phase was extracted with 1,2-dichloroethane (5 ml), and the combined organic phases were dried ($CaCl_2$) and analyzed by gas chromatography. The product yields are given in the Discussion section.

3-(2,6-Dimethylpyridyl)-*N*-phenylbenzimidate. To a solution of sodium ethoxide (0.28 g, 0.0035 mol) in absolute ethanol (10 ml) were added in quick succession 2,6-dimethyl-3-hydroxypyridine (0.43 g, 0.0033 mol) in absolute ethanol (10 ml) and distilled *N*-phenylbenzimidoyl chloride (0.70 g, 0.0033 mol) in dry ether (5 ml). The mixture was allowed to stand for 3 hr at room temperature then filtered through Celite filter-aid. The solvent was evaporated to give a crystalline material. Recrystallization from light petroleum–acetone gave 3-(2,6-dimethylpyridyl)-*N*-phenylbenzimidate (0.75 g, 75%), identical with the compound obtained above.

Acknowledgments. This work was carried out with the financial support of a National Institutes of Health grant (GM 16626) for which we are grateful. We also wish to thank Reilly Tar & Chemical Corp. for the gift of pyridine derivatives.

Registry No.—**1**, 1613-37-2; **2**, 53112-31-5; **3**, 5468-85-9; **4**, 32888-92-9; **7**, 32888-93-0; **10**, 32953-48-3; **11**, 2405-06-3; **12**, 3099-29-4; **14**, 32888-94-1; **15**, 4637-59-6; **17**, 32888-95-2; *N*-phenylbenzimidoyl chloride, 4903-36-0; *N*-phenylbenzonitrilium hexachloroantimonate, 51293-24-4; *o*-nitro-*N*-benzylformanilide, 53112-32-6; 2-anilino-1-benzylbenzimidazole, 24068-33-5; 1-anilinoisoquinoline, 13797-20-1; 3-hydroxyquinoline, 580-18-7; 4-nitroquinoline 1-oxide, 56-57-5; 4-chloro-3-hydroxyquinoline, 32435-60-2.

References and Notes

(1) For prelimary communication of a portion of this work, see R. A. Abramovitch and R. B. Rogers, *Tetrahedron Lett.*, 1951 (1971).
(2) (a) R. A. Abramovitch and G. M. Singer, *J. Org. Chem.*, **39**, 1795 (1974); (b) R. A. Abramovitch and R. B. Rogers, *ibid.* **39**, 1802 (1974).
(3) W. E. Parham and K. B. Sloan, *Tetrahedron Lett.*, 1947 (1971).
(4) T. Kato and T. Niitsuma, *Chem. Pharm. Bull. (Tokyo)*, **13**, 963 (1965); *Chem. Abstr.*, **63**, 14804 (1965).
(5) E. Matsumura, T. Hirooka, and K. Imagawa, *Nippon Kagaku Zasshi*, **82**, 616 (1961).
(6) The same product was isolated in low yield (4.3%) in the reaction of *N*-1-adamantylbenzonitrilium bromopentachloroantimonate with **1** (G. M. Singer, Ph.D. Thesis, University of Saskatchewan, 1970).
(7) W. Dymek and Z. Zlorowska, *Rocz. Chem.*, **38**, 925 (1964).
(8) S. Kajihara, *Nippon Kagaku Zasshi*, **86**, 1060 (1966); *Chem. Abstr.*, **65**, 16936f (1966).
(9) R. A. Abramovitch and E. M. Smith in "Pyridine and its Derivatives: a Supplement," Part 2, (R. A. Abramovitch, Ed.), Wiley-Interscience, New York, N.Y., 1974, Chapter IV, pp 165–170.
(10) V. I. Klimko, V. A. Mikhalev, A. P. Skoldinov, *Zh. Obshch. Khim.*, **30**, 1258 (1960); *Chem. Abstr.*, **55**, 550h (1961).
(11) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 343 (1946).
(12) S. Takahashi and H. Kano, *Chem. Pharm. Bull. (Tokyo)* **11**, 1475 (1963).
(13) S. M. Gadekar, J. L. Frederick, J. Semb, and J. R. Vaughan, *J. Org. Chem.*, **26**, 468 (1961).
(14) H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).
(15) M. Hamana and O. Hoshino, *Yakagaku Zasshi*, **84**, 35 (1964); *Chem. Abstr.*, **61**, 3069 (1964).
(16) W. H. Mills and W. H. Watson, *J. Chem. Soc.*, **97**, 741 (1910).
(17) A. E. Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, **55**, 7 (1924); *Chem. Abstr.*, **19**, 1572 (1925).
(18) P. Oxley, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 1618 (1948).
(19) T. Okamoto, H. Hayatsu, and Y. Baba, *Chem. Pharm. Bull. (Tokyo)* **78**, 892 (1960); *Chem. Abstr.*, **55**, 23528i (1961).
(20) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 28 (1964); *Chem. Abstr.*, **61**, 3069a (1964).

Pyridazino[1,2-*a*]pyridazine Chemistry. An Attempted Synthesis of 1,6-Diazacyclodecapentaene

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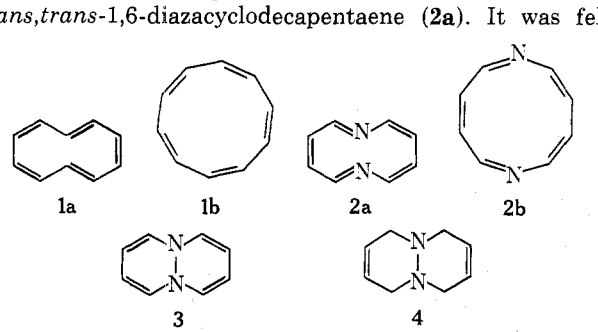
Some new derivatives of the pyridazino[1,2-*a*]pyridazine ring system have been prepared and their chemistry has been studied as possible synthetic precursors to 1,6-diazacyclodecapentaene.

Several years ago it was suggested[1] that the destabilizing effect[2a] of interior nonbonded hydrogen repulsion in *trans,trans*-cyclodecapentaene (**1a**) could be avoided in *trans,trans*-1,6-diazacyclodecapentaene (**2a**). It was felt



1a **1b** **2a** **2b**

3 **4**

that interaction between electron pairs on nitrogen in **2a** might not be serious and therefore the molecule might possibly exist in a nearly strain-free planar configuration. Furthermore, differences in bond angle requirements for the carbon–nitrogen bonds might be sufficient to enable the *all-cis*-1,6-diazacyclodecapentaene (**2b**) to exist as a stable planar species as opposed to the all carbon system **1b**.[2a,b]

The above considerations, as related to obtaining a monocyclic 10π-electron system exhibiting aromatic stability, indicated **2** to be an interesting synthetic objective.

Results and Discussion

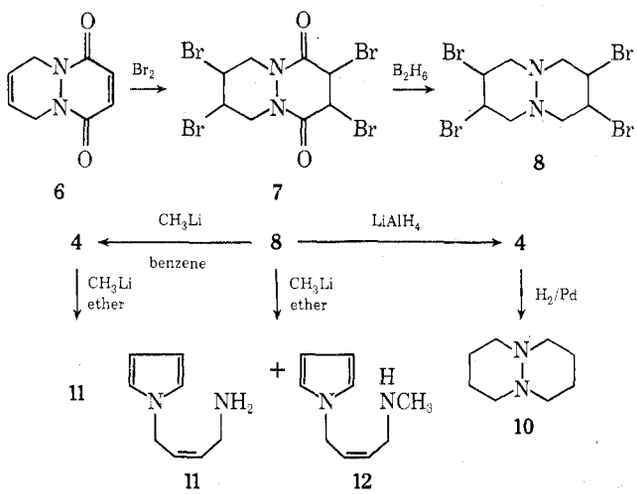
Consideration of various synthetic approaches to **2** suggested a "valence-bond"[3] route as an attractive possibility. Accordingly, the synthetic objective was reduced to one of devising a suitable method for the preparation of the unknown pyridazino[1,2-*a*]pyridazine (**3**).

Scrutiny of the literature reveals no known derivatives of ring system **3**; indeed, even saturated derivatives of **3** have been little studied.[4] A reasonable synthetic path appeared to be to prepare a partially saturated derivative of **3** (*e.g.*, **4**) and introduce the additional unsaturation *via* a halogenation–dehydrohalogenation sequence.

The readily available dihydropyridazino[1,2-*a*]pyridazinedione **6**[5] appeared an obvious precursor to **4** if reduction of the hydrazide function to the corresponding hydrazine could be carried out. In practice, this was accom-

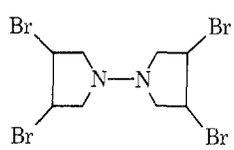
plished by first protecting the troublesome α,β-unsaturated system in **6** followed by reduction (Scheme I).

Scheme I



Treatment of **6** in chloroform with 2 equiv of bromine at room temperature led to the tetrabromo derivative **7** in high yield as evidenced by the elemental analysis, correct molecular weight by mass spectroscopy, and the nmr spectrum, which exhibited a sharp singlet at δ 5.05 assignable to the equivalent protons α to the hydrazide carbonyl groups.

Reduction of **7** with diborane in boiling tetrahydrofuran[6] gave **8** in 60% yield as a white crystalline solid, probably a mixture of bromo isomers. The formulation of **8** as the desired tetrabromoperhydropyridazino[1,2-*a*]pyridazine and not as the isomeric *N,N'*-bispyrrolidine ring system (*e.g.*, **9**)[7] followed from chemical degradation studies. Thus, pro-



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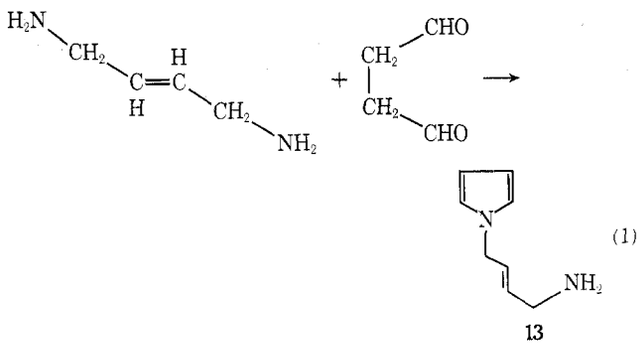
longed treatment of **8** with lithium aluminum hydride in boiling tetrahydrofuran gave a liquid product assigned structure **4** (see below).[8] Catalytic hydrogenation of this product at room temperature and atmospheric pressure gave perhydropyridazino[1,2-*a*]pyridazine (**10**) which had identical ir and nmr spectra and picrate melting point with those of an authentic sample.[9] In addition, the nmr spectrum of authentic[10] *N,N'*-bispyrrolidine was different from the spectrum of **10** obtained from **8** *via* **4**. These results established that no rearrangement[7] of the pyridazino[1,2-*a*]pyridazine ring system had taken place either during the bromination of **6** or the reduction of **7** to **8**.

The last step in the proposed synthetic sequence, the elimination of four molecules of hydrogen bromide from **8** in hopes of producing the desired **3**, unfortunately, proved completely frustrating. Treatment of **8** with a variety of bases in various solvents under nitrogen resulted in either no reaction (*e.g.*, boiling triethylamine, bis(1,8-dimethylamino)naphthalene in boiling tetrahydrofuran) or black, intractable tars (potassium *tert*-butoxide in tetrahydrofuran, sodium amide in liquid ammonia, sodium isopropoxide in tetrahydrofuran). Boiling a solution of **8** and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in tetrahydrofuran for several hours under nitrogen gave intractable dark mixtures, whereas limiting the reaction to shorter periods gave mixtures of partially brominated products. When these mixtures were treated again with DBU, dark products were obtained from which no identifiable materials could be isolated.

In contrast to the above results, treatment of a suspension of **8** in ether with ethereal methyllithium under nitrogen gave a rapid reaction. Work-up with water and separation of the mixture by vpc gave two products assigned structures **11** and **12** on the basis of the following lines of evidence. First, mass spectroscopy established a molecular formula of $C_8H_{12}N_2$ and $C_9H_{14}N_2$ for **11** and **12**, respectively. In addition, the cracking patterns of both compounds were very similar with fragments in **12** that suggested an $NHCH_3$ group.

Second, the nmr spectra of the two compounds were essentially identical except for the presence in **12** of a sharp three-proton singlet in the region expected for an $NHCH_3$ (δ 2.42). A characteristic AA'XX' pattern in both compounds suggested an N-substituted pyrrole derivative, whereas absorptions attributable to two different allylic methylene groups and two vinyl protons were clearly recognizable in kind and number (see Experimental Section).

Finally, synthesis of a model compound[11] was carried out, eq 1. Addition of an aqueous solution of succindial-



(1)

13

dehyde to *trans*-2-butene-1,4-diamine[11,12] gave **13** in low yield. Spectral data clearly established the similarity between **11** and **13**. For example, the nmr spectrum of **13** was very similar to that of **11** with only small differences (see Experimental Section) in chemical shift and coupling constants of the vinyl and allylic methylene protons, attributable to different stereochemistry about the double bond.[14] The above observations establish a cis stereochemistry about the double bond in **11** and **12**.

That **12** arises as a secondary product from **11** (or precursor to **11**) during the reaction was established from consideration of the intermediate in the rearrangement (see below) and the fact that varying reaction conditions dramatically affected the ratio of **11** and **12** in the product mixture. For example, when the reaction between **8** and methyllithium was carried out at room temperature with a stream of nitrogen passing through the solution, much less **12** than **11** was produced. On the other hand, running the reaction in a closed system led to a marked increase in the yield of **12** relative to **11**. These results point to the formation of **12** *via* methylation of a nitrogen anion of **11** (or precursor to **11**) by methyl bromide produced from initial metal–halogen exchange between **8** and methyllithium in the early stages of the reaction.

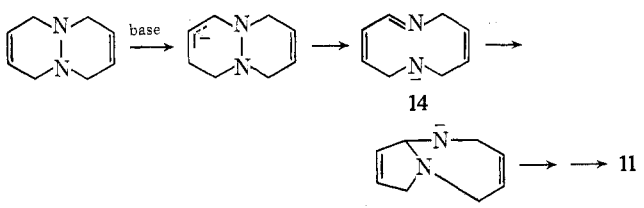
When a benzene suspension of **8** was treated with ethereal methyllithium, a single new product was obtained which proved identical with the product previously obtained from $LiAlH_4$ reduction of **8**, *i.e.*, **4**. The structure of **4** followed from the previous hydrogenation results giving the known perhydropyridazino[1,2-*a*]pyridazine and the fact that the nmr spectrum of **4** showed only a broadened singlet (δ 5.55) assignable to the vinyl hydrogen and a broad multiplet (δ 3.6–2.8) for the remaining allylic hydro-

gens. This nmr spectrum is consistent only with the symmetrical disposition of double bonds indicated in **4**.

That **4** is an intermediate in the formation of **11** (and ultimately **12**) was established by the fact that pyrrole **11** was readily produced when an ether solution of **4** was treated with methyllithium. Furthermore, when the reaction between **8** and methyllithium in ether was interrupted after short reaction time, nmr and vpc analysis definitely established the presence of **4** in the reaction mixture.

While there exists no direct experimental evidence regarding the mechanism of the rearrangement of diene **4** to pyrrole **11**, a possibility is outlined in Scheme II.

Scheme II



It is interesting to compare the proposed cyclization of anion **14** to the cyclization step in the generally accepted mechanism of the classical Fischer indole synthesis;[15] the overall driving force for both rearrangements, of course, is related to the formation of pyrrole rings.

Experimental Section[16]

2,3,7,8-Tetrabromoperhydropyridazino[1,2-*a*]pyridazine-1,4-dione (7). To a solution of 10.7 g (0.065 mol) of 6,9-dihydropyridazino[1,2-*a*]pyridazine-1,4-dione (**6**)[5] in 200 ml of chloroform cooled in a water bath was added dropwise a solution of 20.8 g (0.13 mol) of bromine in 50 ml of chloroform. The resulting mixture was stirred at room temperature for 2 days. After this time the yellow solution was filtered from a small amount of insoluble solid and the solvent was removed under reduced pressure leaving 30.7 g (98%) of yellow solid, mp 164–166°. Recrystallization of a small portion from a minimum volume of chloroform gave an analytical sample: mp 181–183° dec; ir (KBr) 5.97 μ (C=O); mass spectrum *m/e* 480 (M^+), 401 (M − Br).

Anal. Calcd for $C_8H_8Br_4N_2O_2$: C, 19.9; H, 1.67; N, 5.77; Br, 66.1. Found: C, 19.6; H, 2.0; N, 5.7; Br, 66.0.

2,3,7,8-Tetrabromoperhydropyridazino[1,2-*a*]pyridazine (8). To a slurry of 10.0 g (0.021 mol) of **7** in 50 ml of tetrahydrofuran was added 55 ml (0.055 mol) of commercially available 1 *M* borane in tetrahydrofuran. The mixture was stirred and refluxed under nitrogen for 30 min and cooled, and 10 ml of 6 *N* hydrochloric acid was carefully added. The acidic reaction mixture was then refluxed for 4 min and then concentrated to about one-quarter volume under reduced pressure. The white solid was collected, washed well with a large volume of water, and dried. A white product was obtained: 5.8 g (60%); mp 198–199° dec. An analytical sample was prepared by recrystallization from tetrahydrofuran: mp 210–211° dec; mass spectrum *m/e* 452 (M^+), 373 (M − Br).

Anal. Calcd for $C_8H_{12}Br_4N_2$: C, 21.1; H, 2.65; N, 6.14; Br, 70.1. Found: C, 20.9; H, 2.8; N, 5.9; Br, 69.8.

Reaction of 8 in Benzene With Methyllithium. To 300 ml of benzene under nitrogen was added 44 ml (0.088 mol) of 2 *M* methyllithium in ether. To this stirred mixture was added all at once 9.12 g (0.02 mol) of **8**. The reaction mixture was stirred at room temperature for 2 hr under nitrogen, after which 40 ml of water was added. The clear benzene layer was separated, dried over anhydrous calcium sulfate, and concentrated by distillation through a 6-in. Vigreux column. The residue was distilled under reduced pressure giving 1.1 g (41%) of **4** as a colorless liquid: bp 72–75° (4 Torr); nmr (CCl_4) δ 5.55 (br s, 4 H), 3.6–2.8 (br m, 8 H); mass spectrum *m/e* 136 (M^+). A yellow monopicrate was prepared in the usual manner, mp 138–139° (from methanol).

Anal. Calcd for $C_{14}H_{15}N_5O_7$: C, 46.0; H, 4.14; N, 19.2. Found: C, 46.1; H, 4.2; N, 19.2.

Reaction of 8 with Lithium Aluminum Hydride in Tetrahydrofuran. To a slurry of 2.0 g of $LiAlH_4$ in 200 ml of tetrahydrofuran was added all at once 2.28 g (0.005 mol) of **8**. The mixture was heated at reflux for 72 hr and cooled, and 1 ml of water was carefully added followed by 1 ml of 15% aqueous sodium hydroxide solution and then 2 ml of water. The precipitate was removed by filtration and the clear tetrahydrofuran filtrate was dried over anhydrous calcium sulfate. The solvent was removed by distillation leaving a colorless liquid residue. Nmr analysis showed only absorptions attributable to **4** (in addition to butanol). A small sample of the material was treated with ethanolic picric acid giving a yellow picrate, mp 136–138°, with ir spectrum identical with that of the picrate of **4** prepared above. A sample of **4** in ether was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon. Concentration of the filtered ether solution gave a colorless liquid with ir and nmr spectra identical with those of an authentic sample[9] of perhydropyridazino[1,2-*a*]pyridazine, picrate mp 152–153° (lit.[9] mp 155°).

Reaction of 8 in Ether with Methyllithium. A slurry of 4.56 g (0.01 mol) of **8** in 15 ml of dry ether was cooled in an ice bath under nitrogen. To this stirred slurry was added dropwise 30 ml (0.06 mol) of 2 *M* methyllithium in ether. The solid material slowly dissolved. The reaction mixture was stirred an additional hour after all the solid had dissolved and then water was carefully added. The ether layer was separated, dried over anhydrous calcium sulfate, and concentrated to an oil. The crude product was separated into two major components by preparative vpc (5 ft × 0.25 in. 15% SE-30 on Anakrom ABS) at 130°. The first component (**11**) was collected as a colorless liquid: nmr ($CDCl_3$, 90 MHz) δ 6.64 (t, 2 H), 6.15 (t, 2 H), 5.67 (m, 2 H), 4.53 (d, 2 H), 3.40 (d, 2 H), 1.24 (s, 2 H (exchangeable)); mass spectrum *m/e* calcd for $C_8H_{12}N_2$, 136.1000; found, 136.1013. The second component (**12**) also was a colorless liquid: nmr ($CDCl_3$, 90 MHz) δ 6.64 (t, 2 H), 6.15 (t, 2 H), 5.71 (m, 2 H), 4.55 (d, 2 H), 3.31 (d, 2 H), 2.42 (s, 3 H), 1.40 (s, 1 H (exchangeable)); mass spectrum *m/e* calcd for $C_9H_{14}N_2$, 150.1157; found, 150.1169.

Reaction of *trans*-2-Butene-1,4-diamine with Succindialdehyde. Preparation of 13. An aqueous solution containing 0.0025 mol of succindialdehyde[17] was added dropwise to a solution of 0.215 g (0.0025 mol) of *trans*-2-butene-1,4-diamine[18] in 10 ml of water at room temperature. The mixture was stirred for 30 min and then filtered from a solid which had formed. The filtrate was extracted with ether. The combined dried ether extracts were concentrated to an oil, 0.049 g, which was purified by preparative vpc (5 ft × 0.25 in. 15% SE-30 on Anakrom ABS) at 140° to give **13** as a colorless liquid: nmr ($CDCl_3$, 90 MHz) δ 6.64 (t, 2 H), 6.15 (t, 2 H), 5.73 (m, 2 H), 4.46 (m, 2 H), 3.31 (m, 2 H), 1.21 (br s, 2 H (exchangeable)); mass spectrum *m/e* calcd for $C_8H_{12}N_2$, 136.1000; found, 136.0986.

Acknowledgment. The author wishes to thank Mr. D. P. Maier and Dr. T. H. Regan of these laboratories for assistance in obtaining and interpreting mass spectral and nmr data, respectively.

Registry No.—**4**, 38704-81-3; **4** monopicrate, 53166-04-4; **6**, 3661-09-4; **7**, 53166-05-5; **8**, 53166-06-6; **11**, 53166-07-7; **12**, 53166-08-8; **13**, 53166-09-9; *trans*-2-butene-1,4-diamine, 40930-37-8; succindialdehyde, 638-37-9; methyllithium, 917-54-4; lithium aluminum hydride, 16853-85-3.

References and Notes

(1) A. E. Blood and C. R. Noller, *J. Org. Chem.*, **22**, 873 (1957).
(2) (a) T. L. Burkoth and E. E. van Tamelen, "Nonbenzenoid Aromatics," J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, Chapter 3. (b) S. Masamune, K. Hojo, G. Bigam, and D. L. Rabenstein, *J. Amer. Chem. Soc.*, **93**, 4966 (1971).
(3) E. E. van Tamelen and B. C. T. Pappas, *J. Amer. Chem. Soc.*, **93**, 6111 (1971).
(4) R. N. Castle, "The Chemistry of Heterocyclic Compounds; Condensed Pyridazines Including Cinnolines and Phthalazines," Vol. 27, A. Weissberger, Ed., Wiley, New York, N. Y., 1973, pp 1017–1030.
(5) R. A. Clement, *J. Org. Chem.*, **27**, 1115 (1962).
(6) H. Feuer and F. Brown, Jr., *J. Org. Chem.*, **35**, 1468 (1970).
(7) For a related rearrangement see E. Hedaya, R. L. Hinman, V. Schomaker, S. Theodoropulos, and L. M. Kyle, *J. Amer. Chem. Soc.*, **89**, 4875 (1967).
(8) Reduction of vicinal dihalides with $LiAlH_4$ generally leads to olefins; see N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 903.

(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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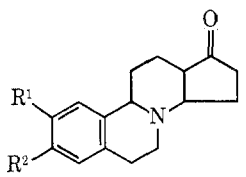
Received July 25, 1974

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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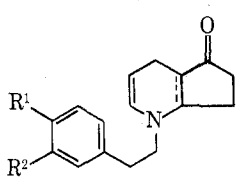

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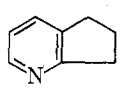

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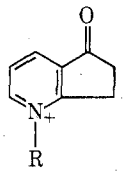
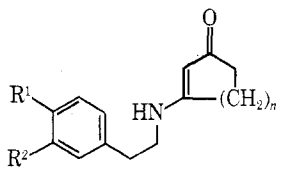


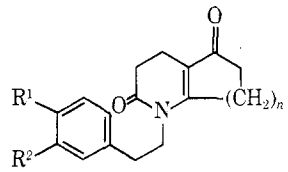
3a, R = $ArCH_2CH_2$
b, R = H

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