Synthesis of (−)-α-Acetylmethadol Metabolites and Related Compounds

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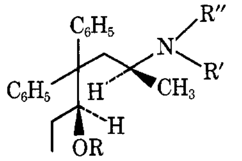
Improved syntheses of two (−)-α-acetylmethadol (**1a**) metabolites, (−)-α-*N*-normethadol (**1d**) and (−)-α-acetyl-*N*,*N*-dinormethadol (**1e**), and of (−)-α-*N*,*N*-dinormethadol (**1f**) are reported. In addition, syntheses of (−)-α-*N*-acetyl-*N*-normethadol (**1g**) and (−)-α-*N*-acetyl-*N*,*N*-dinormethadol (**1h**) are described. A comparison of our methods to previously reported synthetic procedures is presented.

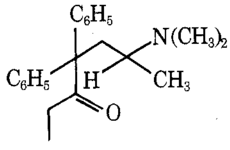
(−)-α-Acetylmethadol (**1a**) is an orally effective analgesic in man which is of current interest as an alternative to methadone (**2**) in the maintenance of opiate addicts.[1,2] Metabolism and pharmacology studies have indicated that **1a** exerts its activity, at least in part, through active metabolites.[3] (−)-α-Acetyl-*N*-normethadol (**1b**), (−)-α-methadol (**1c**), (−)-α-*N*-normethadol (**1d**), and (−)-α-acetyl-*N*,*N*-dinormethadol (**1e**) have been identified as biotransformation products of **1a**.[3–6] Each of these metabolites has been synthesized and shown to possess analgesic activity.[5–7]

In this paper we report the synthesis of **1b**, **1d**, and **1e** and compare our methods to the previously reported synthetic procedures. In addition, we report the synthesis of (−)-α-*N*,*N*-dinormethadol (**1f**), (−)-α-*N*-acetyl-*N*-normethadol (**1g**), and (−)-α-*N*-acetyl-*N*,*N*-dinormethadol (**1h**). The latter two compounds are rearrangement products of **1b** and **1e**, respectively, and are used in a GLC determination of these metabolites.

Booher and Pohland[6] reported that **1b** could be prepared by the demethylation of **1a** with diethyl azodicarboxylate[8] and that reduction of **1b** with lithium aluminum hydride afforded **1d**.[10] In our laboratory we found that **1a** was indeed smoothly converted to **1b** in good yield using diethyl azodicarboxylate. However, our attempts to prepare **1d** by reductive deacetylation of **1b** employing lithium aluminum hydride in refluxing ether[6] gave very little **1d**. The major product from our reactions was consistently (−)-6-(*N*-ethyl-*N*-methylamino)-4,4-diphenyl-3-heptanol (**1i**). Compound **1i** undoubtedly resulted from an *O*- to *N*-acyl migration to give **1g** prior to reduction. The facility of this migration was demonstrated by the isolation of **1i** from an experiment in which an ethereal solution of **1b** was added to the lithium aluminum hydride suspension at room temperature and the reaction quenched immediately after addition. Variation of the reaction temperature, the mode of addition, the solvent, the batch of reducing agent, and the source[11] of **1b** failed to repress the formation of **1i**. Addition of an acid catalyst such as calcium sulfate also had little effect on the reaction.

Chart I





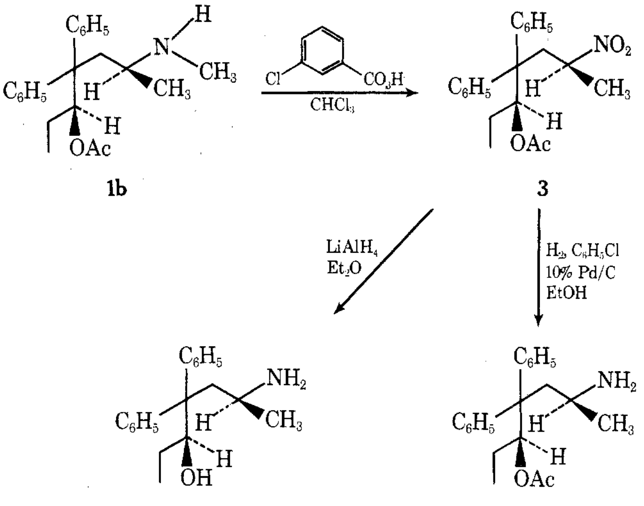
2

1a, R = CH_3CO; R′ = R″ = CH_3
b, R = CH_3CO; R′ = CH_3; R″ = H
c, R = H; R′ = R″ = CH_3
d, R = H; R′ = CH_3; R″ = H
e, R = CH_3CO; R′ = R″ = H
f, R = R′ = R″ = H
g, R = H; R′ = CH_3; R″ = CH_3CO
h, R = R′ = H; R″ = CH_3CO
i, R = H; R′ = CH_3; R″ = C_2H_5
j, R = CH_3CO; R′ = CH_3; R″ = $C_6H_5CH_2$
k, R = H; R′ = CH_3; R″ = $C_6H_5CH_2$

We found that **1b** could be converted to **1d** using refluxing ethanolic hydrochloric acid. However, the yield was low, and the workup was somewhat tedious. Moreover, unless the reaction conditions were carefully controlled, undesirable olefinic by-products were formed. In order to circumvent these difficulties, we devised another route to **1d**. Alkylation of **1b** with benzyl bromide gave (−)-6-(*N*-benzyl-*N*-methyl)-4,4-diphenyl-3-heptanol acetate (**1j**).[12] Hydrolysis of **1j** with lithium hydroxide gave the alcohol **1k** which yielded **1d** on catalytic debenzylation.[13] Although two extra steps were involved in this synthesis, the overall yield was 36%, and the reactions were reproducible and easily scaled up.

The synthesis of **1e** and **1f** is outlined in Chart II. Oxidation of **1b** with *m*-chloroperbenzoic acid (4–6 mol of oxidant per mole of **1b**) in chloroform gave exclusively (−)-6-nitro-4,4-diphenyl-3-heptanol acetate (**3**) in 88–96% yield. The reaction failed completely on (−)-α-acetylmethadol (**1a**) and proceeded only sluggishly on **1b** if smaller quantities of oxidant were used. The product was obtained as a yellow gum which upon standing crystallized to a yellow-white solid sufficiently pure for the subsequent reactions. Consequently, this procedure was considerably more advantageous than the previously reported synthesis of **3** by permanganate oxidation of **1b**.[5,6] Moreover, to our knowledge, it represented the first example of a *m*-chloroperbenzoic acid oxidation of an alkylamino group to a nitro group.

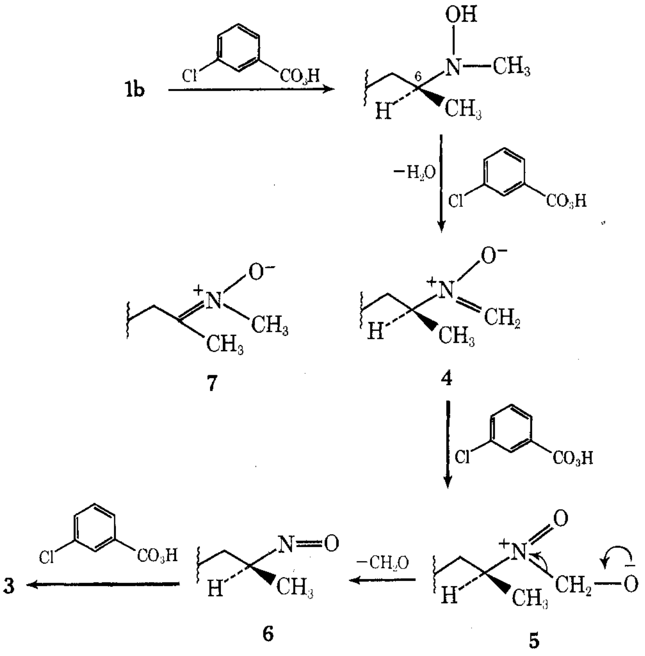
Chart II



1b 3 1f 1e

A key feature of the *m*-chloroperbenzoic acid oxidation is the maintenance of stereochemical integrity at C-6 (vide infra). A postulated mechanism consistent with this fact is shown in Chart III. Oxidation of aliphatic secondary amines with peracids generally leads to nitrones.[14] If the present ox-

Chart III



idation follows the same course, the intermediate nitrone must be **4** rather than **7** on the basis of the C-6 stereochemistry.[15] Furthermore, the subsequent oxidation of **4** would lead to intermediate **5**, which can decompose with loss of formaldehyde to the aliphatic nitroso compound **6**. This accomplishes the removal of the *N*-methyl group. Oxidation of **6** to **3** occurs rapidly enough to prevent formation of the tautomeric oxime. Further study is required to determine if this mechanism is correct and if the oxidation procedure is applicable to other aliphatic secondary amines.

Catalytic hydrogenation of **3** using 10% palladium on charcoal provided (−)-α-acetyl-*N,N*-dinormethadol (**1e**). We initially isolated **1e** as the maleate salt.[5,6] However, we observed that the salt was difficult to purify and that the yield was lowered by the occurrence of some *O*- to *N*-acyl migration during the reaction and subsequent purification. Consequently, we experimented with the use of different catalysts and the addition of 1 equiv of either hydrochloric or perchloric acid to the reaction mixture. We found the best procedure to be catalytic hydrogenation of **3** over 10% palladium on charcoal in the presence of 1 equiv of chlorobenzene. The product was obtained as the hydrochloride salt in yields approaching 50%. In our hands, this procedure was more reliable than the use of iron and hydrochloric acid[5] and more convenient than hydrogenation over Raney nickel at 1000 psi.[6]

Reductive deacetylation of **3** with lithium aluminum hydride afforded (−)-α-*N,N*-dinormethadol (**1f**) which was isolated as the bis fumarate salt. Methylation of **1e** and **1f** under modified Clarke–Eschweiler conditions[16] gave **1a** and **1c**, respectively, thus demonstrating the stereospecific nature of the synthetic routes.

If the reduction of **3** was carried out with hydrazine and Raney nickel, (−)-α-*N*-acetyl-*N,N*-dinormethadol (**1h**) was obtained in 50% yield. (−)-α-*N*-Acetyl-*N*-normethadol (**1g**) was prepared by converting **1b** to the *O,N*-diacetate followed by selective hydrolysis of the ester using lithium hydroxide in methanol.

Experimental Section

Infrared (ir) spectra were recorded on a Perkin-Elmer 467 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were obtained on a Varian HA-100 spectrometer. All chemical shifts are reported in δ values relative to a tetramethylsilane standard. Optical rotations were run on a Perkin-Elmer 141 polarimeter using a 1-dm sample cell. Analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

(−)-α-Acetyl-*N*-normethadol (1b). (−)-α-Acetylmethadol (**1a**) was demethylated with diethyl azodicarboxylate using the procedure of Booher and Pohland.[6,10]

(−)-α-Acetyl-*N*-benzylnormethadol (1j). A mixture of **1b** (3 g, 9 mmol), K_2CO_3 (2.2 g), and benzyl bromide (2 g) in MeOH (60 ml) was stirred at room temperature for 24 h, then diluted with H_2O (300 ml) and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated to get 3.45 g (100%) of **1j** as a viscous, pale yellow gum: ir (CH_2Cl_2) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.50 (d, 3 H), 0.72–0.84 (m, 3 H), 1.80–2.20 (m, 3 H), 1.98 (s, 3 H), 2.02 (s, 3 H), 2.40–2.90 (m, 2 H), 3.46 (broad s, 2 H), 6.13 (distorted d, 1 H), 7.20–7.38 ppm (m, 15 H). The product was generally used without further purification.

Treatment of a solution of **1j** in aqueous MeOH with 70% $HClO_4$ afforded a perchlorate salt, mp 225–226 °C after recrystallization from MeOH–Et$_2$O, $[\alpha]^{25}$D −13.1° (*c* 0.98, 100% EtOH).

Anal. Calcd for $C_{29}H_{36}ClNO_6$: C, 65.70; H, 6.85; N, 2.64. Found: C, 65.49; H, 6.92; N, 2.45.

(−)-α-*N*-Benzylnormethadol (1k). Compound **1j** (2.6 g, 6 mmol) was dissolved in MeOH–H_2O (5.2:1, 155 ml) and the resulting solution treated with LiOH·H_2O (0.88 g). Additional LiOH·H_2O (0.88-g portions) was added after 23, 72, and 94 h. After the reaction mixture had stirred for 144 h at room temperature, the solvent was evaporated and the residue partitioned between CH_2Cl_2 and H_2O. The aqueous phase was washed with additional CH_2Cl_2 (twice), and the combined organic extracts then dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on silica gel to remove a small amount of unreacted ester. The product was obtained from the chromatography as a pale yellow foam: ^{1}H NMR ($CDCl_3$) 0.77–0.90 (m, 6 H), 1.04–1.86 (m, 3 H), 1.97 (s, 1 H), 2.06 (s, 3 H), 2.42–2.96 (m, 2 H), 3.46 (q, 12 H, J = 12.5 Hz), 3.94 (dd, 1 H), 7.16–7.64 (m, 15 H). A solution of **1k** in aqueous MeOH was treated with 70% $HClO_4$ to get 1.29 g (46%, corrected) of the perchlorate salt, mp 186–187 °C, $[\alpha]^{25}$D +2.3° (*c* 0.75, 100% EtOH).

Anal. Calcd for $C_{27}H_{34}ClNO_5$: C, 66.43; H, 7.03; N, 2.87. Found: C, 66.47; H, 7.11; N, 2.80.

(−)-α-Normethadol (1d). A. From 1k. A mixture of **1k** perchlorate (900 mg, 1.85 mmol) and 10% Pd/C (250 mg) in 100% EtOH (100 ml) was hydrogenated on a Parr shaker at 40 °C and 40 psi for 6.5 h. The mixture was then filtered and the filtrate evaporated to dryness. The resulting white solid was recrystallized from MeOH–Et$_2$O to get 584 mg (79.5%) of **1d** perchlorate, mp 184.5–186 °C, $[\alpha]^{25}$D −13.4° (*c* 0.95, 100% EtOH). The overall yield of **1d** from **1b** by the three-step synthesis was 36% as compared to the 30% reported for the reductive deacylation.[6]

Anal. Calcd for $C_{20}H_{28}ClNO_5$: C, 60.35; H, 7.10; N, 3.52. Found: C, 60.27; H, 7.29; N, 3.54.

A sample of the perchlorate salt was converted to the free base and thence to the hydrochloride salt, mp 168.5–170 °C, $[\alpha]^{25}$D −38.8° (*c* 1, H_2O). The literature reports mp 167–168 °C and $[\alpha]^{25}$D −38.0 (*c* 1, H_2O).[6]

B. From 1b. A mixture of **1b** hydrochloride (2 g, 5.3 mmol), H_2O (35 ml), concentrated HCl (40 ml), and EtOH (80 ml) was refluxed for 7 h. The mixture was evaporated almost to dryness and the residue dissolved in H_2O (250 ml). The aqueous solution was extracted twice with Et$_2$O, made basic with concentrated NH_4OH, and reextracted with several portions of $CHCl_3$. Evaporation of the combined and dried (Na_2SO_4) organic extracts afforded 1.53 g of a viscous mass, ir ($CHCl_3$) 1730 cm^{-1} (very weak). The crude product was dissolved in aqueous MeOH and treated with 70% $HClO_4$. The mixture was allowed to stand for several days, after which time 0.68 g (32.1%) of **1d** perchlorate, mp 175–180 °C, was collected. Recrystallization from MeOH–H_2O raised the melting point to 184–186 °C.

(−)-6-Nitro-4,4-diphenyl-3-heptanol Acetate (3). In one batch *m*-chloroperbenzoic acid (1.27 g)[17] was added to a solution of **1b** (500 mg, 1.5 mmol) in $CHCl_3$ (15 ml). The resulting mixture was refluxed for 2 h, during which time the initial blue color gave way first to green and later to yellow. After reflux the mixture was chilled and the precipitated acid removed by filtration. The filtrate was washed with 10% Na_2SO_3 (2 × 40 ml), saturated $NaHCO_3$ (2 × 40 ml), and H_2O (3 × 60 ml). The organic phase was then dried (Na_2SO_4) and evaporated to get 470 mg (89%) of **3** as a yellow oil. After several hours of standing, the oil crystallized to a yellow-white solid which was chromatographically pure by TLC: ir ($CHCl_3$) 1740, 1552 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.74–0.94 (m, 3 H), 1.27 (d, 3 H, J = 6.5 Hz), 1.50–1.90 (m, 2 H), 2.02 (s, 3 H), 2.21 (dd, 1 H, J = 3.0, 14.8 Hz), 3.19 (dd, 1 H, J = 6.5, 14.8 Hz), 4.55 (dectet, 1 H, J = 3.0, 6.5, 6.5 Hz), 5.76 (distorted d, 1 H), 7.15 (broad s, 10 H). The product was generally used with no further purification. Recrystallization of a small sample from 100% EtOH afforded a white solid, mp 103–105 °C (lit.[6] 108–109 °C), $[\alpha]^{22}_{\mathrm{D}}$ −36.9° (*c* 1, 100% EtOH).

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.09, N, 3.94. Found: C, 70.96; H, 7.19; N, 3.92.

(−)-*α*-Acetyl-*N,N*-dinormethadol (1e). A. A mixture of **3** (2.0 g, 5.6 mmol) and 10% Pd/C (400 mg) in 95% EtOH (115 ml) was hydrogenated overnight at 40 °C and 40 psi. When TLC showed incomplete reaction, additional catalyst (200 mg) was added and hydrogenation contained for 24 h. Afterwards the mixture was filtered through Super-cel and the filtrate evaporated to get an oil. This was dissolved in EtOAc and treated with an equivalent weight of maleic acid in EtOAc. The resulting solution was evaporated, and the resulting off-white foam was recrystallized twice from *i*-PrOH–Et_2O to get 0.7 g (30.2%) of **1e** maleate, mp 149–150.5 °C, $[\alpha]^{25}_{\mathrm{D}}$ −40.0° (*c* 0.16, 100% EtOH). The literature reports mp 148–149 °C and $[\alpha]^{25}_{\mathrm{D}}$ −53.3° (*c* 1, H_2O).[6]

B. A mixture of **3** (20.0 g, 56 mmol), chlorobenzene (5.6 ml), and 10% Pd/C (8 g) in 100% EtOH (1.2 l.) was hydrogenated at 40 °C and 40 psi for 127 h. Additional 10% Pd/C (1–2 g) was added after 17, 31, and 103 h.[18] Afterwards the reaction mixture was filtered as before and the filtrate evaporated to get a greenish-white powder. The powder was dissolved in H_2O (1.5 l.) containing 10% HCl (5 ml) and the solution extracted twice with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and evaporated to get 3.87 g of brown residue. Chromatography of this material on silica gel afforded 2.5 g of **3** (12.5% recovery).

The aqueous phase was filtered through charcoal and concentrated in vacuo until the flask was coated with a sticky white gum. This was dissolved in CH_2Cl_2, and the remaining aqueous phase was extracted with two additional portions of CH_2Cl_2. Evaporation of the combined and dried (Na_2SO_4) organic extracts then afforded 9.8 g of an off-white foam. This was redissolved in a minimum volume of CH_2Cl_2 and the solution diluted with a copious quantity of Et_2O containing a small amount (ca. 3 ml) of H_2O.[19] After several hours, 8.2 g (44%, corrected) of **1e** hydrochloride crystallized as a white powder, mp 120–122 °C, $[\alpha]^{25}_{\mathrm{D}}$ −45.1° (*c* 1, 95% EtOH). The overall yield of **1e** from **1b** was 39% as compared to previously reported 17.5%.[6]

Anal. Calcd for $C_{21}H_{28}ClNO_2 \cdot H_2O$: C, 66.37; H, 7.96; Cl, 9.34; N, 3.69. Found: C, 66.22; H, 7.91; Cl, 9.31; N, 3.61.

In a small-scale experiment **1e** hydrochloride crystallized from the concentrated aqueous phase as a white powder, mp 128–130 °C. Vacuum drying at 50° reduced the melting point to 119–121 °C. The difference in the melting points was evidently due to the degree of hydration.

(−)-*α*-*N,N*-Dinormethadol (1f). To a well-stirred slurry of $LiAlH_4$ (200 mg, 53 mmol) in dry Et_2O (80 ml) was added, dropwise, a solution of **3** (500 mg, 14 mmol) in dry Et_2O (100 ml). The resulting mixture was stirred at room temperature for 1 h, then was cooled in ice and treated with H_2O (10 ml). A solution of 20% sodium potassium tartrate (200 ml) was added and the mixture stirred overnight. Afterwards, two phases were present. The Et_2O phase was separated, washed once with H_2O, dried (Na_2SO_4), and evaporated to get 3.8 g of light tan foam. This was dissolved in fresh Et_2O (500 ml), and the solution was added dropwise to a solution of fumaric acid (1.5 g) in Et_2O (1500 ml). The resultant gel was collected and briefly dried at 60 °C. Recrystallization from EtOAc–THF–MeOH afforded 2.14 g of white powder having a broad melting point. A second recrystallization from 100% EtOH–EtOAc then gave 1.04 g (22%) of **1f** bisfumarate, mp 211–212 °C, $[\alpha]^{25}_{\mathrm{D}}$ −68.2° (*c* 0.11, 100% EtOH). The ^1H NMR spectra (Me_2SO-d_6) of the salt consistently showed a 10:1 ratio between the amine aromatic protons and the acid olefinic protons. In spite of the low yield on the reduction step the overall yield of **1f** from **1b** was 19.5% as compared to the previously reported 5% for the maleate salt.[6]

Anal. Calcd for $C_{42}H_{54}N_2O_6 \cdot \frac{3}{4}H_2O$: C, 72.42; H, 8.03; N, 4.02. Found: C, 72.41; H, 7.86; N, 4.00. (Analyses on several samples gave the same result.)

(−)-*α*-*N*-Acetyl-*N,N*-dinormethadol (1h). Anhydrous H_2NNH_2 (10 ml) was added dropwise over 50 min to a solution of **3** (1.0 g, 2.8 mmol) in MeOH (100 ml) containing Raney nickel. Following addition, the mixture was stirred for 10 min and then filtered through Super-cel. The filtrate was concentrated by in vacuo removal of MeOH and the residue partitioned between Et_2O and 3 N HCl. Subsequent workup of the Et_2O phase yielded 778 mg of white foam. TLC analysis indicated one major component and several minor ones. Preparative chromatography on silica gel plates then afforded 480 mg (49%) of **1h** as an off-white foam: ir ($CHCl_3$) 1660 cm^{-1}; ^1H Nmr)cdcl$_3$) 0.94–1.06 (m, 6 H), 1.46 (s, 3 H), 1.46–2.16 (m, 4 H), 2.89 (dd, 1 H), 3.92–4.66 (m, 3 H), 7.14 (broad s, 10 H); mass spectrum *m/e* 326 (M + 1), 296, 267, (100). A sample recrystallized from C_6H_6 gave a light tan solid, mp 134.5–136.5 °C, $[\alpha]^{29}_{\mathrm{D}}$ −32.3° (*c* 1, CH_2Cl_2).

Anal. Calcd for $C_{21}H_{28}NO_4$, 326.2120; $C_{18}H_{21}NO$, 267.1623. Found: 326.2121, 267.1626.

(−)-*α*-*N*-Acetyl-*N*-normethadol (1g). Acetyl chloride (20 ml) was added dropwise to a solution of **1b** (10.6 g, 31 mmol) in C_6H_6 (150 ml) containing pyridine (1 ml). After overnight stirring, the mixture was filtered and washed with H_2O (2 × 100 ml), 0.5 N HCl (2 × 120 ml), and water (2 × 150 ml). The C_6H_6 was then dried (Na_2SO_4) and evaporated to get 7.9 g (66%) of the *O,N*-diacetate as a viscous oil, ir ($CHCl_3$) 1628, 1732 cm^{-1}.

A mixture of the *O,N*-diacetate (6.9 g) and $LiOH \cdot H_2O$ (700 mg) in MeOH (300 ml) was stirred at room temperature for 96 h. Additional $LiOH \cdot H_2O$ (1.25 g) was added in 250-mg portions over 48 h. Afterwards the solvent was evaporated and the residue subjected to high-pressure liquid chromatography on silica gel using $CHCl_3$ as the eluting solvent. The chromatography afforded 1.45 g (24%) of **1g** as a white solid: mp 96–98 °C; ir ($CHCl_3$) 1625 cm^{-1}; $[\alpha]^{25}_{\mathrm{D}}$ −31.5° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.81; H, 8.55; N, 4.12. Found: C, 77.77; H, 8.70; N, 4.02.

Methylation of 1e. A solution of **1e** (700 mg, 2.2 mmol) in MeOH (90 ml) was treated with boric acid (700 mg), 37% formaldehyde (9 ml), and $NaBH_4$ (2.2 g) after the procedure reported by Wildman and Bailey.[16a] The resulting amine was dissolved in EtOH and treated with concentrated HCl. The solution was then evaporated to dryness and the resulting foam redissolved in hot EtOAc with traces of insoluble matter being removed by filtration. Upon cooling, **1a** hydrochloride precipitated as a white solid, mp 203–205 °C, $[\alpha]^{26}_{\mathrm{D}}$ −25.2° (*c* 1, 100% EtOH). A reference sample[20] had mp 213–215 °C and $[\alpha]^{26}_{\mathrm{D}}$ −23.7° (*c* 1, 100% EtOH).

Methylation of 1f. A sample of **1f** was methylated using the same procedure described for the methylation of **1e**. The experiment yielded **1c** hydrochloride as a white solid, mp 172–175 °C, $[\alpha]^{25}_{\mathrm{D}}$ −33° (*c* 1, H_2O). A reference sample[20] had mp 173–175 °C and $[\alpha]^{25}_{\mathrm{D}}$ −32.7° (*c* 1, H_2O).

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Registry No.—**1a,** 1477-40-3; **1b,** 43033-71-2; **1b** HCl, 55096-75-8; **1b** *O,N*-diacetate, 59803-30-4; **1d** perchlorate, 60045-87-6; **1e** HCl, 59872-11-6; **1f** bisfumarate, 59872-12-7; **1g,** 59803-24-6; **1h,** 51733-62-1; **1j,** 59803-26-8; **1j** perchlorate, 59803-27-9; **1k,** 59803-28-0; **1k** perchlorate, 59803-29-1; **3,** 55123-65-4; benzyl bromide, 100-39-0; *m*-chloroperbenzoic acid, 937-14-4; sodium potassium tartrate, 304-59-6.

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(7) N. Chatterjie and C. E. Inturrisi, *J. Med. Chem.,* **18,** 630 (1975).

(8) Compound **1a** has also been demethylated to **1b** using mercuric acetate[7] and by a two-step procedure involving treatment of **1a** with 2,2,2-trichloroethyl chloroformate followed by cleavage of the carbamate with zinc and formic acid.[6,9]

(9) J. A. Montzka, J. D. Matiskella, and R. A Partyka, *Tetrahedron Lett.,* 1325 (1974).

(10) We are grateful to Dr. A. Pohland for providing us his experimental procedures prior to publication.

(11) We obtained the same result irrespective of whether **1b** was purified and stored as the free base or the hydrochloride salt.

(12) A. Pohland, U.S. Patent 3 021 360 (1962); *Chem. Abstr.,* **57,** 4594*d* (1962).

(13) A. F. Casy and M. M. A. Hassan, *J. Med. Chem.,* **12,** 337 (1969). These investigators prepared racemic **1d** by reduction of *N*-benzyl-*N*-normethadone to racemic **1k** followed by catalytic debenzylation. No yields were reported.

(14) (a) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 330–331; (b) S. N. Lewis in "Oxidation", Vol. 1, R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1969, p 250.

(15) A somewhat analogous situation exists in the mercuric acetate oxidation of **1a** to **1b.**[7] In this case the key imine intermediate is formed by proton

abstraction from one of the *N*-methyl groups rather than C-6. The result is formation of **1b** with preservation of the C-6 stereochemistry.

(16) (a) W. C. Wildman and D. T. Bailey, *J. Org. Chem.*, **33**, 3749 (1968); (b) G. A. Brine, Ph.D. Dissertation, Duke University, 1974.

(17) The *m*-chloroperbenzoic acid used was a technical grade containing 85% of the oxidant (Aldrich Chemical Co.).

(18) Use of fresh catalyst substantially reduced the amount required and the reaction time.

(19) Since the hydrochloride salt crystallizes as a hydrate, omission of the H_2O substantially reduces the quantity obtained.

(20) The reference sample was supplied by Regis Chemical Co., Morton Grove, Ill.

Synthesis and Reactivity Patterns of *meso*- and *dl*-Bistriquinacene. Efficient Route to the Diastereomeric Bivalvanes

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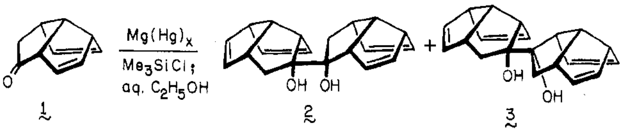
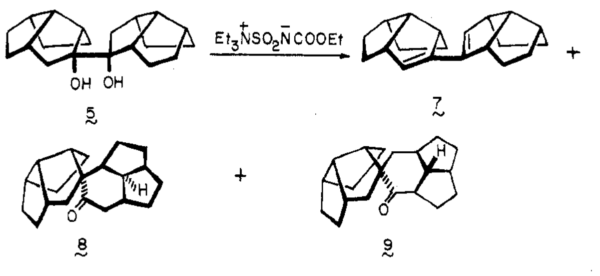
Pinacolic reduction of *dl*-2,3-dihydrotriquinacen-2-one and its tetrahydro derivative gives rise to an equal mixture of *dl* and meso diols. In order to effect the rapid, efficient, yet nondestructive separation of the two pairs of "dimers", the individual mixtures were dehydrated directly with (preferably) phosphorus oxychloride in pyridine and treated with 0.5 molar equiv of *N*-methyltriazolinedione at low temperature. Under these conditions, only the meso isomers enter into Diels–Alder reaction since the s-cis conformation of their conjugated diene moieties makes possible simultaneous exo bonding of the dienophile to both termini. In contrast, concerted $_\pi4_s$ bonding to a *dl* isomer requires concurrent exo,endo attack and is more sterically impeded. The *dl* isomers are consequently left in solution in a pure state. The homogeneous dihydro and tetrahydro adducts submit to hydrolysis–oxidation with formation of azo compounds which extrude nitrogen readily to return the meso hydrocarbons. By this procedure, nonimmolative chemical separation of the isomer pairs is conveniently effected. Their individual catalytic hydrogenation affords pure *dl*- and *meso*-bivalvane. The alkali metal–ammonia reduction of the dehydration products has been examined for its stereochemical outcome.

Because of the many exciting structural features inherent in the dodecahedrane molecule, among which may be cited the existence of a cavity of 2.0–2.5 Å diameter completely enclosed within the carbon network, we have developed an interest in the synthesis of this $(CH)_{20}$ polyhedron. In one approach based upon the concept of stepwise dimerization of two triquinacene halves,[1] the pinacolic reduction of *dl*-2,3-dihydrotriquinacen-2-one (1) was studied and shown to give the desired *dl* diol 2 admixed with an approximately equal amount of meso isomer 3.[2] When starting with enantiomerically pure (+)-1, 2 becomes the exclusive reductive coupling product because of enforced enantiomer recognition. Identical behavior was noted in the fully saturated series involving (±)- and (+)-hexahydrotriquinacen-2-one (4). However, the existing method for preparing optically pure 1 and 4 is laborious and nonconducive to scale-up. High-pressure liquid chromatographic separation of 2, 3, and their perhydro counterparts can be effected with somewhat greater efficiency, but we desired a rapid, high-yield, and nondestructive means of cleanly separating the *dl* and meso series. Were this goal to be achieved, rapid access to *dl*-bivalvane and its derivatives could be gained with limited expenditures of time and effort starting entirely with racemic 1 and 4.



We now describe the successful adaptation of this plan to the preparation of *dl*- and *meso*-bistriquinacene and their octahydro counterparts, together with the conversion of these polyolefins to the respective bivalvanes and to diastereomeric "dimers" which have previously eluded synthesis.

The Perhydrotriquinancene Series. To gain information on the susceptibility of the four diols to directed twofold dehydration, preliminary studies were carried out on pure samples of 5 and 6. We desired introduction of the pair of double bonds into the less substituted sites (cf. 7 and 10) and therefore made initial recourse to ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt because of its well-established propensity for directing cis elimination.[3] Reaction of 5 with this reagent in tetrahydrofuran at −5 °C for 2 h led to formation of 7 (68.5%) and a mixture of isomeric spiro ketones 8 and 9 (28%). With less polar solvents such as benzene and cyclohexane, dehydration proceeded less rapidly and required more elevated temperatures, but still gave a predominance of 7 (Table I). The definitive spectral data for 7 include a particularly revealing two-proton olefinic singlet at δ 5.27 and a ^{13}C NMR spectrum comprised of only ten signals. This last pattern is of course consistent only with strict maintenance of C_2 symmetry. Were dehydration to have occurred instead toward the bridgehead positions, the resulting fully substituted diene would also belong to this point group but would lack olefinic protons. No contamination from this product was seen. The electronic spectrum of 7 in isooctane consists of three absorption maxima at 237, 245, and 255 nm.



The infrared spectra of several crops obtained by fractional crystallization of the ketone fraction showed pronounced variations in the intense 1410-cm^{-1} absorption characteristic of methylene groups adjacent to carbonyl, thereby indicating the presence of both 8 and 9. Their ratio in the reaction mixture was determined by mass spectral analysis of their base-