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Stereochemical Aspects of Analgetics. Preparation of Isomeric 1-Methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines[1]

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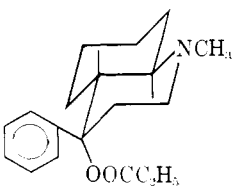
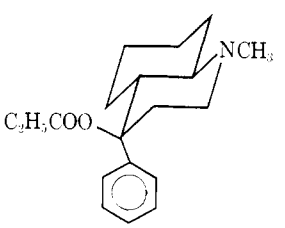
The two isomeric 1-methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines were prepared from *trans*-4-ketodecahydroquinoline by treatment with either phenyllithium or phenylmagnesium bromide to afford the quinolinols. The alcohols were separated and their propionate esters prepared. They were tested for analgetic activity and the results are reported.

Since Beckett first postulated his analgetic receptor site theory,[3,4] controversy as to the necessity of an axial aromatic function as a requirement for analgetic action has appeared in the literature continuously. In order to resolve this controversy, a system was desired which would be rigid and in which the only variable would be the conformation of the aromatic ring.

The prodine-type analgetics, derivatives of 1-methyl-4-piperidinol, have been studied by Beckett and others.[4] To make as close a comparison to their work as possible and still maintain a rigid structure, 1-methyl-4(e)-phenyl-*trans*-decahydro-4(a)-propionoxyquinoline hydrochloride (I), and 1-methyl-4(a)-phenyl-*trans*-decahydro-4(e)-propionoxyquinoline hydrochloride (II) were selected as the compounds which would have the desired physical and biological properties. According to



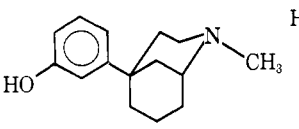
I



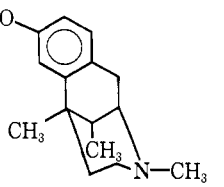
II

the Beckett theory, the only compound with analgetic potency would be the axial phenyl isomer II.

There are no reports in the literature in which isomers differing exclusively in the stereochemistry of the aromatic group have been tested. Eddy has reported compounds III and IV to be almost equally active as analgetics[5] but these two compounds have skeletal differences along with the conformational change of the phenyl ring.



III



IV

The required quinolinols were synthesized *via* 1-methyl-*trans*-4-ketodecahydroquinoline (V) which was prepared by modifications of the methods of Clemo[6] and Horii[7] and their co-workers. When ketone V was allowed to react with either phenyllithium or phenylmagnesium bromide, a mixture of 1-methyl-4-phenyl-*trans*-decahydro-4-quinolinols (VI and VII) was obtained. The alcohols were separated, esterified, and converted to the hydrochloride salts of I and II (VIII and IX) (Scheme I).

The reaction utilizing phenyllithium afforded VI and VII in a ratio of 7:1 and the reaction with phenylmagnesium bromide gave VI and VII in a ratio of 6:1 as determined by gas–liquid partition chromatography (glpc). The alcohols were obtained in a pure state by chromatographic separation on alumina and checked for homogeneity by thin layer chromatography (tlc) (Table I). The alcohols were assigned the structures VI and VII on the basis of their infrared and nmr spectra (Tables II and III).

The *trans* stereochemistry was indicated by the Bohlmann bands (3.46–3.70 μ) in the infrared; these bands appear when there is a free electron pair on a tertiary nitrogen which is *trans* to two axial adjacent protons. Other workers have found these bands in the spectra of

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(2) National Institutes of Health Predoctoral Fellow, 1963–1965.

(3) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954); *Nature*, **173**, 1231 (1954).

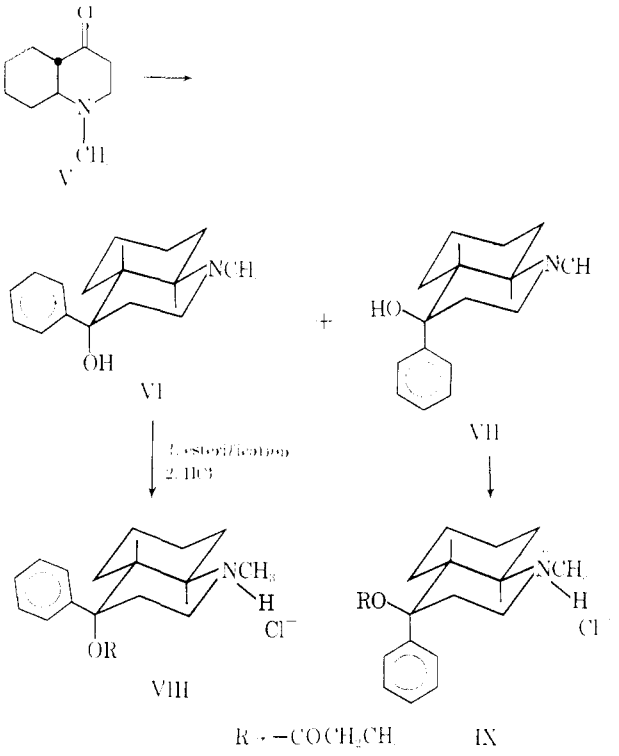
(4) A. H. Beckett in "Fortschritte der Arzneimittelforschung," Vol. 1, E. Jucker, Ed., Birkhäuser Verlag, Basel, 1959, pp 519–529.

(5) N. B. Eddy, *Chem. Ind.* (London), 1462 (1959).

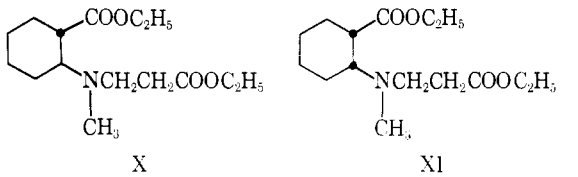
(6) G. R. Clemo, J. G. Cook, and R. Raper, *J. Chem. Soc.*, 1183 (1938).

(7) Z. Horii, T. Watanabe, M. Ikeda, and Y. Tamura, *J. Pharm. Soc. Japan*, **83**, 930 (1963).

SCHEME I



aza steroids,[8] alkaloids,[9] and other heterocyclic systems.[10,11] Bands may appear in this region for compounds containing merely an N-methyl group; however, neither compounds X nor XI show these bands. Compounds X and XI were both used to synthesize the perhydroquinolone system (V). Therefore the bands in the region 3.46–3.70 μ in the infrared indicate the *trans* stereochemistry in alcohols VI and VII.[12]



The alcohols VI and VII were esterified by the method of deStevens, *et al.*,[13] and converted to the hydrochloride salts. The ester hydrochlorides, VIII and IX, were submitted for testing by the Eddy hot plate method[14] using subcutaneous administration (Table IV). The two compounds are of about equal acute toxicity, LD_{50} *ca.* 160 mg/kg, and somewhat less acutely toxic than either meperidine or codeine. Optical resolution of VIII and IX is being investigated; however, the activity of the *dl* forms compares with ED_{50} values of 1.2, 7.5, and 4.7 mg/kg for morphine hydrochloride, codeine hydrochloride, and meperidine hydrochloride, respectively.[15]

The majority of the animal results reported in the prodine and the meperidine series have been obtained by the hot plate method.[16] From the results obtained utilizing this assay method with a system having an energetically restricted conformation for the phenyl group (VIII and IX), it appears that no definitive conformational requirements of the phenyl group are necessary for analgetic action.

TABLE I

GLPC AND TLC DATA FOR 1-METHYL-4-PHENYL-*trans*-DECAHYDRO-4-QUINOLINOLS

	VI (axial)	VII (equatorial)
Mp, °C	126	106–108
Retention time,[a] min	17.5	21.4
R_f[b]	0.17	0.24

[a] Measured from point of injection of a 10 ft × 0.25 in. column of Carbowax 20 M (15%) on Gas-Chrom P support at 225° and 60 cc/min (He). [b] Measured on 1 × 3 in. microscope slides using aluminum oxide G (E. Merck AG., Darmstadt) with ethyl acetate–petroleum ether (2:1).

TABLE II

INFRARED SPECTRAL DATA[a] FOR 1-METHYL-4-PHENYL-*trans*-DECAHYDRO-4-QUINOLINOLS

	VI (axial)	VII (equatorial)
KBr pellets		
Bohlmann bands	3.58[b]	3.58[b]
Ar	3.26, 3.30, 3.33	3.24, 3.26, 3.31
C–O stretching	9.38, 9.93	9.38, 9.50, 9.80, 9.96
CCl_4 solution		
4-OH	2.77	2.77
Bohlmann bands	3.58[b]	3.58[b]
C–O stretching	9.37, 9.93	9.38, 9.50, 9.80, 9.91

[a] Absorption maxima are given in microns. [b] In each case there are several shoulders on the high-wavelength side of the Bohlmann band. [c] K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, Inc., San Francisco, Calif., 1962, p 33, and references therein.

TABLE III

NMR SPECTRAL DATA[a] FOR 1-METHYL-4-PHENYL-*trans*-DECAHYDRO-4-QUINOLINOLS

	VI (axial)	VII (equatorial)
N-Methyl	2.2	2.2
Aromatic multiplet	7.1–7.5	7.3–7.8
N–CH and N–CH_2 multiplets	2.6–2.9	2.6–2.9

[a] Obtained for CCl_4 solutions using TMS as internal standard. Values are expressed in δ units.

TABLE IV

ANALGETIC ACTIVITIES OF 1-METHYL-4-PHENYL-*trans*-DECAHYDRO-4-PROPIONOXYQUINOLINES

Compound	ED_{50}, mg/kg (std dev)
Axial ester hydrochloride (VIII)	12.14 (10.52–14.01)
Equatorial ester hydrochloride (IX)	12.92 (11.68–14.31)

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(9) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963).

(10) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *ibid.*, **86**, 3364 (1964).

(11) H. P. Hamlow and S. Okuda, *Tetrahedron Letters*, 2553 (1964).

(12) While this work was in progress a report on the reaction of 1-methyl-4-ketodecahydroquinolone (VI) with phenyllithium to yield the mixture of alcohols VI and VII was published: E. A. Mistryukov, N. I. Aronova, and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1599 (1962).

(13) G. deStevens, A. Halamandaris, P. Strachan, E. Donoghue, L. Dorfman, and C. F. Huebner, *J. Med. Chem.*, **6**, 357 (1963).

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

(15) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

(16) R. A. Hardy, Jr., and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, pp 179–279.

Experimental Section[17]

1-Methyl-4-phenyl-*trans*-decahydro-4-quinolinols (VI and VII).—The reaction of the ketone V with phenyllithium was performed according to Ziering and Lee[18] and Beckett, *et al.*[19] Lithium (1.33 g, 0.192 g-atom) was placed in 100 ml of dry ether, a few drops of bromobenzene was added, and the mixture warmed to start the reaction. The remaining bromobenzene (a total of 15.1 g, 0.096 mole) was added at a rate to cause the mixture to reflux vigorously. After all the bromobenzene was added, the mixture was refluxed 45 min. The flask was cooled in an ice–salt water bath and the ketone V (8 g, 0.048 mole) was added over 15 min. The mixture was stirred at room temperature for 2 hr, refluxed for 1 hr, and allowed to stand for 5 hr. Hydrochloric acid (15 ml of concentrated acid in 125 ml of water) was added while the mixture cooled in an ice bath. The ether layer was separated. The aqueous layer was made alkaline with 100 ml of concentrated NH_4OH and extracted five times with 150-ml portions of ether. The ether layers were combined and dried ($MgSO_4$), and the ether was removed to yield a viscous oil. Gas–liquid partition chromatography indicated that the isomeric alcohols VI and VII were present in the ratio of 7:1.

The mixture was chromatographed on a column of 398 g of Woelm alumina (grade III) using 20% ethyl acetate in petroleum ether (63–68°). For the final fraction, 67% ethyl acetate in petroleum ether was used. After 240 ml of eluent was collected, all further fractions (50 ml) yielded only the axial alcohol VI. After recrystallization from ethyl acetate and petroleum ether, 6.7 g (57%) of VI was obtained mp 126°.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.47; H, 9.39; N, 5.78.

The physical and spectral data for VI are shown in Tables I–III.

The supernatants obtained from recrystallization of the chromatographic fractions were combined, and after removal of the solvents, a viscous brown liquid (4 g) was obtained and glpc indicated that VI and VII were present in the ratio of 1.9:1. This material was then chromatographed on a column of 400 g of Woelm alumina (grade III) and eluted with 10% ethyl acetate in petroleum ether and finally 67% ethyl acetate in petroleum ether for the last two fractions. The course of the chromatography was followed by tlc (see Table I). The amounts of VI and VII obtained were 1.0 and 0.7 g. The total yields from the two chromatographic separations for VI and VII were 66 and 6%.

The equatorial alcohol melted at 106–108° upon recrystallization from petroleum ether. The physical and spectral data for compound VII are shown in Tables I–III.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.11; H, 9.50; N, 5.67.

1-Methyl-4-phenyl-*trans*-decahydro-4-quinolinols (VI and VII) by a Grignard Reaction.—The ketone V (1 g, 0.006 mole) in 10 ml of dried ether was added slowly to a cooled, stirred, ethereal solution of the Grignard reagent prepared from Mg (0.292 g, 0.012 g-atom) and bromobenzene (1.89 g, 0.012 mole). The mixture was refluxed for 7 hr and allowed to stand for 3 hr. It was then cooled and decomposed with 12 ml of 20% HCl. The ether layer was separated and the aqueous layer was washed with ether. The aqueous layer was saturated with K_2CO_3 and extracted with ether. The ether solution was dried ($MgSO_4$), the latter was removed, and the solvent was evaporated. Gas–liquid partition chromatography indicated the ratio VI:VII to be 6:1.

1-Methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinoline Hydrochloride Salts (VIII and IX).—The esterifications were performed according to deStevens, *et al.*[13] The axial alcohol VI (1.95 g, 0.00796 mole) in 10 ml of dried toluene was added to 1.91 g (0.0207 mole) of freshly distilled propionyl chloride in 10 ml of dried toluene. The mixture was stirred and heated at 100–110° for 8 hr. At the end of this time, the toluene was evaporated and the residue was made basic with aqueous $NaHCO_3$. After six extractions with ether, the latter solutions were combined, dried ($MgSO_4$), and evaporated to yield an oil.

The infrared spectrum of the ester ($CHCl_3$) showed bands at 3.58 with shoulders on the high-wavelength side (Bohlmann bands), a band at 5.77 (C=O), and bands at 8.15, 8.47, and 8.70 (C–O stretching for axial ester).[20]

The axial ester hydrochloride was obtained in an 80% yield (2.14 g), mp 135°. The salt was hygroscopic and could not be recrystallized; it was purified by treatment with activated charcoal in acetone solution. Spectral data are given in Tables V and VI.

TABLE V

INFRARED SPECTRAL DATA[a] FOR 4-PHENYL-*trans*-DECAHYDRO-4-PROPIONOXYQUINOLINE HYDROCHLORIDE SALTS

	VIII (axial ester)	IX (equatorial ester)
C=O stretching	5.77	5.77
C—O stretching	8.14, 8.49, 8.66	8.27, 8.51

[a] Absorption maxima are given in microns. The spectra were taken with KBr pellets.

TABLE VI

NMR SPECTRAL DATA[a] FOR 4-PHENYL-*trans*-DECAHYDRO-4-PROPIONOXYQUINOLINE HYDROCHLORIDE SALTS

	VIII (axial ester)	IX (equatorial ester)
N-methyl	3.00	3.05
Aromatic multiplet	7.14–7.68	7.48–7.83
N–CH and $N–CH_2$ multiplets	3.18–3.80	3.18–3.95

[a] Obtained for D_2O solutions using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard. The values are expressed in δ units.

Anal. Calcd for $C_{19}H_{28}ClNO_2$: C, 67.54; H, 8.35; Cl, 10.49; N, 4.15. Found: C, 67.85; H, 8.45; Cl, 10.95; N, 3.97.

The equatorial alcohol VII (0.750 g, 0.00306 mole) was esterified by the deStevens method[13] and the hydrochloride salt was obtained; yield 0.821 g (80%), mp 132–133°. This salt was also hygroscopic and could not be recrystallized; it was purified by treatment with activated charcoal in acetone solution. Spectral data are given in Tables V and VI.

Anal. Calcd for $C_{19}H_{28}ClNO_2$: C, 67.54; H, 8.35; Cl, 10.49; N, 4.15. Found: C, 67.20; H, 8.30; Cl, 10.94; N, 4.56.

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(17) Melting points were obtained on a calibrated Kofler micro hot stage and a Thomas–Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR5 and IR8 spectrophotometers. Values are expressed in microns. Nmr data were recorded on a Varian Associates Model A-60 spectrophotometer using TMS as the internal standard or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt when D_2O was used as solvent. All chemical shifts are in parts per million downfield from the standard. Gas chromatographic data were obtained on F and M Model 810 research chromatograph using a 3.05 m × 0.63 cm (10 ft × 0.25 in.) column of Carbowax 20 M (15%) on Gas-Chrom P support at 225° and 60 cc/min (He).

(18) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

(19) A. H. Beckett, A. F. Casy, G. Kirk, and J. Walker, *J. Pharm. Pharmacol.*, **9**, 939 (1957).

(20) S. Bory and M. Fetizon, *Bull. Soc. Chim. France*, 570 (1964).