arylmagnesium bromide and butyronitrile or valeronitrile.[51] Both 2-methyl-2-octen-4-one and 2-methyl-2-hepten-4-one were prepared from dimethylacrylic acid *via* the acid chloride and the dialkylcadmium.[52] Both benzene and hexane were washed with sulfuric acid, dried, and distilled from phosphorus pentoxide.

Apparatus. All relative quantum yields were measured in a precisely machined "merry-go-round" apparatus so that each sample received the same amount of light. In the center was a 450-w Hanovia lamp in a quartz immersion well surrounded by a quartz filter jacket containing 46 g of $NiSO_4 \cdot 6H_2O$ and 14 g of $CoSO_4 \cdot 7H_2O$ per 100 ml of water. The water solution permitted the following wavelength distribution to pass through the 1-mm walls of the Pyrex tubes employed: 6% 2967 A, 20% 3025 A, 62% 3130 A, 10% 3340 A.

(51) C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *J. Am. Chem. Soc.*, 70, 426 (1948).
(52) J. Cason, *ibid.*, **68**, 2078 (1946).

Procedure. All reactions were run in 13-mm Pyrex tubes. After solutions of the proper concentrations had been prepared, 3.4 ml of each was placed in a tube with a syringe, and the tubes were degassed three or four times to 2×10^{-4} mm in freeze–thaw cycles and finally sealed *in vacuo*. For any given run, two samples containing no quencher and one sample for each quencher concentration were irradiated for the same length of time, and then stored in the dark until vpc analysis. The aliphatic ketones were analyzed with 5-ft columns packed with 25% Carbowax 20M on 42–60 Firebrick. Injector temperature was 180°, and the columns were programmed upward from 100° at 10°/min. The aromatic ketones were analyzed on 6-ft columns containing 5% Carbowax 20M on Chromosorb G, programmed upward from 125° at 10°/min. All analyses were performed on a Loenco Model 70 dual column–dual thermal detector machine with helium flows of 150 ml/min.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

Acid-Catalyzed Isomerization in the Peptide Part of Ergot Alkaloids[1]

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Contribution from the Research Laboratories of Sandoz Pharmaceuticals, Hanover, New Jersey, and Research Laboratories, Sandoz Ltd., Basle, Switzerland. *Received November 12, 1965*

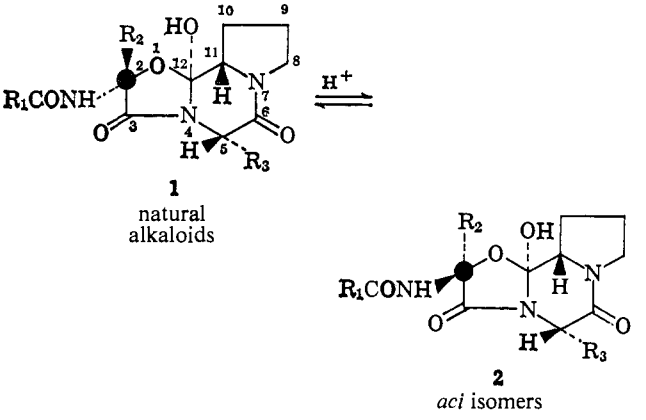
Abstract: Chemical evidence and a probable reaction mechanism for the acid-catalyzed isomerization at C-2 of the peptide part of ergot alkaloids is presented.

From X-ray crystal-structure analysis[2] it has become evident that the reversible acid-catalyzed isomerization of the peptide ergot alkaloids, as described for the first time in 1961 by Schlientz, Brunner, Thudium, and Hofmann,[3] represents an epimerization at position 2 of the peptide part as depicted by the stereo formulas **1** and **2** (Chart I).

This result prompts us to report some of our chemical investigations in connection with this problem, since these findings gave the clue to the interesting mechanism of this acid-catalyzed isomerization called, in short, "*aci* isomerization."

The *aci* isomerization is not the only reaction observed when natural ergot peptide alkaloids are heated in aqueous acidic solution, but it is accompanied by the long known epimerization at C-8 of lysergic acid,[4] thus leading to a mixture of four isomers. If, however, one of the corresponding $\Delta^{9,10}$-dihydro alkaloids is refluxed in dilute acetic acid, an equilibrium solely between the dihydro alkaloid and its *aci* isomer is established and almost no irreversible cleavage products can be detected. The same holds true for cyclols (**1**)

Chart I



1
natural alkaloids

2
aci isomers

R_1CO = lysergyl or 9,10-dihydrolysergyl
R_2 = CH_3 (ergotamine group) or $CH(CH_3)_2$ (ergotoxine group)
R_3 = $CH_2C_6H_5$, $CH(CH_3)_2$, or CH_2-$CH(CH_3)_2$

in which R_1CO stands for a simple acyl group like acetyl, benzoyl, *p*-nitrobenzoyl, or *p*-iodobenzoyl.

The reversibility of this epimerization in dilute acetic acid at C-2 of the peptide part is well documented by the observation that, no matter whether one starts with compound **1** or **2**, the same approximate 1:1 mixture of the two isomers is formed as an end result. The rate by which this equilibrium is reached depends mainly on reaction temperature, pH of the reaction

(1) (a) This is our 65th publication on ergot alkaloids; 64th communication: D. Stauffacher, H. Tscherter, and A. Hofmann, *Helv. Chim. Acta*, **48**, 1379 (1965). (b) Research Laboratories, Sandoz Ltd., Basle, Switzerland.
(2) A. T. McPhail, G. A. Sim, A. J. Frey, and H. Ott, *J. Chem. Soc.*, in press.
(3) W. Schlientz, R. Brunner, F. Thudium, and A. Hofmann, *Experientia*, **17**, 108 (1961).
(4) A. Stoll, T. Petrzilka, J. Rutschmann, A. Hofmann, and H. Günthard, *Helv. Chim. Acta*, **37**, 2039 (1954); A. Stoll, A. Hofmann, and F. Troxler, *ibid.*, **32**, 506 (1949).

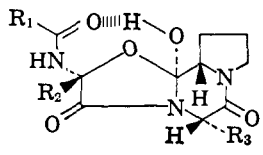
Table I

Name	Formula	R_1CO	R_2	R_3	Mp, °C	$[\alpha]^{20}D$, deg[a]	pK in DMF–H_2O (8:2)
Dihydroergotamine	1	Dihydrolysergyl	CH_3	$CH_2C_6H_5$	239	−64	13.3
aci-Dihydroergotamine	2	Dihydrolysergyl	CH_3	$CH_2C_6H_5$	188	−96	12.6
Dihydroergocristine	1	Dihydrolysergyl	$CH(CH_3)_2$	$CH_2C_6H_5$	180	−56	13.5
aci-Dihydroergocristine	2	Dihydrolysergyl	$CH(CH_3)_2$	$CH_2C_6H_5$	204–205	−138	12.8
Dihydroergocryptine	1	Dihydrolysergyl	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	235	−41	13.7
aci-Dihydroergocryptine	2	Dihydrolysergyl	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	180	−135	12.8
Dihydroergocornine	1	Dihydrolysergyl	$CH(CH_3)_2$	$CH(CH_3)_2$	187	−48	13.6
aci-Dihydroergocornine	2	Dihydrolysergyl	$CH(CH_3)_2$	$CH(CH_3)_2$	179	−133	13.0
Acetylaminocyclol	1	CH_3CO	CH_3	$CH_2C_6H_5$	207–208	+55	13.9
aci-Acetylaminocyclol	2	CH_3CO	CH_3	$CH_2C_6H_5$	222–223	−75	12.8
p-Nitrobenzoylaminocyclol	1	*p*-NO_2–C_6H_4–CO–	CH_3	$CH_2C_6H_5$	203–205	+6	
aci-p-Nitrobenzoylaminocyclol	2	*p*-NO_2–C_6H_4–CO–	CH_3	$CH_2C_6H_5$	199–200	−61	

[a] In pyridine.

medium, and structural features to be discussed later.

Table I gives some physicochemical data of these *aci* isomers, and the following facts can be derived therefrom. (1) The *aci* isomers (**2**) show higher negative specific rotation as compared to the parent compounds (**1**). (2) The cyclol hydroxyl group in the natural compounds of the type **1** is, by approximately 1 pK unit, less acidic than in *aci* isomers **2** and many other cyclols mentioned earlier.[3,6] This fact, we believe, results from intramolecular hydrogen bonding in compounds **1** represented in formula **3** which is excluded



3

R_1 and R_3 are the same as in Chart I

in *aci* compounds (**2**) for steric reasons. Stereo models of **1** permit such an eight-membered chelate ring without any strain.

Chemically, the higher acidity of the *aci* isomers (**2**) makes them more soluble in dilute alkali in contrast to the natural compounds (**1**), rendering the separation of a mixture of such isomers very easy.

Methylation of the cyclol hydroxyl group with CH_3I–Ag_2O, CH_2N_2, or CH_3I–$NaNH_2$ in liquid ammonia can only be accomplished with *aci* isomers (**2**) and fails completely with the natural alkaloids (**1**). Thus *aci*-DHE[3] (**4**) yields O-methyl-*aci*-DHE[7] (**5**) on standing for 3 days in methanolic diazomethane solution, whereas natural DHE (**6**) stays completely unchanged (see Chart II). This different behavior might be due to increased shielding of the backside and/or the intramolecular chelation in the stereoisomers (**1**), *i.e.*, **6**.

Mild acidic hydrolysis of O-methyl-*aci*-DHE (**5**), *e.g.*, standing in dilute hydrochloric acid at room temperature, leads back to *aci*-DHE as the sole reaction product. This type of reaction has been described earlier[3] with several O-methylated model cyclols and is formulated as a SN1 reaction through the carbonium ion (**12**) as an intermediate. Unlike most SN1 reactions, the nucleophile adds stereospecifically only from the backside of the carbonium ion. These facts are best represented by the acid-catalyzed reaction sequence **5** ⇌ **12** ⇌ **4**.

We shall show that the resonance-stabilized, ambident cation **12** also plays a central role as the starting point of the isomerization at C-2. Ambident cations similar to **12**, in particular carboxonium and oxazolinium ions, have been postulated as intermediates in solvolytic displacement reactions with participation of neighboring acetoxy groups[8] and in the thermal decomposition of imino ether hydrochlorides.[9] More recently, Meerwein[10] has isolated several ambident cation systems in the form of their tetrafluoroborates, and the reactions of these cations have been rationalized by Hünig.[11]

These principles can logically be applied to the ambident oxazolinium ions of the *aci* isomers (**2**) and natural alkaloids (**1**), respectively. These ions can be represented as hybrids of several canonical forms outlined in Chart III (partial structures). *aci* Isomerization of the natural alkaloids (**1**) occurs in a reasonable rate only

(5) H. Ott, A. J. Frey, and A. Hofmann, *Tetrahedron*, **19**, 1675 (1963); R. G. Griot and A. J. Frey, *ibid.*, **19**, 1661 (1963); W. Schlientz R. Brunner, A. Hofmann, B. Berde, and E. Stürmer, *Helv. Pharm. Acta*, **36**, 472 (1961).

(6) A. Hofmann, H. Ott, R. Griot, P. A. Stadler, and A. J. Frey, *Helv. Chim. Acta*, 46, 2306 (1963).

(7) DHE stands for $\Delta^{9,10}$-dihydroergotamine. In our publication on the synthesis and stereochemistry of ergotamine,[6] we described the synthesis of DHE (**6**) by the reaction sequence **7** → **8** → **6** (Chart II). The analogous reaction sequence with the C-2 diastereoisomeric carbobenzoxyaminocyclol (**9**) supposedly led to the C-2 isomeric compound **4**, which, as we know now, corresponds to *aci*-DHE. Since our synthetic DHE isomer was, however, not identical with *aci*-DHE (**4**), our structural assignment at this time must have been incorrect. A reinvestigation revealed that this DHE isomer is actually identical in every respect (infrared, nmr, melting point, mixture melting point, thin layer chromatography, etc.) with O-methyl-*aci*-DHE (**5**). The hydrogenolytic removal of the carbobenzoxy group from the carbobenzoxyaminocyclol (**9**) was evidently accompanied by the substitution of the cyclol hydroxyl group by the methoxyl group to form the amine hydrochloride (**10**) (obtained as an amorphous crude product), which on acylation with 9,10-dihydrolysergyl chloride led to O-methyl-*aci*-DHE (**5**). We know that the cyclol OH group at C-12 is replaced by the methoxyl group preceding the hydrogenolytic cleavage of the carbobenzoxy group because, when the carbobenzoxyaminocyclol (**9**) is dissolved in methanolic hydrochloric acid at room temperature, O-methylcarbobenzoxyaminocyclol (**11**) forms almost quantitatively within 3 min, whereas, under the same conditions, hydrogenolytic removal of the carbobenzoxy group requires approximately 30 min.

(8) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2780 (1942); S. Winstein and R. Boschan, *ibid.*, **72**, 4670 (1950); S. Winstein, C. B. Anderson, and E. C. Friedrich, *Tetrahedron Letters*, **29**, 2037 (1963).

(9) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2233 (1951).

(10) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Sprille, *Chem. Ber.*, **89**, 2060 (1956); H. Meerwein, K. Bodenbrenner, P. Borner, F. Kunert, and K. Wunderlich, *Ann. Chem.*, **632**, 38 (1960); H. Meerwein, W. Florian, N. Schön, and G. Stopp, *ibid.*, **641**, 1 (1961).

(11) S. Hünig, *Angew. Chem. Intern. Ed. Engl.*, **3**, 548 (1964).

Chart II

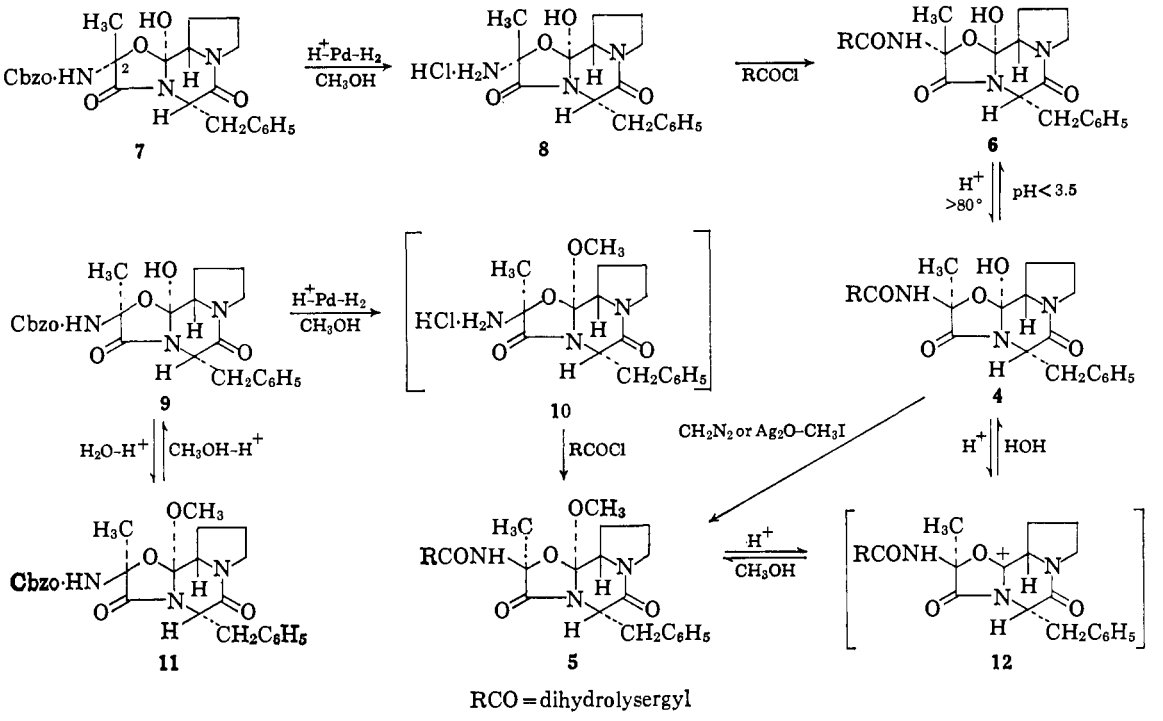
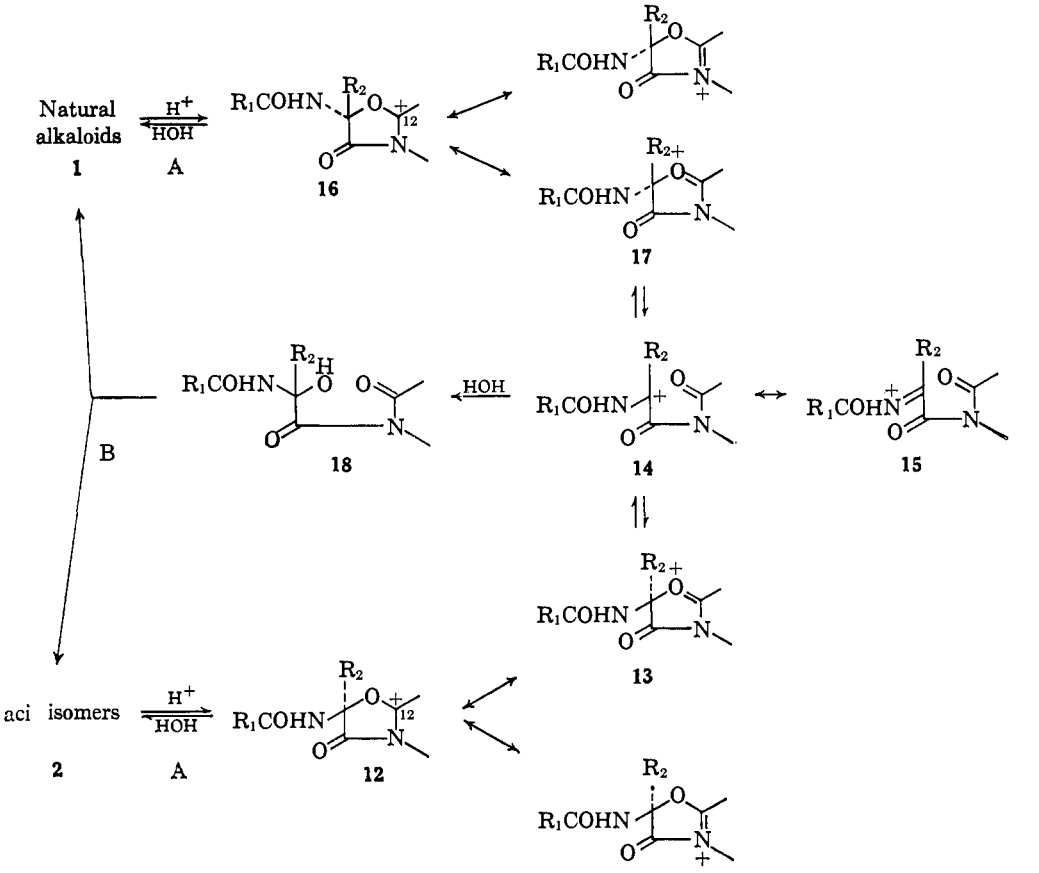
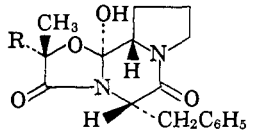


Chart III



when energy is applied, *e.g.*, under mild acidic conditions (pH 3–4) at temperatures over 80°. Therefore, the cyclic canonical ions **13** and **17** apparently require energy to be transformed into the acyclic ions **14** ↔ **15**, respectively. It is obviously only through this ring-opening step that the partial racemization at the asymmetric center C-2 can occur. That the possibility of the ammonium ion formation **15** is an essential prerequisite for the *aci* isomerization can be derived from the fact that analogous compounds of type **19**, where the amide function at C-2 is replaced by a hydrogen atom or a carboxylic ester, do not undergo any isomerization at this center under the same reaction conditions, although a carbonium ion of type **14** could theoretically be formulated.

Whether the cation **14** ↔ **15** independently reverts



19

R = H or $COOCH_3$

back to the cyclol forms **1** and **2** through the cyclic carbonium ions **12** ↔ **13** and **16** ↔ **17** by nucleophilic attack of water at C-12 *via* pathway A, or whether it (**14** ↔ **15**) combines first with water to form **18** and then cyclizes stereospecifically *via* pathway B directly, the observed results would be the same. But, since pathway A calls for the exchange of the cyclol hydroxyl group only, whereas in pathway B the oxygen in the oxazolidine ring is exchanged as well, it was possible to differentiate between reaction mechanisms A or B by the following ^{18}O isotope techniques.

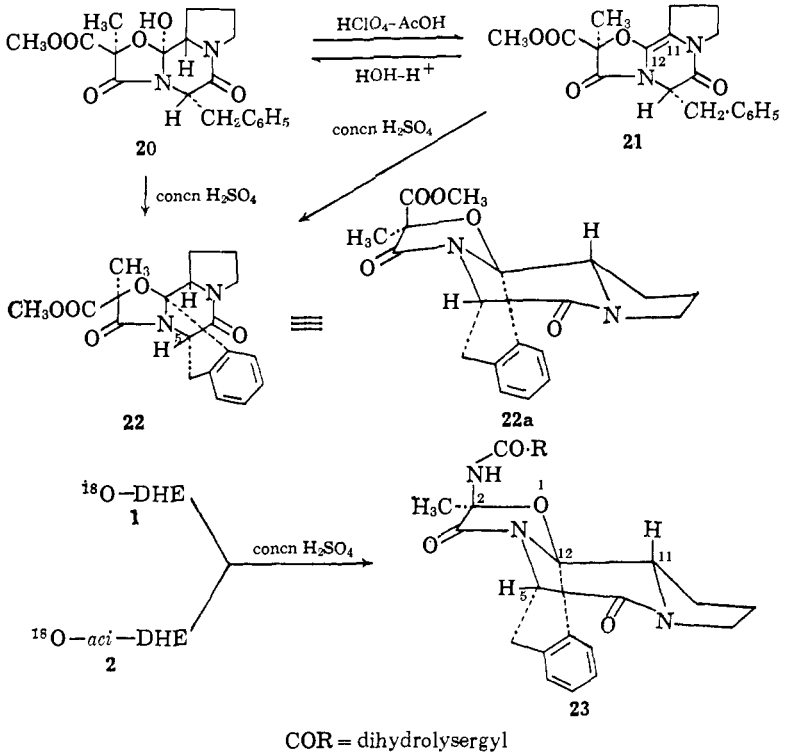
Table II

Tested compounds	Tracer ^{18}O found (calcd for one O atom) %: 1st detmn	2nd detmn
DHE unlabeled	7.4	8.7[a]
aci DHE unlabeled	8.9	1.6[a]
DHE labeled	86	85
aci DHE labeled	77	88.5
Dehydration product from labeled *aci*-DHE (**23**)	0	0

[a] Blind value.

However, if the dehydration of **20** is carried out in concentrated sulfuric acid, a product of structure **22** is obtained.[13] This unexpected cage-like structure is strongly supported by the nmr spectrum which revealed, after careful evaluation of the integrals, that only four

Chart IV



COR = dihydrolysergyl

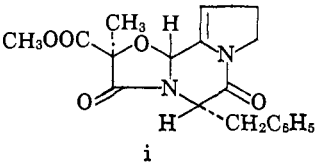
Pure DHE and *aci*-DHE were isomerized independently in aqueous acetic acid enriched in $H_2{}^{18}O$ (approximately 1% abundance) at reflux temperature, and the isomerization products, *aci*-DHE and DHE, respectively, were isolated and submitted to analysis by mass spectroscopy.[12] The results of these analyses (Table II) indicate clearly that, within the error limits of the applied method, one and only one oxygen atom has been substituted by ^{18}O in the equilibrium reaction. This speaks strongly for mechanism A and rules out pathway B.

Further evidence for the single labeling could be gained from dehydration experiments of the cyclols ^{18}O-DHE and ^{18}O-*aci*-DHE.

It was known[6] that, *e.g.*, the dehydration of the cyclol ester (**20**) with perchloric acid in acetic acid leads, *via* an E1 reaction, to the $\Delta^{11,12}$ ester (**21**) (Chart IV). aromatic protons are present in the molecule. The doublet of a doublet centered at 299 cps results from coupling of the proton at C-5 in **22** with the two adjacent benzylic protons in the newly formed six-membered ring. The coupling constants of this quartet (J_1 = 6.5 cps, J_2 = 2 cps) are in reasonably good agreement

(12) We wish to thank Professor H. Dahn, University of Lausanne, for the analysis by mass spectroscopy of our ^{18}O products. The method used has been described by H. Dahn, H. Moll, and R. Menassé, *Helv Chim. Acta*, 42, 1225 (1959).

(13) In our earlier publication[6] in this matter, we attributed to compound **22** the incorrect structure of a $\Delta^{10,11}$ dehydration product (i). Professor Warnhoff, University of Western Ontario, informed us then privately about his doubts as to the correctness of this formula based on his different ultraviolet spectra of simpler compounds containing the chromophoric system C=C—N—C=O. We wish to thank Professor Warnhoff for kindly drawing our attention to this conflict.

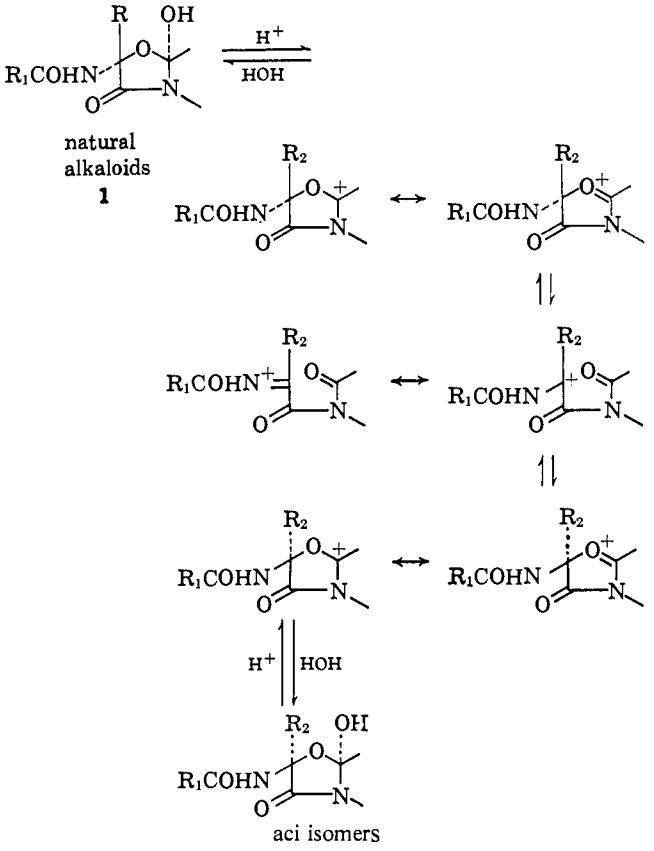


i

with the dihydral angles involved. The dehydration product (**22**) conceivably forms by electrophilic attack of the initial carbonium ion at C-12 on the *ortho* position of the phenyl ring. If we consider the proximity of the phenyl ring and the cyclol hydroxyl group as evinced in the X-ray analysis of *aci*-*p*-iodobenzoylaminocyclol,[14] the course of this dehydration reaction is plausible. Indeed, the Dreiding stereo model of the molecule (**22a**) is practically free of strain.

When ^{18}O-labeled DHE or *aci*-DHE are now separately treated with sulfuric acid at room temperature, one and only one identical and *unlabeled* (see Table II) dehydration product can be isolated in crystalline form. Its structure (**23**) follows from a comparison of its nmr spectrum with that of ester **22**. The open-chain cation, **14** ↔ **15**, is again postulated as an intermediate in the dehydration reaction in order to explain the formation of the same product (**23**) from both DHE and *aci*-DHE. The complete loss of the tracer element ^{18}O in this dehydration confirms our earlier deduction that only the cyclol hydroxyl group is labeled during the *aci* isomerization in $H_2{}^{18}O$.

In conclusion, we have, therefore, presented strong evidence that the mechanism of the *aci* isomerization is best represented by the following reaction scheme.



R_1CO = lysergyl or dihydrolysergyl
R_2 = CH_3, C_2H_5, or $CH(CH_3)_2$

Experimental Section[15]

***aci*-Dihydroergocristine.** A solution of 12.0 g of dihydroergocristine in 400 ml of glacial acetic acid and 8 l. of water was refluxed for 15 hr. To the cooled solution 400 g of sodium carbonate was added in small portions under vigorous stirring, and the reaction mixture was then thoroughly extracted with chloroform–methanol (9:1). The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated. The amorphous residue, consisting of a mixture of dihydroergocristine and *aci*-dihydroergocristine (as shown by thin layer chromatography), was dissolved in 300 ml of methylene chloride, and this solution extracted three times with 100 ml of 1 *N* sodium hydroxide. The combined aqueous phases containing the sodium salt of *aci*-dihydroergocristine were neutralized with concentrated hydrochloric acid and extracted with methylene chloride. The amorphous residue (4.62 g), on crystallization from acetone, yielded 3.73 g of *aci*-dihydroergocristine: white prisms, mp 204–205°, $[\alpha]^{20}D$ −138° (*c* 0.3, pyridine).

Anal. Calcd for $C_{35}H_{41}N_5O_5$: C, 68.7; H, 6.8; N, 11.5; O, 13.1. Found: C, 68.4; H, 6.9; N, 11.2; O, 13.5.

***aci*-Dihydroergocryptine.** This *aci* compound was prepared from dihydroergocryptine in an analogous manner as described for *aci*-dihydroergocristine. For analysis, it was crystallized from methanol: white prisms, mp 180°, $[\alpha]^{20}D$ −135° (*c* 0.3, pyridine).

Anal. Calcd for $C_{32}H_{43}N_5O_5$: C, 66.5; H, 7.5; N, 12.1; O, 13.9. Found: C, 66.3; H, 8.1; N, 12.4; O, 14.1.

***aci*-Dihydroergocornine.** This *aci* compound was prepared from dihydroergocornine in an analogous manner as described for *aci*-dihydroergocristine. For analysis, it was crystallized from methanol: white prisms, mp 179°, $[\alpha]^{20}D$ −133° (*c* 0.3, pyridine). The sample was hygroscopic and was therefore difficult to analyze.

Anal. Calcd for $C_{31}H_{41}N_5O_5$: C, 66.0; H, 7.3; O, 14.2. Found: C, 64.6; H, 7.5; O, 14.7.

Acetylaminocyclol (1, R_1 = R_2 = CH_3; R_3 = $CH_2C_6H_5$). At −50°, 10 ml of acetyl chloride was added to a suspension of 7.3 g of aminocyclol hydrochloride (**8**) in 175 ml of dry methylene chloride, followed by the addition of 20 ml of pyridine within 1 min. The mixture was stirred for 30 min at −50° and then for 2 hr at 0°. The resulting solution was extracted with dilute hydrochloric acid and sodium hydrogen carbonate, dried over sodium sulfate, and filtered. The solvent was then evaporated *in vacuo*. The crude crystalline residue was recrystallized from ethanol to yield 6.45 g (87%) of acetylaminocyclol, mp 207–208°, $[\alpha]^{20}D$ +41° (*c* 0.2, methanol).

Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.1; H, 6.2; N, 11.3; O, 21.4. Found: C, 60.8; H, 6.3; N, 11.4; O, 21.2.

***aci*-Acetylaminocyclol (2, R_1 = R_2 = CH_3; R_3 = $CH_2C_6H_5$).** A solution of 5.0 g of acetylaminocyclol in 25 ml of glacial acetic acid and 475 ml of water was refluxed for 15 hr. The clear yellow solution was evaporated to dryness *in vacuo*, and the residue crystallized from ethyl acetate to yield 2.1 g of *aci*-acetylaminocyclol, mp 222–223°, $[\alpha]^{20}D$ −75° (*c* 0.25, methanol).

Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.1; H, 6.2; N, 11.3; O, 21.4. Found: C, 61.0; H, 6.3; N, 11.8; O, 21.4.

***p*-Nitrobenzoylaminocyclol (1, R_1 = *p*-$NO_2C_6H_4$; R_2 = CH_3; R_3 = $CH_2C_6H_5$).** At −50°, 1.02 g of *p*-nitrobenzoyl chloride was added to a suspension of 1.84 g of aminocyclol hydrochloride (**8**) in 15 ml of dry methylene chloride, followed by addition of 5 ml of pyridine. The mixture was stirred for 30 min at −50°, and then for 1 hr at 0°. The resulting solution was diluted with methylene chloride and extracted with dilute hydrochloric acid and sodium hydrogen carbonate. The organic phase was dried over sodium sulfate and evaporated to dryness *in vacuo*. On crystallization from ethyl acetate, 1.65 g (69%) of *p*-nitrobenzoylaminocyclol, mp 200–202°, was obtained. For analysis, a sample was recrystallized from methanol: light yellow prisms, mp 203–205°, $[\alpha]^{20}D$ +6° (*c* 0.2, pyridine).

Anal. Calcd for $C_{24}H_{24}N_4O_7$: C, 60.0; H, 5.0; N, 11.7; O, 23.3. Found: C, 59.9; H, 5.1; N, 11.7; O, 23.6.

***aci*-*p*-Nitrobenzoylaminocyclol (2, R_1 = *p*-$NO_2C_6H_4$; R_2 = CH_3; R_3 = $CH_2C_6H_5$).** A solution of 500 mg of *p*-nitrobenzoylaminocyclol in a mixture of 12 ml of glacial acetic acid, 120 ml of ethanol, and 120 ml of water was refluxed for 150 hr. The clear yellow solution was evaporated to dryness *in vacuo*. On treating the obtained residue with 50 ml of chloroform, 211 mg of *aci*-*p*-nitrobenzoylaminocyclol remained undissolved. For analysis, this product was recrystallized from ethanol: light yellow prisms, mp 199–200°, $[\alpha]^{20}D$ −61° (*c* 0.2, pyridine).

Anal. Calcd for $C_{24}H_{24}N_4O_7$: C, 60.0; H, 5.0; N, 11.7; O, 23.3. Found: C, 59.3; H, 5.3; N, 11.4; O, 23.9

O-Methyl-*aci*-acetylaminocyclol (5, R = CH_3). To a solution of 1.0 g of *aci*-acetylaminocyclol in 30 ml of methylene chloride and 30 ml of methyl iodide, 2.0 g of freshly prepared silver oxide was

(14) A. T. McPhail and G. A. Sim, *Chem. Commun.* (London), 124 (1965).

(15) Melting points are corrected; nmr spectra were obtained using the Varian Associates A-60 spectrometer.

added and the suspension was stirred at room temperature for 5 hr. The insoluble inorganic material was filtered off. The filtrate was diluted with methylene chloride, and this solution was extracted twice with ice-cold 0.5 *N* sodium hydroxide to remove the unreacted starting material. The organic phase was dried over sodium sulfate and evaporated to dryness *in vacuo*. On crystallization of the oily residue from ethyl acetate, 475 mg of O-methyl-*aci*-acetylaminocyclol was obtained, mp 207–209°.

Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.0; H, 6.5; N, 10.8; O, 20.6. Found: C, 61.9; H, 6.7; N, 10.8; O, 20.6. Nmr spectrum in $CDCl_3$ (ppm): $C-CH_3$, δ 1.56; $COCH_3$, δ 1.95; and OCH_3, δ 2.83.

O-Methyl-*aci*-DHE (5, RCO = 9,10-dihydrolysergyl). To a solution of 400 mg of *aci*-DHE in 80 ml of methylene chloride and 20 ml of methanol, 70 ml of an etheral solution of diazomethane was added; this reaction mixture was kept at 4° for 60 hr. After evaporation to dryness, the crude residue was dissolved in methylene chloride, and the unreacted starting material was extracted twice with ice-cold 0.5 *N* sodium hydroxide. O-Methyl-*aci*-DHE crystallized from ethyl acetate in white prisms, mp 196–200°. It was pure by tlc but contained probably some crystal solvent and, therefore, did not give a correct analysis.

Anal. Calcd for $C_{34}H_{39}N_5O_5$: C, 68.3; H, 6.6; N, 11.7; O, 13.4. Found: C, 66.6; H, 7.0 N, 11.6; O, 14.6. Nmr spectrum in $CDCl_3$: OCH_3, δ 2.83 ppm.

O-Methylcarbobenzoxyaminocyclol (11). To a solution of 250 mg of carbobenzoxyaminocyclol (**9**) in 15 ml of dry methanol was added 6 ml of 0.7 *N* hydrochloric acid in methanol. The exchange of the cyclol hydroxyl group by a methoxy group can easily be followed by tlc. The reaction proceeded rapidly at ambident temperature and was nearly complete after 3 min. After standing for 30 min, the clear, slightly yellow solution was concentrated *in vacuo* at 30°, diluted with methylene chloride, and extracted once with sodium hydrogen carbonate solution. The organic phase was dried over anhydrous sodium sulfate, and the solvent was then evaporated *in vacuo* to yield 240 mg of O-methylcarbobenzoxyaminocyclol (**11**) as a colorless oil. All attempts to crystallize this product failed. In tlc, the product was pure and showed a considerably higher R_f value than the carbobenzoxyaminocyclol **9**. The nmr spectrum in $CDCl_3$ showed $C-CH_3$, δ 1.47, and OCH_3, δ 2.65 ppm.

Hydrolysis to Carbobenzoxyaminocyclol (9). A solution of 100 mg of the above-described O-methylcarbobenzoxyaminocyclol (**11**) in 2 ml of ethanol and 1.2 ml of 2 *N* aqueous hydrochloric acid was allowed to stand at ambident temperature for 15 hr. The reaction mixture was then diluted with water, made slightly alkaline with sodium hydrogen carbonate, and extracted with methylene chloride. After drying the organic phase over sodium sulfate and evaporating to dryness *in vacuo*, the oily residue (100 mg) crystallized from ethyl acetate to yield 70 mg (72%) of carbobenzoxyaminocyclol (**9**), mp 217–218°. The product was identical in melting point, mixture melting point, and tlc with an authentic sample of carbobenzoxyaminocyclol (**9**).

^{18}O-DHE. A solution of 1.0 g of *aci*-DHE in 5 ml of glacial acetic acid and 100 ml of $H_2{}^{18}O$ (approximately 0.8% abundance of ^{18}O) was refluxed for 6 hr. The clear solution was evaporated to dryness *in vacuo*, the residue was dissolved in methylene chloride–methanol (6:1), and the solution was extracted three times with 1 *N* sodium hydroxide. The organic phase was dried over sodium sulfate and the solvent evaporated *in vacuo*. The resulting crude ^{18}O-DHE (275 mg) was crystallized from methanol. The sample was pure and identical in tlc with DHE.

^{18}O-*aci*-DHE. A solution of 2.5 g of DHE in 12.5 ml of glacial acetic acid and 250 ml of $H_2{}^{18}O$ (approximately 0.8% abundance of ^{18}O) was refluxed for 6 hr. The clear solution was evaporated to dryness *in vacuo*, the residue was dissolved in methylene chloride–methanol (6:1), and the solution was extracted three times with 15-ml portions of 1 *N* sodium hydroxide. The aqueous phases were combined, neutralized with 5 *N* hydrochloric acid, and extracted four times with methylene chloride–methanol (6:1). After drying and evaporating the organic solvent, the crude residue was crystallized from methanol to give pure ^{18}O-*aci*-DHE, identical in tlc with *aci*-DHE.

Dehydration Product from ^{18}O-*aci*-DHE (23). Under stirring, 680 mg of ^{18}O-*aci*-DHE was added in small portions to 7 ml of concentrated sulfuric acid (96%) at 0°. The brown solution was kept for 2 hr between 0 and 10° and was then added dropwise to an ice-cold mixture of excess saturated sodium hydrogen carbonate solution and methylene chloride under vigorous stirring. The organic phase was separated and the aqueous layer extracted three more times with methylene chloride. After drying and evaporating the organic solvent, the remaining residue was chromatographed on a column of 15 g of aluminum oxide with chloroform containing 0.5% of methanol. The purest fraction (by tlc) was crystallized from acetone to yield 155 mg of the dehydration product, mp 230–240°, $[\alpha]^{20}D$ −153° (*c* 0.2, pyridine).

Anal. Calcd for $C_{33}H_{35}N_5O_4 \cdot CH_3COCH_3$: C, 69.4; H, 6.6; N, 11.2; O, 12.8. Found: C, 69.2; H, 6.3; N, 11.1; O, 12.8