react at 600°,[14] is good evidence for the high reactivity of sulfur lost from the benzyne–thiophene 1,4 adduct I. The formation of thiols in the reactions of other arynes with thiophene and benzothiophene is being investigated; in addition, we are looking at the reactions of other arynes generated by pyrolysis of aromatic anhydrides with sulfur, carbon disulfide, and S-containing heterocyclic compounds other than thiophene.

Experimental Section

Reaction of Phthalic Anhydride with Thiophene.—A filtered solution of 14.8 g (0.1 mol) of phthalic anhydride in 78.65 ml (1 mole) of thiophene was pyrolyzed at 690° in a Vycor tube filled with Vycor chips in a stream of dry nitrogen flowing at 20 cc/min. The pyrolysate was distilled to recover 67.5 ml of thiophene and obtain 12.15 g of residue.

A solution of the residue in 200 ml of ether was extracted with two 50-ml portions of 10% aqueous potassium hydroxide; the acidified aqueous extract was extracted with three 50-ml portions of ether. The dried ether solution, evaporated on the steam bath, gave 1.6 g of a light yellow semisolid mixture of thiols.

Reaction of Sulfur with Thiophene.—A mixture of 3.2 g (0.1 g-atom) of sulfur and 31.46 ml (0.4 mol) of thiophene was refluxed for 18 hr, by which time all of the sulfur was in solution. Although a small amount of hydrogen sulfide evolved during the refluxing, there had been no appreciable reaction; both sulfur and thiophene were recovered unchanged in a separate experiment. The thiophene solution was pyrolyzed and the thiols were worked up as described in the phthalic anhydride reaction. Yield of mixed thiols was 0.25 g.

Phthalic anhydride-d_4 was made by oxidation of naphthalene-d_8 with potassium permanganate.

Analysis.—Mass spectral analyses were performed on a Consolidated Model 21-103c instrument with the inlet system at 250°. The usual 70-V spectrum was supplemented by a low-voltage (7.5 ionizing V, uncorrected) spectrum to help identify parent peaks.

Gas chromatographic analyses were performed on a stainless steel column 6 ft long and 0.25-in. o.d., packed with 10% diethylene glycol sebacate on 30–60 mesh acid-washed Chromosorb W. The column temperature was programmed from 70 to 200° at 2°/min; helium flow was 50 cc/min. Temperature of the injector was 240°; that of the thermal conductivity cell was 300°.

Directly coupled gas chromatography–mass spectrometry is described in ref 8.

Registry No.—Thiophene, 110-02-1; benzyne, 462-80-6.

[14] H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p 61.

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

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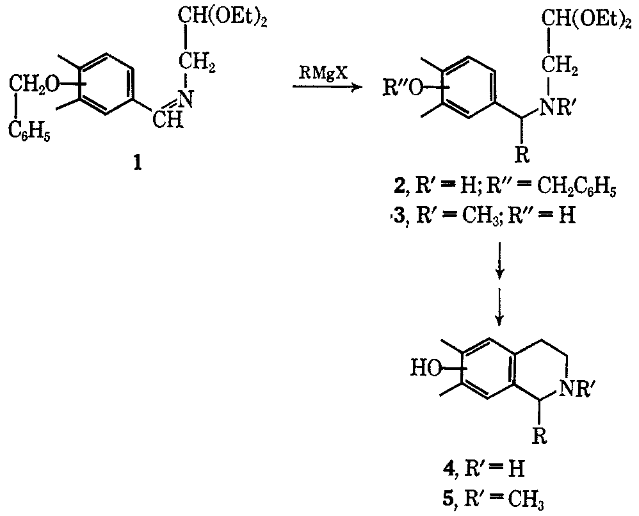
In recent years, we have developed some facile syntheses of various oxygenated isoquinolines.[3] In connection with our work on the oxidative coupling of phenolic isoquinolines,[4,5] we required a series of 1-alkyl-N-methyl-1,2,3,4-tetrahydroisoquinolines. In this paper, we would like to describe a general synthesis of these compounds.[6] The reactions are shown in Scheme I.

Scheme I



This route for the preparation of 1-alkylisoquinolines was originally developed by Quelet and Vinot.[7] However, their method involved the use of boron trifluoride as a cyclizing agent. This was found to be generally unsuitable for the preparation of oxygenated isoquinolines, and thus, for the various cactus alkaloids.[8] Vanillin and isovanillin were benzylated[9] (75–85% yield) and allowed to react with aminoacetaldehyde diethyl acetal to yield the Schiff bases **1** (95% yield). Veratraldehyde was converted directly to the Schiff base. The Schiff bases were allowed to react with various aliphatic Grignard reagents to yield the amines (**2**, R = CH_3, CH_3CH_2, and $CH_3CHCH_3CH_2$). At this point, there were two alternatives. Compounds **2** could be debenzylated (H_2-Pd/C), hydrolyzed, and cyclized (HCl), and reduced to give 1-alkyl-1,2,3,4-tetrahydroisoquinolines (**4**, Table I).[10] Second, compounds **2** could be debenzylated, N-methylated (HCHO, H_2, Pt) to **3**, hydrolyzed, cyclized, and reduced to yield 1-alkyl-N-methyl-1,2,3,4-tetrahydroisoquinolines (**5**, Table II).[11]

Several alkaloids were prepared in this work. These are salsoline (**6**),[8] salsolidine (**8**),[8] carnegine (**13**),[8] and lophocerine (**16**).[12]

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[1] (a) Paper IX. M. Bobbitt and C. P. Dutta, *J. Org. Chem.*, **34**, 2001 (1969). (b) This work was sponsored, in part, by Training Grant GM-1139 from the National Institutes of Health.

[2] Abstracted in part from the Ph.D. Dissertations of A. S. S. (University of Connecticut, 1968) and K. H. W. (University of Connecticut, 1969).

[3] See ref 1 and the preceding papers of this series.

[4] J. M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Lett.*, 575 (1963).

[5] J. M. Bobbitt, J. T. Stock, A. Marchand, and K. H. Weisgraber, *Chem. Ind.* (London), 2127 (1966).

[6] This work was partially reported at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

[7] N. Vinot, *Ann. Chim.* (Paris), [13] **3**, 461 (1958); N. Vinot and R. Quelet, *Bull. Soc. Chim. Fr.*, 1164 (1959).

[8] These compounds have been previously synthesized, generally by more laborious routes. The work is summarized by L. Reti in "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1954, p 7.

[9] R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

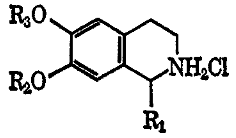
[10] J. M. Bobbitt, J. M. Kiely, K. W. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1963).

[11] J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *ibid.*, **32**, 2225 (1967).

[12] J. M. Bobbitt and T.-t. Chou, *ibid.*, **24**, 1106 (1959).

TABLE I

1-ALKYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES

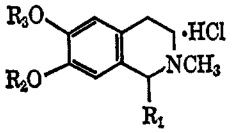


Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Lit. mp, °C
6	CH_3	CH_3	H	65	200	200–202[b]
7	CH_3	H	CH_3	83	236–237	237–238[c]
8	CH_3	CH_3	CH_3	66	189–191	196–197[d]
9	C_2H_5	CH_3	H	68	190–191	186–188[e]
10[f]	C_2H_5	H	CH_3	81	218–220	

[a] The yields are based upon the starting Schiff bases **1**. [b] N. Proskurnina and A. Orekhoff, *Bull. Soc. Chim. Fr.*, [5] **4**, 1265 (1937). The literature contains melting points for this compound ranging from 145 to 220°. [c] H. Bruderer and A. Brossi, *Helv. Chem. Acta*, **48**, 1945 (1965). [d] E. Späth and F. Dengel, *Ber.*, **71**, 113 (1938). [e] D. Beke and C. Szántay, *Magy. Kém. Folyóirat*, **60**, 346 (1954); *Chem. Abstr.*, **52**, 4648 (1958). [f] *Anal.* Calcd: C, 59.09; H, 7.39; N, 5.74. Found: C, 59.06; H, 7.52; N, 5.93.

TABLE II

1-ALKYL-N-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES



Compd	R_1	R_2	R_3	Yield,[a] %	Mp, °C	Lit. mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	CH_3	CH_3	H	28	253–255		59.13	7.39	5.74	58.51	7.22	6.07
12	CH_3	H	CH_3	62	195–198	190–192[b]						
13	CH_3	CH_3	CH_3	62	209–210	210–211[c]						
14	C_2H_5	H	CH_3	51	174–178		60.56	7.82	5.43	60.28	7.84	5.49
15	C_2H_5	CH_3	H	30	260		60.56	7.82	5.43	59.95	7.44	5.74
16	$CH_3CHCH_3CH_2$	H	CH_3	45	186–187 (picrate)	191–193[d]						

[a] The yields are based upon the starting Schiff bases **1**. [b] J. T. Strukov, *Zh. Obshch. Khim.*, **31**, 2709 (1961); *Chem. Abstr.*, **56**, 11567 (1962). [c] E. Späth, *Ber.*, **62**, 1021 (1929). [d] Reference 12.

Experimental Section[13]

Benzylation of Phenolic Aldehydes.—The aldehyde (0.5 mol) was dissolved in 250 ml of absolute ethanol and added to a mixture of benzyl chloride (83 g, 0.66 mol) and K_2CO_3 (72 g, 0.52 mol) in 200 ml of absolute ethanol. The solution was heated to reflux for 15 hr with stirring. Activated carbon (5 g) and 100 ml more of ethanol were added and the mixture was heated for 0.5 hr more and filtered hot. The products precipitated when the filtrate was cooled and were collected by filtration. Benzylvanillin melted at 61–62°, lit.[9] 64–65°, and benzylisovanillin melted at 63–65°, lit.[14] 63°.

The Schiff Bases 1.—The aromatic aldehydes (0.1 mol) were dissolved in 100 ml of benzene, combined with 13.3 g (0.1 mol) of aminoacetaldehyde diethyl acetal, and allowed to stand overnight. The solution was heated to reflux under a Dean–Stark tube for 2 hr or until all of the water had collected. The benzene was removed on a rotary evaporator and the products were crystallized from hexane. The base from veratraldehyde melted at 60–62°, lit.[15] 61–63°.

The base from benzylvanillin melted at 34°.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.45; H, 7.61; N, 3.95.

The base from benzylisovanillin melted at 70–71°.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.23; H, 7.72; N, 4.15.

Grignard Synthesis of 2.—Commercial Grignard reagent[16] (0.06 mol) was diluted with 200 ml of dry ether in an anhydrous system. The reaction mixture was cooled to 0° and stirred, and a solution of 0.02 mol of Schiff base **1** in 100 ml of dry ether was added slowly (0.5 hr). The mixture was stirred at reflux temperature until tlc showed the absence of starting material[17] (18–24 hr). The reaction was cooled to 0° and hydrolyzed with NH_4Cl (9 g in 25 ml of H_2O). The mixture was heated to reflux for 1 hr, cooled, and separated. The aqueous layer was extracted twice with ether and the combined ether layer and extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to a thick oil **2** on a rotary evaporator.

The benzyl compounds were debenzylated by dissolving them in 30 ml of ethanol and hydrogenating them over 3.5 g of 5% Pd on C. The catalyst was removed by filtration and the solvent was evaporated on a rotary evaporator to yield oily products.

1-Alkyl-1,2,3,4-tetrahydroisoquinolines (4).—The appropriate benzylamino acetals (from 0.02-mol runs) obtained from debenzylation were dissolved in 50 ml of 4 *N* HCl, extracted twice with ether-benzene, and allowed to stand for 14–18 hr. The last traces of the organic solvents were removed on a rotary evaporator, and the acid solutions were hydrogenated over 3.5 g of 5% Pd on C. The catalyst was removed by filtration and the solvent was evaporated on a rotary evaporator (below 50°). The residue was dissolved in 50 ml of absolute ethanol and again evaporated. The process was repeated two or three times until the products crystallized. The products were collected and recrystallized from ethanol.

1-Alkyl-N-methyl-1,2,3,4-tetrahydroisoquinolines (5).—The appropriate benzylamino acetals (from 0.02-mol runs) obtained from debenzylation were dissolved in 30 ml of ethanol, mixed with 1.6 ml of acetic acid and 1.5 g of 37% formaldehyde solution, and hydrogenated over 0.3 g of prereduced platinum oxide. The catalyst was filtered and the solvent was removed on a rotary evaporator to yield oily N-methylbenzylamino acetals. These were cyclized in 4 *N* HCl and reduced as described above for **4**.

Registry No.—**10**, 19886-92-1; **11**, 19072-60-7; **14**, 19886-94-3; **15**, 19922-52-2; base from benzylvanillin, 19886-95-4; base from benzylisovanillin, 19922-53-3.

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[13] Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. Microanalyses were performed by the Baron Consulting Co., Orange, Conn. Tlc was carried out on silica gel GF-254 layers and visualized under uv light at 254 mμ.

[14] A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930).

[15] R. Forsyth, C. I. Kelly, and F. L. Pyman, *ibid.*, **127**, 1659 (1925).

[16] Methylmagnesium bromide and ethylmagnesium bromide was from the Arapahoe Chemical Co., Boulder, Colo. Isobutyl Grignard reagent was prepared in ether from isobutyl bromide and Mg.

[17] Small samples were removed and hydrolyzed with a few drops of water. The ether layer was spotted and the chromatograms were developed with benzene–methanol, 20:1.