mp 220–221°; λ_{max}^{Nujol} 3.70 μ; λ_{max}^{EtOH} 216, 255 mμ (ϵ 17,160, 120, respectively).

Anal. Calcd for $C_{17}H_{30}I_2N_2$: C, 39.55; H, 5.86; N, 5.43. Found: C, 39.63; H, 5.93; N, 5.46.

Registry No.—**1a**, 2997-20-8; **1c**, 13128-08-0; **2**, 13128-09-1; **3**, 13128-10-4; **4**, 13128-11-5; **5**, 13128-12-6; **6**, 13128-13-7; picrate of **6**, 13128-14-8; **7**, 3293-73-0; **8**, 2997-07-1; 1-mono-2,4-dinitrophenylhydrazone of **8**, 2997-08-2; **10**, 13128-18-2; **12**, 13128-19-3; bis-2,4-dinitrophenylhydrazone of **12**, 13128-20-6; monooxime of **12**, 13128-21-7; **13**, 13128-22-8; **14**, 13221-17-5; oxime of **14**, 13168-37-1; *cis* **15a**, 13128-23-9; *trans* **15a**, 13128-24-0; **15b**, 13128-25-1; **15d**, 13128-26-2; **16a**, 13128-27-3; hydrochloride of **16a**, 13168-38-2; **16b**, 13128-28-4; hydrochloride of **16c**, 13192-30-8; hydrochloride of **17a**, 13128-29-5; hydrochloride of **18a**, 13128-30-8; hydrochloride of **18b**, 13128-31-9; **19**, 13168-39-3; **20**, 13128-32-0; **22**, 13128-33-1; **23**, 13128-34-2; **24a**, 2997-09-3; **24b**, 2997-10-6; **24c**, 2997-40-2; **24d**, 2997-38-8; **25**, 13128-40-0; hydrochloride of **26**, 13128-41-1; **27a**, 3277-16-5; hydrochloride of **27a**, 2997-11-7; picrate of **27a**, 13128-44-4; **27b**, 2959-93-5; hydrochloride of **27b**, 3118-09-0; **28a**, 13128-47-7; hydrochloride of **28a**, 13128-48-8; N-acetyl derivative of **28a**, 13128-49-9; hydrochloride of **28b**, 13128-50-2; **29a** (X = I), 2997-13-9; **29a** (X = I·H_2O), 13128-52-4; **29a** (X = Cl·H_2O), 13128-53-5; **29a** (X = Cl·1.5H_2O), 13128-54-6; **29a** (X = Br), 3196-51-8; **29b** (X = I), 2959-88-8; **30a**, 2997-34-4; **31a**, 13128-58-0; picrate of **31a**, 13128-59-1; hydrochloride of **31a**, 13128-60-4; hydroiodide of **31a**, 13128-61-5; methyl iodide of **31a**, 3048-72-4; hydroiodide of **31b**, 13128-63-7; **32a**, 2997-33-3; **33a**, 13128-65-9; **36**, 13128-66-0; 4,4-diphenyl-1,3-cyclohexanedione, 13128-74-0; $C_{18}H_{16}O_2$ (mp 244–248), 13128-75-1; 2-benzyl-3,4-dimethyl-1,4-dihydro-1,4-ethanoisoquinolinium bromide, 2959-89-9; 2-benzyl-3,4-dimethyl-1,4-dihydro-1,4-ethanoisoquinolinium iodide, 3123-56-6; $C_{20}H_{22}IN$, 2997-14-0; $C_{22}H_{26}IN$, 2997-15-1; $C_{21}H_{24}IN$, 2997-18-4; $C_{25}H_{24}ClN \cdot 0.5H_2O$, 2997-16-2; $C_{26}H_{26}IN$, 2997-17-3; $C_{22}H_{25}BrNO_2$, 2997-19-5; $C_{22}H_{24}ClNO_2 \cdot 0.5H_2O$, 3123-45-3.

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Synthesis of Isoquinolines. VI. N-Alkyl-1,2,3,4-tetrahydroisoquinolines[1]

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A reaction scheme has been worked out which allows the synthesis of substituted N-methyl-1,2,3,4-tetrahydroisoquinolines from substituted benzaldehydes in high over-all yields. Using this method, two alkaloids, corypalline and hydrohydrastinine, have been prepared. Secondly, a method has been devised for preparing N-substituted 1,2,3,4-tetrahydroisoquinolines where the alkyl group is varied from methyl to *t*-butyl. The method uses glycidol followed by periodate oxidation to produce carbons 3 and 4 of the isoquinoline.

Recently, we[3] have described an efficient method for converting substituted benzaldehydes to 1,2,3,4-tetrahydroisoquinolines (**1** → **2** → **3** → **6**) (Scheme I). We have now extended the method to the preparation of N-alkyl-1,2,3,4-tetrahydroisoquinolines.

N-Methylation was carried out as a part of the first reduction step. Thus, the appropriate substituted benzaldehyde was combined with aminoacetal and reduced over platinum oxide. The hydrogenation vessel was opened and a slight excess of formaldehyde and some acetic acid were added after which hydrogenation was continued to carry out the N-methylation.[4] The N-benzyl-N-methylaminoacetals (**4**) were then treated with dilute hydrochloric acid and hydrogenated to yield the desired products (**5**). The reaction was tested on three compounds, vanillin (**1a**), isovanillin (**1b**), and piperonal (**1c**). The yields of **5a**, **5b** (corypalline), and **5c** (hydrohydrastinine) were 59, 94, and 67%, respectively, based on the starting aldehydes. Compound **5b** was isolated as a free base while **5a** and **5c** were isolated as hydrochlorides. As in the original synthesis,[3] there must be an oxygen function in the 3 position of the starting aldehyde for effective cyclization; free phenolic groups do not interfere. It is of interest to note that corypalline (**5b**)[5] and hydrohydrastinine (**5c**)[6] have been prepared previously in yields of approximately 0.3 and 10%.[7]

(1) (a) Paper V: J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (London), 2127 (1966). (b) This work was supported in part by Grant CA-3905 from the National Cancer Institute of the National Institutes of Health.

(2) On leave from the Bengal Immunity Research Institute, Calcutta 16, India; recipient of a Fulbright Travel Grant.

(3) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(4) W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).

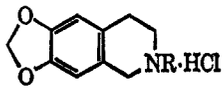
(5) R. H. F. Manske, *Can. J. Res.*, **15B**, 159 (1937).

(6) P. Fritsch, *Ann.*, **286**, 1 (1895).

(7) It should be noted that these compounds were prepared for structure elucidation studies in which yields are less important.

TABLE I

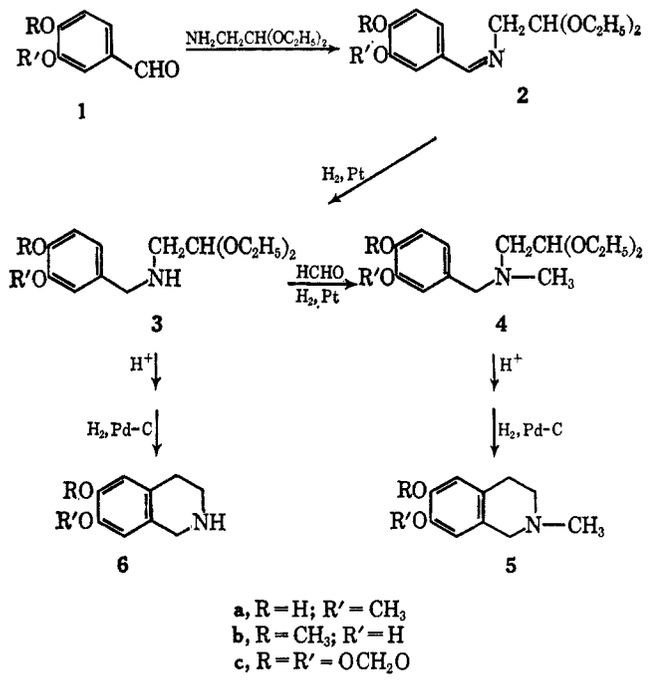
N-ALKYL-6,7-METHYLENEDIOXY-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



R	Yield,[a] %	Mp,[b] °C	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
CH_3	35	276–278	58.01	6.21	6.15	15.59	57.55	6.36	6.38	15.63
CH_3CH_2	65	278–280	59.64	6.69	5.79	14.69	59.25	6.52	6.06	14.61
$CH_3CH_2CH_2$	36	262–264	61.03	7.12	5.47	13.87	61.10	6.94	5.36	13.36
CH_3CHCH_3	42	268–270	61.03	7.12	5.47	13.87	60.88	6.85	5.26	13.78
$(CH_3)_3C$	28	294–296	62.30	7.49	5.19	13.16	62.16	7.49	5.01	12.81

[a] Yields are calculated from piperonal and are based upon the product obtained after at least one recrystallization from ethanol. [b] The melting points are measured on the amounts reported in the yield column and refer to the analytical samples.

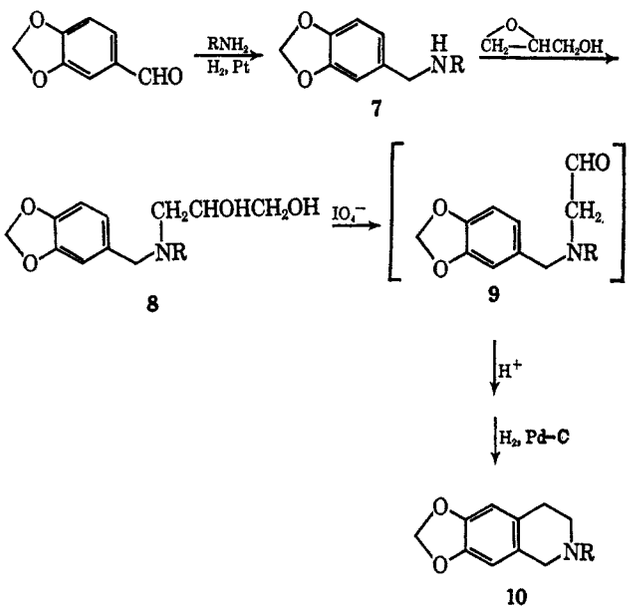
SCHEME I



a, R = H; R′ = CH_3
b, R = CH_3; R′ = H
c, R = R′ = OCH_2O

When attempts were made to extend this preparation to N-alkyl derivatives other than N-methyl by using aldehydes other than formaldehyde, no products were isolated. We then searched for another source of carbons 3 and 4 of the isoquinoline. A series of substituted benzylamines [**7**, R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $(CH_3)_2CH$, $(CH_3)_3C$] was prepared by reductive alkylation of the appropriate amines with piperonal.[4] Attempts to alkylate these amines with chloroacetal[8] were unpromising, perhaps owing to steric hindrance. An alternate procedure using glyoxal semiacetal[9] for carbons 3 and 4 has a serious disadvantage in that the glyoxal derivative is difficult to prepare. It appeared that a reaction of these amines with glycidol to yield substituted 3-benzylamino-1,2-propanediols (**8**) should take place with a minimum of steric interference. Moreover, glycidol is commercially available. Periodate oxidation[10] of **8** should yield the substituted aminoacetaldehydes (**9**) which could be converted to isoquinolines (**10**) by the procedure shown above (**3** → **6**). The adducts (**8**) were obtained with little difficulty and oxidized in a water–chloroform system to **9**. This step requires that a glycol be oxidized in preference to an amino alcohol. Since the periodate oxidation of compounds containing a tertiary amine is slow,[10] this was possible. The aminoacetaldehydes (**9**) were converted to the isoquinolines (**10**, Scheme II) with the over-all yields

SCHEME II



shown in Table I. The compounds were isolated as hydrochlorides. The nmr spectra were in complete agreement with the structures. Since phenols react with periodate,[10,11] only those compounds containing blocked phenols can be used. When R is phenyl or benzyl, the reaction does not proceed satisfactorily. Attempts to extend the reaction using substituted glycidols or to use oxidizing agents other than periodate have not been successful.

Experimental Section[12]

6-Hydroxy-7-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (5a).—Aminoacetaldehyde diethyl acetal (2.66 g, 0.02 mole) and vanillin (3.04 g, 0.02 mole) were dissolved in 15 ml of absolute ethanol and added to a hydrogenation flask containing platinum (from 0.2 g of platinum oxide, prereduced in the flask) and 20 ml of absolute ethanol. The mixture was reduced at room tempera-

(8) I. A. Kaye and I. Minsky, *J. Am. Chem. Soc.*, **71**, 2272 (1949).
(9) W. J. Gensler, *Org. Reactions*, **6**, 191 (1951).
(10) J. M. Bobbitt, *Advan. Carbohydrate Chem.*, **11**, 1 (1956).
(11) E. Adler, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962).
(12) All melting points were taken on a Kofler micro hot-stage apparatus and are corrected. The microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich, Zürich, Switzerland.

ture and atmospheric pressure[13] until about 0.02 mole of hydrogen had been absorbed. The flask was opened; acetic acid (2 ml)[4] and 1.78 g (0.022 mole) of 37% formalin in 20 ml of absolute ethanol were added; and the reduction was continued until 0.02 additional mole of hydrogen was absorbed. The catalyst was removed by filtration and the ethanol was removed on a rotary evaporator. The thick oil was dissolved in 150 ml of 6 *N* hydrochloric acid, extracted with ether, and allowed to stand overnight. The last traces of ether were removed on a rotary evaporator and the solution was hydrogenated over 2 g of 10% palladium on carbon, again at room temperature and atmospheric pressure. After 0.02 mole of hydrogen had been taken up,[14] the catalyst was removed by filtration and the solution was concentrated to about 20 ml and cooled. Crystals formed and were collected to yield 2.73 g (59.3%) of crude 6-hydroxy-7-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, mp 276–280°. Five recrystallizations from ethanol raised the melting point to 285–290° for the analytical sample.

Anal. Calcd for $C_{11}H_{15}NO_2 \cdot HCl$: C, 57.47; H, 7.02; Cl, 15.43; N, 6.09. Found: C, 57.90; H, 7.11; Cl, 15.44; N, 6.06.

The **free base** was prepared by basification of an aqueous solution of the hydrochloride with ammonia. Two recrystallizations from benzene yielded an analytical sample, mp 164–165°.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.23; H, 7.69; N, 7.33.

7-Hydroxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (5b).—The reactions were carried out exactly as described for **5a** except for the product isolation. The aqueous acid solution was evaporated completely to dryness and dissolved in a minimum amount of water. The solution was made strongly basic (pH 10) with ammonium hydroxide and the product (3.64 g, 94%, mp 166–170°) precipitated. One recrystallization from benzene raised the melting point to 171–173° (lit.[5] mp 168°). A **picrate** melted at 174–177° (lit.[5] mp 178°).

6,7-Methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (5c).—The reactions were carried out exactly as described for **5a** except for the product isolation. The aqueous acid solution was evaporated to a small volume and 50 ml of absolute ethanol was added and subsequently evaporated. The alcohol addition was repeated twice more. The product crystallized during this process and was removed by filtration to yield 3.06 g (67%) of **5c** as its hydrochloride, mp 263–269°.[15] The **free base**, mp 60–61.5° (lit. mp 60–61°,[5] 66°[16]), was prepared as described above for **5b**. A **picrate** was prepared from the free base and melted at 175–179° (lit.[16] mp 175–176°).

6,7-Methylenedioxy-N-alkyl-1,2,3,4-tetrahydroisoquinolines (10). General Procedure.—Piperonal (15 g, 0.1 mole) and the appropriate amine (0.1 mole)[17] were dissolved in 50 ml of absolute ethanol and added to a hydrogenation flask containing platinum (from 0.4 g of platinum oxide, prereduced in the flask) and 20 ml of absolute ethanol. The mixture was reduced at room temperature and atmospheric pressure until 0.1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the residue was taken up in 30 ml of 6 *N* hydrochloric acid and washed with ether. The aqueous solution was made strongly basic with sodium hydroxide (30%) and extracted three times with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to a residual oil. The oils were not further purified and were not analyzed.

The crude, oily amines (0.015 mole) and glycidol (1.3 g, 0.0175 mole) were mixed in a test tube protected from moisture with a drying tube and heated in a boiling water bath for 2 hr.

The adducts were dissolved in 25 ml of chloroform, added to 25 ml of water, and cooled to 0°. Sodium metaperiodate (3.3 g, 0.015 mole) in 20 ml of water was added dropwise to the stirred, two-phase system. After the addition was complete (15 min), the mixtures were made basic to pH 8 with 1 *N* sodium hydroxide and stirred for 3 hr. The layers were separated and the chloroform layer was extracted with three, 20-ml portions of 6 *N* hydrochloric acid.

The aqueous acid solutions were allowed to stand overnight and reduced over 2.5 g of 5% palladium on carbon until hydrogenation essentially ceased. The catalyst was removed by filtration and the aqueous solutions were evaporated on a rotary evaporator to dryness. The residue was recrystallized from ethanol to give the hydrochlorides listed in Table I in the specified yields and with the specified melting points. Analytical samples were prepared by recrystallization from ethanol.

The nmr spectra of the hydrochlorides listed in Table I were measured in deuterium oxide against tetramethylsilane as an external standard. The spectra showed the predicted peaks for the various N-alkyl residues as well as the following peaks in common: two singlets of one proton each at about τ 3.25 (C-6 and C-8 protons), one singlet of two protons at 4.1 (methylenedioxy), a singlet or doublet of two protons at 5.7 (C-1 protons), and two, broad multiplets of two protons each at 6.3 and 6.8 (C-3 and C-4). When the N-alkyl group was primary (**10**, R = CH_3, CH_3CH_2, and $CH_3CH_2CH_2$) the C-1 protons appeared as a doublet in the spectra. When the N-alkyl group was secondary or tertiary [**10**, R = $(CH_3)_2CH$, and $(CH_3)_3C$] the C-1 protons appeared as a singlet.

(13) Pressures up to 10 psi were safe, but decomposition sometimes occurred at higher pressure.

(14) The reaction was terminated after 0.02 mole of hydrogen had been absorbed, even though it had not completely stopped.

(15) The melting point of this compound was erratic, sometimes being as high as 300°.

(16) E. Späth and P. L. Julian, *Ber.*, **64**, 1131 (1931).

(17) In the cases of methylamine and ethylamine, these were 8 g of a 40% aqueous solution and 6.5 g of a 70% aqueous solution, respectively. Otherwise, the liquid amines were used.

The Electron Paramagnetic Resonance Detection of Aryl Ether Cleavage. II. The Anion Radicals of Polyphenyl Ethers[1,2]

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The cleavage of the anion radicals of *m*-polyphenyl ethers has been found to produce, initially, the diphenoxide radical of diphenyl ether and biphenyl anion radical.

Metal reduction techniques exercised upon aryl ethers have, in the past, resulted in ready scission.[1,3] The reductive stability of several polyphenyl ethers was investigated in this research to determine if increased stability over simple diaryl ethers might accrue from increased chain length or if possible unusual cleavage reactions might be observed. The compounds investigated and tabulated in Table I produced cleavage products detectable by electron paramagnetic resonance (epr) within seconds; all the fragments were not those which might have been predicted from earlier research. As might be expected from knowledge of the fate of previously studied diaryl ethers, the diether $(Ph)_3O_2$ was found to cleave off both phenyl groups, forming biphenyl and the dipotassium salt of hydro-

(1) Paper I. Diaryl Ethers: D. H. Eargle, Jr., *J. Org. Chem.*, **28**, 1703 (1963).

(2) Research performed at the U. S. Naval Research Laboratory and presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.

(3) E. J. Strojny, *J. Org. Chem.*, **31**, 1662 (1966).