being stirred until all the material dissolved, HCl was added to the mixture to a pH of 1.5. Ethanol was evaporated leaving an oily product in aqueous solution. A small amount of cold water was added and a solid precipitated on scratching. The solid was collected and yielded after drying 17.9 g (92%) of **3a**: mp 105–6 °C (lit.[8] mp 106 °C); IR (KBr) 3485 cm^{-1}, 1590; NMR ($CDCl_3$) δ 1.9 (s, 3 H), 3.5 (s, 2 H), 7.2 (m, 5 H), 11.2 (s, 1 H, disappeared with D_2O).

4-Bromo-3-methyl-4-benzyl-2-isoxazolin-5-one (4a). To 9.45 g (0.05 mol) of **3a** in 100 mL of chloroform was added 8.0 g (6.05 mol) of bromine in 50 mL of chloroform. The resulting mixture was warmed for 0.5 h at 50 °C and evolution of HBr was observed. The chloroform was evaporated leaving an oil which, on cooling in an ice bath and addition of small portions of ligroin, solidified. The product obtained in 85% yield had a mp of 60–65 °C and on recrystallization from benzene–petroleum ether melted at 76–78 °C: IR (KBr) 1800 cm^{-1}, 1585 (w); NMR ($CDCl_3$) δ 2.2 (s, 3 H), 3.32 (1 H, d, J = 14.0 Hz), 3.71 (1 H, d, J = 14.0 Hz), 7.20 (m, 5 H).

Anal. Calcd for $C_{10}H_{10}NO_2Br$: C, 49.25; H, 3.73; N, 5.22; Br, 29.85. Found: C, 49.32; H, 3.75; N, 5.16; Br, 30.05.

Formation of 2-Benzal-3-hydroxyiminobutanoic Acid (5). To a solution of sodium hydroxide (4.60 g, 0.115 mol) in 150 mL of H_2O was added with cooling and stirring 6.70 g (0.025 mole) of **4a**. After 0.5 h, the ice bath was removed and stirring was continued for 6 h. Acidification was carried out at −3 °C with 3 N HCl and the resulting product (4.92 g, 96% yield) was filtered and dried and had mp 174–76 °C dec: IR (KBr) 1576 cm^{-1}, 1620, 1715, 3300; NMR (Me_2SO) δ 2.5 (s, 3 H), 6.8 (s, 1 H), 7.4 (m, 5 H), 11.5 (s, 2 H, disappeared with D_2O); UV (95% C_2H_5OH) 278 nm (4.44 log ϵ).

Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.52, H, 5.48; N, 6.75.

Ethyl α-Phenylbenzoylacetate (2b). This compound was prepared in 65% yield utilizing the method of Howk and McElvain[9] and using cyanodesoxybenzoin[10] as the starting material.

3,4-Diphenyl-2-isoxazolin-5-one (3b). Ethyl α-phenylbenzoylacetate (30 g, 0.11 mol) was placed in 300 mL of absolute alcohol in a 1-L flask and 36 g (0.51 mol) of hydroxylamine hydrochloride was added; the mixture was refluxed for 2 h. After standing overnight, most of the product precipitated. The remaining product was precipitated by diluting the solution with water. After drying, the product was boiled with anhydrous ether, filtered, and obtained in 78% yield, mp 150–52 °C (lit.[10] 146–49 °C).

4-Bromo-3,4-diphenyl-2-isoxazolin-5-one (4b). Finely powdered **3b** (15 g, 0.040 mol) was suspended in 600 mL of anhydrous CCl_4 and the mixture was treated with 10 g (0.045 mol) of anhydrous bromine. The mixture was shaken periodically and the isoxazolone dissolved with the evolution of white fumes. After all the isoxazolone had been dissolved, the CCl_4 was removed by rotary evaporator and the product **4b** was recrystallized from CH_3OH in 75% yield, mp 68–70 °C (lit.[10] mp 72 °C).

Attempted Synthesis of 2,3-Diphenyl-3-nitrosopropenoic Acid Formation of Benzil 11. To 150 mL of aqueous NaOH (94.60 g, 0.11 mol) cooled in an ice bath was added 7.3 g (0.024 mol) of **4b** at 0 °C. After 0.5 h the ice bath was removed and stirring was continued for 6 h. The resulting yellow solution was acidified with 6 N HCl and the solid product formed was recrystallized from benzene and then from acetone and was obtained in 72% yield, mp 95–6 °C: Anal. (C, 80.0, H, 4.90, no nitrogen); IR (1681 cm^{-1}, 1540, 1445); NMR ($CDCl_3$) δ 7.4 (m, 10 H); mass spectrum (m/e at 210, 105, 77 (1.00)); UV (C_2H_5OH) 259 nm (4.31 log ϵ) gave support to the product as being benzil.

Acknowledgments. We would like to express our gratitude to the National Science Foundation and the Central Awards Committee, State University of New York, Faculty Grants for the Improvement of Undergraduate Instruction for partial support of this work. We would also like to thank the organic chemistry class who participated in project-oriented laboratories and accomplished some of the preliminary work.

Registry No.—**2a**, 620-79-1; **2b**, 58929-02-5; **3a**, 68708-06-5; **3b**, 68708-07-6; **4a**, 68708-08-7; **4b**, 68708-09-8; **5**, 68708-10-1; **11**, R_1 = R_2 = Ph, 134-81-6.

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Potassium Permanganate Oxidation of Methadone and Its Convenient Transformation to Metabolites

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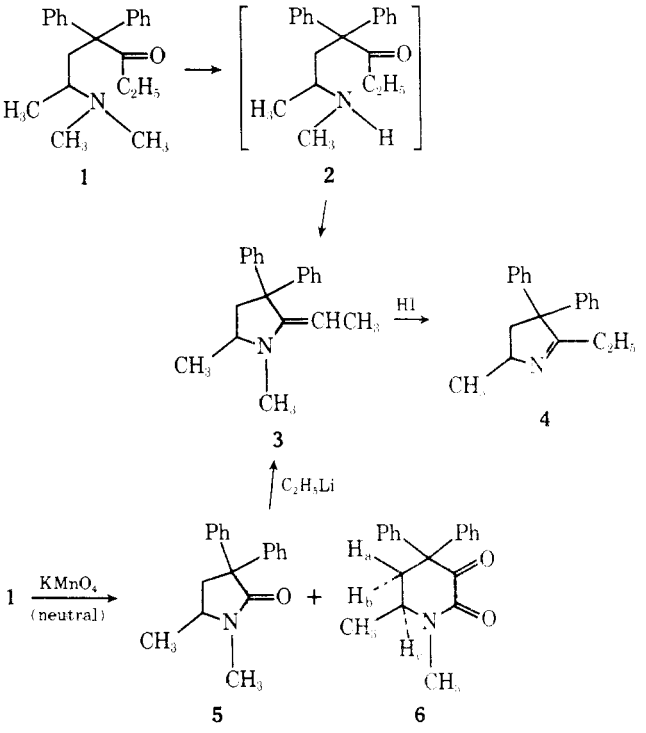
Received September 19, 1978

The major metabolite of the important drug methadone 1 in humans and in rats has been identified as 1,5-dimethyl-3,3-diphenyl-2-ethylidenepyrrolidine (3) together with its



N-demethylated analogue 4 and their aryl hydroxylation products as minor metabolites.[1-5] Formation of these metabolites, in vivo, is considered to proceed via hitherto unknown *N*-demethylmethadone 2.[1,2] Attempts to prepare the major metabolite 3 by treatment of 1 with either cyanogen bromide[6] or chloroformate esters[7] were not fruitful, and were reported in both cases to give 3,3-diphenyl-2-ethylidene-5-methyltetrahydrofuran. While inert to oxidation with mercuric acetate, methadone was cleaved to benzophenone with alkaline potassium permanganate.[8,9] To our knowledge in vitro chemical transformation of methadone to its metabolites has not been accomplished so far. The metabolites, however, have been prepared in overall poor yields involving long synthetic sequences.[2,4] We have reinvestigated[10] the demethylation problem and found that treatment of 1 with potassium permanganate[11] under neutral conditions cleanly affords 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (5),[12] a precursor

0022-3263/79/1944-0874$01.00/0

to methadone metabolites, together with a new compound **6**.

Oxidation of methadone with neutral potassium permanganate proved to be very rapid under mild conditions. Thus, when **1** was stirred with the excess oxidant at 25 °C, the reaction was complete in minutes and afforded in a high yield a mixture of two neutral, crystalline compounds, **5** and **6**, in a 4:1 ratio.[13] The ratio of these products was independent of the temperature and concentration of the reactants. The major compound was characterized as 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (**5**) by comparison with an authentic sample.[14] According to Pohland's observations, it underwent nearly quantitative reaction with ethyllithium to yield the metabolite **3**.[4] The transformation of **3** with hydroiodic acid to the second metabolite **4** has already been reported by other workers.[3,4] The above procedure thus represents a convenient method for preparation of methadone metabolites from the drug.

The minor product analyzed for $C_{19}H_{19}NO_2$, showed two carbonyl absorption bands at 1660 and 1735 cm^{-1} in its IR spectrum, and exhibited a 60-MHz proton NMR spectrum very similar to that of **5** except in the aromatic region, where it displayed a ten-proton multiplet. The UV spectrum of **6** showed a long wavelength n–π^* transition at 340 nm due to an α-dicarbonyl system.[15,16] Its mass spectrum showed a weak molecular ion at *m/e* 293 (6%) followed by a base peak at *m/e* 265 ($M^+ - CO$). The peak at *m/e* 265 and subsequent fragments were identical with those for **5**, thereby indicating their close structural relationship. Based on the above data, the minor product is considered to be 4,4-diphenyl-3-keto-2-piperidone (**6**), and the structure is in accord with its ^{13}C and 300-MHz proton NMR spectra (see Experimental Section).

Experimental Section[17]

Oxidation of Methadone 1 with Neutral Potassium Permanganate. Formation of Pyrrolidone 5 and α-Keto Lactam 6. To a stirred solution of methadone hydrochloride (9.0 g) in water (125 mL) at 25 °C was added dropwise 10% aqueous sodium hydroxide solution until the reaction mixture was distinctly basic (pH 10–12). The solution was extracted with ether, and the extract was dried and evaporated to afford free methadone as a thick, colorless oil (ca. 8 g). The oil was dissolved in acetone (700 mL), and to this was added a solution of potassium permanganate in acetone/water (2 L, 1:1). The reaction mixture was vigorously stirred for 20 min at room temperature and then cooled in an ice bath. The excess oxidant was removed by bubbling sulfur dioxide through the cold solution until it was nearly colorless. The solution was filtered through a bed of Celite, and the filtrate was concentrated on a rotary evaporator. After an oily material had separated, the aqueous solution was extracted with ether. The organic extract was washed with 5% aqueous sodium carbonate and water. Removal of the solvent from the dried extract gave a mixture of **5** and **6** as a thick, pale yellow oil (6.4 g). Preparative silica gel TLC (chloroform/methanol, 9:1) afforded 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (**5**) as a white, crystalline compound (3.7 g, 55%) which, when recrystallized from ethanol, had mp 120–121 °C (lit.[12] mp 121–122 °C) and showed the following spectral data: ν_{max} (KBr) 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, J = 6 Hz, 3 H), 2.05–2.4 (m, 2 H), 2.9 (s, 3 H), 3.3–3.8 (m, 1 H), and 7.3 (broad singlet, 10 H); mass spectrum (70 eV), *m/e* 265 (M^+, 100), 250 (13), 208 (32), 193 (58), 179 (25), 165 (29), 130 (32), 115 (40), 91 (29), and 56 (40).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.84; H, 7.04; N, 5.17.

The second compound, **6** (1.1 g, 15%), was crystallized from ethanol, mp 212–213 °C, and it showed the following spectral data: ν_{max} (KBr) 1660 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, J = 6 Hz, 3 H), 2.5–2.9 (m) and 2.85 (s) (total 5 H), 3.0–3.6 (m, 1 H), and 6.8–7.5 (m, 10 H); λ_{max} (EtOH) 258 nm (ϵ 3700) and 340 (75); ^{13}C NMR ($CDCl_3$) δ 21.0, 31.0, 39.3, 50.0 ($N-CH_3$), 58.5 ($>CPh_2$), 126–129 (aromatic), 136.7 and 140 (aromatic quaternary carbons), 158.5 ($CONH_2$), and 191.5 (C=O);[18] mass spectrum (70 eV), *m/e* 293 (M^+, 6), 265 (100), 250 (11), 208 (36), 193 (70), 179 (30), 165 (26), 130 (45), 115 (44), 91 (30), and 56 (20).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.81; H, 6.48; N, 4.77. Found: C, 77.29; H, 6.44; N, 4.78.

The 300-MHz NMR spectrum ($CDCl_3$) exhibited signals at δ 1.35 (d, J = 6 Hz, 3 H), 2.66 (d of d, J = 15.0 and 10.5 Hz, 1 H, H_a), 2.85 (s, 3 H), 2.99 (d of d, J = 15.0 and 4.5 Hz, 1 H, H_b), 3.43 (m, 1 H, H_c), and 6.97–7.50 (m, 10 H).

Preparation of Metabolite 3. The methadone metabolite **3** and its perchlorate salt were prepared according to Pohland et al.[4] and found to be identical in all respects with the previously synthesized material.[4]

Acknowledgments. The authors would like to thank Dr. E. F. Ullman for helpful discussions and Mr. J. Shoolerey of Varian Associates, Palo Alto, for recording the ^{13}C and 300-MHz NMR spectra.

Registry No.—1 HCl, 1095-90-5; **3**, 30223-73-5; **3** $HClO_4$, 66729-78-0; **5**, 30223-75-7; **6**, 68715-73-1.

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N-Alkylation of β-Ketocarboxylic Acid Amides

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Received June 12, 1978

A recent synthesis of indeno[1,2,3-*de*]quinolin-2-ones involves the acid-catalyzed cyclization of 2,2-dichloro-*N*-substituted β-ketoamides of type **1**; compounds **1** are derived by sulfuryl chloride chlorination of the corresponding amide **2**.[1] We present here an alternative route to **1** which obviates the need for **2** and its prerequisite *N*-alkylarylamine[1-3] and utilizes as substrate the usually more accessible β-ketoamide **3**. Indeed, compound **2** itself can be obtained, if desired, using this method.

To our knowledge direct N-alkylation of **3** as a preparative route to **2** has not been described. When treated with sodium

0022-3263/79/1944-0875$01.00/0