presumably unreacted allylbenzene, was removed under a high vacuum. The residual viscous liquid, 28.4 g., was crystallized by the use of a small amount of Skellysolve E and recrystallized twice from methanol to yield 6.8 g. of white needles, m.p. 94.0–94.5° (lit.[29] m.p. of 1,1,4-triphenyl-3-butene-1-ol 94.0–94.5°). Vacuum distillation of 3.1 g. of the product with a trace of iodine gave, after one recrystallization from ethanol, 1.5 g. of white needles, m.p. 100.5–101.5° (lit.[17] m.p. of 1,1,4-triphenyl-1,3-butadiene 101.5–102.0°).

The liquid product, 16.7 g., from the filtrates of the recrystallization of the alcohol was not crystallizable, so it was dehydrated to the diene which, recrystallized three times from ethanol, had a m.p. of 101.0–101.5°. Based on combined alcohol and diene, the yield of crude 1,1,4-triphenyl-3-butene-1-ol was 41% and of pure product 25%.

2-Methyl-1-phenylhexane.—α-Methylcaprophenone[18] was reduced by the Huang-Minlon modification of the Wolff–Kishner reduction[34] in 43% yield. Redistillation gave the hydrocarbon, b.p. 228–230°, $n^{20}D$ 1.4868.

The sulfonamides[35] from the authentic 2-methyl-1-phenylhexane and from the material obtained by quenching the products of reaction of propenylbenzene and butyllithium both had m.p. and mixed m.p. of 93–94° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{13}H_{21}O_2NS$: C, 61.15; H, 8.23; N, 5.5; S, 12.55. Found: C, 61.32; H, 8.03; N, 5.6; S, 12.59.

(34) D. Todd in "Organic Reactions," R. Adams, editor, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 378.

(35) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 197.

TROY, NEW YORK

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

Alkyl and Diethylaminoethyl Esters of N-Substituted Aminoacylaminobenzoic Acids

BY ELIAS EPSTEIN AND DANIEL KAMINSKY

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Several alkyl esters of *o*- and *p*-N-substituted aminoacetyl- and propionylaminobenzoic acids as well as diethylaminoethyl esters of *p*-N-substituted aminoacetylaminobenzoic acids were prepared. They were tested as salts for anesthetic potency, toxicity and for irritation. The anesthetic efficiencies (ratio of potency to toxicity) of some of these compounds were sufficiently high to warrant further study.

At the turn of the century and prior to his discovery of procaine, Einhorn and his associates synthesized a group of alkylaminoacetylaminobenzoates.[1,2] The clinical use of one of these, methyl 5-diethylaminoacetylaminosalicylate (Nirvanine), was discontinued because of its irritating properties. Since then several investigators[3–8] have prepared substituted anilide anesthetics and found them too irritating for clinical use.

In 1946, Lofgren[9] prepared ω-diethylamino-2,6-dimethylacetanilide (lidocaine), which had a high anesthetic potency and was sufficiently non-irritating for clinical use. His success in finding this relatively non-irritating anilide anesthetic encouraged other investigators to prepare many other anilide derivatives.

Since Lofgren[10] has shown that relatively small changes in the molecular structure of his group of anilides can produce substantial changes in their toxicity, potency and irritating properties, it was of interest to us to reinvestigate the alkylaminoacylaminobenzoates of Einhorn. We extended the series to other alkyl and diethylaminoethyl esters of alkyl- and heterocyclic aminoacylaminobenzoic acids in order to determine the effect of molecular structure on the anesthetic potency, toxicity and irritating properties of this group of compounds.

Three series of N-substituted aminoacylamino benzoates were prepared: alkyl esters of *o*- and *p*-N-substituted aminoacetylaminobenzoic acids, alkyl esters of *o*- and *p*-N-substituted aminopropionylaminobenzoic acids and diethylaminoethyl esters of *p*-N-substituted aminoacetylaminobenzoic acids.

The method of preparation consisted of treating a chloroacyl chloride with an ester of aminobenzoic acid and subsequent condensation of the resulting chloroanilide with a primary or secondary amine to yield the anesthetic base. The hydrochloride salts of the anesthetic bases were purified by recrystallization from isopropyl alcohol or isopropyl alcohol–water mixtures. Table I lists the chloroacylamino benzoates with their melting points and analyses. Table II lists the melting points of the free bases together with the melting points, analyses and molecular weight determination of the hydrochlorides.

Pharmacology

A preliminary pharmacological investigation of these compounds as local anesthetics on experimental animals was conducted. The toxicities were determined intraperitoneally and subcutaneously on white mice. The irritation was determined by topical application on the rabbit cornea and by intradermal injection in the rabbit skin. The topical anesthetic potency was determined by noting the length and depth of anesthesia on the rabbit cornea produced by varying concentrations of the compound. The method of blocking the sciatic nerve of

(1) A. Einhorn, German Patent 106,502 (1898).

(2) A. Einhorn and M. Oppenheimer, *Ann.*, **311**, 155 (1900).

(3) E. Puxeddu and G. Sanna, *Gazz. chim. ital.*, **60**, 126 (1930) (*C. A.*, **24**, 3770 (1930)).

(4) G. Sanna and M. Grannata, *Rend. seminar facolta sci. univ. Cagliari*, **5**, 88 (1935) (*C. A.*, **33**, 5827 (1939)).

(5) G. Sanna, *Ann. chim. applicata*, **25**, 638 (1936) (*C. A.*, **30**, 5722 (1936)).

(6) H. Erdtman and N. Lofgren, *Svensk Kem. Tid.*, **49**, 163 (1937).

(7) K. Gaind, J. Ray and J. Yajnik, *J. Indian Chem. Soc.*, **17**, 400 (1940).

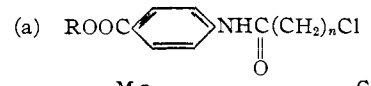
(8) K. Gaind, J. Ray and B. Sarin, *ibid.*, **17**, 619 (1940).

(9) N. Lofgren, *Arkiv Kemi, Mineral. Geol.*, **A22**, No. 18 (1946).

(10) N. Lofgren, "Studies on Local Anesthetics, Xylocaine, A New Synthetic Drug," Ivar Haeggstroms, Stockholm, 1948.

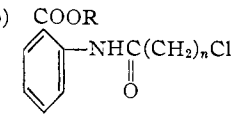
TABLE I

p-CHLOROACYLAMINOBENZOATES

(a) 

R	*n*	M.p., °C.	Formula	Chlorine, % Calcd.	Found
CH_3[a]	1	144–146	$C_{10}H_{10}O_3CNI$	15.58	15.48
C_2H_5[b]	1	116–118	$C_{11}H_{12}O_3NCl$	14.67	14.49
i-C_3H_7	1	105–107	$C_{12}H_{14}O_3NCl$	13.87	13.69
n-C_4H_9	1	91–92	$C_{13}H_{16}O_3NCl$	13.15	13.02
i-C_4H_9	1	113–115	$C_{13}H_{16}O_3NCl$	13.15	13.07
n-C_5H_{11}	1	96–98	$C_{14}H_{18}O_3NCl$	12.50	12.41
$C_6H_{11}(CH_3)CH$	1	48–51	$C_{17}H_{24}O_3NCl$	10.88	10.63
$(C_2H_5)_2NCH_2CH_2$[c]	1	61–64	$C_{15}H_{21}O_3N_2Cl$	11.56	11.45
C_2H_5	2	125–128	$C_{13}H_{14}O_3NCl$	13.87	13.71
i-C_3H_7	2	127–129	$C_{13}H_{16}O_3NCl$	13.15	13.10
n-C_4H_9	2	98–100	$C_{14}H_{18}O_3NCl$	12.50	12.39
i-C_4H_9	2	121–123	$C_{14}H_{18}O_3NCl$	12.50	12.38

o-CHLOROACYLAMINOBENZOATES

(b) 

C_2H_5[d]	1	79–81	$C_{11}H_{12}O_3NCl$	14.67	14.59
i-C_3H_7	1	50–52	$C_{12}H_{14}O_3NCl$	13.87	14.00
n-C_4H_9	1	46–48	$C_{13}H_{16}O_3NCl$	13.15	13.02
C_2H_5	2	67–69	$C_{12}H_{14}O_3NCl$	13.87	13.98

[a] Also prepared by Einhorn.[1,2] [b] Also prepared by Einhorn,[1,2] Sanna,[4,5] Clark and Hams.[11] [c] Also prepared by Jacobs and Heidelberger.[12] [d] Also prepared by Jacobs, Heidelberger and Rolf.[13]

the intact guinea pig was used to determine conductive anesthesia. The details of these procedures have been described previously.[14]

The anesthetic efficiency (ratio of potency to toxicity) of these compounds ranged from poor to excellent. A few compounds exhibited no apparent anesthetic potency in the concentrations tested. In general, the toxicities were low for local anesthetics. Several of these compounds, notably the capryl esters, were highly irritating.

The *n*-butyl ester of *p*-(β-isobutylaminopropionylamino)-benzoic acid hydrochloride was over one hundred times more efficient as a topical anesthetic than cocaine when applied to the rabbit cornea, and over one hundred times more efficient than procaine hydrochloride as a conductive anesthetic when used to block the sciatic nerve of the guinea pig.

Detailed pharmacological and clinical studies of these compounds will be published elsewhere.

Experimental

The methyl, ethyl, isobutyl and *n*-butyl *p*-amino- and the ethyl *o*-aminobenzoates were obtained from commercial sources. The isopropyl *o*- and *p*-aminobenzoates and the *n*-butyl *o*-aminobenzoate were prepared by the Fisher method with anhydrous hydrochloric acid in excess of the alcohol. The *n*-amyl and capryl *p*-aminobenzoates were prepared by treating *p*-nitrobenzoyl chloride with an excess of the appropriate alcohol and subsequent reduction with iron and hydrochloric acid. The diethylaminoethyl *p*-aminobenzoate (procaine) was obtained commercially.

The chloroacetylamino- and β-chloropropionylaminobenzoates were prepared by treating the chloroacyl chloride in glacial acetic acid with the substituted aniline. This method is substantially that of Jacobs and Heidelberger[15] as modified by Lofgren.[9,10] We found that a low temperature was not required and that the chloro compounds could be isolated by diluting the acetic acid with water or sodium acetate solution. The chloroacylaminobenzoates were purified by recrystallization from isopropyl alcohol or isopropyl alcohol–water mixtures. The chloroacetyl derivative of procaine was prepared in a similar manner but was isolated by removing the acetic acid by distillation under high vacuum.

The anesthetic compounds were prepared by treating the chloroacylaminobenzoates with an excess of the appropriate amine below 100° or at the reflux temperature.

Preparation of *n*-Amyl *p*-Aminobenzoate Hydrochloride.—Six hundred grams (7 moles) of *n*-amyl alcohol was added to 558 g. (3 moles) of *p*-nitrobenzoyl chloride and the mixture stirred for two hours without heating. The solution was then refluxed until no more hydrogen chloride was evolved, which took approximately six hours. The excess alcohol was removed by vacuum distillation on a steam-bath and the residue washed with a 5% sodium hydroxide solution. To the residual oil were added 250 ml. of isopropyl alcohol, 10 ml. of concentrated hydrochloric acid and 250 ml. of water. The mixture was heated to 70°, and 550 g. (10 moles) of iron filings in 50-g. portions were added with stirring at a rate sufficient to maintain the temperature between 60 to 70°. The mixture was stirred for an additional two hours at 70° and then filtered. The alcohol was removed by distillation, and to the residue were added 100 g. of citric acid and 10 g. of sodium hydrosulfite. The solution was made strongly alkaline with excess concentrated ammonium hydroxide and extracted with three 300-ml. portions of ether. The ether extract was washed once with water and dried over anhydrous sodium sulfate. After bone-charring, the ether solution was acidified with anhydrous hydrochloric acid. The precipitate on recrystallization from 99% isopropyl alcohol yielded 592 g. (83%) of *n*-amyl *p*-aminobenzoate hydrochloride as white crystals, m.p. 92–95°.

Isobutyl Ester of *p*-(β-Chloropropionylamino)-benzoate.—To a solution of 19.3 g. (0.1 mole) of isobutyl *p*-aminobenzoate in 150 ml. of glacial acetic acid was added rapidly, with vigorous stirring, 14.1 g. (0.11 mole) of β-chloropropionyl chloride. The solution was stirred for 0.5 hour and 100 g. of sodium acetate dissolved in 500 ml. of water was added. After stirring for an additional hour, the mixture was filtered. The product was recrystallized from 90% isopropyl alcohol to yield 26.8 g. (94%) of the isobutyl ester of *p*-(β-chloropropionylamino)-benzoate as white crystals, m.p. 122–125°.

Diethylaminoethyl Ester of *p*-Chloroacetylaminobenzoic Acid.—To 71 g. (0.3 mole) of procaine base in 100 ml. of glacial acetic acid was added dropwise, with constant stirring at room temperature, a solution of 37.5 g. (0.33 mole) of chloroacetyl chloride in 50 ml. of acetic acid over a period of 0.5 hour. The mixture was stirred for an additional hour and the excess acid removed by distillation under vacuum on a steam-bath. The residue was dissolved in ether and neutralized with a cold 5% solution of potassium carbonate. The ether layer was bone-charred and dried over anhydrous potassium carbonate. The ether was removed by distillation under vacuum at room temperature and the residue recrystallized from petroleum ether. The yield of diethylaminoethyl ester of *p*-chloroacetylaminobenzoic acid was 90 g. (95%) as white crystals, m.p. 61–64°.

Isobutyl Ester of *p*-(β-Diethylaminopropionylamino)-benzoic Acid Hydrochloride.—A mixture of 11.4 g. (0.04 mole) of isobutyl ester of *p*-(β-chloropropionylamino)-benzoic acid and 14.6 g. (0.2 mole) diethylamine was refluxed for four hours. The excess amine was removed by distillation under vacuum on a steam-bath and the residue taken up in 250 ml. of ether. The ether extract, after being washed twice with water and dried over anhydrous sodium sulfate, was bone-charred at room temperature. The solution was

(11) N. G. Clark and A. F. Hams, *Biochem. J.*, **55**, 839 (1953).

(12) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 139 (1915).

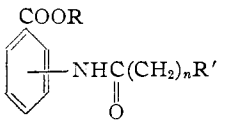
(13) W. A. Jacobs, M. Heidelberger and I. P. Rolf, THIS JOURNAL, **41**, 469 (1919).

(14) E. Epstein, M. Meyer and H. Ginsberg, *Current Res. Anes. & Analg.*, **34**, 171 (1954).

(15) W. A. Jacobs and M. Heidelberger, THIS JOURNAL, **39**, 1439, 1447 (1917).

TABLE II

ALKYL AND DIETHYLAMINOETHYL ESTERS OF N-SUBSTITUTED AMINOACYLAMINOBENZOIC ACIDS



R	R′	n	Position	M.p., °C., base[a]	M.p., °C., HCl	Formula	Chlorine, % Calcd.	Chlorine, % Found	Mol. wt. Calcd.	Mol. wt. Found
CH_3	NHC_2H_5	1	*p*	104–106	231–233[b]	$C_{12}H_{17}O_3N_2Cl$	13.00	12.99	273	273
CH_3	NHC_3H_7	1	*p*	56–60	242–244	$C_{13}H_{19}O_3N_2Cl$	12.36	12.21	287	289
CH_3	NHC_4H_9	1	*p*	71–75	229–232	$C_{14}H_{21}O_3N_2Cl$	11.79	11.52	301	300
CH_3	NHC_4H_9(iso)	1	*p*	Oil	180–182	$C_{14}H_{21}O_3N_2Cl$	11.79	11.85	301	301
CH_3	$N(C_2H_5)_2$	1	*p*	60–62	192–194[c]	$C_{14}H_{21}O_3N_2Cl$	11.79	11.71	301	303
CH_3	Morpholino	1	*p*	113–114	233–235	$C_{14}H_{19}O_4N_2Cl$	11.26	11.19	315	318
CH_3	Cyclohexylamino	1	*p*	103–104	286–287	$C_{16}H_{23}O_3N_2Cl$	10.85	10.61	327	320
C_2H_5	NHC_2H_5	1	*p*	66–70	206–208	$C_{13}H_{19}O_3N_2Cl$	12.36	12.57	287	290
C_2H_5	NHC_4H_9	1	*p*	69–72	243–245	$C_{15}H_{23}O_3N_2Cl$	11.26	11.23	315	310
C_2H_5	NHC_4H_9	2	*o*	Oil	145–149	$C_{16}H_{25}O_3N_2Cl$	10.78	10.57	329	325
C_2H_5	NHC_4H_9(iso)	1	*o*	60–64	180–183	$C_{15}H_{23}O_3N_2Cl$	11.26	11.43	315	318
C_2H_5	NHC_4H_9(iso)	1	*p*	42–45	235–237	$C_{15}H_{23}O_3N_2Cl$	11.26	11.32	315	318
C_2H_5	$N(C_2H_5)_2$	1	*o*	55–57	123–127	$C_{15}H_{23}O_3N_2Cl$	11.26	11.46	315	319
C_2H_5	$N(C_2H_5)_2$	1	*p*	[d]	171–174	$C_{15}H_{23}O_3N_2Cl$	11.26	11.30	315	318
C_2H_5	$N(C_2H_5)_2$	2	*o*	Oil	163–165	$C_{16}H_{25}O_3N_2Cl$	10.78	10.68	329	324
C_2H_5	$N(C_2H_5)_2$	2	*p*	Oil	88–90	$C_{16}H_{25}O_3N_2Cl$	10.78	10.84	329	327
C_2H_5	Morpholino	1	*o*	69–71	129–133	$C_{15}H_{21}O_4N_2Cl$	10.75	10.91	330	335
C_2H_5	Morpholino	1	*p*	77–80	182–185	$C_{15}H_{21}O_4N_2Cl$	10.75	10.74	330	330
C_2H_5	Morpholino	2	*o*	59–64	186–188	$C_{16}H_{23}O_4N_2Cl$	10.34	10.23	343	340
C_2H_5	Morpholino	2	*p*	Oil	219–221	$C_{16}H_{23}O_4N_2Cl$	10.34	10.26	343	342
C_2H_5	Cyclohexylamino	1	*p*	104–107	287–288	$C_{17}H_{25}O_3N_2Cl$	10.40	10.21	341	339
i-C_3H_7	NHC_2H_5	1	*p*	52–55	227–229	$C_{14}H_{21}O_3N_2Cl$	11.79	11.59	301	300
i-C_3H_7	NHC_3H_7	2	*p*	Oil	162–165	$C_{16}H_{25}O_3N_2Cl$	10.78	10.63	329	328
i-C_3H_7	NHC_4H_9	1	*p*	84–87	242–244	$C_{16}H_{25}O_3N_2Cl$	10.78	10.76	329	329
i-C_3H_7	NHC_4H_9	2	*p*	45–48	202–203	$C_{17}H_{27}O_3N_2Cl$	10.34	10.39	343	343
i-C_3H_7	NHC_4H_9(iso)	1	*p*	89–92	196–199	$C_{16}H_{25}O_3N_2Cl$	10.78	10.69	329	325
i-C_3H_7	$N(C_2H_5)_2$	1	*o*	Oil	179–182	$C_{16}H_{25}O_3N_2Cl$	10.78	10.69	329	327
i-C_3H_7	$N(C_2H_5)_2$	1	*p*	Oil	134–136	$C_{16}H_{25}O_3N_2Cl$	10.78	10.64	329	324
i-C_3H_7	$N(C_2H_5)_2$	2	*p*	Oil	182–185	$C_{17}H_{27}O_3N_2Cl$	10.34	10.46	343	340
i-C_3H_7	Morpholino	1	*p*	88–90	194–196	$C_{16}H_{23}O_4N_2Cl$	10.34	10.16	343	347
n-C_4H_9	NHC_2H_5	1	*p*	Oil	197–199	$C_{15}H_{23}O_3N_2Cl$	11.26	11.18	315	309
n-C_4H_9	NHC_3H_7	2	*p*	Oil	189–191	$C_{17}H_{27}O_3N_2Cl$	10.34	10.18	343	343
n-C_4H_9	NHC_4H_9	1	*p*	70–72	244–247	$C_{17}H_{27}O_3N_2Cl$	10.34	10.30	343	344
n-C_4H_9	NHC_4H_9	2	*p*	85–89	192–194	$C_{18}H_{29}O_3N_2Cl$	9.93	9.98	357	359
n-C_4H_9	NHC_4H_9(iso)	1	*p*	Oil[e]	225–227	$C_{17}H_{27}O_3N_2Cl$	10.34	10.42	343	347
n-C_4H_9	NHC_4H_9(iso)	2	*p*	Oil	125–128	$C_{18}H_{29}O_3N_2Cl$	9.93	9.74	357	353
n-C_4H_9	NHC_4H_9(tert)	2	*p*	63–67	178–180	$C_{18}H_{29}O_3N_2Cl$	9.93	9.93	357	352
n-C_4H_9	$N(C_2H_5)_2$	1	*o*	Oil	127–130	$C_{17}H_{27}O_3N_2Cl$	10.34	10.22	343	340
n-C_4H_9	$N(C_2H_5)_2$	1	*p*	Oil	118–122	$C_{17}H_{27}O_3N_2Cl$	10.34	10.21	343	339
n-C_4H_9	$N(C_2H_5)_2$	2	*p*	Oil	144–146	$C_{18}H_{29}O_3N_2Cl$	9.93	9.81	357	352
n-C_4H_9	Morpholino	1	*o*	Oil	136–139	$C_{17}H_{25}O_4N_2Cl$	9.93	9.84	357	356
n-C_4H_9	Morpholino	1	*p*	71–73	196–198	$C_{17}H_{25}O_4N_2Cl$	9.93	10.06	357	358
n-C_4H_9	Morpholino	2	*p*	Oil	217–219	$C_{18}H_{27}O_4N_2Cl$	9.56	9.39	371	370
i-C_4H_9	$NHCH_3$	1	*p*	68–71	176–179	$C_{14}H_{21}O_3N_2Cl$	11.79	11.54	301	294
i-C_4H_9	NHC_2H_5	1	*p*	83–86	216–219	$C_{15}H_{23}O_3N_2Cl$	11.26	11.01	315	317
i-C_4H_9	NHC_3H_7	1	*p*	Oil	211–213	$C_{16}H_{25}O_3N_2Cl$	10.78	10.94	329	333
i-C_4H_9	NHC_4H_9	1	*p*	80–82	246–249	$C_{17}H_{27}O_3N_2Cl$	10.34	10.38	343	340
i-C_4H_9	NHC_4H_9(iso)	1	*p*	Oil	207–209	$C_{17}H_{27}O_3N_2Cl$	10.34	10.12	343	337
i-C_4H_9	NHC_4H_9(iso)	2	*p*	Oil	220–222	$C_{18}H_{29}O_3N_2Cl$	9.93	9.97	357	358
i-C_4H_9	$N(C_2H_5)_2$	1	*p*	Oil	153–155	$C_{17}H_{27}O_3N_2Cl$	10.34	10.22	343	340
i-C_4H_9	$N(C_2H_5)_2$	2	*p*	Oil	150–152	$C_{18}H_{29}O_3N_2Cl$	9.93	9.93	357	359
i-C_4H_9	$N(C_4H_9)_2$	1	*p*	Oil	294–296	$C_{21}H_{35}O_3N_2Cl$	8.89	8.64	399	397
i-C_4H_9	Pyrrolidino	1	*p*	69–71	178–179	$C_{17}H_{25}O_3N_2Cl$	10.40	10.44	341	339
i-C_4H_9	Piperidino	1	*p*	86–89	193–196	$C_{18}H_{27}O_3N_2Cl$	9.99	9.80	355	349
i-C_4H_9	Morpholino	1	*p*	92–95	198–200	$C_{17}H_{25}O_4N_2Cl$	9.93	10.08	357	361
i-C_4H_9	Morpholino	2	*p*	109–112	223–224	$C_{18}H_{27}O_4N_2Cl$	9.56	9.47	371	369
i-C_4H_9	2,6-Dimethylmorpholino	1	*p*	94–96	203–205	$C_{19}H_{29}O_4N_2Cl$	9.21	9.14	385	387
i-C_4H_9	Cyclohexylamino	1	*p*	155–159	286–288	$C_{19}H_{29}O_3N_2Cl$	9.61	9.50	369	372

i-C_4H_9	Cyclohexylmethylamino	1	p	90–94	262–264	$C_{20}H_{31}O_3N_2Cl$	9.26	9.36	383	385
i-C_4H_9	Furfurylamino	1	p	Oil	244–247	$C_{18}H_{23}O_4N_2Cl$	9.66	9.39	367	363
i-C_4H_9	Benzylamino	1	p	103–106	240–242	$C_{20}H_{25}O_3N_2Cl$	9.41	9.56	377	384
i-C_4H_9	$NH(CH_2)_3N(CH_3)_2$	1	p	Oil	226–228	$C_{18}H_{30}O_3N_3Cl$	9.54	9.31	372	368
n-C_5H_{11}	NHC_2H_5	1	p	Oil	206–208	$C_{16}H_{25}O_3N_2Cl$	10.78	11.01	329	332
n-C_5H_{11}	NHC_4H_9	1	p	Oil	244–246	$C_{18}H_{29}O_3N_2Cl$	9.93	9.91	357	359
n-C_5H_{11}	NHC_4H_9(iso)	1	p	57–59	205–208	$C_{18}H_{29}O_3N_2Cl$	9.93	9.85	357	358
n-C_5H_{11}	$N(C_2H_5)_2$	1	p	Oil	138–142	$C_{18}H_{29}O_3N_2Cl$	9.93	9.81	357	353
n-C_5H_{11}	Morpholino	1	p	88–91	162–164	$C_{18}H_{27}O_4N_2Cl$	9.56	9.72	371	373
n-$C_6H_{13}(CH_3)CH$	$N(C_2H_5)_2$	1	p	Oil	110–114	$C_{21}H_{35}O_3N_2Cl$	8.89	8.70	399	394
n-$C_6H_{13}(CH_3)CH$	Morpholino	1	p	Oil	112–115	$C_{21}H_{33}O_4N_2Cl$	8.59	8.89	413	420
n-$(C_2H_5)_2NCH_2CH_2$	NHC_4H_9(iso)	1	p	Oil	187–191	$C_{19}H_{33}O_3N_3Cl_2$	16.78	16.40	422	416
n-$(C_2H_5)_2NCH_2CH_2$	$N(C_2H_5)_2$	1	p	18–22	193–195	$C_{19}H_{33}O_3N_3Cl_2$	16.78	17.02	422	426
n-$(C_2H_5)_2NCH_2CH_2$	Morpholino	1	p	Oil	151–154	$C_{19}H_{31}O_4N_3Cl_2$	16.26	16.61	436	441

[a] Most of these bases form crystalline hydrates. However, the anhydrous form is reported in this column. Since they crystallize with difficulty, some of these compounds reported as oils may crystallize on long standing. [b] Reported[2] m.p. of base 101–102°, m.p. of hydrochloride 218°. [c] Reported[2] m.p. of base 59–60°, m.p. of hydrochloride 186–187°. [d] Reported[4,5] m.p. of base 115°, m.p. of hydrochloride 211°. [e] B.p. 152–156° at 20 μ.

acidified with anhydrous hydrochloric acid. The precipitated salt was recrystallized from 99% isopropyl alcohol to yield 12.8 g. (89%) of the isobutyl ester of p-(β-diethylaminopropionylamino)-benzoic acid hydrochloride as white crystals, m.p. 150–152°.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Unsaturated Macrocyclic Compounds. III.[1] Synthesis of Cyclohexadeca-1,3,9,11-tetrayne by a Novel Cyclization Reaction[2]

BY F. SONDHEIMER AND Y. AMIEL

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The terminal diacetylene octa-1,7-diyne (I) on oxidation with oxygen in the presence of cuprous chloride and ammonium chloride in aqueous ethanol has been found to give 8% of cyclohexadeca-1,3,9,11-tetrayne (VI) by a novel cyclization reaction. The major products of the reaction are hexadeca-1,7,9,15-tetrayne (II) and dotriaconta-1,7,9,15,17,23,25,31-octayne (IV). Under milder conditions essentially only the linear tetraacetylene II is formed.

The oxidative coupling of terminal acetylenes (R—C≡CH) to the corresponding α-diacetylenes (RC≡C—C≡CR), first discovered by Glaser nearly ninety years ago,[3] is one of the few reactions in organic chemistry in which two molecules are linked together directly to give a symmetrical product. The reaction has become of considerable synthetic importance, since not only acetylenic hydrocarbons[3] but also alcohols,[4a,b] amines,[4c] nitro compounds,[4d] carboxylic acids[4e,f] and esters[4g] usually give the coupled products smoothly and in high yield. The reaction, which takes place under very mild conditions, may be brought about by oxidizing the cuprous derivative of the acetylene with air or oxygen,[3,4a,b] cupric chloride,[5a] hydrogen peroxide,[5b] potassium ferricyanide[4d,e,5c] or simply by heating[5d] and by oxidizing the Grignard derivative with iodine[5e,f] or cupric halides.[5e,g] Very recently Eglinton and Galbraith[6] made the interesting discovery that the coupling can be brought about simply and under homogeneous conditions by treating the acetylene with excess cupric acetate in methanol and pyridine.

Although the aforementioned type of oxidative coupling of acetylenes has been studied extensively, when we started our investigation only compounds containing a single terminal acetylene had been submitted to it. It seemed to be of interest to investigate the reaction with terminal diacetylenes of type HC≡C—n—C≡CH. Firstly the normal coupled product (HC≡C—n—C≡C—C≡C—n—C≡CH), being again a terminal diacetylene, might react further to give an unsaturated linear long-chain compound of high molecular weight, or if isolated, could be a useful intermediate in synthetic

(1) (a) The paper by F. Sondheimer and Y. Amiel (THIS JOURNAL, **78**, 4178 (1956)) is to be considered Part I of this series; (b) for Part II see Y. Amiel, F. Sondheimer and R. Wolovsky (*Proc. Chem. Soc.*, 22 (1957)).

(2) Presented before the Organic Chemistry Division at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1956.

(3) C. Glaser, *Ber.*, **2**, 422 (1869); *Ann.*, **154**, 159 (1870).

(4) *Inter al.* (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and K. H. Sargent, *J. Chem. Soc.*, 1579 (1947); (b) J. B. Armitage, C. L. Cook, N. Entwistle, E. R. H. Jones and M. C. Whiting, *ibid.*, 1998 (1952); (c) J. D. Rose and B. C. L. Weedon, *ibid.*, 782 (1949); (d) A. Bayer, *Ber.*, **15**, 50 (1882); (e) **18**, 674, 2269 (1885); (f) H. K. Black and B. C. L. Weedon, *J. Chem. Soc.*, 1785 (1953); (g) T. Bruun, P. K. Christensen, C. M. Haug, J. Stene and N. A. Sörensen, *Acta Chem. Scand.*, **5**, 1244 (1951); **6**, 602 (1952); J. P. Riley, *J. Chem. Soc.*, 2193 (1953).

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(6) G. Eglinton and A. R. Galbraith, *Chemistry & Industry*, 737 (1956); see also F. Bohlmann and J. Politt, *Ber.*, **90**,130 (1957).