That the ion formed initially during the hydrolysis of **4** had considerable charge delocalization is suggested by considering a comparison of the solvolysis rate of **4** in aqueous ethanol[13] with that of cyclopropyl chloride (Table I). Although a direct comparison of all the numerical values in the table is not possible because of the variety of solvents, temperatures, and leaving groups employed by various workers, it seems clear that the introduction of a cyclopropyl group into the 1 position of cyclopropyl chloride has a very large accelerating effect compared with the introduction of a 1-methyl or even a 1-phenyl group on cyclopropyl bromide and tosylate, respectively. Extensive charge delocalization in the ion formed initially during the solvolysis of 4 would be expected on the basis of the well-known behavior of the cyclopropylcarbinyl system[14] and is undoubtedly responsible for the unique solvolysis behavior of chloride **4**. Further studies on systems of this type are in progress.[15]

Table I. Solvolysis Rates of Selected Cyclopropyl Derivatives

Compound	Temp, °C	Solvent	k, sec^{-1}
Cyclopropyl chloride	95	50% EtOH	2.5×10^{-10} [a]
1-Chlorobicyclopropyl	95	50% EtOH	1.58×10^{-4} [b]
Cyclopropyl bromide	130	50% EtOH	2.6×10^{-6} [c]
1-Methylcyclopropyl bromide	130	50% EtOH	1.05×10^{-4} [c]
Cyclopropyl tosylate	108	HOAc	1.5×10^{-7} [d]
1-Phenylcyclopropyl tosylate	108	HOAc	1.93×10^{-3} [e]

[a] Extrapolated data from ref 1; see J. A. Landgrebe and D. E. Applequist, *J. Am. Chem. Soc.*, **86**, 1536 (1964). [b] This work. [c] E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 2719 (1961). [d] Extrapolated from data in ref 1. [e] Reference 2b.

(13) A substantial amount of ketone **8** was also formed during the solvolysis of **4** in 50 vol. % aqueous ethanol, *i.e.*, under the conditions of the kinetic study. Most if not all of the other silver ion assisted hydrolysis products appear to be present as products of the aqueous ethanolysis.

(14) P. von R. Schleyer and G. W. Van Dine, *J. Am. Chem. Soc.*, **88**, 2321 (1966), and references cited therein.

(15) NOTE ADDED IN PROOF. Recent evidence for trapping a cyclopropyl cation in very low yield has been reported by W. Kirmse and H. Schütte, *ibid.*, **89**, 1284 (1967).

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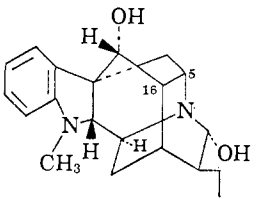
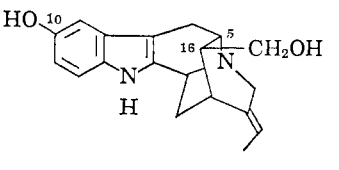
The Synthesis of Ajmaline[1]

Sir:

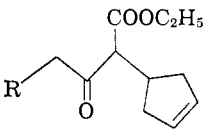
Numerous naturally occurring ajmaline–sarpagine type alkaloids[2] are structurally characterized by the presence of the quinuclidine ring and the C_5 and C_{16} bond linkage, *e.g.*, ajmaline (**1**) and sarpagine (**2**).[3] Since the structural elucidation of ajmal ne by Woodward[4a] and Robinson,[4b] the unique features of the alkaloids have presented a considerable challenge to synthetic organic chemists. We describe herein the first total synthesis of ajmaline.



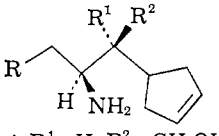
1



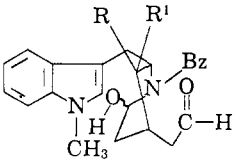
2



3, R = N-Methyl-3-indolyl



4, $R^1 = H$; $R^2 = CH_2OH$
4a, $R^1 = CH_2OH$; $R^2 = H$



6, R = CH_2OBz; $R^1 = H$
6a, R = H; $R^1 = CH_2OBz$

Condensation[5] of the magnesium chelate of ethyl hydrogen Δ^3-cyclopentenylmalonate[6] with N-methyl-3-indolacetyl chloride, mp 9–11°, provided in 80% yield a keto ester (**3**), mp 20–23°. Reaction of **3** with methoxyamine followed by lithium aluminum hydride afforded in 70% yield an approximately 2:1 mixture of readily separable epimeric α,γ-amino alcohols **4** [diacetyl derivative, mp 140–141°; dibenzoyl derivative **5**, amorphous] and **4a**, mp 113.5–114.5° [diacetyl derivative, mp 117–118°; dibenzoyl derivative **5a**, mp 170–172°]. These epimeric series of compounds are both useful for the synthesis of natural products, and they are interconvertible at a later stage of the synthesis (*vide infra*). Treatment of **5** and **5a** with osmium tetroxide and then sodium metaperiodate afforded quantitatively aldehydes **6** and **6a**,[7] which were warmed with acetic acid at 50° for 1 hr to give tetracyclic aldehydes **7** and **7a** in 40 and 50% yield, respectively. Structures **7** and **7a** were compatible with spectral data[8] of the respective compounds and

(1) This work was presented before the Chemical Institute of Canada Symposium, Banff, Alberta, Canada, Aug 31–Sept 2, 1966.

(2) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, Germany, 1964, p 67.

(3) W. I. Taylor, *Alkaloids*, **8**, 785 (1965).

(4) (a) R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956); (b) R. Robinson, *ibid.*, **69**, 40 (1957).

(5) R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).

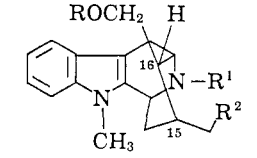
(6) Prepared from the corresponding diethyl ester: C. C. Lee and E. W. C. Wong, *Tetrahedron*, **21**, 539 (1965).

(7) The preparation of dialdehydes by this procedure was utilized in earlier indole alkaloid syntheses: (a) E. E. van Tamelen, M. Sharma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Am. Chem. Soc.*, **80**, 5006 (1958); (b) E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Letters*, **No. 19**, 30 (1960).

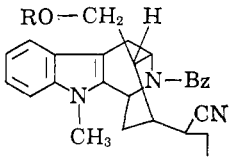
(8) Spectral data included ultraviolet, infrared, nmr, and mass spectra. Compounds with no description of melting points have been amorphous. These compounds were purified until each gave a single spot on thin layer chromatography, using several solvent systems. All new crystalline compounds gave satisfactory elemental analyses.

further characterized by converting them in more than 90% yield into the corresponding dihydroxy secondary amines **7′**, mp 208–209°, and **7a′**, mp 162–163°, with lithium aluminum hydride and then catalytic hydrogenation.

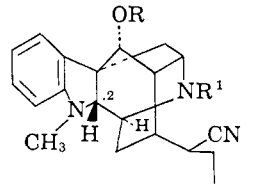
Conversion of **7** into the cyano compound **8** was readily achieved by treatment with hydroxylamine followed by benzoyl chloride in warm pyridine. The anion of **8** (triphenylmethylsodium–tetrahydrofuran) was treated with excess ethyl iodide to provide in 70% yield monoethyl compounds, from which a pure ethyl cyano compound **9**[8] was isolated in 60–70% yield. Brief treatment of **9** with sodium methoxide removed the benzoyl group from the ester to give a hydroxy compound (**10**), mp 202.5–204.5°. Similarly, **8a** was converted into **9a**[8] and **10a**.[8] Spectra[8] of **9**, **10**, **9a**, and **10a** were identical with those of the corresponding degradation products of ajmaline, as shown below.



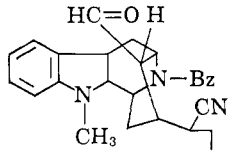
7, R = R¹ = Bz; R² = CHO
7′, R = R¹ = H; R² = CH_2OH
8, R = R′ = Bz; R² = CN



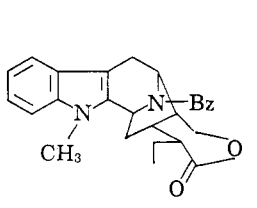
9, R = Bz
10, R = H
13, R = H
14, R = Bz



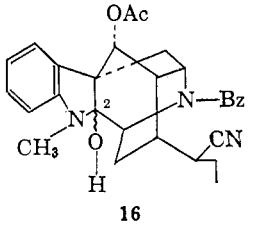
11, R = H; R¹ = Bz
17, R = Ac; R¹ = Bz
18, R = H; R¹ = $CH_2C_6H_5$
19, R = R¹ = H



12



15



16

Compounds **7a**, **7a′**, **8a**, etc., are epimeric at C_{16} with **7**, **7′**, **8**, etc., respectively. Compounds **9** and **10** are racemates; **13** and **14** are the *d* (or *l*) isomers.

Treatment of ajmaline oxime[9] with benzoyl chloride in warm pyridine followed by sodium hydroxide provided a cyanobenzamide (**11**), mp 265–266°. Reaction of **11** with lead tetraacetate[3] followed by neutral work-up afforded an aldehyde (**12**), mp 219–220°, nmr ($CDCl_3$, 60°)[10] τ 0.45 (CHO) and 6.46 (N–CH_3), which was reduced with sodium borohydride to the corresponding hydroxy compound **13**, mp 228–230° and 261–262°, O-benzoate (**14**).[10] In the presence of alumina **12** was equilibrated with its epimer, **12a**; nmr ($CDCl_3$, 60°)[10] τ 0.32 (CHO) and 6.54 (N–CH_3), in a 3:7 ratio in favor of **12a**. Thus **12** and **12a** were interconvertible. The sodium borohydride reduction of **12a** provided a hydroxy compound (**13a**) which was converted with hydrochloric acid to a lactone (**15**), mp 312–313°. Compounds **13** and **13a** were oxidized with dimethyl sulfoxide and acetic anhydride (or carbodiimide)[11] to afford **12** and **12a**, respectively. Identity of spectral data[8] of **13**, **14**, **13a**, and **14a** with those of **10**, **9**, **10a**, and **9a**, respectively, established the structures and stereochemistry of synthetic intermediates.

Compound **12** upon treatment with hydrochloric acid in acetic acid and acetic anhydride underwent cyclization to afford in 65% yield compound **16**, which was hydrogenated with platinum catalyst in 6 *N* hydrochloric acid to yield in 60% yield compound **17**, mp 202–204°, and the corresponding 2 epimer in 30% yield.[12,13] Reduction of **17** with lithium triethoxyaluminum hydride provided the corresponding benzyl derivative **18**, mp 170.5–171.5°, which was in turn hydrogenolyzed to a secondary amine (**19**), mp 260–262°.[9] Since **19** has already been converted into **1** with lithium aluminum hydride,[9] we have completed the first synthesis of ajmaline.[14]

Acknowledgment. The authors are grateful to the National Research Council of Canada for financial support.

(9) F. A. L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, *J. Chem. Soc.*, 1242 (1954).

(10) All compounds containing the benzamide group showed temperature-dependent nmr spectra.

(11) A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 1762 (1966), and references cited therein.

(12) Compound **16** existed exclusively in the indoleninium form under these conditions: λ_{max}^{6NHCl} 294 mμ (ε 7200), 244 (11,700), and 236 (13,200).

(13) Catalytic hydrogenation of 21-deoxyajmalal-A[3] and 2-hydroxyvincamedine under acidic conditions proceeded from the α side of the compounds to yield 2-*epi* series of ajmaline type compounds [J. Gosset-Garnier, J. Le Men, and M.-M. Janot, *Bull. Soc. Chim. France*, 676 (1965)]. Dreiding models of these compounds reveal that the α and β sides present only a slight difference in steric hindrance toward hydrogenation. The exclusive α attack reported above was presumably due to the presence of the protonated nitrogen atom in the α side. In accord with this view, **16**, in which the amine was benzoylated, provided predominantly a compound of the normal series.

(14) Compound **15** was readily converted into N-methyl-10-desoxydihydrosarpagine[3] through a sequence of four steps in 35% over-all yield.

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The Stereospecific Introduction of a Vicinally Functionalized Angular Methyl Group. A Synthesis of *l*-Valeranone

Sir:

The molecular rearrangement accompanying the transformation of β-diketones and related substances into monoketones by the action of zinc and acid has been interpreted in terms of reductive formation of cyclopropanols followed by acid-induced ring cleavage.[1]

(1) (a) E. Wenkert and E. Kariv, *Chem. Commun.*, 570 (1965); (b) B. R. Davis and P. D. Woodgate, *J. Chem. Soc.*, 2006 (1966), and references therein.