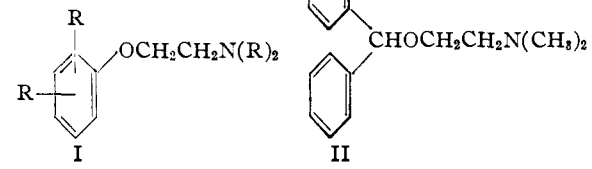
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Pyridyl-aryloxy Alkamine Ethers as Histamine Antagonists[1]

BY DOMENICK PAPA, NATHAN SPERBER AND MARGARET SHERLOCK

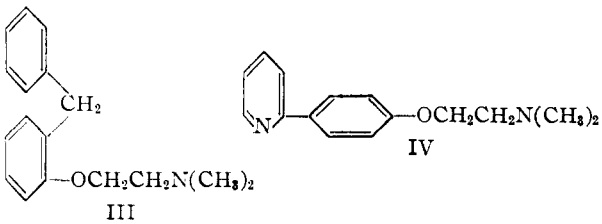
The ortho, meta and/or para dimethylaminoethoxy derivatives of 2-phenylpyridine, 2-benzylpyridine, 2-styrylpyridine and 4-phenethylpyridine have been prepared by the condensation with sodamide of β-dimethylaminoethyl chloride and the respective hydroxy compounds. Only the alkamine ethers of 2-benzylpyridine show a high order of antihistaminic activity in guinea pigs.

Although phenolic alkamine ethers (I) were the first synthetic compounds[2] to exhibit protective action against the toxic effects of histamine in guinea pigs, these substances as a class were unsuitable for clinical application because of toxicity and untoward reactions. The first alkamine ether which met with general clinical acceptance was β-dimethylaminoethylbenzhydryl ether (II),[3] this

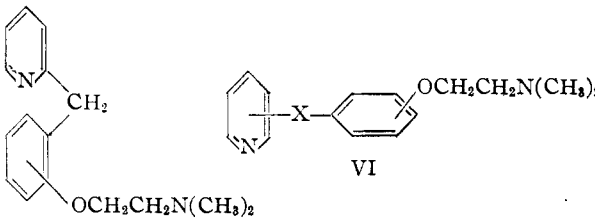


I II

R = lower alkyl groups



III IV



V VI

X = —CH=CH—; —CH_2—CH_2—

ether differing from the phenolic ethers of Fourneau in: (a) having a second phenyl group; and (b) the relative position of the β-dimethylaminoethoxy moiety. In I, this group is attached directly to the benzene ring; whereas, in II, the alkamine ether residue has been shifted to an aliphatic carbon atom. Recently there has been described[4] a series of compounds which can be viewed as intermediate in structure between I and II. In the most active compound of this series, III, the original position of the β-dimethylaminoethoxy radical was retained and the second phenyl group was introduced as an ortho benzyl radical. It has been reported[4b] that III shows greater antihistaminic potency in guinea pigs than II.

In continuation of our studies on antihistaminic agents,[5] we have prepared a number of alkamine ethers of homologous compounds of formulas IV, V[6] and VI. Only one or two members of each type was synthesized, since our primary interest in this investigation was to examine the pharmacological spectra of these configurations.

Of the substituted phenylpyridines (IV), only the 2-(*p*-dimethylaminoethoxyphenyl)-pyridine was prepared. *p*-Methoxyphenyllithium and pyridine,[7] yielded 2-(*p*-methoxyphenyl)-pyridine, which was demethylated and the resulting hydroxy compound converted to the alkamine ether with sodamide and β-dimethylaminoethyl chloride. The ethers of formulas V and VI were prepared by similar alkylation of the 2-(*o*- and *p*-hydroxybenzyl)-pyridines and the hydroxystilbazoles and dihydro derivatives, respectively.

Pharmacology.—The compounds were tested by the standard procedure previously described.[5c] Only the ethers of general formula V exhibited pronounced antihistaminic activity comparable to that of the presently available clinical drugs of the alkamine ether type.

Experimental

(1) **2-(*o*-Dimethylaminoethoxybenzyl) pyridine.**—To a stirred suspension of sodium amide (2 g. of sodium) in 150 ml. of dry xylene, there was added 7 g. (0.038 mole) of 2-(*o*-hydroxybenzyl)-pyridine.[8] After heating for 1 hour on the steam-bath, 14 g. (0.13 mole) of β-dimethylaminoethyl chloride was added and the resulting mixture heated and stirred for about 10 hours. The alkamine ether was isolated by adding water to the alkaline solution and separating the organic layer. After removing the xylene, the residue was distilled; yield 7.7 g. (80%), b.p. 156–164° (1.5 mm.), $n^{28}D$ 1.5450. The analytical sample was taken at 161° (1.5 mm.), $n^{28}D$ 1.5440; literature,[6] b.p. 142–144° (0.2 mm.).

Anal. Calcd. for $C_{16}H_{20}N_2O$: N, 10.93. Found: N, 11.26.

(2) **2-(*p*-Dimethylaminoethoxybenzyl)-pyridine.**—2-(*p*-Hydroxybenzyl)-pyridine[8] was converted to the ether by the procedure for the ortho isomer; yield 80%, b.p. 148–

(1) Presented in abstract before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Sept. 6, 1950.

(2) Fourneau and Bovet, *Arch. internat. pharmacodynamie*, **46**, 178 (1933); Bovet and Staub, *Compt. rend. soc. biol.*, **124**, 547 (1937).

(3) Loew, Kaiser and Moore, *J. Pharmacol. Exptl. Therap.*, **83**, 120 (1945); Rieveschl, U. S. Patent 2,421,714 (1947).

(4) (a) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949); (b) Wheatley, Cheney and Binkley, *ibid.*, **71**, 64, 3795 (1949).

(5) For previous papers from this Laboratory on antihistaminic agents, see: (a) Sperber, Papa, Schwenk, Sherlock and Fricano, Abs. 113th Meeting of the Amer. Chem. Soc., pg. 4K, April 20, 1948; (b) Sperber and Papa, THIS JOURNAL, **71**, 886 (1949); (c) Sperber, Papa, Schwenk and Sherlock, *ibid.*, **71**, 887 (1949), and (d) Villani, Sperber, Lang and Papa, *ibid.*, **72**, 2724 (1950).

(6) In a recent paper, Morel and Stoll, *Helv. Chim. Acta*, **33**, 516 (1950), have described the synthesis of 2-(*o*-dimethylaminoethoxybenzyl)-pyridine.

(7) "Organic Syntheses," Coll. Vol. II, p. 517.

(8) 2-(*o*-Hydroxybenzyl)-pyridine and 2-(*p*-hydroxybenzyl)-pyridine were prepared by the conversion of the corresponding *o*- and *p*-methoxyphenyl-2-pyridyl carbinols[5c] to the chlorides with thionyl chloride, followed by the reductive replacement of the halogen with zinc and acetic acid. The chemistry of a series of substituted 2-benzylpyridines will appear shortly in another publication.

151° (1 mm.), $n^{26}D$ 1.5531. The analytical sample was taken at 149° (1 mm.), $n^{25}D$ 1.5536.

Anal. Calcd. for $C_{16}H_{20}N_2O$: N, 10.93. Found: N, 11.16.

(3) **2-(*p*-Dimethylaminoethoxyphenyl)-pyridine.**—(a) 2-(*p*-Methoxyphenyl)-pyridine was prepared in 50% yield by the reaction of *p*-methoxyphenyllithium[9] and pyridine in xylene, essentially as described for 2-(phenyl)-pyridine[7]; b.p. 127–130° (0.5 mm.), m.p. 53–54° after recrystallization from benzene–petroleum ether, literature,[10] m.p. 49–50°.

Anal. Calcd. for $C_{12}H_{11}NO$: N, 7.57. Found: N, 7.67.

(b) **2-(*p*-Hydroxyphenyl)-pyridine.**—A solution of 8 g. of 2-(*p*-methoxyphenyl)-pyridine, 25 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid was refluxed for 20 hours. The mixture was poured on ice, made alkaline with sodium hydroxide solution and, after ether extraction, was neutralized carefully with dilute hydrochloric acid. A tan solid precipitated; m.p. 148–153°. After recrystallization from benzene, the hydroxy compound was obtained as a white crystalline solid; yield 5 g. (68%), m.p. 164–165°.

Anal. Calcd. for $C_{11}H_9NO$: N, 8.18. Found: N, 8.47.

(c) **The 2-(*p*-dimethylaminoethoxyphenyl)-pyridine** was prepared by treating 16 g. (0.093 mole) of 2-(*p*-hydroxyphenyl)-pyridine, 14 g. (0.13 mole) of dimethylaminoethyl chloride and sodamide (3 g. of sodium) in 200 cc. of xylene as described previously; yield 13 g. (58%), b.p. 176–180° (2 mm.). The oil solidified and was recrystallized from benzene–petroleum ether, m.p. 52–53°.

Anal. Calcd. for $C_{15}H_{16}N_2O$: N, 11.56. Found: N, 11.26.

(4) **2-(*p*-Dimethylaminoethoxystyryl)-pyridine.**—This ether was obtained in a yield of 88% by the reaction of *p*-hydroxy-α-stilbazole[11] with sodamide and β-dimethylaminoethyl chloride in xylene, b.p. 182–192° (1 mm.), m.p. 70–71°, from benzene–petroleum ether.

Anal. Calcd. for $C_{17}H_{20}N_2O$: N, 10.44. Found: N, 10.67.

(5) **2-(*m*-Dimethylaminoethoxystyryl)-pyridine.**—*m*-Hydroxy-α-stilbazole was prepared according to the procedure described for the para isomer[11]; yield 20%, m.p. 137–138°.

Anal. Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 7.32.

The alkamine ether was prepared in the manner described for the para compound and was obtained as a yellow oil; yield 43%, b.p. 182–186° (1 mm.).

Anal. Calcd. for $C_{17}H_{20}N_2O$: N, 10.44. Found: N, 10.01.

(6) **4-(*o*-Dimethylaminoethoxy-β-phenethyl)-pyridine.**—*o*-Hydroxydihydro-γ-stilbazole was converted to the corresponding alkamine ether as described; yield 85%, b.p. 160–164° (1 mm.).

Anal. Calcd. for $C_{17}H_{22}N_2O$: N, 10.36. Found: N, 10.42.

(9) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

(10) Haworth, Heilbron and Hey (*J. Chem. Soc.*, 358 (1940)) obtained 2-(*p*-methoxyphenyl)-pyridine by the fractional crystallization of the mixed picrates of 2- and 4-(*p*-methoxyphenyl)-pyridines, the latter being obtained by the action of diazotized *p*-anisidine on pyridine.

(11) Chiang and Hartung, *J. Org. Chem.*, **10**, 21 (1945).

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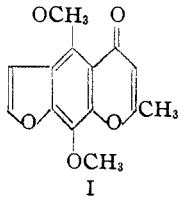
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA]

Chromones. III. A Total Synthesis of Khellin[1]

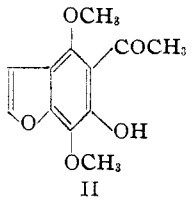
BY T. A. GEISSMAN AND T. G. HALSALL[2]

Interest in the chemistry of khellin (I) and of the related chromones which accompany it in the seeds of the umbelliferous plant *Ammi visnaga* has been heightened by the reports of the ability of khellin to produced a sustained coronary vasodilatation and to be effective in the clinical treatment of the anginal syndrome.[3] Preliminary studies indicate that the drug may be of potential usefulness in the treatment of other kinds of smooth muscle spasm.[4]

The structure of khellin has been elucidated by degradative methods by Späth and Gruber,[5] who also accomplished its partial synthesis by reconstruction of the chromone ring starting from khellinone (II), its alkaline degradation product.



I



II

Because Späth and Gruber's resynthesis was not entirely unequivocal, the synthesis of khellin from khellinone was carried out by another method which established its structure as that of a 2-methylchromone.[1]

Although these results seemed to establish conclusively the structure of khellin, it appeared desirable to effect its total synthesis, partly to determine whether it might be prepared synthetically more advantageously than it could be isolated from the natural source, and partly to explore the synthetic methods with a view to the preparation of analogs. A study of the dependence of coronary activity upon structure should prove to be of considerable interest because of the nearly unique position of khellin in being a non-nitrogenous spasmolytic agent.

While the present work was in progress three reports[6,7,8] of the synthesis of khellin appeared from other laboratories. While all of these confirmed the structure I adopted for khellin, none appeared to have the potential utility as preparative routes as the method developed in this Laboratory, although the syntheses of Baxter, *et al.*, and Clarke and Robertson bear a similarity to ours in that all three proceed to khellinone by way of 2,5-dimethoxyresorcinol.[9] The elegant synthesis of Murti

(1) For the second paper in this series see Geissman and Hinreiner, THIS JOURNAL, **73**, 782 (1951).

(2) Visiting Fellow, 1949, from the University of Manchester, Manchester, England.

(3) For references to the clinical and pharmacological literature, see Anrep, Barsoum and Kenawy, *Amer. Heart. J.*, **37**, 531 (1949); Osher and Katz, *Boston Med. Quart.*, **1**, 11 (1950).

(4) Rosenman, Fishman, Kaplan, Levin and Katz, *J. Am. Med. Assoc.*, **143**, 160 (1950).

(5) Späth and Gruber, *Ber.*, **71B**, 106 (1938).

(6) Baxter, Ramage and Timson, *J. Chem. Soc.*, S30 (1949).

(7) Clarke and Rohertson, *ibid.*, 302 (1949).

(8) Murti and Seshadri, *Proc. Indian Acad. Sci.*, **30**, 107 (1949).

(9) Baker, Nodzu and Robinson, *J. Chem. Soc.*, 74 (1929).