Preparation of *p*- and *m*-Aminomethylcyclohexylcarboxylic Acid

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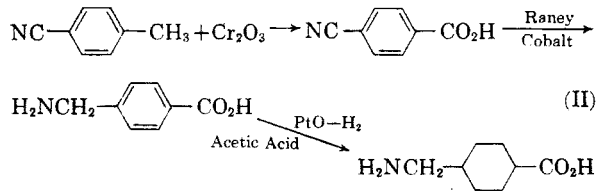
Amino acids containing cycloaliphatic groups have been neglected in the search for fiber-forming polymers although ω-aminocarboxylic acids and their derivatives have received considerable attention. Two cycloaliphatic amino acids, *p*- and *m*-aminomethylcyclohexylcarboxylic acid, were prepared in our laboratory. The meta compound (I) has not previously been reported in the literature; the only preparation of the para compound (II) reported involved a chemical reduction of *p*-aminomethylbenzoic acid prepared from *p*-cyanobenzylchloride.[1] Our three-step synthesis is illustrated in



the accompanying scheme. The starting material may be *m*- or *p*-tolunitrile depending upon the amino acid desired.

The *p*-cyanobenzoic acid prepared from *p*-tolunitrile by chromium trioxide oxidation was first reported by Adkins and Scanley[2] who credited B. F. Aycock with the experimental procedure. Apparently Aycock has not published experimental details; therefore, a procedure for oxidation with chromium trioxide is included. The yields obtained by using this method are higher than those obtained by the Sandmeyer method.

The Albert and Magrath[3] method, using Raney nickel in ammonia, was followed for the reduction of *p*-cyanobenzoic acid. This method resulted in higher yields but the product contained more impurities than when the reduction was carried out using palladium in ammonia. Practically a quantitative yield of (II) (m.p. 238–240°—probably preferential preparation of *cis* isomer) was obtained when the aromatic nucleus was reduced in glacial acetic acid using platinum oxide as catalyst. It is interesting to note that the chemical reduction method[1] for the preparation of (II) produced two forms, an α-form which softened at 270° and a β-form which decomposed between 220–229°.

The *m*-aminomethylcyclohexylcarboxylic acid (I) was prepared from *m*-tolunitrile. A chromic acid oxidation, followed by the reduction of the nitrile group and the aromatic ring gave the new compound (I), melting point 203–204°. Acetyl derivatives of (I) and (II) were prepared and characterized for the first time, and the reduction product of *p*-acetamidomethylbenzoic acid was also prepared.

EXPERIMENTAL

Chromic oxide oxidation of p-tolunitrile. A solution of 35.1 g. (0.3 mole) of *p*-tolunitrile and 570 ml. of glacial acetic acid was placed in a 1-l., three necked flask equipped with a stirrer and a thermometer. Concentrated sulfuric acid, 45 ml., was added slowly to this solution. The reaction flask was cooled to 5° and 90 g. (0.9 mole) of chromic oxide was added in small portions at such a rate that the temperature did not rise above 10°. The reaction materials were stirred at 0–10° for 2 hr., and the temperature was then allowed to rise to 25° during an additional hour. The contents of the reaction flask were poured onto ice, and the solid products were filtered off. The crude material was dissolved in sodium carbonate, and the *p*-cyanobenzoic acid was precipitated with hydrochloric acid. The purification was repeated and the crude acid was recrystallized from water. The product, obtained in 57% yield, melted at 219–220°, in agreement with the value reported by Adkins and Scanley.[3]

Reduction of p-cyanobenzoic acid with Raney Cobalt. A mixture of 14 g. (0.09 mole) of *p*-cyanobenzoic acid, about 2 g. of Raney Cobalt (W-6 or W-7), 40 ml. of 28% aqueous ammonia and 150 ml. of water was shaken in the Parr Hydrogenerator at 25° under a starting hydrogen pressure of 3 atm. The theoretical amount of hydrogen was taken up within 3 hr. After removing the catalyst by filtration, the violet solution was boiled to remove ammonia, and a solid product precipitated. After recrystallization from water, a pink colored product, *p*-aminomethylbenzoic acid, m.p. 347–350° (closed tube), was obtained in 80% yield. This melting point is in agreement with Dewing.[4] Several recrystallizations from water with the aid of carbon black were necessary in order to obtain a white product.

Reduction of p-aminomethylbenzoic acid. *p*-Aminomethylbenzoic acid, 6.12 g. (0.04 mole) was reduced in glacial acetic acid, 100 ml., with 0.2 g. platinum oxide as catalyst. The reduction was carried out in the low pressure Parr Hydrogenerator at 60° and the reaction was completed in 16–24 hr. After filtering the catalyst, the solution was evaporated to dryness. The residue, the acetate of the amino acid, was dissolved in water. Sulfuric acid was added in order to release the acetic acid upon boiling. After the last traces of acetic acid were removed, enough barium hydroxide was added to remove all the sulfate ions as barium sulfate. After evaporating the filtrate to a small volume, the aliphatic amino acid was then obtained on diluting with acetone. Practically a quantitative yield of (II) was obtained, m.p. 237–240°.

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

Acetylation of p-aminomethylbenzoic acid. The amino acid, 5 g., was heated on a steam cone with 60 cc. of acetic anhydride and 8 drops of sulfuric acid for 0.5 hr. The product, *p*-acetamidomethylbenzoic acid, after standing 2 hr. at 25° was poured onto ice. The solid product, obtained on evaporation of the liquid, was extracted with potassium hydroxide solution and was recrystallized from a large volume of xylene, m.p. 199–120° (compound was not previously reported).

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

Reduction of p-acetamidomethylbenzoic acid. Reduction of *p*-acetamidomethylbenzoic acid in acetic acid with platinum oxide gave *p*-acetamidomethylcarboxylic acid.

Anal. Neut. equiv.: Calcd. 199. Found: 198.

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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.

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Mannich Derivatives of Analgesic Agents

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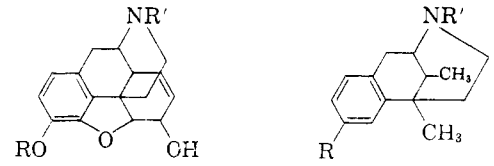
The recent disclosure[1] that replacement of the methyl group on the nitrogen of morphine and meperidine by phenethyl and *p*-aminophenethyl groups, respectively, results in a marked increase in analgesic potency has stimulated renewed interest along these lines.[2–5] In the morphinan[5] series, compounds 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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