(9) H. Stetter and H. Spangenberger, *Chem. Ber.*, **91**, 1982 (1952).
(10) We thank Dr. E. Hedaya for supplying us with a copy of the nmr spectrum of authentic *N,N'*-bispyrrolidine.[7]
(11) Attempted preparation of the unknown *cis*-2-butene-1,4-diamine by partial hydrogenation[12] of butyne-1,4-diamine[13] led only to the isolation of pyrrole. Also, attempted condensation of 2-butyne-1,4-diamine with succindialdehyde gave none of the desired N-substituted pyrrole derivative.
(12) L. H. Amundsen, R. H. Mayer, L. S. Pitts, and L. A. Malentacchi, *J. Amer. Chem. Soc.*, **73**, 2118 (1951).
(13) A. W. Johnson, *J. Chem. Soc.*, 1009 (1946).
(14) Attempted determination of coupling constants by use of rare-earth shift reagents was frustrated by experimental difficulties. However, the gross trends were in accord with those expected for the indicated stereochemistries.
(15) B. Robinson, *Chem. Rev.*, **63**, 373 (1963).
(16) Melting points and boiling points are uncorrected. Nmr spectra were determined on Varian T-60, Varian A-60, and Bruker HX-90 spectrometers. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Mass spectra were taken on a CEC 21-100B instrument. Gas chromatography was performed on a Varian Model 90-P instrument.
(17) J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Amer. Chem. Soc.*, **72**, 869 (1950).

A Novel Synthesis of 8-Aza Steroids[1]

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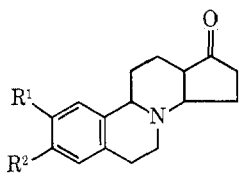
A general synthesis of A-aromatic 18-nor-8-aza steroids have been demonstrated from the enamine of a β-arylethylamine and 1,3-cyclopentandione. The C-ring atoms were introduced by reaction of the enamine with β-propiolactone. Cyclization to form the B ring occurred with redox dispropionation to give an 8-aza steroid with the C-ring aromatic (**7**) and the C ring in the tetrahydro state (**9**). Reductions of **7** and **9** were investigated to form the trans-anti-cis isomer of 2,3-dimethoxy-18-nor-8-azaesterone (**13**). The reaction of **9** with electrophiles occurred at oxygen.

The potential of heterocyclic analogs of the cyclopentanophenanthrenes to function as steroidal antagonists or antimetabolites has prompted an interest in the synthesis of many nitrogen heterocycles as aza or diaza steroids.[2-6] Except for the preparation of 8-aza steroids by Brown and coworkers,[5a] the syntheses usually involve the formation of the 8–14 and/or 12–13 bond(s) in an intermediate having preformed A, B, and D rings. In order to provide for the possibility of introducing 11 and 12 substituents in an 8-aza steroid nucleus, a study was made of synthetic approaches to 8-aza steroids (**1**) *via* formation of the 9–10 bond with an intermediate having preformed A, C, and D rings (**2**).

A logical intermediate for forming the 9–10 bond of an 8-aza steroid, based on the enamine nature of dihydro-[7] and tetrahydropyridines,[8] is the reduced form of 1-(2-arylethyl)-5-pyrindanone salt (**3a**). The 5-pyrindanone (**3b**) was prepared by oxidation of pyrindan (**4**)[9] by buffered po-



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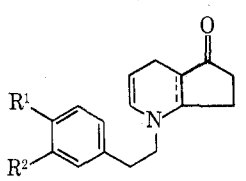

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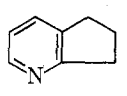

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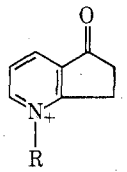
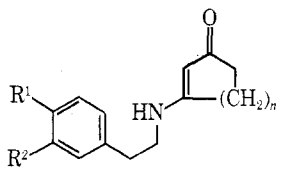


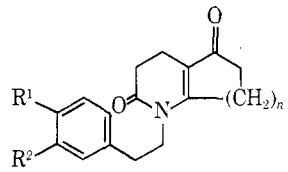
3a, R = $ArCH_2CH_2$
b, R = H

tassium permanganate.[10] This 5-pyrindanone,[11a] unlike the isomeric 7-pyrindanone, prepared from 7-pyrindanol,[11b] showed no evidence of existing as the enolic tautomer. Quaternary salt formation proved to be difficult, because the electron attraction of the 3-carbonyl and steric interference of the α-methylene had the effect of reducing the nucleophilicity of the heterocyclic nitrogen. The competing reaction, dehydrohalogenation of the arylethyl halide, was a serious side reaction. As a result this approach was abandoned.

The synthesis of a similar intermediate which could be used to prepare 11- and/or 12-substituted 8-aza steroids was investigated using a modification of the route of Brown and coworkers[5a] and Nagata and Castle and coworkers.[2] The reaction of methoxylated β-arylethylamines with 1,3-cyclohexadione and 1,3-cyclopentadione gave quantitative yields of enamino ketones (**5**). The vinylogous amide of the



5a, $R^1 = R^2 = CH_3O$; $n = 1$
b, $R^1 = H$; $R^2 = CH_3O$; $n = 1$
c, $R^1 = R^2 = CH_3O$; $n = 2$



6a, $R^1 = R^2 = CH_3O$; $n = 1$
b, $R^1 = H$; $R^2 = CH_3O$; $n = 1$
c, $R^1 = R^2 = CH_3O$; $n = 2$

enamine system of **5** decreases the nucleophilicity of the enamine, and similar systems undergo alkylation largely on oxygen.[12] Thus the choice of the 3-carbon molecule with which to form the C ring was complicated, for the cyclization must occur with formation of a functional group capable of undergoing 9–10 bond formation to form the B ring.

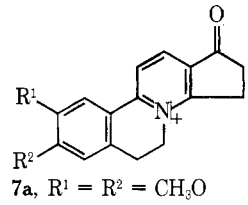
The logical reagent to accomplish this result would be a derivative of acrylic acid in view of the success of this route in the synthesis of lycopodium alkaloids.[13] Acrylonitrile or ethyl acrylate gave no reaction with **5c**. This is surprising in view of the successful reaction of acrylonitrile with comparable systems.[5a] The use of the more reactive acrolein or acrolein dimethyl acetal also failed to undergo reaction. Dimethyl acetylenedicarboxylate gave a reaction with **5c**; however, the product contained more than one of the acetylenic moieties. As might have been predicted from the work of Meyers and coworkers,[3,5] the reaction of **5c** with β-chloropropionic acid did not occur.

The reaction of a limited number of enamines with β-propiolactone was reported to give the substituted propioamide.[14] This suggested that the alkylation of **5c** would

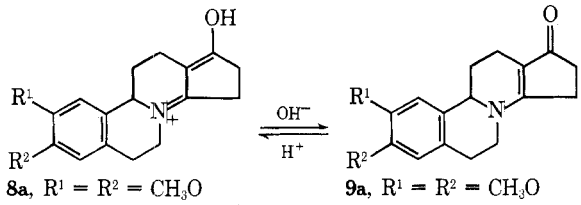
occur with subsequent cyclization to form the desired intermediate **6c**. Reaction did not occur at the reflux temperature of benzene or toluene; however, with chlorobenzene as solvent **5c** gave a moderate yield of **6c**. The isolation of the product was improved by using xylene as solvent. Comparable results were obtained from the reaction of **5a** and **5b** with β-propiolactone, giving good yields of **6a** and **6b**. The dihydropyridone structures for **6a–c** were conclusively evident from the spectral data.

The cyclodehydration reaction of **6a–c** to form the bisnor-8-aza steroids appeared to be analogous to the cyclization used by Meltzer and coworkers to form aza steroids.[5a] However, the reaction of **6a** with polyphosphoric acid gave a high yield of product which was shown by proton magnetic spectrum to be a mixture of two aza steroids. Separation of the two products by precipitation of the perchlorate from acetonitrile–ethanol gave, as the more insoluble material, the A,C-bisaromatic-8-aza steroid (**7a**). The aromatic nature of the heterocyclic ring was clear from the presence of an AB quartet at 9.0-ppm downfield from TMS in the pmr spectrum, and the orientation of the cyclization to give the 2,3-dimethoxy rather than the 3,4-dimethoxy-8-aza steroid was indicated by the sharp singlets for the protons attached to the oxygenated aromatic ring. The formation of this pyridinium derivative required that dehydrogenation as well as cyclodehydration had occurred. This suggested that the second product should be in the oxidation state of a tetrahydropyridine. Evaporation of the solvent from the isolation of **7a** gave an oil which was crystallized. This soluble salt was shown to have the structure **8a** by spectral analysis. Treatment of the salt with base gave the enamino ketone **9a**, which was protonated on oxygen by perchloric acid to give **8a**, identical with the original material.

Protonation of enamino ketones on treatment with acid has been reported with a number of aza steroids.[15–18] The properties reported for these compounds compare well with those observed for **8a** and **8b**.



7a, $R^1 = R^2 = CH_3O$
b, $R^1 = H$; $R^2 = CH_3O$



8a, $R^1 = R^2 = CH_3O$
b, $R^1 = H$; $R^2 = CH_3O$

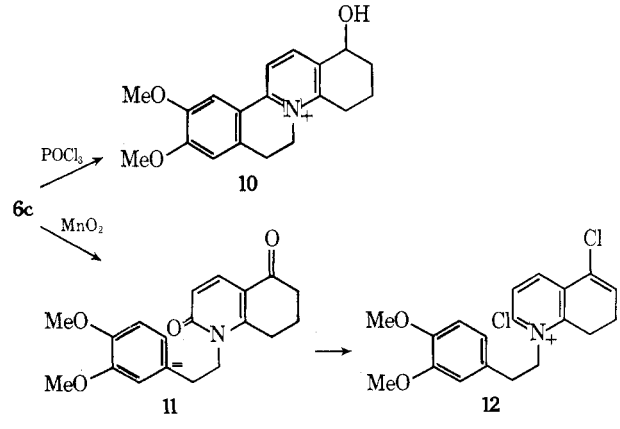
9a, $R^1 = R^2 = CH_3O$
b, $R^1 = H$; $R^2 = CH_3O$

The relative yields of the two cyclization products **7a** and **8a** did not vary with the reaction time for the ratio of 1 to 1 was observed at 80% completion, complete reaction, and two times the reaction time for complete reaction. This suggests that two molecules of an intermediate cyclization product, probably a dihydropyridine, undergo disproportionation to form **7a** and **8a** and argues against the possibility that **7a** or **8a** could be the intermediate in the formation of the other. These results are similar to those described in the synthesis of partially reduced lepidine by cyclization.[19] No evidence for a dihydrointermediate could be obtained for the cyclization.

The reaction of **6b** with polyphosphoric acid also gave two products (**7b** and **8b**) in a ratio of 1 to 1 resulting from disproportionation of the intermediate. The position of cyclization was para to the methoxy group to give 8-aza steroids, **7b** and **8b**, with a 3-methoxy substituent as was shown by the nmr spectra of the aromatic protons of **7b** and **8b**.

The decomposition of the intermediate dihydropyridine, formed by the cyclodehydration of **6c** with phosphorus oxychloride, apparently took a different course. A single product was detected and had the properties of a quaternary salt. The spectral data of the product were consistent with structure **10** in which the carbonyl group was reduced as the dihydropyridine underwent oxidation.

In an effort to avoid the complications of the oxidation–reduction reaction, the dihydropyridone of **6c** was oxidized to the pyridone **11** which was then subjected to cyclodehydration conditions. The oxidation of **6c** was caused most conveniently by activated manganese dioxide. No reaction of **11** was observed with phosphorus oxychloride in a solvent; however, using the reagent itself as solvent gave a dichloro derivative, **12**. Cyclodehydration of **11** by other re-



10

11

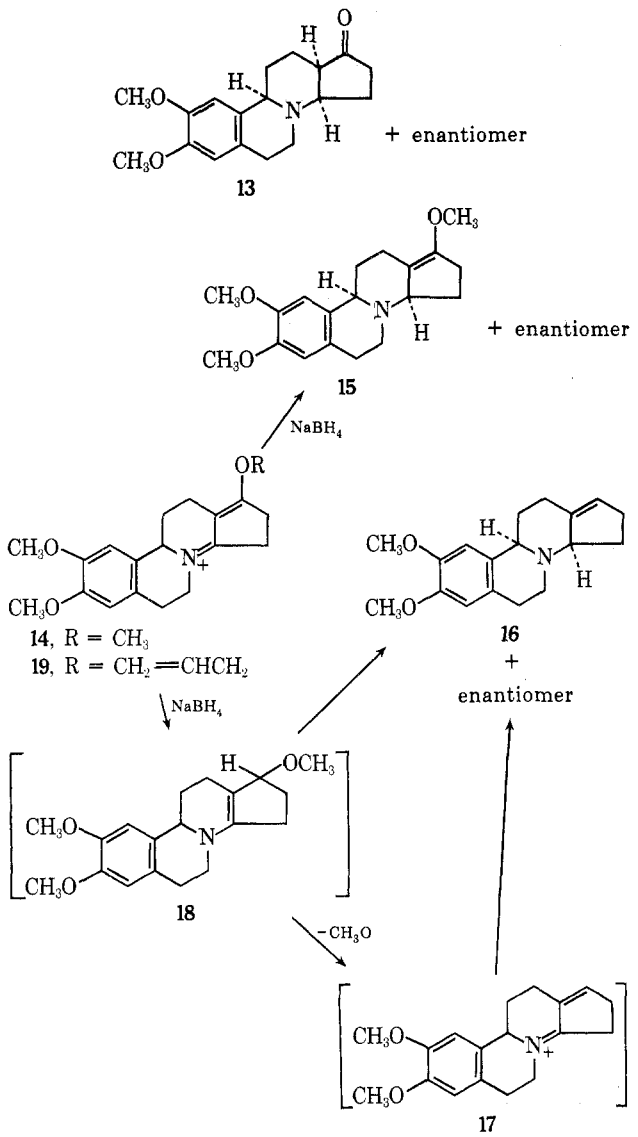
12

agents or cyclodehydrohalogenation of **12** failed and the synthesis of D-homo-8-aza steroids by this route was not investigated further.

The reactions of the A,C-bisaromatic-8-aza steroids **7a** and **7b** and the tetrahydro derivatives **8a** and **8b** were studied as a means for preparing other 8-aza steroid derivatives. The pyridinium ring C of **7a** or **7b** should provide a reactive site for reduction by hydrogenation[20] or complex metal hydrides[21] or addition of cyanide.[22] The catalytic hydrogenations gave no reaction and sodium borohydride reduction of **7a** gave a small yield of **8a**. Addition of cyanide appeared to give formation of a dimer related to viologen.[23]

The reduction of the salt **8a** with hydrogen over catalysts or by complex metal hydrides gave only **9a** on work-up. The reduction of **9** with lithium aluminum hydride did give saturation of the 13–14 double bond, for the infrared spectrum of the product **13** gave the carbonyl stretching vibration at 1740 cm^{-1} indicating the absence of conjugation. The appearance of Bohlmann bands at 2810 and 2890 cm^{-1} in the infrared spectrum[24] and the comparison of the pmr spectrum with related aza steroids[25] allowed the assignment of the trans-anti-cis stereochemistry to the product, 2,3-dimethoxy-1,3,5(10)-triene-8-azagonan-17-one (**13**).[26]

The alkylation of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) was investigated as a means for preparing other 8-aza steroids. The enamino ketone system of **9a** has three possible sites for reaction with electrophiles; however, in view of the exclusive reaction with protons at oxygen, alkylation of **9a** should also occur at oxygen to give **14**. The cisoid enamino ketones have been reported to give reaction at either carbon or oxygen depending on the solvent.[12] The reaction of **9a** with methyl iodide gave a high



yield of the *O*-methyl salt, **14**. The spectral properties of **14** were quite similar to those of the proton salt **8a** and supported the structural assignment of **14**.

The immonium bond of **14** would be expected to undergo reduction to give **15**, the enol ether of **13**. Treatment of **14** with hydrogen over palladium gave no reaction; however, reaction of **14** with sodium borohydride gave two products, **15** and **16**. The spectral data of **15** showed that it was the enol ether of **13**. The strong Bohlmann bands observed in the infrared spectrum of **15** provided evidence for the trans-anti stereochemistry for the **9**, **13**, and **14** positions.

The nmr spectrum of **16** provided the best clue of the structure of this unexpected product. Only two *O*-methyl signals were observed and a signal characteristic of a vinyl proton was evident. These results in conjunction with the other spectral data suggested that **16** was formed by reduction of the immonium bond and reductive cleavage of the 17-methoxyl goup. The loss of the methoxyl group may occur by an elimination reaction to form **17** or reductive cleavage of the allylic methoxyl group of **18** may give **16** directly.

The alkylation of **13** with allyl halides or tosylate proved to be more difficult than methylation; however, heating **13** with neat allyl bromide under reflux gave the O-alkylated product in moderate yield. No C-alkylated product was detected. Attempts to cause a Claisen-type rearrangement of the vinyl allyl ether[27] by heating **19** gave only the dealkylated product **13**.

Experimental Section

Melting points were determined using a Thomas-Hoover Capillary Melting Point apparatus or a Mel-Temp Apparatus and were not corrected for thermometer stem exposure. Elemental analyses were determined using an F and M Model 185 C, H, and N analyzer. Infrared spectra were determined using Perkin-Elmer Model 137 or 337 spectrometers with samples prepared as mulls or KBr pellets. The ultraviolet absorption spectra were measured on a Cary 15 spectrometer in the solvent indicated, and the nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-3-aminocyclopent-2-en-1-one (5a). To a one-neck, 500-ml, round-bottom flask, equipped with a Dean-Stark trap and a condenser, were added 10.0 g (55.3 mmol) of β-3,4-dimethoxyphenethylamine, 5.0 g (51.0 mmol) of 1,3-cyclopentanedione, and 250 ml of dry benzene. The suspension was stirred magnetically and heated under reflux until the theoretical amount of water was collected (*ca.* 2–3 hr). At this time the reaction was homogeneous. The solvent was removed under reduced pressure and the resulting solid was triturated with anhydrous ether to give, on filtration, 13.1 g (98.3%) of *N*-(β-3,4-dimethoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5a**) as an off-white solid: mp 125–128°; pmr ($CDCl_3$) δ 6.61 (broad, 1 H), 6.58 (s, 3 H), 4.87 (s, 1 H), 3.73 (s, 6 H); ir (KBr) 1560 (C=O), 3180 (NH) cm^{-1}; uv (95%, C_2H_5OH) 229 (log ε 3.96), 271 nm (log ε 4.56).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.82; H, 7.20; N, 5.19.

Preparation of *N*-(β-3-Methoxyphenethyl)-3-aminocyclopent-2-en-1-one (5b). Following the procedure for the preparation of **5a**, 3.0 g (19.8 mmol) of β-3-methoxyphenethylamine, 1.94 g (19.8 mmol) of 1,3-cyclopentanedione, and 50 ml of dry benzene were converted to 4.5 g (98.5%) of *N*-(β-3-methoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5b**): mp 104–106°; pmr ($CDCl_3$) δ 7.27 (m, 1 H), 7.13 (m, 1 H), 6.9–6.65 (m, 3 H), 4.98 (s, 1 H), 3.75 (s, 3 H), 3.65–3.2 (m, 2 H), 2.87 (t, 3 H, *J* = 6.5 Hz), 2.7–2.1 (m, 4 H); ir (KBr) 1570 (C=O), 3190 (NH) cm^{-1}; uv max (95% C_2H_5OH) 271 nm (log ε 4.498).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.91; H, 7.42; N, 5.98.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-3-aminocyclohex-2-en-1-one (5c). Using the procedure for the preparation of **5a**, 36.2 g (0.20 mol) of 3,4-dimethoxyphenethylamine, 22.4 g (0.20 mol) of 1,3-cyclohexanedione, and 500 ml of dry benzene gave 55.0 g (100%) of *N*-(β-3,4-dimethoxyphenethyl)-3-aminocyclohex-2-en-1-one (**5c**) which on recrystallization from xylene melted at 116 to 119°: pmr ($CDCl_3$) δ 6.75 (m, 3 H), 5.80 (broad, N-**H**), 5.14 (s, 1 H, vinyl), 3.88 (s, 6 H, OCH_3); ir (KBr) 1575 (C=O) and 3180 (NH) cm^{-1}; uv max (95% C_2H_5OH) 229 (log ε 3.914), 288 nm (log ε 4.538).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.58; N, 4.86.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (6a). A solution of 100.0 g (0.38 mol) of *N*-(β-3,4-dimethoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5a**), 150 g (2.08 mol) of β-propiolactone, and 3 l. of chlorobenzene was heated under reflux for 7 days. Every 24 hr 200 ml of chlorobenzene was distilled off to remove any water formed from the reaction and was replaced by an equal amount of dry chlorobenzene. The solvent was removed under reduced pressure and the resulting red oil was chromatographed on neutral alumina and eluted with ethyl acetate. Evaporation of the ethyl acetate under reduced pressure gave a solid which was recrystallized from 2-propanol to give 81.5 g (67.5%) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (**6a**): mp 156–158°; pmr ($CDCl_3$) δ 6.74 (m, 3 H), 3.88 (m, 8 H); ir (KBr) 1640 (C=O pyridone), 1680 (C=O, conjugated) cm^{-1}; uv max (95% C_2H_5OH) 228 (log ε 4.1), 286.5 nm (log ε 4.2).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.64; H, 6.78; N, 4.43.

Alternatively the reaction could be run using a mixture of xylenes as the solvent. In this case the water was removed with a Dean-Stark trap, the reaction time was decreased to 20 hr, and a slightly larger excess of β-propiolactone was used (approximately 15%). Under these conditions the yields of **6a** varied from 41 to 50%.

Preparation of *N*-(β-3-Methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (6b). Following the procedure for the synthesis of **6a**, except for decreasing the frequency of removing the chlorobenzene–water azeotrope to every 3 days, 4.0 g (17.35

mmol) of *N*-(β-3-methoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5b**), 4.0 g (55.5 mmol) of β-propiolactone, and 125 ml of chlorobenzene were converted to 3.4 g (68.8%) of *N*-(β-3-methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (**6b**): mp 119–120°; pmr ($CDCl_3$) δ 3.82 (t, 2 H, J = 7.0 Hz), 3.74 (s, 3 H), 2.87 (t, 2 H, J = 7.0 Hz), 2.33 (s, 4 H); ir (KBr) 1620 (C=O, pyridone), 1670 (C=O, conjugated) cm^{-1}; uv max (95%, C_2H_5OH) 291 (log ε 4.23), 282 (log ε 4.21), 218 nm (log ε 4.09).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.66; N, 4.82.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione (6c). Using the method described for the preparation of **6a**, 18.0 g (0.065 mol) of *N*-(β-3,4-dimethoxyphenethyl)-1-aminocyclohexen-3-one, 10.0 g (0.139 mol) of β-propiolactone, and 400 ml of xylene gave 13.9 g (65%) of **6c**: mp 82.5–83.5° (recrystallized from ether); nmr ($CDCl_3$) δ 6.74 (s, 3 H), 3.82 (m, 8 H, OCH_3N–CH_2), 2.47 (s, 4 H); ir (KBr) 1510, 1605, 1640 (C=O, pyridone), and 1685 (C=O, keto) cm^{-1}; uv max (95% C_2H_5OH) 230 (log ε 4.071), 299 nm (log ε 4.182).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.46; H, 7.16; N, 4.22.

Cyclization of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (6a). To 30 g of polyphosphoric acid at 90° in a 125-ml beaker was added 3.8 g (12.05 mmol) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione(**6a**). The solution was heated 6 hr with occasional stirring and was quenched with 90 g of crushed ice. Aqueous perchloric acid (10%) was added dropwise with stirring until precipitation ceased, and the beaker was covered and cooled overnight at approximately 5°. The precipitate was removed by filtration, washed with cold water, and dried to a constant weight to yield 4.42 g (92.5%) of the crude mixture of cyclization products **7a** and **8a**. In several reactions the yields ranged between 92 and 100%. The solid was dissolved in 150 ml of boiling acetonitrile. To this was added 300 ml of absolute ethanol. The mixture was concentrated to 175 ml by evaporation and was allowed to cool. After standing overnight at room temperature, the solution deposited crystals which were collected by filtration and dried to give 2.0 g (42.2%) of **2,3-dimethoxy-1,3,5(10),8,11,13-hexaene-8-azagonan-17-one perchlorate (7a)**: mp 294–295° dec; pmr (DMSO-d_6). δ 8.95, 8.86, 8.84, 8.76 (q, 2 H), 7.95 (s, 1 H), 7.42 (s, 1 H), 4.86 (t, 2 H, J = 7.0 Hz), 3.74 (m, 2 H), 3.43 (t, 2 H, J = 7.0 Hz), 3.10 (m, 2 H); ir (KBr) 1720 (C=O), 1605 (s, Ar, C=C); uv max (95% C_2H_5OH) 337 (log ε 3.85), 299 (log ε 3.99), 281 (log ε 3.94), 236 nm (log ε 3.90).

Anal. Calcd for $C_{18}H_{18}ClNO_7$: C, 54.62; H, 4.58; N, 3.54. Found: C, 54.52; H, 4.63; N, 3.56.

Evaporation of the filtrate gave 1.9 g (39.9%) of **2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (8a)**: mp 208–209° dec; pmr (DMSO-d_6) δ 8.44 (s, 2 H), 6.96 (s, 1 H), 6.82 (s, 1 H), 4.76 (d, 1 H, J = 9.0 Hz), 3.74 (s, 6 H); ir (KBr) 3300 (OH), 1610 (C=CC=N), 1500 cm^{-1}; uv max (95% C_2H_5OH) 293.5 nm (log ε 4.58).

Anal. Calcd for $C_{18}H_{22}ClNO_7$: C, 54.35; H, 5.07; N, 3.52. Found: C, 54.22; H, 5.39; N, 3.47.

Cyclization of *N*-(β-3-Methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-pyrindan-2,5-dione (6b). Using the procedure for the cyclization of **6a**, 10 g of polyphosphoric acid caused the conversion of 1.5 g of *N*-(β-3-methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (**6b**) to a 1.9-g (quantitative) yield of a mixture of **7b** and **8b**. The precipitate from ethanol–acetonitrile was 0.78 g (41%) of3-methoxy-1,3,5(10),8,11,13-hexaene-8-azagonan-17-one perchlorate (**7b**): mp 263–264° dec; pmr (DMSO-d_6) δ 8.60 (AB, 2 H), 8.32 (d, 1 H, J = 8.5 Hz), 4.27 (t, 2 H, J = 6.5 Hz), 3.91 (s, 3 H), 3.34 (t, 2 H, J = 6.5 Hz); ir (KBr) 1700 (C=O), 1596 (Ar, C=C) cm^{-1}; uv max (95% C_2H_5OH) 286 (log ε 3.78), 265 nm (log ε 3.83).

Anal. Calcd for $C_{17}H_{16}ClNO_6$: C, 55.82; H, 4.41; N, 3.83. Found: C, 55.65; H, 4.45; N, 4.10

Evaporation of the filtrate and recrystallization of the residue from acetone–petroleum ether gave 0.75 g (39%) of 3-methoxyl-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8b**) as a yellow solid: mp 220–222°; pmr (TFA) δ 7.12 (d, 1 H, J = 8.0 Hz), 4.70 (d, 1H, J = 11.0 Hz), 3.76 (s, 3 H); ir (KBr) 1650 (C=C-C=N) cm^{-1}; uv max (95% C_2H_5OH) 293 nm (log ε 4.52).

Anal. Calcd for $C_{17}H_{20}ClNO_6$: C, 55.22; H, 5.45; N, 3.79. Found: C, 55.37; H, 5.46; N, 3.71.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (11). A solution of 1 g (3.02 mmol) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione (**6c**) in 75 ml of methylene chloride was treated with 12 g of activated MnO_2. After stirring for 24 hr, the mixture was filtered, and the insoluble residue was washed well with methylene chloride. Evaporation of the solvent from the combined methylene chloride solutions gave an oil which crystallized from methanol to give 0.40 g (40%) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**11**): mp 184–185.5°; nmr ($CDCl_3$), δ 7.73 (d, 1 H, J = 9.5 Hz), 6.6–6.4 (m, 3 H), 6.30 (d, 1 H, J = 9.5 Hz), 4.33 (t, 2 H, J = 6.5 Hz), 3.73 (s, 3 H), 3.67 (s, 3 H), 2.88 (t, 2 H, J = 6.5 Hz); ir (KBr) 1510, 1540, 1590 (C=O pyridone), 1665 (C=O, keto) cm^{-1}; uv max (95% C_2H_5OH) 227 (log ε 4.00), 283 nm (log ε 4.32).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.51; H, 6.51; N, 4.14.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-2,5-dichloro-7,8-dihydroquinolinium Perchlorate (12). A solution of 1.0 g (3.06 mmol) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**11**) in 20 ml of phosphorus oxychloride was heated under reflux for 0.5 hr. Excess phosphorus oxychloride was removed by evaporation under reduced pressure, and the red residue was dissolved in 20 ml of water, treated with charcoal, and filtered to give a yellow solution. Perchloric acid (10%, aqueous) was added dropwise until precipitation ceased, and the mixture was cooled overnight at 0–5° to complete precipitation. The solid was isolated by filtration and recrystallized twice from acetone to give 0.74 g (59%) of **12**: mp 206–207.5°; nmr (TFA) δ 8.25 (d, 1 H, J = 9.0 Hz), 7.67 (d, 1 H, J = 9.0 Hz), 6.56 (m, 3 H), 6.21 (t, 1 H, J = 4.5 Hz), 4.73 (t, 2 H, J = 6.5 Hz), 3.51 (s, 6 H); ir (KBr) 1455, 1505, 1575, and 1620 cm^{-1} (no C=O); uv max (95% C_2H_5OH) 231 (log ε 4.10), 252 (log ε 3.85), 281 (log ε 4.02), 327 nm (log ε 3.80).

Anal. Calcd for $C_{19}H_{20}Cl_3NO_6$: C, 49.11; H, 4.33; N, 3.01. Found: C, 49.21; H, 4.46: N, 3.03.

Preparation of 2,3-Dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (9a). A suspension of 0.50 g (1.52 mmol) of 2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8a**) in 25 ml of methylene chloride was treated with 10 ml of 5% aqueous sodium hydroxide. The reaction mixture was stirred under nitrogen for 15 min and the layers were separated. The aqueous phase was extracted twice with 10-ml portions of methylene chloride, and the combined organic layers were washed with two 20-ml portions of water and dried over magnesium sulfate under nitrogen. The drying agent was removed by filtration and the solvent was evaporated. The addition of ether to the residue gave a white solid which was recrystallized from ethyl acetate–hexane to give 0.24 g (64%) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**): mp 158–160°; pmr ($CDCl_3$) δ 6.80 (s, 1 H), 6.68 (s, 1 H), 4.52 (d, 1 H, J = 10.0 Hz); ir (KBr) 1640 (C=O), 1560, 1490 cm^{-1}; uv max (95% C_2H_5OH) 293 (log ε 4.63), 228 nm (log ε 4.00); mass spectrum M^+, 299.

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.04; H, 7.00; N, 4.61.

Preparation of 2,3-Dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol Perchlorate (8a) from 9a. To a solution of 0.10 g (0.33 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) in 5 ml of 95% ethanol was added 10 drops of 10% aqueous perchloric acid. The solution was cooled overnight, and the precipitate which formed was collected by filtration to give 0.10 g (75%) of2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8a**) as the monohydrate, mp 120–122°.

Anal. Calcd for $C_{18}H_{24}ClNO_8$: C, 51.74; H, 5.79; N, 3.35. Found: C, 51.26; H, 5.80; N, 3.28.

The solid was dissolved in 20 ml of acetonitrile and 40 ml of absolute ethanol. The volume of the solution was reduced to 20 ml. Hexane was added and the solution was cooled. The resulting solid, mp 208–209°, was collected by filtration. This material was identical in all respects with the material from cyclization of **6a**.

Anal. Calcd for $C_{18}H_{22}ClNO_7$: C, 54.35; H, 5.07; N, 3.52. Found: C, 54.02; H, 5.70; N, 3.47.

Preparation of 3-Methoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (9b). A stirred suspension of 0.50 g (1.34 mmol) of 3-methoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8b**) in 30 ml of methylene chloride was treated with 10 ml of 5% aqueous sodium hydroxide as in the preparation of **9a** to give 0.30 g (82.4%) of 3-methoxyl-1,3,5(10),13-tetraene-8-azagonan-17-one (**9b**): mp 122–125°; pmr ($CDCl_4$) δ 4.67 (m, 1 H), 3.90 (s, 1 H); ir (neat) 1670 (C=O), 1600 (Ar, C=C) cm^{-1}; uv max (95% C_2H_5OH) 293 nm (log ε 4.5); mass spectrum M^+, 269.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 74.40; H, 7.19; N, 5.02.

Preparation of 2,3-Dimethoxy-1,3-5(10)-triene-9β,13β-8-azagonan-17-one (13). A solution of 1.0 g (3.3 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) dissolved in 80 ml of dry tetrahydrofuran was treated with 0.25 g of lithium aluminum hydride and was heated under reflux for 3 hr. Aqueous 10% sodium hydroxide was added to decompose the excess lithium aluminum hydride, and the resulting solid was removed by filtration. The solution was evaporated under reduced pressure and the residue was recrystallized from hexane to give 0.25 g (25%) of 2,3-dimethoxy-1,3,5(10)-triene-9β,13β,14β-8-azagonan-17-one (**13**): mp 150–152°; pmr ($CDCl_3$ δ 6.71 (s, 1 H), 6.58 (s, 1 H), 3.85 (s, 6 H); ir (KBr) 2900, 2800, 1740 (C=O), 1600, 1520 cm^{-1}; uv max (95% C_2H_5OH) 281 nm (log ε 3.84).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.64. Found: C, 71.65; H, 7.88; N, 4.44.

Preparation of 2,3,17-Trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane Iodide (14). A mixture of 103.6 mg (0.346 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) and 5 of methyl iodide was heated under reflux under a positive pressure of nitrogen for 17 hr. The solid which formed was collected by filtration and washed with dry ether. Recrystallization of the solid from methanol gave 136.6 mg (90%) of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane iodide (**14**): mp 166–167°; pmr (DMSO-d_6) δ 7.01 (s, 1 H), 6.86 (s, 1 H), 4.92 (d, 1 H, J = 10.5 Hz), 4.14 (s, 3 H), 3.74 (s, 6 H), 1.50 (m, 1 H); ir (KBr) 1580 (ROC=CC=N), 1500, 1455 cm^{-1}; uv max (95% C_2H_5OH) 290 nm (log ε 4.58).

Anal. Calcd for $C_{19}H_{24}INO_3$: C, 51.81; H, 5.49; N, 3.18. Found: C, 51.65; H, 5.43; N, 3.07.

Preparation of 2,3-Dimethoxy-17-allyloxy-1,3,5(10),8(14),-13(17)-pentaene-8-azagonane Bromide (19). A solution of 1.0 g (3.35 mmol) of2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) in 25 ml of dry acetone was added 0.5 ml of allyl bromide. The solution was heated under reflux for 24 hr. Dry ether (25 ml) was added to cause the precipitation of all salts. The solid material was removed by filtration and recrystallized from methanol to give 0.35 g (25%) of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane bromide (**19**): mp 142–143°; pmr (DMSO-d_6) δ 7.04 (s, 1 H), 6.88 (s, 1 H), 6.02 (m, 1 H), 5.24–5.64)m, 2 H), 5.00 (m, 2 H), 3.72 (s, 6 H); ir (KBr) 1600, 1575 (C=CC=N), 1515 cm^{-1}; uv max (95% C_2H_5OH) 290 nm (log ε 4.54).

Anal. Calcd for $C_{21}H_{26}BrNO_3$: C, 58.83; H, 6.42; N, 3.43. Found: C, 58.56; H, 6.35; N, 3.73.

Attempted Rearrangement of 2,3-Dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane Bromide (19). A suspension of 25.6 mg (0.061 mmol) of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8,(14),13(17)-pentaene-8-azagonane bromide (**19**) in 25 ml of dry toluene was heated under reflux for 19 hr. At that time all material had dissolved. The solvent was removed under reduced pressure to give an oily residue. An infrared spectrum (neat) of the oil was identical with that obtained for 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**).

Reduction of 2,3,17-Trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane Iodide (14). A solution of 0.50 g (1.13 mmol) of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane iodide (**14**) in 50 ml of absolute ethanol was treated with 30 mg (0.79 mmol) of sodium borohydride in 10 ml of absolute ethanol. The resulting solution was stirred at room temperature for 0.5 hr, and the solvent was evaporated at reduced pressure. The residue was dissolved in 50 ml of methylene chloride and washed twice with 10-ml portions of 5% aqueous sodium bicarbonate and once with 10 ml of water and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was evaporated under reduced pressure. The resulting material was dissolved in a minimum amount of benzene and put on a column of neutral alumina (10 g). Elution of the column with 325 ml of benzene gave 0.10 g (31.1%) of 2,3-dimethoxy-1,3,5(10),13(17)-tetraene-9β,14β-8-azagonane (**16**): mp 135–137° after sublimation at 120° (0.2 mm); pmr ($CDCl_3$) δ 6.73 (s, 1 H), 6.68 (s, 1 H), 5.53 (m, 1 H), 3.91 (m, 7 H); ir (KBr) 2910, 2810, 2700, 1675, 1630, 1600, 1525, 767 cm^{-1}; uv max (95% C_2H_5OH) 282 (log ε 3.58), 286 nm (log ε 3.58).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.45; H, 8.13; N, 5.11.

Elution of the column with 30 ml of ethyl acetate gave 0.13 g (36.5%) of 2,3,17-trimethoxy-1,3,5(10),13(17)-tetraene-9β,14β-8-azagonane (**15**): mp 109–110° (recrystallized from petroleum ether); nmr ($CDCl_3$) δ 6.82 (s, 1 H), 6.68 (s, 1 H), 3.89 (m, 9 H), 3.67 (s, 3 H); ir (KBr) 2900, 2800, 2700 (CH), 1690 (C=O), 1600 1520, 770 cm^{-1}; uv max (95% C_2H_5OH) 282 (log ε 3.61), 286 nm (log ε 3.62).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.38; H, 7.89; N, 4.59.

Registry No.—**5a,** 53129-00-3; **5b,** 53129-01-4; **5c,** 27032-09-3; **6a,** 2349-42-0; **6b,** 2118-99-2; **6c,** 2349-40-8; **7a,** 53129-03-6; **7b,** 53129-05-8; **8a,** 53129-07-0; **8b,** 53129-09-2; **9a,** 53129-10-5; **9b,** 53129-11-6; **11,** 53129-12-7; **12,** 53129-14-9; **13,** 53129-15-0; **14,** 53129-16-1; **15,** 53129-17-2; **16,** 53129-18-3; **19,** 53129-19-4; β-3,4-dimethoxyphenethylamine, 120-20-7; 1,3-cyclopentanedione, 3859-41-4; β-3-methoxyphenethylamine, 2039-67-0; 1,3-cyclohexanedione, 504-02-9; β-propiolactone, 57-57-8; methyl iodide, 74-88-4.

References and Notes

(1) Abstracted from the thesis of G. A. Heavner presented to the graduate faculty of the University of New Hampshire in partial fulfillment of the requirements of the Ph.D. degree. University of New Hampshire Fellow 1968–1969, 1971–1973.
(2) M. Nagata, M. Goi, K. Matoba, T. Yamagaki, and R. N. Castle, *J. Heterocycl. Chem.*, **10,** 21 (1973), and ref 3–9 in this article.
(3) A. I. Meyers and J. C. Sircar, *Tetrahedron,* **23,** 785 (1967).
(4) J. Bowler and R. Clarkson, *J. Chem. Soc. C,* 2975 (1968).
(5) (a) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.,* **31,** 1489 (1966); (b) A. A. Akhrem, A. M. Moiseekov, and A. Poselenov, *Izv. Akad. Nauk SSSR, Ser. Khim.,* 2579 (1972); *Chem. Abstr.,* **78,** 71875K (1973).
(6) (a) H. O. Huisman, *Angew. Chem., Int. Ed. Engl.,* **10,** 450 (1971); (b) J. J. Artus, J. J. Bonet, and A. E. Pena, *Tetrahedron Lett.,* 3187 (1973).
(7) J. H. Supple, D. A. Nelson, and R. E. Lyle, *Tetrahedron Lett.,* 1645 (1963).
(8) E. Wenkert, *Accounts Chem. Res.,* **1,** 78 (1968).
(9) H. L. Lochte and A. G. Pittman, *J. Amer. Chem. Soc.,* **82,** 469 (1960).
(10) R. L. Augustine and W. G. Pierson, *J. Org. Chem.,* **34,** 1070 (1969). Other oxidizing agents used to convert arylmethylenes to phenylketones, such as chromic anhydride in acetic anhydride, cerric ammonium nitrate in nitric acid, molecular oxygen with cobalt acetate or tris(triphenylphosphine)rhodium chloride or selenium dioxide, failed to cause oxidation.
(11) (a) C. Ruangsiyanand, H.-J. Rimek, and F. Zymalkowski, *Chem. Ber.,* **103,** 2403 (1970); (b) M. M. Robison, *J. Amer. Chem. Soc.,* **80,** 6254 (1958).
(12) A. I. Meyers, A. H. Reine, and R. Gault, *Tetrahedron Lett.,* 4049 (1967); *J. Org. Chem.,* **34,** 698 (1969).
(13) K. Wiesner, I. Jirkovsky, M. Fishman, and C. A. J. Williams, *Tetrahedron Lett.,* 1523 (1967).
(14) G. Schroll, P. Klemmensen, and S.-O. Lawesson, *Acta Chem. Scand.,* **18,** 2201 (1964).
(15) W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *J. Org. Chem.,* **30,** 3667 (1965).
(16) A. I. Meyers, G. G. Munoz, W. Sobotka, and K. Baburao, *Tetrahedron Lett.,* 255 (1965).
(17) J. C. Sircar and A. I. Meyers, *J. Org. Chem.,* **32,** 1248 (1967).
(18) A. I. Meyers and W. N. Beverung, *Chem. Commun.,* 877 (1968).
(19) B. D. Tilak, T. Ravindranathan, and K. N. Subbaswami, *Tetrahedron Lett.,* 1959 (1966).
(20) R. E. Lyle and S. Edward Mallett, *Ann. N. Y. Acad. Sci.,* **145,** 83 (1967).
(21) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.,* **6,** 45 (1966).
(22) U. Eisner and J. Kuthan, *Chem. Rev.,* **72,** 1 (1972).
(23) L. J. Winters, A. L. Borror, and N. Smith, *Tetrahedron Lett.,* 2313 (1967).
(24) F. Bohlmann, *Chem. Ber.,* **91,** 2157 (1958).
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(26) R. E. Brown, A. I. Meyers, L. M. Trefonas, R. L. R. Towns, and J. N. Brown, *J. Heterocycl. Chem.,* **8,** 279 (1971).
(27) K. H. Bell and P. S. Portoghese, *J. Med. Chem.,* **16,** 203 (1973).