[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE AND DENTISTRY AND THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Reduction of 9-(2-N-*dl-trans*-Decahydroquinolino-1-oxoethyl)-1,2,3,4-tetrahydrophenanthrene and Its Optical Forms to Alcohols with Pronounced Gonadal Effects

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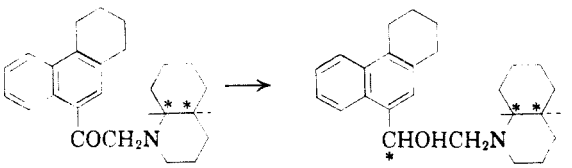
Reduction of 9-(2-N-*dl-trans*-decahydroquinolino-1-oxoethyl)-1,2,3,4-tetrahydrophenanthrene (I) with lithium aluminum hydride has given 70–85% yields of a 6:1 mixture of the two expected alcohols (α and β) as compared with a 60% yield of a 4:1 mixture obtained previously by platinum oxide hydrogenation. With aluminum isopropoxide as the reducing agent, a 50% yield of a 2:3 ratio of the α- and β-alcohols respectively resulted. The optical isomers of I, reduced with lithium aluminum hydride, afforded results similar to those obtained with the racemate I. The racemic α- and β-alcohols are effective in producing atrophic changes in both the male and female gonads of the rat, more pronounced in the male than in the female, and in inhibiting the secretory and developmental changes in the seminal vesicles and prostate and the gynecological tract.

In the pharmacological study of various amino alcohols having antimalarial activity it was observed[2] that 9-(2-N-*dl-trans*-decahydroquinolino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene (II)[3] produced apparent gonadal stimulation in the

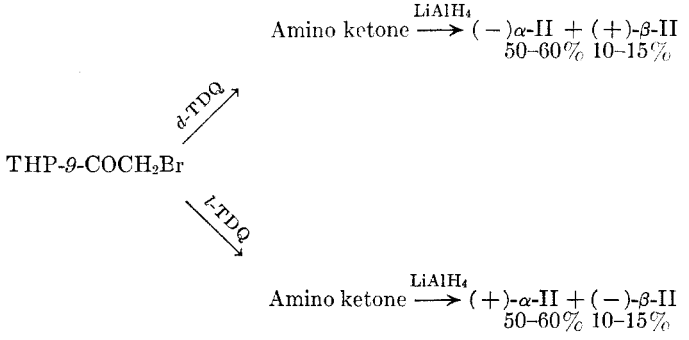


I II

rat and rabbit. Subsequent observations with larger series of animals of different age groups indicated that the SN 1800,[3] instead of having a stimulating effect, produced rather a preliminary transient edema of the sex organs. As additional studies of this nature seemed warranted, we have investigated further the preparation of the pure racemates corresponding to II and the optical isomers comprising these racemates. Results pertaining to the biological studies, however, deal only with the pure racemic alcohols.

The hydrogenation of 9-(2-N-*dl-trans*-decahydroquinolino-1-oxoethyl)-1,2,3,4-tetrahydrophenanthrene (I) has been shown to yield 60–65% of a mixture of the two possible racemic alcohols (II)[3] in an approximate ratio of 4:1. We now find that with ethereal lithium aluminum hydride, I and its optical forms give 50–70% yields of the α- and 10–15% of the β-alcohol[4] corresponding to II. (Figure 1 shows the course of the reductions when the optically active forms of I are used.) Reduction of the hydrochloride of I with aluminum isopropoxide affords a 2:3 mixture of the α- and β-isomers respectively.

FIG. 1



TDQ = *trans*-decahydroquinoline, THP = tetrahydrophenanthrene

(1) Georgetown University Medical Center.

(2) Popovici, Rubin, and Geschickter, *The Bulletin, Georgetown University Medical Center*, **4**, 165 (1951).

(3) May and Mosettig, *J. Org. Chem.*, **11**, 1 (1946). As originally isolated and tested the II was a 4:1 mixture of diastereoisomeric alcohols designated as SN 1800 in Wiselogle, A Survey of Antimalarial Drugs, J. W. Edwards, Ann Arbor, Michigan, 1946.

(4) These diastereomeric alcohols were formerly designated as A and B. For convenience in the experimental nomenclature the A and B designations have now been changed to α and β.

trans-Decahydroquinoline was first resolved by Mascarelli and Nigrisoli[5] with *d*-bromocamphorsulfonic acid. While their procedure readily gave the pure *d-trans*-decahydroquinoline, in our hands it proved unsatisfactory for the preparation of the *l*-isomer. We have obtained the latter in 55–60% yields by treating *dl-trans*-decahydroquinoline with L-threaric (*d*-tartaric) acid.[6]

The *α*- and *β-dl*-II, administered to rats over a three-day period, followed by sacrifice after eight days, produced marked atrophic changes in both the male (reduction in weight of the testes, prostate, and seminal vesicles) and female (about 50% atrophy of the ovaries, tubes, uterus, and cervix). There was also apparent inhibition of the secretory and developmental changes in the seminal vesicles and prostate and in the gynecological tract. Adrenal enlargement ranged from 20–30% above the controls. Details of the pharmacology (unpublished) of these two isomers are presently available at Georgetown University.

EXPERIMENTAL[7]

l-Trans-Decahydroquinolinium hydrogen L-*threarate.* L-Threaric acid (7.5 g., 0.05 mole), 7.0 g. (0.05 mole) of *dl-trans*-decahydroquinoline,[8] and 25 ml. of methanol were warmed to solution, diluted with 25 ml. of dry ether, and kept at 25° for 5 hours to give 10.0 g. of crystals of m.p. 153–160°. Three recrystallizations from methanol (3 ml./g.)-ether (2.5–3 ml./g.) with cooling for 2–2.5 hours at 25° gave 4.1 g. (58%) of the hydrogen L-threarate salt of *l-trans*-decahydroquinoline, m.p. 171.5–173°. The analytical sample was recrystallized from ethanol; clusters of thin prisms, m.p. 172–174°, $[\alpha]_D^{20}$ +14.3° (*c*, 1.19, water).

Anal. Calc'd for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01. Found: C, 53.68; H, 8.10.

l-trans-Decahydroquinoline was prepared from the L-threarate with aqueous sodium hydroxide and ether. A sublimed sample melted at 71–73° and gave $[\alpha]_D^{20}$ −4.6° (*c*, 3.9); lit.[5], m.p. 74–75°, $[\alpha]_D^{25}$ −4.5°.

Reduction of I *with lithium aluminum hydride.* To 5.0 g. of I[3] and 150 ml. of dry ether was added, with stirring during 3–5 minutes, 5 ml. of 1.5 *M* ethereal lithium aluminum hydride. The clear solution was stirred for 5–10 minutes and treated gradually with 10 ml. of water. The ether was decanted, dried, concentrated to 20–25 ml. (to the appearance of crystals), and kept at 5° for 4 hours to give 3.7 g. of 9-(2-*α*-N-*dl-trans*-decahydroquinolino-1-hydroxyethyl)-1,2,-3,4-tetrahydrophenanthrene (II)[4], m.p. 150–155°. After one recrystallization from acetone the yield was 3.0 g., m.p. 158.5–160° alone or in mixture with that designated previously[3] as isomer A.

The filtrate from the 3.7 g. of the *α*-isomer, on concentration to *ca.* half volume, gave 0.5 g. of the *β*-alcohol, m.p. 135–138°[9], identical with the isomer B described previously.[3]

Reduction of I *hydrochloride*[10] *with aluminum isopropoxide.* A mixture of 4.0 g. of I hydrochloride and 25 ml. of *M* aluminum isopropoxide in isopropyl alcohol was distilled (one-foot Vigreux column) so that 5 ml. of liquid was collected during 2.5 hours. The remainder of the solvent was evaporated *in vacuo*, and the residue was partitioned between ether and 5% sodium hydroxide. The dried ether layer was concentrated to 20 ml. and seeded with the pure *β*-alcohol. After 0.5 hour at 25° and 2 hours at 5° the yield of almost pure *β*-alcohol was 1.0 g. The filtrate was concentrated somewhat and kept at 5° overnight to give 1.5 g. of a mixture of the *α*- and *β*-alcohols, m.p. 125–150°. Fractional crystallization of this mixture from ether gave 0.8 g. of the *α*-alcohol and then 0.2 g. of the *β*-isomer.

(+)-α-9-(2-N-trans-Decahydroquinolino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. 9-*ω*-Bromoacetyl-1,2,3,4-tetrahydrophenanthrene[3, 11] (2.7 g.) and 2.5 g. of *l-trans*-decahydroquinoline in 40 ml. of dry ether were kept at 25° for 20 hours (occasional shaking during the first two hours), cooled to 0°, and filtered. To the stirred filtrate was added 5 ml. of 1.5 *M* ethereal lithium aluminum hydride during 5–10 minutes. The mixture was decomposed gradually with 5 ml. of water, and the precipitate was washed twice with hot benzene. The combined filtrate and washings were dried and evaporated *in vacuo*. The residue was dissolved in *ca.* 75 ml. of boiling acetone and the solution was concentrated to 25–30 ml. when crystals began separating. After 1.5 hours at 25° and one hour at 5°, 1.5 g. of thick square plates, m.p. 167–170°, was obtained. An additional 0.1 g. (total yield based on bromo ketone 50%) was obtained as described below. The analytical sample melted at 169–171° and had $[\alpha]_D^{20}$ +107° (*c*, 0.22).

Anal. Calc'd for $C_{25}H_{33}NO$: C, 82.60; H, 9.15. Found: C, 82.36; H, 9.09.

The *hydrochloride* crystallized from alcohol-ether in needles of m.p. 226–228° (dec.), $[\alpha]_D^{20}$ +71.3° (*c*, 1.59).

Anal. Calc'd for $C_{25}H_{34}ClNO$: C, 75.05; H, 8.57. Found: C, 74.70; H, 8.64.

(−)-β-(2-N-trans-Decahydroquinolino-1-hydroxyethyl)-1,2,-3,4-tetrahydrophenanthrene. The filtrate from the 1.5 g. of the (+)-*α*-alcohol above was concentrated slightly and kept at 5° for 2 hours to give 0.4 g. of principally rods, m.p. 145–154°. A recrystallization from acetone gave 0.3 g. (10% based on bromo ketone) of almost pure *β*-isomer, m.p. 159–161°. Concentration of the filtrate from the 0.4 g. and cooling gave an additional 0.1 g. of the (+)-*α*-alcohol. The analytical sample (rods) of the (−)-*β*-alcohol melted at 162–163°; $[\alpha]_D^{20}$ −33.9° (*c*, 0.28).

Anal. Calc'd for $C_{25}H_{33}NO$: C, 82.60; H, 9.15. Found: C, 83.08; H, 9.08.

The *hydrochloride* crystallized from alcohol-ether in needles of m.p. 225–226.5° (dec.), $[\alpha]_D^{20}$ −48.4° (*c*, 0.31).

Anal. Calc'd for $C_{25}H_{34}ClNO$: C, 75.05; H, 8.57. Found: C, 75.04; H, 8.57.

(−)-α-9-(2-N-d-trans-Decahydroquinolino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene. This isomer,[12] prepared as described for its enantiomorph melted at 170–171°; thick square plates, $[\alpha]_D^{20}$ −108.6° (*c*, 0.28).

Anal. Calc'd for $C_{25}H_{33}NO$: C, 82.60; H, 9.15. Found: C, 82.46; H, 8.99.

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(5) Mascarelli and Nigrosoli, *Gazz. chim. ital.*, **45**, 106 (1915); *cf.* also Mascarelli, *Gazz. chim. ital.*, **45**, 127 (1915).

(6) These results indicate that *d*-bromocamphorsulfonic acid and L-threaric acid, used in the order given, would provide an excellent combination of reagents for effecting the complete resolution of *trans*-decahydroquinoline.

(7) Melting points are uncorrected. Rotations were taken in alcohol unless otherwise noted.

(8) An Eastman Kodak preparation; *cf.* Adkins and Cramer, *J. Am. Chem. Soc.*, **52**, 4349 (1930).

(9) Prolonged boiling of an acetone solution of this material converted it to another crystalline modification, m.p. 163–164°.

(10) Reduction of the base gave a 40% yield of a 1:1 ratio of the *α*- and *β*-alcohols.

(11) Bachmann and Struve, *J. Org. Chem.*, **4**, 472 (1939).

(12) The *d-trans*-decahydroquinoline[5] used in this experiment melted at 74–75° and had $[\alpha]_D^{20}$ +4.9° (*c*, 4.0).

The *hydrochloride* crystallized from alcohol-ether in needles of m.p. 226–228.5°, $[\alpha]_D^{20}$ −71.9° (*c*, 1.28).

Anal. Calc'd for $C_{25}H_{34}ClNO$: C, 75.05; H, 8.57. Found: C, 75.00; H, 8.41.

(+)-*β-9-(2-N-d-trans-Decahydroquinolino-1-hydroxyethyl)-1,2,3,4-tetrahydrophenanthrene.* This compound obtained, as described for the (−)-β-alcohol, melted at 162.5–163.5°, $[\alpha]_D^{20}$ +34.8 (*c*, 0.46).

Anal. Calc'd for $C_{25}H_{33}NO$: C, 82.60; H, 9.15; N, 3.85. Found: C, 82.47; H, 9.29; N, 3.80.

The *hydrochloride* melted at 223–226° (dec.), $[\alpha]_D^{20}$ +48.6° (*c*, 1.07).

Anal. Calc'd for $C_{25}H_{34}ClNO$: C, 75.05; H, 8.57; N, 3.50. Found: C, 75.08; H, 8.44; N, 3.63.

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