3–7, 35.5 g., 85° (29 mm.), 1.4260; residue, 0.8 g. Fractions 3–7 were a 92% yield of *n*-propylneopentylcarbinol. *Anal.* Calcd. for $C_9H_{20}O$: C, 75.0; H, 14.0. Found: C, 74.5; H, 14.5. The phenylurethan had m. p. 82°.

Preparation of *n*-Butylneopentylcarbinol.—*n*-Butyl neopentyl ketone, b. p. 69° (13 mm.), $n^{20}D$ 1.4204, d^{20}_4 0.8143, was prepared in 77% yield by the action of *n*-butylmagnesium bromide on *t*-butylacetamide, m. p. 132°. Heating of 26.7 g. (0.17 mole) of the ketone with 20.4 g. (0.1 mole) of aluminum isopropylate in 120 cc. of dry isopropyl alcohol was conducted for twenty-four hours with the removal of acetone, during the course of the reaction, through column VI: 1–2, 3.1 g., 90–99° (30 mm.), 1.4254–1.4300; 3–5, 22.2 g., 95° (24 mm.), 1.4308, d^{20}_4 0.8212; residue, 2.0 g. Fractions 3–5 represented a 93% yield of *n*-butylneopentylcarbinol. *Anal.* Calcd. for $C_{10}H_{22}O$: C, 75.9; H, 13.9. Found: C, 75.7; H, 14.1. The α-naphthylurethan had m. p. 70–70.5°.

Preparation of *n*-Amylneopentylcarbinol.—*n*-Amylneopentyl ketone, b. p. 86° (13 mm.), $n^{20}D$ 1.4247, d^{20}_4 0.8184, was prepared in 60% yield from *n*-amylmagnesium bromide and *t*-butylacetamide. Heating of 51 g. (0.25 mole) of aluminum isopropylate in 400 cc. of dry isopropyl alcohol with 90 g. (0.53 mole) of the ketone for thirty-three hours gave a crude carbinol which, on fractionation through column VI, gave: 1–2, 3.4 g., 80–94° (12 mm.), 1.4271–1.4326; 3–12, 80.7 g., 96° (13 mm.), 1.4338, d^{20}_4 0.8225. Fractions 3–12 represented an 89% yield of *n*-amylneopentylcarbinol. *Anal.* Calcd. for $C_{11}H_{24}O$: C, 76.7; H, 14.0. Found: C, 76.9; H, 14.0. Phenylurethan, m. p. 60.5–61°; α-naphthylurethan, m. p. 63–63.5°.

Summary

1. The action of *n*-propyl-, *n*-butyl- and *n*-amylmagnesium bromides on *t*-butylacetyl chloride produced, together with the expected tertiary carbinols and olefins, *n*-propylneopentylcarbinol in 24.4% yield, *n*-butylneopentylcarbinol in 20.5% yield, *n*-amylneopentylcarbinol in 19.3% yield, respectively. No reduction product could be isolated when ethylmagnesium bromide was used.

2. The preparation and physical constants of *n*-propylneopentyl-, *n*-butylneopentyl-, and *n*-amylneopentylcarbinols have been reported.

STATE COLLEGE, PENNA. RECEIVED JUNE 29, 1938

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. XXI. Morpholino Alcohols Derived from Phenanthrene[1]

BY ERICH MOSETTIG, FORREST W. SHAVER AND ALFRED BURGER

As part of a systematic search for substances with central narcotic action, which, eventually, might replace morphine, we have synthesized in previous years a large variety of amino alcohols derived from phenanthrene.[2] Dr. N. B. Eddy at the University of Michigan has shown[3] that some of these phenanthryl amino alcohols produce in the cat marked analgesia and a physiological picture very like that of morphine. Furthermore, a distinct interdependence of degree of analgesic action and nature of the tertiary amino group became evident when, in the various groups of amino alcohols, individual members differing only in the basic group were compared. Thus, for example, the diethylamino derivatives of types I and II are superior to the dimethylamino derivatives.[4]

Extension of these studies to morpholino alcohols (I–VI) seemed justified, in order that comparison with the corresponding diethyl and piperidino compounds might be made.

The preparation of the various amino alcohols proceeded quite normally except that in the catalytic hydrogenation of 2-morpholino-1-keto-1,2,-3,4-tetrahydrophenanthrene the two diastereoisomeric forms (A and B) of the corresponding amino alcohol (type III) were formed. We have

(1) (a) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. (b) Communications XIX and XX of this series have been submitted to the *Journal of Organic Chemistry*.

(2) (a) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933); (b) Burger and Mosettig, *ibid.*, **56**, 1745 (1934); (c) van de Kamp and Mosettig, *ibid.*, **57**, 1107 (1935); (d) Mosettig and Burger, *ibid.*, **57**, 2189 (1935); (e) van de Kamp and Mosettig, *ibid.*, **58**, 1568 (1936); (f) Burger and Mosettig, *ibid.*, **58**, 1570 (1936); (g) Burger and Mosettig, *ibid.*, **58**, 1857 (1936); (h) van de Kamp, Burger and Mosettig, *ibid.*, **60**, 1321 (1938); (i) Burger, *ibid.*, **60**, 1533 (1938).

(3) (a) Eddy, *J. Pharmacol.*, **55**, 419 (1935); (b) Eddy, *ibid.*, (*Proc.*) **54**, 140 (1936); (c) Mosettig, Eddy and co-workers, "Attempts to Synthesize Substances with Central Narcotic and, in Particular, Analgesic Action." Supplement 138 to the U. S. Public Health Reports, Government Printing Office, Washington, D. C., in press.

(4) Such regularities have been observed also in the dibenzofuran series [Eddy, *J. Pharmacol.*, **58**, 159 (1936); Mosettig and Robinson, THIS JOURNAL, **57**, 2186 (1935); Robinson and Mosettig, *ibid.*, **58**, 688 (1936)] and in the carbazole series [Ruberg and Small, *ibid.*, **60**, 1591 (1938)].

No.	Derivatives of phenanthrene	Appearance	Solvent	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	2-(2-Morpholino-1-oxo-ethyl)-[a]	Light yellow plates	MeOH	154–156	$C_{20}H_{19}O_2N$	78.65	78.49	6.28	6.30
2	-Hydrochloride[b]	Light yellow plates	MeOH–Et_2O	268, dec.	$C_{20}H_{20}O_2NCl$	70.25	70.32	5.90	6.05
3	2-(2-Morpholino-1-hydroxy-ethyl)-[c]	Colorless	MeOH	129–131	$C_{20}H_{21}O_2N$	78.13	78.06	6.89	6.67
4	-Hydrochloride[d]	Colorless leaflets	MeOH–Et_2O	244–245, dec.	$C_{20}H_{22}O_2NCl$	69.84	69.61	6.46	6.35
5	3-(2-Morpholino-1-oxo-ethyl)-[e]	Light yellow	MeOH	136.5–137.5	$C_{20}H_{19}O_2N$	78.65	78.44	6.28	6.13
6	-Hydrochloride	Light yellow needles	MeOH–Et_2O	237, dec.	$C_{20}H_{20}O_2NCl$	70.25	69.95	5.90	6.03
7	3-(2-Morpholino-1-hydroxy-ethyl-	Colorless leaflets	MeOH	115–117	$C_{20}H_{21}O_2N$	78.13	78.18	6.89	6.56
8	-Hydrochloride[f]	Colorless leaflets	MeOH–Et_2O	214, dec.	$C_{20}H_{22}O_2NCl$	69.84	69.59	6.46	6.32
9	2-(3-Morpholino-1-oxo-propyl)-[g]	Colorless leaflets	MeOH	120–130	$C_{21}H_{21}O_2N$	78.95	79.34	6.63	6.39
10	-Hydrochloride[b]	Colorless leaflets	MeOH	224–226, dec.	$C_{21}H_{22}O_2NCl$	70.86	71.15	6.24	6.19
11	2-(3-Morpholino-1-hydroxy-*n*-propyl)-[h]	Colorless		98–100	$C_{21}H_{23}O_2N$	78.46	78.30	7.22	7.36
12	-Hydrochloride[i]	Needles	MeOH–Et_2O	177–179, dec.	$C_{21}H_{24}O_2NCl$	70.46	70.18	6.76	6.99
13	2-(3-Morpholino-1-acetoxy-*n*-propyl)-HCl[j]	Colorless plates	MeOH–Et_2O	253, dec.	$C_{23}H_{26}O_3NCl$	69.05	69.36	6.56	6.84
14	3-(3-Morpholino-1-oxo-propyl)-[k]	Colorless leaflets	MeOH	114–116	$C_{21}H_{21}O_2N$	78.95	78.96	6.63	6.75
15	-Hydrochloride[l]	Colorless prisms	MeOH–Et_2O	207–208, dec.	$C_{21}H_{22}O_2NCl$	70.86	71.06	6.24	6.22
16	3-(3-Morpholino-1-hydroxy-*n*-propyl)-		MeOH	83–86	$C_{21}H_{23}O_2N$	78.46	78.36	7.22	7.32
17	-Hydrochloride[m]	Colorless	MeOH–Et_2O	172–174, dec.	$C_{21}H_{24}O_2NCl$	70.46	70.72	6.76	6.80
18	3-(3-Morpholino-1-acetoxy-*n*-propyl)-HCl[n]	Colorless prisms		226–227, dec.	$C_{23}H_{26}O_3NCl$	69.05	69.44	6.56	6.74
19	3-Methoxy-9-(2-morpholino-1-oxo-ethyl)-HCl[o]	Yellow	MeOH–Et_2O	240–242, dec.	$C_{21}H_{22}O_3NCl$	Nitrogen, 3.77			3.72
20	3-Methoxy-9-(2-morpholino-1-hydroxy-ethyl)-HCl[o]	Glittering leaflets	MeOH–Et_2O	217–219, dec.	$C_{21}H_{24}O_3NCl$	67.44	67.04	6.47	6.52
	Derivatives of 1,2,3,4-tetrahydrophenanthrene								
21	2-Morpholino-1-keto-[p]	Yellow clusters	Me_2CO	141–171, dec.	$C_{18}H_{19}O_2N$	76.83	77.04	6.81	6.81
22	-Hydrochloride	Colorless	EtOH- Et_2O	230–231, dec.	$C_{18}H_{20}O_2NCl$	Nitrogen, 4.41			4.62
23	2-Morpholino-1-hydroxy-(A)[q]	Colorless needles	EtOH	179–180	$C_{18}H_{21}O_2N$	76.28	75.90	7.48	7.70
24	-Hydrochloride	Colorless	EtOH	245, dec.	$C_{18}H_{22}O_2NCl$	67.57	67.39	6.94	6.68
25	2-Morpholino-1-acetoxy-HCl (A)		EtOH–Et_2O	189, dec.	$C_{20}H_{24}O_3NCl$	66.36	66.70	6.69	6.65
26	2-Morpholino-1-hydroxy-(B)	Stout prisms	EtOH	139–140.5	$C_{18}H_{21}O_2N$	76.28	76.16	7.48	7.52
27	-Hydrochloride	Colorless	EtOH–Et_2O	252–253, dec.	$C_{18}H_{22}O_2NCl$	67.57	67.43	6.94	7.33
28	2-Morpholino-1-hydroxy-(B_1)	Colorless flat plates	EtOH	153–154	$C_{18}H_{21}O_2N$	76.28	76.28	7.48	7.71
29	2-Morpholino-1-acetoxy-HCl (B_1)		MeOH–Et_2O	208–210, dec.	$C_{20}H_{24}O_3NCl$	66.36	65.72	6.69	7.10
30	2-Morpholinomethyl-1-keto-	Glittering plates	Dil. MeOH	121	$C_{19}H_{21}O_2N$	Nitrogen, 4.75			4.77
31	-Hydrochloride[r]	Colorless prisms	EtOH	182–183, dec.	$C_{19}H_{22}O_2NCl$	Nitrogen, 4.22			4.26
32	2-Morpholinomethyl-1-hydroxy-	Colorless prisms	EtOH	120–121	$C_{19}H_{23}O_2N$	76.72	76.82	7.80	7.73
33	-Hydrochloride[s]	Stout prisms	EtOH	230–240, dec.	$C_{19}H_{24}O_2NCl$	68.33	68.36	7.25	6.96
34	3-Morpholino-4-keto-[t]	Colorless needles	Dil. MeOH	127–128	$C_{18}H_{19}O_2N$	Nitrogen, 4.98			5.08
35	-Hydrochloride	Colorless	MeOH–Et_2O	227–228, dec.	$C_{18}H_{20}O_2NCl$	68.00	68.38	6.35	6.21
36	3-Morpholino-4-hydroxy-	Colorless prisms	MeOH	185–186	$C_{18}H_{21}O_2N$	76.28	76.45	7.48	7.36
37	-Hydrochloride[u]	Whetstone-shaped	EtOH	238–240, dec.	$C_{18}H_{22}O_2NCl$	67.57	67.24	6.94	7.52
38	3-Morpholino-4-acetoxy-HCl	Colorless needles	EtOH–Et_2O	203–204, dec.	$C_{20}H_{24}O_3NCl$	Nitrogen, 3.87			4.00
39	3-Morpholinomethyl-4-keto-HCl[v]	Prisms	EtOH–Et_2O	170–172, dec.	$C_{19}H_{22}O_2NCl$	Nitrogen, 4.22			4.40
40	3-Morpholinomethyl-4-hydroxy-HCl	Colorless flat plates	EtOH–Et_2O	173, dec.	$C_{19}H_{24}O_2NCl$	68.33	68.62	7.25	7.07

[a] To a solution of 5 g. of 2-ω-bromoacetylphenanthrene[2a] in 40 ml. of dry benzene was added 3.5 g. of morpholine ($n^{20}D$ 1.4547), and the mixture was allowed to stand overnight. It was diluted with ether, the solution was washed with water, and the solvent was evaporated under reduced pressure; yield 89%.

[b] The hydrochloride was obtained by adding an ethereal solution of hydrogen chloride to an acetone solution of the free base.

[c] Liberated from No. 4 with sodium hydroxide solution and extracted into ether.

[d] A suspension of 4 g. of No. 2 and 0.16 g. of platinum oxide in 160 ml. of ethanol absorbed the required amount of hydrogen in about ten hours. The catalyst was filtered out and the solvent was evaporated under reduced pressure. The residue was dissolved in acetone, the acetone solution was diluted with ether, and allowed to crystallize; yield 75%.

[e] Obtained like No. 1, by employing 8.3 g. of 3-ω-bromoacetylphenanthrene, 40 ml. of benzene, and 5.6 g. of morpholine. The amino ketone was purified through the hydrochloride; yield 85%.

[f] Prepared like No. 4; yield 70%.

[g] A mixture of 3 g. of 2-acetylphenanthrene,[5] 1 g. of paraformaldehyde, 2 g. of morpholine hydrochloride (prepared by neutralizing morpholine with alcoholic hydrogen chloride and precipitating the salt with ether), and 12 ml. of isoamyl alcohol was boiled under reflux for six minutes. The amino ketone hydrochloride precipitated out within this time, and the precipitation was completed by addition of ether to the cooled reaction mixture. The free base was liberated from the salt with ammonium hydroxide, and extracted into ether. The ether solution was washed with water. The base was purified by sublimation in an oil-pump vacuum, and crystallization; yield 73%.

[h] Prepared from No. 12 and purified by sublimation in an oil-pump vacuum.

[i] Prepared like No. 4; yield 63%.

[j] A suspension of 0.3 g. of the amino alcohol in 5 ml. of dry pyridine and 1 ml. of acetic anhydride was allowed to stand for forty-eight hours. The solvent was evaporated under reduced pressure, the residue was washed with acetone and recrystallized.

[k] Prepared from No. 15.

[l] Prepared like No. 9, except that the hydrochloride, as precipitated from the reaction mixture, was purified by crystallization; yield 76%.

[m] Prepared by catalytic hydrogenation of No. 15; yield 82%.

[n] Ten and two-tenths grams of 3-methoxy-9-ω-bromoacetylphenanthrene[2b] was allowed to react with 7.5 g. of morpholine in 50 ml. of benzene for one hour. The mixture was extracted with water, the benzene solution was dried, evaporated in a vacuum, and the oily residue was converted to the hydrochloride in acetone solution; yield 82%.

[o] Prepared by catalytic hydrogenation of No. 19 (methanol, platinum oxide); yield 70%. The free base could not be obtained crystalline.

[p] Nine grams of 1-keto-2-bromo-1,2,3,4-tetrahydrophenanthrene[2d] and 7.5 g. of morpholine were allowed to react in 30 ml. of benzene for forty-eight hours. The red mixture was extracted with water and a crystalline residue was obtained by evaporation of the benzene layer; yield 55%.

[q] Seventeen and five-tenths grams of No. 22 in 400 ml. of methanol and 0.5 g. of platinum oxide absorbed approximately the calculated amount of hydrogen in a week. The mixture of crystalline hydrochlorides was converted to the bases, m. p. 95–127°; yield 16 g. This mixture was dissolved in 100 ml. of hot ethanol and allowed to crystallize. The first crop (A) was filtered when the temperature of the solution had reached 30°. Another crop (B) was obtained by allowing the filtrate to crystallize slowly. The base A was recrystallized from ethanol three times to the constant m. p. 179–180°; yield 1 g. The hydrochloride was formed from the base in acetone suspension with ethereal hydrogen chloride. The acetyl derivative was obtained by the action of acetic anhydride in pyridine solution. The base B was recrystallized from ethanol three times to the constant m. p. 139–140.5°; yield 1 g. In a second experiment, similarly, two bases were obtained. The one was base A of m. p. 179–180°, the other one melted at 153–154° (B_1). A new determination of the melting point of B showed that this compound had changed, in the meantime, to the higher-melting form.

[r] Prepared by the Mannich reaction, by heating to boiling a solution of the reactants (10 g. of 1-ketotetrahydrophenanthrene, 12 g. of paraformaldehyde, and 7 g. of morpholine hydrochloride) in 50 ml. of isoamyl alcohol for four minutes. The crude hydrochloride was washed with acetone; yield 41%.

[s] Prepared by catalytic hydrogenation of No. 31; yield 94%.

[t] Prepared like No. 21 by allowing 3-bromo-4-keto-1,2,3,4-tetrahydrophenanthrene to react with morpholine in benzene solution; yield 63%.

[u] Prepared by catalytic hydrogenation of No. 35; yield 68%.

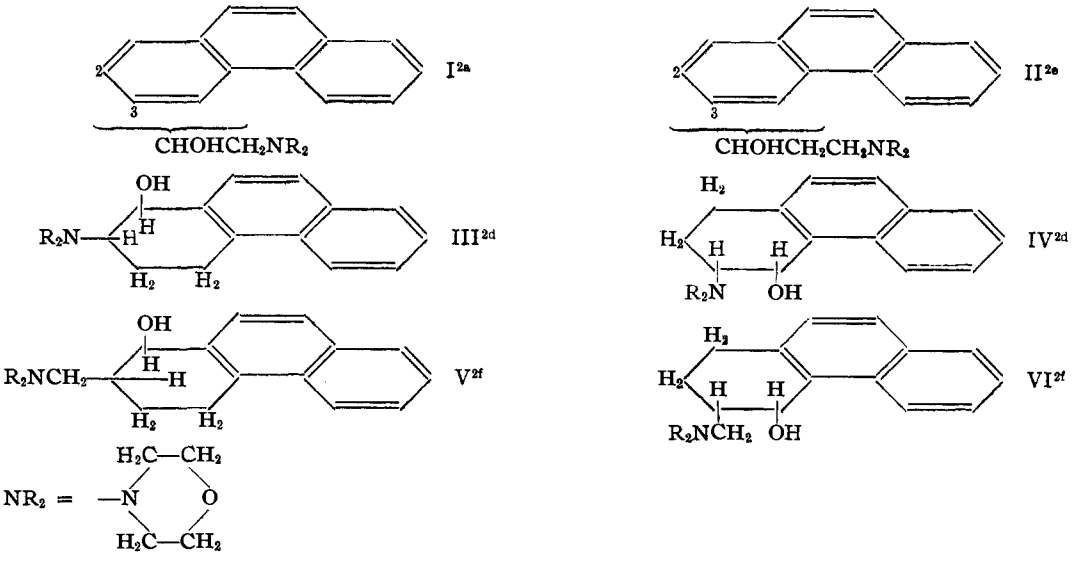
[v] Six grams of 4-keto-1,2,3,4-tetrahydrophenanthrene was boiled with 4.2 g. of morpholine hydrochloride, 7.2 g. of paraformaldehyde, and 24 ml. of isoamyl alcohol for twenty-five minutes. The reaction mixture was worked up in the usual manner; yield 30%.

never observed in our previous work the simultaneous formation of diastereoisomeric amino alcohols under analogous conditions. When a noble metal catalyst is employed in the reduction of amino ketones, generally only one of the two possible amino alcohols is formed, while in the sodium amalgam reduction both forms may be obtained.[6]

The possibility that one of the two compounds A or B is a hexahydro derivative cannot be excluded entirely, since, because of lack of material, we did not attempt to demonstrate the isomerism by converting A and B to identical desoxy compounds.

(5) Mosettig and van de Kamp, THIS JOURNAL, **52**, 3704 (1930).

(6) See Hyde, Browning and Adams, *ibid.*, **50**, 2287 (1928), and Mannich, Borkowsky and Wan Ho Lin, *Arch. Pharm.*, **275**, 54 (1937). See also Shriner and Teeters, THIS JOURNAL, **60**, 936 (1938).



All of the amino alcohols that have been tested so far (Nos. 4, 8, 20, 24, 27, 33, 37, 40 of the accompanying table)[7] show only low analgesic action or none at all. In the instances where a comparison with analogous diethylamino and piperidino compounds was possible, it became apparent that replacement of the diethyl or piperidino group by the morpholino group resulted in a decrease of analgesia in the ratio from 2:1 to about 8:1.

(7) Eddy, unpublished results.

Summary

The synthesis of a series of morpholino alcohols from 2-acetylphenanthrene, 3-acetylphenanthrene, 3-methoxy-9-acetylphenanthrene, 1-keto-tetrahydrophenanthrene and 4-keto-tetrahydrophenanthrene is described.

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[CONTRIBUTION FROM THE DEPT. OF CHEMICAL ENGINEERING, UNIVERSITY OF CINCINNATI, AND THE RESEARCH LABORATORIES OF THE WM. S. MERRELL COMPANY]

An Investigation of the Effect of Chemical Structure on Local Anesthetic Action of Diothane Analogs[1]

BY ELSIE M. WALTER[2]

Most local anesthetics in general use contain a benzene ring somewhere in their structure. In fact, many early experimenters claimed that a compound must contain a benzoyl group to exhibit anesthetic action. In 1925, Gilman and Pickens[3] studied the effect of various aromatic rings on the anesthetic action of procaine. They prepared the furan, thiophene, and pyrrole analogs of procaine. Their results indicate that the order of decreasing activity is benzene > pyrrole > thiophene > furan > methyl. More recently, however, Phatak and Emerson[4] prepared various alkyl esters of 2-furoic acid where the alkyl varied from methyl to amyl. They found that all of the compounds possess local anesthetic action which increases with the size of the alkyl from methyl to amyl. The amyl furoate has approximately the same activity as cocaine. It was pointed out by the authors that the corresponding benzoates show either incomplete or no anesthetic action.

Since very little work has been done on the effect of substituting various aromatic rings for the benzene ring in the structure of local anesthetics, it was decided to prepare some furan analogs of Diothane (piperidinopropanediol diphenylurethan hydrochloride[5]) and compare their

(1) From a thesis in partial fulfilment of the requirements for the degree of Chemical Engineer, University of Cincinnati, June, 1938.

(2) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(3) H. Gilman and R. M. Pickens, THIS JOURNAL, 47, 245 (1925).

(4) N. M. Phatak and G. A. Emerson, *J. Pharmacol.*, 58, 174 (1936).

(5) T. H. Rider, THIS JOURNAL, 52, 2115 (1930); T. H. Rider and E. S. Cook, *J. Pharmacol.*, in press.