in vacuo, and the remaining solid was recrystallized from a mixture (30:70 v/v) of ether and petroleum ether (bp 30–60 °C) to afford 8.25 g (60.2%) of ethyl *P*-ethylphosphoramidate: mp 62.5–63.5 °C; IR (KBr) 1180 (P=O), 1570 (P-NH_2), and 3230 (NH_2) cm^{-1}; NMR ($CDCl_3$) δ 1.35 (m, 8-PCH_2CH_3 and OCH_2CH_3), 3.45 (s, 2, NH_2), and 4.05 (m, 2, OCH_2). Anal. Calcd for $C_4H_{12}NO_2P$: C, 35.04; H, 8.82; N, 10.21; P, 22.59. Found: C, 35.13; H, 9.01; N, 10.06; P, 22.88.

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Registry No.—**3**, 78-38-6; **4**, 78-46-6; **5**, 67774-24-7; **6**, 67774-25-8; **7**, 52468-61-8; **9**, 67774-26-9; dibutyl pentylphosphonate, 995-48-2; diisopropyl 1-nitrobutylphosphonate, 67774-27-0; diisopropyl *n*-propyl phosphate, 67774-28-1; ethyl *P*-ethylphosphoramidate, 62992-28-3; dibutyl propyl phosphate, 7242-63-9; propyl nitrate, 627-13-4.

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N-Methylpyruvanilide and 1,3-Dimethyl-3-hydroxyoxindole[1]

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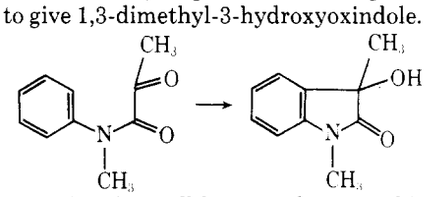
The preparation of *N*-methylpyruvanilide seems to have been reported twice: by Wohl and Lips in 1907 and by Adams, Bramlet, and Tendick in 1920–1922. The reports do not agree with each other. Wohl and Lips[2] utilized the reaction of *N*-methylaniline with the pyridine "salt" of hydroxymaleic anhydride, a procedure which they used and which we also have used to prepare a variety of N-monosubstituted as well as N,N-disubstituted pyruvamides. They reported analytical data for C, H, and N, along with cryoscopic molecular weight determinations in two solvents. The melting point reported for the product, 152–153 °C, is some 50 °C *higher* than that of pyruvanilide, a finding which surprised us somewhat, and no carbonyl group reactions or derivatives are mentioned. Adams, Bramlet, and Tendick reacted methylmagnesium iodide with *N,N'*-dimethyloxanilide and obtained the product resulting from addition of the Grignard reagent to only one of the two carbonyl groups. They at first[3a] reported the *N*-methylpyruvanilide thus produced as being a solid melting at 83–84 °C, but in a correction[3b] two years later they reported it as being a liquid boiling at 148–150 °C (10 mm). The only characterization offered was an elemental analysis for nitrogen, an analysis which agrees neither with the calculated percentage of nitrogen reported nor the theoretical percentage required. The molecular formula is wrong in both the article and the correction, no identifying chemical or physical properties other than the boiling (melting) point are given, and the earlier work of Wohl and Lips is not cited.

N-Methylpyruvanilide is central to certain of our studies[4] of pyruvamides as model compounds which simulate both in structure and in reactivity the α-ketoamide prosthetic groups of a number of enzymes.[5] Accordingly, we deemed it necessary to repeat the preparation by both procedures in order to resolve the situation and to have the compound and a method for its preparation reliably in hand. We find that when solid pyridinium hydroxymaleic anhydride[6] is stirred into a solution of *N*-methylaniline in benzene at room temperature as described by Wohl and Lips, gas evolution (CO_2) commences smoothly and can be brought to completion by gentle heating. Removal of solvent and distillation of the product under reduced pressure affords *N*-methylpyruvanilide directly in 65% yield, but as a pale yellow liquid, bp 108–110 °C (0.5 torr), rather than as a solid. The same compound is obtained from the reaction of dimethyloxanilide with methylmagnesium iodide in ether (Adams' procedure) and also by the reaction of pyruvyl chloride, a reliable procedure for the preparation of which was reported[7] while this work was in progress, with *N*-methylaniline in pyridine–chloroform mixture. The product from the Grignard procedure contained a persistent impurity, probably unreacted dimethyloxanilide, recognizable by virtue of an enhancement of the intensity of the two downfield peaks in the NMR spectrum.

Wohl and Lips' crude product had been worked up with concentrated hydrochloric acid, a procedure of considerable value in the preparation of pyruvanilide itself and other pyruvyl derivatives of aromatic primary amines by the hydroxymaleic anhydride procedure since it effects a clean separation from otherwise troublesome byproducts. Accordingly, we warmed *N*-methylpyruvanilide with concentrated HCl, whereupon it did indeed yield a white solid, mp 152–153 °C, exactly as reported by the German workers. The spectroscopic properties of this substance suggested to us that cyclization might have occurred, hydrogen chloride being the Lewis acid catalyst, to give 1,3-dimethyl-3-hydroxyoxindole. This compound, it transpires, is a well-known substance which has been prepared by at least three different methods[8] but which has not previously been recognized as being identical with Wohl and Lips' product. A comparison with the very full range of properties most recently reported leaves no doubt as to the identity.



That *N*-methylpyruvanilide should undergo cyclization so smoothly, in sharp contrast to pyruvanilide which does not, a difference cogently corroborated by the fact that pyruvanilide can be nitrated[9] by sulfuric–nitric acid mixture to the *p*-nitroanilide while *N*-methylpyruvanilide is destroyed by this reagent, is curious. Nevertheless, given the ready availability of α-ketoacyl derivatives of aromatic secondary amines on the one hand and the known synthetic versatility of oxindoles on the other, the facile cyclization should afford a convenient route for the preparation of a variety of 1,3-disubstituted indoles and related compounds.

Experimental Section

NMR Varian EM 360 and A 60; IR, Beckman "Acculab"; Analyses, Galbraith Laboratories.

***N*-Methylpyruvanilide.** a. Solid pyridinium hydroxymaleic anhydride (20 g) was added to a stirred solution of *N*-methylaniline (10 g) in benzene (50 mL). Gas evolution (CO_2) commenced spontaneously and was brought to completion by gentle heating. The turbid

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solution was filtered and concentrated under reduced pressure to give the crude product as a brown oil (13.3 g, 80%), spectroscopically almost indistinguishable from pure material. Simple distillation under reduced pressure afforded pure material, a pale yellow oil: 10.8 g; 65%; bp 108–110 °C (0.5 torr); freezes at ca. 15 °C; n^{27}_D 1.5325; IR (liquid) 3050, 2950, 1750, 1680, 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3 H, $CH_3C{=}O$), 3.2 (s, 3 H, CH_3N), 7.1 (s, 5 H, C_6H_5). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26. Found: C, 67.80; H, 6.32%.

b. Pyruvyl chloride (1.1 g) was added dropwise to a solution of *N*-methylaniline (0.75 g) and pyridine (1.1 g) in $CHCl_3$ (5 mL). The solution was washed with water and concentrated under reduced pressure to give essentially pure product (1.25 g) in practically quantitative yield. Distillation (0.5 torr) afforded almost colorless material, 1.0 g, 80%.

c. Finely powdered *N,N'*-dimethyloxanilide (26 g) was added portionwise to a stirred solution of methylmagnesium iodide (from Mg, 10.5 g, and CH_3I, 53 g) in ether (500 mL). The mixture was stirred for 3 h, ice and 6 M HCl (160 mL) then were added, the ether layer was isolated, dried ($MgSO_4$), and evaporated, and the crude product was obtained as a red-brown oil (11.2 g), the spectroscopic properties of which were consistent with a 1:1 mixture of *N*-methylpyruvanilide and unreacted dimethyloxanilide. Simple distillation did not effect separation but fractionation by means of a Nester-Faust annular adiabatic spinning band column afforded 4.4 g, 26%, of reasonably pure material.

1,3-Dimethyl-3-hydroxyoxindole. *N*-Methylpyruvanilide (1 g) was placed on a large watch glass, covered with concentrated HCl (2–3 mL), and heated on the steam bath until the aqueous acid was evaporated away (20–30 min). Occasionally, the product obtained upon cooling being oily or pasty, the acid treatment would be repeated. Crystallization of the solid product from water afforded the oxindole as snowy crystals: 0.55 g; 55%; mp 152–3 °C; spectroscopic and analytical properties were in complete agreement with published data.[8]

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Registry No.—*N*-Methylpyruvanilide, 61110-50-7; pyridinium hydroxymaleic anhydride, 52060-80-7; *N*-methylaniline, 100-61-8; pyruvyl chloride, 5704-66-5; *N,N'*-dimethyloxanilide, 14288-22-3; methylmagnesium iodide, 917-64-6; 1,3-dimethyl-3-hydroxyoxindole, 54279-13-9.

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Revision of Some 16-Alkylated Steroids

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The introduction of a 16-methyl substituent into the steroid nucleus is a common procedure to enhance biological activity in the corticoid series. This effect, however, is not observed with the other classes of steroidal hormones, such as androstanes, estranes, and aldosterone antagonists, which upon 16-alkyl substitution show a marked decrease in hormonal activity. These less active classes of compounds, however, have become of new interest since some 16-ethylestranes have recently been shown to exhibit antihormonal activity.[1]

Our first aim was to find a stereoselective introduction of 16α-alkyl substituents starting from 17-ketosteroids, for we believe that the apparent lack of methods in this respect is largely responsible for certain shortcomings and errors in the literature.

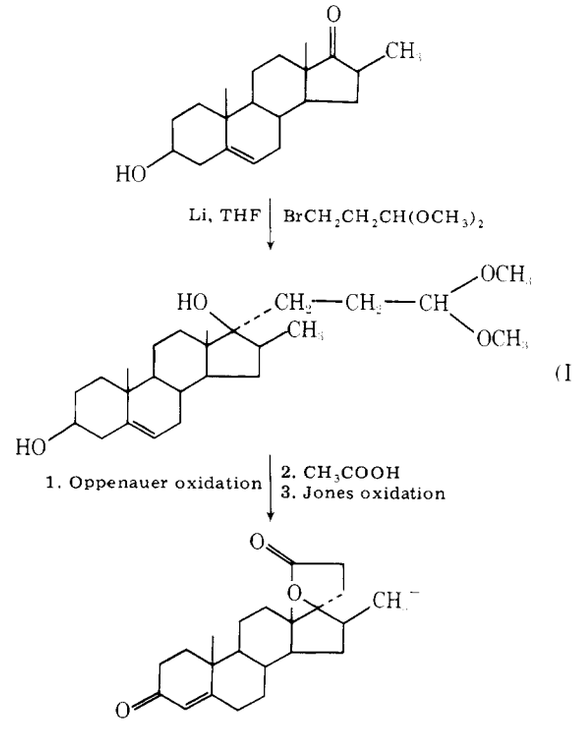
The problem was solved by adopting the procedure of Corey and Enders.[2] Alkylation of 17-ketodimethylhydrazones resulted in clean and quantitative formation of the 16α-alkyl derivatives. Hydrazone cleavage with cuprous chloride in aqueous tetrahydrofuran led to regeneration of the parent ketone without isomerization at C-16.[3,4]

The application of the Corey–Enders procedure to a rigid five-membered ring ketone demonstrates that, in this case, stereoselectivity can only be explained on the basis of steric factors, as orbital control would not be expected to distinguish between α or β side attack.[10]

The stereoselective synthesis of 16β-methyl steroids was performed according to known methods.[5] With pure 16α- and 16β-methyl isomers at hand[6] we investigated the question of thermodynamic stability which had been a point of controversy between several research groups.[7–9] Treatment of 3β-hydroxy-16β-methyl-5-androsten-17-one as well as 3β-hydroxy-16α-methyl-5-androsten-17-one under acidic or alkaline conditions led to the same equilibrium mixture which contained the 16β-methyl derivative in about 80% and the 16α-methyl isomer in about 20%. This is not in agreement with Atwater's[7] result who claimed complete conversion of the β isomer into the α compound.

A comparison between our material and Atwater's[7] revealed significant differences as far as the 16α-methyl compound is concerned.

The steric hindrance exercised by a 16α or β substituent is another point of discussion. Atwater et al.[7] reported that their repeated attempts to ethynylate 3β-hydroxy-16β-methyl-5-androsten-17-one were unsuccessful. Our results show,



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