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Synthesis of a Tetracyclic Ajmalicine Analogue

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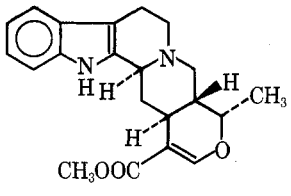
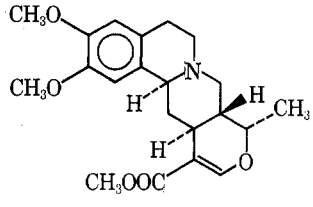
The synthesis of a tetracyclic analogue (**2**) of the heteroyohimbine alkaloid ajmalicine (**1**) is described. The synthesis makes use of a novel alternative to the Korte reaction for the preparation of the dihydropyran ester portion (**11**) of the molecule.

A number of syntheses of indole alkaloid analogues lacking the pyrrole ring of the natural products has been reported.[1] These syntheses were undertaken either with the aim of obtaining medicinally useful substances or as model studies for the synthesis of the natural alkaloids. With the former goal in mind it appeared worthwhile to prepare such a tetracyclic version of the heteroyohimbine alkaloid ajmalicine (**1**)[2] as a potential hypotensive agent.

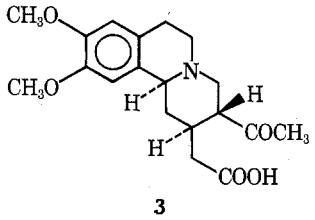


1

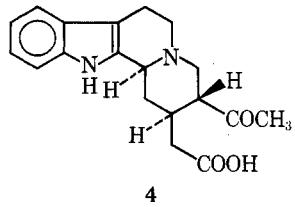


2

We selected **2** as our target, reasoning that it could be prepared from the intermediate **3**, used in van Tamelen's emetine synthesis,[3] by applying the methods developed for the synthesis of ajmalicine from the corresponding indole-containing intermediate **4**, described in the same paper.[3]



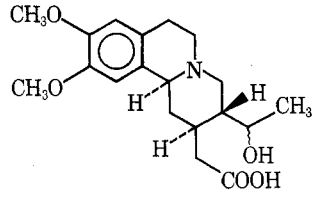
3



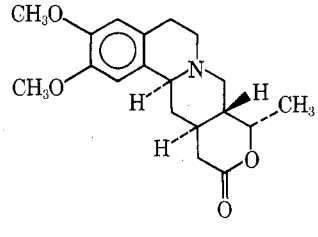
4

Reduction of **3** with sodium borohydride in aqueous potassium hydroxide gave the hydroxy acid **5**. The NMR spectrum of this substance showed that it was a 50:50 mixture of the two epimeric alcohols [a methyl doublet at δ 1.26 (J = 6.75 Hz) collaped on irradiation at δ 4.71, while a doublet at δ 1.30 (J = 6.20 Hz) collapsed on irradiation at δ 4.29].

The lactone **6** was prepared from **5** either with 1-cyclohexyl-3-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate in pyridine or with ethanolic hydrogen chloride. One recrystallization of the crude lactone gave material which was a single isomer (NMR), presumably having the configuration indicated by analogy with van Tamelen's pentacyclic lactone **7** which was converted to ajmalicine.[3] Surprisingly, although a variety of conditions was tried, treatment of **6** with triphenylmethylsodium in dioxane followed by addition of methyl formate did not lead to the formation of the α-hydroxymethylene lactone. van Tamelen found that the lactone **7** underwent condensation under these conditions.[3] Conceivably, in the case of **7**, proton abstraction α to the carbonyl group was facilitated by an intramolecular process involving initial deprotonation of the indole N–H.



5



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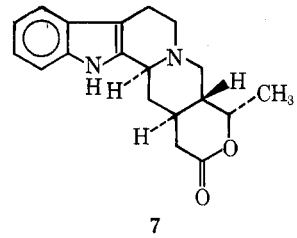
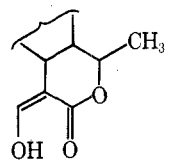


7

We had intended to complete the synthesis of **2** by making use of the Korte reaction,[4] which involves treatment of a hydroxymethylene lactone **8** with methanolic HCl at room

temperature to give an α-formyl-δ-hydroxy ester **9**. This then cyclizes to the acetal **10**. Elimination of methanol with polyphosphoric acid[4] or with methanolic HCl[3] at the reflux gives the dihydropyran ester **11**.



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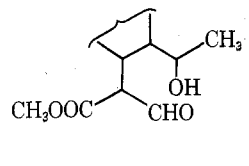

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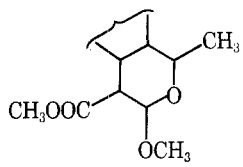
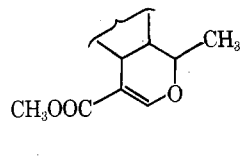
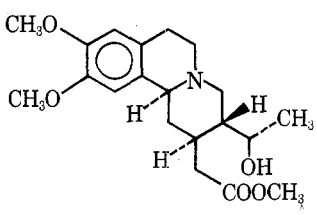


10

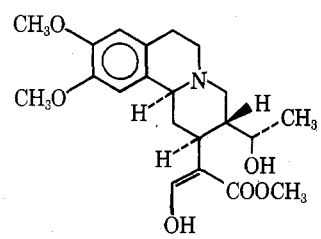


11

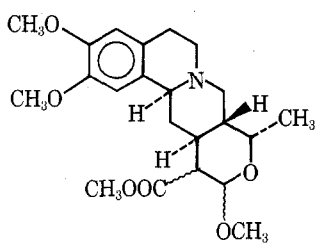
An alternative to this procedure was obviously required. We realized that the ring-opened intermediate **9** is merely the hydroxymethylene derivative of the hydroxy ester corresponding to the original lactone, and we therefore decided to attempt to complete the synthesis of **2** via the hydroxy ester **12**. This substance was obtained by treatment of **5** with diazomethane. Again, as in the case of the lactone, one recrystallization gave material which was a single isomer (NMR). Condensation of **12** with methyl formate was readily achieved, and gave the hydroxymethylene derivative **13**, which was not purified. Cyclization to the acetal **14** was effected with



12



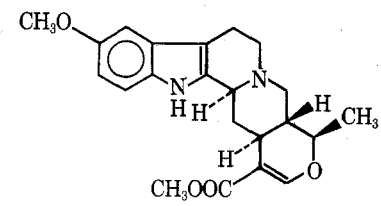
13



14

methanolic hydrogen chloride. Cyclization was accompanied by some elimination of methanol (to give **2**) but elimination was not increased by prolonging the reaction time. More complete elimination leading to isolation of **2** was achieved by refluxing a solution of **14** and *p*-toluenesulfonic acid in chloroform using a sulfuric acid trap to absorb the methanol produced in the reaction. The product was converted to the hydrochloride; one recrystallization gave analytically pure material.

The NMR spectrum of the purified product indicated that the substance was stereochemically homogeneous; in particular the methyl doublet at δ 1.16 (J = 6.5 Hz) was very similar to that reported by Shamma and Richey[5] for ajmalicine (δ 1.16, J = 6.7 Hz), whereas in raumitorine (**15**), an alkaloid stereochemically identical with ajmalicine except for the orientation of the methyl group, the doublet appears at δ 1.29.[6] In synthetic 19-epiajmalicine[7] the doublet is at δ 1.33 (J = 6.5



15

Hz). The configuration of the remaining three asymmetric centers of **2** must be as shown, as the substance was prepared from **3** which in turn was converted to emetine by van Tamelen.[3] The presence of complex bands in the ir between 2700 and 2900 cm^{-1} confirmed the trans nature of the quinolizidine system in **2**.[8] The mass spectrum of **2** was analogous to that of ajmalicine.[9] The only important difference (apart from the obvious shift in molecular weight of the fragment ions) was the low intensity of the m/e 177 peak of **2** relative to the corresponding peak (m/e 156) of ajmalicine. These peaks presumably arise from reverse Diels–Alder fragmentation of the tetrahydropyridine rings of **2** and ajmalicine. Such a process would appear to be more favorable in the case where the indole double bond was involved.

The ajmalicine analogue **2** demonstrated significant hypotensive activity in the anesthetized cat and dog when administered intraduodenally at 30 mg/kg; however, the hypotension was accompanied by an unacceptable level of CNS stimulation.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer 137 spectrophotometer and NMR spectra on a Varian A-60D spectrometer in Me_2SO-d_6 solution.

2-Carboxymethyl-3-(1-hydroxyethyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Hydrochloride (5 HCl). A solution of **3** (30 g) and sodium borohydride (11.7 g) in water (550 ml), adjusted to pH 11 with KOH, was refluxed for 25 h. After cooling, the solution was made acidic (pH 2) with concentrated HCl and the solvent removed on the rotary evaporator. The residue was extracted with boiling ethanol to give 29.2 g of **5** hydrochloride, mp 250–262 °C. The melting point was unchanged after recrystallization from water.

Anal. Calcd for $C_{19}H_{28}ClNO_5$: C, 59.14; H, 7.31; N, 3.64; Cl, 9.19. Found: C, 59.05; H, 7.13; N, 3.56; Cl, 9.06.

2,3-Dimethoxy-9-methyl-5,8,8a,11,12,12a,13,13a-octahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizin-11-one (6). Method A. A solution of **5** HCl (2.8 g) and 1-cyclohexyl-3-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate (3.6 g) in pyridine (400 ml, freshly distilled from KOH) was maintained at 100 °C for 4.5 h under a nitrogen atmosphere. The reaction mixture was evaporated under reduced pressure and the resulting oil dried for 17 h at 20 °C (0.05 mm). The residue was dissolved in $CHCl_3$ (150 ml) and extracted with 5% H_2SO_4 (3 × 50 ml). The combined acid extracts were washed with $CHCl_3$ (2 × 10 ml), then neutralized with solid $NaHCO_3$ and extracted with $CHCl_3$ (3 × 75 ml). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give the lactone as an oil (1.5 g) which crystallized on treatment with ethyl acetate. This material was apparently a mixture of **6** and the epimer with the methyl group in the β configuration, with **6** predominating: NMR δ 1.36 (d, J = 6.6 Hz) more intense than δ 1.42 (d, J = 6.6 Hz). Recrystallization from ethanol gave **6** (0.7 g): mp 211–214 °C; NMR δ 1.36 (d, J = 6.6 Hz).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.66; H, 7.89; N, 4.43.

Method B. A solution of **5** HCl (2.0 g) in 5% ethanolic HCl was refluxed for 2.5 h. The reaction mixture was evaporated to dryness, dissolved in water (200 ml), made basic by the addition of solid K_2CO_3, and extracted with $CHCl_3$ (2 × 150 ml). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give the lactone as a colorless oil (0.7 g) which crystallized on treatment with ethyl acetate. Recrystallization from ethanol gave **6** (0.6 g), mp 211–214 °C, identical with the material obtained using method A.

2-Carbomethoxymethyl-3-(1-hydroxyethyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (12). A solution of diazomethane in ether[10] (100 ml), prepared from *N*-nitrosomethylurea (10.3 g), was added to a solution of **5** HCl (6.4 g) in

methanol (75 ml) at 0–5 °C. After 18 h at room temperature, the solution was heated on the steam bath until ether boiled mildly and then the solvent was removed on the rotary evaporator. The residue (6.8 g) was dissolved in ether/$CHCl_3$ (1:1, 300 ml) and extracted with 2% K_2CO_3 (300 ml). The organic layer was dried over anhydrous K_2CO_3 and evaporated to give 4.2 g of **12**. This material was dissolved in methanol (10 ml) and excess methanolic HCl added. Evaporation and recrystallization of the residue from methanol/benzene gave **12** HCl as the hydrate: 2.0 g; mp 142–144 °C; NMR δ 1.14 (d, 3, J = 6.6 Hz), 3.66 (s, 3), 3.78 (s, 6), 6.8 (s, 2).

Anal. Calcd for $C_{20}H_{32}ClNO_6$: C, 57.44; H, 7.72; N, 3.35; Cl, 8.48; H_2O, 4.34. Found: C, 57.05, H, 7.82; N, 3.31; Cl, 8.26; H_2O, 4.56.

12-Carbomethoxy-2,3,11-trimethoxy-9-methyl-5,8,8a,11,-12,12a,13,13a-octahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizine (14). A solution of triphenylmethylsodium in ether[11] was prepared from triphenylmethyl chloride (42 g) in anhydrous ether (1000 ml). This was added under nitrogen pressure to a solution of **12** (6.1 g) in dry dioxane[12] (150 ml) at 15 °C until the deep red color of triphenylmethylsodium persisted. Methyl formate (4.8 g) was added and the solution stirred for 16 h while the ice water cooling bath warmed to room temperature. The entire mixture was poured into 2.4 M HCl (320 ml). The aqueous layer was extracted with ether (2 × 300 ml) and evaporated to dryness under reduced pressure and the resulting solid azeotroped twice with methanol. The residue (11.1 g) containing crude product and inorganic material was dissolved in 3.4% methanolic HCl (38 g) and refluxed for 3.5 h. The reaction mixture was evaporated to dryness and the residue distributed between ether (200 ml) and 5% K_2CO_3 (100 ml). The aqueous layer was separated and extracted with ether (2 × 100 ml). The combined ether solutions were dried over anhydrous K_2CO_3 and evaporated to give 3.9 g of **14**.

12-Carbomethoxy-2,3-dimethoxy-9-methyl-5,8,8a,12a,13,-13a-hexahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizine Hydrochloride (2 HCl). A solution of 14 (3.9 g) and *p*-toluenesulfonic acid (2.3 g) in $CHCl_3$ (350 ml) was azeotroped for 120 h using a Dean-Stark apparatus containing concentrated H_2SO_4 (20 ml) in the trap. The reaction mixture was poured into 5% K_2CO_3 (100 ml). The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ solutions were dried over anhydrous K_2CO_3 and the solvent removed on the rotary evaporator. The crude oil was triturated with benzene to give four crops of crystalline material. Infrared spectroscopy indicated that three crops (1.8 g) consisted essentially of the desired compound. Intense bands at 1680 and 1600 cm^{-1} indicated the carbonyl and the conjugated double bond, respectively, of the desired compound; a small band at 1725 cm^{-1} indicated the presence of an impurity. The remaining crop of material (164 mg) showed strong absorption at 1725 cm^{-1} and was not combined with the above material for purification as the hydrochloride. The 1.8-g sample described above and 4.2 g of material obtained from 16 g of **14** in five separate reactions were combined and dissolved in ether (900 ml). The solution was dried (Na_2SO_4) and the hydrochloride salt was precipitated with anhydrous hydrogen chloride. The entire mixture was evaporated under reduced pressure and the remaining semisolid recrystallized from methanol/ether to give 3.7 g of **2** HCl as the two-thirds hydrate, mp 181–186 °C.

Anal. Calcd for $C_{21}H_{28}ClNO_5 \cdot \frac{2}{3}H_2O$: C, 59.81; H, 7.07; N, 3.31; Cl, 8.31; H_2O, 2.82. Found: C, 60.10; H, 7.06; N, 3.41; Cl, 8.47; H_2O, 2.55.

Acknowledgments. We thank Dr. V. Boekelheide for valuable discussions, the Analytical Research Department for analyses and spectral data, and the Pharmacology Department for biological data.

Registry No.—**2**, 60184-19-2; **2** HCl, 60209-13-4; **3**, 60209-14-5; **5** HCl epimer A, 60184-20-5; **5** HCl epimer B, 60209-15-6; **6**, 60184-21-6; **6** β-methyl epimer, 60209-16-7; **12**, 60184-22-7; **12** HCl, 60209-17-8; **14**, 60184-23-8.

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Stereospecific Synthesis of the Four 20,22-Epoxycholesterols and of (*Z*)-20(22)-Dehydrocholesterol[1]

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(20*R*,22*S*)-, (20*R*,22*R*)-, and (20*S*,22*R*)-epoxycholesterol have been synthesized stereospecifically from (20*R*,22*R*)-, (20*R*,22*S*)-, and (20*S*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a**, **5a**, and **21**), respectively, via their 22-mesylates. (*Z*)-20(22)-Dehydrocholesterol has been prepared by pyrolysis of the 1,3-dioxolane derivative of (20*R*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**5a**). The stereoselective oxidations of (*E*)-3β-acetoxy-5,20(22)-cholestadiene with *m*-chloroperbenzoic acid gave (20*S*,22*S*)-20,22-epoxycholesterol (after hydrogenolysis of the 3β-acetate) and with osmium tetroxide yielded **21**. A total stereoselectivity has been obtained in the synthesis of the glycol (20*R*,22*R*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a**) from the aldehyde (20*R*)-3β-acetoxy-20-tetrahydropyranyloxypregn-5-ene-20-carbaldehyde (**10b**) by an isoamylmagnesium bromide Grignard reaction.

In continuation of our work[3–5] on the mechanism of the biochemical conversion of cholesterol to pregnenolone and in view of suggestions[6–8] that 20,22-epoxycholesterol (**1a–d**)[9] and 20(22)-dehydrocholesterol (**2a,b**)[9] are obligatory intermediates in the biochemical transformation of cholesterol to pregnenolone, mediated by mitochondrial preparations of the rat adrenal cortex, it appeared important to prepare such sterols by stereospecific syntheses. There is no mention of the configuration of either the 20,22 double bond or of the 20,22-epoxide by these authors.[6–8] However, since