Oxidation of m-tolunitrile. Oxidation of *m*-tolunitrile to *m*-cyanobenzoic acid was carried out with chromium trioxide in a mixture of acetic and sulfuric acids as described above for *p*-tolunitrile. The conversion was 66% and the product, *m*-cyanobenzoic acid, melted at 218–220°. The compound had previously been prepared using the Sandmeyer method,[5] m.p. 217°.

Reduction of m-cyanobenzoic acid with Raney Cobalt. The techniques used in the reduction were similar to those used with the *para* isomer. The product obtained was considerably more soluble than *p*-aminomethylbenzoic acid in water. The melting point was 273–275° (closed tube). This value is not in agreement with the melting point reported by Reinglass[6] (215–218°).

Anal. Calcd. for $C_8H_9O_2N$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.33; H, 5.42; N, 9.17.

Reduction of m-aminomethylbenzoic acid to m-aminomethylcyclohexylcarboxylic acid. The reduction was carried out in glacial acetic acid using platinum oxide as catalyst. The product (I), not previously reported, melted at 203–204° using the method of isolation reported above for the *para* derivatives.

Anal. Calcd. for $C_8H_{15}O_2N$: C, 61.14; H, 9.55. Found: C, 60.30; H, 9.36.

Acetylation of m-aminomethylbenzoic acid. The acetylation was carried out as previously described using acetic anhydride. The product obtained, not previously reported, melted at 162–164°.

Anal. Neut. equiv.: Calcd. 193. Found: 196.

HIGH POLYMER RESEARCH LABORATORY
INDUSTRIAL RAYON CORP.
CLEVELAND, OHIO

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Mannich Derivatives of Analgesic Agents

E. M. FRY AND EVERETTE L. MAY

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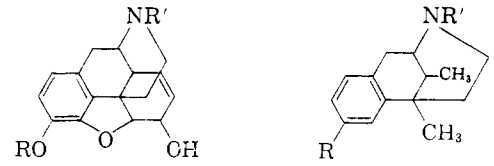
The recent disclosure[1] that replacement of the methyl group on the nitrogen of morphine and meperidine by phenethyl and *p*-aminophenethyl groups, respectively, results in a marked increase in analgesic potency has stimulated renewed interest along these lines.[2–5] In the morphinan[5] series, compounds have emerged with activities some fifty times that of the *N*-methyl parent. Perhaps the most dramatic increase in potency (500 fold) has been that resulting from substitution of 3-oxo-3-phenylpropyl for the methyl radical of ethyl 1-methyl-4-phenylisonipecotate (meperidine).[6] We wish to report an extension of this last-mentioned modification to other series of analgesics.

FIGURE 1



Ia. R = R′ = H
b. R = CH_3, R′ = H
c. R = H, R′ = CH_2CH_2COPh
d. R = CH_3, R′ = CH_2CH_2COPh
e. R = R′ = CH_3
IIa. R = R′ = H
b. R = OH, R′ = H
c. R = H, R′ = CH_2CH_2COPh
d. R = OH, R′ = CH_2CH_2COPh
e. R = OH, R′ = CH_3
f. R = OCH_3, R′ = CH_3

II

The substitution of 3-oxo-3-phenylpropyl for the hydrogen of a secondary amine can usually be achieved by the Mannich reaction using acetophenone and paraformaldehyde. With the bases under consideration, normorphine (Ia), norcodeine (Ib), 5,9-dimethyl-6,7-benzomorphan (IIa), and 2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIb), normal procedures[5b,7] failed. Ultimately the desired compounds, Ic, Id, IIc, and IId, were obtained by means of the amine replacement reaction. In this reaction as originally presented by Snyder and Brewster[8] the secondary amine in large excess was heated with a Mannich base or its methiodide; the resulting amine exchange gave the new Mannich base. The reaction has proved useful in preparing Mannich bases of amines which do not undergo the normal condensation.[9] Conditions were modified on finding that equivalent amounts of the secondary amine and Mannich quaternary salts in dimethylformamide reacted at room temperature to give the expected product in good yield. Sodium carbonate was used to bind released acid and nitrogen to agitate the mixture and remove trimethylamine.

In the case of the phenolic compounds (Ia, IIb) the possibility of ring substitution was eliminated by subjecting the presumed Mannich bases (Ic, IId) to the action of base in the presence of methyl iodide. Loss of the 3-oxo-3-phenylpropyl group took place readily and the resultant *N*-methyl analogs were identified as the methiodides.

3-Phenyl-3-oxopropyl-normorphine (Ic) and norcodeine (Id) are from two to three times less potent analgesics in mice than morphine and codeine respectively, while the benzomorphans IIc

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and IId are somewhat more effective than the *N*-methyl counterparts.[10,11]

EXPERIMENTAL

Melting points are uncorrected unless otherwise noted. Microanalyses are by Paula M. Parisius of the Institutes Service Analytical Laboratory, Dr. William C. Alford, director.

5,9-Dimethyl-6,7-benzomorphan (IIa) *picrate.* A solution of 1.7 g. of 2,5,9-trimethyl-6,7-benzomorphan (from 2.2 g. of hydrochloride)[10] in 8 ml. of chloroform was added during 0.7 hr. to a stirred solution of 1.0 g. of cyanogen bromide (Eastman) in 10 ml. of chloroform. The solution was refluxed for 2 hr. and evaporated to dryness *in vacuo*. The residue and 36 ml. of 6% hydrochloric acid were refluxed for 20 hr. Cooling and ammonium hydroxide addition liberated an oil which was dried in ether. Evaporation of the ether left 1.5 g. of base which with 1.5 g. of picric acid and 10 ml. of alcohol (heated to solution), gave on cooling to 25° 1.7 g. (50%) of IIa picrate m.p. 232–233° (dec., corr.).

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.60; H, 5.16.

The *hydrochloride* crystallized from acetone-ether in long needles, m.p. 171.5–173.5° (corr.). It was dried 0.5 hr. at 139° for analysis.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 70.71; H, 8.48. Found: C, 70.39; H, 8.35.

2'-Hydroxy-5,9-dimethyl-6,7-benzomorphan (IIb). Two g. of 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan[10] and 4 ml. of acetic anhydride were kept at 95–100° for 0.5 hr., cooled, diluted with ice water, and after 5 min. made alkaline with aqueous potassium hydroxide while keeping ice cold. The oil was quickly shaken into ether. Drying and evaporation of the ether left 2.3 g. of ester which was subjected to *N*-demethylation (1 g. of cyanogen bromide) as described above, except that chloroform or 2:1 benzene butanol was used to extract the crude IIb which weighed 1.8 g. It crystallized from 5 ml. of acetone in a yield of 1.1 g. (60%); m.p. 225–231°, and 232–235° (corr.) after two recrystallizations from methanol.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.20; H, 8.86.

The *hydrochloride*, small prisms from absolute ethanol-ether, melted at 291–294° (dec., corr.).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.25; H, 7.94. Found: C, 66.14; H, 8.13.

N-(3-Oxo-3-phenylpropyl)normorphine (Ic). Normorphine[12] (Ia, 10 g.), 12 g. (1.1 equivalent) of β-dimethylaminopropiophenone methiodide, 3.6 g. (2 equivalents) of sodium carbonate, and 50 ml. of dimethylformamide were agitated with a slow stream of nitrogen which also removed trimethylamine. After 4 hr. addition of water gave an oil which readily crystallized. Filtration and washing with water, then alcohol gave 11.2 g. of Ic which melted at 179–182°. Recrystallization from alcohol yielded 10.0 g. (74%), m.p. 180–183°.

Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25. Found: C, 74.13; H, 6.20.

The Ic, alcoholic sodium hydroxide, and excess methyl iodide were left overnight. The recovered crude product was put in acetone suspension with methyl iodide. The resultant methiodide gave no depression in melting point on admixture with codeine methiodide.

N-(3-Oxo-3-phenylpropyl)norcodeine (Id) *hydrochloride.* This compound was prepared from norcodeine (Ib)[12] as described above. The hydrochloride of Id crystallized from water as the dihydrate, m.p. 168–171°.

Anal. Calcd. for $C_{26}H_{28}ClNO_4.2H_2O$: H_2O, 7.3. Wt. loss (100°), 7.2. For the anhydrous hydrochloride: C, 68.79; H, 6.22. Found: C, 68.80; H, 6.13.

2-(3-Oxo-3-phenylpropyl)-5,9-dimethyl-6,7-benzomorphan (IIc) *hydrochloride.* As described in the synthesis of Ic, the yield of IIc from IIa was 70%. The hydrochloride salt was purified from alcohol; m.p. 181–183°.

Anal. Calcd. for $C_{23}H_{28}ClNO$: C, 74.67; H, 7.63. Found: C, 74.35; H, 7.78.

2'-Hydroxy-5,9-dimethyl-2-(3-oxo-3-phenylpropyl)-6,7-benzomorphan (IId). This compound prepared in 85% yield as described above was freed of a little iodide with dilute aqueous sodium hydroxide. Recrystallized from alcohol, it melted at 175–176°.

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79. Found: C, 78.71; H, 7.89.

2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan (IIf) *methiodide.* Alcoholic sodium hydroxide, IIe[10] and methyl iodide gave after 1 hr. at 25° crystals which were collected and purified from alcohol; m.p. 173–178°.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.71; H, 6.77. Found: C, 52.78; H, 6.98.

Similar treatment of IId gave the same compound, m.p. 170–177°, after purification from alcohol. The melting point was not lowered on admixture with the above sample and the infrared spectra were identical.

NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MD.

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Indoxyl Acetate from Indole

ROBERT D. ARNOLD, WILLIAM M. NUTTER, AND WILLIAM L. STEPP

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The observation of Barrnett and Seligman,[1] later extended by others,[2–4] that indoxyl acetate was suitable for the detection of acetylcholinesterase in tissue slices suggested to us that this technique could be adapted to the determination of this enzyme in serum. In the course of our investigations for a method of synthesizing substituted indoxyl acetates that would lend themselves to a colorimetric procedure for the determination of the activity of the enzyme, a new method of preparation of indoxyl acetate was found. Oxidation of indole with various reagents has been reported to give indoxyl[5] but the yields are not good. Halogenated indoles are reported to be inert to alkaline hydrolysis.[6] The usual greater reactivity of iodine compounds compared to that of other halogen compounds, cou-

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