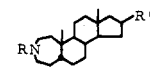
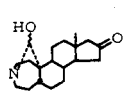
(c) R. G. Shulman, B. K. Teo, P. Eisenberger, G. S. Brown, and B. M. Kincaid, to be submitted for publication; (d) J. Reed, P. Eisenberger, B. K. Teo, and B. M. Kincaid, submitted for publication; (e) B. K. Teo, P. Eisenberger, and B. M. Kincaid, to be submitted for publication.
(15) The fitting error for each parameter is calculated by changing that particular parameter (while least-squares refined the others) until the chi-square doubled.
(16) R. W. Lane, J. A. Ibers, R. B. Frankel, G. C. Papaefthymiou, and R. H. Holm, *J. Am. Chem. Soc.*, **99**, 84 (1977).

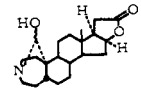
P. A. Lee,* Boon-Keng Teo,* A. L. Simons
Bell Laboratories
Murray Hill, New Jersey 07974
Received December 27, 1976



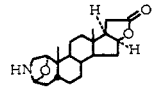
1a, R = Ac; R′ = H
N-acetylsamane
b, R = H; R′ = OH
samanine



2



3



4, samandaridine

Denial of the Proposed Structure of Salamander Alkaloid, Cycloneosamandaridine. Total Synthesis of Cycloneosamandione and Supposed Cycloneosamandaridine

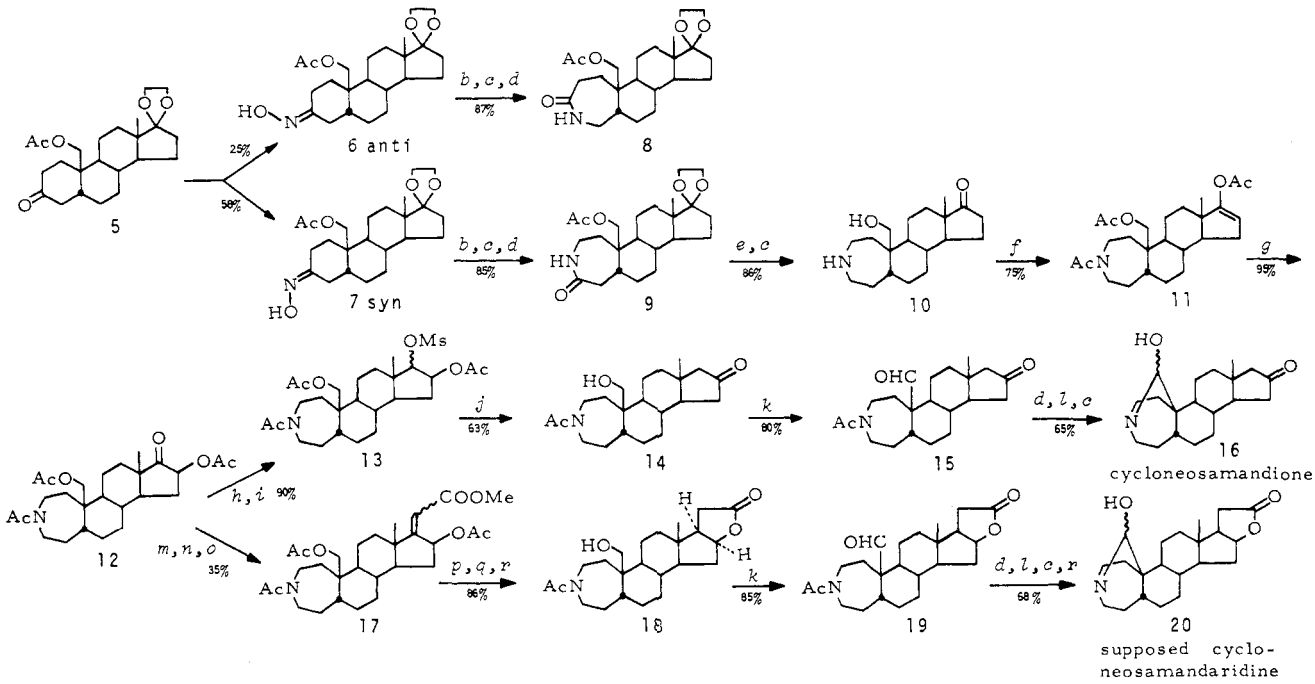
Sir:

The unique 10-retro-steroidal structure of cycloneosamandione **2**,[1] one of the biologically active salamander alkaloids,[2] proposed by Habermehl and Göttlicher by their x-ray study, has been revised to a normal configuration (**2** → **16**). This interesting revision is a result of their synthetic studies,[3,4] and seems to be supported by our synthesis[5,6] of *N*-acetylsamane **1a** (one of the degradation products).[7] The key step of our synthetic sequence involves a specific Beckmann rearrangement of the geometrically pure isomers of steroidal 3-ketoximes.[5] We have used this method also in the synthesis of the other natural alkaloid, samanine **1b**.[8] The accuracy of this method has been proved by Weiler's independent synthesis of the samanine type alkaloids.[9] However, we have been shaken by Habermehl's comments[10] to the effect that our synthetic specimen was contaminated with a small amount of the regioisomer.

We will show in this paper that our method is still an excellent one for the synthesis of 5β-3-aza-A-homo ring system in the salamander alkaloids by the synthesis of cycloneosamandione **16** and cycloneosamandaridine **20**. The main object of the present synthesis is to confirm the structure of cycloneosamandaridine which had been believed to be **3** by Habermehl and Haaf[11] who, at that time, compared its IR and mass spectra[12] with those of cycloneosamandione **2** and samandaridine **4**.[13] Since the structure of cycloneosamandione has been revised (**2** → **16**), it follows that the 10-retro configuration of cycloneosamandaridine must now be revised to a normal one (**3** → **20**). However, the absence of an M − 29(CHO) peak in the mass spectrum of cycloneosamandaridine[11] compelled us to synthesize the supposed structure **20** and compare its mass spectrum with those of the related alkaloids, especially cycloneosamandione **16** where the M − 29 peak is very strong.[1] Our synthetic sequence of these two alkaloids is shown in Scheme I.

The baseline resolution of a mixture of ketoximes prepared from the corresponding ketone **5**[19] into the geometrical isomers was achieved by silica gel column chromatography: anti isomer **6** (less polar, 25%, mp 238–240 °C; δ (pyr-d_5) 3.65 (2β-H)) and the desired syn isomer **7** (more polar, 58%, mp 234–236 °C; δ (pyr-d_5) 3.50 (4β-H)). The assignment of these isomers was based on the NMR of each isomer.[20] For the large scale

Scheme I



[a] $NH_2OH \cdot HCl$, pyr, room temp. [b] TsCl, pyr, 37 °C, 3 h. [c] Dilute HCl, room temperature. [d] Ethylene glycol, TsOH (trace), C_6H_6, reflux. [e] LAH, Et_2O–THF, reflux, 3 h. [f] Isopropenyl acetate, H_2SO_4 (trace), reflux, 7 h. [g] $Pb(OAc)_4$, HOAc, Ac_2O (trace), room temp, over night. [h] $NaBH_4$, MeOH, room temp. [i] MsCl, pyr, room temp. [j] KOH, 95% EtOH, reflux, 1.5 h. [k] CrO_3, H_2SO_4, 0 °C. [l] KOH, *n*-BuOH, H_2O, reflux. [m] $BrCH_2COOMe$, Zn (powder), I_2 (trace), Et_2O–C_6H_6, reflux, 2 h. [n] Ac_2O, pyr, room temp. [o] TsOH (trace), PhMe. [p] Pt. H_2, HOAc, room temp. [q] NaOH, MeOH, room temp. [r] TsOH (trace), C_6H_6, reflux.

experiment, recrystallization of the original mixture from chloroform–ethyl acetate at room temperature yielded the desired syn isomer **7** specifically. The contents of the mother liquor which is rich in anti isomer **6** were converted easily into the equilibrium mixture on heating in ethanol.

Regiospecific Beckmann rearrangement followed by reketallization[21] was achieved with each isomer to give the pure regioisomers, 4-aza-**8** (mp 230–232 °C; δ ($CDCl_3$) 2.95–3.35 (N–CH_2)) and 3-aza-ε-lactams **9** (mp 242–244 °C; δ ($CDCl_3$) 2.65–2.95 (one hydrogen of N–CH_2, another overlapped with the ethylenedioxy hydrogen signal)). The assignment of these structures was also based on the remarkable differences between the two NMR spectra.[6]

Reduction of **9** with lithium aluminum hydride and subsequent hydrolysis afforded the amino ketone **10** (mp 213–215 °C). The enol acetate **11** (mp 139–141 °C) prepared from **10** was oxidized by lead tetracetate to give an acetoxy ketone **12** (oil; δ ($CDCl_3$) 4.90 (t, J = 9.0 Hz, 16α-H)). The configuration of the 16α-hydrogen was determined by the comparison of its NMR spectrum with those of 3β,16β-diacetoxy-5-androsten-17-one[22] (δ ($CDCl_3$) 4.99 (t, J = 9.5 Hz, 16α-H)) and 3β,16α-diacetoxy-5α-androstan-17-one[23] (δ ($CDCl_3$) 5.45 (d.d, J = 9.0, 2.0 Hz, 16β-H)). This acetoxy ketone **12** was a common key intermediate of the two alkaloids.

Firstly we converted **12** into cycloneosamandione **16** which seemed to be indispensable in our efforts to confirm the structure of cycloneosamandaridine **20.** Reduction of **12** with sodium borohydride and methanesulfonylation afforded the mesylate **13** (oil) which was immediately subjected to an elimination reaction to give the 16-oxo derivative **14** (oil; IR ($CHCl_3$) 1738 (C=O)). Mild oxidation of **14** with an equimolar amount of Jones reagent afforded an aldehyde **15** (oil; IR ($CHCl_3$) 2770 (CHO)). The conversion of **15** to the final product, which involves protection of the carbonyl groups, cleavage of the *N*-acetyl group, and removal of the protecting groups, was accomplished successively to give cycloneosamandione **16** (mp 120–122 °C; natural[7] mp 118–119 °C). The IR spectrum was superimposable with that of the natural product.[7]

Secondly, we aimed to synthesize cycloneosamandaridine **20.** Reformatsky reaction of **12** followed by reacetylation and dehydration was achieved to give an unsaturated carboxylate **17** (oil; δ ($CDCl_3$) 5.98 (t.d, J = 8.0, 1.8 Hz, 16α-H), 5.62 (d, J = 1.8 Hz, C=CH)). Catalytic hydrogenation of **17** and subsequent hydrolysis and cyclization afforded a γ-lactone **18** (mp 245–246 °C; IR (KBr) 3240 (OH), 1772 (γ-lactone); δ ($CDCl_3$) 4.90 (m, 16α-H)). The β-cis-configuration of the γ-lactone ring was confirmed by the chemical shift of the 16α-hydrogen which was fully compatible with that of our model compound, 3β-acetoxy-16β-hydroxy-5α-pregnan-21-oic acid γ-lactone (mp 215–217 °C; δ ($CDCl_3$) 4.88 (m, 16α-H)).[24]

Jones oxidation of **18** afforded an aldehyde **19** (oil; δ ($CDCl_3$) 9.70 and 9.75 (two s, CHO)).[25] Successive protection of the formyl group, deacetylation, hydrolysis, and recyclization of the γ-lactone gave a final product **20** (mp 270–272 °C; MS 345 (M^+, 15%), 330 ($M^+ - 15$, 32%), 316 ($M^+ - 29$, base peak); δ ($CDCl_3$) 0.79 (s, CH_3), 4.90 (s, 19-H), 4.95 (m, 16α-H), 7.10 (b, OH); IR (KBr) 3400 (OH), 1771 (γ-lactone)).

The spectral data of our synthetic specimen were consistent with the assigned structure **20.** However, it was not identical with the natural product (mp 281–283 °C).[11] The characteristic pattern of mass fragmentation of our sample clearly showed the preferential elimination of CHO from the original carbinol amine structure, while in the spectrum of the natural product it is distinctly absent.[11] The mass spectrum of the synthetic cycloneosamandione **16** revealed also an $M^+ - 29$ peak of 23% intensity. Furthermore, the natural cycloneosamandaridine showed an $M^+ - 1$ peak rather than the molecular peak, while **20** exhibited the molecular peak and no $M^+ - 1$ peak.

From the data described above we have decided that the structure of cycloneosamandaridine is not **20.** Although a true structure is not known, we suppose that the most probable one might involve a 3,6-cyclic carbinol amine ring system.

Acknowledgment. The authors wish to express their gratitude to Dr. Yoshimasa Ike for valuable discussions and help in the preparation of the starting material.

References and Notes

(1) G. Habermehl and S. Göttlicher, *Chem. Ber.*, **98,** 1 (1965).
(2) G. Habermehl, *Naturwissenschaften*, **12,** 615 (1969); "Progress in Organic Chemistry", Vol. VII, Butterworth, London, 1968, p 35; "The Alkaloids", Vol. IX, Academic Press, New York, N.Y., 1967, p 427.
(3) G. Habermehl and A. Haaf, *Z. Naturforsch. B*, **23,** 1551 (1968).
(4) G. Habermehl and A. Haaf, *Z. Naturforsch. B*, **24,** 1414 (1969).
(5) K. Oka and S. Hara, *Tetrahedron Lett.*, 1189 (1969).
(6) K. Oka and S. Hara, *Chem. Ind. (London)*, 168 (1969).
(7) C. Schöpf and O. W. Müller, *Justus Liebigs Ann. Chem.*, **633,** 127 (1960): the name "neosamane" was used in place of "samane".
(8) K. Oka and S. Hara, *Tetrahedron Lett.*, 1193 (1969).
(9) R. B. Rao and L. Weiler, *Tetrahedron Lett.*, 4971 (1973).
(10) G. Habermehl and A. Haaf, *Tetrahedron Lett.*, 3815 (1969).
(11) G. Habermehl and G. Haaf, *Chem. Ber.*, **98,** 3001 (1965).
(12) Unfortunately, the quite limited amount of the natural sample has dissuaded them from taking the NMR spectrum of cycloneosamandaridine.[11]
(13) The structure of samandaridine has been confirmed by our total synthesis of samandarone[14,15] and the conversion of samandarone to samandaridine by Habermehl.[16] Other syntheses of the samandarine-type alkaloids have also appeared.[17,18]
(14) S. Hara and K. Oka, *J. Am. Chem. Soc.*, **89,** 1041 (1967).
(15) K. Oka and S. Hara, *Tetrahedron Lett.*, 1987 (1969).
(16) G. Habermehl, *Chem. Ber.*, **96,** 840 (1963).
(17) Y. Shimizu, *Tetrahedron Lett.*, 2919 (1972); *J. Org. Chem.*, **41,** 1930 (1976).
(18) M. H. Benn and R. Shaw, *J. Chem. Soc., Chem. Commun.*, 288 (1973).
(19) Y. Ike, a thesis for a degree at Tokyo College of Pharmacy, 1970.
(20) K. Oka and S. Hara, *Chem. Ind. (London)*, 911 (1968).
(21) Acid hydrolysis of iminopyridinium salts as an intermediate of the Beckmann rearrangement in pyridine was needed.
(22) T. Aoki, Y. Yamamura, K. Takei, and H. Mori, *Chem. Pharm. Bull.*, **12,** 808 (1964).
(23) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Am. Chem. Soc.*, **76,** 2943 (1954).
(24) K. Oka and S. Hara, unpublished data.
(25) The formyl proton of this series revealed two singlets in the NMR spectrum at room temperature: R. Binder and H. Wehrli, *Helv. Chim. Acta*, **51,** 1989 (1968).

Kitaro Oka,* Shoji Hara
Tokyo College of Pharmacy
Horinouchi, Tokyo 192-03, Japan
Received February 9, 1977

A Totally Synthetic Bilayer Membrane

Sir:

We wish to report for the first time the formation of biomembrane-like bilayer structures from a simple organic compound.

Didodecyldimethylammonium bromide (Eastman) was recrystallized twice from ethyl acetate, mp 55–56 °C, and suspended in deionized water. A clear solution (10 mM) was obtained by sonication (Bransonic 12 ultrasonicator, water-bath type) for 4 h at 50 °C. A few drops of this solution was applied to a 150-mesh copper grid coated with a carbon film, which was then dried in a desiccator. A 2% aqueous solution of uranyl acetate was applied in a similar way.

An electron micrograph (Hitachi, Model H-500) of this sample is shown in Figure 1. Spheric objects with diameters of 300–500 Å can be clearly seen. This picture is indistinguishable from that of dipalmitoyllecithin vesicles reported, for example, by Sheetz and Chan.[1] When the sonication pro-