Synthesis of a New Metabolite of Acetylmethadol

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The primary amine metabolites of α-(±)- and α-(−)-acetylmethadol were synthesized. A neutral permanganate oxidation of noracetylmethadol gave a nitroalkane. This unusual oxidation product was readily converted to the primary amine metabolite of acetylmethadol.

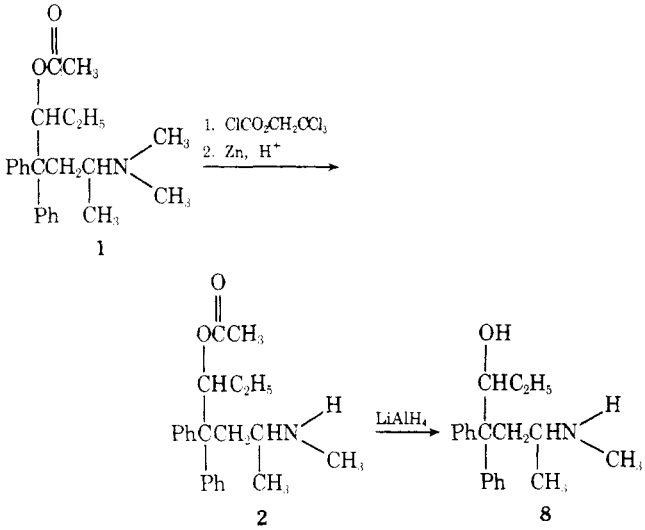
The metabolism of α-(±)-acetylmethadol (**1**), an orally effective analgesic, has been the subject of several studies in these laboratories.[1-3] Results reported in 1965 by McMahon, *et al.*,[1] indicated that an important metabolic route of **1** was N-demethylation to α-(±)-noracetylmethadol (**2**). Noracetylmethadol has been synthesized and found to be a potent analgesic.[4] A recent communication[2] on the metabolism of **1** in rodents identified a new metabolite which was the result of N-demethylation of **2** to α-(±)-6-amino-4,4-diphenyl-3-heptanol acetate (**3**). The metabolite **3** has also been found in man.[3]

In this paper we wish to report the detailed synthesis of metabolites **2** and **3** given in earlier communications.[2,4] A synthesis of **3** by degrading readily available **1** or **2** to an entity such as **6** seemed appropriate. The conversion of ketone **6** to a primary amine analog followed by separation of diastereoisomers[5] would give **3**. Chemical conversion of **3** to α-(±)-methadol would relate its stereochemistry to **1** and **2**.

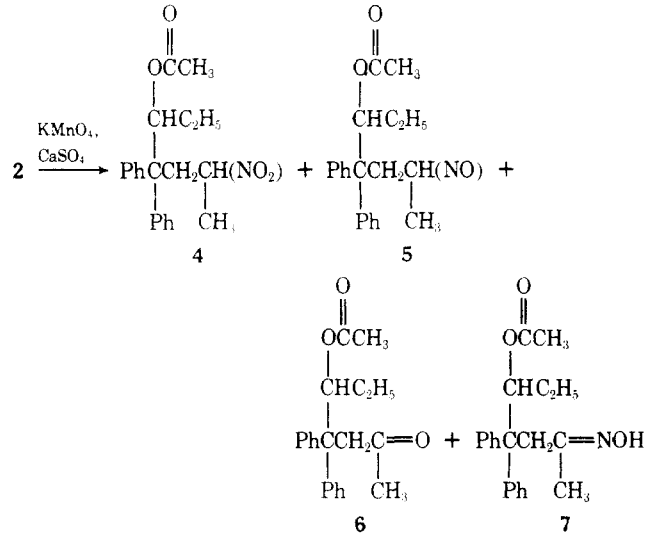
Synthesis. α-(±)-Acetylmethadol (**1**) was allowed to react with 2,2,2-trichloroethyl chloroformate[6] to give α-(±)-*N*-2,2,2-trichlorocarbethoxynoracetylmethadol in 87% yield. The reduction of the carbamate with zinc in 90% formic acid provided α-(±)-noracetylmethadol (**2**) in 34% yield. The demethylation of **1** with diethyl azodicarboxylate will also give **2**.[4] Reduction of **2** with lithium aluminum hydride afforded α-(±)-normethadol (**8**) (Scheme I).[4]

Oxidation of **2** with neutral permanganate[7] in aqueous *tert*-butyl alcohol gave very little of the expected α-(±)-4,4-diphenyl-6-keto-3-heptanol acetate (**6**). The major product of oxidation of **2** was identified as α-(±)-4,4-diphenyl-6-nitro-3-heptanol acetate (**4**). Other products isolated were the nitroso compound **5** and the oxime **7**. A qualitative test[8] for an aliphatic nitro group on **4** was positive. Compound **4** gave an ir absorption band at 1550 cm^{-1}, which was characteristic for an aliphatic nitro group. An nmr absorption spectrum and elemental analysis were consistent for the assigned structure of **4** (Scheme II).

Scheme I



Scheme II



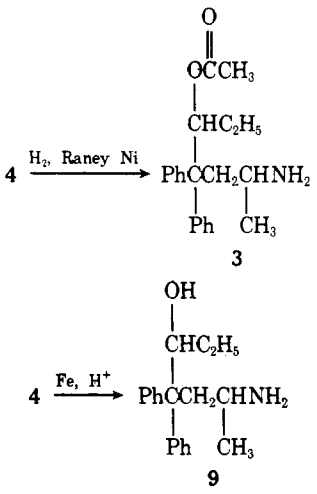
The only related permanganate oxidation of an amino group to a nitro group reported in the literature was Kornblum's[9] conversion of tertiary carbinamines to tertiary nitroparaffins. Of course, no further oxidation could occur to give an aldehyde or ketone, which are usual products of oxidation of primary or secondary carbinamines.[7] Oxidation of **1** with neutral permanganate gave only α-(±)-*N*-formylnoracetylmethadol.

The reduction of **4** with iron in glacial acetic acid or hydrogenation of **4** in the presence of Raney nickel in glacial acetic acid at 1000 psi provided α-(±)-6-amino-4,4-diphenyl-3-heptanol acetate (**3**). A comparison of the synthetic **3** with metabolically formed **3** showed that the gc retention times and the mass fragmentation patterns were identical.[2] Exhaustive reduction of **4** with iron in 5 *N* hydrochloric acid gave α-(±)-6-amino-4,4-diphenyl-3-heptanol (**9**). The stereochemistry of **3** and **9** was related to **1** by reacting crude product **9** with 38% formalin in 90% formic acid to provide only α-(±)-methadol (**10**).[5] An identification of α-(±)-methadol over β-(±)-methadol can clearly be established by nmr spectra analysis. The branched methyl group of α-(±)-methadol hydrochloride appears as a doublet at δ 0.75, whereas the methyl doublet for β-(±)-methadol hydrochloride appears at δ 0.5. Therefore, no racemization occurred during oxidation of **2** to **4** (Scheme III).

The above sequence of reactions was performed, beginning with α-(−)-acetylmethadol to provide the α-(−) isomers of **2, 3, 4, 8,** and **9.**

Biological Results. The analgesic activity of the α-(−) isomer of **3** in the mouse writhing test was reported recently.[10] Following subcutaneous administration significant inhibition of writhing was apparent within 15 min, peaked at 1 hr, and persisted for 3–5 hr. The ED_{50} was found to be 2.0 mg/kg sc, which approached that of other potent analgesics such as morphine and methadone. The α-(−) isomer of **3** also has potent opiate activity in the guinea pig isolated

Scheme III



ileum.[11] The high potency of this compound and the reported[4] analgesic activity of **2** indicate that these metabolites may contribute significantly to the pharmacologic effects seen after administration of **1**.

Experimental Section

All new compounds were identified by nmr, ir, and mass spectroscopy. Where analyses are indicated by symbols of the elements, the microanalytical results were within ±0.4% of the theoretical values. Melting points are uncorrected.

α-(±)-Noracetylmethadol (2). Method A. To a solution of α-(±)-acetylmethadol (**1**, 105.2 g, 0.3 mol) in 300 ml of C_6H_6 at reflux was added dropwise 2,2,2-trichloroethyl chloroformate (70 g, 0.33 mol) in 100 ml of C_6H_6 over a period of 2 hr. The reaction mixture was refluxed an additional 1 hr and then cooled with an ice bath. To the cooled reaction mixture was added 5 ml of 98% HCOOH, followed by addition of 11 ml of Et_3N. The reaction mixture was stirred at room temperature for 30 min, poured into H_2O, and extracted with two portions (500 ml) of Et_2O. The Et_2O solution was washed with 5 *N* HCl and H_2O and dried ($MgSO_4$) and the solvent evaporated *in vacuo* to yield 135 g (87%) of α-(±)-*N*-2,2,2-trichlorocarbethoxynoracetylmethadol as an oil. The crude carbamate was dissolved in 330 ml of DMF and HCOOH (23.2 g, 0.505 mol) was added. The reaction mixture was cooled to 15° and Zn dust (42.5 g, 0.652 mol) was added in portions over a 30-min period. The rate of addition of Zn was such that the reaction temperature was maintained at 15–20°. After the addition of Zn, the reaction mixture was stirred for 1 hr at 0° and then overnight at room temperature. The reaction mixture was filtered through a sintered glass funnel and the filtrate was poured into an ice–water mixture. Excess 12 *N* HCl was added to the aqueous solution followed by extraction with Et_2O. The acidic solution was made alkaline with excess NH_4OH in the cold and then extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and evaporated *in vacuo* to yield 66 g of an oil. The oil was redissolved in Et_2O and saturated with anhydrous HCl to give a precipitate which was recrystallized from MeOH–EtOAc to provide 33 g (34%) of **2** hydrochloride: mp 233–235°. *Anal.* ($C_{22}H_{30}ClNO_2$) C, H, N.

In a similar manner (−)-**1** (102 g, 0.29 mol) was N-demethylated to provide 48 g (44%) of (−)-**2** hydrochloride: mp 234–235°; $[\alpha]^{25}D$ −70.1° (*c* 1, H_2O). *Anal.* ($C_{22}H_{30}ClNO_2$) C, H, N.

Method B. To a solution of **1** (388 g, 1.10 mol) in 2 l. of C_6H_6 was added at once diethyl azodicarboxylate (200 g, 1.14 mol). The reaction mixture was warmed at 50° overnight. The reaction mixture was concentrated to dryness *in vacuo*. To the residual oil was added 1 l. of EtOH and 500 ml of saturated aqueous NH_4Cl solution. The reaction mixture was refluxed for 2 hr and then concentrated to 0.25 vol *in vacuo*. To the concentrate was added 1 l. of H_2O and the aqueous solution was extracted with Et_2O. To the aqueous solution was added excess concentrated NH_4OH. The basic solution was extracted with Et_2O. The Et_2O solution was washed with H_2O and dried ($MgSO_4$). The Et_2O solution was saturated with anhydrous HCl to give a precipitate which was recrystallized from MeOH–EtOAc to provide 282 g (68%) of **2** hydrochloride: mp 233–235°. *Anal.* ($C_{22}H_{30}ClNO_2$) C, H, N.

α-(±)-Normethadol (8). A solution of **2** (9.83 g, 0.032 mol) in 100 ml of Et_2O was added to a suspension of $LiAlH_4$ (2.5 g, 0.065 mol) in 100 ml of Et_2O at such a rate as to maintain gentle reflux. After complete addition, the reaction mixture was heated to reflux for an additional 3 hr. The reaction mixture was hydrolyzed by careful addition of a saturated aqueous NH_4Cl solution. The Et_2O solution was decanted from the inorganic solid and the latter was washed with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and then saturated with anhydrous HCl to give a precipitate. The precipitate was recrystallized from MeOH–EtOAc to yield 3.6 g (37%) of **8** hydrochloride: mp 172–173°. *Anal.* ($C_{20}H_{28}ClNO$) C, H, N.

In a similar manner (−)-**2** (5 g, 0.013 mol) was reduced to provide 1.3 g (30%) of (−)-**8** hydrochloride: mp 167–168°; $[\alpha]^{25}D$ −38.0° (*c* 1, H_2O). *Anal.* ($C_{20}H_{28}ClNO$) C, H, N.

Oxidation of α-(±)-Noracetylmethadol (2). A solution of **2** (32 g, 0.094 mol) in 200 ml of *t*-BuOH was added in one portion to a mixture of $KMnO_4$ (89.2 g, 0.564 mol) and $CaSO_4 \cdot 2H_2O$ (48.5 g, 0.282 mol) in 2 l. of 50% aqueous *t*-BuOH. The reaction mixture was stirred an additional 4 hr, followed with external cooling and cautious acidification with 12 *N* HCl. Portions of powdered $NaHSO_3$ were added to the reaction mixture to reduce MnO_2. The reaction mixture was extracted twice with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to yield 21 g of an oil. Chromatography of this reaction product on silica gel by eluting with C_6H_6 containing increasing amounts of EtOAc provided four components. Elution with C_6H_6–EtOAc (97:3) and recrystallization with Skelly F gave 8.3 g (24.4%) of α-(±)-4,4-diphenyl-6-nitro-3-heptanol acetate (**4**): mp 128–129°. *Anal.* ($C_{21}H_{25}NO_4$) C, H, N, O.

Elution with C_6H_6–EtOAc (95:5) and recrystallization with Skelly F gave 2 g (6.3%) of α-(±)-4,4-diphenyl-6-nitroso-3-heptanol acetate (**5**): mp 179–180°. *Anal.* ($C_{21}H_{25}NO_3$) C, H, N, O.

Further elution with C_6H_6–EtOAc (95:5) and recrystallization with Skelly F gave 1.2 g (3.9%) of α-(±)-4,4-diphenyl-6-keto-3-heptanol acetate (**6**): mp 74–75°. *Anal.* ($C_{21}H_{24}O_3$) C, H, O.

Final elution with C_6H_6–EtOAc (9:1) and recrystallization with Skelly F gave 0.8 g (2.5%) of α-(±)-4,4-diphenyl-6-oximino-3-heptanol acetate (**7**): mp 143–144°. *Anal.* ($C_{21}H_{25}NO_3$) C, H, N.

In a similar manner (−)-**2** (48 g, 0.128 mol) was oxidized with neutral $KMnO_4$ to provide 11 g (24.3%) of (−)-**4**: mp 108–109°; $[\alpha]^{25}D$ −39.4° (*c* 1, EtOH). *Anal.* ($C_{21}H_{25}NO_4$) C, H, N, O.

α-(±)-6-Amino-4,4-diphenyl-3-heptanol Acetate (3). A mixture of W4 Raney nickel (1.0 g) and **4** (2.85 g, 0.008 mol) in 100 ml of glacial AcOH was shaken at room temperature under 1000 psi of H_2 for 16 hr. The catalyst was removed from the reaction mixture and the solvent was evaporated *in vacuo*. To the oily residue was added excess cold NH_4OH; then the basic solution was extracted twice with Et_2O. The Et_2O solution was washed with H_2O and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* from the Et_2O solution provided 2 g of an oil. The oil was dissolved in 50 ml of EtOAc and mixed with a hot solution of maleic acid (0.93 g, 0.008 mol) in 50 ml of EtOAc to give 1 g (28%) of **3** maleate: mp 171–172°. *Anal.* ($C_{25}H_{31}NO_6$) C, H, N, O.

The melting point of **3** maleate was reported earlier[2] to be 165–166°. The above higher melting point for **3** maleate reflects a more pure sample. In a similar manner (−)-**4** (10 g, 0.028 mol) was hydrogenated to provide 9 g (72%) of (−)-**3** maleate: mp 148–149°; $[\alpha]^{25}D$ −53.3° (*c* 1, H_2O). *Anal.* ($C_{25}H_{31}NO_6$) C, H, N, O.

α-(±)-6-Amino-4,4-diphenyl-3-heptanol (9). A mixture of **4** (3 g, 0.0085 mol) and 5 g of Fe powder in 100 ml of 2B EtOH and 100 ml of 5 *N* HCl was stirred at reflux for 16 hr. The reaction mixture was cooled to room temperature then concentrated to 0.25 vol *in vacuo*. To the acidic solution was added excess 5 *N* NaOH. The basic solution was extracted with Et_2O. The Et_2O soluton was washed with H_2O, and then extracted with 5 *N* HCl. The acidic extract was made alkaline with excess NH_4OH. The basic solution was extracted twice with Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to yield 1.5 g (62%) of **9**. A portion of crude product **9** (0.2 g) in EtOAc was mixed with an equivalent amount of maleic acid in EtOAc to yield **9** maleate: 0.2 g; mp 156–158°. *Anal.* ($C_{23}H_{29}NO_5$) C, H, N, O.

In a similar manner (−)-**4** (2.85 g, 0.008 mol) was reduced to provide 0.6 g (20%) of (−)-**9** maleate: mp 172–173°; $[\alpha]^{25}D$ −31.1° (*c* 1, H_2O). *Anal.* ($C_{23}H_{29}NO_5$) C, H, N, O.

Conversion of (±)-9 to α-(±)-Methadol (10). The balance of crude reaction product (±)-**9** (1.3 g, 0.0046 mol) was dissolved in 10 ml of cold 90% HCOOH; then 10 ml of 38% aqueous HCHO was added. The solution was warmed at 100° for 16 hr. The reaction mixture was poured into ice–water, and the aqueous solution was made alkaline with excess 2 *N* NaOH. The basic mixture was extracted twice with Et_2O. The Et_2O solution was washed with H_2O

and dried ($MgSO_4$). The Et_2O solution was saturated with anhydrous HCl and evaporated to dryness *in vacuo* to yield 1.2 g (76%) of crude α-(±)-methadol hydrochloride (**10**). The nmr spectrum of crude **10** was identical with an nmr spectrum of an authentic sample of **10**.[5] The crude product **10** was recrystallized with MeOH–EtOAc to yield 1 g (64%) of **10**: mp 199–200° (lit.[12] mp 200–203°).

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Synthesis of 15-Keto-6β,7β-methyleneprogesterone. Effect of the 6β,7β-Methylene Group on Mineralocorticoid Activity†

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15-Ketoprogesterone is as active as spironolactone in blocking the mineralocorticoid effect of deoxycorticosterone acetate. This activity is reduced when a methylene group is attached to the 6β,7β position. The title compound was prepared from 15α-acetoxy-6-dehydroprogesterone. Methylenation of the Δ^6 double bond with dimethyloxosulfonium methylide proceeds stereoselectively from the β side of the molecule.

Information gained from metabolic and pharmacokinetic studies[1] and knowledge of the characteristics of various substituents[2] have proved useful in the design of new drugs. By altering the biotransformation of a substance through structural changes, compounds with differing profiles of activity can be obtained.

In seeking to develop more potent blockers of aldosterone, we have applied the knowledge acquired from the studies on the spirolactones to the development of antagonists which are structurally more closely related to progesterone. The latter substance had been shown by Landau, *et al.*, to block the activity of aldosterone when administered at a high dose.[3] Subsequently, Tweit and Kagawa showed that the antialdosterone effect of progesterone can be notably enhanced by introduction of an oxygen function at C-15, either in the form of a keto or a β-hydroxy group, and by insertion of a Δ^1 or Δ^6 double bond (**1a,b**).[4]

This report is concerned with the attachment of a methylene group to the 6,7 position of 15-oxygenated progesterone derivatives and the effect which this group has on antimineralocorticoid activity. Earlier we had found that the spirolactone with a β-methylene group at the 6,7 position (**2**) has an activity somewhat greater than that of spironolactone (**3a**).[5] Recently, it was reported that an inactive metabolite of spironolactone contains a hydroxyl group at the 6β position (**3b**).[6] Attachment of a β substituent to C-6 would, of course, prevent hydroxylation from occurring at this site. Hence, the 6β,7β-methylene group could be expected to produce a desirable effect by this means. Alternatively, this effect could be produced by π-complex formation with the receptor site as a consequence of the unique electronic characteristic of the cyclopropane ring. Such a process had previously been proposed by Wolff, *et al.*, to account for the androgenic effects of certain 2,3-methyleneandrostanes.[7] It was our hope that the present study would provide some insight as to whether either of these processes is involved in blocking the effect of the mineralocorticoids.

Methylenation at the 6,7 position of a steroid is generally achieved by the addition of dimethyloxosulfonium methylide to a 3-keto-$\Delta^{4,6}$-dienone system. Previous investigators had shown that the methylenation of 6-dehydrotestosterone acetate by this procedure furnishes a pair of stereoisomers, **4** and **5**, of which the one possessing the methylene group in the β configuration (**4**) predominates, the ratio of the β/α isomers being about 1.5:1.[8,9]

The starting material for our study was 15α-acetoxy-6-dehydroprogesterone (**6**). Addition of dimethyloxosulfonium methylide results not only in methylenation of the 6,7 double bond but also in oxirane formation at C-20. Oxirane formation can readily be discerned from the upfield shift of the C-21 methyl group and the accompanying downfield shift of the C-18 methyl group in the nmr spectrum. To prevent formation of the oxirane, the 20-carbonyl group of **6** was reduced with lithium tri-*tert*-butoxyaluminum hydride. Although the reduction was conducted at 0°, some reduction of the 3-keto group occurred. The allylic hydroxyl group at C-3 was selectively converted back to the keto group by means of dichlorodicyanobenzoquinone (DDQ).

Treatment of the product (**7**) with dimethyloxosulfon-

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