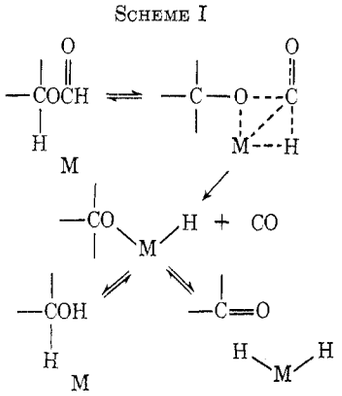
hydrogen bond would be similar to that of aldehydes[12] and would produce the corresponding alkoxycarbonyl radical. Recent investigations indicated that this radical is quite stable at moderate temperatures and undergoes coupling rather than decarboxylation.[13] Loss of CO_2 has been observed[14] in instances where decarboxylation leads to stable alkyl radicals. Products of radical coupling or significant amounts of products derived from loss of CO_2 were not observed under our reaction conditions, even with benzyl formate where substantial driving force for formation of the stable benzyl radical might be expected. As indicated in Table I, toluene was likely formed from hydrogenolysis of benzyl alcohol.

A probable mechanism involves initial cleavage of the ester linkage to yield catalyst-bound alkoxy and carbonyl species. Loss of carbon monoxide would produce an adsorbed alcohol intermediate similar to that proposed for hydrogen–deuterium exchange and oxidation of alcohols over metallic surfaces.[15-17] This intermediate could then partition to either or both alcohol and carbonyl products (Scheme I). The product

SCHEME I



composition obtained from treatment of formate esters in the presence of Raney nickel is compatible with the intermediacy of highly polar species. The initial ester cleavage likely involves closely bound ionic or radical moieties which are formed *via* electron transfer with the metal surface.

Experimental Section

Materials.—The chemicals used in this investigation were obtained from suitable commercial sources and checked for purity prior to use or were synthesized using literature methods. Raney nickel was obtained from W. R. Grace, Davison Chemical Division, as Davison Raney nickel, grade 28. The material possessed approximately the same activity as Raney nickel, W2.[1] The following compounds were prepared by the indicated methods and were used as reactants or for comparison purposes: benzyl formate, prepared by the method of Stevens and Van Es;[18] cyclohexyl formate and *exo*-2-norbornyl formate, prepared by addition of formic acid to the corresponding olefins;[19] cyclohexyl acetate, prepared from cyclohexanol by treatment with acetic anhydride–pyridine and product purity confirmed by ir analysis;[20] 8-*exo*-tricyclo[5.2.1.$0^{2,6}$]dec-4- (or 5-) enyl formate and 8-*exo*-tricyclo[5.2.1.$0^{2,6}$]decyl formate, prepared by the method of Bergman and Japhe;[21] and 8-tricyclo[5.2.1.$0^{2,6}$]dec-4- (or 5-) enone, 8-tricyclo[5.2.1.$0^{2,6}$]decanone, and 8-exo-tricyclo[5.2.1.$0^{2,6}$]decanol, prepared by the method of Bruson and Reiner.[22]

Analyses.—Glc analyses were performed on an F & M 5750 chromatograph using both a 10 ft × 0.25 in. stainless-steel column of 15% FFAP on Chromosorb W (60/80 mesh) and a similar column of 10% W-98 on Chromosorb G (60/80 mesh). Individual peaks were identified by comparison with authentic materials and by infrared spectral comparisons[20] of the product mixtures. Further confirmation was provided by nmr spectral analyses.

Typical Procedure.—In a typical experiment, a 50-ml, three-neck flask was equipped with a distillation head with provision for variable take-off, a thermometer, and a nitrogen inlet tube. Weighed amounts of 2-*exo*-norbornyl formate (15 g) and Raney nickel (0.3 g) were added to the flask. The system was maintained under a positive nitrogen pressure and the contents were stirred magnetically and heated to reflux (170–175°). Reaction progress was followed by glc analysis. When heating was discontinued (19 hr), the reaction vessel was allowed to cool and a small amount of filter aid was introduced. The contents of the flask were then collected by suction filtration and subjected to analysis by ir–glc (Table I). Typical material balances ranged from 85 to 97%.

Registry No.—Nickel, 7440-02-0.

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New Lossen Rearrangement Precursors. The Relative Rates of Rearrangement of Nitrophenylbenzhydroxamates in Aqueous Base

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Data in the literature support the theory that the rate of the Lossen rearrangement is directly proportional to the acidity of the leaving group or its conjugate acid where the leaving group is a basic anion.[2-6] However, all of the examples of hydroxamic acid derivatives which have been studied are acylhydroxamates where the leaving group is a carboxylic acid or its conjugate base. Therefore, the data available to test this theory are limited to a relatively narrow range of acidities (pK_a = 2–5) for the leaving group or its conjugate acid. The objective of this study was to prepare Lossen rearrangement precursors where the conjugate acids of the basic anion leaving groups have pK_a values >5 in order to test the classical theory over

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TABLE I

RATE CONSTANTS AND ACTIVATION ENERGIES FOR THE LOSSEN REARRANGEMENT[a]

Registry no.	Compd	Temp, °K	k, min^{-1}	Av dev, %[b]	E_a, kcal	pK_a[c]
41828-26-6	*p*-Nitrophenylbenzhydroxamate	342	0.00301	2.1		
		351	0.0108	3.7	34.5	7.14
		356	0.0193	1.6		
41828-27-7	*o*-Nitrophenylbenzhydroxamate	333	0.00895	4.3		
		342	0.0288	2.7	30.4	7.23
		351	0.0861	4.6		
41828-28-8	2,4-Dinitrophenylbenzhydroxamate	303	0.0168	3.5	25.6	4.13
		313	0.0692	2.6		
7340-13-8	*m*-Nitrobenzoylbenzhydroxamate	313	0.0216	1.0	25.4	3.5
		323	0.0685	1.2		

[a] All of the rearrangement reactions were run in water at pH 11. [b] These are the average relative deviations from the mean for the rate constants. [c] These are literature values for the conjugate acids of the leaving groups.

a wider range of relative acidities for the conjugate acids of the leaving groups.

Two new nitrophenylbenzhydroxamate derivatives were synthesized where the conjugate acids of the nitrophenoxide leaving groups have pK_a values of 7.14 and 7.23,[7] namely, *p*-nitrophenylbenzhydroxamate and *o*-nitrophenylbenzhydroxamate. In addition to studying the rates for the Lossen rearrangement of these new benzhydroxamic acid derivatives, we undertook to study the rearrangement rate for 2,4-dinitrophenylbenzhydroxamate which had been synthesized by Gallop and Seifter,[8,9] who did not provide data concerning its relative rate of rearrangement. We also studied the rate of rearrangement for *m*-nitrobenzoylbenzhydroxamate in order to relate our data to the previously published data.[2,3]

The Lossen rearrangement reactions were first order and were followed spectrophotometrically to determine the rate constants. The activation energies were determined from the slope ($-E_a/R$) of the plot of ln k *vs.* $1/T$. The results are summarized in Table I.

The activation energy for the rearrangement of *m*-nitrobenzoylbenzhydroxamate was found to be 25.4 kcal with a rate constant of 0.0216 min^{-1} at 40°. These values are in reasonable agreement with the 26.3 kcal for the activation energy and 0.0231 min^{-1} for the rate constant at 40° reported by Bright and Hauser.[2]

Table I reveals that the classical theory of relating the rate of the Lossen rearrangement directly to the relative acidity of the conjugate acid of the anionic leaving group continues to hold, at least qualitatively, in the higher range of pK_a values for the conjugate acids. However, owing to the fact that only three nitrophenol derivatives of benzhydroxamic acid could be synthesized for study, and that two of them involve phenols with ortho nitro groups which show an "ortho effect," no quantitative correlation between conjugate acid pK_a values and rate constants or activation energies for these rearrangements could be made. Judson and Kilpatrick have shown that the ortho nitro group on *o*-nitrophenol has a definite "acid weakening effect."[10] This effect is most obvious when one compares the pK_a of 7.14 for *p*-nitrophenol, which cannot participate in intramolecular hydrogen bonding, with the pK_a value of 7.23 for *o*-nitrophenol. Therefore, it is not possible to correlate the pK_a values for *o*-nitrophenol and 2,4-dinitrophenol quantitatively with the relative rates of rearrangement for their respective benzhydroxamic acid derivatives.

Despite these limitations it is obvious that there is a correlation between the relative base strengths of the phenoxide anion leaving groups and the rate constants and their related activation energies for the Lossen rearrangement. The *p*-nitrophenoxide anion would be expected to be the strongest base and the conjugate base of the weakest acid in the series of nitrophenylbenzhydroxamates. This would lead one to predict that *p*-nitrophenylbenzhydroxamate would have the highest activation energy (34.5 kcal) and the slowest reaction rate, which is substantiated by the fact that the rearrangement had to be run at the highest temperatures in order to obtain reasonable rates. At the other end of the scale the 2,4-dinitrophenylbenzhydroxamate showed the lowest activation energy (25.6 kcal) and the fastest reactions even at relatively low temperatures. This is to be expected since the 2,4-dinitrophenoxide anion is the weakest base and the conjugate base of the strongest acid. The *o*-nitrophenylbenzhydroxamate falls in between the other two with an activation energy of 30.4 kcal as would be predicted.

Experimental Section

Kinetic Measurements.—The rate studies were carried out using a Beckman DB-G spectrophotometer. The reactions were followed by continuously recording the absorbance of an appropriate concentration of benzhydroxamate in a pH 11.0 water solution at a previously determined wavelength, *i.e.*, 4.0×10^{-5} *M* *m*-nitrobenzoylbenzhydroxamate at 250 mμ, 3.6×10^{-5} *M* 2,4-dinitrophenylbenzhydroxamate at 400 mμ, 3.0×10^{-5} *M* *p*-nitrophenylbenzhydroxamate at 400 mμ, and 9.3×10^{-5} *M* *o*-nitrophenylbenzohydroxamate at 420 mμ. Infinite absorbance readings were obtained by allowing the sample to stand overnight at the appropriate temperature to ensure complete reaction.

Instruments.—Nmr spectra were determined on a Varian A-60 spectrometer, infrared spectra were run on a Beckman IR-20 A spectrophotometer, and melting points (uncorrected) were taken in open capillary tubes with a Thomas-Hoover melting point apparatus.

Potassium benzhydroxamate was prepared according to the method of Hauser and Renfrow,[11] as was the *m*-nitrobenzoylbenzhydroxamate.[3] The 2,4-dinitrophenylbenzhydroxamate was prepared in a manner analogous to that in the literature.[8,9]

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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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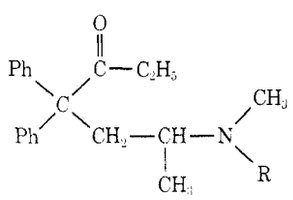
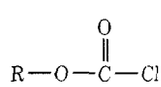
Current interest in the biotransformations of methadone[1] (4,4-diphenyl-6-dimethylamino-3-heptanone, **1b**), and the identification of its metabolites[2,3] prompted us to investigate the chemical demethylation of this compound. In an attempt to synthesize authentic *N*-demethylmethadone (4,4-diphenyl-6-methylamino-3-heptanone, **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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