Acknowledgments.—We thank Drs. C. C. Christman and E. Buhle, Development Division, Wyeth Laboratories Inc., for providing compound I, Dr. R. A. Edgren, and his associates of the Endocrinological Department, Wyeth Laboratories Inc., for obtaining and discussing the biological data, and Dr. K. Mislow and Mr. M. Axelrod (Princeton University) for the optical rotatory dispersion data.

8-Aza Steroids. IV.[1] 8-Aza-19-norprogestogens

Richard E. Brown, David M. Lustgarten, R. John Stanaback, and Robert I. Meltzer

Warner-Lambert Research Institute, Morris Plains, New Jersey

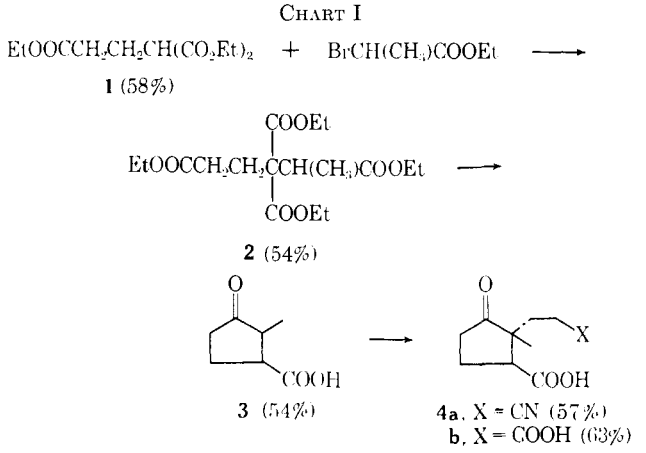
Received October 31, 1966
Revised Manuscript Received January 25, 1967

The synthesis of 8-aza-19-norprogesterone, 17α-hydroxy-8-aza-19-norprogesterone, and several isomeric products has been accomplished by application of the previously described sequence. Spectral data are described on the basis of which the stereochemical assignments are made. The products were essentially inactive as progestogens.

Previous papers[2] in this series have described the synthetic route to the 8-aza steroid nucleus developed in these laboratories, and application of the method to the synthesis of 8-azaestrogens and 8-aza-19-norandrogens. The present communication deals with the preparation of the 8-aza analog of 19-norprogesterone and related products. Subsequent publications will be concerned with applications of the method to the preparation of the 8-aza analogs of other 19-nor steroid hormones.

Preparation of the known[3] 2-methyl-2-β-carboxyethylcyclopentanone-3-carboxylic acid (**4b**) was carried out by modifications of published procedures as summarized in Chart I. Triethyl 2-carboxyglutarate[4] (**1**)

Chart I



was prepared by adaptation of the method of Floyd and Miller.[5] This was alkylated with ethyl α-bromopropionate to give the known[6] **2**, which was converted to acid **3**[6,7] by the procedure of Shimyakin, *et al.*[6]

Michael addition of **3** to ethyl acrylate failed under a variety of conditions. Addition of acrylonitrile, however, did take place exothermally under strongly basic conditions and led to adduct **4a**. That addition to the cyanoethyl group occurred at the more substituted carbon atom, as desired, was established by the unsplit methyl nmr signal at 1.02 ppm. Hydrolysis to the required ketodicarboxylic acid **4b** was accomplished with HCl.[3] On the basis of thermodynamic considerations, the methyl and secondary carboxyl groups in this product were assumed in previous work[3] to have a *cis* relationship to each other. Some additional evidence relative to the configuration of **4b** was obtained in the present work (see ref 8).

Condensation of **4b** with *m*-methoxyphenethylamine[2b] was carried out by both of the previously described[1,2] procedures. Direct condensation in refluxing xylene afforded the unsaturated lactam **5** in 77% yield. Catalytic reduction of **5** proceeded stereospecifically to afford a single saturated lactam **7** (Chart II[9]). This was also obtained as the sole product of reductive condensation of the amine and **4b**. Proof of the *trans* fusion of the pyrindone rings in **7** was obtained in later work (see ref 10).

Lactams **5** and **7** were treated in succession with $POCl_3$, ethanol, and dilute base to give the unsaturated esters **6** and **8**, respectively, in high yields, the reactions

(1) Part III: R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966).

(2) (a) R. I. Meltzer, D. M. Lustgarten, R. J. Stanaback, and R. E. Brown, *Tetrahedron Letters*, 1581 (1963); (b) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, M. W. Osborne, and R. I. Meltzer, *J. Med. Chem.*, **7**, 232 (1964).

(3) P. C. Dutta, *J. Indian Chem. Soc.*, **31**, 875 (1954).

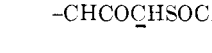
(4) L. Ruzicka, A. de Almeida, and A. Brack, *Helv. Chim. Acta*, **17**, 183 (1934).

(5) D. E. Floyd and S. E. Miller, *J. Org. Chem.*, **16**, 882 (1951).

(6) M. M. Shemyakin, L. A. Shchukina, E. I. Vinogradova, M. N. Kolosov, R. G. Vdovina, M. G. Karapetyan, V. Ya. Rodionov, G. A. Ravdel, Yu. B. Shvetsov, E. M. Bamdas, E. S. Chaman, K. M. Ermolaev, and E. P. Semkin, *Zh. Obshch. Khim.*, **27**, 742 (1957).

(7) K. Toki, *Bull. Chem. Soc. Japan*, **30**, 450 (1957).

(8) Some additional evidence on the configuration of **4b** may now be derived in the following way. In **12a**, the acetyl group is β and therefore *cis* to the angular methyl. Since no change in configuration during acid-catalyzed hydrolysis would be expected, ketone **10a** (as obtained by the Corey procedure) must also have the acetyl group *cis* to the methyl. Likewise, the Corey procedure probably proceeds without change in configuration (the stable anion

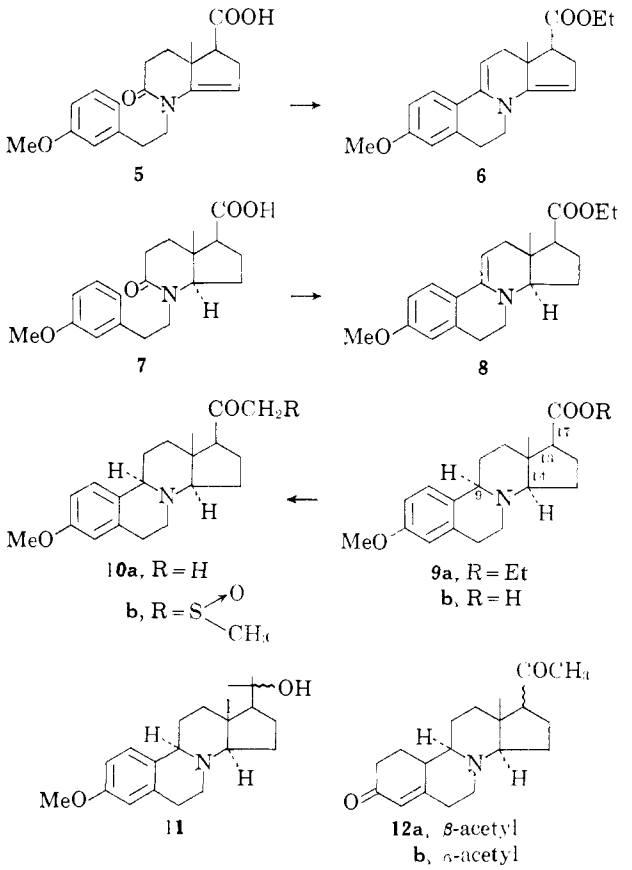


presumably preventing abstraction of the proton at C-17), leading to the conclusion that the COOR group in **9** is also *cis* to the CH_3. The same must then be true in the precursor **4b**.

(9) All compounds described in this paper were obtained as *dl* pairs. For convenience, the structures depict only one of the optical antipodes.

(10) The C–D *trans* ring junction in the saturated lactam **7** was established in the following way. When sulfoxide **10b** was treated with acetic acid followed by Raney Ni, a minor product isolated from the reaction was identified as hydroxy ketone **15c**. Since the ring junction of **15c** was established unequivocally as *trans* by its preparation from keto lactam **13a** of known *trans* ring junction, it follows that sulfoxide **10b**, its precursors **7–9**, and its transformation products **11** and **12** must also have the C–D *trans* ring junction. This work will be discussed in detail in a subsequent publication.

CHART II[a]



proceeding through acid chloride intermediates. Both **6** and **8** were reduced either catalytically or chemically (KBH_4 in ethanol) to a single saturated base, **9a**. Assignment of the α configuration to the hydrogen thus introduced was based on the presence of Bohlmann bands[11] in the infrared and an upfield nmr signal[12] (no signal downfield from 3.2 ppm) for this proton, thereby establishing its axial nature. With the *trans*-fused pyridine rings, this is possible for an all-chair conformation only if the hydrogen at position 9 and the angular methyl group are *anti*[13] to each other.

Introduction of the 2-carbon pregnane side chain was initially accomplished by application of the Arens–van Dorp procedure.[14] Hydrolysis of **9a** with dilute HCl gave amino acid **9b**, isolated as its hydrochloride. Treatment of the hydrochloride of **9b** with ethereal methyllithium in tetrahydrofuran (THF) gave a crystalline product for which the analytical and infrared data were consistent with ketone structure **10a**, but which was subsequently shown to be impure.[15] Conversion of this material to its ethylene ketal followed by Birch reduction and acid hydrolysis furnished the two C-17 epimers of 8-aza-19-norprogesterone (**12a** and **12b**), separated by chromatography on alumina.

An alternate route which furnished **12a** in better yield utilized Corey's procedure[17] for ketone synthesis. To this end, ester **9a** was allowed to react with the anion of dimethyl sulfoxide (DMSO), to give the β-keto sulfoxide **10b**. Reductive cleavage of this product with aluminum amalgam proceeded smoothly according to the published procedure to furnish a single isomer of ketone **10a**. Conversion of this to its ethylene ketal followed by Birch reduction and acid hydrolysis readily gave 8-aza-19-norprogesterone (**12a**), uncontaminated by its epimer **12b**.

Assignments of the configurations of the two epimers of 8-aza-19-norprogesterone (**12a** and **12b**) were based on a comparison of the chemical shifts of the angular methyl groups of the two epimers. It has been well established in carboxylic steroids[16] that the 17α-acetyl group shifts the methyl signal to lower field by a factor of *ca.* 0.28 ppm relative to that of the 17β-acetyl epimer. In the case of the two epimers in question, **12a** exhibited the methyl signal at 0.82 ppm, whereas **12b** resonated at 1.12 ppm. Thus the nmr data supported the conclusion that **12a**, the major product of the equilibrium mixture, had a 17β-acetyl group (the expected more stable pseudo-equatorial conformation).[5] Assignment of the (more stable) β configuration to the hydrogen introduced at the newly formed center of asymmetry at C-10 in **12a** and **12b** (and in **16a** and **16b**, see below) is based on well-established precedent in the acid treatment of Birch reduction products from various aromatic steroids.[18]

Experiments designed to introduce the 17α-hydroxyl group into **10a** or **12a** by methods standard to steroid chemistry were in progress when the following alternate sequence, summarized in Chart III, was developed. The keto lactam **13a**,[1] of known *trans* ring junction, was converted to cyanohydrin **13b** by the usual procedure[18] which affords epimeric mixtures of cyanohydrins with carbocylic steroids. Although only one of the expected epimeric cyanohydrins was isolated, treatment of the mother liquors with base resulted in recovery of the remainder of the material as starting ketone, indicating the probability that both cyanohydrins had been formed. The stereochemistry of this product became evident later in the sequence as described below.

Acid hydrolysis of the cyanohydrin lactam afforded mixtures of ill-defined products; however, cyclization with $POCl_3$ in benzene proceeded in high yield to give

(11) (a) F. Bohlmann, *Ber.*, **91**, 2157 (1958); (b) W. E. Rosen, *Tetrahedron Letters*, 481 (1961).

(12) M. Uskokovic, H. Broleccr, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

(13) In this series of papers, the terms *syn* and *anti* refer to the relationship of the C-9 hydrogen and the C-13 methyl group. The question of the configuration of the C-9 hydrogen in the 8-aza steroid nucleus was discussed in detail in part III[1] of this series and the reader is referred to this work in connection with the stereochemistry of **9a**.

(14) (a) H. Gilman and P. R. Van Ess, *J. Am. Chem. Soc.*, **55**, 1258 (1933); (b) J. F. Arens and D. A. van Dorp, *Nature*, **157**, 190 (1946).

(15) It would be expected that both C-17 epimers would be present in this product by equilibration through the common enol in the strongly basic medium encountered during work-up. The nmr spectrum of the material indicated that both C-17 epimers were indeed present but also indicated the presence of at least one by-product. Thus the expected[16] two methyl signals, (integration ratio *ca.* 3:2) appeared at 0.78 and 1.02 ppm, respectively, consistent with the presence of both C-17 epimers. Two additional singlets of equal intensity at 1.22 and 1.32 ppm were not consistent with structure **10a**. No attempt was made to isolate the material responsible for these signals, but it is suggested that they are due to the presence of carbinol **11**, formed by over-reaction with methyllithium. Since only two extraneous signals are present, which are equal in intensity, the indication is that a single isomer of **11** is present (with the side chain in the β orientation) in which the adjacent asymmetric carbon at C-17 renders the carbinol methyl groups, shifted downfield due to proximity to the alcohol, magnetically nonequivalent.

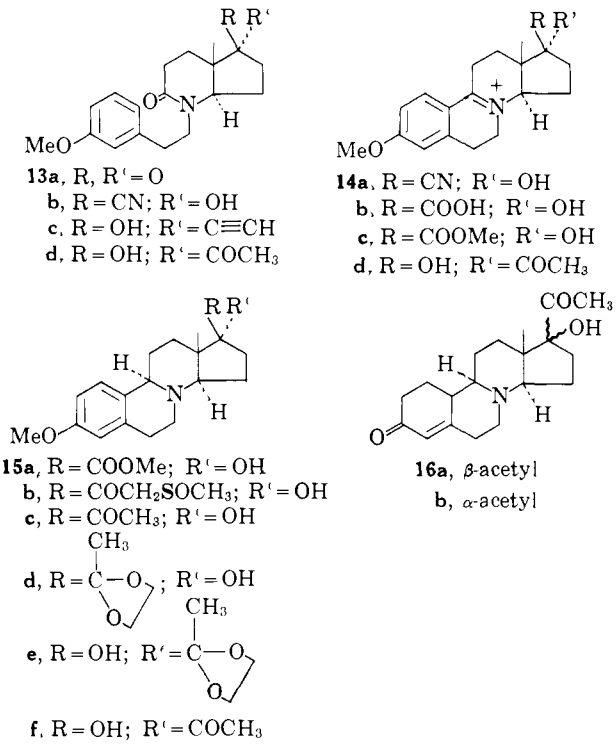
(16) (a) M. B. Rubin and E. C. Blossey, *J. Org. Chem.*, **29**, 1932 (1964); (b) J. D. Cocker, H. B. Hanbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965); (c) M. B. Rubin, *Steroids*, **2**, 561 (1963).

(17) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

(18) C. Djerassi, A. E. Lipmann, and J. Grossman, *ibid.*, **78**, 2479 (1956).

(19) H. Heusser, P. Th. Herzig, A. Furst, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

Chart III[9]



quaternary salt **14a**. Acid hydrolysis at this stage proceeded cleanly to give the hydroxy acid **14b**, which was directly esterified to **14c**. Reduction of **14c** by KBH_4 in ethanol gave a single isomer of the saturated hydroxy ester **15a**. Assignment of the 9α-configuration to **15a** was made, as described for **9a**, on the basis of spectral data (presence of Bohlmann bands[11] in the infrared and absence of a downfield nmr signal for the angular hydrogen).[12] Treatment of the ester with the anion of DMSO[16] gave β-ketosulfoxide **15b**. This product underwent cleavage with aluminum amalgam to give ketone **15c**[10] in quantitative yield. The ketone was converted to its ethylene ketal, **15d**, which was subjected to Birch reduction and acid hydrolysis to give the target compound, 17α-hydroxy-8-aza-19-norprogesterone (**16a**).

Reaction of *trans* ketolactam **13a**[1] with ethynylmagnesium bromide gave adduct **13c**. Hydration of the ethynyl alcohol was accomplished by suitable modification of the literature procedure[20] and gave ketone **13d**. Cyclization of **13d** with $POCl_3$ in benzene gave ketone **14d** which was converted to its ethylene ketal and reduced (KBH_4) to give ketal **15e**. Hydrolysis of this gave a ketone (**15f**) different from that (**15c**) obtained *via* the cyanohydrin. When ketal **15e** was subjected to Birch reduction and acid hydrolysis, a base **16b**, epimeric to **16a**, was obtained. That this product was epimeric at position 17, and not at position 9 was clear from the presence of Bohlmann bands[11] and the upfield nmr signal[12] due to the axial angular protons in both isomers of **17**.

Configurational assignments to **16a** and **16b** were based on nmr data and method of synthesis. It is well known[21] that addition of acetylene to 17-keto steroids gives almost exclusively the epimer of the ethynyl alcohol in which the hydroxy group is β. Extension of this generalization to keto lactam **13a** would lead to the prediction that **16b**, prepared from the ethynyl adduct **13c**, has the pseudo-equatorial, or β-hydroxyl group. Epimer **16a** prepared through cyanohydrin **13b**, would then have the 17α-hydroxy configuration of natural steroids. Comparison of the chemical shifts of the angular methyl groups[16] of the two epimers, as described for **12a** and **12b**, confirmed that this was indeed the case. Thus the methyl signal of the product from the cyanohydrin (**16a**) resonated at 0.90 ppm, whereas in the epimeric product from the ethynyl derivative (**16b**), it resonated at 1.14 ppm, consistent with the prediction made on the basis of the known direction of addition of acetylene. Configurational assignments to **16a** and **16b** were accordingly made as shown.[22]

Biological Tests.—When tested for progestational activity by the method of Clauberg[25] as modified by McPhail,[26] **16a** and **16b** were inactive at doses of 5 and 25 mg/kg/day sc, respectively (total doses 25 and 125 mg). Product **12a** likewise was inactive at a dose of 5 mg/kg/day; however, at 50 mg/kg/day, this compound gave a full progestational response.

Product **12a**, as the most interesting of the series, was selected for further studies. When given subcutaneously at doses up to 4 mg/animal/day with or without the concomitant administration of 17β-estradiol (1 μg/animal/day sc), it failed to maintain pregnancy[27] in rats spayed on the 9th day of pregnancy. Doses above 4 mg/animal/day were toxic. Product **12a** also did not exert progesterone-like activity *in vitro* on rat uterine motility,[28] nor did it antagonize the uterotropic action of estrone in spayed mice at a dose of 1 mg/animal sc over a 3-day period.

Experimental Section[29]

Tetraethyl 2-Methyl-3,3-dicarboxyadipate (2).—A suspension of 1.275 kg of 53% NaH–mineral oil dispersion in 10 l. of dry benzene was prepared under N_2 in a 50-l. flask. To this was added 7.012 kg of triethyl 2-carboxyglutarate[4] in 3 l. of dry benzene over 6 hr, the temperature being maintained at 12–18°. The temperature was then raised to 50° and, with stirring, a solution of 4.93 kg (27 moles) of ethyl α-bromopropionate in 3 l. of dry benzene was added over 3 hr at this temperature. The mixture was then refluxed gently for 3 hr, cooled to room temperature, and washed with three 3-l. portions of water. The benzene solution was dried and the solvent was removed. The residual oil was distilled at 1.8 mm to give a forecut of 607 g, bp 30–145° (1.8 mm), followed by 5.512 kg of water white oil, bp

(20) M. S. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1953).

(21) (a) H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, *Ber.*, **71**, 1024 (1938); (b) T. Reichstein and C. Meystre, *Helv. Chim. Acta*, **22**, 728 (1939); (c) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Academic Press Inc., New York, N. Y., 1955, p 158.

(22) The possibility that either **16a** or **16b** was a homoannulation[23] product was eliminated by the presence of nmr singlets (3 protons) at 2.21 ppm in both compounds. This value is in agreement with the known values for the 21-methyl group of 20-keto steroids and contrasts with the observation that homoannulation (which changes the methyl group to a methyl carbinol function) shifts the methyl signal upfield by 0.9 ppm.[24]

(23) N. L. Wendler in "Molecular Rearrangements," Vol. II, Paul DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1114.

(24) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).

(25) C. Clauberg, *Zentr. Gynaekol.*, **54**, 27 (1930).

(26) M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1934).

(27) J. C. Stucki, *Proc. Soc. Exptl. Biol. Med.*, **99**, 500 (1958).

(28) W. H. Sawyer, E. H. Frieden, and A. C. Martin, *Am. J. Physiol.*, **172**, 547 (1953).

(29) Melting points were taken on a Fisher-Johns block and are uncorrected. Ultraviolet, infrared, and nmr spectra were determined on Beckman DK-1, Baird Model 455, and Varian A-60 instruments, respectively. The silica gel G used for tlc was according to Stahl and was purchased from Brinkmann Instruments, Inc. The spots were visualized in an iodine chamber. All samples for which analytical data are reported showed a single spot.

145–160° (1.8 mm) (lit.[6] 168–70° (3 mm)); yield 54% of material satisfactory for cyclization.

2-Methyl-2-β-cyanoethylcyclopentanone-3-carboxylic Acid (4a).—A solution of 100 g (0.7 mole) of **3**[6] in 110 ml of 40% aqueous KOH (0.78 mole) was adjusted to 30°, and, with vigorous stirring, freshly distilled acrylonitrile (44 ml, 0.7 mole) was added in one portion. After an induction period of *ca.* 1 min, a vigorous exothermic reaction began. When the temperature reached 45°, the flask was submerged in an ice bath to control the temperature at not more than 50°. When the exothermic reaction subsided, the ice bath was removed, and the reaction mixture was allowed to cool slowly to room temperature with stirring. The mixture was stirred at room temperature overnight and, with cooling, was acidified (HCl). The suspension was extracted with three portions of ethyl acetate. The extracts were combined, dried ($MgSO_4$), and concentrated to an oil which slowly crystallized. Trituration with a small amount of isopropyl ether gave 63.3 g of white solid, mp 131–133°. From the mother liquor, an additional 8.6 g of product was obtained; total yield 71.9 g (57%). The analytical sample (from ethyl acetate) had mp 136–137°; ν_{max}^{Nujol} 1710, 1735, 2300 cm^{-1}; δ_{CH_3} 1.02 ppm (s).

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.48; H, 6.88; N, 6.98.

Lactam 5.—A mixture of 12.0 g of **4b** (0.056 mole), 8.5 g of *m*-methoxyphenethylamine[2b] (0.056 mole), and 400 ml of xylene was refluxed with stirring under a Dean–Stark trap. After 2 hr, 1.8 ml of water had been collected (theoretical, 2.0 ml). The mixture was cooled and extracted with 5% NaOH. The alkaline solution was extracted with ether and then acidified with concentrated HCl. The acid suspension was extracted with three portions of ether. The ether solution was dried and concentrated to an oil. The oil solidified on trituration with ether to give 14.0 g (77%) of white solid, mp 123–126°. A sample was recrystallized from ethyl acetate; mp 125–127°; ν_{max}^{Nujol} 1720, 1610 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}NO_4$: C, 69.49; H, 6.75. Found: C, 69.54; H, 6.84.

Catalytic Reduction of 5 to 7.—A solution of 10 g of **5** in 200 ml of acetic acid was reduced over 0.1 g of PtO_2 catalyst at room temperature and 4.2 kg/cm^2. After 6 hr, 1 equiv of H_2 had been absorbed, and the rate of uptake was very slow. The catalyst and solvent were removed, and the residue was recrystallized from ethyl acetate to give 7.1 g of white solid, mp 169–171°, yield 71%. A sample was recrystallized from ethyl acetate: mp 173–174°; ν_{max}^{Nujol} 1610, 1730 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.13; H, 7.84; N, 4.56.

Lactam 7 by Reductive Condensation. A mixture of 15 g (0.07 mole) of **4b**, 10.6 g (0.07 mole) of *m*-methoxyphenethylamine, 250 ml of ethanol, and 0.025 g of PtO_2 catalyst was shaken for 24 hr at 60° and 2.45 kg/cm^2 initial H_2 pressure. The catalyst and solvent were removed, and the solid residue was recrystallized from ethyl acetate to give 18 g of white crystals, mp 171–173°. The infrared spectrum of this material was superimposable with that of the material prepared by catalytic reduction of **5**.

Cyclization of 5 to 6.—A mixture of 6 g of **5** and 30 ml of $POCl_3$ was heated for 2 hr on the steam bath. The mixture was evaporated under reduced pressure to an oil. The infrared spectrum of this oil showed a strong band at 1800 cm^{-1} (acid chloride). The oil was taken up in 50 ml of absolute ethanol, and the solution was refluxed for 0.5 hr. The solvent was removed, and the residue was dissolved in ice water and made basic with 5% NaOH. The supernatant liquid was decanted from the resulting gum, and the gum was recrystallized from ethanol to give 5.4 g of tan crystals, mp 87–90°, yield 88%. A sample was recrystallized from ethanol: mp 92–93°; ν_{max}^{Nujol} 1615, 1635, 1740 cm^{-1}; $\lambda_{max}^{95\%\ EtOH}$ 260 mμ (ε 18,400).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.12; H, 7.66; N, 4.36.

Cyclization of 7 to 8.—Lactam **7** was cyclized and esterified in 95% yield as described above for lactam **5**. Base **8** was recrystallized from 95% ethanol; mp 109–111°; ν_{max}^{Nujol} 1605, 1615, 1725 cm^{-1}.

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.08; H, 8.20; N, 4.08.

Base **8** was conveniently isolated and stored as its quaternary perchlorate, mp 154–156° after recrystallization from ethanol: ν_{max}^{Nujol} 1605, 1725 cm^{-1}.

Catalytic Reduction of 6 to 9a.—A solution of 4.0 g of **6** in 50 ml of ethanol was hydrogenated over 0.2 g of PtO_2 catalyst at room temperature and 3.5 kg/cm^2 H_2 pressure. After shaking for 15 min, 2 equiv of H_2 had been absorbed. The catalyst and solvent were removed, and the residue was taken up in ether. The ether was dried ($MgSO_4$) and dry HCl was passed in. The solid was filtered and recrystallized from ethanol–ether to give 3.6 g of white crystalline product: mp 209–211°; ν_{max}^{Nujol} 1620, 1730, 2550 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}ClNO_3$: C, 66.38; H, 7.96; Cl, 9.33. Found: C, 66.52; H, 8.15; Cl, 9.31.

The free base was obtained by treatment of a cold aqueous ethanolic solution of the salt with 5% NaOH; mp 89–90° from acetone–water; ν_{max}^{Nujol} 1610, 1730 cm^{-1}; $\nu_{max}^{CCl_4}$ 2760, 2820 cm^{-1}.

Borohydride Reduction of the Salt of 8 to Base 9a.—A solution of 42 g of the quaternary perchlorate of **8** in a mixture of 800 ml of methanol and 100 ml of water was treated with 20 g of $NaBH_4$ in small portions over an 0.5-hr period. The yellow solution became colorless, and a heavy white precipitate formed. The mixture was stirred at room temperature for an additional 15 min and then poured into 2 l. of water, stirred, cooled in an ice bath for 1 hr and filtered. The product after drying weighed 31 g (95%), mp 85–87°. It was identical with the base obtained by catalytic reduction of **6** as described in the preceding experiment.

Hydrolysis of 9a to 9b.—A solution of 21.0 g of the hydrochloride of **9a** in 450 ml of 4 *N* HCl was refluxed for 6 hr. The solution was evaporated to dryness and the residual paste was triturated with acetone. The suspension was filtered to give 17.4 g white solid, mp 196–198°. A sample was recrystallized twice from ethanol–ether: mp 202–203°; ν_{max}^{Nujol} 1610, 1730, 2700, 3200 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}ClNO_3$: C, 64.85; H, 7.45; Cl, 10.08. Found: C, 64.60; H, 7.67; Cl, 9.85.

Ketone 10a. A. By Use of Methyllithium.—A suspension of 15 g of **9b**·HCl in 200 ml of dry THF[a] was cooled at 10° and treated dropwise over a 1-hr period with 200 ml of *ca.* 1 *N* methyllithium in ether.[3b] The suspended solid slowly dissolved to give a clear colorless solution. The mixture was stirred for 1 additional hr, then the excess methyllithium was decomposed by cautious addition of water. The mixture was finally diluted with 80 ml of water, and the ether and THF distilled from the two-phased system. The gummy residue was extracted with ethyl acetate. The organic phase was dried and concentrated to give 11.5 g of white solid:[15] mp 121–123°; ν_{max}^{Nujol} 1615, 1705 cm^{-1}. The hydrochloride melted at 214–217° after recrystallization from ethanol–ether. On tlc (methanol–$CHCl_3$, 20:80) the base showed two spots with R_f values of 0.7 and 0.4 g. It is considered that the less polar spot represents both C-17 epimers of **10a** while the more polar spot represents a single isomer of **11** (see ref 15).

B. By Reductive Cleavage of Sulfoxide 10b.—A solution of 6.6 g of **10b** in 200 ml of refluxing 15% aqueous THF was treated with 0.91 g of amalgamated aluminum[17] in small pieces over an 0.5-hr period. The mixture was stirred at reflux for 1.5 hr, by which time no Al remained. The mixture was filtered while hot and the gelatinous cake was washed well with hot THF. The filtrate was concentrated until a slurry was obtained. The slurry was cooled for 3 hr and filtered. The cake was washed with water and dried to give 5.0 g of off-white solid, mp 141–144°, yield 91%. A sample was recrystallized twice from ethanol: mp 148–149°; ν_{max}^{Nujol} 1615, 1705 cm^{-1}.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.74; H, 8.87; N, 4.32.

On thin layer chromatography, both the crude and recrystallized samples of **10a** prepared from the sulfoxide revealed a single spot. Using a developing agent composed of 1-butanol–acetic acid–water (5:1:1.5), the R_f was 0.2 while a developing agent composed of 20% methanol and 80% $CHCl_3$ gave R_f 0.7.

Sulfoxide 10b.—A suspension of 4.2 g of 50% NaH–mineral oil dispersion in 75 ml of dry DMSO was warmed with stirring under nitrogen to 60° for 2 hr. The resulting cloudy solution was cooled to 5°, and a solution of 12 g of **9a** in 30 ml of dry THF was added over a 5-min period. The mixture was stirred for 3 hr while the temperature was allowed to rise to ambient. Water was

(a) A solution of 51 g (0.5 mole) of CH_3I in 100 ml of anhydrous ether was added dropwise with stirring to a cold (0–10°) suspension of 8.0 g (1.16 g-atoms) of Li in 100 ml of ether. The mixture was refluxed for 10 min after the addition and cooled. The cloudy solution thus prepared contained suspended LiI and excess Li and was filtered through glass wool and titrated before use.

added cautiously to decompose the reaction mixture. After dilution with 600 ml of water, the mixture was acidified with 4 *N* HCl, and the mineral oil was removed by extraction with petroleum ether. The pH was adjusted to 7.5 with 5% NaOH, and the mixture was extracted with four portions of CH_2Cl_2. The combined organic phases were washed with water and dried, and the solvent was removed. The oil crystallized readily on scratching. The solid was slurried in ether and filtered to give 13 g (98%) of tan solid, mp 95–100°. The crude material was satisfactory for cleavage with aluminum amalgam. A sample was recrystallized from ethanol; mp 123–125°; ν_{max}^{Nujol} 1030, 1610, 1710 cm^{-1}.

Anal. Calcd for $C_{21}H_{29}NO_3S$: C, 67.17; H, 7.78; S, 8.54. Found: C, 66.98; H, 7.90; S, 8.35.

8-Aza-19-norprogesterone (12a) and 8-Aza-19-nor-17-α-progesterone (12b).—A mixture of 15 g of the hydrochloride of ketone **10a**, prepared by the MeLi procedure, 10 ml of ethylene glycol, 200 mg of *p*-toluenesulfonic acid, and 400 ml of benzene was refluxed for 2 hr, during which time 1.6 ml of water (theoretical, 0.8 ml) was collected in a Dean-Stark trap. The reaction mixture was cooled and washed with 5% NaOH. The benzene was dried and evaporated to a solid residue. The solid was triturated with petroleum ether (bp 30–60°) to give 12.0 g of product which was transparent in the carbonyl region of the infrared.

The ketal was dissolved in 200 ml of anhydrous ether and added to *ca.* 400 ml of liquid NH_3. Lithium (2.5 g) was added in small pieces over 20 min, and the blue solution was stirred at reflux for 1.5 hr. Ethanol was then added dropwise until the blue color was discharged. The NH_3 was allowed to evaporate with stirring, and the mixture was diluted with 300 ml of water. The layers were separated and the aqueous phase was extracted twice with ether. The combined ether phases were washed with water, dried (K_2CO_3), and concentrated to a solid residue weighing 10.7 g. The enol ether ketal thus obtained (end absorption only in the ultraviolet) was refluxed for 1 hr in 50 ml of 10% H_2SO_4. The solution was cooled in an ice bath and made basic with 20% NaOH. The precipitated oil was extracted with two portions of ether. The combined ether fractions were washed with water and dried ($MgSO_4$). The ether was evaporated and the oily residue was scratched with ethyl acetate. The slurry was filtered to give a first crop of 1.9 g of white solid. The mother liquor was concentrated to a small volume and cooled to afford a second crop of 0.9 g, total yield of crude **12a**, 2.8 g (31%). A sample was recrystallized twice from ethyl acetate; mp 152–154°; ν_{max}^{Nujol} 1630, 1670, 1705 cm^{-1}; $\lambda_{max}^{95\% EtOH}$ 235 mμ (ε 15,200).

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.87; H, 9.17; N, 4.57.

The mother liquor from the second crop of **12a** was concentrated to an oil and placed on 300 g of neutral alumina (Merck). The column was washed well with benzene and anhydrous ether which removed small amounts of oily material. Elution of the column with ethyl acetate removed 1.4 g of yellow solid. After two recrystallizations from ethyl acetate, 0.7 g of **12b** was obtained as off-white crystals: mp 151–153°; mmp (with **12a**) 123–137°; ν_{max}^{Nujol} 1625, 1665, 1700 cm^{-1}; $\lambda_{max}^{95\% EtOH}$ 236 mμ (ε 16,100).

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.41; H, 9.16; N, 4.61.

On tlc (ethanol–$CHCl_3$, 15:85), **12a** and **12b** migrated at clearly different rates, R_f *ca.* 0.7 and 0.6, respectively.

In the same way, the pure ketone **10a**, prepared *via* the sulfoxide, was converted to its ethylene ketal and subjected to Birch reduction and acid hydrolysis. Thin layer chromatography of the crude semisolid reaction product revealed no spot corresponding to **12b**. Likewise, the nmr spectrum of the crude product revealed no signal at 1.12 ppm. By trituration with anhydrous ether, a 50% yield of pure **12a** was obtained.

Cyanohydrin 13b.—A mixture of 30.2 g (0.10 mole) of **13a**, 126 g (1.95 moles) of KCN, and 460 ml of methanol was treated with stirring with 126 ml (2.2 moles) of acetic acid added dropwise over a 6-hr period. The mixture was stirred overnight and concentrated under reduced pressure to a paste, the temperature being maintained below 30°. Water (150 ml) was added, and the solid was filtered, washed well with water, and dried in a desiccator. The product (24.6 g, 75%) melted over a wide range due to loss of HCN on heating. The product was analyzed without purification; ν_{max}^{Nujol} 1615, 2250 (weak), 3250 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.34; N, 8.53. Found: C, 70.33; H, 7.45; N, 8.54.

The mother liquor and water washings were combined and extracted (CH_2Cl_2). The solvent was removed to leave a dark oil composed of unreacted ketone and cyanohydrin. The oil was dissolved in 100 ml of ethanol, 20 ml of 20% NaOH was added, and the solution was warmed for 0.5 hr on the steam bath. The ethanol was removed, and the residue was diluted with water and extracted with ethyl acetate. The ethyl acetate was dried and removed to recover 7.2 g of starting ketone.

Cyclization of 13b to 14a.—A suspension of 8.5 g of cyanohydrin **13b** in 200 ml of benzene and 30 ml of $POCl_3$ was refluxed with stirring for 45 min. The mixture was concentrated under reduced pressure to a heavy oil. This was dissolved in 100 ml of hot water, and the clear solution was cooled and treated with 10% $HClO_4$ solution. The solid was filtered and recrystallized from methanol to give 7.4 g yellow crystals, mp 205–207°. A second crop of 1.2 g, mp 204–206°, was obtained by partial concentration of the filtrate, yield 81%. A sample was recrystallized from methanol; mp 205–207°; ν_{max}^{Nujol} 1610, 3350 cm^{-1}.

Anal. Calcd for $C_{19}H_{23}ClN_2O_3$: C, 55.55; H, 5.64; Cl, 8.63. Found: C, 55.45; H, 5.80; Cl, 8.59.

Ester Quaternary Salt 14c.—A solution of 7.2 g of **14a** in 110 ml of concentrated HCl was stirred at 75° for 12 hr. The solution was concentrated under high vacuum to a heavy oil. This was taken up in 100 ml of methanol and the solution was refluxed for 1 hr, the esterification being catalyzed by the residual HCl. Chloroform (100 ml) was added and the mixture was concentrated to dryness. The process was repeated with an additional 100 ml each of methanol and $CHCl_3$ (the $CHCl_3$ served to aid attainment of anhydrous conditions and thereby ensure completion of the esterification). The residue was dissolved in cold water (methanol being added to aid solubility), and the clear solution was treated with 10% $HClO_4$ until precipitation of the salt was complete. The slurry was cooled overnight and filtered to give 7.0 g of crystalline product, mp 159–161°, yield 90%. A sample was recrystallized from methanol; mp 161–163°; ν_{max}^{Nujol} 1605, 1735, 3500 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}ClNO_3$: C, 54.12; H, 5.90; Cl, 7.99. Found: C, 54.23; H, 6.06; Cl, 8.13.

Reduction of 14c to 15a.—A solution of 7.0 g of **14c** in 200 ml of ethanol was treated with 3 g of KBH_4 added in portions over a 0.5-hr period. The mixture was stirred for 0.5 hr and filtered. The filtrate was concentrated to dryness and the residue was partitioned between water and ether acetate. The ethyl acetate was dried and concentrated to 5.0 g of solid residue. The base was converted to its hydrobromide salt for analysis. After two recrystallizations from ethanol, the product melted at 222–223°; ν_{max}^{Nujol} 1620, 1720, 2550, 2680, 3400–3500 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}BrNO_4$: C, 56.34; H, 6.62; Br, 18.74. Found: C, 56.56; H, 6.66; Br, 18.55.

Sulfoxide 15b.—Ester **15a** (5.0 g of the free base) was converted to the sulfoxide using 3.0 g of the NaH mineral oil dispersion as described for preparation of **10b**. The crude product weighed 4.95 g (87.5%), mp 192–195°. A sample was recrystallized from acetonitrile; mp 196–197°; ν_{max}^{Nujol} 1030, 1610, 1710, 3360 cm^{-1}.

Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.56; H, 7.60; N, 3.40.

Ketone 15c.—Reductive cleavage of sulfoxide **15b** was carried out as described for ketone **10a**. The free base, obtained in quantitative yield, melted at 195–197° after recrystallization from acetone–water. It was converted to its hydrobromide salt for analysis, mp 250–252° from 2-propanol; ν_{max}^{Nujol} 1615, 1690, 2550, 2650, 3450 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}BrNO_3$: C, 58.54; H, 6.88; Br, 19.47. Found: C, 58.45; H, 6.86; Br, 19.26.

17α-Hydroxy-8-aza-19-norprogesterone (16a).—A mixture of 3.3 g of ketone **15c** (free base), 3.5 g of *p*-toluenesulfonic acid, 25 ml of ethylene glycol, and 300 ml of benzene was refluxed with stirring under a Dean–Stark trap for 4 hr. The solution was cooled and washed with K_2CO_3 solution and water. The benzene layer was dried and concentrated to 3.9 g of heavy oil which crystallized. The ketal (**15d**, transparent in the C=O region of the infrared) was dissolved in 50 ml each of dry THF and *t*-butyl alcohol and added to *ca.* 400 ml of liquid NH_3. Lithium (3.5 g) was added in small pieces over a 20-min period, and the blue solution was stirred for 1.5 hr at reflux. Ethanol was added dropwise to discharge the blue color, and the NH_3 was allowed to evaporate. Water (100 ml) was added, and the THF was removed by distillation. The mixture was extracted with ethyl acetate, and the organic phase was dried and concentrated to give 3.4 g of white solid enol ether ketal which showed end absorption

only in the ultraviolet. This was hydrolyzed directly by refluxing for 30 min in 60 ml of methanol and 40 ml of 3 *N* HCl. The methanol was removed by distillation and the solution was made basic with 10% NH_4OH. The precipitate was extracted with ethyl acetate, and the solution was dried and concentrated to 2.1 g of solid, mp 191–193°. The product was recrystallized twice from 2-propanol; mp 195–197°; ν_{max}^{Nujol} 1630, 1670, 1710, 3500 cm^{-1}; $\nu_{max}^{CCl_4}$ 2750, 2840 cm^{-1}; λ_{max}^{EtOH} 235 mμ (ε 15,800).

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.76; H, 8.74; N, 4.44.

Ethynyl Lactam 13c.—A solution of ethylmagnesium bromide was prepared from 2.4 g of Mg and 12 g of ethyl bromide in 30 ml of dry THF. Acetylene (purified by passage through concentrated H_2SO_4 and activated alumina, Alcoa S–14 mesh) passed through the solution for 2 hr. A solution of 3 g of **13a** in 10 ml of dry THF was added over a 10-min period. The mixture was stirred for 0.5 hr, cooled in an ice bath, and decomposed by addition of saturated NH_4Cl solution. The layers were separated and the THF was removed. The oil was taken up in 100 ml of ethyl acetate and a small amount of insoluble material (bis addition compound) was filtered off. The filtrate was concentrated to 25 ml and cooled to give a first crop of 2.1 g, mp 141–143°. From the mother liquor a second crop of 0.4 g was obtained. Recrystallization from ethyl acetate gave 2.3 g of material, mp 142–143°. A sample was recrystallized again from ethyl acetate; mp 142–143°; ν_{max}^{Nujol} 1615, 2050 (very weak), 3280 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.43; H, 7.83; N, 4.35.

Acetyl Lactam 13d.—A solution of 11.5 g of ethynyl lactam **13c** in 1800 ml of methanol and 36 ml of water was refluxed for 2 hr with vigorous stirring with 48 g of Dowex 50 resin impregnated with $HgSO_4$.[20] The methanol was removed from the mixture by distillation under reduced pressure, and the residue was suspended in 200 ml of water. The mixture was made basic with 5% NaOH, and the aqueous suspension of resin and product was extracted with four portions of CH_2Cl_2. The combined organic layers were washed with water and dried, and the solvent was removed to give 11.65 g of white solid, mp 173–176°, yield 91%. A sample was recrystallized twice from ethyl acetate; mp 177–179°; ν_{max}^{Nujol} 1610, 1705, 3280 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.80; H, 7.79; N, 4.23.

Acetyl Quaternary Salt 14d.—To a solution of 11.6 g of **13d** in 200 ml of refluxing benzene was added, in one portion, 20 ml of $POCl_3$. The solution was refluxed for 30 min and concentrated under reduced pressure to an oil. The residue was dissolved in warm water, and a small amount of insoluble material was extracted with ethyl acetate. The aqueous solution was treated with 10% $HClO_4$ until precipitation of the oil was complete. The supernatant liquid was decanted, and the oil was rubbed with ethanol to induce crystallization. The slurry was cooled and filtered to give 5.0 g of solid, mp 218–220°. A second crop of 1.4 g was obtained from the mother liquor, mp 214–217°, total yield of crude product, 46%. A sample was recrystallized twice from methanol: mp 219–221°; ν_{max}^{Nujol} 1600, 1695, 3450 cm^{-1}.

Anal. Calcd for $C_{26}H_{26}ClNO_5$: C, 56.14; H, 6.12; Cl, 8.29. Found: C, 56.40; H, 6.41; Cl, 8.29.

Ketal 15e.—A mixture of 4.95 g of quaternary perchlorate **14d**, 100 ml of ethylene glycol, 1 l. of benzene, and 2 g of *p*-toluenesulfonic acid was refluxed under a Dean–Stark trap for 18 hr with vigorous stirring. The solution was cooled to room temperature, and with vigorous stirring a solution of 10 g of KBH_4 in 100 ml of ethylene glycol was added dropwise over a 1-hr period. The mixture was stirred at room temperature for an additional 15 min. Water (1 l.) was added and the layers were separated. The aqueous layer was extracted with ether, and the combined ether and benzene layers were dried and concentrated to 4.6 g of oil which crystallized spontaneously on standing overnight under a small amount of ether. The product absorbed at 1605 and 3500 cm^{-1} and was used without further characterization.

Ketone 15f.—A solution of 50 mg of ketal **15e** in 10 ml of 4 *N* HCl was warmed on the steam bath for 0.5 hr. The solution was made basic with 5% NaOH and the precipitated base was extracted with ethyl acetate. The ethyl acetate solution was dried and concentrated to 5 ml. Petroleum ether (3 ml) was added and the solution was allowed to crystallize. The solid was filtered and recrystallized from ethyl acetate–petroleum ether. The crystalline product, mp 140–142°, absorbed at 1605, 1700, and 3500 cm^{-1}. On thin layer chromatography (1-butanol–acetic acid–water, 5:1:1.5), **15f** migrates slightly faster than the epimeric ketone **15c**, R_f *ca.* 0.3.

17β-Hydroxy-8-aza-19-nor-17α-progesterone (16b).—Ketal **15e** (4.6 g) was subjected to Birch reduction and acid hydrolysis as described for the preparation of **16a**. Removal of the ethyl acetate left a residue of 3.4 g of yellow solid, mp 170–178°. Two recrystallizations from 2-propanol gave 1.3 g of pure material: mp 191–194°, mmp (with **16a**) 172–175°; ν_{max}^{Nujol} 1630, 1675, 1705, 3400 cm^{-1}; $\nu_{max}^{CCl_4}$ 2750, 2840 cm^{-1}; λ_{max}^{EtOH} 235 mμ (ε 15,400).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 71.89; H, 8.17; N, 4.41. Found: C, 71.59; H, 8.70; N, 4.35.

On tlc (methanol–$CHCl_3$, 20:80), **16b** migrated slower than **16a**; R_f *ca.* 0.6 and 0.8, respectively.

Acknowledgment.—The authors wish to thank Professor E. L. Eliel for his helpful suggestions. We also wish to thank Mr. A. D. Lewis and the members of his Analytical and Physical Chemical Section, Mrs. Umi Zeek, Mr. Robert Puchalski, and Mr. Robert DeSimone, for the microanalyses and spectra. The assistance of Mr. S. A. Robinson and Mr. G. Conrad of the Chemical Development Department, under the direction of Dr. A. W. Ruddy, is also gratefully acknowledged. The biological studies were carried out by Drs. A. Meli and B. Steinetz of this institute to whom the authors express their appreciation.