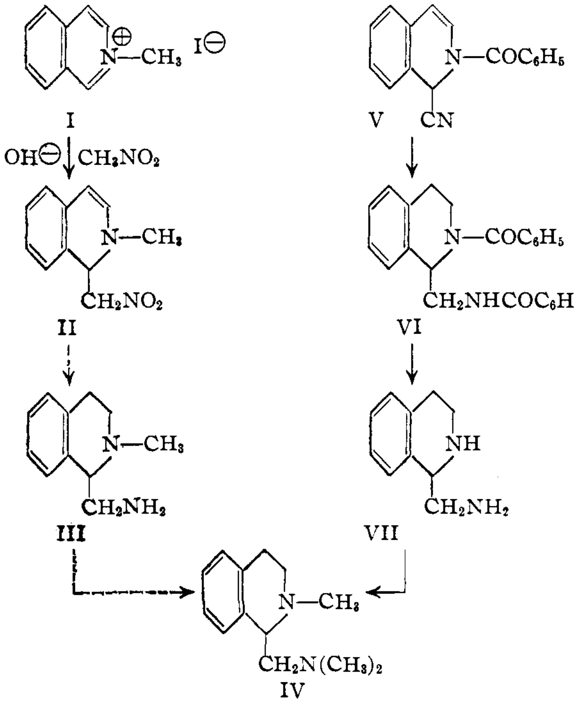
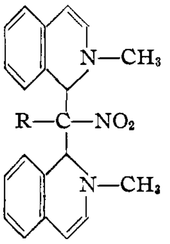
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reactions of Nitroparaffins with Isoquinolinium Compounds

BY NELSON J. LEONARD AND GERHARD W. LEUBNER[1,2]

One method for the synthesis of substituted 1-aminomethyltetrahydroisoquinolines (*e. g.*, III, IV), which are of pharmacological interest,[3] would appear to be the condensation of nitroparaffins with isoquinolinium salts in the presence of alkali, followed by stages of reduction and alkylation. For example, the mono-condensation product (II) of nitromethane with 2-methylisoquinolinium iodide (I) should be convertible to 1-dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV). Positive comparison of this product with that obtained (VI → VII → IV)[4] from Reissert's isoquinoline compound (V)[5] would serve to establish the structure of the compounds in the nitroparaffin series. Surprising results were encountered in the proposed synthesis of II in that *2-nitronaphthalene* (XV) was obtained from the reaction of nitromethane with 2-methylisoquinolinium iodide in the presence of alkali. In addition, the alkaline condensation of nitromethane with I furnished some disubstituted nitroparaffin to which has been assigned the structure VIIIa. The alkaline condensation of nitroethane and 1-nitropropane with I yielded VIIIb and VIIIc.





VIII (a, R = H; b, R = CH_3; c, R = C_2H_5)

The condensation of nitromethane with 2-methylisoquinolinium iodide in the presence of two molecular equivalents of potassium hydroxide has been described in the patent literature.[6] Kaufmann reported a product melting at 99°, but further characterization was lacking. In our hands, the same condensation in the presence of varying amounts of alkali invariably led to a non-homogeneous product, the components of which were difficult to separate. Recrystallization, sublimation, distillation and chromatographic adsorption of the crude reaction product were investigated. A single, pure chemical individual was isolated (in about 9% yield) by the methods of sublimation and chromatography. The pale yellow crystalline solid, m. p. 78–79°, thus obtained possessed a melting point and an analytical composition which were suggestive of 2-nitronaphthalene (XV); indeed, the product was found to be identical with an authentic sample of 2-nitronaphthalene. Moreover, it was converted by reduction and acetylation to acet-2-naphthalide, identical with an authentic sample of this compound.

Since the transformation of an isoquinoline ring system to a naphthalene ring system is unusual, it is interesting to speculate on the method whereby 2-nitronaphthalene is produced. A plausible series of reactions can be written in which the first step supposes the formation of 1-nitromethyl-2-methyl-1,2-dihydroisoquinoline (II) from 2-methylisoquinolinium hydroxide and nitromethane. Compound II has a Mannich base structure so that its conversion to the open chain nitroölefin (IX) might be expected to occur.[7] Hope and Robinson[8] have reported the isolation of a similar type of compound from the reaction of methyl iodide with anhydrocotarninenitromethane. The 1,3-shift of hydrogen corresponding to the conversion of a vinyl secondary amine (IX) to a Schiff

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[3] (a) Magidson and Gorbovizkii, *Ber.*, **68**, 656 (1935); (b) Dey and Kantam, *J. Indian Chem. Soc.*, **14**, 91 (1937); (c) Takase and Sato, *J. Pharm. Soc. Japan*, **49**, 1096 (1929).

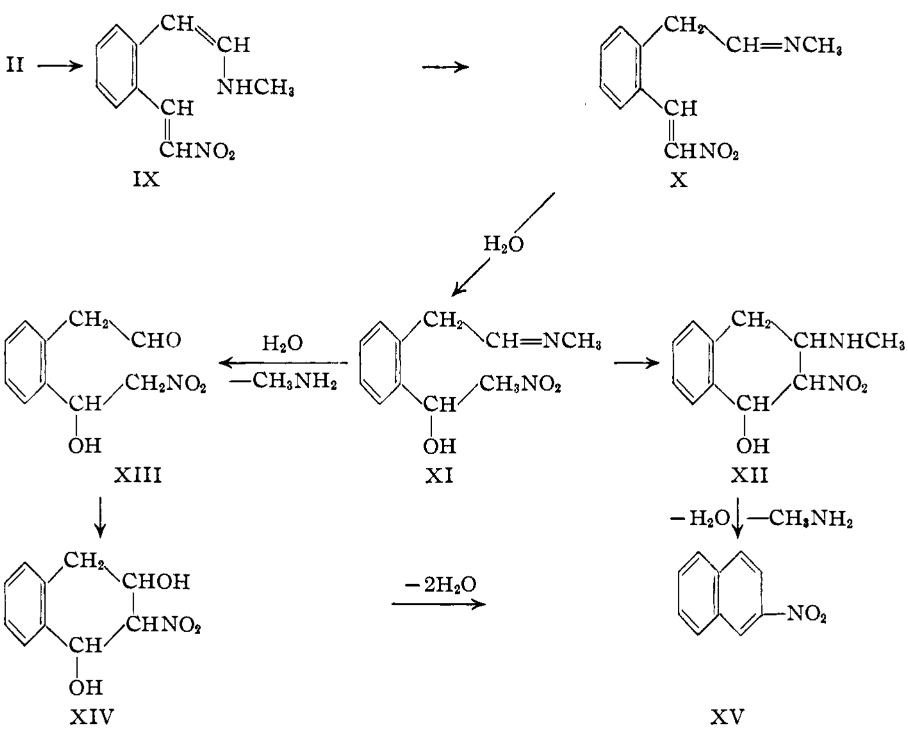
[4] Rupe and Frey, *Helv. Chim. Acta*, **22**, 673 (1939).

[5] Reissert, *Ber.*, **38**, 3415 (1905).

[6] Kaufmann, German Patent 250,154, July 15, 1912; *Frdl.*, **10**, 1317 (1910-1912).

[7] Blicke, in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. I, p. 318.

[8] Hope and Robinson, *J. Chem. Soc.*, **99**, 2114 (1911).



base (X) has been observed,[9] as has the addition of water (X → XI) to a nitroölefin.[10,11] The sequence of these and subsequent reactions is not to be considered inflexible. The conversion of the Schiff-base hydrolysis product (XIII) to XIV represents a common reaction of aldehydes with nitroparaffins[11] and the conversion of XI to XII represents a known reaction of nitroparaffins with imines.[12] The transformation of both XIV and XII to 2-nitronaphthalene (XV) would be expected to occur readily. Further study is planned to determine the scope and course of the over-all transformation.

Also obtained from the reaction of nitromethane and 2-methylisoquinolinium iodide in the presence of alkali was a compound, isolated as the monohydrochloride and monopicrate, which had a composition represented by the structure VIIIa, An analogous product was isolated as the free base (in 44% yield) from the condensation of nitroethane with two moles of 2-methylisoquinolinium iodide and potassium hydroxide and was assigned the structure, 1,1-bis-[1′-2′-methyl-1′,2′-dihydroisoquinolyl)]-nitroethane (VIIIb), on the basis of analysis and infrared absorption spectrum. A similar product, 1,1-bis-[1′-(2′-methyl-1′,2′-dihydroisoquinolyl)]-1-nitropropane (VIIIc) was obtained in a 21% yield using 1-nitropropane, Previously reported examples of the reaction of nitroparaffins with isoquinolinium compounds have never disclosed the formation of dicondensation products.[3b,6,8,13,14,15,16]

In the preparation of IV from Reissert's isoquinoline compound,[5] with certain modifications of the method of Rupe and Frey,[4] the intermediates VI and VII were isolated. The anhydrous hydrochloride of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII) was obtained, rather than the hydrated salt, and the dipicrate of 1 - dimethylaminomethyl - 2 - methyl-1,2,3,4-tetrahydroisoquinoline (IV) was formed from IV, rather than the monopicrate, as observed by Rupe and Frey.

Experimental[17]

Reaction of Nitromethane with 2-Methylisoquinolinium Hydroxide.—Fifty grams (0.185 mole) of 2-methylisoquinolinium iodide, m. p. 161–162°, and 33.8 g. (0.554 mole) of freshly distilled nitromethane[18] were dissolved in 250 ml. of hot absolute ethanol. To this was added a hot solution of 25 g. (0.38 mole) of potassium hydroxide pellets (85% KOH) in 100 ml. of absolute ethanol. The color of the solution changed immediately from yellow to red, and potassium iodide began to precipitate. After allowing the solution to stand for ten minutes, 250 ml. of water was added. The solution was cooled in an ice-bath and was acidified slowly with approximately 300 ml. of 5% aqueous acetic acid, with rapid stirring. The light brown solid which formed was allowed to settle and the supernatant liquid was decanted. The solid was stirred with water and the supernatant liquid was again decanted. After the washing process was repeated three times, the solid was collected and air-dried (25 g.). The wide melting range of the solid was not improved by recrystallization (ethanol, methanol, petroleum ether). In one run, a picrate was made from a filtered ether solution of the solid and an ethereal solution of picric acid. Four recrystallizations from ethylene dichloride–ethanol gave tiny yellow needles, which decomposed at 200° and were found to have an elementary composition corresponding to the **monopicrate of bis-[1-(2-methyl-1,2-dihydroisoquinolyl)]-nitromethane** (VIIIa).

Anal. Calcd. for $C_{27}H_{24}N_6O_9$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.28; H, 4.10; N, 14.16.

In a second run, using 1.1 moles of potassium hydroxide per mole of nitromethane and 2-methylisoquinolinium iodide, the crude dry product (1 g.) was dissolved in 100 ml. of ether and treated with anhydrous hydrogen chlo-

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(9) Marz, Diss. Techn. Hochsch., München, 1913; see Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).

(10) Lambert, *J. Chem. Soc.*, 1474 (1947).

(11) Levy and Rose, *Quarterly Reviews*, **1**, 358 (1948).

(12) Mayer, *Bull. soc. chim. France*, [3] **33**, 395 (1905).

(13) Dey and Srinivasan, *J. Indian Chem. Soc.*, **12**, 526 (1935).

(14) Haworth, Perkin and Rankin, *J. Chem. Soc.*, **127**, 1444 (1925).

(15) Malan and Robinson, *ibid.*, 2653 (1927).

(16) Robinson and Robinson, *ibid.*, **111**, 958 (1917).

(17) All melting points are corrected. The authors are indebted to Mrs. James L. Johnson for determination of the infrared absorption spectra.

(18) Freund and Bode, *Ber.*, **42**, 1746 (1909).

ride. The precipitated salt was recrystallized four times from absolute ethanol to yield 0.33 g. of colorless prisms, which decomposed at 184° after initial sintering and darkening at 170°. In elementary composition the compound corresponded to the **monohydrochloride of bis-[1-(2-methyl-1,2-dihydroisoquinolyl)]-nitromethane.**

Anal. Calcd. for $C_{21}H_{22}ClN_3O_2$: C, 65.70; H, 5.78; N, 10.95. Found: C, 65.74; H, 6.13; N, 11.00.

The **picrate** prepared from this hydrochloride salt was identical with that described above.

In a duplicate of the original run (two moles of potassium hydroxide per mole of nitromethane and 2-methylisoquinolinium iodide) the crude condensation product was dissolved in benzene and chromatographed on a column of Harshaw 2-350 aluminum oxide. The chromatogram was developed with benzene to give successive canary yellow, lighter yellow, and brown bands. The lowest yellow band was eluted with benzene and the benzene solution was evaporated to dryness. The light yellow crystalline solid, after purification by sublimation and recrystallization from water (as needles), melted at 78–79°. The analytical composition corresponded to the empirical formula $C_{10}H_7NO_2$.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.70; H, 4.10; N, 7.72.

Analysis and melting point were suggestive of 2-nitronaphthalene.[19] An authentic sample of 2-nitronaphthalene, m. p. 78–79°, was prepared by the method of Hodgson, Birtwell and Marsden[19] from 2-nitro-1-naphthylamine. Mixtures of the two samples gave no depression in melting point. The $C_{10}H_7NO_2$ product was reduced by means of iron powder in acetic acid and acetic anhydride to give a product, m. p. 131–132°, which separated as colorless plates from aqueous ethanol. This product gave no depression in melting point when mixed with an authentic sample, m. p. 131–132°, of acet-2-naphthalide.[20] The amount of 2-nitronaphthalene isolated by means of chromatography corresponded to a yield of 9% based on the 2-methylisoquinolinium iodide used. Approximately the same yield of 2-nitronaphthalene, similarly characterized, was realized by sublimation of the crude condensation product of 2-methylisoquinolinium hydroxide and nitromethane. The sublimation was carried out in the range of 80–150° and 0.01–0.5 mm. No other pure compounds could be isolated by chromatography and sublimation methods. It is probable that the yield of 2-nitronaphthalene can be raised by further examination of the conditions of the reaction.

1,1-bis-[1′-(2′-Methyl-1′,2′-dihydroisoquinolyl)]-nitroethane (VIIIb).—To a hot solution of 75 g. (0.28 mole) of 2-methylisoquinolinium iodide, 62 g. (0.83 mole) of nitroethane and 30 ml. of methanol was added a heated solution of 27.4 g. (0.42 mole) of potassium hydroxide in 100 ml. of methanol. The solution was allowed to stand one-half hour and was then evaporated at 25° with a stream of dry air. After the crystalline material began to separate, evaporation was aided by mechanical stirring. A thick paste of crystals and dark red oil resulted. The oil was removed by repeated washing with cold methanol, and potassium iodide was removed by water washing. The colorless organic solid (22 g., 44% yield) crystallized as prisms from acetone; m. p. 210–212°.

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.14; H, 6.55; N, 11.72.

The infrared absorption spectrum agreed well with the structure assigned on the basis of analysis. The strong characteristic nitro absorption band was observed at 1535 cm.$^{-1}$, and the bands at 741 and 751 cm.$^{-1}$ were characteristic of the *o*-substituted phenyl grouping.

1,1-bis-[1′-(2′-Methyl-1′,2′-dihydroisoquinolyl)]-1-nitropropane (VIIIc).—The reaction between 1-nitropropane and 2-methylisoquinolinium iodide was carried out in the same manner as that described for nitroethane. When the reaction mixture was allowed to stand for several days at 25°, crystalline material separated. The solid (21% yield) was obtained as colorless prisms upon recrystallization from acetone; m. p. 201.5–202°.

Anal. Calcd. for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.58; H, 6.87; N, 10.99.

The infrared absorption spectrum was very similar to that observed for the lower homolog (VIIIb).

1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII) Hydrochloride.—The preparation of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (V) was effected by the method of Reissert[5] with some modifications. Hydrogenation of V in ethanol over Raney nickel catalyst at 150 atm. and 100° gave 1-benzoylaminomethyl-1,2,3,4-tetrahydroisoquinoline as an oil which was converted to solid 1-benzoylaminomethyl-2-acetyl-1,2,3,4-tetrahydroisoquinoline (VI), m. p. 196–197.5° (reported, 201°).[4] Hydrolysis of VI to 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII), b. p. 154–159° (15 mm.), $n^{20}D$ 1.5779, was effected with 20% hydrochloric acid. To a cooled solution of 11.5 g. (0.071 mole) of VII in 20 ml. of absolute ethanol was added slowly with stirring 6.8 ml. of absolute ethanol containing 2.6 g. (0.071 mole) of hydrogen chloride. The mixture containing some crystalline solid was heated, 25 ml. additional of absolute ethanol was added, and the material was allowed to crystallize. The monohydrochloride was obtained as colorless plates which darkened at 171° and melted at 179–184°. Recrystallization from absolute ethanol failed to improve the melting point.

Anal. Calcd. for $C_{10}H_{15}ClN_2$: C, 60.44; H, 7.61; N, 14.10. Found: C, 60.39; H, 7.37; N, 13.92.

Rupe and Frey[4] prepared the monohydrochloride in absolute ether and recrystallized from ethanol containing a small amount of water to obtain a dihydrate of the salt, m. p. 281° (dec.).

1-Dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV).—The formaldehyde–formic acid method of methylation[21] was adapted to the conversion of VII to IV, rather than the methyl iodide–potassium hydroxide method of Rupe and Frey.[4] Twenty-one grams (0.13 mole) of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (VII) was dissolved with cooling in 51.1 g. (0.97 mole) of 87.5% formic acid and to this was added 34.7 g. (0.43 mole of formaldehyde) of formalin. After a short period of heating on the steam-bath, the initially vigorous evolution of carbon dioxide subsided in fifteen minutes. Heating on the steam-bath was continued for eight hours, 23 ml. of 12 *N* hydrochloric acid was added, and the solution was then evaporated to dryness under reduced pressure. The sirup which remained was dissolved in water, and the cold aqueous solution was made strongly alkaline with sodium hydroxide. The alkaline mixture was extracted with ether, the ethereal solution was dried, and the ether was removed. Fractional distillation of the residue *in vacuo* gave 12.6 g. (48%) of colorless oil, b. p. 143–146° (16 mm.) (reported, b. p. 135° (12 mm.)[4]); $n^{20}D$ 1.5331.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.72. Found: C, 76.23; H, 9.78; N, 14.07.

The methiodide, recrystallized from ethanol, melted at 196–197° (reported, 199°).[4] Two new derivatives of 1-dimethylaminomethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline were formed. The **dihydrobromide monohydrate** was prepared by the slow addition of 12.2 g. (0.072 mole of HBr) of 48% hydrobromic acid with stirring to an ice-cold solution of 7.4 g. (0.036 mole) of IV in 15 ml. of absolute ethanol. During the addition the crystalline salt began to separate. The mixture was heated and additional absolute ethanol was added to bring about solution. After filtration and cooling, 11.7 g. (88%) of colorless elongated prisms separated. Recrystallization from ethanol plus a small amount of water gave a 94% recovery of material which began sintering at 138° and melted with decomposition at 152–153°,

Anal. Calcd. for $C_{13}H_{24}Br_2N_2O$: C, 40.64; H, 6.30; N, 7.29. Found: C, 40.46; H, 6.48; N, 6.90.

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[19] Hodgson, Birtwell and Marsden, *J. Chem. Soc.*, 112 (1944).

[20] Leonard and Hyson, *J. Org. Chem.*, **13**, 164 (1948).

[21] "Organic Syntheses," **25**, 89 (1945).

A small sample was well crushed and dried in an Abderhalden apparatus over phosphorus pentoxide at 110° for ten hours. The melting point of the anhydrous **dihydrobromide** was 216-220°.

Anal. Calcd. for $C_{13}H_{22}Br_2N_2$: C, 42.64; H, 6.06. Found: C, 42.76; H, 6.31.

We were unable to isolate the monopicrate, m. p. 202°, described by Rupe and Frey,[4] but we obtained a **dipicrate** when the amine in ethanol was treated with a large excess of ethanolic picric acid. Recrystallization from acetone-ethanol gave yellow crystals which softened at 158° and melted at 171-174°.

Anal. Calcd. for $C_{25}H_{26}N_8O_{14}$: C, 45.32; H, 3.96; N, 16.91. Found: C, 45.56; H, 4.18; N, 17.17.

Summary

It has been established that 2-nitronaphthalene is produced from the condensation of 2-methylisoquinolinium iodide with nitromethane in the presence of potassium hydroxide, and a plausible series of reactions has been suggested to account for this unusual transformation. The alkaline condensation of 2-methyliosquinolium iodide with nitromethane also produced some bis-[1-(2-methyl - 1,2 - dihydroisoquinolyl)]-nitromethane, that with nitroethane produced 1,1-bis-[1′-(2′-methyl - 1′,2′ - dihydroisoquinolyl)]-nitroethane, and that with 1-nitropropane gave 1,1-bis-[1′-(2′-methyl-1′,2′-dihydroisoquinolyl)]-1-nitropropane.

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Reactions of Nitroparaffins with Pseudo Bases Related to Dihydroisoquinolinium Hydroxide

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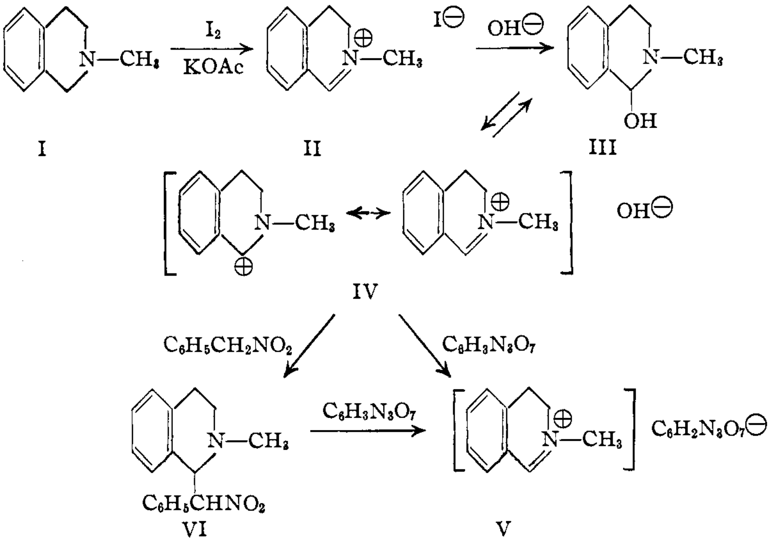
In an investigation[3] of the reaction of nitroparaffins with a pseudo base of type III,[4] the attempted characterization of the nitromethane product (analogous to VI) by picrate formation gave an unusual result. The supposed picrate derivative always reverted to the picrate of the pseudo base (V)! This observed elimination of nitromethane prompted a reëxamination of the picrate derivatives of anhydrocotarninenitromethane (VIII) and anhydrohydrastininenitromethane (VIII without methoxyl) reported by Hope and Robinson.[5] It has now been found that these reported derivatives are, in fact, cotarnine picrate (IX) and hydrastinine picrate (IX without methoxyl), both products of nitromethane elimination.



The method of synthesis of the pseudo base III required the initial preparation of 2-methyl-1,2,3,4-tetrahydroisoquinoline (I). The previously described directions for obtaining I by the reduction of 2-methylisoquinolinium iodide with tin and hydrochloric acid[6] or with sodium and ethanol[7] were less convenient than the formaldehyde–formic acid methylation[8] of 1,2,3,4-tetrahydroisoquinoline. 2-Methyl-1,2,3,4-tetrahydroisoquinoline (I) was oxidized to 2-methyl-3,4-dihydroisoquinolinium iodide (II) by means of iodine and potassium acetate. Compound II had been prepared previously, but by a degradation process.[9] The conversion of tetrahydro- to dihydro-compounds by iodine oxidation had been realized previously with several highly substituted tetrahydroisoquinolines,[10,11,12] but Schmidt had reported that iodine oxidation of tetrahydroisoquinoline itself gave iso-

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(3) For previous paper, see Leonard and Leubner, THIS JOURNAL, **71**, 3405 (1949).

(4) Compound III results from alkali treatment of a 3,4-dihydroisoquinolinium salt (II).

(5) Hope and Robinson, *J. Chem. Soc.*, **99**, 2114 (1911).

(6) Wedekind and Oechslen, *Ber.*, **34**, 3986 (1901).

(7) Emde, *Ann.*, **391**, 88 (1912).

(8) "Organic Syntheses," **25**, 89 (1945).

(9) Pyman, *J. Chem. Soc.*, **95**, 1738 (1909).

(10) Haworth, Perkin and Rankin, *ibid.*, **127**, 1444 (1925).

(11) Haworth and Perkin, *ibid.*, **127**, 1434 (1925).

(12) German Patent 267,272, Jan. 19, 1913; *Frdl.*, **11**, 1004 (1912-1914).