphonium chloride] to the corresponding hexafluorophosphate and picrate. *t*-Butylaminobenzyldiphenylphosphonium chloride was converted to the hexafluorophosphate, picrate, and borohydride. *P*-(Hexamethyldisiloxane)bis[(*t*-butylamino)diphenylphosphonium bromide], which was isolated only in the crude state, was characterized by conversion to the picrate. During the course of these experiments it was found that *t*-butylaminodiphenylphosphine reacts with ethanolic solutions of mercuric chloride and silver nitrate, respectively, to give the compounds $t\text{-}C_4H_9NHP(C_6H_5)_2 \cdot HgCl_2$ and $t\text{-}C_4H_9NHP(C_6H_5)_2 \cdot AgNO_3$.

Experimental[2]

Materials.—*t*-Butylaminodiphenylphosphine was prepared by the previously reported procedure.[3] The previously reported procedure[1] for the synthesis of *t*-butylaminobenzyldiphenylphosphonium chloride was modified by using toluene instead of benzene as solvent and by reducing the reflux time to 10 hr. By this means the yield was improved to 97%. 9,10-Chloromethylanthracene was prepared by the method of Miller, Amidon, and Tawney.[4] *p*-Fluorobenzyl chloride was obtained from Beacon Chemical Industries, Inc. Potassium borohydride was obtained from Callery Chemical Company. Bis(bromomethyl)tetramethyldisiloxane and 1,4-dibromobutene-2 were purchased from Peninsular ChemResearch, Inc. All compounds obtained from commercial sources were used as received.

Reaction of *t*-Butylaminodiphenylphosphine with RCH_2X Compounds.—The reaction of *t*-butylaminodiphenylphosphine with 9,10-chloromethylanthracene is described to illustrate the procedure used. A mixture of 5.2 g. (0.02 mole) of *t*-butylaminodiphenylphosphine and 2.8 g. (0.01 mole) of 9,10-bis(chloromethyl)anthracene in 35 ml. of dimethylformamide was stirred at reflux for 5 hr. The reaction mixture was cooled and then filtered. The yellow micro-crystalline solid was thoroughly washed with benzene and ethyl ether, and dried. The product weighed 6.5 g. (82% yield) and melted with decomposition at 279°.

This general procedure also was used for the preparation of *P*-(*p*-fluorobenzyl)(*t*-butylamino)diphenylphosphonium chloride, *P*-(1,4 - butene - 2)bis[(*t* - butylamino)diphenylphosphonium bromide], and *P*-(hexamethyldisiloxane)bis[(*t*-butylamino)di-

(1) H. H. Sisler and N. L. Smith, *J. Org. Chem.*, **26**, 4733 (1961).

(2) Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points and boiling points were uncorrected.

(3) H. H. Sisler and N. L. Smith, *J. Org. Chem.*, **26**, 611 (1961).

(4) M. W. Miller, R. W. Amidon, and P. O. Tawney, *J. Am. Chem. Soc.*, **77**, 2845 (1955). See also A. E. Kretov and M. R. Rovenskii, *J. Gen. Chem. USSR*, (Eng. Transl.), **30**, 667 (1960), for modifications.