and ammonia protects the formamide from the air, and no trouble is encountered unless the heating is interrupted, or unless the heating is continued after the evolution of gases has ceased.

Standard Method of Carrying Out the Reaction.—Eighty-five grams of benzophenone (0.467 mole) and 110 cc. of 99% formamide (6 × 0.467 mole) (obtained from the Eastman Kodak Co.) together with any substances to be tested for catalytic effect, and a chip of porous plate were placed in a 200-cc. balloon flask equipped with an air-reflux-condenser. The air was displaced with nitrogen, and the flask immersed in an oil-bath kept at 190–200°. After boiling had started, the temperature in the flask was at 180–190°. A small quantity of ammonium carbonate sublimed into the reflux condenser, and ammonia and carbon dioxide were evolved. At exactly four hours after boiling started, the flask was removed from the oil-bath, allowed to cool to about 140°, and cautiously poured into about 200 cc. of cold water. (If it was cooled much below 130°, the formyl derivative crystallized, and removal from the flask was difficult.) The flask was washed out with a little water, and the mixture of benzophenone, N-benzhydryl formamide, and water soluble substances was cooled, seeded with a crystal of benzophenone, and the mixture of solids collected on a Buchner funnel, washed with a little water, and dried. The amount of benzophenone and of N-benzhydryl formamide in the mixture of solids was determined by distillation *in vacuo* without a column. Benzophenone boils at 114° at 1.2 mm., but was collected at 120–130° in order to speed up the distillation. When the benzophenone was all gone, the boiling point rose rapidly; at 160° the receiver was changed, and the remaining formyl derivative was distilled with strong enough heating to prevent crystallization in the side arm of the flask. The amide boils at 173° at 1.2 mm., but as before, it saved time to collect it at 185–190°. A small amount of tar (about a gram) remained in the Claisen flask. The amount of benzophenone determined by this method may be too great by one to two grams (estimated), as a small amount of formamide remains with the solids, and distills over with the first few drops of benzophenone.

All of the reaction mixtures were homogeneous, with the exception of 3-C; the ammonium sulfate added is not completely soluble in the reaction mixture. The results are shown in Table I. The melting point determined by Fischer block method was higher when the reaction was more complete. The value for the pure substance in the literature and in our hands is 132°.[2] In order to judge the purity of the amide, a solution of 2% benzophenone in molten N-benzhydryl formamide was made up and allowed to cool. This material melted at 126.5–130.5°, from which it is concluded that the maximum impurity in the amide samples in Table I is about 2 or 3%.

Summary

1. The Leuckart reaction with benzophenone and formamide has been run under various conditions; with pure formamide (99%) the yield is low unless a large amount of the reagent is used.

2. Ammonium formate, ammonium sulfate, and magnesium chloride have been shown to be effective catalysts for the reaction.

3. A partial mechanism is advanced for the reaction.

PHILADELPHIA 30, PA. RECEIVED AUGUST 20, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Gelsemine

BY BERNHARD WITKOP[1]

Several recent papers[1a,2,3] deal with the structure of gelsemine, $C_{20}H_{22}O_2N_2$, the principal crystalline alkaloid of *Gelsemium sempervirens*, the American "yellow jasmine." Marion[2] isolated an indole derivative as the product of soda-lime or selenium treatment of gelsemine. This is the first major degradation product reported, and relates gelsemine to the indole alkaloids. Indole itself occurs in the oils from the enfleurage of jasmine flowers, where it is present in the form of an unknown complex.[4] Marion and other investigators,[1a,2] studying the degradation of gelsemine, report the presence of bases that were difficult to purify and obtainable only in very small yield.

By the use of a modified mild zinc dust distillation three degradation products have been obtained from gelsemine. Two of basic nature were separated by the difference in basicities. The stronger base is an oil with quinoline or isoquinoline odor, and yields a well-crystallized picrate. Analysis of the latter corresponds to an ethyl- or dimethyl- quinoline or -isoquinoline. It is clear from the data of Table I that gelsemine is such a strong tertiary base that the basic nitrogen atom can neither be attached to a benzene nucleus nor form part of an unreduced pyridine ring, as has been suggested already by Forsyth, Marrian and Stevens.[1a] A more weakly basic product, probably $C_{14}H_{11}N$, was obtained in the form of a picrate. According to the analytical data it might be a methylbenzquinoline (or -isoquinoline). Skatole was isolated as the main non-basic product of indolic nature in the form of the picrate.

TABLE I

pK_a (negative logarithms of acidity constants of the hydrochlorides)

Quinoline	4.89[5]
Isoquinoline	5.36
Py-tetrahydroquinoline	5.03
Py-tetrahydroisoquinoline	9.41
Gelsemine	9.37[1a]

The dimethylindole reported by Marion[2] has not been observed in the present investigation. It should be pointed out, however, that the identification of alkyl indoles is often rendered difficult

(1) Fellow of the Matthew T. Mellon Foundation.

(1a) Forsyth, Marrian and Stevens, *J. Chem. Soc.*, 579 (1945).

(2) Marion, *Can. J. Res.*, **21B**, 247 (1943).

(3) Chu and Chou, THIS JOURNAL, **62**, 1955 (1940); **63**, 827 (1941).

(4) Hesse, *Ber.*, **37**, 1457 (1904).

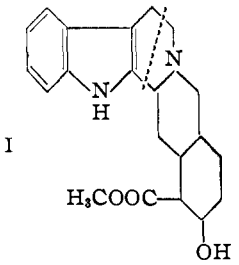
(5) Karrer and Schmid, *Helv. Chim. Acta*, **29**, 1858 (1946).

by the tendency of these substances to form mixed crystals. Soda-lime fusion, zinc dust distillation and dry distillation of yohimbine invariably lead to an isomorphous mixture of 3-ethylindole and skatole,[6] which has been looked upon as an unknown dimethylindole.[7] The same conditions are encountered in the case of C-dihydrotoxiferine-I, an alkaloid of calebash curare. Here, too, an isomorphous mixture of the two β-indole homologs simulates the properties of a new compound.[8] However, in the case of gelsemine purification of skatole could be effected with no great difficulties, which suggests the absence of other homologs.

The isolation from gelsemine of cleavage products containing nine and eleven carbon atoms intimates that the decomposition has taken the simple course

$$C_{20}H_{22}O_2N_2 \longrightarrow C_9H_9N + C_{11}H_{11}N$$

and that the alkaloid may be built up by a combination of the indole and the quinoline or isoquinoline nucleus. The latter possibility further suggests a relationship to the yohimbé alkaloids (*cf.* yohimbine (I)). It must be pointed out however that gelsemine contains an N-methyl group,



I

and that, if the above hypothesis be accepted, it is necessary to assume a migration of the methyl group from nitrogen to carbon. Since this change is somewhat unlikely,[9] the possibility must be considered that the reactions occurring during the degradation may be much more involved than is indicated by the above argument.

TABLE II

MELTING POINTS OF THE PICRATES

1-Ethylisoquimoline	209–210[10]
1,4-Dimethylisoquimoline	221–222[10,11]
1,3-Dimethylisoquimoline	180–181[12,a]
3,4-Dimethylisoquimoline	224–226
$C_{11}H_{11}N$ from gelsemine	185–187[a]

[a] Mixed melting showed large depression.

(6) Witkop, *Ann.*, **556**, 105 (1944)

(7) *Cf.* Marion, *Can. J. Res.*, **25B**, 1 (1947).

(8) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

(9) Migration of blocking alkyl groups is reported in the case only of quaternary ammonium bases [Reher, *Ber.*, **19**, 2996 (1886)] and certain bicyclic ring systems [norlupinane → quinoline, Prelog and Balenovic, *ibid.*, **74**, 1508 (1941)].

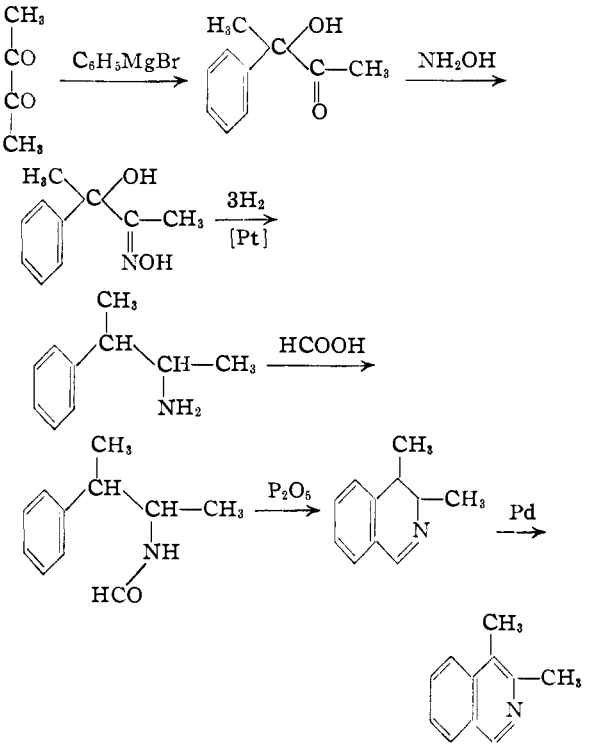
(10) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(11) Krabbe, Schmidt and Eisenlohr, *ibid.*, **74**, 1905 (1941).

(12) Isolated from coal tar, *cf.* P. Karrer, "Organic Chemistry," New York, 1946, p. 898; O. Kruber, *Z. angew. Chem.*, **53**, 69 (1940); E. Jantzen, *C. A.*, **27**, 1064 (1933).

Comparison of the properties of the base $C_{11}H_{11}N$ with those of the previously known dimethyl- and ethylisoquinolines, and further with two new substances, *viz.*, 1,3- and 3,4-dimethylisoquinolines, which have been synthesized in the course of this investigation, has shown that the new base is not identical with any of those substances (Table II).

3,4-Dimethylisoquinoline was prepared by a modification of the method of Pictet and Gams.[13,14] The oxime of dimethylphenylketol,



on catalytic hydrogenation, lost its hydroxyl group and yielded 2-phenyl-3-aminobutane. Formylation, ring closure and dehydrogenation gave the final isoquinoline.

Attempts have been made to prove the presence of an indole ring by ozonolysis[6] or by the very characteristic reaction that is given by indole compounds with perbenzoic acid.[15] Only the reactive double bond present in gelsemine[3] will react with ozone to yield an ozonide explosive in a dry state. Perbenzoic acid gives products that are no longer precipitated on addition of alkali. These findings together with the spectroscopic evidence[16] and the positive "Otto reaction"[17] speak for a hydrogenated indole ring present in gelsemine.

(13) Pictet and Gams, *Ber.*, **43**, 2384 (1910).

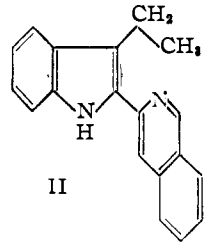
(14) Attempts to use the method of C. Pommeranz, *Monatsh.*, **15**, 299 (1894), recently improved in the synthesis of quinine, Woodward and Doering, THIS JOURNAL, **67**, 860 (1945), failed to give practicable yields in the ring closure reaction of benzylidene-2-aminobutanon (3) diethylacetal with sulfuric acid of varying strength.

(15) Witkop, *Ann.*, **558**, 98 (1947).

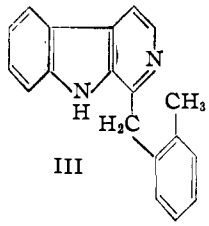
(16) Janot and Berton, *Compt. rend.*, **216**, 564 (1943).

(17) *Cf.* Henry, "The Plant Alkaloids," 1939, p. 507.

Sempervirine.—The concomitant alkaloid sempervirine, $C_{19}H_{16}N_2$, is a very interesting substance. It is isomeric with isoyobyrine (II)[18] and yobyrine (III).[19] In its strong fluorescence and lack of optical activity also it resembles yobyrine.



II



III

On the other hand, the spectra of the three compounds[20,21] are entirely dissimilar. This difference is emphasized by the behavior of sempervirine toward perbenzoic acid. Derivatives of harmine form amine oxides and lose their fluorescence; the reaction is very prompt and characteristic.[15] Sempervirine is very stable to perbenzoic acid; a non-fluorescent amine oxide could not be isolated.[21a]

Experimental[22]

Gelsemine.—*Anal.* Calcd. for $C_{20}H_{22}O_2N_2 \cdot CH_3CO-CH_3$: C, 72.63; H, 7.42; NCH_3, 9.0. Found: C, 72.90; H, 7.64; NCH_3, 11.4.

Gelsemine Hydrochloride.—*Anal.* Calcd. for $C_{20}H_{22}-O_2N_2 \cdot HCl$: C, 67.04; H, 6.42; NCH_3, 8.1. Found: C, 67.21; H, 6.61; NCH_3, 9.49 (no methoxyl; calcd. for NC_2H_5: 12.01).[23]

Zinc Dust Distillation of Gelsemine.—For every distillation 50 mg. of gelsemine is mixed with 5 g. of zinc dust (reagent). The reaction is carried out in an apparatus described previously.[24] The mixture is separated from the constriction by a 2 g.-layer of zinc dust. The temperature inside the oven is regulated to 370°. Nitrogen is passed through a tube at such a velocity that one distillation does not take longer than ten minutes. Eighty such distillations were carried out.

Phenolic Fraction.—The combined ethereal solutions of the volatile degradation products are concentrated to 50 cc. and extracted twice with 5 cc. of dilute alkali. The alkaline solution is acidified and extracted with ether. The solvent is removed and leaves a very small amount of an oil possessing a distinct phenolic odor. It does not give the reaction of Gerngross, Voss and Herfeld[25] and, therefore, cannot be a phenol with a substituent in the *para* position.

Bases.—**A.**—The ether solution which contains a mixture of bases is extracted first with 10 cc. of 2 *N* acetic acid which removes preponderantly the stronger base. This base is liberated by alkali, taken up in ether, and, after evaporation of the solvent, obtained in the form of an oil with a characteristic quinoline or isoquinoline odor. The crude base is purified by steam distillation in a micro-apparatus similar to that described by Gettler and Siegel.[26] The resulting colorless oil is dissolved in little 0.1 *N* hydrochloric acid and precipitated as the picrate by the addition of the necessary amount of an aqueous solution of picric acid. The flocculent picrate is collected, washed with water and dried. Recrystallized twice from acetone, it forms bright yellow needles, m. p. 185–187°.

Anal. Calcd. for $C_{11}H_{11}N \cdot C_6H_3O_7N_3$: C, 52.85; H, 3.64. Found: C, 52.95; H, 3.59.

B.—A weaker base is obtained by extracting the ethereal solution from (A) with 2 *N* hydrochloric acid. It is liberated with alkali and taken up in ether. The ether is boiled off, and the oily residue subjected to steam distillation. Here, too, the resulting colorless oil has a characteristic odor reminiscent of isoquinoline. The picrate of this base is prepared in the same way as described for the stronger base. Twice recrystallized from acetone, it forms beautiful needles, m. p. 218–220°.

Anal. Calcd. for $C_{14}H_{11}N \cdot C_6H_3O_7N_3$: C, 56.87; H, 3.36. Found: C, 56.47; H, 3.36.

Non-basic Fraction.—The ethereal solution, which is now free of bases, is evaporated. The residue is separated by steam distillation into a steam volatile and a non-volatile part. The dry volatile part, which has a strong indolic odor, is distilled in high vacuum. The colorless oil which distills at 80–90° is dissolved in 4 drops of benzene. On addition of 4 drops of a cold benzenic solution of picric acid and not too much petroleum ether one obtains a red picrate (m. p. 153°). The addition of eight further drops of picric acid solution to the mother liquor yields a second purer crop of the red picrate. Recrystallized twice from benzene it forms dark red, glossy needles, m. p. 165°.

Anal. Calcd. for $C_9H_9N \cdot C_6H_3O_7N_3$: C, 50.00; H, 3.33. Found: C, 49.99; H, 3.49.

When mixed with a very pure sample of skatole picrate (m. p. 174°) it melted at 172°. Careful study of the picrate from gelsemine on a micro hot stage proves the identity in all respects with skatole picrate. It shows the two transformation points at 138° and 155° characteristic of skatole picrate.[12]

Admixture of 2,3-dimethylindole picrate with the picrate obtained from gelsemine does not lower the melting point below 156°. Equal parts of pure samples of skatole picrate and 2,3-dimethylindole picrate show a mixed melting point of 165°. In the same way, 2,3-dimethylindole (m. p. 106°) and skatole (m. p. 95°) fail to show a characteristic depression on admixture: the mixed melting point is 96°.

The residue from the steam distillation can be purified by high vacuum distillation. At 130° one obtains an oil which partially crystallizes on cooling. Recrystallization from low boiling petroleum ether yields a very small amount of needles, m. p. 195°, which do not give the reaction of Hopkins–Cole. With dimethylaminobenzaldehyde in alcoholic solution and concentrated hydrochloric acid a purple coloration is obtained at room temperature, slightly intensified on heating.

1,3-Dimethylisoquinoline Picrate.—1,3-Dimethyl-3,4-dihydroisoquinoline[27] is easily dehydrogenated by treatment with palladium black at 200° for thirty minutes. The base is dissolved in *N* hydrochloric acid and precipitated as the picrate. Recrystallized from acetone it forms short needles, m. p. 180–181°.

Anal. Calcd. for $C_{11}H_{11}N \cdot C_6H_3O_7N_3$: C, 52.85; H, 3.64. Found: C, 53.15; H, 3.66.

On admixture with the isomeric picrate from gelsemine (m. p. 185–187°) the melting point is lowered to 145°.

Dimethylphenylketoloxime Hydrochloride.—Dimethylphenylketol[28] (10 g., prepared by the Grignard method)

(18) *Cf.* Julian, Karpel and Magnani, THIS JOURNAL, **70**, 180 (1948).

(19) *Cf.* Clemo and Swan, *J. Chem. Soc.*, 617 (1946).

(20) Pruckner and Witkop, *Ann.*, **554**, 127 (1943).

(21) Private communication and reference (16); the author wishes to express his gratefulness to Prof. Janot, Paris, for his friendly donation of a sample of sempervirine.

(21a) Addendum in proof: very recently Goutarel, Janot and Prelog were able to obtain yobyrine as well as tetrahydroisoyobyrine by dehydrogenation of sempervirine, *Experientia*, **4**, 24 (1948).

(22) All melting points corrected.

(23) Many indole derivatives split off some volatile iodide under the conditions of the N-methyl determination: yohimbol, 3.04%; quinamine [Henry, Kirby and Shaw, *J. Chem. Soc.*, 524 (1945)], 1.63% "NCH_3."

(24) Witkop, *Ann.*, **554**, 123 (1943).

(25) Gerngross, Voss and Herfeld, *Ber.*, **66**, 435 (1933).

(26) Gettler and Siegel, *Arch. of Pathol.*, **19**, 208 (1935).

(27) Hey, *J. Chem. Soc.*, 18 (1930).

(28) Wegmann and Dahn, *Helv. Chim. Acta*, **26**, 101 (1946).

is heated with hydroxylamine hydrochloride (4.1 g.) and anhydrous sodium acetate (4.1 g.) in 200 cc. of absolute ethanol under reflux for four hours. After removal of the sodium chloride the ethanol is evaporated in vacuum. The residue is taken up in 200 cc. of absolute ether. On passing dry hydrogen chloride through the solution the oxime hydrochloride is deposited in form of a sticky oil, which completely crystallizes after twenty hours in the ice box, m. p. 99°.

2-Phenyl-3-aminobutane.—The oxime hydrochloride (4.7 g., 0.2 mole) of 50 cc. of glacial acetic acid with 0.5 g. of platinum oxide takes up somewhat less than three moles of hydrogen. The solvent is removed in vacuum. The residue is taken up in ether, the base extracted with dilute hydrochloric acid, liberated with alkali, and taken up in ether. The amine was obtained as an oil (1.8 g., 60%).

3,4-Dimethyldihydroisoquinoline.—The amine (1.8 g.) is heated with 20 cc. of 87% formic acid on the steam-bath for two hours. The formic acid is evaporated in vacuum and the procedure repeated. The resulting crude formylamino compound still contains some amine which is extracted with dilute acetic acid. The ethereal solution is evaporated to dryness. The carefully dried crude formylamino compound (1.1 g.) is dissolved in 30 cc. of freshly distilled tetralin and treated with 3.5 g. of phosphorus pentoxide. The mixture is refluxed for thirty minutes and another 3.5 g. of pentoxide is added in the middle of this time. The resulting base is isolated in the usual manner and distilled at 120° (10 mm.). It is converted into the picrate and recrystallized from acetone as needles, m. p. 208°.

Anal. Calcd. for $C_{11}H_{13}N \cdot C_6H_3O_7N_3$: C, 52.57; H, 4.12. Found: C, 52.80; H, 4.12.

The hydrochloride is prepared from the picrate by trituration with dilute alkali and extraction with ether. When hydrogen chloride is passed through the dry ethereal solution the hydrochloride crystallizes and forms beautiful needles from ethanol, m. p. 208° (sublimes).

3,4-Dimethylisoquinoline Picrate.—As in the case of the 1,3-dimethyl compound palladium (220°, thirty minutes) easily dehydrogenates the dihydro base in almost quantitative yield. The picrate crystallized immediately from the aqueous solution in short needles, m. p. 224–226°.

Anal. Calcd. for $C_{11}H_{11}N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 50.37; H, 3.95. Found: C, 50.37; H, 3.69.

Acknowledgment.—The author is indebted for support of this work to Prof. L. F. Fieser in whose laboratory part of this work was performed.

Summary

Gelsemine can be degraded to skatole and a base $C_{11}H_{11}N$ which is considered to be a dimethylisoquinoline. None of the three possible dimethylisoquinolines bearing the methyl groups in the pyridine part of the molecule is identical with the base from gelsemine.

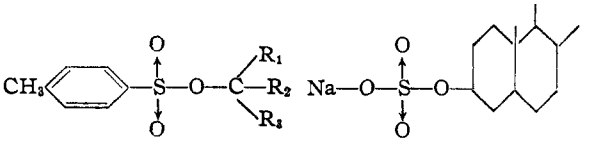
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE 38, MASS. RECEIVED SEPTEMBER 2, 1947

[CONTRIBUTION FROM THE DIVISION OF HORMONE CHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Studies in Steroid Metabolism. V. The Problem of Walden Inversion in the Reactions of Steroid Hydrogen Sulfates and Steroid Sulfites[1,2]

BY SEYMOUR LIEBERMAN, LUCIE B. HARITON AND DAVID K. FUKUSHIMA

This paper deals with the problem of Walden inversion in the reactions of steroid hydrogen sulfates and with the point of cleavage of the S-O-R linkage in these compounds. Since urinary steroids are excreted, at least in part, as water-soluble sulfates,[3] this problem is of biological interest as well as chemical. The isolation of these conjugates is difficult, their quantitative estimation impractical, and therefore it is the general practice to hydrolyze these conjugates with boiling acid in order to estimate or identify the free steroids. Although it has been recognized that various artefacts result from this hydrolytic procedure, the possibility that another type of transformation product might be formed has been overlooked. This type of artefact would result from a Walden inversion accompanying the hydrolysis of those urinary steroids conjugated with sulfuric acid. The supposition is based on the results obtained on the cleavage of analogous sulfonoxy compounds.



I II

Kenyon and Phillips[4] have shown that displacement reactions of *p*-toluenesulfonates of optically active alcohols (I) are accompanied by inversion of configuration, and there are at least three reports[5] demonstrating that steroid toluenesulfonates undergo displacement reactions accompanied by Walden inversion. Esters of sulfonic acids, therefore, unlike esters of carboxylic acids react by a rupture of the alkyl oxygen (SO-R) linkage.

(1) This paper was presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York City, September, 1947.

(2) A portion of this paper was taken from the Master's Thesis of Lucie B. Hariton, June, 1947, Department of Chemistry, New York University.

(3) The following steroids have been isolated from urine as their sulfuric acid esters: (a) Estrone [Schachter and Marrian, *J. Biol. Chem.*, **126**, 663 (1938)]; (b) androsterone [Venning, Hoffman and Browne, *J. Biol. Chem.*, **146**, 369 (1942)]; (c) dehydroisoandrosterone [Munson, Gallagher and Koch, *ibid.*, **152**, 67 (1944)]; (d) Δ^{16}-allopregnenol-3β-one-20 [Klyne and Marrian, *Biochem. J.*, **39**, Proc. xiv (1945)]; (e) uranediol [Klyne, *ibid.*, **40**, Proc. lv (1946)].

(4) Kenyon, Phillips, *et al.*, *J. Chem. Soc.*, **123**, 44 (1923); **127**, 399, 2552 (1925); 1676 (1930); 1072, 1663 (1935); *Trans. Faraday Soc.*, **26**, 451 (1930).

(5) (a) Prelog and Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944); (b) Plattner and Furst, *ibid.*, **26**, 2226 (1943); (c) Gallagher, private communication.