TABLE III—RELATIVE RETENTION TIMES OF ALKYL ETHERS OF *p*-HYDROXYBENZOATE ESTERS ON COLUMN PACKED WITH 1.5% SE-30 POLYESTER ON ANAKROM ABS

Ester	Retention Time of Alkyl Ether Relative to Naphthalene[a] Internal Std.		
	Ethyl	*n*-Propyl	*n*-Butyl
Methyl	2.0	2.5	3.8
Ethyl	2.4	3.2	4.8
Propyl	3.3	4.6	7.3
Butyl	5.0	7.0	11.2

[a] The absolute retention time of naphthalene was 1.0 min. at 135°, 240 ml. argon per min.

of ethyl and propyl *p*-hydroxybenzoate. These two derivatives each gave two overlapping peaks, the first being symmetrical, the second being lower with considerable tailing. The author suspects this effect was due to decomposition on the column. Single peaks without tailing were observed for the *n*-butyl ethers when the column temperature was lowered to 170°. For this reason selected derivatives were chromatographed on a column packed with 1.5% SE-30 polyester on 90-100 mesh Anakrom ABS at a temperature designed to give similar retention times. The data which appear in Table III indicate that this packed column under these conditions is more suitable than the capillary column. The four esters thus may be resolved within each set of ether derivatives under appropriate conditions. Quantitative work was restricted to diazoethane and diazopropane since they produced stable derivatives in good yields. Plots of peak height *versus* concentration were linear for the lower three esters, as were plots of peak area *versus* concentration for the butyl ester when using ethyl derivatives on the capillary column. Plots of peak height *versus* concentration were linear when using propyl derivatives of the four esters on the packed column. This was true whether the esters were alone or mixed on either column.

The results indicate that higher diazoalkanes, when catalyzed with boron trifluoride, are useful for preparation of derivatives for gas chromatography of *p*-hydroxybenzoate esters. Now that *N*-alkyl-*N*-nitroso-*N'*-nitroguanidine precursors of higher diazoalkanes are commercially available,[2] their use should be considered for gas chromatography of these or other phenolic acids.

SUMMARY

Methyl through butyl esters of *p*-hydroxybenzoic acid have been converted to alkyl ethers by means of diazoalkanes catalyzed with .007% boron trifluoride. These ethers were easily resolved on the gas chromatograph. Ethers prepared from diazoethane and diazopropane were found suitable for quantitative work. The method seems generally applicable among phenolic acids where alkylating activity greater than that of diazomethane is needed.

REFERENCES

(1) Lach, J. L., and Sawardeker, J. S., *J. Pharm. Sci.*, **54**, 424(1965).
(2) Inamine, S., Obatake, A., and Matsuda, T., *Hakko Kogaku Zasshi*, 43, 97(1965).
(3) Higuchi, T., Patel, K. P., Bonow, E. R., and Landsman, J., *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 293(1952).
(4) Donato, S. J., *J. Pharm. Sci.*, **54**, 917(1965).
(5) Wilcox, M., *Anal. Biochem.*, **16**, 253(1966).
(6) Muller, E., and Rundel, W., *Angew. Chem.*, **70**, 105 (1958).
(7) Williams, C. M., *Anal. Biochem.*, **11**, 224(1965).

[2] Cyclo Chemical Corp., Aldrich Chemical Co., and K & K Chemical Co.

Syntheses of Some Hydroindolizines by Reductive Cyclization

By JOSEPH SAM and K. APARAJITHAN

The syntheses of dodecahydrobenzo[*b*] indolizine, octahydrocyclopenta[*b*] indolizine, decahydronaphth[2,1-*b*] indolizine, and 7-methoxydecahydronaphth[2,1-*b*]-indolizine are reported. The preparations of pyridylmethylene and pyridylmethyl derivatives of cyclopentanone, cyclohexanone, 1-tetralone, and 7-methoxy-1-tetralone also are described. Some preliminary pharmacological observations in mice are included.

THE SYNTHESIS of dodecahydrobenzo[*b*] indolizine (11-perhydroazafluorene) (II*b*) involving several steps was reported by Prelog and associates (1). Subsequently the authors reported (2) a two-step synthesis of II*b* by reductive cyclization of I at 200° and 2000 p.s.i. (Scheme I) and also the low pressure (50–60 p.s.i.) catalytic reductive cyclization of 2-pyridylmethylene-1-indanones (III) to the corresponding hydroindolizine (IV) (3, 4). (Scheme II.) The authors have now utilized the latter method for the synthesis of other hydroindolizines (II and XII) from 2-(2-pyridylmethylene)-cycloalkanones (IX and XI). The formation of IX*b* by the reaction of cyclohexanone (V*b*) with 2-pyridinealdehyde (VI) was investigated; however, only 2,6-bis-(2-pyridylmethylene) cyclohexanone (VII) was obtained. The synthesis of IX was accomplished by the reaction of 2-pyridinealdehyde with the morpholine enamine (VIII) (5, 6) of the cycloalkanone (V). The 3-, and 4-pyridylmethylenecycloalkanones also were prepared by this method using the appropriate pyridinealdehydes. The reaction of 2-pyridinealdehyde with 1-tetralones (X) occurred satisfactorily to yield the corresponding pyridylmethylene derivatives (XI). Some of the properties of the products from the reaction of pyridinealdehydes with various cycloalkanones are summarized in Table I.

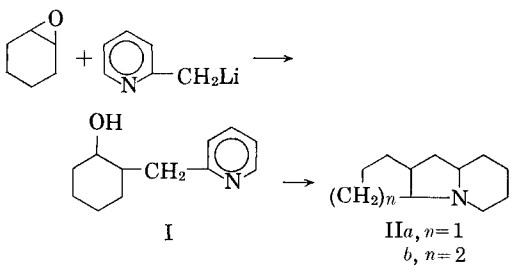
A number of the unsaturated compounds (IX,

Received December 27, 1966, from the Department of Pharmaceutical Chemistry, University of Mississippi, University, MS 38677

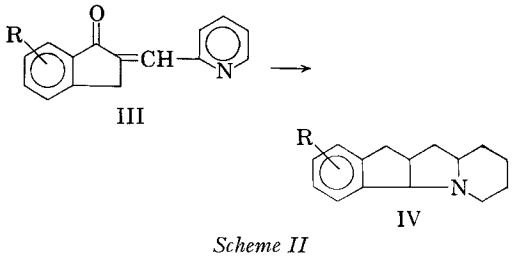
Accepted for publication February 8, 1967.

This work was done during the tenure of a Mississippi Heart Association Research fellowship to K. Aparajithan.

Presented to the Medicinal Chemistry Section, A.PH.A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.



Scheme I



Scheme II

XI, and the corresponding 3- and 4-pyridyl derivatives) were catalytically (Pd-C) hydrogenated at 50–60 p.s.i. to the corresponding dihydro derivatives. The properties of the latter compounds are summarized in Table II.

The cyclization of IX and XI to the hydroindolizines (II and XII) was accomplished by low pressure catalytic (PtO_2) hydrogenation as described in earlier reports (3, 4). (Scheme III.) Elemental analysis and infrared spectrophotometry were used for the identification of the products. Gas–liquid chromatography of the hydroindolizines (Table III) indicated the presence of trace quantities of impurities. These, however, were readily removed during the recrystallization of the corresponding salts.

PHARMACOLOGY[1]

Acute effects after intraperitoneal administration to albino mice were observed for five of the pyridylmethylenecycloalkanones (Table I, compounds *13, 16, 17, 18, 20*), six of the pyridylmethylcycloalkanones (Table II, compounds *21, 22, 24, 27, 28, 33*) and three of the indolizines (Table III, compounds *38, 42, 46*). Gross symptomatology at toxic and subtoxic dosages was noted in a fashion similar to that described by Irwin (7) and approximate LD_{50}'s (48 hr.) were determined by the method of Horn (8) utilizing five mice per dosage level.

Most of the compounds showed LD_{50}'s in a moderate dosage range (147 to 562 mg./Kg.) with the exceptions of compound *20* which produced deaths only at greater than 1.0 Gm./Kg., and of the three indolizines which all had LD_{50}'s below 100 mg./Kg. (26 to 93 mg./Kg.). Excitation was prominent after compounds *13, 16, 17, 18, 20, 24, 27,* and *28*. Compound *20* differed in that it evoked convulsions which were delayed 2–3 hr. after administration. Muscular incoordination and/or tremors were prominent after compounds *21, 28, 33, 38, 42,* and *46*. Predominant symptoms of CNS depression were seen at all dosages of compounds *21* and *22*. Sedation seemed to occur at lower dosages of compounds *13* and *24*.

EXPERIMENTAL[2]

2-(Pyridylmethylene) Cycloalkanones (Table I)—*Method A*—A mixture of 0.4 mole of freshly distilled cycloalkanone, 40 Gm. (0.45 mole) of freshly distilled morpholine, 0.5 Gm. of *p*-toluenesulfonic acid, and 100 ml. of dry benzene was heated under reflux for 18 hr. with a Dean-Stark water separator. The benzene solution was distilled under reduced pressure (water-aspirator) to give the desired enamine (5) of cyclopentanone and cyclohexanone.

A solution of 0.3 mole of *N*-(1-cycloalkenyl)morpholine and 28 Gm. (0.26 mole) of pyridinealdehyde in 100 ml. of dry toluene or benzene was refluxed for 1 to 7 days with a Dean-Stark apparatus. The reaction mixture was cooled, treated with 120 ml. of 6 *N* hydrochloric acid, and thereafter stirred for 2 hr. The lower acid layer was separated, washed with ether, and then neutralized with sodium bicarbonate. The oil (or solid) that separated was extracted with benzene, washed with water, and dried (anhydrous magnesium sulfate). Distillation of the benzene solution under reduced pressure gave the desired product (Table I). The infrared spectrum showed strong absorption at about 5.75–5.9 μ.

2-(Pyridylmethylene)-1-tetralones—*Method B*—A mixture of 0.15 mole of the 1-tetralone, 4 ml. of acetic acid, 5 ml. of piperidine, and 0.15 mole of pyridinealdehyde was heated on a steam bath for 0.5 to 3 hr. The lower boiling materials were removed by distillation (water-aspirator). The residue was dissolved in benzene and extracted with dilute hydrochloric acid. The acid layer was separated and treated with dilute sodium hydroxide. The solid was removed by filtration and recrystallized from a suitable solvent (Table I). The infrared spectrum showed strong carbonyl absorption at about 5.95 μ.

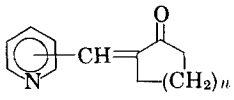
2 - Pyridylmethylcycloalkanones—*Method C*—A solution of 0.1 mole of the 2-pyridylmethylene compound in 100 ml. of ethanol was hydrogenated at 50 p.s.i. at room temperature with 1 Gm. of 5% Pd/C catalyst in a Parr low pressure hydrogenator. The product was isolated in the usual manner and distilled (Table II). The infrared spectrum showed strong carbonyl absorption at about 5.95 μ.

Indolizines (Table III)—A solution of 0.025 mole of cycloalkanone in a mixture of 50 ml. of glacial acetic acid and 15 ml. of freshly distilled acetic anhydride was hydrogenated at 47 p.s.i. with 0.1 Gm. of platinum oxide catalyst. The absorption of hydrogen was rapid in the first hr. and was complete in 24 hr. The catalyst was removed by filtration; the filtrate was treated with 15 ml. of water and then allowed to remain at room temperature for 2 hr. The solvents were distilled; the residue was treated with 75 ml. of water and filtered. The filtrate was saturated with sodium bicarbonate and extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous magnesium sulfate. The chloroform solution was distilled under reduced

[1] The authors are grateful to Dr. W. Marvin Davis, Department of Pharmacology, School of Pharmacy, University of Mississippi, University, for the pharmacological data.

[2] All melting points were taken on a Fisher-Johns apparatus and are uncorrected; boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137 Infracord spectrophotometer.

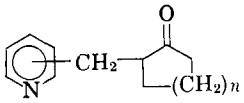
TABLE I—PYRIDYLMETHYLENE CYCLOALKANONES



Compd.	Isomer[a]	n	Method; React. Time, hr.	Recrystn. Solvent[b]	Yield, %	B.p. (mm.) and/or M.p., °C.	Molecular Formula	Anal., % Calcd. C	H	N	Found C	H	N
1	2	1	A; 24	M-W	78	132–4 (0.3) 49–51	$C_{11}H_{11}NO$	76.3	6.4	8.1	76.0	6.3	8.2
2	2	1	...	E	...	162–164	$C_{12}H_{14}INO$[c]	45.7	4.5	4.5	45.6	4.6	4.1
3	2	1	...	W	...	161–162	$C_{17}H_{14}N_4O_8$[d]						
4	3	1	A; 60	...	80	134–138 (0.8)	$C_{11}H_{11}NO$	76.3	6.4	8.1	76.3	6.6	8.2
5	3	1	...	E	...	164–166	$C_{12}H_{14}INO$[c]	45.7	4.5	4.5	45.7	4.8	4.4
6	3	1	...	W-A	...	203–205	$C_{17}H_{14}N_4O_8$[d]						
7	4	1	A; 72	...	68	158–159 (0.2)	$C_{11}H_{11}NO$	76.3	6.4	8.1	75.8	6.5	8.4
8	4	1	...	W	...	190–191	$C_{12}H_{14}INO$[c]						
9	4	1	...	W	...	161–162	$C_{17}H_{14}N_4O_8$[d]						
10	2	2	A; 108	...	29	122 (0.3)	$C_{12}H_{13}NO$	77.0	7.0	7.5	77.1	7.1	7.6
11	3	2	A; 160	...	47	166 (2.1)	$C_{12}H_{13}NO$						
12	3	2	...	W-A	...	171	$C_{18}H_{16}N_4O_8$[d]	51.9	3.9	13.5	52.6	3.9	13.2
13	3	2	...	Ac-P	...	106–107	$C_{13}H_{16}INO$[c]						
14	4	2	A; 96	...	49	141–146 (0.8)	$C_{12}H_{13}NO$						
15	4	2	...	W-A	...	167–168	$C_{18}H_{16}N_4O_8$[d]	51.9	3.9	13.5	51.9	3.9	13.5
16	4	2	...	E-Ea	...	147–148.5	$C_{13}H_{16}INO$[c]	47.4	4.9	4.3	47.4	5.2	4.1
17	2	1-Tetralone[e]	B; 0.5	M	68	119–120	$C_{16}H_{13}NO$	81.7	5.6	6.0	81.4	5.6	6.0
18	3	1-Tetralone[e]	B; 3	C	23	73.5–74	$C_{16}H_{13}NO$	81.7	5.6	6.0	81.8	5.7	5.8
19	4	1-Tetralone[e]	B; 1.5	C	51	114–115	$C_{16}H_{13}NO$	81.7	5.6	6.0	81.6	5.6	6.2
20	2	7-Methoxy-1-tetralone[e]	B; 0.5	C	68	92–93	$C_{17}H_{15}NO_2$	77.0	5.7	5.3	77.1	5.7	5.4

[a] Refers to position of the substituent in the pyridine ring. [b] A, acetic acid; Ac, acetone; C, cyclohexanone; E, ethanol; Ea, ethyl acetate; M, methanol; P, petroleum ether (30–60°); W, water. [c] Methiodide. [d] Picrate. [e] Entire cycloalkanone moiety.

TABLE II—PYRIDYLMETHYLCYCLOALKANONES

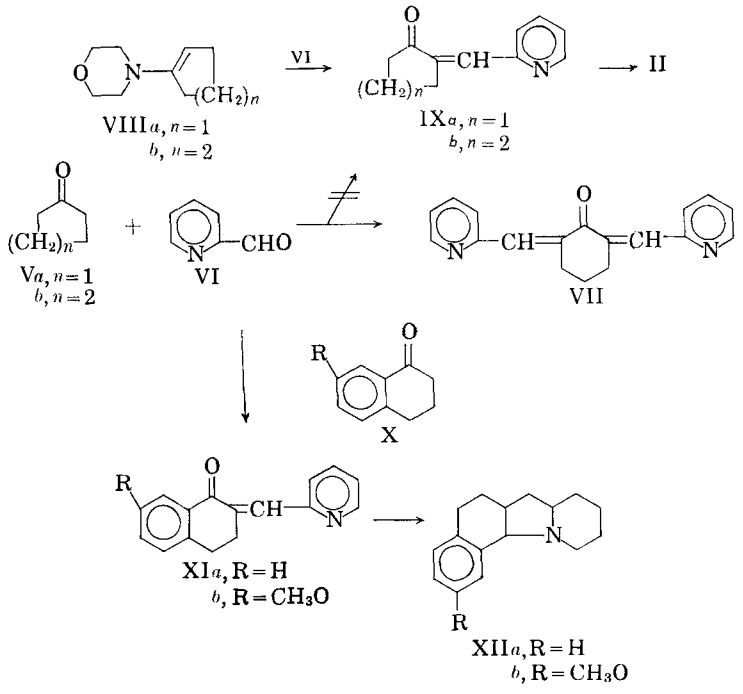


Compd.	Isomer[a]	n	React. Time, hr.[b]	Recrystn. Solvent[c]	Yield, %	B.p. (mm.) and/or M.p., °C.	Molecular Formula	Anal., % Calcd. C	H	N	Found C	H	N
21	2	1	3	...	70	132–133 (1.7)	$C_{11}H_{13}NO$						
22	2	1	...	W	...	191–193	$C_{12}H_{16}N_4O$[d]	62.0	6.9	24.1	61.3	7.1	23.8
23	2	1	...	E	...	123–124	$C_{12}H_{16}INO$[e]	45.4	5.1	4.4	45.5	5.1	4.3
24	3	1	3	...	86	122–123 (0.5)	$C_{11}H_{13}NO$						
25	3	1	...	E	...	114–115	$C_{12}H_{16}INO$[e]	45.4	5.1	4.4	45.5	5.1	4.4
26	3	1	...	W	...	118–119	$C_{17}H_{15}N_4O_8$[f]						
27	4	1	4	...	80	134–136 (1.3)	$C_{11}H_{13}NO$	75.4	7.5	8.0	75.4	7.5	8.2
28	4	1	...	Ac	...	95–96	$C_{12}H_{16}INO$[e]	45.4	5.1	4.4	45.3	5.0	4.3
29	4	1	...	W	...	136–138	$C_{17}H_{16}N_4O_8$[f]						
30	3	2	4	...	84	156–157 (3.0)	$C_{12}H_{15}NO$	76.2	8.0	7.4	75.2	7.9	7.9
31	3	2	...	W	...	142–143	$C_{18}H_{18}N_4O_8$[f]	51.7	4.3	13.4	52.2	4.2	13.3
32	4	2	4	...	80	132–133 (0.5)	$C_{12}H_{15}NO$	76.2	8.0	7.4	76.1	7.8	7.8
33	4	2	...	C	...	103–105	$C_{13}H_{18}INO$[e]	47.2	5.5	4.2	47.1	5.3	4.1
34	4	2	...	W-A	...	175–176	$C_{18}H_{18}N_4O_8$[f]	51.7	4.3	13.4	52.2	4.4	13.4
35	2	1-Tetralone[g]	0.5	P	92	181 (1.2) 70–71	$C_{16}H_{15}NO$	81.0	6.4	5.9	80.9	6.4	5.8
36	4	1-Tetralone[g]	2	P	88	174–177 (0.2) 62–64	$C_{16}H_{15}NO$	81.0	6.4	5.9	80.3	6.4	6.2

[a] Refers to position of substituent in pyridine ring. [b] Method C. [c] A, acetic acid; Ac, acetone; C, cyclohexanone; P, petroleum ether (30–60°); W, water. [d] Semicarbazone. [e] Methiodide. [f] Picrate. [g] Entire cycloalkanone moiety.

pressure to give the desired product. Carbonyl and hydroxyl group absorption was absent in the infrared spectra.

The hydrochlorides, picrates, and methiodides were prepared in the usual manner and recrystallized from a suitable solvent.



Scheme III

TABLE III—INDOLIZINES (II AND XII)

Compd.	Recrystd. from	n_D(°C.)	Yield, %	M.p., °C.	Molecular Formula	Anal., % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
37 (II*a*)	...	1.4922 (23)	65	106–108 (20 mm.)[a]	$C_{11}H_{19}N$						
38 (II*a*)	Acetonitrile	...	...	206–208	$C_{12}H_{22}IN$[b,c]	46.9	7.2	4.6	46.7	7.3	4.7
39 (II*a*)	Ethanol	...	...	211–212	$C_{17}H_{22}N_4O_7$[d]	51.8	5.6	14.2	51.9	5.8	13.9
40 (II*b*)	...	1.4967 (24)	44	126–130 (20 mm.)[a]	$C_{12}H_{22}N$[e]						
41 (II*b*)	Methanol	...	...	207–208	$C_{18}H_{28}N_4O_7$[d]						
42 (II*b*)	Acetonitrile	...	...	260–261	$C_{13}H_{24}IN$[b,f]	48.6	7.5	4.4	48.7	7.5	4.5
43 (XII*a*)	...	1.5620 (22)	68	125 (0.3 mm.)[a]	$C_{16}H_{21}N$	84.5	9.3	6.2	84.6	9.1	6.3
44 (XII*a*)	Methanol	...	...	215–217	$C_{22}H_{24}N_4O_7$[d]	57.9	5.3	12.3	58.1	5.3	12.7
45 (XII*b*)	...	1.5611 (23)	48	144–146 (0.2 mm.)[a]	$C_{17}H_{23}NO$	79.3	9.0	5.4	78.9	9.0	5.6
46 (XII*b*)	Acetonitrile	...	...	217–218	$C_{17}H_{24}ClNO$[g,h]	69.5	8.2	4.8	69.6	8.3	4.9

[a] Boiling point. [b] Methiodide. [c] Calcd. for I: 41.3. Found: 41.0. [d] Picrate. [e] *Reference 1*. [f] Calcd. for I: 39.5. Found: 39.4. [g] Calcd. for Cl: 12.1. Found: 12.1. [h] Hydrochloride.

REFERENCES

(1) Prelog, V., Frenkiel, L., and Szpilfogel, S., *Helv. Chim. Acta*, **29**, 484(1946).
(2) Sam, J., Plampin, J. N., and Alwani, D. W., *J. Org. Chem.*, **27**, 4543(1962).
(3) Sam, J., England, J. D., and Alwani, D. W., *J. Med. Chem.*, **7**, 732(1964).
(4) Sam, J., Alwani, D. W., and Aparajithan, K., *J. Heterocyclic Chem.*, **2**, 366(1965).
(5) Birkofer, L., and Barnikel, C. D., *Ber.*, **91**, 1996(1958) Hunig, S., Benzing, E., and Lucke, E., *ibid.*, **90**, 2833(1957).
(6) Szmuszkovicz, J., "Advances in Organic Chemistry: Methods and Results," vol. 4, Raphael, R. A., Taylor, E. C., and Wynberg, H., eds., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1.
(7) Irwin, S., "Animal and Clinical Techniques in Drug Evaluation," Nodine, J. H., and Siegler, P. E., eds., Year Book Medical Publication, Inc., Chicago, Ill., 1964.
(8) Horn, H. J., *Biometrics*, **12**, 311(1956).