[Contribution from the National Institute of Arthritis and Metabolic Diseases,
National Institutes of Health, Public Health Service,
Department of Health, Education, and Welfare]

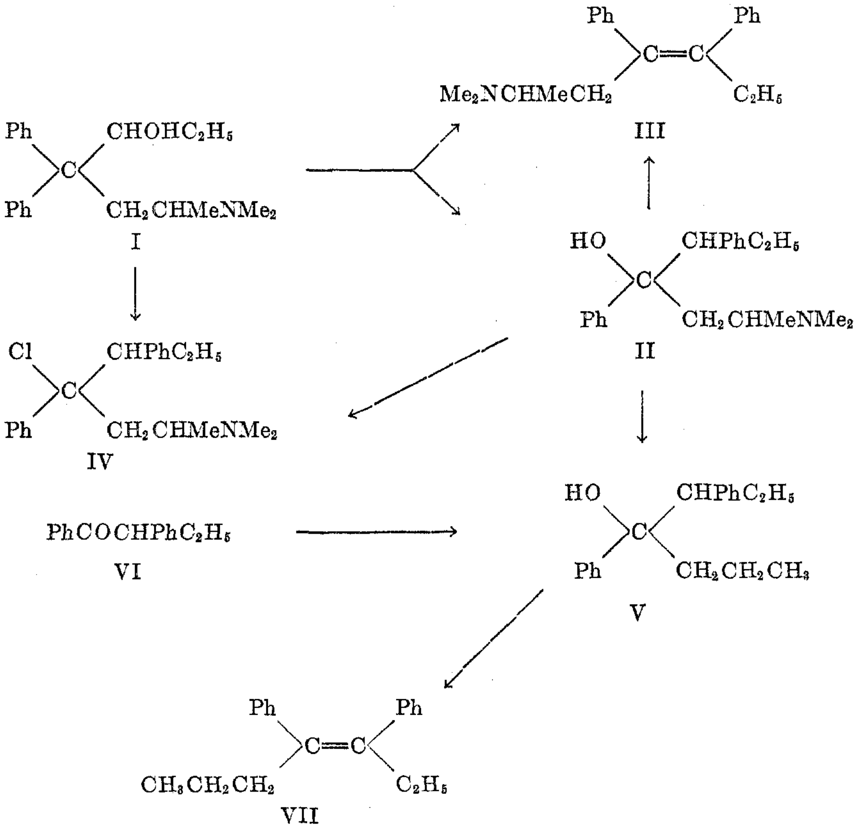
WAGNER REARRANGEMENT OF *α-dl*-6-DIMETHYLAMINO-4,4-DIPHENYL-3-HEPTANOL (*α-dl*-METHADOL)

EVERETTE L. MAY and T. D. PERRINE

Received May 7, 1953

During the last five years several investigators have reported that O-acyl derivatives of *α-dl*-6-dimethylamino-4,4-diphenyl-3-heptanol (I) exhibit pronounced analgesic activity (1–5). The methyl ether of I was therefore thought to be of interest for screening as an analgesic agent.

In an effort to prepare this ether from the sulfate salt of I with excess dimethyl sulfate in boiling ethyl acetate, we obtained instead a carbinol (II) (45% yield) isomeric with I. In addition a desoxy compound (III) was isolated as the picrate in a yield of 5–10%.



Formulation of the isomeric carbinol II as 6-dimethylamino-3,4-diphenyl-4-heptanol is based on the following considerations: It could not be O-acetylated with the same ease as I[1] which was indicative of a tertiary alcohol function.

---

[1] Acetylation of I can be readily effected with acetic anhydride-pyridine at 50° while II

Exhaustive methylation of II followed by hydrogenation of the resultant non-basic, olefinic compound yielded an oily carbinol whose ultraviolet absorption spectrum, refractive index, and *p*-nitrophenylurethan derivative were identical with those of 3,4-diphenyl-4-heptanol (V) which was synthesized from α-ethyldesoxybenzoin (VI) and propyllithium.[2] The infrared spectral curves of V obtained from II and VI were also practically identical; the few differences noted

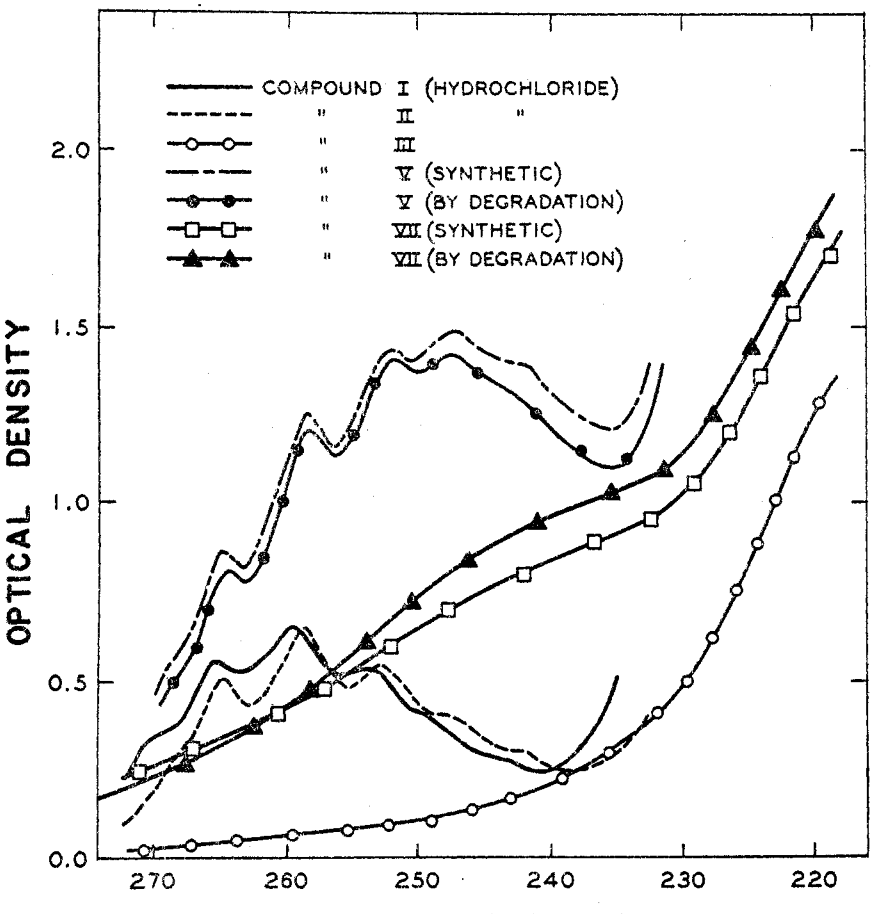


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA. Measurements were made in a Cary spectrophotometer using a 2-dm. cell and the following molar concentrations in absolute ethanol: I, 7.9×10^{-4}; II, 7.9×10^{-4}; III, 5.3×10^{-5}; V (synthetic), 1.0×10^{-3}; V (by degradation), 9.6×10^{-4}; VII (synthetic), 7.0×10^{-5}; VII (by degradation), 7.3×10^{-5}.

---

was substantially unchanged under these conditions. A temperature of 100° was necessary for the acetylation of II.

[2] Although Buu Hoï, *et al.* (6) report the preparation of a series of tertiary alcohols from α-alkyldesoxybenzoins and alkylmagnesium bromides we obtained almost exclusively 1,2-diphenyl-1-butanol when propylmagnesium chloride was used instead of propyllithium.

may be ascribed to traces of impurities. Furthermore formic acid dehydration of V from either source gave the same desoxy compound (VII) whose spectral data and inertness toward catalytic hydrogenation were compatible with a stilbene structure.[3]

The structure of 6-dimethylamino-3,4-diphenyl-3-heptene has been assigned to the desoxy compound III on the basis of its formation in the *vigorous* thionyl chloride treatment of II, its low reactivity toward hydrogenation (platinum oxide), and its ultraviolet absorption spectrum. *Mild* thionyl chloride treatment of II (benzene, 0° to 10°) gave the corresponding chloro compound, 4-chloro-6-dimethylamino-3,4-diphenylheptane (IV) as the principal product.

The desoxy compound III and the chloro compound IV were found to be identical with two compounds[4] previously obtained from I and designated (1) as 6-dimethylamino-4,4-diphenyl-2-heptene and 3-chloro-6-dimethylamino-4,4-diphenylheptane respectively. The latter formulations may now be reassigned to conform to those of III and IV.

Under the conditions of the reactions used in the production of II, III, and IV, I would be expected to undergo Wagner rearrangement. The formulations given for these products are compatible with a reaction mechanism involving the formation of a common carbonium ion intermediate followed by rearrangement (7).

Neither the carbinol (II), nor its O-acetyl derivative had significant analgesic action in mice (8).

EXPERIMENTAL[5]

6-Dimethylamino-3,4-diphenyl-4-heptanol (II) *hydrochloride.* To 7.5 g. of I (1–4) in 140 ml. of ethyl acetate was added 1.2 ml. of conc'd H_2SO_4, then 7.5 ml. of dimethyl sulfate. The mixture was refluxed for 15–20 hours and the solvent was evaporated *in vacuo*. The residue was washed thrice with ice-cold ether to remove dimethyl sulfate and was partitioned between ether and excess dilute NH_4OH. The dried ether layer gave, on evaporation, an oil which was acidified to Congo Red with alcoholic HCl. Addition of *ca.* 30 ml. of dry ether and cooling to 5° gave 3.8 g. (46%) of the hydrochloride of II, m.p. 202–206°. It crystallized from acetone-ether in fine, curved needles which gradually changed to broad needles of m.p. 208–210°.

Anal. Calc'd for $C_{21}H_{30}ClNO$: C, 72.5; H, 8.7.
Found: C, 72.4; H, 8.6.

The *picrate* crystallized from aqueous alcohol in yellow, rectangular plates, m.p. 160–161°.

Anal. Calc'd for $C_{27}H_{32}N_4O_8$: C, 60.0; H, 5.9.
Found: C, 59.7; H, 6.2.

---

[3] Buu Hoï, *et al.* (6) report that the formic acid dehydration of their tertiary alcohols (*cf.* footnote 2) gives stilbenes of probably the *trans* configuration.

[4] Compound IV was obtained (1) in the mild thionyl chloride treatment of I, while III was obtained by reaction of IV with phosphorus and hydriodic acid or by vigorous treatment of I with thionyl chloride, phosphorus pentachloride, phosphorus pentoxide, or phosphorus-hydriodic acid.

[5] Melting points are corrected (Hershberg-type apparatus, total-immersion thermometers). Microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford. Infrared measurements were made by Mrs. Phyllis Smeltzer and Mrs. Alma Hayden of this Institute.

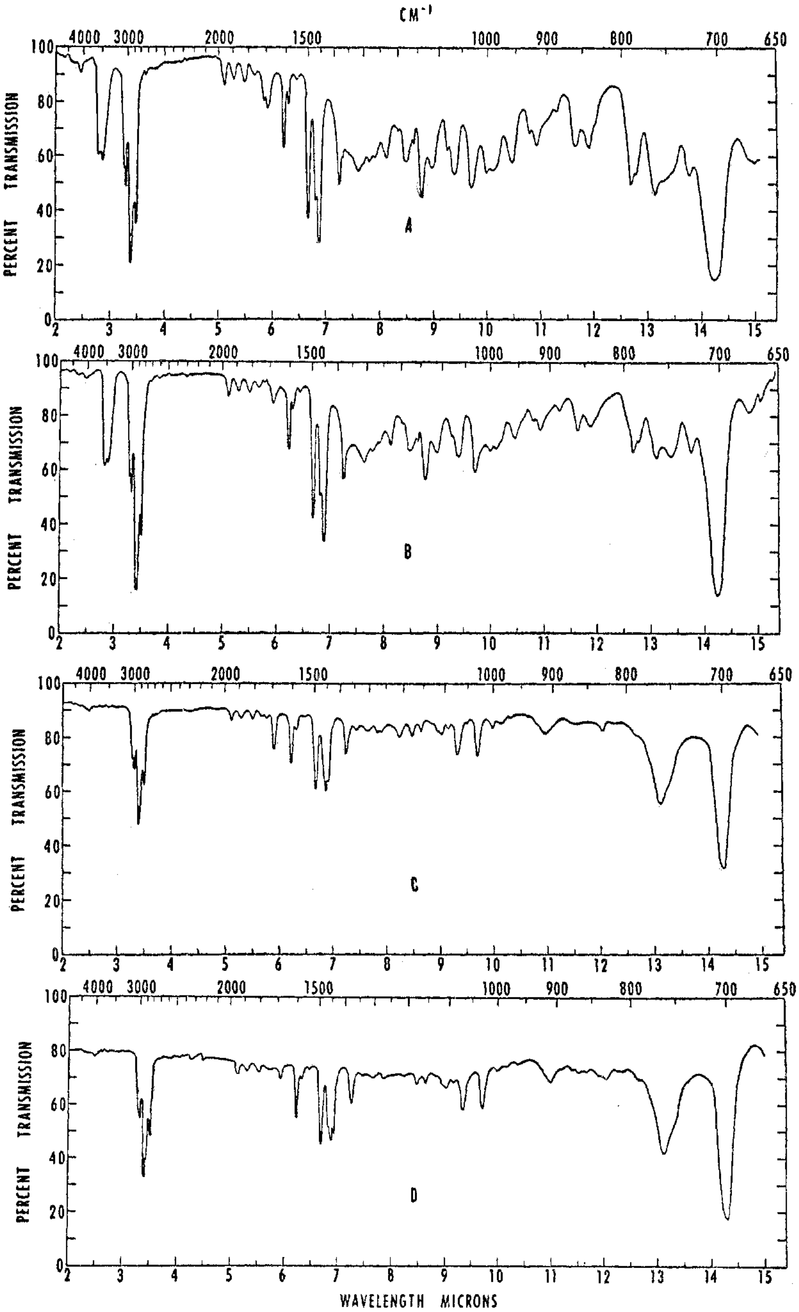


FIG. 2. INFRARED ABSORPTION SPECTRA. Curve A, V (synthetic); Curve B, V (by degradation); Curve C, VII (synthetic); Curve D, VII (by degradation). In all cases liquid smears were used.

6-Dimethylamino-3,4-diphenyl-3-heptene (III). The filtrate of the 3.8 g. of II hydrochloride, kept for two days (finally at 5°) gave 0.5 g. of needles (unidentified). The resultant filtrate was evaporated to dryness and the residue was treated with excess aqueous alcoholic picric acid to give, after seeding, 0.5–1.0 g. (5–10%) of the picrate of III, m.p. 112–114°. It was found to be identical with the desoxy compound described previously (1) as 6-dimethylamino-4,4-diphenyl-2-heptene. III was also obtained in the reaction of II with thionyl chloride in boiling benzene and chromatographing the resultant product on alumina, and on refluxing I and formic acid.

The *chloroplatinate* of III, m.p. 200–201°, crystallized from 95% ethanol in tiny rosettes.

Anal. Calc'd for $C_{42}H_{56}Cl_6N_2Pt$: C, 50.6; H, 5.7; Pt, 19.6.
Found: C, 50.5; H, 5.7; Pt, 19.4.

4-Acetoxy-6-dimethylamino-3,4-diphenylheptane hydrochloride. The hydrochloride of II (1.5 g.), 3 ml. of acetic anhydride, and 3 ml. of dry pyridine, kept on the steam-bath for one hour and diluted to 25 ml. with dry ether gave 1.3 g. (75%) of needles which were recrystallized from acetone-ether (Norit); m.p. 180–182°.

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.8; H, 8.3.
Found: C, 70.7; H, 8.2.

3,4-Diphenyl-4-heptanol (V). (*a*) *By synthesis.* To 64.7 g. of α-ethyldesoxybenzoin (9)[6] in 400 ml. of ligroin[7] was added with stirring 500 ml. of 0.65 *N* propyllithium[8] in ligroin.[7] The mixture was poured into water and the hydrocarbon layer was dried and distilled to give a 95% yield of liquid boiling at 106° (0.1 mm.). This was dissolved in ligroin[9] (1 g./ml.) and the solution kept overnight at 0° to give 10% of a solid[10] of m.p. 98–100°. The residue from the filtrate was again distilled at 0.1 mm.; n_D^{20} 1.5553, final yield of V, 80%.

Anal. Calc'd for $C_{19}H_{24}O$: C, 85.0; H, 9.0.
Found: C, 84.7; H, 8.8.

The *p-nitrophenylurethan* was prepared by heating in a stoppered flask (drying oven, 95–105°) 0.5 g. of V and 0.4 g. of *p*-nitrophenyl isocyanate for 15 hours.

The resultant yellow material was digested with ligroin[9] to give 0.5 g. of solid which was digested with chloroform. The filtrate, diluted with ligroin,[9] gave 0.3 g. (40%)[11] of small white needles, m.p. 188–191°. The analytical sample (from alcohol) melted at 194°.

Anal. Calc'd for $C_{26}H_{28}N_2O_4$: C, 72.2; H, 6.5.
Found: C, 72.1; H, 6.5.

(*b*). *By degradation of* II. Methyl iodide (2 ml.), 5 ml. of methanol, and the base from 2.0 g. of II hydrochloride were kept at 25–30° for 48 hours, warmed to boiling, and diluted with ether to give 2.1 g. of the methiodide of II, m.p. 190–193°. This methiodide, and 60 g. of 20% sodium hydroxide were refluxed for 8 hours. The resultant olefin was dried in ether and hydrogenated (0.02 g. of platinum oxide, methanol, 5–10 minutes). Distillation of the product at 0.5 mm. (bath temperature 100–110°) gave 1.1 g. (71% based on II) of V, n_D^{20} 1.5543 whose IR and UV spectra were virtually identical with those of the synthetic V.

Anal. Calc'd for $C_{19}H_{24}O$: C, 85.0; H, 9.0.
Found: C, 84.8; H, 9.0.

---

[6] The use of potassium *tert*-butoxide in place of sodium ethoxide gave us superior yields.

[7] B.p. 28–38°.

[8] When propylmagnesium chloride was used instead of propyllithium the major product was a solid whose analysis, m.p. (79–80°) and m.p. of its phenylurethan (125°) corresponded to those of 1,2-diphenyl-1-butanol (10). The *p-nitrobenzoate* of this alcohol melted at 106–106.4°. *Anal.* Calc'd for $C_{23}H_{21}NO_4$: C, 73.6; H, 5.6. Found: C, 73.8; H, 5.7.

[9] B.p. 30–60°.

[10] The infrared and ultraviolet absorption spectra of this solid are different from those of V although its analysis indicates that it is isomeric with V. It crystallized from aqueous methanol in prisms, m.p. 99–100°. *Anal.* Calc'd for $C_{19}H_{24}O$: C, 85.0; H, 9.0. Found: C, 84.8; H, 9.2.

[11] The yield varied greatly with the absolute humidity. On some very hot, humid days only traces could be obtained.

The *p-nitrophenylurethan*, prepared as described above, melted at 193–194° alone or in mixture with that prepared from the synthetic V.

3,4-Diphenyl-3-heptene (VII). Formic acid (16 ml.) and 0.8 g. of V (prepared by either method) were heated on the steam-bath for 1–2 hours and were evaporated to dryness *in vacuo*. The residual oil was distilled 3 times at 0.5 mm. (bath temperature 100–110°) to give the desoxy compound,[12] n_D^{20} 1.5580.

Anal. Calc'd for $C_{19}H_{22}$: C, 91.1; H, 8.9.

Found: C, 91.3; H, 8.7.

4-Chloro-6-dimethylamino-3,4-diphenylheptane (IV). To 0.4 g. of II (base) in 2 ml. of ice-cooled, dry benzene was added during one minute (shaking) 0.15 ml. of thionyl chloride. The mixture was kept at room temperature for 25 minutes and was diluted to 10 ml. with dry ether. After 3 days at 5–10° 0.15 g. of a hydrochloride, m.p. 115–120° was obtained. The free base melted at 88–90° alone or in mixture with that designated previously (1) as 3-chloro-6-dimethylamino-4,4-diphenylheptane. The picrate melted at 137–138.5° and was also identical with that described before (1).

SUMMARY

α-*dl*-6-Dimethylamino-4,4-diphenyl-3-heptanol (I) has undergone the Wagner rearrangement to give 6-dimethylamino-3,4-diphenyl-4-heptanol (II), 6-dimethylamino-3,4-diphenyl-3-heptene (III), and 4-chloro-6-dimethylamino-3,4-diphenylheptane (IV) depending upon the reaction conditions.

The structure of II was proved by its degradation to a nitrogen-free alcohol identical with the 3,4-diphenyl-4-heptanol prepared from α-ethyldesoxybenzoin and propyllithium, while that of III is based on its formation from II, its low reactivity toward catalytic hydrogenation, and on spectral data. The structure of IV follows from its formation in the mild chlorination of II.

BETHESDA 14, MD.

REFERENCES

(1) MAY AND MOSETTIG, *J. Org. Chem.*, **13**, 459 (1948).
(2) SPEETER, BYRD, CHENEY, AND BINKLEY, *J. Am. Chem. Soc.*, **71**, 57 (1949).
(3) POHLAND, MARSHALL, AND CARNEY, *J. Am. Chem. Soc.*, **71**, 460 (1949).
(4) EDDY, MAY, AND MOSETTIG, *J. Org. Chem.*, **17**, 321 (1952).
(5) FRASER AND ISBELL, *J. Pharmacol. Exptl. Therap.*, **105**, 458 (1952).
(6) BUU HOÏ, HIONG-KI-WEI, LACASSAGNE, AND LECOCQ, *Compt. rend.*, **219**, 589 (1944).
(7) ALEXANDER, *Ionic Organic Reactions*, John Wiley & Sons, Inc., New York, Chapman and Hall Limited, London, p. 56 (1951).
(8) EDDY (Unpublished results).
(9) MEYER AND OELKERS, *Ber.*, **21**, 1299 (1888).
(10) KAYSER, *Compt. rend.*, **199**, 1424 (1934).

---

[12] This compound absorbed hydrogen (platinum oxide) extremely slowly if at all.