

SYNTHESIS OF THE 3-HYDROXY-4-METHYL DERIVATIVE OF AMPHETAMINE*

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Received November 11th, 1976

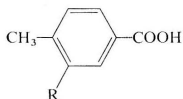
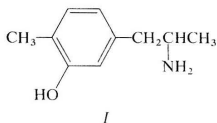
p-Toluic acid was converted in seven steps to (3-methoxy-4-methylphenyl)acetonitrile (*VIII*) which underwent Claisen's reaction with ethyl acetate and subsequent acid hydrolysis to yield the phenylacetone derivative *XI*. Leuckart's reaction and alkaline hydrolysis of the product gave rise to 3-methoxy-4-methylamphetamine (*XIII*) which was demethylated with hydrobromic acid to the title compound *I*.

Carlsson and coworkers^{1,2} prepared the 3-hydroxy-4-methyl derivative of amphetamine *I* which, in histochemical and biochemical experiments on rats and mice, depresses with extraordinary intensity the levels of norepinephrine in central and peripheral neurones (brain and heart) by setting it free from its storage sites. At the same time, a sympathomimetic stimulation and a central excitation are observed. Compound *I* accelerates³ the oxidation of norepinephrine catalyzed by ceruloplasmin in experiments *in vitro*. The mentioned effects of *I* can be suppressed by prophylactic application of antidepressants (protriptyline, desipramine)⁴; amphetamine and methamphetamine, on the other hand, potentiate the effects of *I* as to the washing out of brain norepinephrine⁵. Only higher doses release also brain dopamine¹; this effect is potentiated by the lysergide model *N,N*-diethyl-1-methyl-1,2,3,6-tetrahydronicotinamide (THPC) as long as *I* is applied in combination with mezcaine⁶. For the reported studies, the pharmacokinetics of *I* in mouse brain and heart⁷ was studied and a micromethod for identification of the compound in central and peripheral neurones was developed⁸. *I* acts as antinociceptive toward painful stimuli in the rat⁹ and this effect is antagonized by neuroleptics (chlorpromazine, reserpine) as well as by antidepressants (protriptyline) and potentiated by atropine. Lassen¹⁰ studied the mechanism of hypermotility brought about by *I* in rats and found¹¹ this hypermotility to be antagonized by neuroleptics of the cataleptic type (chlorpromazine, haloperidol) and noncataleptic type (clozapine, thioridazine); he suggested to use the antagonizing of this hypermotility as a test for evaluating potential neuroleptics.

The mentioned paper¹¹ stimulated our interest in *I* as our studies in the series of 10-piperazinodibenzo[*b,f*]thiepins include both highly cataleptic¹² and noncataleptic¹³ neuroleptics. A pharmacological test that would embrace both types of neuroleptics would be an invaluable tool for the prediction of clinical properties of the studied compounds. For this reason we took up the synthesis of *I*. Ref.^{1,2}

* Part CXII in the series Neurotropic and Psychotropic Agents; Part CXI: This Journal 42, 2231 (1977).

describe its preparation in two parallel ways which proceed from 3-methoxy-4-methylbenzaldehyde and from 3-benzyloxy-4-methylbenzaldehyde (obtained from the corresponding acids by Rosenmund's reaction) which react with nitroethane to yield the corresponding substituted nitrostyrenes. Reduction with lithium aluminium hydride yielded 1-(3-methoxy-4-methyl)-2-propylamine and 1-(3-benzyloxy-4-methyl)-2-propylamine; to obtain *I*, the first of these was demethylated with hydrobromic acid, the other was debenzylated by catalytic hydrogenation. We developed an alternative synthesis which, although somewhat longer as to the number of steps, is advantageous because it employs simple reactions and gives a high yield.

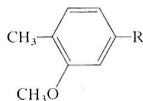


II, R = NO₂

III, R = NH₂

IV, R = OH

V, R = OCH₃

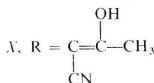


VI, R = CH₂OH

VII, R = CH₂Cl

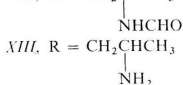
VIII, R = CH₂CN

IX, R = $\begin{array}{c} \text{CHCOCH}_3 \\ | \\ \text{CN} \end{array}$



XI, R = CH₂COCH₃

XII, R = CH₂CHCH₃



The starting compound was *p*-toluic acid which was converted by conventional procedures *via* intermediates *II*–*VI* to 3-methoxy-4-methylbenzyl chloride (*VII*). *p*-Toluic acid was nitrated¹⁴ by a modified method¹⁵ to 4-methyl-3-nitrobenzoic acid (*II*). For reduction of *II* to 3-amino-4-methylbenzoic acid^{14,16} (*III*) we used catalytic hydrogenation on Raney nickel. Transformation to 3-hydroxy-4-methyl-

benzoic acid (IV) was done according to ref.¹⁷. Subsequent methylation was described¹⁸ by treatment with methyl iodide and potassium hydroxide at 140°C when it was necessary in a separate step to hydrolyze the methyl ester formed. We carried it out in a single step with dimethyl sulfate in the presence of excess aqueous sodium hydroxide and thus obtained 3-methoxy-4-methylbenzoic acid (V). A similar procedure was used by El'tsov¹⁹ but he converted the product without isolation to the methyl ester which was then reduced with lithium aluminium hydride in ether to 3-methoxy-4-methylbenzyl alcohol (VI). We observed here that the same result is achieved by reduction of the free acid V. The above author¹⁹ described the conversion of alcohol VI to chloride VII with thionyl chloride in ether in merely a 37% yield. Our modification of this reaction in benzene produced chloride VII in a 75% yield.

Reaction of chloride VII with sodium cyanide in dimethylformamide yielded (3-methoxy-4-methylphenyl)acetonitrile (VIII) which underwent Claisen's reaction (method in^{20,21}) with ethyl acetate to cyano ketone IX. While the ¹H-NMR spectrum of the compound (in deuteriochloroform solution) is compatible with structure IX, the IR spectrum of a solid (in Nujol) indicates that we are dealing here with a stabilized enol-form X. Hydrolysis with a boiling mixture of hydrochloric and acetic acids resulted in (3-methoxy-4-methylphenyl)acetone (XI) which underwent Leuckart's reaction²² with formamide and formic acid to the formamido derivative XII. This was transformed by alkaline hydrolysis without characterization to 1-(3-methoxy-4-methylphenyl)-2-propylamine (XIII) prepared before by a different procedure¹. Patent applications² also mention a method using Leuckart's reaction but do not characterize any of the intermediates XI–XIII. The final demethylation was done with hydrobromic acid^{1,2}; the product was prepared in the form of hydrogen maleate and base I was further characterized by a study of spectra.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at 0.5 Torr over P₂O₅ at room temperature or at 77°C. The UV spectrum (in methanol) was recorded in a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol) were recorded in a Unicam SP 200G spectrophotometer and ¹H-NMR spectra (in CD₃SOCD₃ unless stated otherwise) in a Tesla BC 487 (80 MHz) spectrometer. Homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

3-Amino-4-methylbenzoic Acid (III)

Raney nickel (10 g) was added to a warm solution of 121 g 4-methyl-3-nitrobenzoic acid¹⁵ (II, m.p. 185–190°C) in 1 litre ethanol and the mixture was hydrogenated at normal pressure and with gentle heating. Theoretical consumption of hydrogen was reached in 5 h; it was filtered and the solution was evaporated. A total of 93.8 g (94%) crystalline product was obtained; m.p. 166.5–167.5°C. Ref.¹⁶ reports for a product obtained by reduction of II with stannous chloride a m.p. of 164–165°C.

3-Methoxy-4-methylbenzoic Acid (*V*)

Dimethyl sulfate (54.2 g) was added to a suspension of 26.9 g 3-hydroxy-4-methylbenzoic acid¹⁷ (*IV*, m.p. 206–210°C) in 110 ml methanol, and 117 ml 30% NaOH was then added dropwise under stirring over a period of 40 min. The temperature of the mixture rose spontaneously to the boiling point and a clear solution was formed. It was refluxed for 4 h, methanol was evaporated at reduced pressure and the residue was diluted with water until the sodium salts formed dissolved. After filtration, the filtrate was acidified with 70 ml 5M-HCl, the precipitated product was cooled, filtered, washed with water and dried in air; 23.9 g (82%), m.p. 158–160°C. Ref.¹⁸ reports a m.p. of 156°C.

3-Methoxy-4-methylbenzyl Alcohol (*VI*)

Suspension of 47.4 g *V* in 500 ml ether was added dropwise under stirring over a period of 30 min to a suspension of 21.5 g LiAlH₄ in 250 ml ether. The mixture was refluxed for 2 h, cooled, decomposed by adding 75 ml water and 25 ml 5M-NaOH, stirred for a while and combined with 25 g K₂CO₃. After brief stirring, the solid was filtered and washed with ether. Treatment of the filtrate yielded 34.4 g (80%) product boiling at 96–102°C/0.2–0.5 Torr. Ref.¹⁹ reports for a product obtained by reducing the methyl ester a b.p. of 107–110°C/3 Torr.

3-Methoxy-4-methylbenzyl Chloride (*VII*)

A solution of 87.5 g SOCl₂ in 75 ml benzene was added dropwise over a period of 30 min to a solution of 53.4 g *VI* in 200 ml benzene. The mixture was stirred for 30 min at 50°C and refluxed for 1.5 h. After evaporation of the volatile fractions the residue was dissolved in 200 ml benzene, the solution was filtered with charcoal and CaCl₂ and the filtrate was distilled; 44.8 g (75%), b.p. 76–78°C/0.5 Torr. Ref.¹⁹ reports for a product obtained in a similar reaction in ether a yield of merely 37% and a b.p. of 123°C/17 Torr.

(3-Methoxy-4-methylphenyl)acetonitrile (*VIII*)

Sodium cyanide (19.9 g) was added under stirring to a solution of 35.2 g *VII* in 75 ml dimethylformamide. After cessation of the exothermic reaction the mixture was stirred for 4 h at room temperature. After standing overnight it was diluted with 300 ml water and extracted with chloroform. The extract was washed with water, dried with Na₂SO₄ and distilled: 30.3 g (91%), b.p. 106–108°C/0.5 Torr. Analytical sample, b.p. 99°C/0.1 Torr. For C₁₀H₁₁NO (161.2) calculated: 74.50% C, 6.88% H, 8.69% N; found: 74.57% C, 7.21% H, 8.55% N.

1-Cyano-1-(3-methoxy-4-methylphenyl)acetone (*IX*)

Compound *VIII* (12.6 g) was added to a warm solution of C₂H₅ONa (2.36 g Na and 35 ml ethanol) and then 14.5 g ethyl acetate was added under stirring over a period of 20 min at 70 to 75°C. The mixture was refluxed under stirring for 2.5 h and left to stand overnight at room temperature. The precipitated substance was dissolved by adding 250 ml water, the pH of the solution was adjusted to 10–12 with 20% NaOH and the turbid solution was washed with ether. Acidification of the alkaline aqueous layer with 30 ml acetic acid (pH 4.5) released a product which was isolated by extraction with chloroform; 14.6 g (92%), m.p. 80–81°C. An analytical sample was obtained by crystallization from a mixture of benzene and light petroleum, m.p. 83.5–84.5°C. IR spectrum: 815, 837, 844, 863 (2 adjacent and solitary Ar–H), 1042, 1259 (ArOCH₃), 1139

(OH), 1504, 1572, 1609 (Ar), 1630 (C=C), 2220 (C=C—CN), 3010 (Ar), 3170 cm^{-1} (OH); The IR spectrum thus does not display the band of a keto group but contains bands of the hydroxyl group which suggests the enol form *X*. $^1\text{H-NMR}$ spectrum (CDCl_3): δ 7.12 and 6.82 (2 d, $J = 8.0$ Hz, 2 H, 5,6- H_2), 6.75 (bs, 1 H, 2-H), 4.64 (s, 1 H, Ar—CH—CO), 3.80 (s, 3 H, OCH_3), 2.20 and 2.18 (2 s, 6 H, Ar— CH_3 and COCH_3). For $\text{C}_{12}\text{H}_{13}\text{NO}_2$ (203.2) calculated: 70.91% C, 6.45% H, 6.89% N; found: 70.39% C, 6.68% H, 6.96% N.

(3-Methoxy-4-methylphenyl)acetone (*XI*)

Hydrochloric acid (30 ml) was added to a solution of 8.5 g *IX* in 40 ml acetic acid and the mixture was refluxed for 6 h. After cooling, it was diluted with 500 ml water and extracted with chloroform. Processing of the extract yielded 4.9 g (67%) product boiling at 100–110°C/1 Torr. The analytical sample boiled at 101°C/1 Torr. $^1\text{H-NMR}$ spectrum (CDCl_3): δ 7.04 (d, $J = 8.0$ Hz, 1 H, 5-H), 6.66 (d, $J = 8.0$ Hz, 1 H, 6-H), 6.60 (s, 1 H, 2-H), 3.78 (s, 3 H, OCH_3), 3.60 (s, 2 H, ArCH_2CO), 2.15 (s, 3 H, ArCH_3), 2.11 (s, 3 H, COCH_3). For $\text{C}_{11}\text{H}_{14}\text{O}_2$ (178.2) calculated: 74.13% C, 7.92% H; found: 74.31% C, 8.18% H.

1-(3-Methoxy-4-methylphenyl)-2-propylamine (*XIII*)

A mixture of 18.2 g *XI*, 140 g formamide and 14 g formic acid was refluxed for 12 h in a 190 to 200°C bath. After partial cooling, it was diluted with 250 ml water and the product was isolated by extraction with chloroform. Processing of the extract yielded 15.5 g (75%) oily N-[1-(3-methoxy-4-methylphenyl)-2-propyl]formamide (*XII*) which was processed further without characterization.

A mixture of 15.5 g *XII*, 30 ml ethanol and 28 g KOH was refluxed for 3 h in a 135–140°C bath. After cooling, it was diluted with 100 ml water and the product was isolated by extraction with ether. The extract was dried with K_2CO_3 and evaporated. Base *XIII* was obtained in a theoretical yield (13.4 g) as a viscous oil. After dissolving in ethanol, it was neutralized with an ether solution of hydrogen chloride. A total of 10.5 g (65%) hydrochloride was obtained, melting at 181.5–183.5°C. Analytical sample, m.p. 182.5–183.5°C (ethanol–ether); crystal modification takes place at 166–169°C. IR spectrum: 809, 860 (2 adjacent and solitary Ar—H), 1041, 1262 (ArOCH_3), 1515, 1582, 1600 (Ar), 1617 (NH_2), 2505, 2595, 2645, 2730 cm^{-1} (NH^+). $^1\text{H-NMR}$ spectrum: δ 8.30 (bs, NH_2), 7.00 (d, $J = 8.0$ Hz, 1 H, 5-H), 6.75 (s, 1 H, 2-H), 6.61 (d, $J = 8.0$ Hz, 1 H, 6-H), 3.70 (s, 3 H, OCH_3), 3.30 (bs, 1 H, CH—N), 2.60–3.10 (m, 2 H, ArCH_2), 2.05 (s, 3 H, ArCH_3), 1.10 (d, $J = 6.0$ Hz, 3 H, C— CH_3). For $\text{C}_{11}\text{H}_{18}\text{ClNO}$ (215.7) calculated: 61.24% C, 8.41% H, 16.44% Cl, 6.49% N; found: 61.04% C, 8.54% H, 16.31% Cl, 6.49% N. Ref.^{1,2} describe the preparation of the compound in a different way without characterizing it.

1-(3-Hydroxy-4-methylphenyl)-2-propylamine (*I*)

A mixture of 10.5 g *XIII-HCl* and 60 ml 48% hydrobromic acid was refluxed for 5 h, the solution formed was evaporated *in vacuo*, the residue was made alkaline with NH_4OH and the product was isolated by extraction with chloroform; 7.6 g (94%), m.p. 134–138°C. Analytical sample, m.p. 137.5–138.5°C (light petroleum). UV spectrum: λ_{max} 277 nm ($\log \epsilon$ 3.40). IR spectrum: 810, 859 (2 adjacent and solitary Ar—H), 1261 (ArOH), 1531, 1595 (Ar), 1622 (NH_2), 2620, 2710, 2740 (NH^+ , internal salt), 3040, 3080 (Ar), 3290, 3355 cm^{-1} (NH_2). $^1\text{H-NMR}$ spectrum: δ 6.85 (d, $J = 8.0$ Hz, 1 H, 5-H), 6.50 (bs, 1 H, 2-H), 6.40 (d, $J = 8.0$ Hz, 1 H, 6-H), 4.00 (bs, NH_2), 2.90 (m, 1 H, CH—N), 2.40 (d, $J = 7.0$ Hz, 2 H, ArCH_2), 2.00 (s, 3 H, ArCH_3), 0.90

(d, $J = 6.0$ Hz, 3 H, $\text{C}-\text{CH}_3$). Ref.^{1,2} report a m.p. of 134°C for a base prepared similarly and characterize it as a hydrochloride (m.p. 184°C).

Hydrogen maleate, m.p. $134.5-135.5^\circ\text{C}$ (ethanol-ether). For $\text{C}_{14}\text{H}_{19}\text{NO}_5$ (281.3) calculated: 59.77% C, 6.80% H, 4.98% N; found: 59.75% C, 6.92% H, 4.86% N.

The authors are indebted to Drs B. Kakáč, J. Holubek and E. Svátek (physico-chemical department of this institute) for measuring and interpretation of the spectra shown, to Mrs M. Vlková for technical cooperation with the preparative part of the work and finally to Mrs J. Komancová and Mrs V. Šmídová (analytical department of this institute) for carrying out the analyses.

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Translated by A. Kotyk.