*Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.78; H, 8.20; N, 11.43.

An analytical sample of the nonradioactive material was obtained by crystallization from methanol-ethyl acetate, m.p. 166–167° (s 164°). The ultraviolet and infrared spectra were identical with those of the radioactive sample.

The radioactive sample was found to be homogeneous by paper chromatography in several solvent systems and radioautography of the paper chromatograms.[12]

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(12) F. S. Eberts, Jr., to be published.

## Resolution and Configuration of 1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine

ROBERT H. MAZUR

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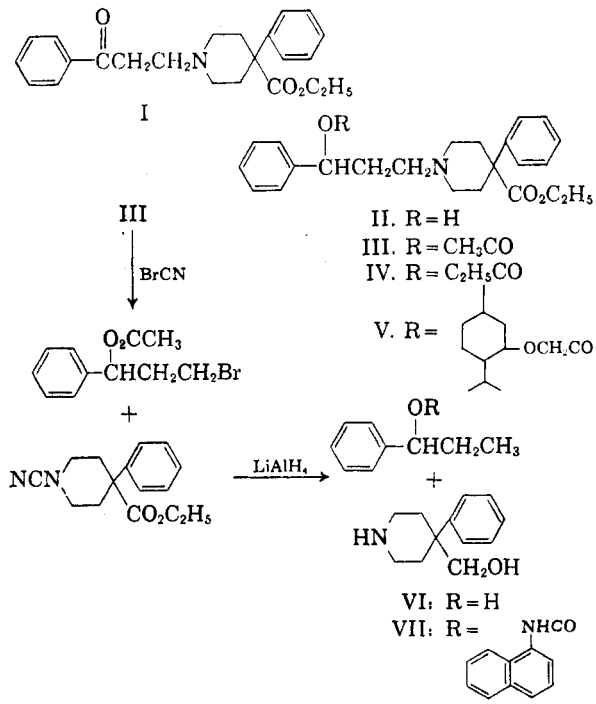
The discovery of the analgesic properties of 3-(4 - ethoxycarbonyl - 4 - phenylpiperidino)propiophenone (I)[1] prompted us to investigate the synthesis and pharmacologic evaluation of the corresponding alcohol, 1-(3-hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine (II)[2a] and some of its derivatives. The carbinol II should exhibit greater stability than the ketone I (a Mannich base) and has the additional attraction that it is capable of resolution which might conceivably lead to a useful separation of analgesic and respiratory depressant activities usually associated with this type of analgesic.

Ketone I was conveniently reduced with sodium borohydride in aqueous ethanol to the desired carbinol II in high yield. The latter was crystalline and was characterized as the hydrochloride. The acetate III and propionate IV of the carbinol were also prepared. The oily esters were converted to crystalline maleates for analysis and testing.

Resolution of carbinol II proved difficult as none of the salts with the usual optically active acids could be induced to crystallize. A suitable derivative was eventually found by esterification with *l*-menthoxyacetyl chloride and formation of the crystalline maleate salt. Fractional crystallization yielded the *l*, *l*-ester maleate which liberated *l*-II on alkaline hydrolysis. The levo-base was characterized as the hydrochloride and converted to the levo-acetate maleate and levo-propionate maleate. Similarly, *d*-menthoxyacetyl chloride[3] was used to obtain *d*-II and its hydrochloride.

As a point of interest, the absolute configuration of levo-base II was determined. The *l*-acetate III was degraded by the von Braun cyanogen bromide method and the crude mixture reduced with lithium aluminum hydride. The chart shows the course of the reactions. The neutral fraction proved to contain *l*-ethylphenylcarbinol (VI) isolated as the α-naphthylurethan (VII) which had the same melting point and rotation as *l*-ethylphenylcarbinyl-α-naphthylurethane prepared from authentic *l*-ethylphenylcarbinol.[4] The latter has been shown to possess the S configuration.[5,6] Therefore, *l*-base II may be written as S-1-(3-hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine.

The analgesic potencies[7] in mice of the various compounds are given in the table. An increase in analgesic activity was accompanied by an approximately corresponding increase in respiratory depression.




### EXPERIMENTAL

*1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrochloride* (II·HCl). Ketone I hydrochloride (12.0 g., 0.03 mole) was suspended in 48 ml. of 50% ethanol

(1) P. A. J. Janssen, A. H. M. Jageneau, P. J. A. Demoen, C. van de Westeringh, A. H. M. Raeymaekers, M. S. J. Wouters, S. Sanczuk, B. K. F. Hermans, and J. L. M. Loomans, *J. Med. Pharm. Chem.*, 1, 105 (1959).

(2*a*) Janssen and Eddy[2b] have recently reported carbinol II as its hydrochloride along with the corresponding acetate hydrochloride, III·HCl, and propionate hydrochloride, IV·HCl. Their analgesic potency values (mice) are in substantial agreement with those obtained in our laboratories.

(2*b*) P. A. J. Janssen and N. B. Eddy, *J. Med. Pharm. Chem.*, 2, 31 (1960).

(3) J. Read and W. J. Grubb, *J. Soc. Chem. Ind.*, 51, 329T (1932).

(4) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 70, 355 (1926).

(5) R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, 82, 876 (1960).

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

(7) N. B. Eddy and D. Leimbach, *J. Pharmacol.*, 107, 385 (1953).

TABLE I

| Compound | Analgesic Potency |
|---|---|
| Morphine | 1 |
| *d,l*-II·HCl | 14 |
| *d,l*-III·Maleate | 8 |
| *d,l*-IV·Maleate | 14 |
| *l*-II·HCl | 25 |
| *l*-III·Maleate | 11 |
| *l*-IV·Maleate | 14 |
| *d*-II·HCl | 7 |

and 1.2 g. (0.03 mole) of sodium hydroxide in 72 ml. 95% ethanol added. The clear solution was treated with 1.1 g. (0.03 mole) of sodium borohydride and stirred 10 min. at room temperature. The solution was diluted with chloroform, washed exhaustively with water, the chloroform dried over sodium sulfate and distilled. The crystalline residue, m.p. 89–91°, was dissolved in 60 ml. of isopropyl alcohol and 6.6 ml. of 6.8 *N* hydrogen chloride in isopropyl alcohol added. Two crops of II·HCl, irregular prisms, m.p. 196–198°, were obtained totaling 11.6 g. (96%). Recrystallization from isopropyl alcohol raised the melting point to 198–199°.

*Anal.* Calcd. for $C_{23}H_{30}ClNO_3$: C, 68.38; H, 7.49; N, 3.47; Cl, 8.78. Found: C, 67.90; H, 7.29; N, 3.33; Cl, 8.74.

*1-(3-Acetoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrogen maleate* (III·Maleate). Base II (3.7 g., 0.01 mole) was dissolved in 40 ml. of pyridine and 10 ml. of acetic anhydride. The solution was heated on the steam bath a few minutes and allowed to stand overnight at room temperature. Excess acetic anhydride was decomposed with water, the solution diluted with ether, washed with 1*M* potassium carbonate and repeatedly with 10% sodium sulfate. The ether was dried over sodium sulfate and distilled. The residue was taken up in ether and treated with 1.3 g. (0.011 mole) of maleic acid in ether which gave III·maleate, 4.9, g. (94%), m.p. 136–138°. Crystallization from ethanol-ether yielded clusters of needles, m.p. 137–139°.

*Anal.* Calcd. for $C_{29}H_{35}NO_8$: C, 66.27; H, 6.71; N, 2.67. Found: C, 65.96; H, 6.89; N, 2.67.

*1-(3-Propionoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrogen maleate* (IV·Maleate). The above procedure was followed using 3.7 g. (0.01 mole) of base II and 3.9 g. (0.03 mole) of propionic anhydride. The yield of IV·maleate was 4.7 g. (87%), m.p. 142–143°. Crystallization from ethanol-ether gave needles with unchanged melting point.

*Anal.* Calcd. for $C_{30}H_{37}NO_8$: C, 66.77; H, 6.91; N, 2.60. Found: C, 66.84; H, 6.95; N, 2.66.

*l,l-1-(3-Menthoxyacetoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrogen maleate* (*l,l*-V·Maleate). Base II (3.7 g., 0.01 mole) in 20 ml. of pyridine was treated with 3.5 ml. (*ca.* 50% excess) of *l*-menthoxyacetyl chloride.[8] The mixture was allowed to stand at room temperature with occasional swirling for 3 hr. during which time a clear solution was obtained. The solution was cooled in an ice bath, 2 ml. of water added to decompose excess acid chloride, the solution diluted with ether and the ether washed once with aqueous potassium carbonate and thrice with aqueous sodium sulfate. The residue from distillation of the ether was dissolved in 15 ml. of ethyl acetate and 1.4 g. (0.012 mole) of maleic acid added. The mixture was heated to effect solution, filtered, the filtrate concentrated to dryness and 50 ml. of anhydrous ether added. The yield of salt was 6.3 g. (93%), m.p. 79–86°; $[\alpha]_D$ −30°.

Crystallization of 50 g. of salt prepared as above from 150 ml. of dry ethanol plus 2.5 l. of dry ether yielded 9.2 g., m.p. 137–139°. Recrystallization from 18 ml. of ethanol plus 450 ml. of ether gave *l,l*-V·maleate as clusters of needles, 8.9 g., (33%), m.p. 139–140°; $[\alpha]_D$ −50°. Further crystallization did not raise the melting point.

*Anal.* Calcd. for $C_{39}H_{53}NO_9$: C, 68.90; H, 7.86; N, 2.06. Found: C, 68.80; H, 7.80; N, 2.15.

*l-1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine* (*l*-II). The above optically pure salt (6.8 g., 0.01 mole) in 70 ml. methanol was hydrolyzed with 2.8 g. (0.05 mole) of potassium hydroxide in 35 ml. 80% methanol at room temperature for 15 min. Dilution of the solution with two volumes of water gave the free base, 3.7 g. (100%), m.p. 83–84°. Crystallization from aqueous methanol yielded *l*-II as glistening plates, m.p. 86–86.5°; $[\alpha]_D$ −21°.

*Anal.* Calcd. for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.36; H, 7.91; N, 3.80.

*l-1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrochloride* (*l*-II·HCl). The free base (1.1 g.) in 5 ml. of isopropyl alcohol was acidified with 1 ml. of 6.8*N* hydrochloric acid in isopropyl alcohol. Dilution with 10 ml. of ether gave the hydrochloride, 0.9 g., m.p. 187–188°. Crystallization from 5 ml. of isopropyl alcohol yielded *l*-II·HCl as irregular prisms, 0.8 g. (67%), m.p. 187–188°; $[\alpha]_D$ −23°.

*Anal.* Calcd. for $C_{23}H_{30}ClNO_3$: C, 68.38; H, 7.49; N, 3.47; Cl, 8.78. Found: C, 68.06; H, 7.42; N, 3.50; Cl, 8.76.

*l-1-(3-Acetoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrogen maleate* (*l*-III·Maleate). Levo base (1.1 g., 0.003 mole) in 10 ml. of pyridine and 5 ml. of acetic anhydride was allowed to stand overnight at room temperature. An excess of acetic anhydride was decomposed with 5 ml. of water, the solution diluted with ether, washed once with aqueous potassium carbonate and thrice with aqueous sodium sulfate. The ether was dried over sodium sulfate and the solution added to 0.4 g. (0.003 mole) of maleic acid in 0.8 ml. of methanol and 10 ml. of ether. The crude product, 1.5 g., m.p. 141–142°, was crystallized from 5 ml. of ethanol plus 75 ml. of ether and yielded *l*-III·maleate as clusters of needles, 1.4 g. (87%), m.p. 142–143°; $[\alpha]_D$ −22°.

*Anal.* Calcd. for $C_{29}H_{35}NO_8$: C, 66.27; H, 6.71; N, 2.66. Found: C, 65.93; H, 6.52; N, 2.76.

*l-1-(3-Propionoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrogen maleate* (*l*-IV·Maleate). Using propionic anhydride instead of acetic anhydride in the above procedure yielded 1.3 g. (80%) of *l*-IV·maleate, m.p. 143–144° $[\alpha]_D$ −23°.

*Anal.* Calcd. for $C_{30}H_{37}NO_8$: C, 66.77; H, 6.91; N, 2.60. Found: C, 66.72; H, 6.97; N, 2.33.

*d,d-1-(3-Menthoxyacetoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrogen maleate* (*d,d*-V·Maleate). The method described for the preparation of the *l,l*-isomer was used. *d*-Menthoxyacetyl chloride[8] (22.1 g., 0.095 mole) and 35.0 g. (0.095 mole) of base II recovered from separation of the *l*-isomer yielded, after fractional crystallization, 15.9 g. (49%) optically pure *d,d*-V·maleate, m.p. 138–139.5°; $[\alpha]_D$ +50°.

*Anal.* Calcd. for $C_{39}H_{53}NO_9$: C, 68.90; H, 7.86; N, 2.06. Found: C, 68.95; H, 8.19; N, 2.34.

*d-1-(3-Hydroxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine hydrochloride* (*d*-II·HCl). The *d,d*-isomer was hydrolyzed and the resulting base converted to the hydrochloride as described above for the *l*-isomer. From 13.6 g. (0.02 mole) of *d,d*-V·maleate was obtained 5.2 g. (65%) d-II·HCl, m.p. 186–187°; $[\alpha]_D$ +25°.

*Anal.* Calcd. for $C_{23}H_{30}ClNO_3$: C, 68.38; H, 7.49; N, 3.47; Cl, 8.78. Found: C, 68.25; H, 7.27; N, 3.67; Cl, 8.78.

*Degradation of l-1-(3-acetoxy-3-phenylpropyl)-4-ethoxycarbonyl-4-phenylpiperidine.* Levo base II (1.9 g., 0.005 mole) was acetylated as described above. The oily ester was dissolved in 100 ml. of dry benzene, 0.6 g. (0.006 mole) of cyanogen bromide added and the solution heated under reflux 5 hr. The benzene was distilled, the residue dissolved in 100 ml. of dry tetrahydrofuran and 0.8 g. (0.02 mole) of lithium aluminum hydride added. The mixture was heated at reflux 5 hr., an excess of hydride destroyed with ethyl acetate, the

(8) M. T. Leffler and A. E. Calkins, *Org. Syntheses*, Coll. Vol. III, 547 (1955).

mixture treated with dilute hydrochloric acid and ether, the ether dried over sodium sulfate and distilled. The residue was heated on the steam bath 2 hr. with 1.0 ml. of α-naphthylisocyanate and an excess of reagent decomposed with 90% aqueous acetone. The mixture was concentrated to dryness, the residue boiled with petroleum ether (b.p. 60–80°) and the extract poured over 20 g. of silica gel. The column was washed with 500 ml. of 1:1 benzene-petroleum ether and the product eluted with benzene. Crystallization of the residue from petroleum ether yielded 0.8 g. *l*-ethylphenylcarbinyl-α-naphthylurethane (VII) as needles, m.p. 113–115°. Recrystallization from the same solvent raised the m.p. to 116–117°, $[\alpha]_D$ −31.5°.

A duplicate experiment using racemic base (3.7 g.) gave racemic ethylphenylcarbinyl-α-naphthylurethane, 1.1 g., needles from petroleum ether, m.p. 102–103° (lit.,[9] m.p. 102°).

Levo-ethylphenylcarbinol[4] was converted to the *l*-α-naphthylurethane, needles from petroleum ether, m.p. 115–116°, $[\alpha]_D$ −31.5°.

*Anal.* Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.55; H, 6.24; N, 4.81.

*Acknowledgment:* We would like to thank C. G. VanArman and Miss Norma Bylenga for the pharmacological results. Discussions with R. M. Dodson on stereochemistry and with R. Pappo on the von Braun degradation were very helpful.

We are indebted to R. T. Dillon, H. W. Sause and their associates for analyses and rotations. Analytical samples were dried under high vacuum one hour at 118° unless otherwise stated. Rotations were determined at 25 ± 3° in methanol at a concentration of 1%.

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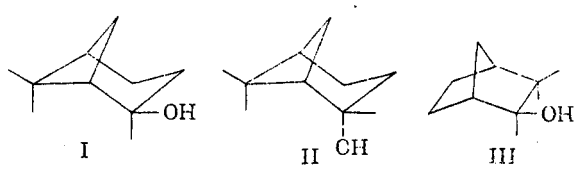
(9) V. T. Bickel and H. E. French, *J. Am. Chem. Soc.*, **48**, 747 (1926).

## Rearrangements During Phosphoryl Chloride–Pyridine Dehydrations

R. R. Sauers and J. M. Landesberg[1]

*Received June 15, 1960*

In an extension of some earlier work[2] on the effect of structure on the course of phosphoryl chloride–pyridine dehydration of tertiary alcohols we have examined the effect of these reagents on *cis*-methylnopinol (I), *trans*-methylnopionol (II),[3] and camphene hydrate (III).

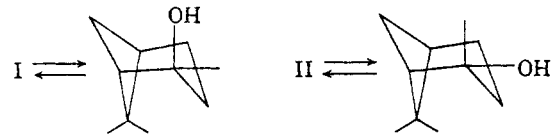



(1) Abstracted in part from the Bachelors thesis of J. M. L. (1960).

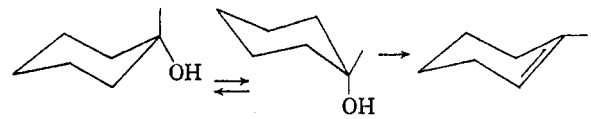
(2) R. R. Sauers, *J. Am. Chem. Soc.*, **81**, 4873 (1959).

(3)(a) W. D. Burrows and R. H. Eastman, *J. Am. Chem. Soc.*, **81**, 245 (1959); (b) W. Huckel and E. Gelchsheimer, *Ann.*, **625**, 12 (1959).

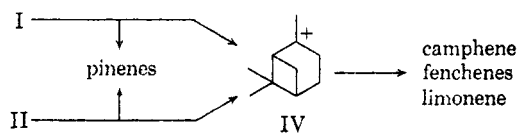
If alcohols I and II are considered in the indicated conformations, the *cis* alcohol would be expected to lead to β-pinene (exocyclic double bond) and the *trans* alcohol would be expected to lead to α-pinene (endocyclic double bond), owing to the equatorial and axial nature of the respective hydroxyl groups.[2] Ring inversion would reverse the axial-equatorial relationships and consequently the dehydration products. It should be noted that ring inversion relieves a 1,3-diaxial interaction and creates a 1,4-methyl-hydrogen interaction. Thus,




if these forms are rapidly equilibrating, both isomers would be expected to lead to α-pinene since 1-methylcyclohexanol gives only 1-methylcyclohexene[2]:




Experimentally, it was found that both alcohols gave mainly α-pinene.[4] Of even greater interest is the formation of considerable amounts of camphene, limonene, β-pinene and some of the fenchenes. The reaction product was too complex (*ca.* ten components) to be completely resolved by vapor phase chromatography and accurate data on the ratios of the components were therefore not attainable. The two mixtures were clearly different, however, ruling out the possibility of a common intermediate. It does not seem unreasonable to assume that part of the elimination proceeds *via* a common symmetrically solvated carbonium ion (IV) and the remainder through either an unsymmetrically solvated carbonium ion or by an $E_2$ mechanism. The carbonium ion IV could be




transformed into the indicated products by well known rearrangements.

It is clear from these results that the use of this reaction for dehydration of alcohols of unknown structure should be accompanied by careful product determination and possible rearrangements considered.

Dehydration of camphene hydrate gave only camphene. In this system, elimination must be

(4) M. Vilkas, G. DuPont, and R. Dulou, *Compt. rend.*, **242**, 1329 (1950) reported that I was dehydrated to a 5:1 mixture of α:β-pinene. These authors did not examine this product by vapor phase chromatography.