[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

SYNTHESIS OF SOME NEW 2-ARYLOXY AND 2-ALKYLOXY PYRIDINES

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Antispasmodic activity of the type exhibited by papaverine and atropine has been demonstrated for a wide variety of materials, with no evidence that such activity is limited to specific structures or configurations. Isoquinoline derivatives, aryl and alkyl amines, and innumerable derivatives of acetic acid have been described as spasmolytic agents.[3]

Studies relating to pyridine compounds as antispasmodics are of recent origin. Winterfeld and Holschneider (1) first indicated possible utility in the pyridine series when they reported on a group of α-pyridyl ketones; one of their materials, α-pyridyl γ-aminopropyl ketone, was said to be active on isolated guinea pig uterus in dilutions of 1:100,000. Krohnke (2) prepared a series of pyridinium 2-ethanols of the type $C_5H_5N(CH_2CHOHR)^+Br^-$ some of which exhibited activity resembling that of papaverine. Amides of the pyridine carboxylic acids have also been investigated (3). Coates and co-workers (4) in their investigation of therapeutic agents of the quinoline series noted that various α-, β-, and γ-pyridylquinolines exhibited some antispasmodic action. Subsequent to the completion of the present study antispasmodic activity was reported for benzyl derivatives of α-aminopyridine (5), and for esters of diphenylacetic acid with some pyridyl alkanols (6). In the latter group 1-(α-pyridyl)-2-ethyl diphenylacetate hydrochloride exhibited 1/16 the activity of atropine.

This investigation was undertaken for the purpose of introducing the α-pyridyl group into compounds so constituted that the final products arising from the syntheses would presumably be physiologically active, particularly antispasmodic or antihistaminic in their action. Ethers of 2-hydroxypyridine were selected as the type of compound to be investigated because they possess the therapeutically important iminoester configuration, $ROC(=N)-$, and because the synthesis of such materials was made attractive by the availability of 2-bromopyridine (7, 8). Had the notable antihistaminic properties of the basic ethers of benzhydrol (9) and of α-methyl-α-phenyl-2-pyridinemethanol (10) been known when this project was initiated, there would have been an even more cogent reason for conducting the investigation.

Simple ethers of 2-hydroxypyridine have been described from time to time and

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[3] For a comprehensive review of the subject see Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

2-pyridyl ethers of certain amino alcohols were the subject of patents (11, 12). The only pharmacological investigation of such materials was that of Renshaw and Conn (13) in which a series of 2-pyridyl aryl ethers was synthesized and examined for acetylcholine activity. More recently ethers of 2-hydroxy-5-aminopyridine have been described as tuberculostatic agents (14).

The pyridyl ethers obtained directly from 2-bromopyridine are shown in Table I. Ethers of the simple phenols were readily prepared according to the method of Renshaw and Conn (13) by heating 2-bromopyridine and the phenol

TABLE I

2-PYRIDYL ETHERS

R IN  —OR	B.P./MM.	M.P.[a]	n_D^t	METHOD OF PREPARATION	% YIELD	ANALYSIS, % N	
						CALC'D	FOUND
o-$C_6H_4OCH_3$		91–92		A	71	6.97	7.06
m-$C_6H_4OCH_3$	133–135/1		1.5805^{24}	A	82	6.97	6.96
p-$C_6H_4OCH_3$	152–153/3	42–43		A	82	6.97	6.91
p-$C_6H_4OC_2H_5$	110–111/0.14	45–45.5		A	47	6.51	6.80
p-$C_6H_4OCH_2C_6H_5$		72.5–73		A	43	5.05	5.24
p-C_6H_4Br	122–123/1		1.6072^{23}	B	18	5.60	5.38
$CH(C_6H_5)_2$		57–58		B	53	5.36	5.31
$CH_2C_6H_3(OCH_3)_2$-(3′,4′)		58–59		B	23	5.71	5.74
o-$C_6H_4COOCH_3$		67–68		B	52	6.11	6.03
o-C_6H_4COOH		117–118		[b]	85	6.51	6.48
m-$C_6H_4COOC_2H_5$	143–144/1		1.5614^{25}	A	56	5.76	5.96
m-C_6H_4COOH		125–126		[b]	90	6.51	6.28
p-$C_6H_4COOC_2H_5$		64–65		A	32	5.76	5.85
p-C_6H_4COOH		174		[b]	80	6.51	[c]
$C_{10}H_6COOC_2H_5$(2′,3′)		96–97		B	38	4.78	4.71
$C_{10}H_6COOH$(2′,3′)		149–150		[b]	75	5.28	5.20
$CH_2COOC_2H_5$	83–84/0.5		1.4970^{20}	C	26	7.73	7.50
$CH(CH_3)COOC_2H_5$	113–115/8		1.4901^{23}	C	24	7.18	6.97
$CH(C_6H_5)COOC_2H_5$	135–137/1		1.5515^{18}	C	28	5.45	5.40
$CH(C_6H_5)COOH$		115		[b]	74	6.11	6.20

[a] Corrected.

[b] By saponification of the ester with 10% alcoholic potassium hydroxide.

[c] Neutral equivalent: Calc'd, 216; Found, 215.

in the presence of anhydrous potassium carbonate (Method A). This procedure was also suitable for the preparation of ethers of ethyl *meta*-hydroxybenzoate and ethyl *para*-hydroxybenzoate, but it failed when applied to methyl salicylate and gave a negligible yield with ethyl 2-hydroxy-3-naphthoate. Ethers of these compounds were successfully prepared by heating the appropriate dry sodium phenoxide with 2-bromopyridine in the presence of a catalytic quantity of copper powder (Method B).

In this connection the salutary effect of copper powder should be mentioned. The catalytic action of this substance was particularly notable in the reaction of 2-bromopyridine with the sodium alkoxide of veratryl alcohol; in the absence

TABLE II

PROPERTIES OF AMINOESTERS AND HYDROCHLORIDES

COMPOUND[a]	B.P./MM.	n_D^t	ANALYSIS, % N		M.P. OF HCL'D[b]
			CALC'D	FOUND	
o-$(C_5H_4N)OC_6H_4COOCH_2CH_2N(C_2H_5)_2$	170–171/1	1.5361^{25}	8.91	8.85	[c]
o-$(C_5H_4N)OC_6H_4COOCH_2CH_2CH_2N(C_2H_5)_2$	179–180/1	1.5364^{25}	8.53	8.49	[c]
m-$(C_5H_4N)OC_6H_4COOCH_2CH_2N(C_2H_5)_2$	169–170/1	1.5200^{27}	8.91	8.91	110–112
m-$(C_5H_4N)OC_6H_4COOCH_2CH_2CH_2N(C_2H_5)_2$	174–175/1	1.5373^{22}	8.53	8.23	129–130
p-$(C_5H_4N)OC_6H_4COOCH_2CH_2N(C_2H_5)_2$	184.5–185.5/1	1.5383^{28}	8.91	8.96	141–142
p-$(C_5H_4N)OC_6H_4COOCH_2CH_2CH_2N(C_2H_5)_2$	187–189/1	1.5353^{28}	8.53	8.48	161–164
2-$(C_5H_4N)OC_{10}H_6$-3-$COOCH_2CH_2N(C_2H_5)_2\cdot HCl$			6.99	6.95	139–140
2-$(C_5H_4N)OC_{10}H_6$-3-$COOCH_2CH_2CH_2N(C_2H_5)_2\cdot HCl$			6.75	6.99	150–151
$(C_5H_4N)OCH_2COOCH_2CH_2N(C_2H_5)_2$	103–105/0.14	1.4940^{20}	11.11	11.60	94–96[d]
$(C_5H_4N)OCH_2COOCH_2CH_2CH_2N(C_2H_5)_2$	114–115/0.2	1.4919^{20}	10.52	10.60	[c]
$(C_5H_4N)OCH(CH_3)COOCH_2CH_2N(C_2H_5)_2$	121–123/1	1.4892^{22}	10.53	10.37	[c]
$(C_5H_4N)OCH(CH_3)COOCH_2CH_2CH_2N(C_2H_5)_2$	122–123/0.4	1.4875^{20}	9.99	9.80	[c]
$(C_5H_4N)OCH(C_6H_5)COOCH_2CH_2N(C_2H_5)_2\cdot HCl$			7.68	7.46	110.5–112
$(C_5H_4N)OCH(C_6H_5)COOCH_2CH_2CH_2N(C_2H_5)_2\cdot HCl$			7.40	7.22	[c]
o-$(C_5H_4N)OC_6H_4OCH_3\cdot HCl$			5.89	5.68	158–159
m-$(C_5H_4N)OC_6H_4OCH_3\cdot HCl$			5.89	5.56	136–139
p-$(C_5H_4N)OC_6H_4OCH_3\cdot HCl$			5.89	5.57	160–162
p-$(C_5H_4N)OC_6H_4Br\cdot HCl$			4.89	4.88	151–152

[a] (C_5H_4N) = 2-pyridyl.

[b] Dihydrochloride unless otherwise indicated.

[c] Not crystallizable.

[d] Monohydrochloride.

of copper powder the reactants could be heated to 210–220° without evidence of reaction, whereas, when this catalyst was present a vigorous reaction set in at 150°. Unfortunately, the beneficial effect of this reagent was not ascertained until after some of the experimental work had been completed. Thus, it is possible that improved yields could be obtained in some of the cases where copper powder was not employed. Copper powder has been employed in reactions of 2-bromopyridine with amines (15, 16).

2-Pyridyl ethers of ethyl glycollate, ethyl lactate, and ethyl mandelate were prepared through interaction of the sodium alkoxide of the ester with an excess of 2-bromopyridine at 110–120° (Method C). Numerous solvents were tried for this reaction but superior results were secured with 2-bromopyridine itself. When applied to ethyl benzilate, Method C yielded none of the expected ethyl diphenyl-(2-pyridoxy)acetate; instead, a small quantity of material was isolated which proved to be the 2-pyridyl ether of benzhydrol. This compound was prepared in quantity from benzhydrol by Method B and it proved to be identical with the product obtained from the reaction involving ethyl benzilate. It was not possible to prepare ethyl diphenyl-(2-pyridoxy)acetate.

The esters which arose from some of these syntheses were converted to alkamine esters of β-diethylaminoethanol and γ-diethylaminopropanol, respectively. For all but two cases the transformation was accomplished through alcoholysis of the alkyl esters with excess amino alcohol containing a small quantity of dissolved sodium metal. The procedure failed when applied to ethyl phenyl-(2-pyridoxy)acetate and ethyl 2-(2′-pyridoxy)-3-naphthoate, so these esters were converted to the corresponding free acids by saponification, and the acids were reacted with β-diethylaminoethyl chloride and γ-diethylaminopropyl chloride in dry isopropyl alcohol, thus yielding the respective alkamine ester monohydrochlorides. The free bases were not isolated.

Treatment of the alkamine esters with an excess of hydrogen chloride in ether yielded dihydrochlorides which were frequently non-crystallizable hygroscopic oils. In a few instances it was possible to prepare monohydrochlorides by limiting the quantity of hydrogen chloride employed and these materials were sometimes more tractable. Monohydrochlorides of some of the simple ethers were also prepared.

Pharmacological evaluation of these compounds has not been completed, but will be reported elsewhere at a later date.

EXPERIMENTAL

Preparation of 2-pyridyl ethers. As noted in the discussion, three methods of synthesis were employed. Selected examples illustrative of each method are given below.

METHOD A. *Ethyl p-(2-pyridoxy)benzoate.* In a flask fitted with an air condenser a mixture of 7.9 g. (0.05 mole) of 2-bromopyridine, 16.6 g. (0.10 mole) of ethyl *p*-hydroxybenzoate, and 6.9 g. (0.05 mole) of anhydrous potassium carbonate was heated at 150–160° for six hours. When it had cooled, the gray solid was taken up in 50 ml. of 8% sodium hydroxide and the mixture was extracted several times with 30-ml. portions of ether. The ether extracts were dried over Drierite. Removal of the ether left an oil which, when heated to 120° at 1 mm. pressure, yielded approximately 3 g. of distillate consisting of 2-bromopyridine and some phenolic material. The undistilled residue solidified on cooling and it

was then crystallized from 95% alcohol in the form of fine needles which melted at 63–65°. Two more crystallizations raised the melting point to 64–65°. Yield, 4.0 g.; 32%.

Anal. Calc'd for $C_{14}H_{13}NO_3$: N, 5.76. Found: N, 5.85.

p-(2-Pyridoxy)benzoic acid. A solution of 1.0 g. of the ester in 10 ml. of 10% alcoholic potassium hydroxide was gently refluxed for three hours and then diluted with twice its volume of water. Acidification with dilute hydrochloric acid gave 0.7 g. of a fine white precipitate which, when crystallized from alcohol, melted sharply at 174°.

Anal. Calc'd for $C_{11}H_8NO\cdot COOH$: Neutral equivalent, 215.

Found: Neutral equivalent, 216.

METHOD B. *Methyl o-(2-pyridoxy)benzoate.* The sodium salt of methyl salicylate was prepared in a 250-ml. round-bottom flask fitted with a dropping-funnel and a condenser with a calcium chloride tube. Methyl salicylate, 15.2 g. (0.10 mole), was added dropwise to a solution of 2.3 g. (0.1 atom) of sodium in 50 ml. of absolute methanol; the sodium salt precipitated as a white crystalline solid. Excess methanol was distilled off, the last traces being removed under diminished pressure (10 mm.) and at a bath temperature of 120°. The caked solid was then broken up and mixed with 15.8 g. (0.10 mole) of 2-bromopyridine and 0.2 g. of copper powder. An air condenser was attached and the mixture was heated to 185°; at this temperature a vigorous reaction took place and the contents of the flask quickly set to a dark brown solid. The temperature was maintained at 180–190° for an hour. When it had cooled, the melt was broken up and treated with 50 ml. of ether which was then decanted and filtered into a separatory funnel. An equal volume of water was added to the residue in the flask and the resulting solution was filtered into the separatory funnel. Failure to filter the ethereal and aqueous portions invariably led to the formation of a very stable emulsion during the ensuing extraction. The green, aqueous layer was extracted twice more with 30-ml. portions of ether and the combined extracts were dried over Drierite. Following the removal of ether, the residue was distilled and the main fraction, b.p. 132–140°/1 mm., solidified on cooling. Crystallization from 95% alcohol gave the pure ester in the form of long needles, m.p. 67–68°. Yield, 11.9 g., or 52%.

Anal. Calc'd for $C_{13}H_{11}NO_3$: N, 6.11. Found: N, 6.03.

o-(2-Pyridoxy)benzoic acid. This acid was obtained by saponification of the methyl ester with alcoholic potassium hydroxide. It was a white solid which, when crystallized from water, melted at 117–118°.

Anal. Calc'd for $C_{12}H_9NO_3$: N, 6.51. Found: N, 6.48.

METHOD C. *Ethyl phenyl-(2-pyridoxy)acetate.* This reaction was carried out in a 500-ml. three-neck flask equipped with a sealed stirrer, a reflux condenser fitted with a calcium chloride tube, and a dropping-funnel. The sodium alkoxide of ethyl mandelate was prepared by the dropwise addition, during a period of from sixty to ninety minutes, of a solution of 27.0 g. (0.15 mole) of ethyl mandelate in 50 ml. of dry ether to a stirred suspension of 3.45 g. (0.15 mole) of sodium sand in 300 ml. of absolute ether. During this time the reactants were kept under an atmosphere of nitrogen. When all of the ester had been added, the creamy suspension was stirred for an hour to make certain that all of the sodium was consumed. Stirring was suspended and the ether was distilled off during the simultaneous dropwise addition of 84 g. (0.53 mole) of 2-bromopyridine. The ether-free mixture was stirred and heated at 110° for six hours. After it had become cool, the chocolate-colored product was taken up with 100 ml. of saturated salt solution and this mixture was extracted three times with 75-ml. portions of ether. The combined extracts were dried over Drierite. Removal of the ether left a dark oil which was distilled and yielded the following fractions: (a) 71 g., b.p. 80–82° (16 mm.); (b) 3 g., b.p. 71° (18 mm.) to 120° (1 mm.); and (c) 6.8 g., b.p. 125–145° (1 mm.). Fraction (a) was unreacted 2-bromopyridine while (b) contained 2-bromopyridine and ethyl mandelate. Distillation of fraction (c) through a ten-inch Vigreux column gave the pure ethyl phenyl-(2-pyridoxy)acetate; it was a pale yellow oil, b.p. 135–137° (1 mm.); n_D^{20} 1.5515. Yield, 6 g. (28.4% based on the amount of 2-bromopyridine consumed).

Anal. Calc'd for $C_{15}H_{15}NO_3$: N, 5.45. Found: N, 5.40.

Phenyl-2-pyridoxyacetic acid. A solution of 1.0 g. of the ethyl ester in 10 ml. of 10% alcoholic potassium hydroxide was gently refluxed for three hours. Then the cherry red solution was diluted with twice its volume of water and dilute hydrochloric acid was added just to the point of neutrality; at this point the solution was colored yellow but no precipitate had formed. After treatment with decolorizing carbon the solution was cooled and further acidified. In this way 0.7 g. of fine white platelets were obtained. The acid was purified by crystallization from a mixture of benzene and low-boiling petroleum ether; m.p. 115°.

Anal. Calc'd for $C_{13}H_{11}NO_3$: N, 6.11. Found: N, 6.20.

Preparation of aminoesters. The following description illustrates the method.

β-Diethylaminoethyl p-(2-pyridoxy)benzoate. Ethyl *p*-(2-pyridoxy)benzoate, 4.86 g. (0.02 mole), was shaken for ten minutes with a solution of 0.1 g. of sodium metal in 16.4 g. (0.14 mole) of β-diethylaminoethanol; then the mixture was set aside for twelve hours, during which time it turned to a gelatinous mass. The flask was fitted with a short (8 inches) Vigreux column to which was attached a condenser and a receiver fitted with a calcium chloride tube. The mixture was kept in a bath at 160–170° for six hours and occasionally the temperature was raised to 180° in order to force over small amounts of ethyl alcohol which had not distilled at the lower temperature. Excess amino alcohol was then removed by distillation under reduced pressure. The solid grayish-colored residue was partially dissolved in 50 ml. of saturated salt solution and this mixture was extracted with three 30-ml. portions of ether. After being treated with Drierite the extracts were distilled to give 3.45 g. (64%) of a pale yellow oil, b.p. 183.5–184.5° (1 mm.); n_D^{28} 1.5383.

Anal. Calc'd for $C_{18}H_{22}N_2O_3$: N, 8.91. Found: N, 8.96.

Esters of γ-diethylaminopropanol were prepared in the same manner except that the reaction temperature was maintained at 170–180°.

Hydrochlorides. Conversion of the simple phenolic ethers and of the aminoesters to hydrochlorides was accomplished by treatment of an ether solution of the base with a solution of hydrogen chloride in the same solvent. Products varied in physical characteristics, a few being readily crystallizable solids while most were gummy, hygroscopic semi-solids which solidified only after prolonged successive treatments with dry ether. Hydrochlorides of the basic esters of phenyl-(2-pyridoxy)acetic acid and 2-(2′-pyridoxy)-3-naphthoic acid were prepared indirectly by the following method.

β-Diethylaminoethyl 2-(2′-pyridoxy)-3-naphthoate. A solution of 6.15 g. (0.23 mole) of 2-(2′-pyridoxy)-3-naphthoic acid and 5.0 g. (0.037 mole) of β-diethylaminoethyl chloride in 40 ml. of dry isopropyl alcohol was refluxed for ten hours under anhydrous conditions. The cold solution was filtered, solvent was removed from the filtrate by evaporation under reduced pressure, and the residual oil was suspended in 50 ml. of dry ether. After two days in the refrigerator the product solidified and was crystallized from a small quantity of isopropyl alcohol; complete precipitation was insured by the addition of dry ether. Yield, 4.2 g. A sample crystallized from acetone as a white, granular, non-hygroscopic solid which sintered at 136° and became clear at 139–140°.

Anal. Calc'd for $C_{22}H_{25}ClN_2O_3$: N, 6.99. Found: N, 6.95.

SUMMARY

A series of new 2-pyridyl aryl and alkyl ethers has been prepared for pharmacological study, particularly as antispasmodic or antihistaminic agents.

Synthesis of 2-pyridyl aryl ethers was achieved by condensing 2-bromopyridine with the given phenol in the presence of anhydrous potassium carbonate or with the sodium phenoxide in the presence of copper powder.

The pyridyl alkyl ethers were prepared by reacting 2-bromopyridine with the appropriate sodium alkoxide; copper powder was an effective catalyst in certain instances.

Esters which arose from several of these syntheses were converted into alkamine esters of β-diethylaminoethanol and γ-diethylaminopropanol.

These new compounds have in common the significant iminoester, $-N=\overset{|}{C}OR$, configuration.

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