[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW HAMPSHIRE]

Resolution of 2,6-Diphenyl-1-methyl-4-piperidone Oxime, a Novel Example of Molecular Isomerism[1,2]

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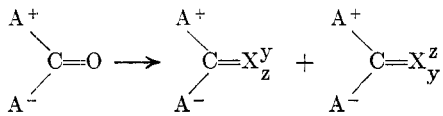
The Michael condensation of dibenzalacetone with methylamine produced *cis*-2,6-diphenyl-1-methyl-4-piperidone (IV). The configuration was proved by failure to resolve IV and reduction of IV to two isomeric alcohols. Configurational assignments of the alcohols were based on the conformational interpretation of equilibration studies, modes of reduction, and infrared spectra of the acetyl derivatives. The oxime of the *cis*-ketone (IV) was shown to be racemic, for it could be resolved. The formation of a racemic mixture by introduction of an unsymmetrically substituted double bond, oximino group, into the *meso* isomer constitutes the first recorded illustration of geometrical enantiomorphic isomerism.

The existence of optical activity may result from the presence of an asymmetric carbon atom in a molecule or from a condition of molecular enantiomorphism in which the lack of symmetry is caused by the restricted rotation of single bonds as in biphenyls[3] and certain aryl amines[4] or by the freezing of a configuration by means of small rings as in allenes,[5,6] cyclohexylidene derivatives,[7] and spiranes.[8,9] One type of molecular asymmetry which was predicted[10] and whose experimental confirmation is the subject of this report has been designated "geometrical enantiomorphic isomerism" by the authors.[1] A compound shows such isomerism when an unsymmetrically substituted double bond



meso *dl*-racemate

is centrally located between two similar asymmetric carbon atoms of opposite configuration.[11]

The earliest attempts to demonstrate geometrical enantiomorphic isomerism was made by Mills who successfully synthesized and resolved the pyridylhydrazone (II) of cyclohexene trithiocarbonate (I).[12] If the bicyclic compound (I) contained a *cis* ring junction, the hydrazone (II) would be optically active because of molecular dissymmetry, and Mills originally made this assignment on the hypothesis that a fusion involving six- and five-membered rings could be stable only in a *cis*-configuration. He therefore made no attempt to ascertain the configuration of I. The discovery that hydrindanes could exist as either *cis* or *trans* isomers caused Mills[13] to withdraw the claims he had made in his earlier paper.

An examination of the recent literature permits an assignment of configuration to I. The hydrolysis of cyclohexene trithiocarbonate (I)[14] produced the same 1,2-dimercaptocyclohexane (III) as that obtained by hydrosulfide ring opening of cyclohexene sulfide.[15] Since the hydrolytic cleavage of I would not disturb the relative configuration of the sulfur atoms of I[16] and since an epithio ring opening produces a *trans* dithiol,[17] I must have a *trans* ring

(1) For preliminary communication, see R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **22**, 856 (1957).

(2) Abstracted from a thesis presented by G. G. Lyle to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Dissertation Abstracts, **19**, 673 (1958).

(3) G. H. Christie and J. Kenner, *J. Chem. Soc.*, 614 (1922).

(4) R. Adams and M. J. Gortakowski, *J. Am. Chem. Soc.*, **79**, 5525 (1957) and preceding papers by R. Adams and coworkers.

(5) P. Maitland and W. H. Mills, *Nature*, **135**, 994 (1935); *J. Chem. Soc.*, 987 (1936).

(6) E. P. Kohler, J. T. Walker, and M. Tishler, *J. Am. Chem. Soc.*, **57**, 1743 (1935).

(7) W. H. Perkin, W. J. Pope, and O. Wallach, *Ann.*, **371**, 180 (1909); *J. Chem. Soc.*, **95**, 1789 (1909).

(8) W. H. Mills and C. R. Nodder, *J. Chem. Soc.*, 1407 (1920).

(9) S. E. Jansen and W. J. Pope, *Chem. & Ind. (London)*, **10**, 316 (1932).

(10) R. L. Shriner, R. Adams, and C. S. Marvel in Gilman's *Organic Chemistry*, **Vol. I**, 2nd Ed., John Wiley and Sons, New York, 1943, p. 240.

(11) The name arises from the introduction of the elements of geometrical isomerism centrally between two enantiomorphic carbon atoms of a *meso* isomer. Since molecular enantiomorphism is a general designation for optically active compounds, geometrical enantiomorphic isomerism denotes the special case in which optical activity is partially the result of geometrical isomerism.

(12) W. H. Mills and H. Schindler, *J. Chem. Soc.*, 3112 (1923).

(13) W. H. Mills and B. C. Saunders, *J. Chem. Soc.*, 537 (1931).

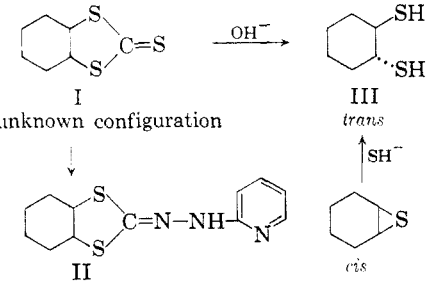
(14) C. C. J. Culvenor and W. Davies, *Australian J. Sci. Research, Series A*, **1**, 236 (1948).

(15) C. C. J. Culvenor, W. Davies, and N. S. Heath, J. Chem. Soc., 282 (1949).

(16) *Cf.* the alkaline hydrolysis of the isothiuronium group to the thiol. T. Taguchi and M. Kojima, *J. Am. Chem. Soc.*, **78**, 1464 (1956).

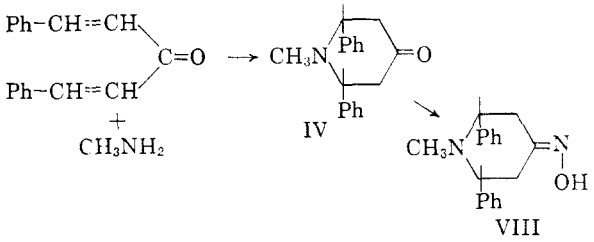
(17) *Cf.* the addition of 2,4-dinitrophenylsulfenyl halides to alkenes *via* sulfonium ion and the stereochemistry of the ring opening reactions of three-membered heterocycles. A. J. Havlik and N. Kharasch, *J. Am. Chem. Soc.*, **78**, 1207 (1956); H. L. Goering, D. I. Relyea, and K. L. Howe, *J. Am. Chem. Soc.*, **79**, 2502 (1957); O. E. Paris and P. E. Fanta, *J. Am. Chem. Soc.*, **74**, 3007 (1952); S. Winstein and R. B. Henderson in *Heterocyclic Compounds*, **Vol. I**, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, 1950, p. 1; D. H. R. Burton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

junction. As a consequence, II was resolvable because of atomic and not molecular asymmetry.



Noller and co-workers attempted the synthesis and resolution of the *p*-dimethylaminobenzylidene derivative of *N,N'*-bis(1-phenylethyl)-malonamide, but the resolution failed because of the decomposition of the salts on recrystallization.[18] Therefore, prior to our preliminary communication,[1] no demonstration of geometrical enantiomorphic isomerism had been made.

The compound selected for this study was the oxime of 2,6-diphenyl-1-methyl-4-piperidone (IV), synthesized by the condensation of dibenzalacetone with methylamine. IV can exist in three isomeric forms, a pair of enantiomorphs in which the two asymmetric carbon atoms have the same configuration, the two isomers constituting a racemic mixture, and a *meso* isomer in which the two similar asymmetric carbons are enantiomorphs. If the ketonic function in the *meso* isomer is replaced by an unsymmetrically substituted double bond, *e.g.*, an oximino group, the resulting racemate would be optically active because of molecular dissymmetry.

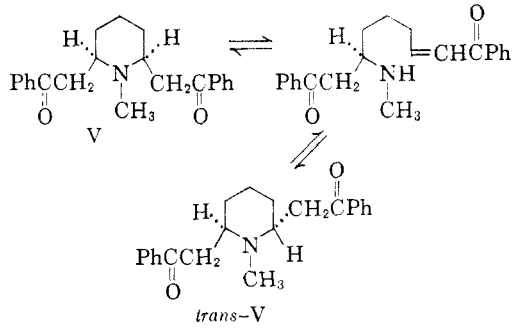


The condensation of dibenzalacetone with methylamine has been reported[19] to produce an isomer of 2,6-diphenyl-1-methyl-4-piperidone (IV), m.p. 152–153°. Repetition of the reaction produced the same compound, and no conditions were found whereby a second modification could be isolated. An alternative synthesis of IV *via* the 3,5-dicarbethoxy derivative[20] failed, for this compound did not undergo hydrolysis and decarboxylation to IV.

The configuration of IV would be expected to show the *cis* relationship of the phenyl groups if thermodynamic control of the formation obtained, for such a configuration would permit the equatorial conformation of the large aromatic groups. At the transition from the acyclic to cyclic forms, the structure showing the least steric interference would be that in which the phenyl groups were *trans* to each other, thus leading to the formation of *trans*-IV by kinetic control. If the formation of the piperidone were irreversible, this should be the only isomer isolated. As will be demonstrated conclusively below, the *cis* isomer was the exclusive product of the Michael condensation. A similar instance has been noted in the formation of *cis*-2,6-dimethyl-4-piperidone *via* the Mannich condensation of diethyl acetonedicarboxylate with acetaldehyde and ammonia followed by hydrolysis and decarboxylation.[21] The conditions for these two reactions are quite similar, and the resultant piperidones would be presumed to undergo equilibration leading to the production of the thermodynamically more stable isomer.

The infrared and ultraviolet absorption spectra of IV were consistent with the structure of the molecule, and the crystalline ketone showed no alteration of properties on standing. Ethanolic solutions of IV, however, changed markedly in ultraviolet absorption on standing at room temperature for several weeks. The carbonyl absorption band (290 mμ, ϵ_{max} 322) for IV underwent a bathochromic shift (to 325 mμ) with a concomitant increase in intensity, ϵ_{max} 2300. The solution became yellow in color during this period. Assuming that the major decomposition product was dibenzalacetone, the ultraviolet absorption spectrum showed that approximately 10% of the piperidone (IV) had disappeared during the three-week period, and subtraction of the absorption of the remaining IV from the spectrum of the mixture gave a differential curve which had maxima at 229 and 325 mμ; dibenzalacetone, $\lambda_{max}^{95\%\ EtOH}$ 208, 230, 330 mμ; ϵ_{max} 15,400; 12,000, 27,000.

The ultraviolet absorption data indicate an equilibration which could reasonably be compared with the isomeric changes observed with some of the lobelia alkaloids.[22] Salts of these alkaloids are stable, and reduction of the carbonyl groups produces stable derivatives. (−)-Lobeline, however, undergoes mutarotation on standing in alcoholic solution



(18) C. R. Noller, A. G. Yartzoff, and W. N. Jones, Jr., *J. Am. Chem. Soc.*, **78**, 5016 (1956).

(19) J. D. Riedel, German Patent **269,429**, July 18, 1913; *Chem. Zentr.*, **85**, 507 (1914).

(20) C. R. Noller and V. Baliah, *J. Am. Chem. Soc.*, **70**, 3853 (1948).

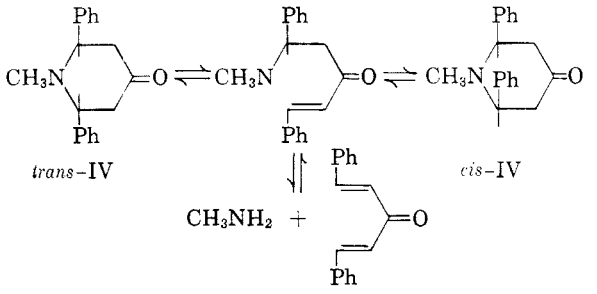
(21) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5444 (1957).

(22) A. Ebnother, *Helv. Chim. Acta*, **41**, 386 (1958).

for several hours, and lobelanine (V), having the *meso* configuration, and *trans*-lobelanine are mutually interconverted on refluxing in ethyl acetate.

The above changes have been explained as resulting from the reversal of the Michael addition in the β-aminoketone leading to ring opening. Closure of the ring could produce the same or a different isomer. This suggests that any compound containing the R—N—CH—CH_2—C—R′ grouping

characteristic of the lobelia alkaloids could undergo a similar reaction, and in the case of cyclic compounds such as IV, the ring could open on both sides of the nitrogen leading to the formation of dibenzalacetone. Such a mechanism would also indicate that production of the more stable *cis* isomer of IV resulted from thermodynamic control.



Evidence for the *meso* configuration of IV came from the failure to resolve IV with the aid of (+)-10-camphorsulfonic acid. Recrystallization of the salt gave fractions which showed essentially the same optical rotation as the salt before recrystallization.

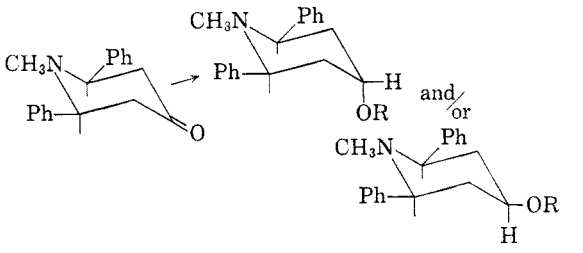
A study of the reduction of IV supplied the proof of configuration as the *meso* isomer. If IV were a DL-racemate, reduction would produce only a DL-racemate, 2,6-diphenyl-1-methyl-4-piperidinol, regardless of the method of hydrogenation. If IV had the *meso* configuration, however, reduction would yield two optically inactive alcohols (VI), the thermodynamically more stable all *cis*-isomer having an equatorial hydroxyl group (VIb) and the epimer with an axial hydroxyl group (VIa). On the basis of reports by Barton[23] and Dauben[24] reduction of an unhindered ketone by lithium aluminum hydride should produce a mixture of alcohols predominating in the isomer having an equatorial hydroxyl. Reduction of IV under these conditions produced only one isolable isomer, m.p. 170–172.5°, designated the β-alcohol, VIb.

Catalytic hydrogenation of IV over Adams' catalyst in neutral medium gave VIb mixed with a different isomer (VIa), m.p. 156–157.5°. The presence of acid in the hydrogenation medium led to a mixture from which only VIb could be isolated in pure form. Attempts to separate the mixture by chromatography over basic alumina yielded only pure VIb.

(23) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953), ref. 23.

(24) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc*, **78**, 3752 (1956).

The reaction of IV with sodium in alcohol led to decomposition of IV. The Meerwein-Ponndorf-Verley reduction of IV produced a mixture of alcohols containing approximately 80% of the axial α-alcohol (VIa), determined as the hydrochlorides of the acetyl derivatives (VII), a value consistent with results from other studies.[25] Equilibration studies of the two alcohols showed that it was possible to convert VIa to VIb but not the reverse. Treatment of VIb with sodium amyloxide produced only unchanged VIb, but a similar reaction with VIa gave a mixture of higher melting point than the starting material. No pure VIb could be isolated, however. When VIa was treated with the lithium aluminum hydride–aluminum chloride mixture described by Eliel[26] for equilibration of cyclohexanol derivatives, a mixture was obtained from which some pure VIb was separated by chromatographic absorption on basic alumina. No attempt was made to ascertain the exact percentage in the equilibrium mixture, but at least 50% of VIb was obtained.



VIa. R = H VIb. R = H
VIIa. R = Ac VIIb. R = Ac

The infrared absorption spectra of VIa and VIb were quite similar, but the melting points and solubilities of the hydrochlorides were distinctly different. Conversion of VI to the acetate hydrochlorides gave compounds having marked differences in all three properties. In the steroid series, the 3-axial acetoxyl group usually gives a complex spectrum in the region from 1200 to 1250 $cm.^{-1}$ while the equatorial acetoxyl group possesses a single, sharp band.[27] The spectrum of VIIa in carbon disulfide revealed a split peak at 1230 and 1237 $cm.^{-1}$ with a shoulder at 1258 $cm.^{-1}$, but VIIb showed a single band at 1236 $cm.^{-1}$. Mulls of the hydrochlorides of VII gave similar bands, that of VIIa being the more complex having a peak at 1243 $cm.^{-1}$ and shoulders at 1235 and 1253 $cm.^{-1}$, while VIIb hydrochloride gave a single band at 1238 $cm.^{-1}$. Thus the modes of formation of the alcohols (VI), the equilibration studies of the alcohols, and the infrared absorption spectra of the acetyl derivatives

(25) H. R. Nace and G. L. O'Connor, *J. Am. Chem. Soc.*, **73**, 5824 (1951).

(26) M. Rerick and E. Eliel, Abstracts of Papers, 133rd Meeting, American Chemical Society, San Francisco, Calif., April, 1958, p. 4 N.

(27) A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 5571 (1952).

(VII) all led to the assignment of the axial hydroxyl to VIa and of the equatorial hydroxyl to VIb.

The conversion of the *meso* ketone (IV) to the racemic oxime (VIII) was accomplished readily. An interesting reaction was observed on heating the racemic oxime with an equimolar amount of D-10-camphorsulfonic acid in 95% ethanol. The specific rotation of the salt solution decreased during the reaction period, and addition of base produced a mixture containing, in addition to the levorotatory oxime, small amounts of 2,6-diphenyl-1-methyl-4-piperidone (IV) and dibenzalacetone. It appeared that the acidic solution effected hydrolysis of the oxime to the ketone which underwent a reversal of the original condensation to produce dibenzalacetone. It is impossible to state whether the reversal of the Michael addition occurred in the acidic solution or during the chromatographic separation on basic alumina. The latter is the more plausible. The optically active acid apparently catalyzed the stereospecific degradation kinetically favoring the decomposition of the dextrorotatory isomer.

The oxime (VIII) formed a crystalline salt on reaction with (+)-10-camphorsulfonic acid in methanol-ether solution, and three recrystallizations yielded a dextrorotatory diastereoisomer of maximum rotation. Regeneration of VIII from the salt produced the dextrorotatory enantiomer with a specific rotation of +31° in either benzene or 95% ethanol. Treatment of the mother liquors with base to obtain the levorotatory isomer failed to yield a crystalline product.

Proof that the asymmetry of the oxime (VIII) was due to molecular asymmetry was obtained by a study of the racemization and hydrolysis of VIII. The rate of acid catalyzed racemization of (+)-VIII could not be measured because of the lack of solubility of the oxime in acidified solutions of water, alcohols, dioxane, nitromethane, acetonitrile, chloroform, carbon tetrachloride, and benzene. When the oxime was allowed to react with thionyl chloride in benzene in a heterogeneous mixture, the oxime was recovered unchanged but racemic, conditions which would alter only the oxime group. Hydrolysis of (+)-oxime by the pyruvic acid method of Hershberg[28] gave 2,6-diphenyl-1-methyl-4-piperidone (IV) which produced no rotation of plane polarized light. The above reactions affected stereochemically only the oximino function and not the asymmetric carbon atoms, thus adding confirmatory proof that this was the first example of geometrical enantiomorphic isomerism.

EXPERIMENTAL[29]

2,6-Diphenyl-1-methyl-4-piperidone (IV). Methylamine was bubbled into a suspension of 20 g. (0.086 mole) of dibenzalacetone[30] in 200 ml. of methanol until solution was effected. The quantity of methylamine dissolved was 8 to 10 g. The solution was allowed to stand for 48 hr. at room temperature. Most of the solvent was removed by distillation at steam bath temperature under reduced pressure, and the residual oil was dissolved in 100 ml. of ether. An equal amount of water was added to the ethereal solution, and on standing crystals were deposited at the interface. The crude product, 32.0 g., from two combined runs was recrystallized from 95% ethanol yielding 24.0 g. (52.6%) of 2,6-diphenyl-1-methyl-4-piperidone (IV), m.p. 151–153°; $\bar{\nu}_{max}^{Nujol}$ 1720 (carbonyl); $\lambda_{max}^{95\%\ EtOH}$ (ϵ_{max}) 210 (19,400); 252 (680); 258 (735); 264 (630); 290 (400); lit.[19] m.p. 152–153°.

Oximation under standard conditions gave a product, m.p. 191–193°, after recrystallization from 95% ethanol; lit.[31] m.p. 190°; $\lambda_{max}^{95\%\ EtOH}$ (ϵ_{max}) 210 (23,800); 252 (565); 258 (608); 264 (506); 289 (246).

Reduction of 2,6-Diphenyl-1-methyl-4-piperidone (IV). (a) *With lithium aluminum hydride.* A suspension of 1.6 g. (0.04 mole) of lithium aluminum hydride in dry ether was prepared in a 500 ml. Grignard apparatus and was stirred vigorously for 15 min. A solution of 5.3 g. (0.02 mole) of 2,6-diphenyl-1-methyl-4-piperidone (IV) in dry ether was added over a period of 45 min. The mixture was heated under reflux with stirring for 1.75 hr. and decomposed cautiously with water. The ethereal layer was separated and dried over potassium carbonate. Removal of the solvent left a white solid, 2,6-diphenyl-1-methyl-4β-piperidinol (VIb), 5.12 g. (95.9%), m.p. 164.5–167°. An analytical sample, m.p. 170–172.5°, was obtained on recrystallization of VIb from 95% ethanol; $\bar{\nu}_{max}^{Nujol}$ 3240, 3150 (bonded OH), 1020 (OH); $\bar{\nu}_{max}^{CS_2}$ 3618 (unbonded OH), 1022 (OH); $\bar{\nu}_{max}^{CCl_4}$ 3618 (unbonded OH); lit.[19] m.p. 167°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 81.03; H, 8.02.

The hydrochloride of VIb was prepared by conventional methods and melted in a sealed tube at 306–309° with decomposition and sublimation.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30. Found: C, 71.02; H, 7.02.

The preparation of the acetyl derivative of the β-alcohol was accomplished by heating 1.0 g. of VIb with 0.5 g. of fused, powdered sodium acetate and 5 ml. of acetic anhydride on a steam bath for 2 hr. The mixture was poured into ice and water causing the precipitation of 4β-acetoxy-2,6-diphenyl-1-methylpiperidine (VIIb). Recrystallization of the ester from ethanol-water gave an analytical sample, m.p. 101–104°; lit.[19] m.p. 105–106°; $\bar{\nu}_{max}^{CS_2}$ 1742, 1236 (acetate).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.71; H, 7.39.

The acetic acid solution, after removal of VIIb, was neutralized with potassium hydroxide solution, and the amine was extracted with ether. After the ethereal extract was dried over sodium sulfate and the solvent removed by distillation, the residual oil was dissolved in anhydrous ether

(28) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(29) Infrared absorption spectra were determined on a Perkin-Elmer spectrophotometer, Model 21. Spectra of solids were determined as mulls in series 11–14 Halocarbon oil from 4000–1300 cm.$^{-1}$ and in Nujol from 1300–650 cm.$^{-1}$ unless otherwise designated. For use of these agents see R. E. Lyle, R. E. Adel, and G. G. Lyle, *J. Org. Chem.*, **24**, 342 (1959); D. S. Crocket and H. M. Haendler, *Anal. Chem.*, **13**, 626 (1959). Optical rotations were determined on a Franz Schmidt and Haensch polarimeter using a sodium vapor lamp as a light source, and all measurements were made in a 2 dcm. tube. Microanalyses were determined by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ultraviolet absorption spectra were obtained using a Perkin-Elmer Model 4000 recording spectrophotometer partially financed by funds from a grant, NSF G 3901, from the National Science Foundation.

(30) C. R. Conard and M. A. Dolliver, *Org. Syntheses*, **Coll. Vol. II**, 167 (1943).

(31) P. W. Neber, A. Burgard, and W. Thier, *Ann.*, **526**, 277 (1936).

and treated with dry hydrogen chloride. Recrystallization of the hydrochloride of VIIb from absolute methanol gave an analytical sample, m.p. 279–281° with sublimation; $\bar{\nu}_{max}^{mull}$ 1737, 1238 (acetate); $\bar{\nu}_{max}^{CHCl_3}$ 1735 (acetate).

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99. Found: C, 68.94; H, 7.06.

(b) *With hydrogen over platinum oxide.* Solution of 2.65 g. (0.01 mole) of 2,6-diphenyl-1-methyl-4-piperidone (IV) in 65 ml. of anhydrous methanol was effected by heating the reagents. On cooling, the piperidone remained in solution, and 0.1 g. of platinum oxide was added. The mixture was shaken under 2.5 atm. of hydrogen at room temperature for 2.5 hr., and the catalyst was removed by filtration. After the solvent was removed by distillation under reduced pressure, the solid residue was triturated with methanol and separated by filtration yielding 0.86 g. of 2,6-diphenyl-1-methyl-4α-piperidinol (VIa), m.p. 155–156°. Four additional crops, m.p. 149–153°, were obtained from the methanol washings. The combined solids represented a 63% yield. A small amount of material, m.p. 166–167°, was obtained from the mother liquors and was shown to be identical with the β-alcohol (VIb). A mixture of the α-alcohol and the starting ketone (IV) melted at 131–141°, while a mixture of the two isomeric alcohols, m.p. 156–157° and 165–168°, melted at 151–154°. Recrystallization of VIa from benzene gave an analytical sample, m.p. 156–157.5°; $\bar{\nu}_{max}^{mull}$ 3500 (w) (unbonded OH), 3270 (bonded OH), 1025 (OH); $\bar{\nu}_{max}^{CS_2}$ 3620 (unbonded OH), 1025 (OH); $\bar{\nu}_{max}^{CCl_4}$ 3630 (unbonded OH).

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.86; H, 7.71.

The hydrochloride of the α-alcohol melted in a sealed tube at 287–288° (dec.) after recrystallization from 70% aqueous isopropyl alcohol.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30. Found: C, 71.11; H, 7.45.

(c) *With aluminum isopropoxide.* Reduction of 5.3 g. (0.02 mole) of IV with 4 g. of aluminum isopropoxide in 50 ml. of isopropyl alcohol was accomplished by standard procedure.[32] The distillate gave a negative acetone test after 1.5 hr. Decomposition of the mixture with dilute hydrochloric acid yielded 4.51 g. (74.3%) of the hydrochloride of 2,6-diphenyl-1-methyl-4α-piperidinol (VIa), m.p. 283–285° (dec.), contaminated with a small amount of the β-alcohol hydrochloride. Neutralization of an aqueous isopropyl alcohol solution of the hydrochloride gave the α-alcohol (VIa), m.p. 155–156° after recrystallization from benzene, which did not depress the melting point of the α-alcohol prepared in (b).

The acetyl derivatives (VII) of the α- and β-alcohols were prepared by heating 1.0 g. of the hydrochlorides of VI, obtained from the Meerwein-Ponndorf-Verley reduction of IV, with 4 ml. of acetic anhydride in 10 ml. of dry pyridine for 20 min. The solution was cooled, diluted with water, and acidified with concentrated hydrochloric acid. The solution was extracted twice with ether, and the extracts were discarded. Strong potassium hydroxide solution was added, and the basic solution was extracted with ether. After drying over potassium carbonate, the ether solution was concentrated, and the residual yellow oil was dissolved in anhydrous ether and treated with hydrogen chloride yielding 0.42 g. of the hydrochlorides of the acetoxy derivatives (VII). Recrystallization from anhydrous ethanol gave 0.07 g. of the hydrochloride of VIIb. Dilution of the ethanolic solution with dry ether gave 0.17 g. of VIIa hydrochloride, m.p. 264–265° (dec.); $\bar{\nu}_{max}^{mull}$ 1737, 1253 (sh.), 1243, 1235 (sh.) (acetate); $\bar{\nu}_{max}^{CHCl_3}$ 1740 (acetate); free amine: $\bar{\nu}_{max}^{CS_2}$ 1748, 1258 (sh.), 1237, 1230 (acetate). From the amounts of the two acetoxy hydrochlorides, it was calculated that the Meerwein-Ponndorf-Verley reduction of IV produced approximately 80% of the α-alcohol (VIa) and 20% of the β-alcohol (VIb).

(32) A. L. Wilds, *Org. Reactions*, II, 203 (1944).

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99. Found: C, 69.40; H, 7.03.

(d) *With hydrogen in weakly acidic solution over platinum oxide.* A solution of 5 g. of the piperidone (IV) in 100 ml. of absolute methanol and 5 ml. of acetic acid was reduced over 0.2 g. of platinum oxide at a pressure of 3 atm. of hydrogen at room temperature for 40 min. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure, and the residue was dissolved in aqueous hydrochloric acid. The acidic solution was extracted once with ether, and the extract was discarded. The aqueous solution was made basic with potassium hydroxide solution and extracted with ether. Concentration of the ethereal extracts yielded crystalline material which, on recrystallization from 95% ethanol, gave 2.32 g. of β-alcohol, m.p. 160–165°. Evaporation of the mother liquor gave 0.72 g. of impure solid, 300 mg. of which was chromatographed on basic alumina using a solution of four parts benzene and one part low-boiling petroleum ether. A dry ether eluent produced 170 mg. of β-alcohol, m.p. 161–166°, and some impure material which was rechromatographed to give 30 mg. of β-alcohol, m.p. 160–165°, and 50 mg. of crude material melting below 130°. It is possible that the basic alumina caused isomerization of the alcohols converting any α-alcohol produced in the reaction to the β-isomer.

(e) *With hydrogen over Raney nickel.* A solution of 4.5 g. of IV in 100 ml. of absolute methanol was hydrogenated at low pressure at room temperature over Raney nickel catalyst. The product was isolated as in (d) yielding 2.37 g. of a mixture consisting chiefly of unreduced IV. Treatment of 0.5 g. of the reduction product, m.p. 135–138°, with hydroxylamine produced 0.52 g. of an oxime, m.p. 186–190°, which did not depress the melting point of an authentic sample of the oxime of 2,6-diphenyl-1-methyl-4-piperidone (IV).

(f) *With hydrogen over platinum oxide in strongly acidic solution.* A solution of 5 g. of the piperidone (IV), 100 ml. of methanol, and 1.6 ml. of concentrated hydrochloric acid was treated with 3 atm. of hydrogen over 0.2 g. of platinum oxide at room temperature for 4.5 hr. The precipitated hydrochloride of VI and catalyst were removed by filtration. The mixture of solids was neutralized, triturated with methanol, and the catalyst separated by filtration. Concentration of the methanolic solution yielded 2.21 g. of VIb, m.p. 167–169°.

The acidic filtrate from the separation of the hydrochloride of VIb was concentrated and neutralized with potassium hydroxide solution yielding 1.28 g. of a mixture of the alcohols, m.p. 154–170°. Recrystallization of the mixture from benzene gave a small amount of the β-alcohol as the only pure component.

Equilibration of the isomeric alcohols (VI). (a) *With sodium methoxide.* A solution of 0.35 of the α-alcohol (VIa), 10 ml. of anhydrous methanol, and 0.2 g. of commercial sodium methoxide was heated under reflux for 2.5 hr. On addition of water, the piperidinol precipitated and was separated by filtration giving a quantitative recovery of the α-alcohol (VIa), m.p. 153–154°.

(b) *With sodium amyloxide and* VIa. Sodium amyloxide was prepared by dissolving 0.5 g. of sodium in 10 g. of amyl alcohol, and the solution was added to 5 ml. of amyl alcohol containing 0.35 g. of VIa recovered from (a) above. The solution was heated under reflux for 3.5 hr., cooled, and poured into 20 ml. of water. The mixture was acidified with hydrochloric acid and was extracted with ether to remove the amyl alcohol. The aqueous solution was made basic with potassium carbonate and extracted with ether. The extracts were dried over potassium carbonate, and the solvent was removed by distillation yielding, as a residue, 0.2 g. of a mixture of the alcohols, m.p. 156–159°. Recrystallization failed to resolve the mixture of alcohols.

(c) *With sodium amyloxide and* VIb. A solution of sodium amyloxide prepared from 1.0 g. of sodium and 15 g. of amyl alcohol was added to 1.0 g. of VIb, m.p. 166–167°,

and the solution was heated under reflux for 3 hr. The product was isolated as in (b) yielding 0.91 g. of material which melted at 166–168°. None of the α-alcohol was isolated from the reaction mixture.

(d) *With lithium aluminum hydride–aluminum chloride.* An ethereal solution of 0.6 g. of the α-alcohol (VIa) was added to a mixture of 0.1 g. of lithium aluminum hydride and 1.38 g. of aluminum chloride in 30 ml. of dry ether. The mixture was heated under reflux for 2.5 hr. and 5 ml. of acetone was added to decompose the reagent. Water was added, and the ether layer was decanted. The basic mixture was acidified with hydrochloric acid and extracted with ether, and the ethereal extracts were discarded. The aqueous solution was made strongly basic with sodium hydroxide solution and extracted with two 30-ml. portions of ether. After the ethereal extracts were dried over sodium sulfate, distillation of the solvent yielded 0.5 g. of crude material, m.p. 148–154°. Chromatographic separation of 300 mg. of the mixture on basic alumina as described in (d), under reduction of IV, yielded 130 mg. of β-alcohol, m.p. 170–173°, 100 mg. of α-alcohol, m.p. 153–156°, and 60 mg. of a mixture of the alcohols.

Attempted resolution of 2,6-diphenyl-1-methyl-4-piperidone (IV). A solution of 4.7 g. of (+)-10-camphorsulfonic acid in methanol-ether solution was added to a solution of 5.0 g. of 2,6-diphenyl-1-methyl-4-piperidone (IV) in methanol-ether. The precipitated salt was removed by filtration and failed to show any change in optical rotation, $[\alpha]_D^{25}$ +10.6° (ethyl alcohol, c = 2.1), on three recrystallizations from ethyl acetate.

Anal. Calcd. for $C_{25}H_{35}NO_5S$: C, 67.58; H, 7.09. Calcd. for $C_{28}H_{35}NO_5S \cdot H_2O$: C, 65.22; H, 7.23. Found: C, 65.67; H, 7.42.

(+)-*2,6-Diphenyl-1-methyl-4-piperidoneoxime* (VIII). A solution of 6 g. of (+)-10-camphorsulfonic acid, prepared by suspending the acid in 60 ml. of dry ether and adding methanol until solution was effected, was added to an ether solution containing 6 g. of the oxime (VIII) of 2,6-diphenyl-1-methyl-4-piperidone. The salt crystallized as needles, 10.9 g., m.p. 155–160°. Fractional crystallization of 22.7 g. of the salt from methanol and ether gave 4.15 g., m.p. 167.5–172° (dec.), $[\alpha]_D^{25}$ +30.08° (95% ethanol, c = 2.0). A portion of the salt was recrystallized from acetone yielding 2.5 g., m.p. 172–175° (dec.), $[\alpha]_D^{25}$ +31.61°. When the methanolic ether solution of the salt was seeded with a small crystal of the dextrorotatory isomer and allowed to stand in a refrigerator overnight, 10 g. of the oxime produced 7.8 g. of the salt, m.p. 164–170° (dec.), $[\alpha]_D^{26}$ +26.35°, after one recrystallization from methanol-ether.

Anal. Calcd. for $C_{28}H_{26}N_2O_5S$: C, 65.60; H, 7.08. Found: C, 65.67; H, 7.43.

A solution of 3.0 g. of the (+)-10-camphorsulfonic acid salt of the oxime (VIII), $[\alpha]_D^{25}$ +30.06°, was neutralized with aqueous potassium carbonate. The precipitated oxime, 1.6 g., was removed by filtration and washed with water. Recrystallization of the crude solid from ethanol gave 1.05 g. of oxime, m.p. 188–192°, $[\alpha]_D^{25}$ +32.63° (95% ethanol, c = 2.2); $[\alpha]_D^{25}$ +31.16° (benzene, c = 1.8).

Attempts to obtain the levorotatory isomer of the oxime by adding base to the filtrates from which the dextrorotatory salt had been isolated failed to yield crystalline material in most cases. A few experiments gave crystalline oxime which had no significant rotation.

Reaction of oxime (VIII) *with* (+)-*10-camphorsulfonic acid.* An equimolar mixture of the oxime (VIII) and (+)-10-camphorsulfonic acid was added to 95% ethanol, and the solution was heated under reflux for 8 hr. The specific rotation of the solution showed a decrease of 4.76°.[33] When the oxime was freed of the acid, the oxime, m.p. 187–189.5°, had a specific rotation of −0.40° ± 0.19°. After removal of the oxime, the oily residue was chromatographed on basic alumina, and small amounts of 2,6-diphenyl-1-methyl-4-piperidone (IV) and dibenzalacetone were obtained.

Hydrolysis of (+)-*2,6-diphenyl-1-methyl-4-piperidoneoxime* (VIII). A mixture of 10 ml. of concentrated hydrochloric acid, 20 ml. of water, 1.0 g. of the oxime, $[\alpha]_D^{25}$ +15°, and 1.0 g. of a 50% aqueous solution of pyruvic acid was heated under reflux on a steam bath for 1 hr., cooled, and diluted with water. On basification of the solution with aqueous potassium carbonate, a precipitate formed and was separated by filtration. Trituration of the solid with ether gave 0.22 g. of 2,6-diphenyl-1-methyl-4-piperidone, m.p. 148–151°, which did not depress the melting point of authentic IV. From 1.5 g. of the oxime, $[\alpha]_D^{25}$ +21°, 0.3 g. of recrystallized ketone (IV) was obtained from a similar reaction. A solution of the two samples of the ketone (IV) in an alcohol-acetone solution gave no significant rotation of plane polarized light.

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(33) When (+)-10-camphorsulfonic acid was heated with 95% ethanol, no change in the specific rotation was observed.