Synthesis of nor-anatoxin-*a* and anatoxin-*a*[1]

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HENRY F. CAMPBELL, OLIVER E. EDWARDS, and RALPH KOLT. Can. J. Chem. **55**, 1372 (1977).

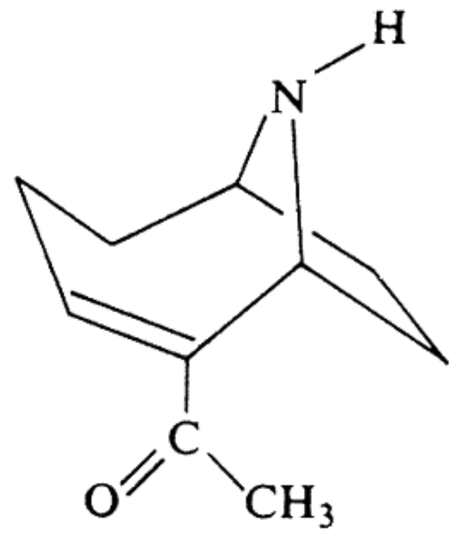
The neuro-muscular post-synaptic depolarizing agent anatoxin-*a* from *Anabaena flos-aquae* (Lyngb.) de Bréb. has been synthesized from cocaine.

Some strains of the fresh-water blue-green algae *Anabaena flos-aquae* (Lyngb.) de Bréb. produce a toxin which has been named anatoxin-*a*. This proved to be a homotropane derivative **1** (1, 2). Anatoxin is of considerable pharmacological interest because of its activity as a post-synaptic depolarizing agent (3). We now report a synthesis of optically active anatoxin-*a* from cocaine (**2**). Since the absolute configuration of the toxin had been determined by X-ray analysis (2), the synthesis confirms the absolute stereochemistry which had been assigned to cocaine (4).

Cocaine was converted by known procedures (5) into the α,β-unsaturated acid **3**. Reaction of the lithium salt of **3** with methyllithium (6) produced the methyl ketone **4** in 76% yield. When this ketone was treated with sodium dimethyloxosulfonium methylide in dimethyl sulfoxide (7) it gave a 65% yield of the *endo* cyclopropane derivative **5** and 35% of the *exo* isomer **6**. Occasionally small amounts of a product with properties corresponding to those expected for the epoxide **7** were produced.

The structures of the two cyclopropanes were assigned on the basis of the ^{1}H nmr shifts shown on the figures. The greater proximity of the acetyl group to the *N*-methyl group and one bridgehead hydrogen, resulting in downfield shifts, identifies the *endo* isomer. The course of the photolysis of the two isomers (see below) made the assignments certain.

Attempts to remove the *N*-methyl group of **5** using 2,2,2-trichloroethyl chloroformate or phosgene led to complications apparently due to



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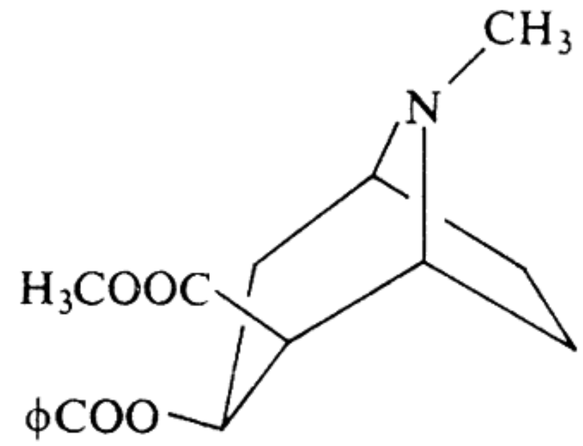

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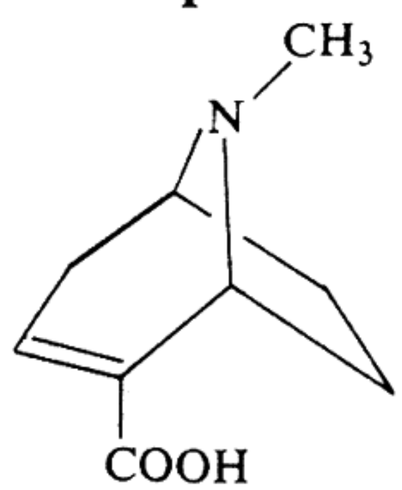

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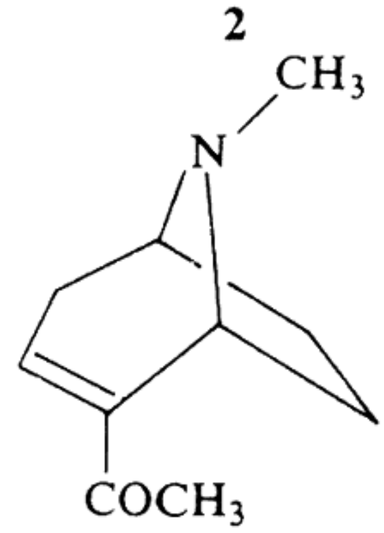

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attack on the cyclopropane ring. The *exo* isomer **6** proved inert to 2,2,2-trichloroethyl chloroformate at room temperature. Hence the demethylation was deferred to a later stage.

Two methods were successful in opening of the cyclopropane ring of **5**, reductive fission using lithium in liquid ammonia or photolytic cleavage. There was reason to expect that the reductive opening of **5** would result in the ring expanded product (see Discussion). Indeed, the action of lithium in ammonia did convert **5** into the enolate anions of the saturated ketone **8**. These were directly converted by acetic anhydride into mixtures of the two enol acetates **9** and **10**. Alternatively, the ketone **8** was isolated, then converted into the enol acetates by acetic anhydride in the presence of hydrogen bromide. Addition of bromine to the enol acetates, followed by aqueous work-up gave the bromo ketone **11**. Elimination of hydrogen bromide

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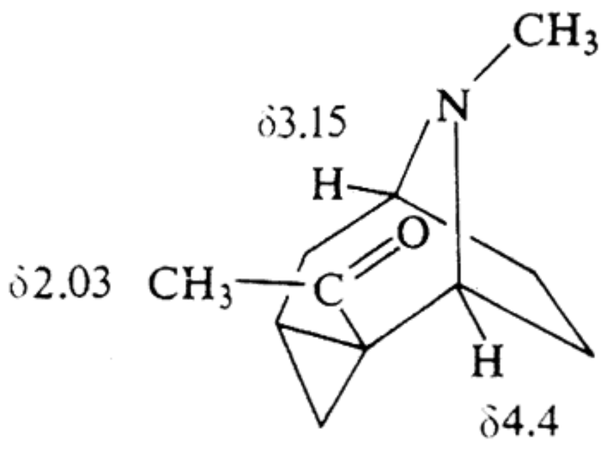

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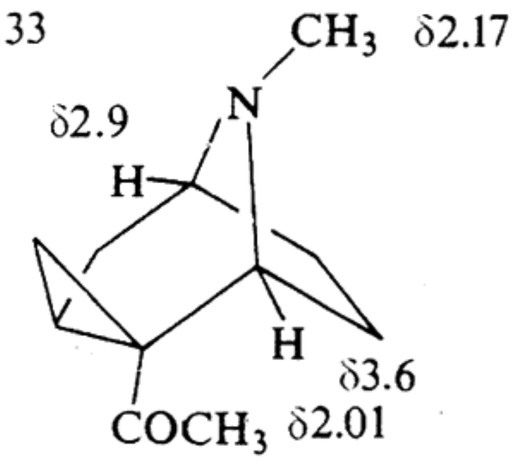

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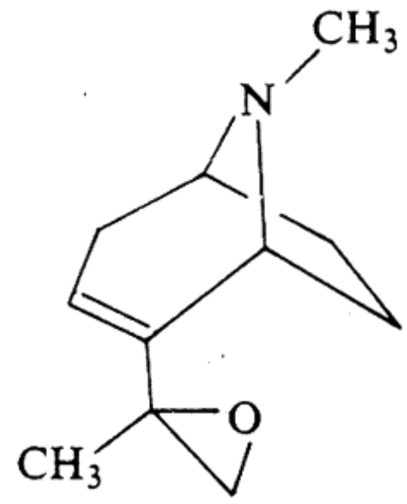

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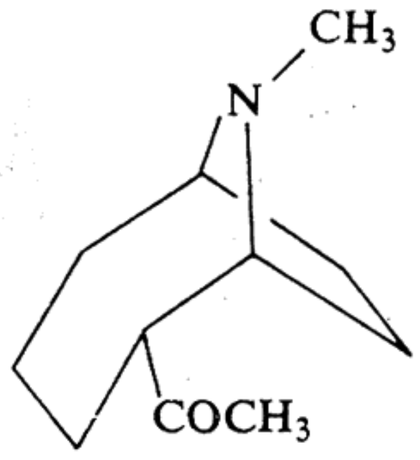

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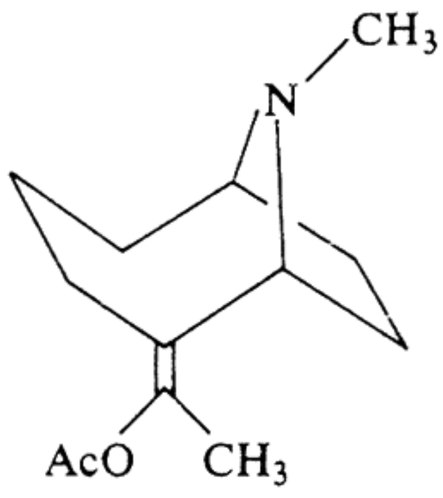
from **11** was achieved by the action of lithium bromide and lithium carbonate in dimethyl formamide, giving *N*-methyl anatoxin-*a* (**12**).

In contrast to the behavior of the *endo* isomer, the action of lithium in ammonia on the *exo* isomer **6** only resulted in reduction of the carbonyl group.

There was literature precedent for the photolytic opening of cyclopropyl ketones to the α,β-unsaturated ketone[3] (8–10). When an aqueous solution of the hydrochloride of the *endo* isomer **5** was irradiated using light with maximum intensity at 300 nm, a 75% yield of the ring expanded *N*-methyl anatoxin-*a* (**12**) resulted.



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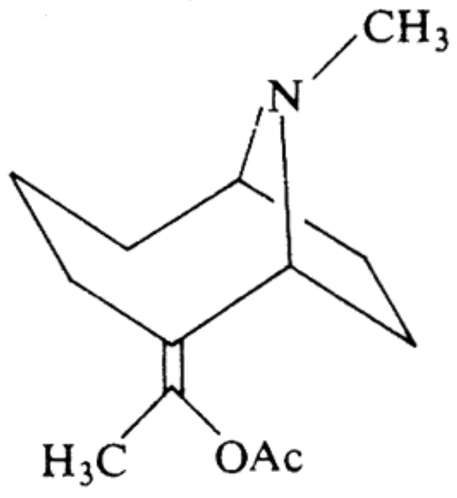

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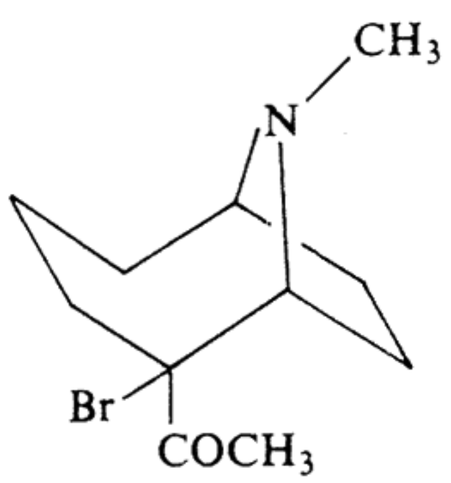

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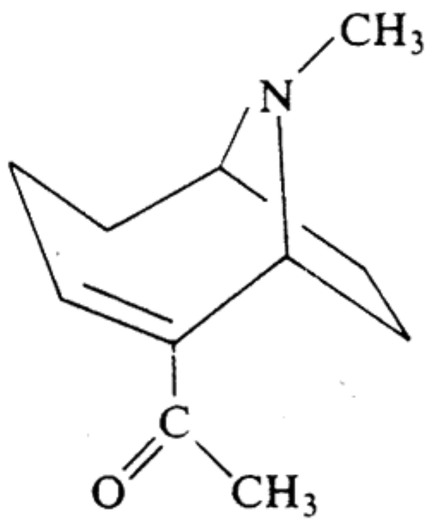
[3]We are grateful to Dr. P. W. Jeffs for drawing our attention to this possibility.

The *exo* isomer **6** photolyzed much more slowly than **5** under comparable conditions, and the reaction took a different course (see below).

De-*N*-methylation of *N*-methyl anatoxin using 2,2,2-trichloroethoxycarbonyl chloride (11) proved to be erratic, and the zinc deblocking of the nitrogen was not clean, so this method was not pursued further.

De-*N*-methylation using phosgene has been reported (13). Preliminary experiments with the methyl ketone **4** (*N*-methyl nor-anatoxin-*a*) showed that phosgene in benzene at room temperature gave extensive demethylation in 0.5 h. The major product, nor-anatoxin-*a* (14) was characterized as its hydrochloride after work-up. However, comparable treatment of *N*-methyl anatoxin-*a* gave messy mixtures of products which have not been characterized.



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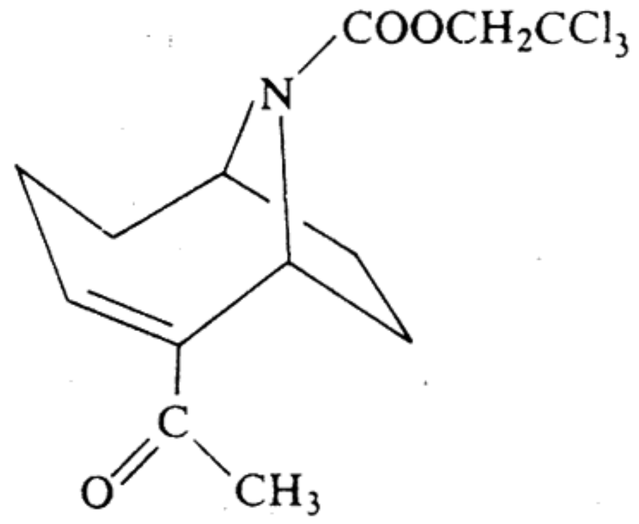

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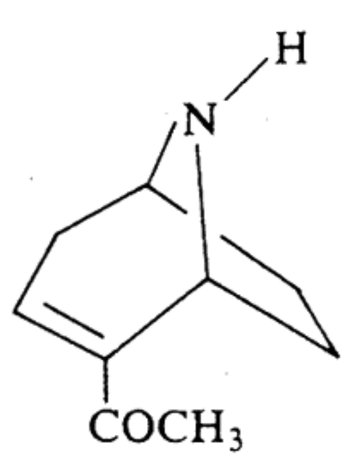

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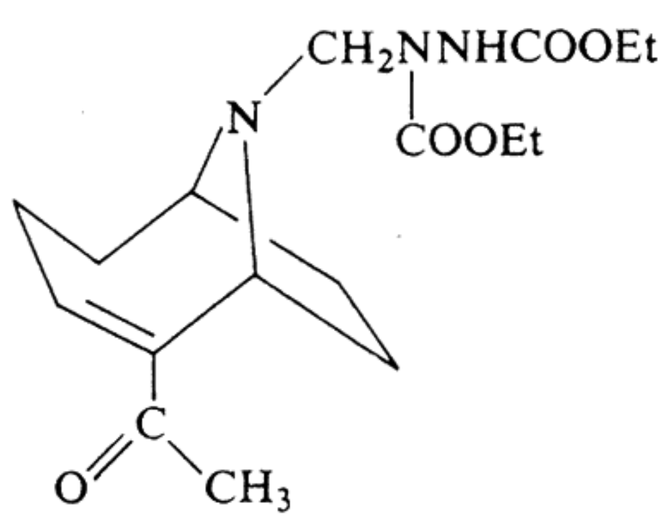

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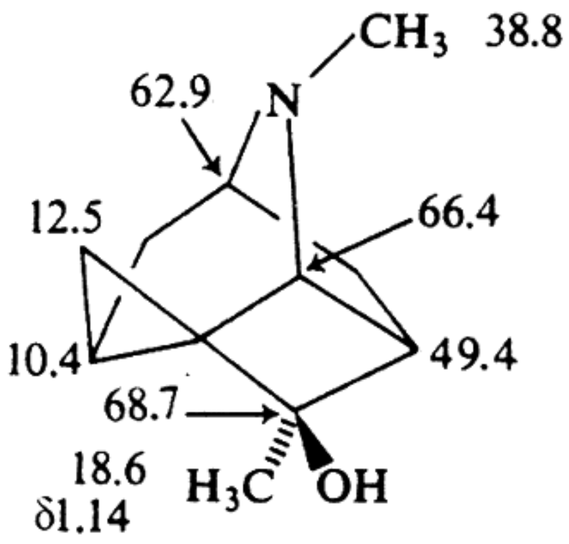
The successful preparation of anatoxin-*a* resulted from the action of diethyl azodicarboxylate (diethyl azodiformate) on the *N*-methyl derivative (14). A benzene solution of **12** and the azo compound was refluxed for 2.5 h, the intermediate (presumably **15**) was hydrolyzed by hydrogen chloride in aqueous ethanol and the products separated by preparative tlc. A 30% yield of anatoxin-*a* hydrochloride was obtained. Its infrared, ultraviolet, and nmr spectra and its toxicity[4] coincided with those of natural anatoxin-*a* hydrochloride. The base was converted to its crystalline *N*-acetyl derivative, which had a melting

[4]Personal communication from Professor P. R. Gorham.

point, spectra, and rotation identical to those of the *N*-acetyl derivative of natural anatoxin-*a* (1).

The photolysis of the *exo*-cyclopropylketone **6** gave no significant amount of enone. Instead two alcohols isomeric with the parent ketone were produced. The ^{1}H and ^{13}C nmr spectra gave convincing evidence that the structures of these were the epimeric alcohols **16** and **17**.



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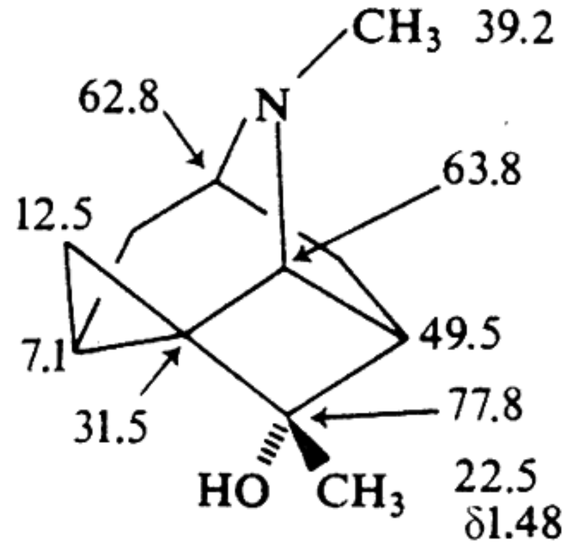

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Discussion

In reaction **1** we outline the possible routes for lithium–ammonia reduction of a cyclopropyl ketone. An equilibrium has been written for path (*c*) since this would only approach delocalization (resonance) if the geometry was ideal for overlap. Path *a* is written as irreversible since the charge repulsion would make the charge-separated ring-opened structure of considerably lower energy.

The accumulated evidence (15, 16) seems only consistent with rapid reduction to the dianion (path *a*). If the geometry is ideal for overlap of the unshared pair on carbon with one bond of the cyclopropane ring, the ring opening may be synchronous with the addition of the second electron.

We are surprised that the reversible process *c* is not more important. Indeed for a number of cases, including that of the *endo* isomer **5**, one could argue that it is the more stable ring-open radical anion which is being preferentially formed. However the observation of Dauben and Wolff (16) that *trans* 1-acetyl-2-methyl-cyclopropane gave 94% of *tert*-butyl acetone is incompatible with this possibility.

The simple reduction of the carbonyl in the case of the *exo* isomer **6** appears to result from poor overlap of the carbanion with the bonds of the cyclopropane ring. It is hence protonated on the carbonyl carbon as in path *b*.

The generally accepted picture of the photoreaction of conjugated cyclopropyl ketones involves excitation to an n–π* singlet followed by transformation into a triplet diradical [2] (17). The question of which of the two possible cyclopropane bonds is cleaved depends on their ability to overlap with the π orbitals of the carbonyl, and the sensing in the transition state of the relative stability of the two possible diradicals (18, 19). Our observations can be explained using these factors and a third, the proximity to the oxygen of an abstractable hydrogen.

The overlap in the favored rotamer **18** and the higher stability of the secondary rather than primary radical combine to cause predominant formation of the ring-expanded product **12** from the *endo* isomer **5**. The formation of an α,β

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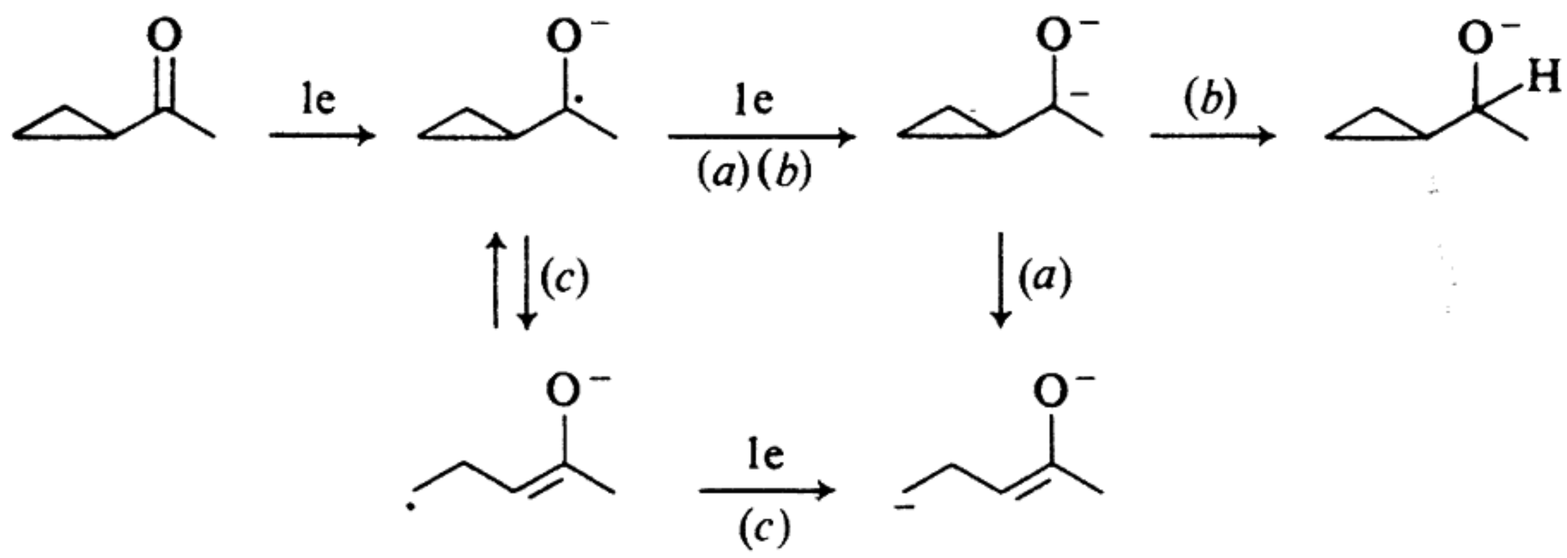

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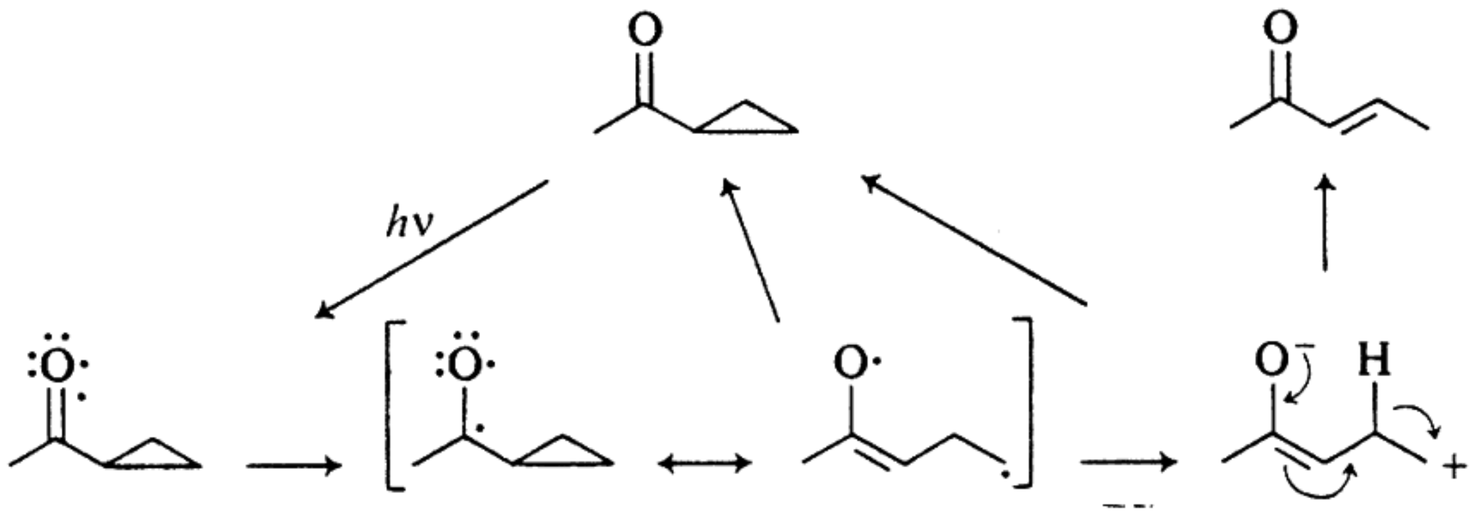
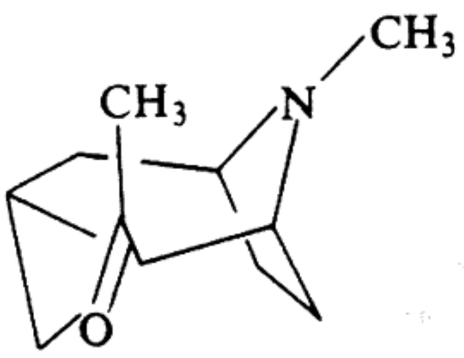


unsaturated ketone from a diradical is most attractively explained [2] by a 1,3-electron jump to give the zwitterion **19**. The zwitterion **19** derived from **18** then undergoes a 1,2-hydride shift to give the observed product. The postulated 1,3-electron jump corresponds to the 'electron



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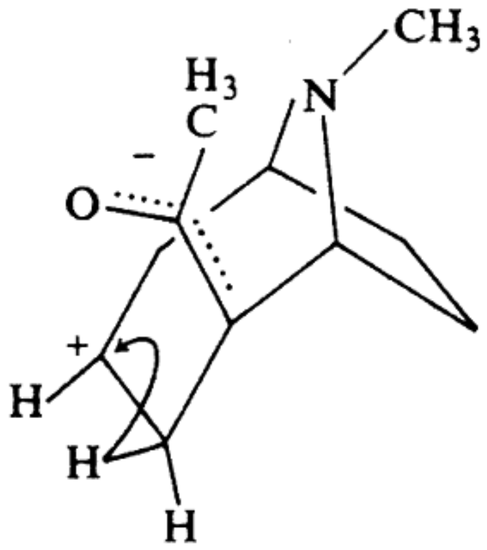

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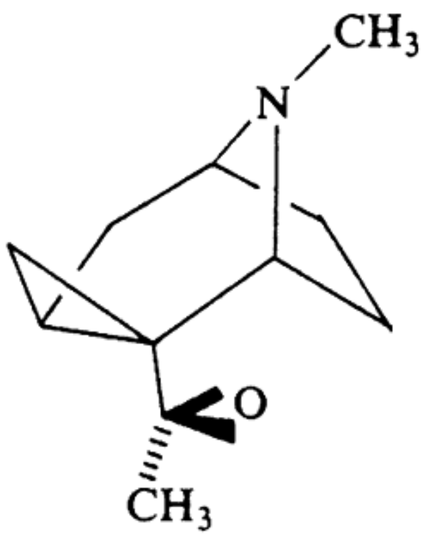
demotion' concept of Zimmerman and co-workers (12). Winter and Lindauer have produced evidence that the conjugated enones are formed by 1,2 hydrogen shifts (9).

The fate of the *exo* isomer **6** seems to be the resultant of the fact that the most favorable rotamers **20** and **21** would lead to a higher-energy primary radical on ring fission, and that the *endo* hydrogen on C-8 can be brought into



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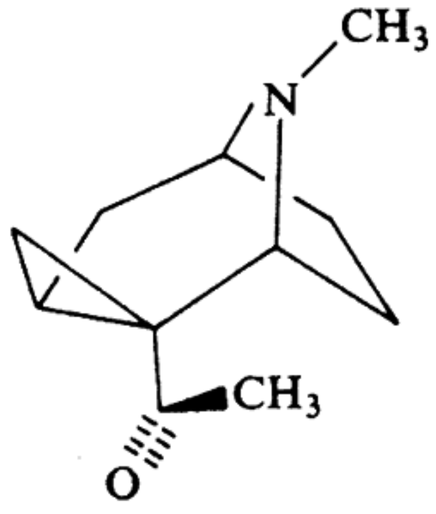

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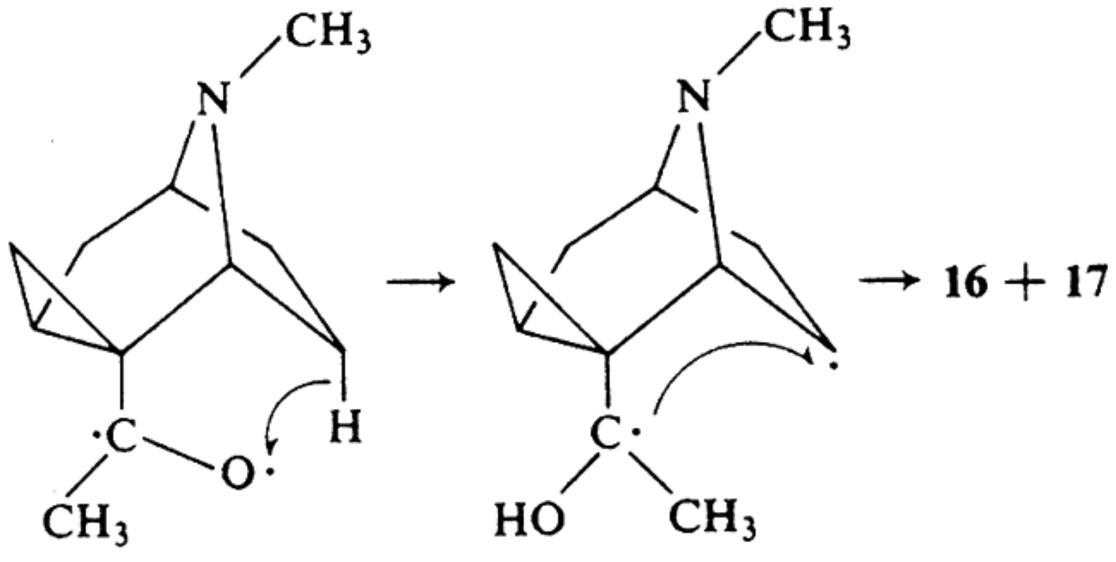
close proximity to the carbonyl oxygen. Consequently hydrogen abstraction followed by cyclization was the dominant reaction [3]. This striking difference in photochemical behavior is so clearly associated with the different geometry of the two isomers, that no ambiguity is left as to which is which.

[3]



Experimental

Infrared spectra were of chloroform solutions, ultraviolet spectra of solutions in 95% ethanol, and unless otherwise stated ^{1}H nmr and ^{13}C nmr spectra were of deuterochloroform solutions with TMS as internal reference. Thin layer and preparative layer chromatography were done using silica gel containing a fluorescent indicator (G_{254}). Gas–liquid chromatography (glc) was on 6 ft × $\frac{1}{4}$ in. column of 10% silicone rubber on silanized Chromosorb W (SE30).

Anhydroecgonine (3)

This was prepared by hydrolysis of cocaine (**2**) in refluxing concentrated hydrochloric acid (5). It was converted to its methyl ester using dry methanol saturated with anhydrous hydrogen chloride at 0°C. This distilled at 55°C/0.5 torr, and had ν_{max} 1710 and 1640 cm^{-1}, λ_{max} 218 nm (ε 10 850), $[\alpha]_D$ −43° (*c* 1.5, methanol), and gave ^{1}H nmr signals at δ 2.38 (s, 3H), 3.75 (s, 3H), and 6.85 (1H).

Lithium Salt of Anhydroecgonine

To a solution of 3.62 g (20 mmol) of redistilled methyl ester of anhydroecgonine in 10 ml of 5% water in methanol was added 880 mg of lithium hydroxide monohydrate (20.1 mmol). After 2 h refluxing the solvent was removed and the solid dried *in vacuo*. After two triturations with ether it was redried at 80°C/0.1 torr for 4 h giving 3.46 g (100%).

Alternatively, an aqueous solution of the hydrochloride of anhydroecgonine was treated with 2 mol equiv. of lithium hydroxide, the water removed under reduced pressure, and the mixture of salts dried at 100°C under 0.1 torr pressure.

Methyl Ketone 4

To a stirred suspension of 2.9 g (16.8 mmol) of the lithium salt of anhydroecgonine in 50 ml of pure dry 1,2-dimethoxyethane under nitrogen at 5°C was added 13.5 ml of methyllithium solution (1.8 *M* in ether). The mixture was stirred for 5 h at room temperature then taken to near dryness under reduced pressure. The products were distributed between ice-cold 2 *N* hydrochloric acid and ether. The aqueous layers were made basic and the product extracted into methylene chloride, giving 2.1 g of nearly pure methyl ketone (79%).

This was converted to its hydrochloride, which after recrystallization from ethanol – ethyl acetate mixture had mp 161–163°C and $[\alpha]_D$ −70°C (*c* 1, methanol). It had λ_{max} 224 nm (ε 12 000). *Anal.* calcd. for $C_{10}H_{16}ClNO$: C 59.54, H 8.00, N 6.95, Cl 17.58; found: C 59.36, H 8.08, N 7.01, Cl 17.34. The free base recovered from the hydrochloride had ν_{max} ($CHCl_3$) 1665 and 1630 cm^{-1} and ^{1}H nmr signals at δ 2.32 (3H), 2.38 (3H), 3.35 (m, 1H), 4.0 (br d, 1H), 6.93 (t, 1H).

Cyclopropyl Ketone Formation

A mineral oil dispersion of sodium hydride (1.01 g, 50%, 21 mmol) was washed three times with pentane. To this was added 4.62 g of trimethyloxosulfonium iodide (21 mmol) then the flask flushed thoroughly with nitrogen. Dry dimethyl sulfoxide (25 ml) was added slowly through a septum using a syringe, while the mixture was stirred magnetically. After 20 min stirring at room temperature,

vigorous hydrogen evolution had ceased. A solution of 3.30 g (20 mmol) of the α,β-unsaturated ketone **4** in 5 ml of dioxane was added through the septum. The reaction mixture was stirred under nitrogen for 2 h at room temperature then 1 h at 50°C. It was poured into 80 ml of cold water then extracted five times with ether. The oil remaining after removal of the ether was distilled. The main fraction, collected between 55 and 80°C under 0.05 torr weighed 2.82 g. Gas–liquid chromatography on SE-30 at 170°C showed this to consist of starting material (9% recovery) and a mixture of the *endo* cyclopropyl ketone **5** (43% yield) and the *exo* isomer **6** (27% yield).

The mixture of products could be partially separated by chromatography on a 65-fold ratio of tlc silica gel using a 10:1 mixture of chloroform and methanol. The order of elution was *exo* isomer, starting material, then *endo* isomer. A slightly better resolution was achieved using a 35-fold ratio of neutral alumina (activity II) and pentane–ether mixtures for elution. The same elution order was observed. In one run a sizeable by-product was observed. It was isolated by chromatography of the base hydrochlorides on silica gel using 3:1 methanol – acetic acid for elution. It was tentatively assigned the epoxide structure **7**.

Epoxide 7

The free base had no carbonyl absorption in its infrared spectrum. Its ^{1}H nmr spectrum had peaks at δ 1.31 (3H), 2.35 (3H), and 5.55 (1H, t, J = 4 Hz).

Endo Cyclopropyl Ketone 5

This was distilled over a short path at 80°C/0.1 torr. It had ν_{max} 1680 cm^{-1} and gave ^{1}H nmr signals at δ 2.03 (s, 3H) and 2.33 (s, 3H) and broad 1H signals at δ 3.15 and 4.4. Its hydrochloride after recrystallization from methanol – ethyl acetate had mp 188–193°C, $[\alpha]_D$ +99° (c 1, methanol) and λ_{max} 271 nm (ε 20 with ε_{210} 710). It gave ^{1}H nmr signals (in D_2O, HOD set at δ 4.70) at 2.0 and 2.7 (3H, s's) and 3.8 and 5.0 (1H, m's).

Exo Cyclopropyl Ketone 6

The early eluates from the chromatograms were nearly pure *exo* isomer. This was distilled over a short path at 80°C/1 torr pressure. It had ν_{max} 1680 cm^{-1} and gave ^{1}H nmr signals at δ 2.01 (s, 3H), 2.17 (s, 3H) and broad 1H signals at 2.9 and 3.6.

It gave a hydrochloride which after recrystallization from methanol – ethyl acetate had mp 192–194°C, $[\alpha]_D^{20}$ −76° (c 1, methanol) and λ_{max} 275 nm (ε 25, with ε_{210} 1220). It gave ^{1}H nmr signals (in D_2O, HOD set at δ 4.70) at 2.01 and 2.75 (3H, s's) and 3.8 and 4.4 (1H, m's). *Anal.* calcd. for $C_{11}H_{18}ClNO$: C 61.25, H 8.41, N 6.50; found: C 61.38, H 8.38, N 6.30.

Reactions of the Endo Isomer 5

Lithium–Ammonia Reduction

Approximately 500 ml of liquid ammonia, distilled from sodium, was collected in a double-walled 2 ℓ flask under a dry ice condensor. The flask was flushed with dry nitrogen, then 4.16 g (60 mmol) of clean lithium metal was added. The mixture was stirred briefly, then a solution of 6.0 g of the *endo* isomer in 150 ml of ether was added slowly with stirring. The mixture was stirred for 3 h, then 67 g of ammonium chloride added. The ammonia was evaporated overnight in a slow stream of nitrogen. The residue was taken up in 900 ml of ether and 900 ml of saturated aqueous sodium chloride solution. The aqueous phase was extracted four times with ether. The dried ether layers gave 5.6 g of crude product (93%). This was placed on top of a column of 500 g of tlc silica gel, then eluted with a 10:1 benzene–diethylamine mixture. The composition of the fractions was monitored using glc (SE-30 at 170°C). After somewhat impure fractions (439 mg) the main product (3.5 g, 58%) was eluted, followed by fractions contaminated with alcohols.

De-N-methylation of Endo Cyclopropyl Ketone 5

A solution of 99 mg of *endo* cyclopropyl ketone **5** and 125 mg of diethylazodicarboxylate (DAD) in 7.5 ml of dry benzene was refluxed for 11 h. At this point only a small amount of starting material remained (tlc in 4:1 benzene–methanol). An extra 30 mg of DAD was added, the solution refluxed for 15 min, then left at room temperature for 10 h. The benzene was removed *in vacuo*, then a solution of the residue in a mixture of 2.5 ml of 2 *N* hydrochloric acid and 2.5 ml of 95% ethanol refluxed for 2.5 h. The resulting solution was taken to a syrup on a rotating evaporator *in vacuo*. The residue was chromatographed on two 20 × 20 cm 500 μm plates using methanol for development. A zone with R_f 0.2–0.5 was extracted with hot 3:2 methanol – acetic acid mixture. Removal of the solvent gave 62 mg of the hydrochloride of the desired de-*N*-methylated base. It had a sharp ^{1}H nmr signal at δ 1.90 relative to the HOD signal (set at δ 4.7).

The corresponding base had ν_{max} 1675 cm^{-1} and gave ^{1}H nmr signals at 2.10 (3H, s) and 0.85, 3.5, and 4.7 (1H, m's).

Ring Expanded Ketone 8

The major product from the lithium–ammonia reduction had ν_{max} 1705 cm^{-1} and gave ^{1}H nmr signals at δ 2.09 and 2.12 (s's, ratio 1:2), 2.38 and 2.48 (s's, ratio 1:2) corresponding to two epimeric ketones. The bases were converted to hydrochlorides using hydrogen chloride in methanol. The major component gave a salt with mp 152–155°C, $[\alpha]_D$ −11° (c 1, methanol). The salt gave ^{1}H nmr signals in heavy water with δ 2.22 (s, 3H) and 2.91 (s, 3H) relative to DSS.

Enol Acetates 9 and 10

(*a*) The lithium in ammonia reduction of the *endo* cyclopropyl ketone **5** (895 mg, 5.0 mmol) was conducted as described above, but the ammonium chloride addition was done carefully until the blue color was just destroyed. The ammonia was then evaporated over 4.5 h in a stream of dry nitrogen. The residue was suspended in 50 ml of pure 1,2-dimethoxyethane, the solution cooled in an ice bath, then added to 5 ml of acetic anhydride. The mixture was stirred for 3 h at room temperature, then poured into a cold mixture of saturated sodium bicarbonate solution and ether. This mixture was stirred for 0.5 h. The ether layer was separated and the aqueous layer extracted twice with fresh ether. The dried ether layers yielded 1.0 g of yellow liquid.

Gas–liquid chromatography (SE-30, 175°C) showed the absence of cyclopropyl ketone and the presence of only a few percent of ring-expanded ketone. Two enol acetates were present in the ratio of 1:3 (identities unknown). A sample distilled over a short path at 100–125°C/0.02 torr had ν_{max} 1740, 1670 cm^{-1}. The bulk of residual acetic anhydride was removed under 0.05 torr during 6 h. The resulting oil gave ^{1}H nmr singlets at δ 2.51 (N—CH_3),

2.13 (CH_3COO), and 2.00 (CH_3—C=C). Signals at δ 2.18 and 1.90 appear to arise from the minor isomer.

(*b*) Ketone **8** hydrochloride (365 mg) was dissolved in 10 ml of acetic anhydride. Hydrogen bromide was bubbled through the solution for 1 min (*ca.* 1 bubble/s). The solution was then heated at 80°C for 24 h. It was evaporated under reduced pressure giving 487 mg of the desired enol acetates as hydrobromides. The mixture had ν_{max} 1755 and 1670 cm^{-1} and gave ^1H nmr signals at δ 1.91 (vinyl methyl), 2.22 (acetate), and a pair of doublets (J = 5 Hz) centered at δ 2.25 and δ 3.0 attributable to the N-CH_3 in the isomers.

*Bromo Ketone **11***

A 0.174 *M* solution of bromine in chloroform was prepared. Ten millilitres of this at 0°C was added to 461 mg of the enol acetate hydrobromides (**9** + **10**) during the course of 15 min. After 2 h at room temperature the ^1H nmr spectrum showed complete bromination. Water was added and the mixture stirred for 1 h, then the solvents evaporated under reduced pressure. The 569 mg of crude bromo ketone hydrobromide was a mixture of two isomers as shown by ^1H nmr signals at δ 1.68 and 1.74 and at δ 2.15 and 2.22 (relative to HOD set at 4.70). One component (the isomer giving the lower-field N-CH_3 and CH_3CO signals) crystallized from acetone giving 224 mg (49%), mp 138–141°C. It gave ^1H nmr signals at δ 2.57 (3H), 2.97 (3H), 5.0 (br s, 1H) and 5.5 (br s, 1H). *Anal.* calcd. for $C_{11}H_{19}Br_3NO$: C 38.74, H 5.61, N 4.11, Br 46.85; found: C 38.59, H 5.72, N 4.19, Br 46.69.

*Dehydrobromination of **11** (N-Methyl Anatoxin-a)*

Bromo ketone hydrobromide (569 mg, 1.67 mmol) and 610 mg (7 mmol) of dry lithium bromide was dried briefly at 100°C/1 × 10^{-2} torr, then 16 ml of dry dimethyl formamide added. The mixture was heated at 60°C for 17 h, and at 130°C for 1 h. The bulk of the dimethyl formamide was removed at 70°C/0.5 torr pressure. The residue was dissolved in 5 ml of water, made basic with solid sodium carbonate, then strongly alkaline with ice-cold 40% sodium hydroxide solution. The product was quickly extracted into ether (4–10 ml portions). After drying and distillation of the ether, the product was converted to its hydrobromide in methanol. This was purified on four 1000 μm plates using 2:1 chloroform–methanol. The most visible band under uv light was collected. This gave 173 mg rich in α,β unsaturated ketone (**12**). This had ν_{max} 1670 cm^{-1} and gave ^1H nmr signals (D_2O) at δ 2.35 (s, 3H), 2.75 (s, 3H), and 7.50 (t, J = 7 Hz, 1H). Repeated purification attempts using silica gel plates failed to remove saturated ketone (ν_{max} 1705 cm^{-1}) and other impurities completely.

*Photolysis of Endo Hydrochloride **5** (N-Methyl Anatoxin-a)*

The *endo* cyclopropyl ketone **5** (105 mg) was converted to its hydrochloride. This was dissolved in 10 ml of water and irradiated in a Vycor flask at 20°C using a Rayonet apparatus with lamps giving peak emission at 300 nm. Reaction was complete in 24 h. The water was removed *in vacuo*, then the product purified using two 20 cm^2, 1 mm thick plates using 4:1 chloroform–methanol as eluate under argon. The broad uv active zone with R_f 0.2 yielded 48 mg (46%) rich in *N*-methyl anatoxin-*a*. This was dissolved in 10:1 chloroform–methanol, filtered, then evaporated and dried *in vacuo*. The glassy solid had $[\alpha]_D$ +42° (*c* 1, methanol); ν_{max} 1670 cm^{-1}; λ_{max} 228 nm (ε 6200); ^1H nmr signals at 2.38 (s, 3H), 2.60 (s, 3H), 3.9 (m, 1H), 4.9 (br d, 1H), and 7.3 (t, J = 6 Hz, 1H).

*De-N-methylation of **12** (Anatoxin-a)*

N-Methyl anatoxin-*a* (**12**) hydrochloride (155 mg) was dissolved in 5 ml of water, the solution made strongly alkaline with cold sodium hydroxide solution, then the base extracted rapidly into methylene chloride. After drying and removal of the solvent, the base was dissolved in 10 ml of dry benzene. After addition of 190 mg of diethylazodicarboxylate the solution was refluxed for 2.5 h. The benzene was removed under reduced pressure and the residue taken up in a mixture of 4 ml of 95% ethanol and 4 ml of 2 *N* hydrochloric acid. This was refluxed for 3 h, then evaporated to dryness on a rotating evaporator. The products were separated on three 20 cm × 20 cm plates (thickness 1 mm) using 4:1 chloroform–methanol under argon. The desired product had R_f approximately 0.2. This zone (65 mg) was replated on one 20 cm × 20 cm × 1 mm plate under the same conditions giving 42 mg (29%) of quite pure anatoxin-*a* hydrochloride (**1**). This had $[\alpha]_D$ +36° (*c* 0.85, ethanol); λ_{max} 226 nm (ε 8500); ν_{max} 1670, 1642, and 1588 cm^{-1}. Its ^1H nmr spectrum had signals at δ 2.40 (s, 3H), 4.4 (m, 1H), 5.3 (m, 1H), 7.3 (t, J = 5 Hz, 1H), and a broad 2H signal between δ 8.3 and 9.0 (2H). These spectra corresponded well to those of natural anatoxin-*a* (**1**).

*N-Acetyl Derivative of **1** (N-Acetyl Anatoxin-a)*

The above hydrochloride (42 mg) was dissolved in 1 ml of acetic anhydride containing 200 mg of sodium acetate. This was heated 1 h at 60°C then left for 60 h at room temperature. The excess anhydride was removed under reduced pressure, the residue warmed with methanol, and the evaporation repeated. The residue was distributed between 5% sodium carbonate and methylene chloride. The organic phase gave 35 mg of product. This crystallized in part from acetone–hexane. The crystals were sublimed over a short path at 95°C/1 × 10^{-4} torr. The crystalline sublimate was washed once with ether, leaving 10 mg of crystals. These were recrystallized once from acetone–hexane. The *N*-acetyl derivative had mp 113–114°C, $[\alpha]_D$ −125 (*c* 0.6, ethanol), ν_{max} 1622 and 1663 cm^{-1} and λ_{max} 226 nm (ε 10 800). Its ^1H nmr spectrum had signals at δ 2.0 (s, 3H), 2.37 (s, 3H), 4.81 (br m, 1H), 5.29 (d, J = 8 Hz, 1H), and 7.02 (t, J = 6 Hz, 1H). Its spectra were identical to those of *N*-acetyl anatoxin-*a* (**1**) and a mixture mp showed no depression. *Anal.* calcd. for $C_{12}H_{17}O_2N$: C 69.54, H 8.27, N 6.75; found: C 69.71, H 8.39, N 6.58.

*Nor-anatoxin-a (**14**)*

(*a*) The *N*-methyl ketone **4** (98 mg, 9.59 mmol) in 1 ml of dry benzene and 0.2 ml of a benzene solution of phosgene (1 mmol) were mixed in an nmr tube in an ice bath, a small precipitate formed. After 30 min at 20°C the *N*-methyl signal had disappeared and a new methyl signal at lower field had appeared (CH_3Cl). After a further 30 min at 20°C the solvent was removed under reduced pressure. The residue was dissolved in water, and the solution left overnight at room temperature. After removal of the water, the product was sublimed at 100°C/1 × 10^{-4} torr. The partially crystalline sublimate was recrystallized from methanol – ethyl acetate mixture giving 15 mg, mp 232–235°C and 40 mg of less pure product.

The crystals had $[\alpha]_D$ −80° (*c* 1.62, methanol) and λ_{max} 225 nm (ε 10 600). Their ^{1}H nmr spectrum in D_2O had a 3H singlet 2.3 ppm upfield from the HOD signal (approximately δ 4.70) and a 1H triplet 2.45 ppm downfield from this reference signal. *Anal.* calcd. for $C_9H_{14}ClNO$: C 57.60, H 7.52, N 7.46; found: C 57.42, H 7.50, N 7.92.

The ^{1}H nmr spectrum of the free base **14** had signals at δ 2.27 (3H, s), 3.70 (1H, m), 4.27 (1H, m), and 6.68 (1H, t, J = 4 Hz).

(*b*) A solution of 207 mg of the *N*-methyl ketone **4** and 366 mg of diethylazodicarboxylate in 10 ml of dry benzene was refluxed for 18 h. After removal of the benzene *in vacuo* the residue was dissolved in a mixture of 6 ml of 2 *N* hydrochloric acid and 6 ml of 95% ethanol. The solution was refluxed for 4.5 h, then concentrated *in vacuo*, dilute sodium hydroxide added, and the base extracted into benzene. It was quickly reconverted to the hydrochloride. Only part was soluble in water, hence the solution was filtered. The filtrate was taken to dryness *in vacuo* then the residue crystallized from methanol – ethyl acetate giving 81 mg of nor-anatoxin-*a* hydrochloride mp 229–231°C. It proved identical to the product from (*a*).

Reactions of Exo Cyclopropyl Ketone 6

Photolysis of Exo Cyclopropyl Ketone 6

A solution of 373 mg of the hydrochloride of **6** in 12 ml of methanol was irradiated in a Vycor flask with lamps peaked at 300 nm in a Rayonet apparatus for 28 h. At the end of this time tlc showed absence of starting material and the presence of two more polar compounds as major products. The solvent was removed under reduced pressure, aqueous sodium hydroxide added, and the base extracted into methylene chloride. It was purified using six 0.5 mm × 20 cm × 20 cm plates with chloroform, acetone, methanol, and diethylamine (15:10:5:1) as developing solvent. The two major products had R_f 0.7 (84 mg) and 0.5 (114 mg). On some silica gel plates (more acidic?) the fast moving product appeared to be destroyed giving a more polar unsaturated alcohol which has not been fully characterized. Photolysis in water gave essentially the same products as above.

Tetracyclic Alcohol 17

The compound with high R_f was sublimed at 100°C 0.1 torr; mp 131°C $[\alpha]_D$ −54° (*c* 1.71, methanol), ν_{max} 3595 cm^{-1}. Its ^{1}H nmr spectrum had signals at δ 3.27 (d, J = 4 Hz, H_A), 3.17 (br m, $W_{1/2}$ 12 Hz, H_B), 2.87 (br m, $W_{1/2}$ 16 Hz, H_C), 2.28 (1H, s, OH), 2.10 (s, NCH_3), 1.50 (s, 3H), and signals for 2.7 hydrogens between δ 0.5 and 1.1. Tentative ^{13}C nmr chemical shift assignments based in part on multiplicities determined using off-resonance decoupling are indicated on the structure **17**. *Anal.* calcd. for $C_{11}H_{19}NO$: C 73.70, H 9.56, N 7.81; found: C 73.58, H 9.70, N 7.69. Yield 22%.

Tetracyclic Alcohol 16

The compound with lower R_t from the photolysis of **6** was distilled over a short path at 100°C/0.1 torr. The distillate crystallized in part. It had $[\alpha]_D$ −43° (*c* 0.97 methanol) and ν_{max} 3595 cm^{-1}. Its ^{1}H nmr spectrum had signals at 3.94 (d, J = 4 Hz, H_A), 3.1 (br m, $W_{1/2}$ = 14 Hz, H_B), 2.8 (br m, $W_{1/2}$ = 17 Hz, H_C), 2.46 (s, OH), 2.10 (s, N—CH_3), 1.13 (s, CH_3) and signals for 3.3H between δ 0.3 and 1.05. Tentative assignments of its ^{13}C nmr spectrum based on multiplicities from an off-resonance decoupled spectrum are indicated on the structure **16**. *Anal.* calcd. for $C_{11}H_{19}NO$: C 73.70, H 9.56, N 7.81; found: C 73.56, H 9.76, N 7.66. Yield 31%.

Lithium in Ammonia on Exo-cyclopropyl Ketone 6

A solution of 1.2 g of lithium in 250 ml of liquid ammonia (distilled over sodium) was prepared in a double-walled flask. To this was slowly added 1.57 g of the *exo* isomer **6** (>90% purity) in 50 ml of ether. The mixture was stirred for 3.5 h after completion of the addition, then 20 g of ammonium chloride added cautiously. After disappearance of the blue color the ammonia was evaporated in a stream of nitrogen. Water (100 ml) was cautiously added to the residue. This was saturated with sodium chloride, then extracted with five 100 ml portions of ether. The ether layers yielded 1.2 g (76%) of product consisting mainly of alcohols (ν_{max} 3600 cm^{-1}) but containing some unchanged cyclopropyl ketones (ν_{max} 1680 cm^{-1}). Its ^{1}H nmr spectrum had signals at δ 1.02 (d, J = 6 Hz) and 1.2 (d, J = 6 Hz) of almost equal intensity, total 3H; 2.14 (s, 3H) and a 6-line multiplet (probably a pair of partially superimposed quartets) at δ 3.9. There were signals for approximately two hydrogens between δ 0.25 and 1.0 (cyclopropane hydrogens).

The structure of these alcohols as simple products of reduction of the carbonyl was confirmed by oxidation. A solution of 113 mg of the alcohol mixture and 53 mg of chromium trioxide in 2 ml of acetic acid and 0.2 ml of water was heated at 45°C for 15 min, then stirred for 1 h at room temperature. The excess reagent was destroyed with methanol then the bulk of the solvents removed under reduced pressure. The residue was made strongly basic with 15% sodium hydroxide solution, then extracted with ether. The 78 mg of product had M^+ 179, and ^{1}H nmr and ir spectra nearly identical to those of *exo*-cyclopropyl ketone **6**.

Sodium in ethanol reduction of the *exo*-cyclopropyl ketone also gave a 1:1 mixture of the two alcohols.

Acknowledgements

We thank Mr. H. Séguin for microanalyses and mass spectra, and Dr. I. C. P. Smith and associates for ^{13}C nmr spectra. We are grateful to Dr. N. R. Hunter for preliminary work on the degradation of cocaine.

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