(11) Unpublished results from this laboratory.
(12) S. Bory, D. J. Lin, and M. Fetizon, *Bull. Soc. Chim. Fr.*, 1298 (1971).
(13) J. A. Svoboda, R. F. N. Hutchins, M. J. Thompson, and W. E. Robbins, *Steroids*, **14**, 469 (1969).
(14) Y. M. Sheikh, B. Twisch, and C. Djerassi, *Tetrahedron Lett.*, 3721 (1972).
(15) E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, **89**, 2755 (1967).
(16) M. F. Semmelhack, *Org. React.*, **19**, 115 (1972).
(17) A. I. Ryer and W. H. Gebert, *J. Amer. Chem. Soc.*, **74**, 45 (1952).
(18) We are thankful to Professor J. Ficini of Paris for helpful suggestions on the preparation of this reagent.
(19) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 2000 (1950).
(20) A. S. Ballsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, *1967 (1957)*.
(21) E. Fernholz, *Justus Liebigs Ann. Chem.*, **507**, 128 (1933).
(22) M. F. Semmelhack, Thesis, Harvard University, 1967.

General Methods of Synthesis of Indole Alkaloids. XIII. Oxindole Alkaloid Models[1,2]

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The synthesis of oxytryptophol and oxindoloindolizidine esters and methyl ketones is described. The determination of the stereochemistry of the acyl derivatives by ^1H and ^{13}C nmr spectral means is portrayed.

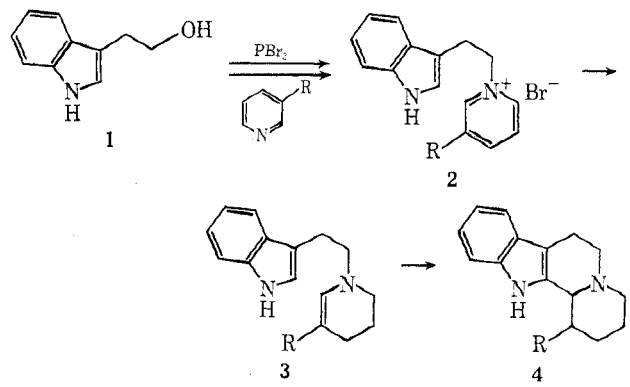
The transformation of tryptophol (**1**) into indoloquinolizidines (**4**) (Scheme I) represents the backbone of a general method of indole alkaloid synthesis.[4] As part of an endeavor to broaden the scope of the method, the possible replacement of the indole ring by the oxindole nucleus among early synthetic intermediates came under scrutiny. This modification offered great promise, since the resulting oxindoloindolizidine (**7**) could be envisaged in various stereochemical and substituted forms to be on the route to oxindole alkaloids of the rhyncophylline and mitraphylline types, to *Aspidosperma* alkaloids,[5] and to structures of even greater complexity. The incorporation of the oxindole system in the present scheme of synthesis appeared feasible at three stages of the reaction sequence: (a) by starting the sequence with oxytryptophol (**5**), (b) by oxidative conversion of indole **3** into oxindole **6** (followed by cyclization), and (c) by a related transformation of **4** into **7**. The following discussion focuses on these variations of Scheme I.

Bromination of tryptophol (**1**) in acetic acid gave a bromooxindole whose hydrogenolysis[6] led to oxytryptophol (**5**).[7] Unfortunately, in analogy with previous experience on *N*-methyloxindole compounds,[8] attempts of conversion of oxytryptophol (**5**) into an alkylating agent by the replacement of its hydroxy function by a leaving group failed. Thus, for example, treatment of **5** with hydrobromic acid yielded cyclopropane **8**.[9,10] As a consequence the preparation of oxindole equivalents of salts **2** appears a difficult task at best and the introduction of the oxindole unit is preferable at a later stage of Scheme I.

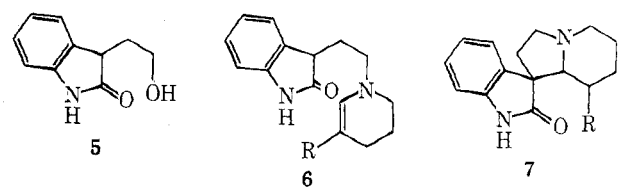
Treatment of ester **3b**[11] with aqueous *N*-bromosuccinimide[12] afforded a bromooxindole whose hydrogenolysis produced oxindole ester **7b** in one operation. Presumably the acid in the halogenating medium had effected the desired cyclization. The formation of three stereoisomers of **7b**, whose configuration is discussed later, indicated the cyclization to be nonspecific.

The customary procedure of an indole–oxindole conversion of type **4** → **7** involves initial oxidation with *tert*-butyl hypochlorite, base-catalyzed alcoholysis of the intermediate β-chloroindolenine, and acid hydrolysis of the resultant imino ether (Scheme II).[13] While this reaction sequence worked well for the simple indoloquinolizidine **4a**[11] and produced the **7a** diastereomers[14,15] therefrom, it proved difficult for **4** (R = Et)[14] and took an unusual course in the case of ketone **4c**.[16] Treatment of the latter with *tert*-butyl hypochlorite and subsequent hydroxide-

Scheme I

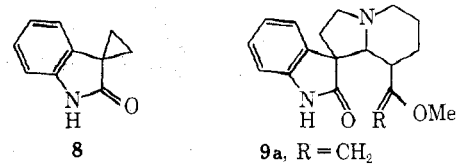


a, R = H; **b**, R = CO_2Me; **c**, R = Ac



a, R = H; **b**, R = CO_2Me; **c**, R = Ac

catalyzed methanolysis led to two oxindoles, instead of methoxyimines, and an unreacted chloroindolenine. The oxindoles proved to be an enol ether (**9a**) and a ketal (**9b**),

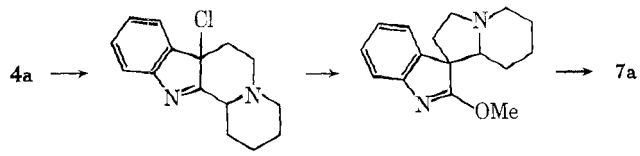


9a, R = CH_2
b, R = Me, OMe

whose mild acid hydrolysis converted them to stereoisomeric ketones (**7c**) of stereochemistry described below.

The unprecedented masking of a keto group in enol ether and ketal forms during a base-catalyzed operation, the formation of oxindoles instead of their imino ethers as a consequence of the rearrangement, and the ease of the reaction sequence appear interrelated and are interpreted most readily in terms of nucleophilic attack on the indolenine α-carbon site occurring intramolecularly. If it be assumed that methoxide first attacks the keto group and

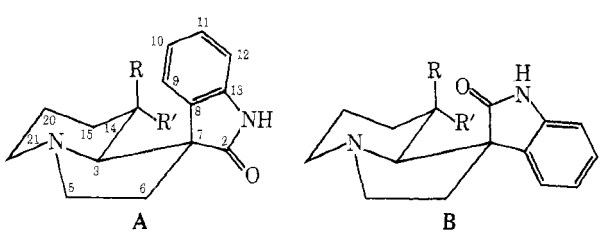
Scheme II



the resultant hemiketal salt adds to the imine, the stage is set for the intermediate with proper stereochemistry to undergo the usual Wagner–Meerwein migration. This sequence of events leads to an unstable imino ketal whose zwitterionic form in the presence of methoxide can be expected to be transformed into an enol ether or ketal (Scheme III).

As the above reactions illustrate, the change in oxidation state inherent in the introduction of an oxindole nucleus into Scheme I can be effected at the intermediate vinylogous amide level (**3b** and probably also **3c**) and, at least in one circumstance (**4c**), at the tetracyclic stage. This clears the way for the application of the general method of indole alkaloid synthesis for the construction of oxindole alkaloids.

Three methods of analysis—an equilibration study and ^1H and ^{13}C nuclear magnetic resonance spectral investigations—were applied to the determination of the stereochemistry of the oxindolyl esters and ketones. It has been known for over a decade[13,17] that solutions of **7a**-like alkaloids undergo thermal C(7) and/or C(3) isomerization by way of C(3)–C(7) bond fission–recombination.[18] It has been assumed that the equilibrium in pyridine yields predominance to structure type **10aA** and in acetic acid to **10aB**.[13,19,20] While the theoretical justification of this phenomenon is still open to question,[21] isomerization results have been used successfully in the determination of the stereochemistry of many oxindole alkaloids.[19]

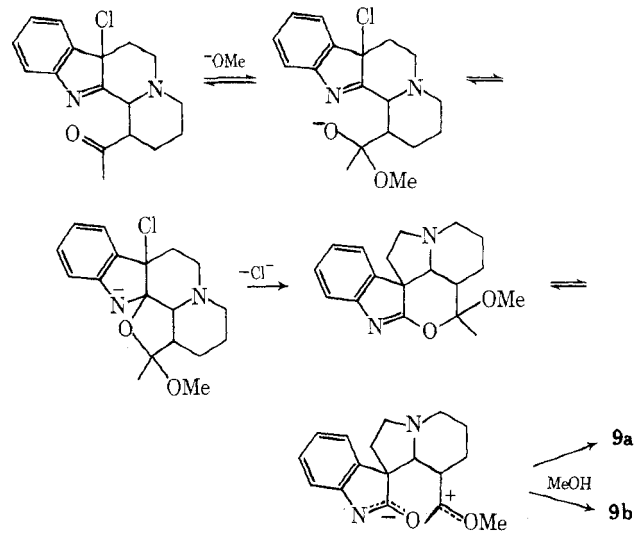


A B

10a, R = R′ = H
b, R = H; R′ = CO_2Me
c, R = CO_2Me; R′ = H
d, R = H; R′ = Ac

Equilibration of the oxindole **7a** isomers, two racemates with mp 146–147° and 195–196°, in pyridine has yielded exclusively the mp 147° isomer, while isomerization in 10% aqueous acetic acid gave a 2.3:1 mixture in favor of the mp 196° isomer.[14] On the asumption of these substances possessing a *trans*-indolizidine structure in solution[21] the mp 147° isomer can be assigned configuration **10aA** and the mp 196° isomer **10aB**.[22] The interconversion of the three isomeric esters **7b**—X, Y, and Z—yielded the following results. Attempted isomerization of C(14)[23] by treatment of the esters with methanolic sodium methoxide left isomers X and Y unfazed, while causing Z to unravel and to produce **6b** along with a trace of isomers X and Y. These data suggest that X and Y are C(7) epimers containing equatorial ester functions, while Z is an axial ester. This conclusion is strengthened by the fact that exposure of X or Y to 10% aqueous acetic acid yielded a 1:1 mixture of only these two isomers. Isomerization of Y in pyridine gave a mixture of **6b**, X, and Y. The overall results support structure **10bA** or **10bB** for isomer X, **10bB** or **10bA** for Y, and **10cA** or **10cB** for Z. Finally, the interconversion of the two ketones **7c**—U and V—proceeded in the following manner. Equilibration of U as well as of V in 10% acetic acid yielded a *ca.* 1.7:1 mixture of only U and V, respectively, while treatment of V with pyridine led to a mixture of **6c** and U. These observations suggest that the two **7c** isomers are equatorial, C(7) epimer ketones.

Scheme III



The pmr spectra define the stereochemistry of the isomeric esters (**7b**) and ketones (**7c**) on the prior assumption of the presence of a *trans*-indolizidine moiety in all substances. As Table I indicates, it has been possible for the first time to pinpoint the H(3) pmr signal and to ascertain its multiplicity. The H(3) coupling behavior reveals all compounds except ester Z to possess equatorial C(14) substituents. In analogy with past experience,[15,19] H(9) exhibits its proximity to N_b by a *ca.* 0.1-ppm downfield shift, thereby differentiating between the 7-epimer pairs. The stereochemically diagnostic $\Delta\delta$ value between 7-epimers can be enhanced to *ca.* 0.2 ppm on carrying out the pmr analysis in trifluoroacetic acid solution. Finally, the

Table I
^1H Chemical Shifts and Coupling Constants

	H(3)		H(9)		Me	
	δ	J, Hz	δ	J, Hz	δ	J, Hz
10bA[a]	2.73	d, 10	7.34	d, 7	3.30	s
10bB[a]	2.55	d, 10	7.20	d, 7	2.98	s
10cA[a]	2.75	d, 5	7.33	d, 7	2.89	s
10dA[b]	2.77	d, 10	7.33	dd, 7, 2	1.44	s
10dB[b]	2.63	d, 10	7.24	dd, 7, 2	1.80	s
10dA[c]	3.99	d, 10	7.60	d, 7	1.74	s
10dB[c]	4.04	d, 10	7.38	d, 7	2.02	s

[a] 220-MHz spectra of $CDCl_3$ solutions. [b] 100-MHz spectra of $CDCl_3$ solutions. [c] 220-MHz spectra of 4:1 trifluoroacetic acid–$CDCl_3$ solutions.

Table II
^{13}C Chemical Shifts

	10aA	10aB	10bA	10bB	10cA	10dA	10dB	12[a]
C-2	182.7	182.6	183.0	181.9	181.7	182.7	181.4	170.0
C-3	72.1	75.4	71.5	73.3	72.0	72.0	72.7	75.9
C-5	54.3	55.3	64.0	54.1	54.6	54.3	54.1	53.6
C-6	34.7	34.4	36.5	35.9	35.8	36.3	35.5	40.8
C-7	57.3	56.6	55.6	55.2	56.5	54.9	55.1	58.0
C-8	134.4	134.1	133.1	134.0	132.2	132.7	133.3	133.7
C-9	125.1	122.9	124.7	123.1	126.7	124.5	122.4	124.4
C-10	122.4	122.4	122.2	122.6	122.0	121.6	122.4	120.9
C-11	127.4	128.0	127.8	127.9	127.9	127.8	127.5	127.9
C-12	109.7	109.8	109.6	109.7	109.6	109.9	109.8	108.4
C-13	140.8	141.7	141.6	141.4	141.1	141.5	140.1	143.2
C-14	26.2	25.6	44.6	42.5	39.3	51.8	51.3	44.1
C-15	23.8	24.3	28.6	28.0	27.7	27.2	28.4	27.9
C-20	25.2	24.8	24.6	23.5	21.4	24.8	24.0	24.1
C-21	53.6	53.8	52.6	52.6	53.6	52.5	52.2	52.6
C=O			173.5	173.5	173.1	175.1	175.9	172.8
Me			50.9	50.8	51.4	27.9	28.4	50.7

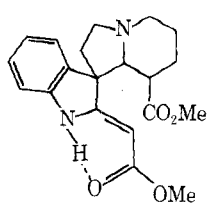
[a] The C-2 acetic ester moiety has the following shifts: α-C, 80.6; C=O, 170.2; and Me, 50.3 ppm.

methoxy group of the esters **7b** shows its proximity to the benzene ring in two of the three isomers by its high field position. All these facts permit assignment of structures **10bA, 10bB,** and **10cA** to the **7b** isomers X, Y, and Z, respectively, and **10dA** and **10dB** to the **7c** isomers U and V.

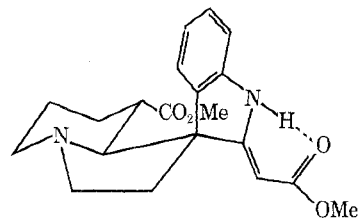
The ^{13}C nmr spectra of the various oxindoles proved to be even more enlightening than the pmr spectra. The chemical shift assignments of esters **10bA, 10bB,** and **10cA** and of ketones **10dA** and **10dB,** listed in Table II, are based on natural abundance, proton-decoupled as well as single-frequency, off-resonance decoupled ^{13}C nmr spectra and on their analysis in the manner described previously for models **10aA** and **10aB.**[24] The introduction of an equatorial carbomethoxy group into the piperidine ring of the oxindoloindolizidine nucleus exerts an α effect of 18.4 and 16.9 ppm (for **10bA** and **10bB,** respectively) reminiscent of the 20.4 ppm $\Delta\delta$ value for C-3 of *N*-methylpiperidine and methyl 1-methyl-1,2,3,4,5,6-hexahydronicotinate,[25] while an axial carbomethoxy function (in **10cA**) produces an expectedly lower α effect (13.1 ppm). The strong α effect of the acetyl group of the ketones **10dA** and **10dB** (25.6 and 25.7 ppm, respectively) reveals their equatorial nature. While the β effect of all acyl groups on C-15 is 4–5 ppm, it is surprisingly low and probably balanced by subtle other effects at C-3. Quaternary C-7 experiences only a minimal (1–2 ppm) γ effect from the acyl functions. The stereochemically most diagnostic carbon shift of ester **10cA** is that of C-20. The 3–4-ppm shielding of this carbon site reveals conclusively the axiality of the carbomethoxy group of this isomer.

The ^{13}C nmr results support strongly the above stereochemical assignments and are consistent only on the basis of a *trans*-indolizidine system. While the C-3 and C-9 carbon shifts have been shown to reflect the C-7 configuration in models **7a** and oxindole alkaloids of the rhyncophylline type,[24] the proximity of the 14-acyl substituents in the esters and ketones to C-3 precludes the use of the latter's chemical shift from being stereochemically determinant. Even the C-9 shift appears to be affected by the C-14 substituent, at least in the case of the axial ester **10cA.**

In view of the success with the ^{13}C nmr analysis of the oxindolyl esters **10bA, 10bB,** and **10cA,** ^{13}C nmr spectroscopy appeared to be an ideal tool for the determination of the configuration of diester **11,** a synthetic intermediate potentially on route to the *Aspidosperma* alkaloids.[26] The shift assignment (Table II) was carried out in the same fashion as for all the aforementioned oxindoles. Replacement of the oxygen of the oxindole carbonyl group by a carbomethoxymethine leads to strong shielding of both C-3 and C-6. The upfield shift of C-3, possible only by the olefinic methine and H-3 being within nonbonded interaction distance, and the C-9 shift show the compound to belong to the **10A** stereochemical series. The C-14 shift and the absence of any γ effect by the piperidino carbomethoxy group on C-20 reveal this substituent to be equatorially oriented. These facts support structure **12** for the diester.



11



12

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared and ultraviolet spectra were recorded on Perkin-Elmer 137 and Cary 14 spectrophotometers. Mass spectra were obtained on an AEI MS-9 spectrometer. Unless otherwise noted, ^1H nmr spectra of deuteriochloroform solutions with TMS as internal standard (δ 0 ppm) were recorded on Varian A-60, HA-100, and HR-220 spectrometers. The ^{13}C nmr spectra of chloroform solutions were taken on a nmr instrument equipped with a Varian Associates DP-60 magnet working at 14 kG with an external ^{19}F lock, a white-noise generator and adjustable, home-built crystal oscillator for proton decoupling, and a Fabri-Tek 1074 time-averaging computer and Digital Electronics Corp. PDP-8/1 computer for signal averaging and Fourier transformation of the free induction decay. The samples were spun in 13-mm-o.d. tubes and the solvent signal was used as internal standard. All δ values are in parts per million downfield from TMS; δ(TMS) = $\delta(CHCl_3)$ + 77.2 ppm.

Oxytryptophol (5). A solution of 7.1 g of bromine in 18 ml of acetic acid was added dropwise to a stirring solution of 3.5 g of tryptophol in 200 ml of 50% aqueous acetic acid in an ice bath. After 1 hr at room temperature the mixture was augmented by 1.5 g of 10% palladium on charcoal and shaken under hydrogen at atmospheric pressure for 20 hr. It then was filtered and the filtrate was evaporated under reduced pressure. A 9:1 ether–chloroform solution of the residual oil was decolorized with charcoal, the mixture was filtered, and the filtrate was concentrated. Crystallization of the residue from hexane–ether yielded 2.0 g of colorless crystals of **5:** mp 110–112° (lit.[7] mp 111–112°); ir (KBr) OH, NH 3.00 (m), 3.18 (m), C=O 5.93 (s), C=C 6.18 μ (m).

Anal. Calcd for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.72; H, 6.42; N, 8.18.

3,3-Dimethyleneoxindole (8). A solution of 49 mg of **5** in 5 ml of 48% hydrobromic acid was refluxed under nitrogen for 10 hr. It

then was cooled, diluted with water, neutralized with 2 *N* sodium hydroxide, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethyl acetate gave 30 mg of crystalline **8**: mp, mmp 185–187°; ir spectrum identical with that of an authentic sample.[8]

Oxindole Esters 7b. Water (25 ml) was added to a solution of 5.1 g of ester **3b**[11] in 50 ml of *tert*-butyl alcohol and 110 ml of glacial acetic acid and the mixture was cooled to 0°. *N*-Bromosuccinimide (7.5 g) then was added over a 5-min period and the mixture was stirred at 0° for 15 min and at room temperature for 1 hr. Palladium on charcoal (1.5 g of 10%) was added and the mixture was hydrogenated at atmospheric pressure for 20 hr. The catalyst was filtered and the filtrate was poured into 800 ml of saturated potassium bicarbonate solution. The precipitate was dissolved in chloroform and the chloroform was washed with 10% sodium hydroxide solution and with water, dried, and evaporated. Chromatography of the residual foam, 6.2 g, on 200 g of Florisil and elution with 99:1 chloroform–methanol gave a small amount of **10cA**, which crystallized from a benzene–ethyl acetate solution, followed by mixtures of **10cA** and **10bA**, whose combination gave 2.0 g of tan foam. Elution with 33:1 chloroform–methanol yielded 2.7 g of crude, crystalline **10bB**. Seeding of an ethyl acetate solution of a mixture of **10cA** and **10bA** with a crystal of **10cA** led to the precipitation of 330 mg of crystalline **10cA** and a solution of mostly **10bA**. Since **10cA** was found to isomerize readily on being heated in several solvents, it was purified by dilution of its methylene chloride solution with hexane and seeding at room temperature and then at 0°. This gave colorless prisms of **10cA**: mp 159–167°; ir (Nujol) NH 3.13 (m), C=O 5.75 (s), 5.86 (s), C=C 6.17 μ (m); uv λ_{max} (EtOH) 252 mm (ϵ 6800), 283 (1300); pmr δ 6.94 (d, 1, J = 7.5 Hz, H-12), 6.97 (t, 1, J = 7.5 Hz, H-10), 7.14 (t, 1, J = 7.5 Hz, H-11).

Anal. Calcd for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.20; H, 6.38; N, 9.33.

Evaporation of the ethyl acetate solution containing **10bA** and chromatography of the residue on Florisil gave 920 mg of crude **10bA** whose crystallization from aqueous methanol at 0–25° yielded 520 mg of crystalline powder, mp 67–100°. Further crystallizations from aqueous methanol produced colorless leaflets of **10bA** hydrate: mp 75–103°; ir (Nujol) OH 2.85 (m), NH 3.12 (m), C=O 5.72 (s), 5.83 (s), C=C 6.14 μ (m); uv λ_{max} (EtOH) 252 nm (ϵ 6700), 283 (1300); pmr δ 6.93 (d, 1, J = 7.5 Hz, H-12), 6.99 (t, 1, J = 7.5 Hz, H-10), 7.16 (t, 1, J = 7.5 Hz, H-11).

Anal. Calcd for $C_{17}H_{20}O_3N_2 \cdot H_2O$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.03; H, 6.59; N, 8.79.

Crystallization of crude **10bB** from benzene–methylene chloride at 0–25° gave 1.5 g of fluffy, colorless crystals, mp 179–180°. Further such crystallizations led to **10bB**: mp 180.5–181.5°; ir (Nujol) NH 3.10 (m), C=O 5.79 (s), 5.89 (s), C=C 6.16 μ (m); uv λ_{max} (EtOH) 253 nm (ϵ 7600), 280 (1400); pmr δ 6.94 (d, 1, J = 7.5 Hz, H-12), 7.00 (t, 1, J = 7.5 Hz, H-10) 7.14 (t, 1, J = 7.5 Hz, H-11).

Anal. Calcd for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.75; H, 6.60; N, 9.18.

A solution of 29 mg of **10bA** and 92 mg of sodium methoxide in 1 ml of methanol was kept at room temperature for 18 hr and then evaporated. The solution of the residue in 5 ml of water was adjusted to pH 8 with acetic acid and saturated potassium bicarbonate solution. The resultant precipitate was taken up in chloroform and the chloroform solution was dried and evaporated. The pmr spectrum of the residue was characteristic exclusively of **10bA**. Crystallization from aqueous methanol yielded 19 mg of **10bA**, identical ir spectrally with **10bA**.

A solution of 29 mg of **10bB** and 116 mg of sodium methoxide in 5 ml of methanol was refluxed for 5 hr and kept at room temperature for 18 hr. Work-up as above gave 20 mg of a crystalline residue whose pmr spectrum revealed the signals of only **10bB**.

A solution of 64 mg of **10cA** and 155 mg of sodium methoxide in 3 ml of methanol was kept at room temperature for 18 hr. Work-up as above yielded 55 mg of pale yellow gum, whose tlc (silica gel, 33:1 chloroform–methanol) showed the presence of **6b** and traces of **10bA** and **10bB** and whose ir and pmr spectra (*vide infra*) were identical with those of **6b**.

A solution of 79 mg of **10bB** in 5 ml of 10% aqueous acetic acid was refluxed for 20 hr. It was neutralized with solid potassium bicarbonate and extracted with chloroform. The extract was dried and evaporated. The 220-MHz pmr spectrum of the residue, 79 mg, showed the presence of a *ca.* 1:1 mixture of **10bA** and **10bB** (unchanged on refluxing an acetic acid solution of **10bB** for 48 hr). The compounds were isolated and identified by the crystallization procedures described above. Treatment of isomer **10aA** for 48 hr under the same conditions and reaction work-up as applied to **10bB** led to the same mixture of products.

A solution of 1.05 g of **10bB** in 50 ml of pyridine was refluxed under nitrogen for 5 hr. Its evaporation produced a dark residue whose pmr spectrum revealed the presence of **10bA**, **10bB**, and **6b**. A benzene solution of the residue was washed with 10% acetic acid solution and with water, dried, and evaporated. Chromatography of the residual oil, 460 mg, on 10 g of Florisil and elution with 99:1 chloroform–methanol afforded 260 mg of oil, which crystallized on trituration with ethyl acetate at −78°. Crystallization from aqueous acetone gave prisms of **6b**: mp 119–124°; ir (Nujol) NH 3.06 (m), C=O, C=C 5.82 (s), 6.04 (s), 6.22 μ (s); uv λ_{max} (EtOH) 250 nm (ϵ 11,000), 294 (25,000).

Anal. Calcd for $C_{17}H_{20}O_3N_2$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.66; H, 6.75; N, 9.40.

Oxindoles 9a and **9b.** A solution of 6.6 g of *tert*-butyl hypochlorite in 440 ml of methylene chloride was added over a 15-min period to a stirring solution of 14.7 g of **4c**[16] and 4.4 ml of triethylamine in 550 ml of methylene chloride at 0°. The mixture was stirred for another 30 min, then washed with water, dried, and evaporated below 40°. A solution of the residue and 3.81 g of potassium hydroxide in 600 ml of methanol was refluxed under nitrogen for 2 hr. It then was concentrated to 50 ml, diluted with water, and extracted with methylene chloride. The extract was dried and evaporated. Passage of a 1:1 benzene–chloroform solution of the residue, 17 g, through a 500-g column of basic alumina (activity III), followed by elution with 2:1 chloroform–benzene gave 10 g of dark, oily chloroindolenine, 2.3 g of brown, gummy ketal **9b**, and 3.6 g of tan, solid ether **9a** in this order.

Rechromatography of the first substance on 100 g of alumina (activity III) and elution with 1:1 benzene–chloroform gave 8.1 g of an oil which crystallized on standing. Crystallization from hexane–benzene yielded the ketochloroindolenine in Scheme III: mp 109.5–110.5°; ir (Nujol) C=O 5.86 (s), C=C 6.29 μ (m); pmr δ 1.2–3.4 (m, 13, saturated H's), 2.32 (s, 3, Me), 3.62 (d, 1, J = 10 Hz, H-3), 7.0–7.5 (m, 4, aromatic H's).

Anal. Calcd for $C_{17}H_{19}ON_2Cl$: C, 67.43; H, 6.32; N, 9.25. Found: C, 67.47; H, 6.33; N, 9.22.

A benzene solution of the ketal was decolorized with activated charcoal, the mixture was filtered, and the filtrate was evaporated. Crystallization of the residue from ethyl acetate gave 1.18 g of crystalline solid whose recrystallization from the same solvent produced prisms of oxindole ketal **9b**: mp 171–172° (with darkening and gas evolution); ir (Nujol) NH 3.14 (m), C=O 5.89 (s), C=C 6.16 μ (m); uv λ_{max} (EtOH) 251 nm (ϵ 7600), 279 (1600); pmr δ 1.5–3.5 (m, 12, saturated H's), 1.18 (s, 3, Me), 2.68, 2.78 (s each, 3, OMe), 6.7–7.6 (m, 4, aromatic H's).

Anal. Calcd for $C_{19}H_{26}O_3N_2$: C, 69.08; H, 7.93; N, 8.48. Found: C, 69.10; H, 7.95; N, 8.56.

A benzene solution of the ether was heated in the presence of activated charcoal, filtered, and concentrated. This led to 1.91 g of crystalline powder, mp 192.5–193.5°. Crystallization from benzene afforded colorless, fibrous crystals of oxindole enol ether **9a**: mp 196.5–197°; ir (Nujol) NH 3.16 (m), C=O 5.86 (s), C=C 5.97 (s), 6.22 μ (m); uv λ_{max} (EtOH) 253 nm (ϵ 7100), 280 (1400); pmr δ 1.5–3.5 (m, 12, saturated H's), 2.63 (s, 3, Me), 3.37, 3.78 (d each, 1, J = 2 Hz, olefinic H), 6.7–7.2 (m, 4, aromatic H's).

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.39; H, 7.61; N, 9.19.

Oxindole Ketones 7c. A solution of 408 mg of ketal **9b** and 0.4 ml of concentrated hydrochloric acid in 40 ml of methanol was kept at room temperature for 6 hr and then evaporated. The residue was taken up in water and treated with sodium carbonate. The methylene chloride solution of the resultant precipitate was dried and evaporated. Several crystallizations of the residual foam, 396 mg, from hexane–ether gave the product in the form of prisms which changed into needles on crystallization from hexane–benzene. Crystallization from hexane–methylene chloride yielded ketone **10dA**: mp 113–114.5°; ir (Nujol) NH 3.02 (m), C=O 5.80 (s), 5.86 (s), C=C 6.17 μ (m); uv λ_{max} (EtOH) 251 nm (ϵ 7950), 284 (1600); pmr δ 6.88 (dd, 1, J = 2, 7 Hz, H-12), 7.00 (dt, 1, J = 2, 7 Hz, H-10), 7.18 (dt, 1, J = 2, 7 Hz, H-11).

Anal. Calcd for $C_{17}H_{20}O_2N_2$: C, 71.82; H, 7.09; N, 9.85. Found: C, 71.76; H, 7.28; N, 9.71.

A solution of 807 mg of enol ether **9a** and 1 ml of concentrated hydrochloric acid in 50 ml of methanol was kept at room temperature for 3 hr and then evaporated. Work-up as for the hydrolysis of **9b** yielded a white foam whose crystallization from benzene–methylene chloride gave 717 mg of needles, mp 154–155°. Further crystallizations from hexane–methylene chloride produced **10dB**: mp 162–162.5°; ir (Nujol) NH 3.10 (m), C=O 5.81 (s), 5.91 (s),

C=C 6.17 μ (m); uv λ_{max} (EtOH) 253 nm (ϵ 5810), 284 (1210); pmr δ 6.88 (dd, 1, J = 2, 7 Hz, H-12), 7.02 (dt, 1, J = 2, 7 Hz, H-10), 7.15 (dt, 1, J = 2, 7 Hz, H-11).

Anal. Calcd for $C_{17}H_{20}O_2N_2$: C, 71.82; H, 7.09; N, 9.85. Found: C, 71.61; H, 7.19; N, 10.03.

A solution of 110 mg of **10dA** in 10 ml of 10% aqueous acetic acid was refluxed for 20 hr and then cooled, neutralized with solid potassium bicarbonate, and extracted with methylene chloride. The extract was dried and evaporated. The pmr spectrum of the oily residue, 102 mg, showed the presence of a 1.6:1 mixture of **10dA** and **10dB**, respectively. A solution of 100 mg of **10dB** in 10 ml of 10% aqueous acetic acid was refluxed for 20 hr. Similar reaction work-up led to 77 mg of product whose tlc (silica gel, 1.6:1 chloroform–methanol) revealed **10dA** and **10dB**, the former predominating, and whose pmr spectrum exhibited signals of a 1.9:1 mixture of **10dA** and **10dB**, respectively.

Registry No.—**3b**, 4695-82-3; **4c**, 2671-38-7; **5**, 51240-38-1; **6b**, 51240-39-2; **8**, 13861-75-1; **9a**, 51240-40-5; **9b**, 51240-41-6; **10aA**, 30671-33-1; **10bA**, 51268-47-4; **10cA**, 51240-42-7; **10dA**, 51240-43-8; **10bB**, 51268-48-5; **10dB**, 51268-49-6; tryptophol, 526-55-6; ketochloroindolenine, 51240-44-9.

References and Notes

(1) This investigation was supported by the U. S. Public Health Service.
(2) Part XII: E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.*, **38**, 4305 (1973).
(3) U. S. Public Health Service Predoctoral Fellow, 1967–1971.
(4) E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).
(5) T. Ohnuma, T. Oishi, and Y. Ban, *J. Chem. Soc., Chem. Commun.*, 301 (1973), and references cited therein.
(6) W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961).
(7) F. J. McEvoy and G. R. Allen Jr., *J. Org. Chem.*, **38**, 3350 (1973).
(8) P. L. Julian, A. Magnani, J. Piki, and W. Karpel, *J. Amer. Chem. Soc.*, **70**, 174 (1948); E. Wenkert and E. C. Blossey, *J. Org. Chem.*, **27**, 4656 (1962).
(9) D. G. Markees and A. Burger, *J. Amer. Chem. Soc.*, **71**, 2031 (1949); E. Wenkert and T. L. Reid, *Chem. Ind. (London)*, 1390 (1953).
(10) It also was the product of attempted mesylation of **5** in pyridine.
(11) E. Wenkert, K. G. Dave, and F. Haglid, *J. Amer. Chem. Soc.*, **87**, 5461 (1965).
(12) M. Ohno, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 343 (1970).
(13) N. Finch and W. I. Taylor, *J. Amer. Chem. Soc.*, **84**, 3871 (1962).
(14) E. Wenkert and J. S. Bindra, unpublished observations.
(15) A. J. Gaskell, H.-E. Radunz, and E. Winterfeldt, *Tetrahedron*, **26**, 5353 (1970).
(16) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **87**, 1580 (1965).
(17) T. Nozoe, *Chem. Pharm. Bull.*, **6**, 300 (1958); J. C. Seaton, M. D. Nair, O. E. Edwards, and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960); N. Finch and W. I. Taylor, *J. Amer. Chem. Soc.*, **84**, 1318 (1962); G. M. Badger, L. M. Jackman, R. F. Sklar, and E. Wenkert, *Proc. Chem. Soc.*, 206 (1963).
(18) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Amer. Chem. Soc.*, **81**, 3763 (1959).
(19) W. F. Trager, C. M. Lee, J. D. Phillipson, R. E. Haddock, D. Dwuma-Badu, and A. H. Beckett, *Tetrahedron*, **24**, 523 (1968), and references cited therein to earlier work.
(20) The indolizidine portion of **10aA** and **10aB** is portrayed usually with C(5), C(6), C(7), and C(3) in coplanar relationship.[13,19] Since this conformation exposes the geminal C(7) substituents to an energetically unfavorable, eclipsing interaction with the C(6) hydrogens, coplanarity between N_b, C(5), C(6), and C(7) is preferred. This latter representation has been illustrated previously without explanation.[15]
(21) All alkaloids have been assumed to possess a *trans*-indolizidine structure in all solutions on the basis of a cis structure being destabilized by extra 1,3-diaxial interactions in the piperidine moiety.[19] While infrared and pmr spectral analyses of simply substituted indolizidines indicate the basic skeleton to be trans fused [H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968); T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971)], the difference of energy between the cis and trans forms is too low and the steric as well as polar interactions of the oxindole ring with the indolizidine nucleus too subtle and complex to permit acceptance of a trans configuration for the latter in compounds **7** without rigorous proof. Equilibration in pyridine leading to **10aA** has been assumed to be the consequence of electron repulsion between the carbonyl oxygen and N_b, while preference of **10aB** in acetic acid has been ascribed to hydrogen bridging of a N_b-protonated species with the carbonyl oxygen.[13,19] However this explanation appears to be oversimplified in view of the fact that the isomer ratio rarely ever exceeds 3:1, indicating a small energy difference, and that substances **7** can be expected to be only minimally protonated in aqueous acetic acid. Merely differences in solvation suffice to give variations of equilibrium positions.
(22) The same configurations were assigned earlier[15] on the basis of pmr data on **7a** with assumed *trans*-indolizidine structures.
(23) For convenience the oxindole alkaloid nomenclature is being maintained for the models **7**.
(24) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, **7**, 46 (1974).
(25) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *J. Amer. Chem. Soc.*, **95**, 4990 (1973).
(26) E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Amer. Chem. Soc.*, **90**, 5251 (1968).

Structure of Aqueous Glutaraldehyde

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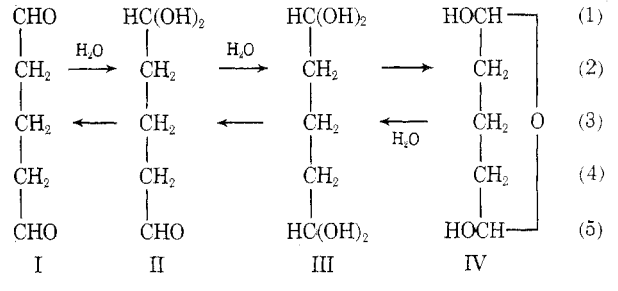
The carbon-13 nmr spectrum of aqueous 25% glutaraldehyde has been assigned to individual components in an equilibrium mixture. The solution is shown to consist primarily of the cyclic hemiacetal, equally present in its two isomeric forms, in equilibrium with the free aldehyde. The ratio of these components varies strongly with temperature. Approximately 25% of the mixture is present as the linear hemihydrate and the dihydrate in about a 2:1 ratio, this fraction being much less temperature dependent. Higher order oligomers contribute very little to the equilibrium mixture.

The structure of gluataraldehyde (pentanedial) in aqueous solution, in which form it is available as a commercial product,[1] has been the subject of several proton magnetic resonance studies,[2-4] not all of which give consistent results. The currently accepted structure,[4] based on the work by Hardy, Nicholls, and Rydon,[3] is that the solution contains roughly equal amounts of the hemihydrate II, the dihydrate III, and the cyclic hemiacetal IV.

It has not been possible to distinguish individual structures in the proton magnetic resonance spectrum owing to the overlapping of complex bands. Carbon-13 nmr is much less subject to these restrictions. With broad band proton decoupling, I, III, and IV should give simple three-line,



2:2:1 intensity patterns, and five equally intense lines should result from II. Higher order oligomers or condensa-