contained 9.6 g. after removal of ether through column X. This was combined with fractions 1–6 to give through column X: 33–36, 14.8 g., 35–122° (750 mm.), 1.3542–1.4040; 37–39, 10.3 g., 122–132°, 1.4040–1.4140; 40–41, 6.6 g., 136°, 1.4158–1.4170; residue, 3.5 g.

The residue above, 37–39, and fractions 7–8 were combined and fractionated through column X to give 5.0 g. of methylneopentylcarbinol, $n^{20}D$ 1.4175–1.4195, which gave an α-naphthylurethan, m. p. and mixed m. p., 86–87°. This was checked with a 3,5-dinitrobenzoate, m. p. and mixed m. p., 95–95.5°. This sample, together with the 6.6 g. of fractions 40–41, represents a 3.4% yield of reduction product. Attempts to find 2-heptanol were unsuccessful. Fractions 9–17 contained dodecenes (0.63 mole) and fractions 18–30 contained methyl-*n*-amylneopentylcarbinol.


## Summary

1. The yields of reduction products from the action of *n*-butylmagnesium bromide on acetyl chloride and trimethylacetyl chloride are reported.

2. Reductions involving *n*-butylmagnesium bromide with ethyl acetate, acetaldehyde and 2-hexanone are also described.

3. The reducing actions of ethyl-, *n*-propyl-, *n*-butyl- and *n*-amyl-magnesium bromides with methyl neopentyl ketone are reported.

4. No evidence was found that ether peroxide was the source of the carbinols.


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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

# The Action of Primary Grignard Reagents on *t*-Butylacetyl Chloride

BY FRANK C. WHITMORE, A. H. POPKIN, J. S. WHITAKER, K. F. MATTIL AND J. D. ZECH

The reduction of trimethylacetyl chloride to neopentyl alcohol in 95% yield[1] and *t*-butylacetyl chloride to neopentylcarbinol[2] in 1% yield when treated with *t*-butylmagnesium chloride has been reported. The results of the present investigation agreed with these observations, the action of ethyl-, *n*-propyl-, *n*-butyl- and *n*-amylmagnesium bromides on *t*-butylacetyl chloride giving no evidence for the formation of neopentylcarbinol in detectable quantities. In view of the yields of primary alcohol obtained by the reduction of isobutyryl-, *n*-butyryl-[3] and pivalyl chlorides using *t*-butylmagnesium chloride and of acetyl chloride using *n*-butylmagnesium bromide,[4] it is possible that the primary, secondary or tertiary character of the groups attached to the α-carbon of the acid chloride may have a more pronounced influence on the extent of reduction than has the branching of the chain. This possibility is being studied.

No reduction product was isolated when *t*-butylacetyl chloride was added to ethylmagnesium bromide, but similar addition to *n*-propyl, *n*-butyl and *n*-amylmagnesium bromides produced the corresponding secondary carbinols in 24.4, 20.5 and 19.3% yields. The chief products were the expected tertiary alcohols, although the recognized instability of such higher molecular weight tertiary carbinols was again evidenced in the partial dehydration of di-*n*-propylneopentyl-, di-*n*-butylneopentyl- and the complete dehydration of di-*n*-amylneopentylcarbinols during fractionation at reduced pressure.

Pure *n*-propyl-, *n*-butyl- and *n*-amylneopentylcarbinols were required for identification of the reduction products obtained. The action of aluminum isopropylate in isopropyl alcohol on *n*-propyl, *n*-butyl and *n*-amyl neopentyl ketones produced the desired secondary carbinols in 92, 93 and 89% yields, respectively. The ketones had been prepared in excellent yields by the action of the appropriate Grignard compound on *t*-butylacetamide.[5]

## Experimental

**Addition of *t*-Butylacetyl Chloride to Ethylmagnesium Bromide.**—The Grignard solution was prepared from 545 g. (5 moles) of ethyl bromide, b. p. 36° (730 mm.), $n^{20}D$ 1.4240, magnesium and 1.5 liter of dry ether. Addition of 182 g. (1.3 moles) of *t*-butylacetyl chloride, b. p. 68° (100 mm.), $n^{20}D$ 1.4226, prepared in 86% yield from the action of thionyl chloride on the acid, was completed in seventy-five minutes. The complex was decomposed with ice, extracted with ether and the product, on removal of solvent using column XII, was fractionated through column XI,[6] to give: fraction 1, 2.6 g., b. p. 35–78° (740 mm.), $n^{20}D$ 1.3770–1.4010; 2, 7.7 g., 50° (10 mm.), 1.4370;

(1) Greenwood, Whitmore and Crooks, THIS JOURNAL, **60**, 2028 (1938).

(2) Whitmore and Heyd, *ibid.*, **60**, 2030 (1938).

(3) Greenwood, Whitmore and Crooks, *ibid.*, **60**, 2028 (1938).

(4) Whitmore, Popkin, Whitaker, Mattil and Zech, *ibid.*, **60**, 2458 (1938).

(5) A detailed description of the synthesis of branched aliphatic ketones from the acid amide and Grignard reagent is in preparation.

(6) The fractionating columns used have already been described, Whitmore, Popkin, Whitaker, Mattil and Zech, THIS JOURNAL, **60** 2458 (1938).

3–12, 89.4 g., 62–64° (10 mm.), 1.4390–1.4400; 13–14, 29.1 g., 76–93° (9 mm.), 1.4440; residue 7.3 g.

Fraction 1 contained ethyl alcohol; 3,5-dinitrobenzoate, m. p. and mixed m. p. 91–92°.

Fractions 3–14 were diethylneopentylcarbinol, $d^{20}_4$ 0.8352, *MR:* calcd. 50.0, obsd. 49.8. Dehydration of the carbinol took place even on standing.

The constants for ethylneopentylcarbinol[7] are b. p. 150–152° (735 mm.), $n^{20}D$ 1.4250. Attempts to find this carbinol in the reaction mixture were not successful. Similar attempts to identify neopentylcarbinol also were unsuccessful.

**Addition of *t*-Butylacetyl Chloride to *n*-Propylmagnesium Bromide.**—Addition of 228 g. (1.7 moles) of *t*-butylacetyl chloride, b. p. 79° (150 mm.), $n^{20}D$ 1.4212 to 4.5 moles of *n*-propylmagnesium bromide in 1.5 l. of ether was completed in one hour and forty minutes. The addition complex was decomposed with ice, extracted with ether and the product fractionated through column XI to give (using 2 solid carbon dioxide traps): 1–8, 137.3 g., 20° (120 mm.) −62° (13 mm.), $n^{20}D$ 1.4142–1.4230; 9–13, 104.4 g., 62° (13 mm.) −88° (9 mm.), 1.4330–1.4410; residue, 19 g.; traps, 85 g. The trap condensate gave 7.5 g. of residue after removal of ether and this, together with fractions 1–8, through column X gave: 14, 2.4 g., 40–82° (733 mm.), 1.3780; 15–16, 4.1 g., 86–96°, 1.3825–1.3970; 17–19, 4.9 g., 135–172°, 1.4156–1.4200; 20–23, 22.9 g., 172°, 1.4220–1.4290; 24–25, 10.5 g., 172°, 1.4340–1.4345; 26–34, 46.0 g., 58–60° (10 mm.), 1.4300–1.4315; 35–37, 30.0 g., 58–59° (8 mm.), 1.4320–1.4330; residue, 1 g.

Fractions 9–13, on refractionation through column X, gave: 38, 55 g., 62–64° (10 mm.), 1.4325; 39–43, 44.8 g., 64° (10 mm.), 1.4330–1.4332, $d^{20}_4$ 0.7759; 44–46, 18.3 g., 66–90° (10 mm.), 1.4340–1.4385; 47–48, 8.4 g., 94–96° (10 mm.), 1.4429, $d^{20}_4$ 0.8376; 49–50, 5.1 g., 108–110° (10 mm.), 1.4390–1.4400; residue, 3.2 g.

Fractions 15–16 were identified as *n*-propyl alcohol by the m. p. and mixed m. p. of the 3,5-dinitrobenzoate, 74–74.5°.

Fractions 20–23 and 26–34 represented a 24.4% yield of *n*-propylneopentylcarbinol, phenylurethan, m. p. and mixed m. p. 82°.

Fractions 24, 25 and 35–43 were dodecenes obtained by dehydration of the tertiary carbinol. Fractions 47–48 were di-*n*-propylneopentylcarbinol. *Anal.* Calcd. for $C_{12}H_{26}O$: C, 77.4; H, 14.0. Found: C, 77.2; H, 13.9. All attempts to identify neopentylcarbinol failed.

**Addition of *t*-Butylacetyl Chloride to *n*-Butylmagnesium Bromide.**—The addition of 228 g. (1.7 moles) of *t*-butylacetyl chloride to 4.5 moles of *n*-butylmagnesium bromide in 1.5 l. of ether was completed in one hour and thirty-five minutes. The product was isolated in the usual manner to give through column XI: 1–14, 83 g., 26–82° (14 mm.), 1.4024–1.4352; 15–21, 43 g., 87–112° (8 mm.), 1.4391–1.4400; 22–24, 132.3 g., 112° (8 mm.), 1.4415–1.4424; residue, 9 g. The solid carbon dioxide trap contents, 95.0 g., were largely ether. Fractions 1–21 contained water, indicating dehydration.

The trap condensates, on removal of ether, yielded 17 g. which on combining with fractions 1–14 gave through column X: 25–28, 11.3 g., 35–75° (733 mm.), 1.3540–1.3680; 29–41, 47.2 g., 102–190°, 1.3840–1.4291; 42–49, 31.2 g., 190–200°; 1.4300–1.4390; residue, 3.4 g.

Fractions 15–24 were refractionated through column X to give: 50, 6.7 g., 90° (8 mm.), 1.4385; 51–53, 23.1 g., 90° (8 mm.), 1.4400–1.4403; 54–61, 84.0 g., 101–110° (8 mm.), 1.4415–1.4458; 62–64, 35.8 g., 112–113° (8 mm.), 1.4460; 65, 10.2 g., 113° (8 mm.), 1.4469; residue, 2 g.

Fractions 29–41, on refractionation through column X, gave: 66–69, 6.5 g., 74–108° (735 mm.), 1.3807–1.3980; 70–74, 10.0 g., 109–113°, 1.4010–1.4050; 75–76, 3.2 g., 113–186°, 1.4170–1.4250; 77–81, 19.0 g., 186–190°, 1.4260–1.4300; residue, 1 g.

Fractions 42–49 and 77–81 represented 54.9 g. (0.35 mole), 20.5% yield of *n*-butylneopentylcarbinol, α-naphthylurethan, m. p. and mixed m. p., 70–70.5°.

Fractions 51–53 were olefins obtained by the dehydration of di-*n*-butylneopentylcarbinol, $d^{20}_4$ of olefins was 0.7824; *MR*, calcd. 66.38; obsd. 66.12.

Fractions 62–64 contained di-*n*-butylneopentylcarbinol $d^{20}_4$ 0.8320; *MR*, calcd. 68.5; obsd. 68.59. Dehydration followed on standing.

Fractions 70–74 were *n*-butyl alcohol, phenylurethan, m. p. and mixed m. p., 62.5–63°. All attempts to identify neopentylcarbinol failed.

**Addition of *t*-Butylacetyl Chloride to *n*-Amylmagnesium Bromide.**—The addition of 200 g. (1.5 moles) of *t*-butylacetyl chloride to 4.1 moles of *n*-amylmagnesium bromide, completed in one hour and twenty minutes, yielded a crude product which gave through column XI: 1–4, 43.9 g., 42–87° (15 mm.), 1.4140–1.4280; 5–7, 36.5 g., 90° (15 mm.) −92° (10 mm.), 1.4310–1.4316; 8–11, 36.7 g., 92–107° (10 mm.), 1.4340–1.4348; 12–18, 186.3 g., 118–130° (13 mm.), 1.4442–1.4460; residue, 5 g.; trap contents, 59 g. Fraction 1–7 contained water, indicating dehydration.

The trap condensate yielded 5.1 g. which was combined with fraction 1. Repeated fractionation of all the fractions using column X gave: 19, 1.4 g., 35–113° (733 mm.), 1.3530; 20–24, 19.9 g., 113–136°, 1.4132–1.4170; 25, 3.7 g., 50–90° (13 mm.), 1.4260; 26–32, 54.5 g., 90–93° (10 mm.), 1.4302–1.4350; 33, 8.0 g., 90–112° (10 mm.), 1.4410; 34–39, 147.7 g., 118° (10 mm.), 1.4450, $d^{20}_4$ 0.7856, *MR* for the hexadecenes; calcd. 75.62; obsd. 75.70; residue, 12.7 g., 1.4452.

Fractions 20–24 were *n*-amyl alcohol, phenylurethan, m. p. and mixed m. p., 48°.

Fractions 26–32 were *n*-amylneopentylcarbinol, phenylurethan, m. p. and mixed m. p., 60–61°. The yield, estimated from the boiling point and refractive index curves, was 19.3%.

Fractions 34–39 were 0.71 mole of olefins from the dehydration of di-*n*-amylneopentylcarbinol. No evidence was obtained for the presence of neopentylcarbinol.

**Preparation of *n*-Propylneopentylcarbinol.**—*n*-Propyl neopentyl ketone, 39 g. (0.27 mole), b. p. 111–112° (150 mm.),[8] was heated for twenty-four hours under column VI with 32.6 g. (0.15 mole), of aluminum isopropylate in 300 cc. of dry isopropyl alcohol, the acetone being removed as formed. The reaction mixture was treated with ice and excess hydrochloric acid, extracted with ether and the product, on removal of the solvent, fractionated through VI to give: 1–2, 1.7 g., 80–84.5° (29 mm.), 1.4193–1.4243;

(7) Prepared by C. I. Noll, this Laboratory.

(8) Prepared by H. C. Crafton, this Laboratory.

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

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[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)].