the tetramethylphenanthrene prepared earlier from 2-butyne and tri-α-naphthylchromium.

Reaction of Triphenylchromium with Tolane.—A solution of phenylmagnesium bromide (0.88 mole) in 100 ml. of tetrahydrofuran was added under nitrogen to 5 g. (0.032 mole) of chromium trichloride suspended in 250 ml. of the same solvent. To this dark red solution containing *ca.* 0.03 mole of triphenylchromium was now added 5.2 g. (0.029 mole) of tolane dissolved in 20 ml. of tetrahydrofuran without a noticeable temperature effect. After refluxing this reaction mixture for 3 hours, the black solution was left overnight before removal of the solvent *in vacuo* and hydrolysis with ice-water. The solid reaction product was collected on a filter and extracted with ether. The insoluble residue consisted of green chromium salt and a small amount of **hexaphenylbenzene.** The yellow ether extract was freed of solvent and then distilled in a ball tube at 0.4 mm. and separated into several fractions. At a bath temperature up to 150°, a fraction consisting of 1 g. of white crystalline material was obtained whose composition according to vapor phase chromatographic analysis was 90% biphenyl, 8% *stilbene*, 1% unreacted tolane and 1% unidentified volatile substance. Between 150–200° 3.4 g. of a yellow glass was collected, leaving 2.3 g. of a brown glass, containing *ca.* 0.01 g. of hexaphenylbenzene as residue. Hexaphenylbenzene was identified in both instances here by infrared spectral comparisons with authentic sample of the benzene prepared from tetraphenylcyclopentadienone and tolane.

The yellow and brown glasses together yielded 2.3 g. of crude **1,2,3,4-tetraphenylnaphthalene** when crystallized from ether–ethanol. Chromatography of the mother liquor on basic alumina with isoöctane yielded another 0.5 g., bringing the total yield to 45% based on tolane. Repeated recrystallization from ether, alcohol and acetic acid gave tetraphenylnaphthalene with unchanged m.p. at 195–198°. However, after melting and resolidifying, the m.p. rose to 201–203°. A sample of 1,2,3,4-tetraphenylnaphthalene prepared by another method[17] showed the same behavior and melted undepressed when mixed with the above sample. Their infrared spectra were also identical in all respects.

Anal. Calcd. for $C_{34}H_{24}$: C, 94.41; H, 5.59. Found: C, 94.85; H, 5.55.

(17) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF NOVOCOL CHEMICAL MFG CO., INC.]

Alkoxyphenyl N-Substituted Aminopropanols

BY ELIAS EPSTEIN

RECEIVED MAY 2, 1959

Several 1-alkoxyphenyl 3-N-substituted aminopropanols-2 were prepared. They were screened on laboratory animals for anesthetic potency, toxicity and for irritation. The anesthetic efficiencies of some of these compounds were sufficiently high to warrant clinical study.

Although two *p*-methoxyphenyl N-substituted aminopropanols were prepared near the beginning of the nineteenth century,[1] there was little to indicate in the literature that these compounds had a pronounced local anesthetic effect. Fernald, in 1953,[2] disclosed that ethoxynaphthyl N-substituted aminopropanols were potent topical anesthetics. On testing these compounds of Fernald, we found that although the topical potency was high and the toxicity on white mice low, they were highly irritating when applied to the eye of the rabbit. To determine whether substitution of the phenyl for the naphthyl group would reduce the irritating qualities of this type of compound, we prepared a series of N-substituted derivatives of methoxy-, ethoxy-, propoxy-, butoxy- and isoamyloxyphenylaminopropanols. These compounds were screened on laboratory animals for possible value as local anesthetics.

The general method of preparation was to treat the alkoxyphenylmagnesium bromide with epichlorohydrin in a Grignard reaction. The resulting chloropropanols were treated with an excess of the appropriate amine to form the anesthetic base. The anesthetic compounds were isolated as their hydrochloride salts and purified by recrystallization from isopropyl alcohol or some other suitable solvent.

The yields of the Grignard reaction ranged from 25 to 60% of theoretical. As discussed in a review by Gaylord and Becker,[3] the reaction proceeded to give two main products in varying yields:

$$ROC_6H_5MgBr + CH_2(O)CHCH_2Cl \longrightarrow ROC_6H_5CH_2CHOHCH_2Cl + BrCH_2CHOHCH_2Cl$$

(1) M. Daufresne, *Compt. rend.*, **145**, 875 (1907).

(2) M. C. Fernald, U. S. Patent 2,629,738 (1953).

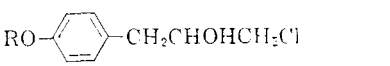
(3) N. G. Gaylord and E. I. Becker, *Chem. Revs.*, **49**, 413 (1951).

Attempts to improve the yield substantially by varying the conditions of the reaction were unsuccessful. The use of the Grignard chloride resulted in a very small or no yield, even when higher boiling solvents such as diisopropyl and dibutyl ether were used.

Table I lists the alkoxyphenyl chloropropanols with their boiling points, refractive indexes and analyses. Table II lists the boiling points of the bases as well as the melting points and analyses of the hydrochlorides of the alkoxyphenylaminopropanols.

TABLE I

ALKOXYPHENYLCHLOROPROPANOLS



R	Position	B.p., °C.	μ	$n^{20}D$	Formula	Chlorine, % Calcd.	Found
CH_3	*o*	99–101	30	1.5458	$C_{10}H_{13}O_2Cl$	17.68	16.92
CH_3	*p*	103–105	40[a]	1.5421	$C_{10}H_{13}O_2Cl$	17.68	17.42
C_2H_5	*o*	86–89	20	1.5231[b]	$C_{11}H_{15}O_2Cl$	16.53	16.99
C_2H_5	*p*	106–108	35	1.5369	$C_{11}H_{15}O_2Cl$	16.53	16.23
C_3H_7	*p*	120–124	60	1.5330	$C_{12}H_{17}O_2Cl$	15.52	15.48
C_4H_9	*m*	121–124	35	1.5270	$C_{13}H_{19}O_2Cl$	14.63	14.43
C_4H_9	*p*	112–115	20	1.5258	$C_{13}H_{19}O_2Cl$	14.63	14.32
i-C_5H_{11}	*m*	125–130	25	1.5210	$C_{14}H_{21}O_2Cl$	13.82	13.77
i-C_5H_{11}	*p*	123–128	30	1.5325	$C_{14}H_{21}O_2Cl$	13.82	14.05

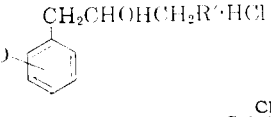
[a] Reported[4] b.p. 188–190° (24 mm.). [b] At 40°.

Pharmacology.—A pharmacological investigation of these compounds was conducted to evaluate their potential use as local anesthetics. The anesthetic potency, toxicity and irritation were determined and compared with cocaine and procaine. The intraperitoneal and subcutaneous toxicities were determined on a Swiss strain of male white mice. An average of twenty mice was used to ob-

(4) E. Fourneau and M. Tiffeneau, *Bull. soc. chim.*, [4] **1**, 1227 (1908).

TABLE II

ALKOXYPHENYL N-SUBSTITUTED AMINOPROPANOL HYDROCHLORIDES



No.	R	Position	R'	B.p., base °C.	μ	M.p., °C., HCl	Formula	Chlorine, % Calcd.	Found
1	CH_3	*p*	CH_3NH	108–110	20	123–124	$C_{11}H_{18}O_2NCl$	15.31	15.03
2	CH_3	*o*	C_2H_5NH	96–98	20	111–113	$C_{12}H_{20}O_2NCl$	14.44	14.43
3	CH_3	*p*	C_4H_9NH	115–120	20	139–140	$C_{14}H_{24}O_2NCl$	12.96	13.28
4	CH_3	*o*	*i*-C_4H_9NH	112–115	20	137–138	$C_{14}N_{24}O_2NCl$	12.96	13.01
5	CH_3	*p*	*i*-C_4H_9NH	120–122	40	146–148	$C_{14}H_{24}O_2NCl$	12.96	12.91
6	CH_3	*o*	$(C_2H_5)_2N$	106–109	40	104–107	$C_{14}H_{24}O_2NCl$	12.96	12.84
7	CH_3	*p*	$(C_2H_5)_2N$	86–90	10[a]	Oil	$C_{14}H_{24}O_2NCl$	12.96	13.10
8	CH_3	*p*	Morpholino	129–131	40	141–143	$C_{14}H_{22}O_3NCl$	12.33	12.60
9	CH_3	*o*	$C_5H_{11}NH$	117–119	30	144–145	$C_{15}H_{26}O_2NCl$	12.33	12.48
10	CH_3	*o*	Furfurylamino	132–135	50	Oil	$C_{15}H_{20}O_3NCl$	11.91	12.20
11	CH_3	*p*	Furfurylamino	135–137	50	140–142	$C_{15}H_{20}O_3NCl$	11.91	11.82
12	CH_3	*p*	Cyclohexylamino	153–156	50	160–161	$C_{16}H_{26}O_2NCl$	11.83	11.99
13	CH_3	*p*	Benzylamino	150–152	60	166–168	$C_{17}H_{22}O_2NCl$	11.52	11.76
14	CH_3	*p*	Heptyl-2-amino	145–150	20	122–123	$C_{17}H_{31}O_2NCl$	11.20	11.25
15	C_2H_5	*p*	CH_3NH	118–120	30	122–124	$C_{12}H_{20}O_2NCl$	14.44	14.29
16	C_2H_5	*p*	C_2H_5NH	128–130	30[b]	143–144	$C_{13}H_{22}O_2NCl$	13.65	13.73
17	C_2H_5	*p*	C_3H_7NH	125–127	30[c]	151–152	$C_{14}H_{24}O_2NCl$	12.96	13.05
18	C_2H_5	*o*	*i*-C_4H_9NH	120–125	30	126–127	$C_{15}H_{26}O_2NCl$	12.33	12.23
19	C_2H_5	*p*	*i*-C_4H_9NH	128–130	30[d]	144–146	$C_{15}H_{26}O_2NCl$	12.33	12.12
20	C_2H_5	*o*	$(C_2H_5)_2N$	110–112	60	99–100[e]	$C_{15}H_{26}O_2NBr$	24.05[e]	24.18
21	C_2H_5	*p*	$(C_2H_5)_2N$	110–112	30	99–100	$C_{15}H_{26}O_2NCl$	12.33	12.20
22	C_2H_5	*o*	Pyrrolidino	119–122	125	137–138	$C_{15}H_{24}O_2NCl$	12.42	12.72
23	C_2H_5	*o*	Morpholino	140–145	40	189–193	$C_{15}H_{24}O_3NCl$	11.75	12.08
24	C_2H_5	*p*	$C_5H_{11}NH$	121–124	40[f]	189–190	$C_{16}H_{28}O_2NCl$	11.75	11.72
25	C_2H_5	*o*	2-Pyridineamino	175–180	125	83–85	$C_{16}H_{20}O_2N_2Cl$	11.53	
26	C_2H_5	*o*	Furfurylamino	160–163	100	90–92	$C_{16}H_{22}O_3NCl$	11.38	11.68
27	C_2H_5	*o*	$(C_4H_9)(CH_2CH_2OH)N$	144–146	20	111–113	$C_{17}H_{30}O_3NCl$	10.72	10.90
28	C_2H_5	*o*	Benzylamino	145–147	250	100–102	$C_{18}H_{24}O_2NCl$	11.03	11.11
29	C_2H_5	*o*	Heptyl-2-amino	116–119	30	Oil	$C_{18}H_{32}O_2NCl$	10.76	
30	C_2H_5	*p*	$(C_4H_9)_2N$	134–136	30	80–83	$C_{19}H_{34}O_2NCl$	10.34	10.24
31	C_2H_5	*o*	$(C_4H_9)_2N$	120–122	20	84–85	$C_{19}H_{34}O_2NCl$	10.34	10.55
32	C_3H_7	*p*	*i*-C_4H_9NH	136–140	200	154–156	$C_{16}H_{28}O_2NCl$	11.75	11.80
33	C_3H_7	*p*	$(C_2H_5)_2N$	123–128	200	85–88	$C_{16}H_{28}O_2NCl$	11.75	11.89
34	C_4H_9	*m*	*i*-C_4H_9NH	155–160	800	114–116	$C_{17}H_{30}O_2NCl$	11.23	11.26
35	C_4H_9	*p*	*i*-C_4H_9NH	170–174	800	160–162	$C_{17}H_{30}O_2NCl$	11.23	11.18
36	C_4H_9	*m*	$(C_2H_5)_2N$	135–137	90	102–103	$C_{17}H_{30}O_2NCl$	11.23	11.33
37	C_4H_9	*p*	$(C_2H_5)_2N$	146–150	800	Oil	$C_{17}H_{30}O_2NCl$	11.23	11.41
38	*i*-C_5H_{11}	*p*	*i*-C_4H_9NH	124–126	20	125–135	$C_{18}H_{32}O_2NCl$	10.76	10.80
39	*i*-C_5H_{11}	*p*	$(C_2H_5)_2N$	120–125	30	Oil	$C_{18}H_{32}O_2NCl$	10.76	
40	*i*-C_5H_{11}	*m*	*i*-C_4H_9NH	150–153	50	115–118	$C_{18}H_{32}O_2NCl$	10.76	10.92
41	*i*-C_5H_{11}	*m*	$(C_2H_5)_2N$	137–140	20	87–90	$C_{18}H_{32}O_2NCl$	10.76	10.98

[a] $n^{24}D$ 1.5062, d^{24} 0.999, *MR* 70.39 (calcd. 70.52), mol. wt. 223 (calcd. 237); reported[1] b.p. 166–167° at 12 mm. [b] M.p. 59–60°. [c] M.p. 64–66°. [d] M.p. 47–51°. [e] Hydrobromide. [f] M.p. 74–76.°

tain the LD_{50} (lethal dose where 50% of the animals die). This value was compared with the LD_{50} for procaine hydrochloride of 750 mg. per kg. The intravenous toxicity on rabbits was determined for those compounds that were to be tested clinically.

The irritating properties of the compounds were checked by observing the effect of a 2% solution on the rabbit eye one hour and twenty-four hours after application. Those compounds to be tested clinically were also tested for irritation on intradermal injection in the rabbit by means of the trypan blue test.

Relative topical anesthetic potency was determined by application to the rabbit eye of successively lower concentrations of the compound until no response was obtained and comparing the result with that obtained in the literature for cocaine hydrochloride. Relative conductive and infiltration anesthetic potencies were obtained by comparing the anesthetic effect of successively lower doses of the compounds on blocking the sciatic nerve of the intact guinea pig and by the wheal test on the back of the guinea pig with that of procaine hydrochloride. These procedures have been described previously.[5]

An attempt was made to correlate molecular structure to physiological activity, with little success. However, a few general observations could be made: 1. Effect of the position and size of the alkoxy group R: (a) *ortho* and *meta* alkoxy derivatives appear to be more potent and more toxic than their *para* counterpart; (b) the methoxy deriva-

(5) E. Epstein and D. Kaminsky, *J. Am. Pharm. Assoc.*, **47**, 347 (1959).

tives appear to have a lower anesthetic efficiency (ratio of potency to toxicity) than the higher alkoxy derivatives. 2. Effect of varying the N-substituted group R′: (a) branched chain groups were less potent and toxic than straight chain groups; (b) heterocyclic and aromatic amino groups had a lower anesthetic efficiency than the alkyl amino groups.

Compounds 38, 40 and 41 proved to be more potent topically and less toxic than cocaine hydrochloride while compounds 13, 27, 29, 31, 32, 34, 35, 36, 40 and 41 were more potent on nerve block and infiltration anesthesia than procaine hydrochloride. The toxicity of this group ranged from equal to eight times as toxic as procaine hydrochloride. Several of these compounds when tried clinically in dental procedures were found to be as effective as procaine hydrochloride. The clinical evaluation is being continued and will be published elsewhere.

Experimental

The *o*- and *p*-anisole and phenetoles were obtained from commercial sources. The *p*-bromophenyl propyl ether and the *m*- and *p*-bromophenyl butyl and isoamyl ethers were prepared by alkylating the bromophenol with the appropriate alkyl halide, with a method similar to that described for alkylating nitrophenols.[6]

1-*p*-**Ethoxyphenyl-3-chloropropanol-2.**—The Grignard reagent prepared from 42 g. (1.8 moles) of magnesium and 300 g. (1.5 moles) of *p*-bromophenetole in 850 ml. of dry ether was treated with 280 g. (3 moles) of freshly distilled epichlorohydrin in one liter of dry ether with stirring. The mixture was refluxed for one hour after addition of the epichlorohydrin and allowed to stand overnight. To the mixture was added dropwise 150 ml. of water and then 850 ml. of a 20% sulfuric acid solution with stirring. The ether solution was separated, dried over anhydrous sodium sulfate and distilled over a water-bath to remove the ether. The residue was distilled under high vacuum and the fraction boiling 106–108° at 35 μ yielded 185 g. (58%) of a colorless liquid, $n^{20}D$ 1.5369, d^{20} 1.157, molecular refraction 57.94 (calcd. 57.43).

1-*p*-**Ethoxyphenyl-3-*n*-propylaminopropanol-2 Hydrochloride.**—A mixture of 25 g. (0.12 mole) of 1-*p*-ethoxyphenyl-2-chloropropanol-2, 40 g. (0.7 mole) of *n*-propylamine and 50 ml. of isopropyl alcohol was refluxed for 24 hours. The alcohol and excess amine were removed by evaporation on a steam-bath and the residue dissolved in 100 ml. of 2 *N* hydrochloric acid. The solution was extracted with three 50-ml. portions of ether to remove the unreacted chloropropanol and then made alkaline with 25 ml. of concentrated ammonium hydroxide solution, and extracted twice with 100-ml. portions of ether. The ether solution was dried over anhydrous sodium sulfate and the ether removed by distillation on a water-bath. The residue was distilled under high vacuum and the fraction at 125–127° at 30 μ was dissolved in 50 ml. of isopropyl alcohol and acidified with anhydrous hydrochloric acid to yield on recrystallization from isopropyl alcohol 19 g. (60%) of the anesthetic salt, m.p. 151–153°, as white crystals.

Acknowledgment.—We are indebted to Richard Sriubas for assistance in the analyses and to Michael Fisher for assistance in the pharmacological testing of these compounds.

BROOKLYN 7, N. Y.

(6) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 140.

[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Alkaloids of *Lunasia amara* Blanco. Isolation Studies

BY SIDNEY GOODWIN, A. F. SMITH, A. A. VELASQUEZ AND E. C. HORNING

RECEIVED APRIL 2, 1959

The isolation and characterization of fourteen leaf alkaloids of *Lunasia amara* Blanco are described.

A number of chemical and pharmacological studies of *Lunasia* alkaloids have been recorded since the initial observations of Lewin[1] and Boorsma,[1] but the structures of these compounds have been unknown until recently. Both leaves and bark of trees of this genus of the Rutaceae contain "water-soluble" alkaloids which are quaternary salts, and the organic bases include representatives of five classes of compounds. The following sections summarize what is known about the occurrence and structure of each of the alkaloids, and the Experimental section contains data relating to the isolation and characterization of the leaf bases of *Lunasia amara* Blanco of Philippine origin. With one exception (lunamaridine), all of the previously known bases have been found, together with a number of new ones. Table I contains formulas, melting points and yields of the leaf bases.

2-Arylquinolines.—An earlier report[2] described the isolation, structural identification and synthesis

(1) L. Lewin, "Lehrbuch der Toxikologie," 2nd Ed., Urban and Schwarzenberg, Vienna and Leipzig, 1897, p. 271; W. G. Boorsma, *Bull. Inst. Bot. Buitenzorg*, **6**, 15 (1900).

(2) S. Goodwin, A. F. Smith and E. C. Horning, THIS JOURNAL, **79**, 2239 (1957)

TABLE I

	Name	Formula	M.p., °C.	Yield,[a] %
I	4-Methoxy-2-phenylquinoline	$C_{16}H_{13}ON$	66–67	0.04
II	4-Methoxy-2-(3′,4′-methylenedioxyphenyl)-quinoline	$C_{17}H_{13}O_3N$	116–117	.002
III	7-Methoxy-1-methyl-2-phenyl-4-quinolone	$C_{17}H_{15}O_2N$	198–200	.002
IV	Lunamarine	$C_{18}H_{15}O_4N$	245–247	.004
V	Kokusagine	$C_{13}H_9O_4N$	195–197	.0003
VI	Skimmianine	$C_{14}H_{13}O_4N$	179–180	.0001
VII	Lunacrine	$C_{16}H_{15}O_3N$	117–118	.1
VIII	Lunine	$C_{16}H_{17}O_4N$	228–229	.004
IX	Hydroxylunacrine	$C_{16}H_{15}O_4N$	201–203	.002
X	Hydroxylunine	$C_{16}H_{17}O_5N$	228–230	.001
XII	Lunacridine	$C_{17}H_{23}O_4N$	85–86	...
XIII	Hydroxylunacridine	$C_{17}H_{23}O_5N$	100–102	.003
XIV	Hydroxylunidine	$C_{17}H_{21}O_6N$	124–125	.001
	Lunacrinol	$C_{16}H_{15}O_4N$	187–188	.0005
	Lunolone	.....	100–103	.001

[a] These yields are for pure material and are approximate.