Fraction A, 0.40 g., eluted by ligroin–benzene (3:1), after several recrystallizations proved to be **24-chloro-3-cholene (XI)** m.p. 67–69°, m.p. not lowered on admixture with an authentic sample.

Fraction B, 2.13 g., eluted by 2% ethanol in ether, was a chlorine-containing mixture which would not separate by recrystallization or on a second chromatographic column. A portion of the mixture, 1.24 g., was acetylated with acetic anhydride and pyridine, and the crude product, 0.95 g., in ligroin solution was chromatographed on 28.5 g. of alumina. The first fraction, eluted by ligroin, 268 mg., crystallized out of acetone–water (4:1) to give needles of **3-cholen-24-yl acetate (IXb)**, m.p. 68.5–69.2°, m.p. not lowered on admixture with an authentic sample. After a small intermediate fraction a second major fraction was eluted with ligroin–benzene (1:1), 173 mg., which crystallized nicely by slow concentration of its acetone–water (5:1) solution, two recrystallizations giving **24-chloro-3β-cholanyl acetate (XIVb)**, platelets, m.p. 149–152°, mixed with IVb melted at 120–130°, $[\alpha]_D$ +18.8°; λ_{max}^{KBr} 3.47, 3.53, 5.78, 6.92, 7.29, 7.33, 7.66, 7.98, 8.08, 8.16(sh.), 8.63, 9.78, 10.15, 10.42, 14.01 μ.

Anal. Calcd. for $C_{26}H_{43}O_2Cl$: C, 73.81; H, 10.24; Cl, 8.38. Found: C, 73.61; H, 10.34; Cl, 8.31.

Fraction C, 2.32 g., eluted by 5% ethanol in ether, crystallized from acetone–water (4:1) to give **3α-tosyloxy-24-cholanol (XVI)** as platelets, 1.46 g., m.p. 125.8–128.3°, $[\alpha]_D$ +38.7°; λ_{max}^{KBr} 3.49, 6.95, 7.45, 8.45, 8.55, 10.52, 10.72, 10.85, 11.58, 11.95, 15.0 μ. The analytical sample, m.p. 127.5–129.5°, crystallized from methanol–water (10:1). Its mixture with the isomeric III melted at 103–118°.

Anal. Calcd. for $C_{31}H_{48}O_4S$: C, 72.05; H, 9.36; S, 6.20. Found: C, 72.13; H, 9.32; S, 6.05.

Fraction D, 1.69 g., also eluted by 5% ethanol in ether, but almost completely separated from fraction C, crystallized from acetone–water (4:1) as needles, **3β,24-cholanediol (XVIIa)**, m.p. 151–154°, m.p. not lowered on admixture with authentic sample, $[\alpha]_D$ +23.3°.

Anal. Calcd. for $C_{24}H_{42}O_2$: C, 79.49; H, 11.68; mol. wt., 362.6. Found: C, 79.50; H, 11.76; mol. wt., 354.

The diacetate XVIIIb crystallized out of methanol–water (20:1) as needles, m.p. 99–101°, $[\alpha]_D$ +13.3°; $\lambda_{max}^{CS_2}$ 3.45, 5.75, 8.00(sh.), 8.08, 8.14(sh.), 9.78 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.03; H, 10.33.

Fraction E, 0.60 g., eluted by 10% ethanol in ether, crystallized from ethyl acetate to give **3α,24-cholanediol (IIa)**, m.p. 176–178°.

Lithium Aluminum Hydride Reduction of 3α-Tosyloxy-24-cholanol (XVI).—Reduction of 1.42 g. of 3α-tosyloxy-24-cholanol by the method described above for 3α-cholanol gave a crude product, 1.14 g., which was chromatographed from ligroin–benzene (5:1) solution on 36 g. of alumina. The first fraction, 255 mg., eluted by ligroin–ether (5:1), crystallized from acetone–methanol or from ethanol as laths, m.p. 85.2–86.0°, m.p. not lowered on admixture with an authentic sample of **24-cholanyl acetate (XVIIIb)**.[26]

Anal. Calcd. for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.06; H, 11.53.

After a small intermediate fraction, the second major fraction, 296 mg., eluted by ligroin–ether (1:2) crystallized from methanol–water (20:1) as laths, m.p. 124.5–125.1°, m.p. unchanged on admixture with authentic **24-cholanol (XVIIIa)**, $[\alpha]_D$ +26° (95% EtOH).

After another small intermediate fraction, a final fraction consisting of 126 mg. of 3α,24-cholanediol (IIa) was obtained.

24-Chloro-3α-cholanyl Tosylate (XIII).—Another room temperature tosylation of 3α,24-cholanediol stood for 2 days. Working up the reaction mixture as described above, and rapidly chromatographing the neutral, ether-soluble portion on alumina gave a fraction, eluted by ether, m.p. 109–117°. Four recrystallizations from benzene–ligroin (30–60°) (1:10) gave platelets, m.p. 116.8–119.0°, in 10% yield; λ_{max}^{KBr} 3.49, 6.96, 7.45, 8.45, 8.55, 10.52, 10.72, 10.85, 11.60, 11.95, 15.0 μ. A comparison of the infrared spectra of this compound and those of III and XVI indicates that this is the 3α-tosylate. In addition, under the reaction conditions 3-chloro substitution does not take place, as mentioned earlier.

Anal. Calcd. for $C_{31}H_{47}O_3ClS$: C, 69.56; H, 8.85; Cl, 6.63; S, 5.99. Found: C, 69.28; H, 8.91; Cl, 6.60; S, 5.73.

(26) Probably formed by ester interchange between 24-cholanol and ethyl acetate during decomposition of excess $LiAlH_4$.

MEMPHIS, TENNESSEE

[CONTRIBUTION FROM THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Effects of Ionizing Radiation on Choline Chloride and its Analogs. II[1]

BY RICHARD M. LEMMON, PEGGY KWONG GORDON, MARGARET A. PARSONS AND FRANCO MAZZETTI

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The radiation sensitivities of crystalline choline chloride and nineteen crystalline analogs have been compared. The chloride is extremely radiation sensitive and appears to decompose by a free-radical chain mechanism. Choline bromide is about one-third as sensitive as the chloride; none of the other analogs show abnormal radiation instability. That choline chloride's susceptibility to radiation damage is a function of its crystal structure is shown by its contrasting stability in solution. Determinations were made of the radiation sensitivity of crystalline choline chloride at low temperature, in the presence of added iodide or iodine, and after repeated recrystallizations. The electron spin resonance signal from irradiated choline chloride also was observed.

An earlier report[2] described the abnormal sensitivity of crystalline choline chloride toward ionization radiation. *G* values (molecules decomposed/100 e.v.) as high as 1250 were found. In addition, the failure of six crystalline choline analogs to show similar abnormal behavior was recorded. The present work describes the efforts which have been made toward an understanding of choline chloride's radiation sensitivity. This work comprises studies on (1) the sensitivity of thirteen additional analogs; (2) the sensitivity of choline chloride in solution; and (3) the rates of decomposition observed when crystalline choline chloride is irradiated (a) at low temperatures, (b) in the presence of added iodide or iodine and (c) after repeated crystallization from different solvents. In addition, this report includes some observations on the electron spin resonance spectrum of irradiated choline chloride.

(1) The work described in this paper was sponsored by the U. S. Atomic Energy Commission.

(2) R. M. Lemmon, *et al.*, THIS JOURNAL, **77**, 4139 (1955).

Experimental

Preparation of Choline Analogs.—The thirteen additional analogs were prepared as follows: The choline salts (bromide, nitrate, sulfate, acetate and cyanide) were prepared from choline iodide by conversion to the quaternary base with Ag_2O, followed either by titration with the appropriate

acid or by passage through a Dowex-2 ion exchange column containing the desired replaceable anion. The preparation of the carnitine hydrochloride, $[(CH_3)_3NCH_2CH(OH)CH_2COOH]^+Cl^-$, was described previously.[3] The 2-hydroxypropyltrimethylammonium chloride was prepared by treating trimethylamine with 1-chloro-2-propanol in aqueous alcoholic solution. The ethyl analogs of choline chloride (with one, two or three methyl groups replaced by a like number of ethyl groups) were prepared by treating either ethyl iodide or methyl iodide with the appropriate dimethylaminoethanol or diethylaminoethanol, followed by conversion of the iodide to chloride. The phenyl analog was prepared by the reaction of dimethylaniline with ethylene chlorohydrin. The preparation of dimethyl-bis-(2-hydroxyethyl)-ammonium chloride was effected by treating 2 moles of methyl iodide with one mole of diethanolamine, followed by conversion of the iodide to chloride. The 2-hydroxyethyltrimethylphosphonium chloride was prepared by treating trimethylphosphine[4] with ethylene chlorohydrin.

Several attempts were made to prepare choline fluoride from the iodide or chloride. The salt is extremely hygroscopic but could be crystallized from ethanol–ether upon rigid exclusion of water. Satisfactory C, H and N analyses were obtained on the choline fluoride. However, the compound decomposes very quickly (1–2 days) at room temperature and in the absence of light. Consequently, no irradiation experiments were attempted with this material.

All of the choline analogs were recrystallized either from ethanol–ether or from dimethylformamide solutions. Acceptable carbon, hydrogen, nitrogen and halogen analyses (all within 0.3% of the calculated values) were obtained on all compounds used in these irradiation studies.

Irradiation Procedures.—Two sources of radiation were used in this work: a 3–5 mv. linear electron accelerator and a 100-curie Co^{60} γ-ray source. A description of these sources, their use in the irradiation experiments, and the estimations of radiation doses were described previously.[1,5] The only modification in the present work was to alter the target area of the electron accelerator so that samples could be irradiated at temperatures near that of liquid nitrogen. This was accomplished by placing a thin-walled (10-mil aluminum) well in the vacuum tank in the path of the electron beam. The glass sample holder was then placed inside the well. During an irradiation, nitrogen gas (from boiled liquid nitrogen) was forced through the well at such a rate that the sample was maintained at $-170 \pm 20°$.

Analytical Procedures.—Three analytical procedures were used to determine the extent of radiation decomposition of the choline analogs. Two of these (reineckate analysis and paper chromatography) were described earlier.[1] The third procedure was to precipitate the undecomposed choline analog with sodium tetraphenylboron.[6]

Electron Spin Resonance Spectrum.—The ESR spectrum was taken at a frequency of 9.6 kmc./sec. on a recording differentiating spectrometer (similar to one developed by Beringer and Castle[7]), using a transmission cavity and bolometer detection. Before a sample was placed in the cavity, the upper half of the tube in which it was contained was annealed in a burner flame in order to remove the F centers. The upper half was then cooled and the tube inverted so that the sample was situated in glass which itself gave no signal response.

Results

Decomposition of Crystalline Choline Analogs.—The data obtained from the irradiations of choline chloride and its analogs are summarized in Table I; the G values found for choline chloride and choline bromide illustrate the unique sensitivity of these crystalline salts toward ionizing radiation. Since G values vary somewhat depending on the percentage of decomposition, and since the analytical procedures are inaccurate at very small amounts of decomposition, all the G values listed in Table I were obtained at 10% decomposition. Choline chloride and the six analogs reported earlier[1] are also listed in Table I, both for the sake of comparison and for the reason that their G values were redetermined at 10% decomposition.

TABLE I

RADIATION DECOMPOSITION OF CHOLINE ANALOGS

Compound	Type of radiation[a]	Method of analysis[b]	G value at 10% decomp.[c]
$[(CH_3)_3NCH_2CH_2OH]^+Cl^-$	e^-	R	98
$[(CH_3)_3NCH_2CH_2OH]^+Cl^-$	γ	R	354
$[(CH_3)_3NCH_2CH_2OH]^+Br^-$	e^-	R, TPB	30
$[(CH_3)_3NCH_2CH_2OH]^+Br^-$	γ	R, TPB	92
$[(CH_3)_3NCH_2CH_2OH]^+I^-$	e^-	R	1.0
$[(CH_3)_3NCH_2CH_2OH]^+I^-$	γ	R	2.5
$[(CH_3)_3NCH_2CH_2OH]^+NO_3^-$	e^-	R	1.4
$[(CH_3)_3NCH_2CH_2OH]^+NO_3^-$	γ	R, TPB, PC	4.9
$[(CH_3)_3NCH_2CH_2OH]_2^+SO_4^=$	e^-	R	14
$[(CH_3)_3NCH_2CH_2OH]_2^+SO_4^=$	γ	R	29
$[(CH_3)_3NCH_2CH_2OH]^+CH_3CO_2^-$	e^-	R, TPB	8.2
$[(CH_3)_3NCH_2CH_2OH]^+CH_3CO_2^-$	γ	R	11
$[(CH_3)_3NCH_2CH_2OH]^+CN^-$	e^-	R	19
$[(CH_3)_3NCH_2CH_2OH]^+CN^-$	γ	R	16
$[(CH_3)_3NCH_2CH_2OCOCH_3]^+Cl^-$	e^-	R, PC	2.7
$[(CH_3)_3NCH_2CH_2OCOCH_3]^+Cl^-$	γ	R, PC	3.5
$[(CH_3)_3NCH_2CH_2CH_2OH]^+Cl^-$	e^-	PC	1.9
$[(CH_3)_3NCH_2CH_2CH_2OH]^+Cl^-$	γ	TPB	4.8
$[(CH_3)_3NCH_2CH(OH)CH_3]^+Cl^-$	e^-	TPB	6.7
$[(CH_3)_3NCH_2CH(OH)CH_3]^+Cl^-$	γ	TPB	6.9
$[(CH_3)_3NCH_2COOH]^+Cl^-$	e^-	R, TPB	16
$[(CH_3)_3NCH_2COOH]^+Cl^-$	γ	R, TPB	15
$[(CH_3)_3NCH_2CH(OH)CH_2COOH]^+Cl^-$	e^-	R	14
$[(CH_3)_3NCH_2CH(OH)CH_2COOH]^+Cl^-$	γ	R, PC	14
$\left[\begin{matrix}C_2H_5\\(CH_3)_2\end{matrix}NCH_2CH_2OH\right]^+Cl^-$	e^-	R	6.1
$\left[\begin{matrix}C_2H_5\\(CH_3)_2\end{matrix}NCH_2CH_2OH\right]^+Cl^-$	γ	R	26
$\left[\begin{matrix}(C_2H_5)_2\\CH_3\end{matrix}NCH_2CH_2OH\right]^+Cl^-$	e^-	R	6.0
$\left[\begin{matrix}(C_2H_5)_2\\CH_3\end{matrix}NCH_2CH_2OH\right]^+Cl^-$	γ	R	7.9
$[(C_2H_5)_3NCH_2CH_2OH]^+Cl^-$	e^-	R	5.5
$[(C_2H_5)_3NCH_2CH_2OH]^+Cl^-$	γ	R	14
$\left[\begin{matrix}C_6H_5\\(CH_3)_2\end{matrix}NCH_2CH_2OH\right]^+Cl^-$	e^-	R	4.8
$\left[\begin{matrix}C_6H_5\\(CH_3)_2\end{matrix}NCH_2CH_2OH\right]^+Cl^-$	γ	TPB	1.9
$[(CH_3)_2N(CH_2CH_2OH)_2]^+Cl^-$	e^-	PC	5.6
$[(CH_3)_2N(CH_2CH_2OH)_2]^+Cl^-$	γ	PC	14
$[(CH_3)_3NCH_2CH_2Cl]^+Cl^-$	e^-	R, PC	4.3
$[(CH_3)_3NCH_2CH_2Cl]^+Cl^-$	γ	R	2.6
$[(CH_3)_3NCH_2CH_3]^+Cl^-$	e^-	R	1.6
$[(CH_3)_3NCH_2CH_3]^+Cl^-$	γ	R	1.7
$[(CH_3)_3PCH_2CH_2OH]^+Cl^-$	e^-	TPB	4.9
$[(CH_3)_3PCH_2CH_2OH]^+Cl^-$	γ	TPB	4.9

[a] e^- = 3–5 Mv. electrons, γ = CO^{60} γ's (1.1 and 1.3 Mev.). [b] R = reineckate analysis, TPB = tetraphenylboron analytical procedure, PC = determination of means of paper chromatography. The particular method (or methods) used was the one (or ones) found to be most reliable for the particular analog. [c] The estimated range for the choline chloride and choline bromide G values is ±25%. For all other compounds the G values given may be in error by as much as a factor of 2. The values are all averages of from 2 to 11 experiments.

Decomposition of Choline Chloride in Solution.—The G values found for choline chloride in solution in water or ethanol are recorded in Table II. These data indicate that choline chloride's radiation sensitivity is a function only of its crystal structure and not of any inherent instability in

(3) F. Mazzetti and R. M. Lemmon, *J. Org. Chem.*, **22**, 228 (1957).
(4) F. G. Mann and A. F. Wells, *J. Chem. Soc.*, 702 (1938).
(5) R. M. Lemmon and D. F. Mosier, *Rad. Res.*, **4**, 373 (1956).
(6) P. Marquardt and G. Vogg, *Z. physiol. Chem.*, **291**, 143 (1952).
(7) R. Beringer and J. G. Castle, *Phys. Rev.*, **78**, 581 (1950).

the isolated choline cation. The data also indicate that all of the energy given to the solution is transferred to the choline, and that a given energy dose per gram of solution causes decomposition of the same number of solute molecules, regardless of concentration.

TABLE II

RADIATION SENSITIVITY OF CHOLINE CHLORIDE IN SOLUTION

Solvent	Concn., mg./ml.	Rads[a] × 10^6	Decompn., %	G = molecules decomp. / 100 e.v. to soln.
Water	9.4	4.3	15	2.2
Water	33	16	20	2.9
Water	52	16	14	3.2
Water	130	18	15	4.4
Water	205	58	18	4.4
Water	405	177	16	2.5
Abs. EtOH	24	125	5	2.8
Abs. EtOH	99	118	3	1.9

[a] The rad equivalent to 100 e.v./gram.

Irradiation of Crystalline Choline Chloride at −170°.—Eighteen samples of crystalline choline chloride were irradiated in the electron beam at −170 ± 20°. The samples all received 4 × 10^6 rads, an energy dose which would cause approximately 10% decomposition at room temperature. Five of the samples were kept at −196° until they could be analyzed for the amount of undecomposed choline present; the samples were then dissolved in water as they were warming up to room temperature and the analyses performed by the reineckate or tetraphenylboron procedure. Two samples each were allowed to stand at room temperature, before solution and analysis, for 2, 4, 7 and 10 hours. Five samples were kept 15 hours at room temperature before analysis. The amounts of decomposition determined in these samples are recorded in Table III. These data indicate that the chain mechanism is propagated very slowly, if at all, at −170°. On warming to room temperature, the free radicals can initiate the chain mechanism. However, the radicals appear to be fairly stable at room temperature and, therefore, several hours are required before all the chains have been initiated.

TABLE III

RADIATION[a] DECOMPOSITION OF CRYSTALLINE CHOLINE CHLORIDE IRRADIATIONS AT −170°, STORAGE AT ROOM TEMPERATURE

No. of samples	Time of storage, hr.	Average % decompn.
5	0	0
2	2	1
2	4	5
2	7	7
2	10	7
5	15	9

[a] 4 × 10^6 rads of 3 Mv. electrons.

Irradiation of Crystalline Choline Chloride in the Presence of Added Iodide or Iodine.—Choline chloride was crystallized from alcohol solutions containing differing concentrations of iodide ion. The amounts of iodide present in the crystals were determined by oxidation with nitrite in acid solution and measurement of the iodine by the optical density of the solution at 425 mμ. The first preparation of the crystalline chloride–iodide contained 4.7 mole % of iodide (*i.e.*, 4.7% of the anions were iodide). Three samples of these crystals were given a dose of 2.5 × 10^6 rads Co^{60} rays. Their measured amounts of decomposition were 14, 16 and 17% and the average G value of the choline chloride in the sample was 433. The same experiment also was performed on two samples of crystals having 29 mole % iodide. The energy dose was 4 × 10^6 rads and the measured amounts of decomposition were 11 and 12%; the average G value for the choline chloride present was 268. These two G values show that the chain mechanism is still operating in spite of the large percentages of iodide. However, choline iodide has a different crystal form (monoclinic) than that of choline chloride (orthorhombic). Therefore, the iodide was doubtless present as separate crystals and there was no alternation in the crystal structure of the choline chloride.

Two samples of crystalline choline chloride were sealed in evacuated tubes to each of which had been added a small crystal of iodine. The samples were given 3 × 10^6 rads in the Co^{60} source. The measured decompositions in the samples were 18 and 20% and the average G value was 350. The presence of the iodine vapor has, therefore, no effect on the chain length in the radiation decomposition of choline chloride.

Crystallization Experiments.—All previous work with crystalline choline chloride has been performed on samples crystallized from ethanol–ether solutions. The salt is obtained as orthorhombic crystals from this solvent mixture. To determine if any possible chain-stopping impurity could be removed by recrystallizations from this solvent mixture, three samples of choline chloride were recrystallized either once, twice or three times from a mixture of the redistilled solvents. Each sample was subjected to 2.1 × 10^6 rads from the Co^{60} source. The measured amounts of decomposition were found to be 13, 13 and 14%, respectively. It is therefore apparent that repeated recrystallization from these solvents has no large effect on the radiation sensitivity.

A sample of choline chloride, previously crystallized from ethanol–ether, was recrystallized from redistilled dimethylformamide. Again, orthorhombic crystals were obtained. Four samples of these crystals were separately subjected to 2.5 × 10^6 rads in the Co^{60} source. Reineckate analyses showed decompositions in the extent of 16, 15, 13 and 14%. Therefore, choline chloride crystallized from dimethylformamide has the same radiation sensitivity as it shows when crystallized from ethanol–ether.

Electron Spin Resonance Spectrum of Irradiated Choline Chloride.—In order to look for some direct evidence of the operation of a free-radical mechanism in the radiation decomposition of choline chloride the irradiated compound was examined for paramagnetism in an electron spin resonance (ESR) spectrometer. Approximately 50 mg. of crystalline, analytically-pure choline chloride was

sealed in a 3-mm. o.d. Pyrex tube under high vacuum. The sample was then subjected at room temperature to 2.2×10^6 rads (enough to cause 10% decomposition) of γ-radiation from the Co^{60} source. During the 45 minutes which elapsed between removal from the source and placing it in the spectrometer cavity, the sample was kept at $-196°$. An unirradiated control gave no signal response. However, the irradiated sample showed an ESR spectrum with a sharp peak at a g value of approximately 2.0 and the height of the peak corresponded to about one free radical developed for every 10^4 e.v. of energy expended in the sample. The free radical signal was fairly stable at room temperature and decayed with a half-time of about four hours, in good agreement with data of Table III. Work leading to the identification of the free radical is now in progress.

Discussion

The radiation sensitivities of crystalline choline chloride and bromide is a matter of considerable interest since they are the only examples known at present of solid-state free-radical chain mechanisms. A recent investigation into the crystal structure of choline chloride has uncovered,[8] however, no unusual features which can account for the radiation instability. The explanation of why the chloride and bromide crystals propagate a chain mechanism, whereas the other analogs do not, must await more detailed comparisons among the various crystal structures.

An interesting facet of choline chloride's great radiation instability was uncovered in the recent work of Serlin.[9] He showed that the crystalline compound is more radiation unstable at 50° than it is at room temperature. Furthermore, and quite unexpectedly, when the temperature is raised to 150° the compound "becomes markedly radiation-resistant." This observation might indicate the presence of a reaction involving the free radicals which competes with the chain mechanism, and that this reaction becomes the predominant one at the higher temperature. It might also mean that the choline chloride had assumed a different crystal form at the higher temperature.

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(8) Michael E. Senko. "The Crystal Structure of a Triazole and Choline Chloride," University of California Radiation Laboratory Report No. UCRL-3521, September, 1956.

(9) I. Serlin, *Science*, **126**, 261 (1957).

BERKELEY, CALIF.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Alkaloids of *Tabernanthe Iboga*. VII.[1] Derivatives of Isoquinuclidine

BY L. H. WERNER AND S. RICCA, JR.

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A number of N-alkylated derivatives of 3-isoquinuclidone and isoquinuclidine were prepared. They did not show any pharmacological activity of interest. Isoquinuclidine was obtained in a pure form by catalytic debenzylation of N-benzylisoquinuclidine. Hofmann degradation of N-benzylisoquinuclidine methiodide resulted in cleavage at the bridgehead.

Recently[2] it was found that the Tabernanthe alkaloids contain an isoquinuclidine ring as part of their structure. Very few derivatives of isoquinuclidine have been reported, and we therefore considered it of interest to prepare a small series of derivatives (Table I).

3-Isoquinuclidone (II) was prepared by fusion of *cis*-4-aminocyclohexanecarboxylic acid (I) according to Ferber and Brückner[3]; likewise *cis*-methyl 4-aminocyclohexanecarboxylate (III) could be cyclized to 3-isoquinuclidone but at a somewhat lower temperature. Refluxing with 2 *N* hydrochloric acid cleaved the 3-isoquinuclidone ring again to give the *cis*-4-aminocyclohexanecarboxylic acid. This could be shown by thermal recyclization to 3-isoquinuclidone. The *trans*-acid does not yield 3-isoquinuclidone, even on prolonged heating. Likewise 2-benzyl-3-isoquinuclidone (IV) was cleaved by refluxing with 2 *N* hydrochloric acid to *cis*-4-benzylaminocyclohexanecarboxylic acid (V). This acid also cyclized readily again on heating. The N-substituted 3-isoquinuclidones given in Table I were obtained by reaction of the sodio derivative of 3-isoquinuclidone with the appropriate alkyl- or aralkyl halide. Reduction of the N-substituted 3-isoquinuclidones with lithium aluminum hydride yielded the corresponding isoquinuclidines. The quaternary bases formed very readily in alcoholic solution at 25° on treatment with an excess of methyl iodide. Isoquinuclidone itself could not be reduced directly to isoquinuclidine (VII); this compound was obtained by lithium aluminum hydride reduction of 2-benzyl-3-isoquinuclidone (IV) to 2-benzylisoquinuclidine (VI), followed by reductive debenzylation. Isoquinuclidine (VII) was found to be a crystalline solid melting and also boiling at 173–175°. Previously,[3] this compound had been isolated only as a picrate and as the N-benzoyl derivative.

It was also of interest to determine the structure of the cleavage product (IXa or b) obtained by the Hofmann degradation of 2-benzylisoquinucli-

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(3) E. Ferber and H. Brückner, *Ber.*, **76**, 1019 (1943).