extended conformation in which the terminal acetoxy group is coplanar with the carbon chain may be regarded as the favored rotamer state.

While rotation about the C–C bonds in the side chain undoubtedly occurs at room temperature, the resolution of the spectrum indicates a high degree of conformational purity, and is in agreement with an extended, planar zig-zag arrangement as the favored conformation. This conformation corresponds to attainment of the minimum nonbonded interactions between the small–medium–large sets of groups at the ends of each carbon–carbon bond.

Experimental

N.m.r. Spectra.—Spectra were measured at approximately 30° with a Varian A-60 60-Mc.p.s. n.m.r. spectrometer. Tetramethylsilane (τ 10.00) was used as the internal reference standard. The spectrum for substance I was measured in dimethyl sulfoxide solution; that for III was measured in deuteriochloroform.

2-(D-*arabino*-Tetrahydroxybutyl)quinoxaline (I).—This compound was prepared by the method of Lohmar and Link[1]: m.p. 190–191°; n.m.r. data, τ 0.80 (singlet, 1 proton, H-3 of quinoxaline), 1.89 (multiplet, 2 protons, H-5 and H-8 of quinoxaline), 2.17 (multiplet, 2 protons, H-6 and H-7 of quinoxaline), and no other resonances below 4.6.

2-(D-*arabino*-Tetraacetoxybutyl)quinoxaline (III).—This compound was prepared[1] by acetylation of I with pyridine and acetic anhydride: m.p. 119–120°; λ_{max}^{EtOH} 211.1 mμ (ε 24,000), 236.9 (ε 32,000), 317.4 (ε 7600); for n.m.r. data, see Table I.

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Synthesis of Isoquinolines. IV.[1] 4-Benzylisoquinolines

J. M. BOBBITT, D. P. WINTER,[2] AND JUDITH M. KIELY[2]

Department of Chemistry, University of Connecticut, Storrs, Connecticut

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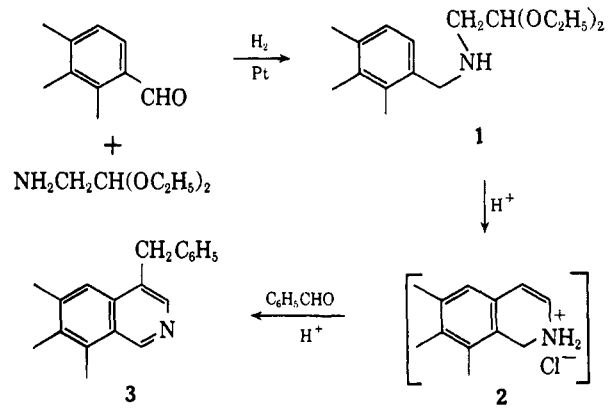
Recent work in this laboratory has yielded a new synthesis of 1,2,3,4-tetrahydroisoquinolines[1,3] based upon the Fischer modification of the Pomeranz–Fritsch synthesis.[4] In that case, the unstable 1,2-dihydroisoquinolines (**2**) formed by dilute acid treatment of the reduced Schiff bases (**1**) were catalytically hydrogenated to 1,2,3,4-tetrahydroisoquinolines. It now appears that, when such intermediates (**2**) are treated with benzaldehyde, 4-benzylisoquinolines (**3**) are formed in good yield and with a minimum of experimental difficulty.

During the course of this work, a similar reaction was reported by Grewe, Krüger, and Vangermain.[5] They obtained a separable mixture of 4-benzyl-1,2,3,4-tetrahydroisoquinoline and 4-benzylisoquinoline by catalytic hydrogenation of isoquinoline in the presence of acetic acid and benzaldehyde. Furthermore, they proposed a 1,2-dihydroisoquinoline intermediate. This is, in turn, quite similar to work reported by Burrows and Burrows[6] who proposed an enamine or 1,2-dihydroisoquinoline intermediate for the condensation of 1,2,3,4-tetrahydroisoquinoline and benzaldehyde. This latter reaction led to 4-benzylisoquinoline in 34% yield. The work reported in this paper, is, in a sense, complementary to previous papers in that properly substituted benzaldehydes can be used as starting materials in place of the more difficultly obtainable heterocyclic molecules.



The reduced Schiff bases (**1**), derived from vanillin (4-hydroxy-3-methoxybenzaldehyde), isovanillin (3-hydroxy-4-methoxybenzaldehyde), and *o*-vanillin (2-hydroxy-3-methoxybenzaldehyde), were prepared by atmospheric pressure hydrogenation of the appropriate aldehyde and aminoacetaldehyde diethylacetal in the presence of a platinum catalyst. The bases were not isolated as such, but were treated with acidic, ethanolic solutions of benzaldehyde to yield the desired 4-benzylisoquinolines. The yields were calculated from the initial aldehydes and were as follows: 4-benzyl-6-hydroxy-7-methoxyisoquinoline (**4**, from vanillin), 63%; 4-benzyl-7-hydroxy-6-methoxyisoquinoline (**5**, from isovanillin), 54%; and 4-benzyl-8-hydroxy-7-methoxyisoquinoline (**6**, from *o*-vanillin, isolated as the hydrochloride), 61%. The three bases were characterized as picrates. In the case of **6**, the free base as obtained by basification of an aqueous solution of hydrochloride was not amenable to further purification. However, when this neutralization was carried out by passing a solution of hydrochloride over a column of basic alumina, the free base was obtained. A similar difficulty was observed[1,3] with 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline.

The structures of the products were established by their elemental analyses and by their unique n.m.r. spectra. Each of the three showed two single protons, on C-1 and C-3, with τ values corresponding to the α hydrogens on an aromatic nitrogen ring. The C-1 protons of **4**, **5**, and **6** were at τ 1.1, 1.1, and 0.5 (hydrochloride), respectively, and the C-3 protons were at τ 1.78, 1.78, and 1.8. The recorded values for isoquinoline itself are τ 1.4 for C-1, 2.0 for C-3, and 3.3 for C-4.[7] There was no evidence in the n.m.r. spectra which would indicate ring closure *ortho* to oxygen functions rather

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(2) Abstracted in part from the M.S. Theses of D. P. W., University of Connecticut, 1964, and J. M. K., University of Connecticut, 1963.

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(6) W. D. Burrows and E. P. Burrows, *J. Org. Chem.*, **28**, 1180 (1963). This paper also contains a literature survey of a number of similar reactions.

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 268.

than the *para* as indicated. Since yields were not quantitative, however, such reactions cannot be ruled out.

Experimental[8]

4-Benzyl-6-hydroxy-7-methoxyisoquinoline (4).—Vanillin (3.04 g., 0.02 mole) was dissolved in a minimum amount of absolute ethanol, combined with 2.66 g. (0.02 mole) of aminoacetaldehyde diethylacetal, diluted to 15 ml. with absolute ethanol and hydrogenated at atmospheric pressure[9] and room temperature over 200 mg. of previously reduced platinum oxide. Hydrogen consumption stopped at about 90% completion after about 3 hr. The catalyst was removed by filtration and the solvent was evaporated under vacuum. The residual oil was dissolved in 50 ml. of concentrated hydrochloric acid. The solution which had become hot was cooled and washed with three 30-ml. portions of 3:2 ether–benzene to remove starting aldehyde. A twofold excess of benzaldehyde (4.24 g., 0.04 mole) dissolved in 50 ml. of ethanol was added to the acidic solution which was subsequently boiled for 30 min. The cooled solution was diluted with an equal volume of water and washed with three 50-ml. portions of ether to remove the excess benzaldehyde. The solution was made basic with ammonium hydroxide to pH 8. The precipitate was removed by filtration and crystallized once from water–ethanol to give 3.33 g. of product, m.p. 185–190°, 63%. The analytical sample, m.p. 192–193°, was recrystallized three more times and dried.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.94; H, 5.91; N, 5.49.

A **picrate** was prepared in ethanol and recrystallized twice from the same solvent to give the analytical sample, m.p. 235–238°.

Anal. Calcd. for $C_{23}H_{18}N_4O_9$: C, 55.87; H, 3.67; N, 11.33. Found: C, 55.64; H, 3.81; N, 11.59.

4-Benzyl-7-hydroxy-6-methoxyisoquinoline (5).—These reactions were carried out exactly like those leading to **4**. The starting material was isovanillin. The crude product, m.p. 200–205°, amounted to 2.88 g., 54%. The analytical sample, m.p. 207–209°, was recrystallized four times from water–ethanol.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.61; H, 5.79; N, 5.25.

A **picrate** was prepared in ethanol–benzene and recrystallized three times from the same solvents to give an analytical sample, m.p. 204–206°.

Anal. Calcd. for $C_{23}H_{18}N_4O_9$: C, 55.87; H, 3.67; N, 11.33. Found: C, 56.08; H, 3.69; N, 11.38.

4-Benzyl-8-hydroxy-7-methoxyisoquinoline (6).—The reduction and acid treatment steps were the same as those described above leading to **4**. The starting material was *o*-vanillin. When the acid–benzaldehyde–isoquinoline mixture was cooled (to 5°), however, the product precipitated as a hydrochloride salt and was removed by filtration. It amounted to 3.68 g., m.p. 204–207°, 61%. The analytical sample, m.p. 207–209°, was recrystallized three times from 6 *N* hydrochloric acid.

Anal. Calcd. for $C_{17}H_{16}ClNO_3$: C, 67.73; H, 5.33; Cl, 11.77; N, 4.64. Found: C, 67.45; H, 5.57; Cl, 11.61; N, 4.78.

The **free base** was prepared by passing an ethanolic solution of the hydrochloride over a column of 50 g. of basic alumina (Woelm). The main fraction of the eluate was yellow and gave, on evaporation, the free base. The analytical sample, m.p. 220–222°, was recrystallized three times from acetone–water.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.86; H, 5.85; N, 5.21.

A **picrate** was prepared from the hydrochloride by neutralization of an aqueous solution, filtration of the solid base, and final salt formation in ethanol. The analytical sample, m.p. 220–223°, was recrystallized three times from acetone–ethanol.

Anal. Calcd. for $C_{23}H_{18}N_4O_9$: C, 55.87; H, 3.67; N, 11.33. Found: C, 56.03; H, 3.77; N, 11.24.

(8) Melting points were recorded on a Kofler hot stage microscope and are corrected. The n.m.r. spectra were measured on a Varian A-60 instrument. The microanalyses were performed by Mr. H. Fröhofer of the Organic Chemistry Institute, University of Zürich, Zürich, Switzerland.

(9) Pressures up to 10 p.s.i. or so were safe, but decomposition sometimes occurred at higher pressures.

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Absence of Direct Participation of *sec*-Butyl Chloride in Acetolysis of Isopropyl *p*-Nitrobenzenesulfonate

DOUGLAS E. APPLEQUIST AND GILBERT W. BURTON

Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61803

Received March 4, 1965

The nucleophilic character of covalent organohalogen compounds is strongly suggested both by the existence of stable diarylhalonium salts[1] and by the commonplace neighboring-group participation by halogen in carbonium ion reactions, both from the β position[2] and from greater distances.[3] There are nevertheless still no reports of stable dialkylhalonium ions, nor is there definitive evidence for intermolecular participation by an alkyl halide in a carbonium ion reaction. This Note reports an attempt to detect such participation in one system, chosen as fairly typical and easy to deal with experimentally, and not necessarily the optimum case for dialkylhalonium ion formation.

When isopropyl nosylate was solvolyzed in a 12:1 mixture (mole ratio) of *sec*-butyl chloride and acetic acid at 95°, the initial products were isopropyl acetate and propene, and only secondarily did other products (*sec*-butyl acetate, isopropyl chloride, and butenes) appear. Thus from 1.85 mmoles of nosylate after various reaction times were observed the product distributions shown in Table I.

TABLE I

SOLVOLYSIS PRODUCTS FROM 1.85 MMOLES OF ISOPROPYL NOSYLATE

	Products, mmoles[a]				
Time, hr.	Propene	*i*-PrOAc	*i*-PrCl	*sec*-BuOAc	Butenes
0.5	0.025	0.031	...	...	...
3	0.23	0.80	0.05	0.009	0.054
6	0.09	1.12	0.18	0.08	0.11
12	0.06	0.98	0.42	0.23	0.21

[a] The numbers are averages of several runs at each time. The scatter in the data[7] indicates precisions of 5–10% for the saturated products and 10–30% for the volatile olefins.

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(3) (a) P. E. Peterson and J. E. Duddey, *ibid.*, **85**, 2865 (1963); (b) P. E. Peterson and G. Allen, *ibid.*, **85**, 3608 (1963); (c) R. E. Glick, Ph.D. Thesis, University of California at Los Angeles, 1954.