were taken using a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60 spectrophotometer, and are reported as parts per million relative to internal TMS. Mass spectra were taken on a JMS-01SG Mattauck-Herzog type double focusing mass spectrometer by Jeolco, Inc., Medford, Mass. Gas chromatography was performed on an Aerograph Model A-90-P instrument. Microanalyses were done by Robertson Laboratory, Florham Park, N. J.

**Materials.**—Pentane (Eastman Organic Chemicals), purified by oleum and permanganate, was used as received. Acetone (Fisher Scientific, Certified A. C. S.) was used as received. *n*-Hexane used for column chromatography was purified by shaking with concentrated sulfuric acid, washing with water, drying with calcium chloride, and distilling from phosphorus pentoxide. Benzene used for column chromatography was distilled from sodium. Silver nitrate–alumina was prepared by the procedure of Murray and coworkers.[22]

**Hexasubstituted Cyclohexane-1,3,5-triones.**—Hexamethylcyclohexane-1,3,5-trione was prepared by the procedure described by Erickson and Kitchens.[23] This trione exhibited infrared absorption ($CCl_4$) at 1698 $cm^{-1}$, exhibited a singlet at $\delta$ 1.38 ppm ($CDCl_3$) in the nmr, and showed uv absorption maxima ($CH_3OH$) at 226 ($\epsilon$ 340) and 297 nm ($\epsilon$ 85). The properties and spectral data for the trispirocyclohexane-1,3,5-triones **5** ($n$ = 4, 5, 6, or 7) are tabulated in Table I.

**General Irradiation Procedure.**—The solvent employed was degassed by slowly bubbling nitrogen through the solution for 5 min. A degassed solution of the compound in pentane or acetone (generally 1.7–2.7 mmol of compound in 170 ml of solvent) was irradiated with a 450-W Hanovia mercury-vapor lamp, No. 6-79A-36, in a quartz immersion well apparatus fitted with a Pyrex or Corex filter. The reaction progress was monitored periodically by infrared analysis. Upon termination of the irradiation, the solution was filtered in those cases where insoluble material formed. The solution was concentrated and the residue was subjected to purification by column chromatography on neutral alumina or vpc separation or the residual material was crystallized.

**Typical Irradiation. Photolysis of Hexamethylcyclohexane-1,3,5-trione.**—A degassed solution of 422 mg (2.0 mmol) of the trione in 170 ml of pentane was irradiated using a Pyrex filter for 4 hr. After removal of the solvent, hexamethylcyclopentane-1,3-dione was isolated by vpc (6 ft 20% GE-SS-96 on Firebrick; column operated at 196° with an He flow rate of 75 ml/min). There was obtained 174.3 mg (48.0%) of the dione, mp 49.5–51.5° (lit.[8] mp 51°).

A degassed solution of 535 mg (2.54 mmol) of hexamethylcyclohexane-1,3,5-trione in 700 ml of acetone was irradiated for 4 hr using a Pyrex filter. After removal of the acetone, crystallization from ether yielded 349 mg (65.4%) of starting trione.

The pertinent experimental conditions and results for the irradiations of the trispirocyclohexane-1,3,5-triones are summarized in Table II.

**Irradiation of 10.**—A degassed solution of **10** (468 mg, 1.55 mmol) in 170 ml of acetone was irradiated for 73 hr using Pyrex optics. After solvent removal, the residue was dissolved in hexane and chromatographed on neutral alumina. A hydrocarbon fraction was collected which was rechromatographed on a silver nitrate impregnated alumina column to yield 2.3 mg (1%) of **4** ($n$ = 6). Elution with ether yielded starting material (30% recovery).

The physical properties and the spectral data for the photolysis products are tabulated in Table III.

**Base-Catalyzed Thermal Rearrangement of 6 to 5** ($n$ = 4).—A solution of 135 mg (0.55 mmol) of **6** in 2.0 ml of dry benzene was heated to reflux. Upon adding 40 mg of $NaOCH_3$ an exothermic reaction occurred. Following 15 min of additional heating, the orange-colored solution was cooled and neutralized with a few drops of glacial acetic acid. The mixture was extracted with ether and the organic phase was dried over $K_2CO_3$. After solvent removal, 80.0 mg (59.2%) of an oil was obtained. Vpc analysis (6 ft 20% Silicone GE-SS-96 on Firebrick, column operated at 185°) yielded 34.5 mg of a component that had ir and vpc retention time identical with those of **5** ($n$ = 4).

**Registry No.**—**4** ($n$ = 5), 29150-89-8; **4** ($n$ = 6), 33780-60-8; **4** ($n$ = 7), 33777-05-8; **6**, 33777-06-9; **7**, 33777-07-0; **8**, 29798-98-9; **9**, 29798-99-0; **10**, 33777-10-5; **11**, 33777-11-6; **12**, 33777-12-7; **13**, 33777-13-8.

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# A Model Iron-Catalyzed Biomimetic Cyclization of a Cyclic Tryptamine *N*-Oxide

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The tryptamine *N*-oxide **5** is cleanly converted to the tetracyclic amine **6** with hydrated ferrous sulfate in methanolic acetic acid. The biosynthetic significance, synthetic potential, and mechanistic implications of the reaction are considered.

The iminium ion **1**, derived from stemmadenine,[2] appears to be a key intermediate in the biogenetic relationship between preakuammicine **2** and precondylocarpine **3**, and thus occupies a central position in the later stages of indole alkaloid biogenesis. The elegant cyclization reactions of Kutney,[3] Schmid,[4] and their coworkers clearly illustrate the potential of synthetically generated iminium ions for realizing analogous conversions. We now report that an iminium species, generated under very mild conditions from an *N*-oxide function, can undergo clean internal cyclization to give a $\beta$-carboline which may serve as a model in indole alkaloid biogenesis; in addition, we record some findings which relate to the mechanisms of analogous reactions *in vitro* and *in vivo*.

The dealkylation of tertiary amine oxides with aqueous $Fe^{2+}$ has been extensively investigated, and the following mechanism has been proposed[5] for trimethylamine *N*-oxide.

$$Me_3N^+-OH + Fe^{2+} + H^+ \longrightarrow Me_2N^{\cdot+} + H_2O + Fe^{3+}$$

$$Me_3N^{\cdot+} + Fe^{3+} \longrightarrow Me_2\overset{+}{N}{=}CH_2 + H^+ + Fe^{2+}$$

$$Me_2\overset{+}{N}{=}CH_2 \xrightarrow{H_2O} Me_2\overset{+}{N}H_2 + HCHO$$

$$Me_3N^{\cdot+} + Fe^{2+} + H^+ \longrightarrow Me_3\overset{+}{N}H + Fe^{3+}$$

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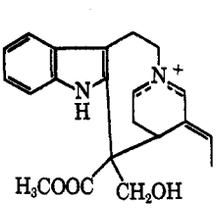

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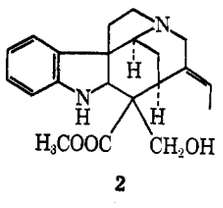

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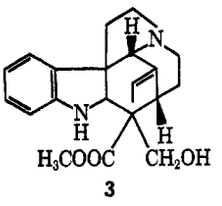

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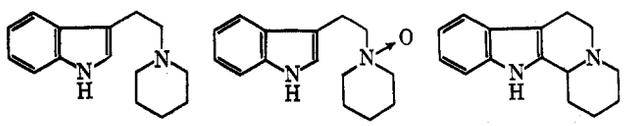
In accord with this mechanism, Ghosal and Mukherjee found[6] that *N*,*N*-dimethyltryptamine *N*-oxide with aqueous ferrous sulfate gave formaldehyde, *N*-methyltryptamine, and indole-3-acetaldehyde, and that 5-methoxy-*N*,*N*-dimethyltryptamine gave 6-methoxy-2-methyl-1,2,3,4-tetrahydrocarboline in *ca.* 12% yield. This carboline could have arisen either by cyclization of an iminium species or by condensation between a dealkylated amine and formaldehyde formed by hydrolysis. Norman and his coworkers[7] found that 3,4-dimethoxy-*N*,*N*-dimethyl-β-phenethylamine *N*-oxide under similar conditions gave dealkylated amine and some 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline. Deuterium labeling implicated formaldehyde in the cyclizations, and increases in $Fe^{3+}$ concentration led to increases (up to 20%) of isoquinoline. These observations also support the mechanism of Ferris and coworkers.[5]

We have investigated the cyclization of the amine oxide **5** as a model for more complex polycyclic indole alkaloid systems. The amine **4**[8] on treatment with 30% $H_2O_2$ gave the *N*-oxide **5**, in 95% yield.



4 5 6

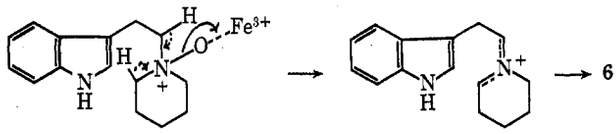
This compound was treated with $FeSO_4 \cdot 7H_2O$ in refluxing methanol–acetic acid, followed by removal of iron salts with $H_2S$ and work-up *via* $NaBH_4$ reduction (compare ref 9). Only three products were obtained; sulfur from the work-up, the uncyclized amine **4**, and the cyclized amine **6**, in approximately 30% yield. These yields have not yet been maximized, but the exceptionally mild conditions and complete absence of side products suggest a considerable synthetic potential for the method.

The yields of cyclized amine **6** were not improved when $Fe^{3+}$ salts were added to the $Fe^{2+}$ salt already present. Attempted cyclizations of the *N*-oxide **5** with $FeSO_4 \cdot 7H_2O$ in the presence of cyclohexanol gave only minute traces of cyclized product, strongly supporting the intermediacy of radical cations in the cyclization, as advocated by Ferris and coworkers.[5] Under strictly anhydrous conditions in the presence of acetic anhydride no cyclization was observed. This suggests that some water is necessary for the reaction, although no hydrolysis products were observed either chromatographically or on work-up. Tlc studies showed that both the uncyclized amine **4** and the cyclized amine **6** were strongly chelated by ferrous and ferric salts; moreover, the separation of iron from the amines using $H_2S$ at the end of the reaction was often slow.

Reaction of the *N*-oxide **5** with hydrated $Fe_2(SO_4)_3$ containing <0.01% $Fe^{2+}$ in methanol–acetic acid gave a trace of the cyclized amine **6**. This suggests that the ionic reaction below may take place to a small extent; however, it is clearly not the major pathway in the $Fe^{2+}$ reactions (Scheme I).

SCHEME I

POSSIBLE FERRIC ION INDUCED CYCLIZATION OF *N*-OXIDE **5**



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The strong similarity between this reaction and the mercuric acetate cyclization[8,9] of amines such as **4** suggests the intermediacy of iminium ions **7**, which arise in our work from *N*-oxides by the mechanism of Ferris and his coworkers.[5] Under these conditions only the desired product and starting material are obtained. These results strongly support the suggestion, adumbrated previously,[6] that tryptamine *N*-oxides may be involved in biogenetic cyclizations, and describe a potentially useful biomimetic synthetic method. Strong added support for such an involvement is offered by studies of enzyme-catalyzed dealkylation of *N*-oxides,[10] and by the natural occurrence of *N*-oxides both of simple[11] and more complex[12] indole alkaloids. Further experiments to test the selectivity of this reaction for diastereomeric *N*-oxides of chiral substrates are underway in our laboratory.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 237 spectrophotometer and mass spectra on an A. E. I. MS-902 instrument.

**Preparation of Amines 4 and 6.**—The tricyclic amine **4** was prepared from 3-indolylglyoxalic acid piperidide[13] by reduction with lithium aluminum hydride.[14] It was crystallized conveniently from absolute ethanol, mp 150–151.5° (lit.[13] mp 150–152°). The amine **6** was prepared by mercuric acetate cyclization of **4** in methanol–acetic acid by the methods of Wenkert,[8] Kutney[9] and coworkers, mp 149–150° (lit.[8] mp 153–155°).

**Preparation of 3-(β-Piperidinoethyl)indole *N*-Oxide 5.**[15]—To a solution of the amine **4** (2.5 g, 11 mmol) in absolute ethanol (85 ml), hydrogen peroxide (30 ml of 30%) was added and the solution was allowed to stir at room temperature for 24 hr. The excess hydrogen peroxide was destroyed by adding a small amount

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of manganese dioxide and stirring in an ice bath until the evolution of bubbles ceased. The solution was then filtered through Celite and the ethanol was evaporated under vacuum. The oily residue crystallized on standing to furnish a quantitative yield of the N-oxide **5**. Tlc (silica gel with 10% methanol–chloroform) was used to show the presence of only one compound ($R_f$ 0.14) which was different from starting material ($R_f$ 0.44): mp 162–163; ir (KBr) 3450 (NH), 3000–2200 (quaternary N-salt absorption), 1620 (indole absorption), 740 (ortho-disubstituted phenyl absorption), and 960 $cm^{-1}$ (characteristic band due to N-oxide not present in the starting material). The picrate salt formed yellow needles, mp 168–171°. *Anal.* Calcd for $C_{21}H_{23}N_5O_8$: C, 53.28; H, 4.9; N, 14.79. Found: C, 53.84; H, 5 01; N, 14.80.

**General Procedure for the Small Scale N-Oxide Cyclization.**[6]—Several scrapings of the pure N-oxide **5** (4–5 mg) were dissolved in methanol (8 ml), and acetic acid (1.5 ml) was added slowly. The iron salt was then added and the solution was refluxed. After refluxing the reaction was cooled and filtered through Celite. Hydrogen sulfide was passed through the solution for about 5 min and sodium borohydride (excess) was added slowly with cooling. The reaction mixture was let stand for 30 min and then filtered through Celite.

The yellow solution was evaporated to a yellow slurry under vacuum, dissolved in water, and extracted several times with benzene. The benzene layer was dried ($K_2CO_3$) and evaporated under vacuum, leaving a small amount of brown oil. The oil was analyzed by tlc (silica gel plates with ethyl acetate as the eluent). Three products were found: $R_f$ 0.72, 0.35, 0.18. The furthest moving component corresponded to sulfur ($R_f$ 0.72), mp 119°. The spot of lowest $R_f$ corresponded to 3-(β-piperidinoethyl)indole (**4**) ($R_f$ 0.18), while the compound with $R_f$ 0.35 was identical with the cyclized tetracyclic amine **6** ($R_f$ 0.35). No N-oxide **5** was found at any time after work-up.

The reaction was run under the conditions that follow.

**Ferrous and Ferric Ions. Experiment I.**—To a solution of the N-oxide **5** (5 mg) in methanol (5 ml) and acetic acid (1 ml), $FeSO_4 \cdot 7H_2O$ (0.2 g) was added, and, after refluxing for 30 min, $Fe_2(SO_4)_3 \cdot xH_2O$ (0.15 g) was also added. Tlc showed the presence of the uncyclized 3-(β-piperidinoethyl)indole (**4**) in the highest yield, a small amount of sulfur, and only a very small amount of the cyclized product.

**Ferric Ion under Anhydrous Conditions. Experiment II.**—The reaction was carried out using anhydrous ferric chloride (50 mg) under anhydrous conditions (8 drops of acetic anhydride were added to the solvents before the reaction was started) and refluxed for 1.5 hr. Tlc showed spots for the uncyclized amine **4** and sulfur, but no cyclized amine was observed.

**Ferrous Ion. Experiment III.**—The solution was allowed to react as in experiment I except that $FeSO_4 \cdot 7H_2O$ (0.1 g) was used and the reaction was refluxed for 2 hr. No ferric sulfate was used. Tlc showed sulfur and uncyclized amine, while the cyclized amine appeared to be present in higher yield than in experiment I.

**Ferrous Ion. Experiment IV.**—The mixture was allowed to react as in experiment III except that $FeSO_4 \cdot 7H_2O$ (0.2 g) was employed and the reaction was refluxed for 20 hr. Again sulfur and the uncyclized amine **4** were shown to be present by tlc. However, the cyclized product **6** was the strongest spot on the tlc plate and was present in much higher concentration than in experiments I and III.

**Ferric and Ferrous Ions under Anhydrous Conditions. Experiment V.**—To a solution of the N-oxide **5** in methanol, anhydrous ferric chloride (50 mg) was added under anhydrous conditions. The solution was refluxed for 1.5 hr. Tlc showed presence of uncyclized amine **4** and sulfur. No cyclized amine **6** was present.

**Ferric Ion. Experiment VI.**—To a solution of the N-oxide **5** (0.5 g) in methanol, $Fe_2(SO_4)_3 \cdot xH_2O$ (0.5 g) was added and the solution was refluxed for 20 hr. After work-up tlc showed the absence of the cyclized amine; however, after chromatography of the crude oil on Woelm activity III alumina, a trace of the cyclized material **6** was evident in one of the fractions.

**Ferrous Ion and Cyclohexanol. Experiment VII.**—The solution was allowed to react as in experiment III except that cyclohexanol (2 ml) was added and the solution was refluxed for 4 hr. Tlc showed the presence of uncyclized amine **4**, sulfur, and only a trace of the cyclized amine **6**.

**Preparation of the Cyclized Tetracyclic Amine 6 on a Large Scale.**—To a solution of the N-oxide **5** (2.5 g, 10 mmol) in methanol (400 ml), acetic acid (75 ml) was added slowly. Then $FeSO_4 \cdot 7H_2O$ (10.0 g) was added and the solution was allowed to reflux for 18 hr. The reaction turned a dark orange-brown color. After cooling, hydrogen sulfide was bubbled through the reaction mixture and the characteristic black precipitate of FeS began to form. Sodium borohydride (30.0 g) was added in small portions and a vigorous reaction took place. The reaction was cooled in an ice bath during the borohydride reduction. Again hydrogen sulfide was passed through the solution and the precipitate was allowed to settle for 30 min. The reaction was then filtered through Celite and the filtrate was evaporated under vacuum to leave a yellow slurry. Water (200 ml) was added and the solution was made basic with 25% sodium hydroxide. The alkaline solution was extracted four times with benzene and filtered to break up an emulsion. The benzene extracts were washed with water and dried over anhydrous potassium carbonate. Evaporation of the benzene left a viscous oil which was chromatographed on Woelm activity III neutral alumina packed with cyclohexane. The column was eluted with cyclohexane (eight fractions of 150 ml). The sulfur was eluted in the first three fractions. The solvent polarity was increased to 10:1 cyclohexane–benzene and gradually increased to 1:1 cyclohexane–benzene; 24 fractions were taken. Fractions 8–18 (75 ml each) were combined to yield the cyclized amine **6** (520 mg, $R_f$ 0.35) in a 22.5% yield. Fractions 18–20 contained both the cyclized product **6** and the uncyclized amine **4** (total 300 mg) while fractions 21–24 (including the chloroform washing of the column) contained 3-(β-piperidinoethyl)indole (**4**) (900 mg) of $R_f$ 0.18.

**Registry No.**—**5**, 33777-27-4; **5** picrate, 33777-28-5; **6**, 4802-79-3; $Fe^{3+}$, 20074-52-6; $Fe^{2+}$, 15438-31-0.

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