TABLE I

EFFECT OF METAL SALTS UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

Salt	Crude yield, %	M.p., °C.	Recrystn. yield, %
$CuCl_2$	44	257–259	37
$FeSO_4$	15	260–262	7
$MnCl_2$	11	256–259	11
$ZnCl_2$	21	254–258	18
$NiCl_2$	11	250–255	9
$CoCl_2$	11	258–261	10
$HgCl_2$	26, 27	254–258	22
$HgCl_2$[a]	9	262–265	. .
H_2PdCl_4	8	259–262	6
MgO	9	254–258	7
$CdCl_2$	19, 21	256–261	16
$CdCl_2$[a]	9	256–258	. .
$SnCl_2$	5	260–262	4
$Pb(OAc)_2$	16	255–257	8
$CrO_3 + Na_2SO_3$	6	260–262	5
$AlCl_3$	12	242–250	9
$FeCl_3$	16	259–261	10
$KMnO_4$	8	254–256	7
$Na_2Cr_2O_7$	13	261–263	8
None (blank)	11	255–258	8
Cu powder[a]	16	258–260	. .
None (blank)[a]	9	. . .	. .

[a] *p*H adjusted to 3.5 ± 0.05 with a *p*H meter. Worked up by removing volatiles *in vacuo* without heating.

nitrogen evolution was complete, the solvent was removed *in vacuo* without heating, or by steam distillation. The product was washed with water and acetone, then recrystallized from anisole.

TABLE II

EFFECT OF SOLVENTS UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

Solvent	Crude yield, %	Crude m.p., °C.	Recrystn. yield, %
Acetone	41[a]	257–260	38
Acetone	44[b]	248–253	. .
Acetonitrile	26[a]	259–261	23
Acetonitrile	34[b]	248–253	. .
Tetrahydrofuran	5[a]	264–265	5
Tetrahydrofuran	23[b]	256–259	. .
Dimethylformamide	19[c]	261–264	17
Dimethylformamide	26[b]	251–255	. .
Ethanol	8[a]	257–258	4
Glycol dimethyl ether	23[a]	258–260	21
Glycol dimethyl ether	26[b]	253–257	. .

[a] Worked up by evaporating solvent *in vacuo*. [b] Worked up by steam distillation. [c] The insoluble product was collected by filtration; a second crop was obtained by steam distilling the filtrate.

***p*H Experiments.**—*p*-Nitrobenzenediazonium chloride (0.03 mole), prepared as before, was brought to the desired *p*H by addition of sodium acetate solution. Cupric chloride (0.0045 mole) was added and the *p*H was again adjusted (*p*H meter). The solution was added to 0.03 mole of coumarin and 90 ml. of acetone. The product was worked up as before, without heating.

TABLE III

EFFECT OF *p*H UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

*p*H	Crude yield, %	Crude m.p., °C.	Color crude	Recrystn. yield, %
1	22	258–260	Yellow	21
2	30	257–260	Yellow	28
3	35	258–261	Yel.-brown	30
4	30	251–256	Dark brown	27
5	17	250–256	Black	15

Buffer Experiments.—*p*-Nitroaniline (0.03 mole) was diazotized as before. The filtered solution was brought to *p*H 3 ± 0.05 (*p*H meter) by addition of a concentrated solution of the appropriate sodium salt. Cupric chloride (0.0045 mole) was added and the *p*H again was adjusted. The solution then was added to a cold solution of 0.03 mole of coumarin in 90 ml. of acetone. Nitrogen evolution commenced immediately. The solution was stirred while the ice-bath melted and allowed to stand overnight. After removal of the solvent *in vacuo*, the precipitate was washed with water, dried, and stirred with acetone. It was then recrystallized from anisole.

TABLE IV

EFFECT OF BUFFER COMPONENT UPON THE YIELD OF 3-*p*-NITROPHENYLCOUMARIN IN THE MEERWEIN REACTION

Buffer	Crude yield, %	Crude m.p., °C.	Recrystn. yield, %
Acetate	40–45	257–260	33–40
Succinate	21	258–260	19
Citrate	28	252–256	24
Citrate	26	253–258	23
Versene	7	257–260	6
Tartrate	13	253–258	11
Phosphate	13	251–256	11

Acknowledgment.—We are indebted to the Horace H. Rackham Fund, University of Michigan, for a grant in support of this work.

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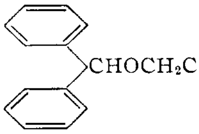
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

1-Aryloxy-3-[N-heterocyclicamino]-2-propanols[1]

BY C. B. POLLARD AND R. W. INGWALSON

RECEIVED JANUARY 26, 1955

In recent years numerous pharmacological investigations have resulted from the synthesis of alkylamine ethers of phenols and arylalkanols and the synthesis of amino alcohols due to the discovery of the potent antihistaminic action of benzhydryl β-dimethylaminoethyl ether [Benadryl (I)] and



I

many of its derivatives.[2] Because of this physiological activity of basic ethers and basic alcohols,

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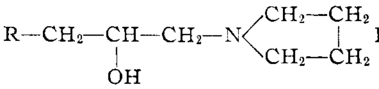
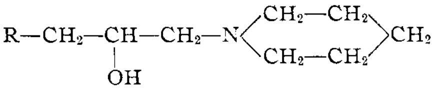
(1) This paper is abstracted from a portion of a dissertation submitted by Raymond W. Ingwalson to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, February, 1952.

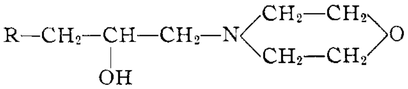
(2) E. R. Loew, *Physiol. Revs.*, **27**, 542 (1947) [a review]; L. C. Cheney, Richard R. Smith and S. B. Binkley, THIS JOURNAL, **71**, 60 (1949); W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 64 (1949); Howard B. Wright and M. B. Moore, *ibid.*, **73**, 2281 (1941); W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 3795 (1949); Howard B. Wright and M. B. Moore, *ibid.*, **73**, 5525 (1951); J. J. Denton, H. P. Schedl, Virginia A. Lawson and W. B. Neier, *ibid.*, **72**, 3795 (1950); J. J. Denton, H. P. Schedl, W. B. Neier and R. J. Turner, *ibid.*, **71**, 2050 (1950); J. J. Denton, W. B. Neier and Virginia A. Lawson, *ibid.*, **71**, 2053 (1949); A. Wayne Ruddy and Jay S. Buckley, Jr., *ibid.*, **72**, 718 (1950); M. Borovicka and M. Vondracek, *Chem. Listy*, **43**, 261 (1949); J. Kolinsky and M. Protiva, *Casopis Ceskeho Lekarnictva*, **60**, 25 (1947).

TABLE I

1-ARYLOXY-3-(N-HETEROCYCLICAMINO)-2-PROPANOLS


Type A

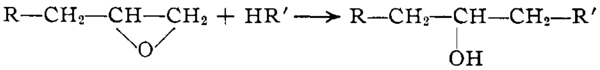

Type B


Type C

Type	R	Formula	B.p., °C.	Mm.	M.p., °C. cor.	Yield, %	Nitrogen, %		Neut. equiv.		Chlorine, %		Bromine, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
A	Phenoxy	$C_{13}H_{19}NO_2$	130–166	1	....	83.2	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{13}H_{20}ClNO_2$	.....	..	118.2–119.2	..	5.43	5.31	...	...	13.76	13.70	...	...
	Hydrobromide	$C_{13}H_{20}BrNO_2$	.....	..	116.2–118.2	..	4.63	4.56	...	...	...	...	26.44	26.37
A	*p*-Chlorophenoxy	$C_{13}H_{18}ClNO_2$	.....	..	90–91	Quant.	5.48	5.46	255.7	256	...	...	...	...
A	*o*-Chlorophenoxy	$C_{13}H_{18}ClNO_2$	144–145	0.7	61–62	79	5.48	5.34	255.7	254	...	...	...	...
A	2,4-Dichlorophenoxy	$C_{13}H_{17}Cl_2NO_2$	162–165	1	79.1–79.6	93.3	4.83	5.02	...	...	...	...	...	...
A	*m*-Toloxy	$C_{14}H_{21}NO_2$	135–139	1	....	92.8	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{14}H_{22}ClNO_2$	.....	..	117.2–117.7	..	5.15	4.94	...	...	13.05	12.80	...	...
A	*o*-Toloxy	$C_{14}H_{21}NO_2$	124–128	1	48.7–50.2	87.8	5.95	5.69	235.3	238	...	...	...	...
A	α-Naphthoxy	$C_{17}H_{21}NO_2$	178–186	0.5	71.5–72.5	76.4	..	..	...	...	...	....	...	...
	Hydrochloride	$C_{17}H_{22}ClNO_2$	.....	..	161.5–163	..	4.55	4.24	...	...	11.52	11.34	...	...
B	Phenoxy[a]	$C_{14}H_{21}NO_2$	155–180	1	....	84.4	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{14}H_{22}ClNO_2$	.....	..	150.9–151.9	..	..	..	271.8	276	13.04	12.97	...	...
	Hydrobromide	$C_{14}H_{22}BrNO_2$	.....	..	134.1–135.1	..	..	..	...	...	...	...	25.27	25.03
B	*p*-Chlorophenoxy[a]	$C_{14}H_{20}ClNO_2$	.....	..	74.6–75.1	Quant.	..	..	269.8	266.	...	...	...	...
	Hydrochloride	$C_{14}H_{21}Cl_2NO_2$	.....	..	157–158	..	..	..	...	...	11.58[b]	11.51[b]	...	...
B	*o*-Chlorophenoxy[a]	$C_{14}H_{20}ClNO_2$	158–159	0.9	70.1–71.1	87	..	..	269.8	267	...	...	...	...
	Hydrochloride	$C_{14}H_{21}Cl_2NO_2$	.....	..	151.4–152.4	..	..	..	...	...	11.58[b]	11.39[b]	...	...
B	2,4-Dichlorophenoxy	$C_{14}H_{19}Cl_2NO_2$	168–170	1	88–89	87.6	..	..	304.2	300	...	...	...	...
	Hydrochloride	$C_{14}H_{20}Cl_3NO_2$	.....	..	149.9–150.9	..	..	..	...	...	10.40[b]	10.29[b]	...	...
B	*m*-Toloxy[a]	$C_{15}H_{23}NO_2$	132–136	1	....	91.8	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{15}H_{24}ClNO_2$	.....	..	128.6–129.6	..	..	..	...	...	12.41	12.32	...	...
B	*o*-Toloxy	$C_{15}H_{23}NO_2$	.....	..	59–60	80.3	..	..	249.3	248	...	...	...	...
	Hydrochloride	$C_{15}H_{24}ClNO_2$	.....	..	134.5–135.5	..	..	..	...	...	12.41	12.29	...	...
B	α-Naphthoxy[a,c]	$C_{18}H_{23}NO_2$	182–187	0.3	82.1–83.1	84.2	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{18}H_{24}ClNO_2$	.....	..	183.6–184.6	..	..	..	...	...	11.02	10.89	...	...
C	Phenoxy[d]	$C_{13}H_{19}NO_3$	150–184	1	67.5–68	94.1	5.90	5.97	...	...	...	...	...	...
C	*p*-Chlorophenoxy	$C_{13}H_{18}ClNO_3$	.....	..	65.5–66.6	Quant.	5.16	5.07	271.7	275.	...	...	...	...
C	*o*-Chlorophenoxy	$C_{13}H_{18}ClNO_3$	170–177	1	69–70	88.2	5.16	5.12	271.7	271.	...	...	...	...
C	2,4-Dichlorophenoxy	$C_{13}H_{17}Cl_2NO_3$	176–183	1	....	90.5	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{13}H_{18}Cl_3NO_3$	.....	..	147.5–149	..	4.09	4.34	...	...	10.35[b]	10.28[b]	...	...
C	*m*-Toloxy	$C_{14}H_{21}NO_3$	148–152	1	....	83.3	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{14}H_{22}ClNO_3$	.....	..	143.9–144.9	..	4.87	5.04	...	...	12.32	12.32	...	...
C	*o*-Toloxy	$C_{14}H_{21}NO_3$	139–141	1	66–67	90.4	5.57	5.47	251.3	252	...	...	...	...
C	α-Naphthoxy	$C_{17}H_{21}NO_3$	190–206	0.5	....	86.4	..	..	...	...	...	...	...	...
	Hydrochloride	$C_{17}H_{22}ClNO_3$	.....	..	190.1–191.1	..	4.33	4.23	...	...	10.95	10.82	...	...

[a] Since this work was completed the hydrochlorides of these compounds have been reported by H. R. Ing and W. E. Omerod, *J. Pharm. Pharmacol.*, **4**, 21 (1952). [b] Ionic chlorine. [c] Reported by Fourneau, *et al.*, *Bull. soc. chim.*, **43**, 454 (1928). [d] Reported by Geigy, Swiss Patent 227,033 (August 2, 1943).

efforts were directed toward the synthesis of compounds which were both ethers and alcohols, as shown by the general equation



$$\underset{\diagdown O \diagup}{R-CH_2-CH-CH_2} + HR' \longrightarrow R-CH_2-\underset{OH}{\underset{|}{CH}}-CH_2-R'$$

R = an aryloxy group
R′ = 1-pyrrolidyl, 1-piperidyl or 4-morpholinyl

Twenty-one of these compounds were synthesized by slow addition of the intermediate epoxide to the amine at gentle reflux, using catalytic amounts of water, with subsequent distillation or recrystallization. Table I shows their structures and some pertinent physical and analytical data. The hydrochlorides and hydrobromides were made by passing the dry gas into solutions of the bases in ether.

Experimental[3]

Epoxides.—The epoxides required for this investigation were prepared[4] by heating a mixture of the phenol and dichlorohydrin[5] to 70° and then adding a 27% solution of sodium hydroxide over a period of about two hours. The temperature of the mixture was maintained below 80° throughout the addition period. The mixture was then heated for 15 to 60 minutes at 100°, cooled, extracted with ether, dried, and distilled at reduced pressure. The yields varied from 22.8 to 56%. The residues were shown to contain 1,3-diaryloxy-2-propanols in two cases, and it is suspected that analogous by-products were obtained in all similar reactions.

1-(Phenoxy)-3-pyrrolidine-2-propanol.—Thirty grams (0.20 mole) of 1,2-epoxy-3-phenoxypropane was added dropwise to 15.6 g. (0.22 mole) of boiling pyrrolidine containing catalytic amounts of water. After all of the epoxide had been added (45 minutes), the mixture was heated at temperatures below 150° for 135 minutes. The reaction mixture was distilled *in vacuo;* 36.7 g. of product was collected (83.2% crude yield). The hydrochloride was prepared by saturating an ice-cold solution of the compound with dry hydrogen chloride. The insoluble hydrochloride was collected by filtration and recrystallized from butanol–hexane. The same procedure was used in preparing the hydrobromide.

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UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

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(3) All melting and boiling points are corrected.

(4) Arthur Fairbourne, George Philip Gibson and David William Stephens, *J. Chem. Soc.*, 1965 (1932).

(5) Dichlorohydrin used was approximately 70% 2,3-dichloro-1-propanol and 30% 1,3-dichloro-2-propanol.

Esterification of Hindered Carboxylic Acids

BY RUSSELL REED, JR.

RECEIVED JANUARY 11, 1955

Bourne[1] found that trifluoroacetic anhydride was

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(1) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949).