p-**Nitrophenylbenzhydroxamate.**—In a 250-ml flask equipped with a mechanical stirrer, a powder dropping funnel containing 5.80 g (0.0331 mol) of powdered potassium benzhydroxamate, a dropping funnel containing 40 ml of dimethyl sulfoxide, and a thermometer were placed 27 ml (0.338 mol) of dry, freshly distilled pyridine and 55.62 g (0.395 mol) of distilled *p*-fluoronitrobenzene. The system was flushed with dry nitrogen gas and sealed from the atmosphere. The reaction was initiated at room temperature by simultaneously adding small amounts of the powdered potassium benzhydroxamate and dimethyl sulfoxide to the stirred reaction flask. The reaction mixture immediately turned yellow with the color gradually deepening through orange to a dark red as the reaction proceeded. The balance of the potassium benzhydroxamate was added in small increments over a period of 1 hr along with just sufficient dimethyl sulfoxide to dissolve any solid products that formed. The temperature of the reaction mixture rose to 38° in about 15 min and was maintained between 38 and 40° for the balance of the reaction. The reaction mixture was evaporated to dryness in a rotary evaporatory at 40° (0.28 mm). The solid residue was dissolved in a minimum (200–300 ml) of 0.1 *N* sodium hydroxide solution. The solution was acidified with hydrochloric acid to pH 8.4 to precipitate the crude product. Subsequent crops of less pure product may be obtained by further lowering the pH to 7. The crude product was purified by repeated recrystallizations from chloroform to give a 30% yield of white crystals: mp 139.8–141.3°; ir (KBr) 3400, 3100, 2900, 1650 (C=O), 1580 (aromatic C=C), 1510 and 1340 (nitro), 1210 (*O*-phenyl), 1155, 1110, 1020, 910, 852, and 752 (nitro), 710, and 690 cm^{-1}; nmr (DMSO-d_6) δ 7.45 (d, 2, J = 9 Hz, H ortho to O), 8.32 (d, 2, J = 9 Hz, H ortho to NO_2), 7.55 (d, 1, J = 2 Hz, H para to C=O), 7.64 (d, J = 2 Hz), 7.92 (d, J = 4 Hz), 8.05 (d, J = 2.5 Hz), 3.3 (s, 1, NH); uv max (water, pH 10) 350 nm.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.44; H, 3.90; N, 10.85. Found: C, 60.37; H, 3.97: N, 10.98.

Further proof for the structure of *p*-nitrophenylbenzhydroxamate was obtained by rearranging a sample of its potassium salt in aniline solution to produce the expected products, *i.e.*, *sym*-diphenylurea and *p*-nitrophenol. The potassium salt was prepared by treating *p*-nitrophenylbenzhydroxamate in absolute ethanol solution with potassium ethoxide in equivalent amounts. The orange potassium *p*-nitrophenylbenzhydroxamate salt was then dissolved in freshly distilled aniline and heated to 120° for 1 hr to ensure complete rearrangement. The insoluble potassium *p*-nitrophenoxide salt was recovered from the reaction mixture and converted to *p*-nitrophenol, which was positively identified by comparison (mixture melting point and ir) with an authentic sample. The diphenylurea was isolated from the aniline solution to yield a sample which was also identical (mixture melting point and ir) with an authentic sample.

o-**Nitrophenylbenzhydroxamate.**—The reaction was run essentially as described for *p*-nitrophenylbenzhydroxamate except that 10.00 g (0.057 mol) of potassium benzhydroxamate, 50.28 g (0.354 mol) of *o*-fluoronitrobenzene, and no pyridine were used. The reaction mixture was dumped into 90 ml of 0.1 *N* sodium hydroxide solution at 0°. The excess *o*-fluoronitrobenzene separated as an oil and was removed. The resulting clear red solution was acidified by the dropwise addition of concentrated hydrochloric acid to precipitate the crude product as a greenish oil which crystallized within 5 min. The crude crystals were purified by recrystallizations from the following solvents in the order listed—chloroform, chloroform–carbon tetrachloride, 1,1,1-trichloroethane, and 4-octyne—followed by several washings with low-boiling petroleum ether to give a 14% yield of cream-colored needles: mp 107–111° dec; ir (KBr) 3440 (NH), 3100 (aromatic CH), 2920 (H-bonded NH), 1680 (C=O), 1615 (aromatic C=C), 1535 and 1367 (nitro), 1300, 1233 (*O*-phenyl), 1172, 1098, 1022, 912, 862, 743, and 705 cm^{-1}; uv max (water, pH 11) 357 nm.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.44; H, 3.90; N, 10.85. Found: C, 60.60; H, 3.91; N, 10.79.

Further proof for the structure of *o*-nitrophenylbenzhydroxamate was obtained by rearranging a sample of its potassium salt in an aniline solution to yield the expected products, *i.e.*, *o*-nitrophenyl and *sym*-diphenylurea, which were identified by comparison with authentic samples.

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Registry No.—Potassium benzhydroxamate, 32685-16-8; *p*-fluoronitrobenzene, 350-46-9; *o*-fluoronitrobenzene, 1493-27-2.

An Anomalous Reaction of Methadone with Chloroformate Esters

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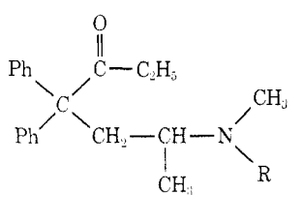
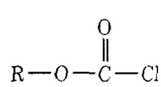
Current interest in the biotransformations of methadone[1] (4,4-diphenyl-6-dimethylamino-3-heptanone, **1b**), and the identification of its metabolites[2,3] prompted us to investigate the chemical demethylation of this compound. In an attempt to synthesize authentic *N*-demethylmethadone (4,4-diphenyl-6-methylamino-3-heptanone, **1a**), which has not been isolated, the reactions of methadone (**1b**) with ethyl chloroformate (**2a**) and phenyl chloroformate (**2b**) were carried out



1a, R = H
b, R = CH_3
c, R = —C(=O)OC_2H_5
d, R = —C(=O)OPh



2a, R = C_2H_5
b, R = Ph

following essentially the procedure of Abdel-Monem and Portoghese.[4] The product obtained in both instances was a neutral, nitrogen-free compound, 2-ethylidene-5-methyl-3,3-diphenyltetrahydrofuran[5] (**3**), in yields of 25 and 50%, respectively. We did not observe formation of the expected carbamate esters **1c** and **1d**. The conditions employed in our reactions were considerably milder than those employed by other workers,[6] who used cyanogen bromide under reflux in their futile attempts to prepare **1a** by demethylation of **1b**. Our reactions were carried out by suspending the compound **1b** in the form of its hydrochloride in a mixture of tetrahydrofuran and sodium bicarbonate and stirring with **2a** or **2b** for 24 hr at room temperature. The reactions, on usual work-up, showed no evidence of a

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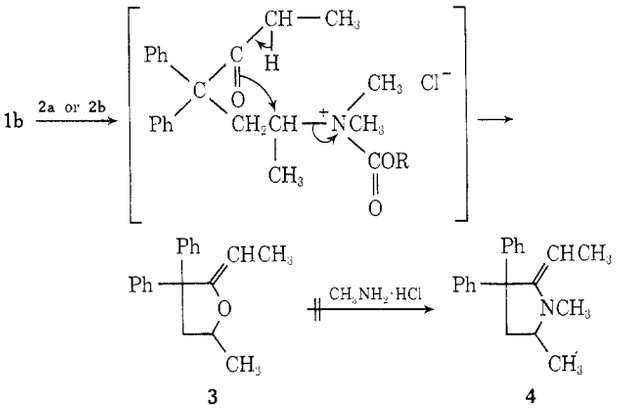
product containing nitrogen. The product **3** (Scheme I) was characterized by it smelting point and ir, nmr,[7] and

SCHEME I



mass spectra, and was found to be identical with the compound obtained by Easton and others on pyrolysis of the methiodide of methadone.[8] An attempt was made by us to convert **3** to **4** (by a variety of conditions; see Scheme I) which was unsuccessful. The compound **4** is a primary metabolite of methadone, which results from demethylation and cyclization.[1,2] However, it is not known whether **3** could result from the biotransformation of methadone, in view of its facile formation, under such mild conditions as employed in our attempted demethylation reaction.

Experimental Section

Melting points of compounds were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infracord (KBr disk). Proton magnetic resonance spectra were obtained with a Varian XL 100 instrument ($CDCl_3$, TMS). Mass spectra were obtained with a Du Pont 492 mass spectrometer. Thin layer chromatography was performed on Analtech plates with florescent indicator. Methadone hydrochloride (racemic) was obtained from Eli Lilly and Co., Indianapolis, Ind. Phenyl chloroformate was obtained from Eastman Kodak Co., Rochester, N. Y. Ethyl chloroformate was obtained from J. T. Baker and Co., Phillipsburg, N. J.

Reaction of Methadone Hydrochloride with Phenyl Chloroformate. Formation of 3.—To a suspension of racemic **1b** hydrochloride (346 mg, 1 mmol) in 25 ml of tetrahydrofuran was added $NaHCO_3$ (2 g, 6 mmol) and **2b** (1.4 g, 8.9 mmol). The resulting mixture was magnetically stirred at room temperature for 24 hr. The reaction mixture was then treated with NaOH (50% solution) until alkaline in pH (about 11) and the solvent was carefully evaporated *in vacuo*. The residue was extracted with chloroform and aqueous NaOH (pH 11) and the chloroform extract was chromatographed preparatively on precoated silica plates (solvent benzene). Some unreacted methadone was found to be present at the origin.[9] The major band close to the solvent front was eluted with chloroform and the extract was evaporated *in vacuo*. A syrupy residue was obtained. This syrupy residue was treated with the minimum of ethanol and water, and allowed to stand overnight at room temperature. The following day, 132 mg (yield 50%) of white crystals, mp 79–81° (lit.[5] mp 78–80°), of **3** was obtained by filtration.

Reaction of Methadone Hydrochloride with Ethyl Chloroformate (2a). Formation of 3.—To a suspension of racemic **1b** hydrochloride (346 mg, 1 mmol) in 20 ml of tetrahydrofuran was added $NaHO_3$ (2 g, 6 mmol) and **2a** (0.8 g, 7.4 mmol). The resulting mixture was magnetically stirred at room temperature for 24 hr. Then the mixture was worked up as in the previous experiment to give 69 mg (25%) of **3**, mp 79–81°.

Acknowledgment.—This research was supported in part by the Narcotic Antagonist Research Program of the New York City Department of Health and Grant No. DA-00297.

Registry No.—(±)-**1b** HCl, 297-88-1; **2a**, 541-41-3; **2b**, 1885-14-9; **3**, 17494-37-0.

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(8) We are thankful to Dr. N. R. Easton for kindly sending us the ir and nmr spectra of the compound.

(9) No effort was made to quantitatively estimate the minute amounts of starting material in this reaction.

Conformations of Carbon-13-Labeled Phenylsuccinic Acid

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Various papers have commented upon the apparent relationship between vicinal ^{13}C–H nmr coupling constants and the geometry of these groups.[1-4] Roughly, the relationship appears to be analogous to the well-known Karplus relationship describing the dependence of H–H coupling constants on dihedral angle.[5] Similar relationships have been postulated for the interaction of ^{31}P–H, ^{31}P–^{13}C, and F–H pairs of nuclei.[6-13] Recently, the effect of molecular geometry on ^{13}C–^{13}C coupling constants has been reported.[14]

From the plot of $J_{^{13}CH}$ *vs.* dihedral angle, given by Lemieux and coworkers, a coupling constant of *ca.* 1 Hz would be expected for gauche ^{13}C–H groups, and *ca.* 8 Hz for trans groups. Somewhat earlier, Perlin and Casu had given values of 0.7 Hz for gauche and 7.8 Hz for trans groups. Lemieux and coworkers caution that ^{13}C–H couplings are quite sensitive to certain structural parameters, including electronegativity of groups, carbon hybridization, and steric relationships.

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