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AN INTERESTING SYNTHESIS OF 3-METHOXY-2,6-DIMETHYLPHENETHYL ALCOHOL*

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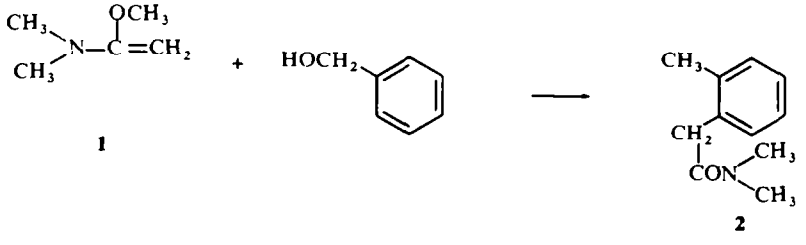
Abstract—A simple procedure for the conversion of *m*-methoxyphenethyl alcohol into 3-methoxy-2,6-dimethylphenethyl alcohol by internal methylation is described.

IN CONNECTION with other synthetic interests we required 3-methoxy-2,6- dimethylphenethyl alcohol **13** as starting material. This substance has been prepared previously by Mandell, Caine and Kilpatrick[1] in approximately 7% overall yield by an 11-step sequence commencing with 2,6-dimethylaniline. In view of the considerable latitude for improvement presented by this procedure, we were prompted to undertake a search for a more satisfactory synthesis of the compound in question.

The structural simplicity of **13** is deceptive, and several obvious approaches to the problem failed, presumably owing to steric hindrance. Thus, for example, Michael addition of malonic ester or of cyanoacetic ester to 2,4-dimethyl-2-cyclohexenone[2] under a wide variety of conditions resulted only in recovery of unaltered starting material.

Eschenmoser and his associates[3] have recently reported details of a procedure in which benzyl alcohol is converted in good yield into N,N-dimethyl-2-methylphenylacetamide **2** by the action of 1-dimethylamino-1-methoxyethylene **1** in DMF.



1 **2**

The reaction is applicable to a wide variety of allylic and benzylic alcohols, but it was noted that complex mixtures resulted in the case of *p*-methoxybenzyl alcohol. Our experience with 2-hydroxymethyl-5-methylanisole **3** was likewise discouraging.[4] Reaction of this substance with 1-dimethylamino-1-ethoxyethylene[5] gave N,N-dimethyl-(2-methoxy-5-methylphenyl)-propionamide **6a** as the major isolable product and in extremely poor yield.

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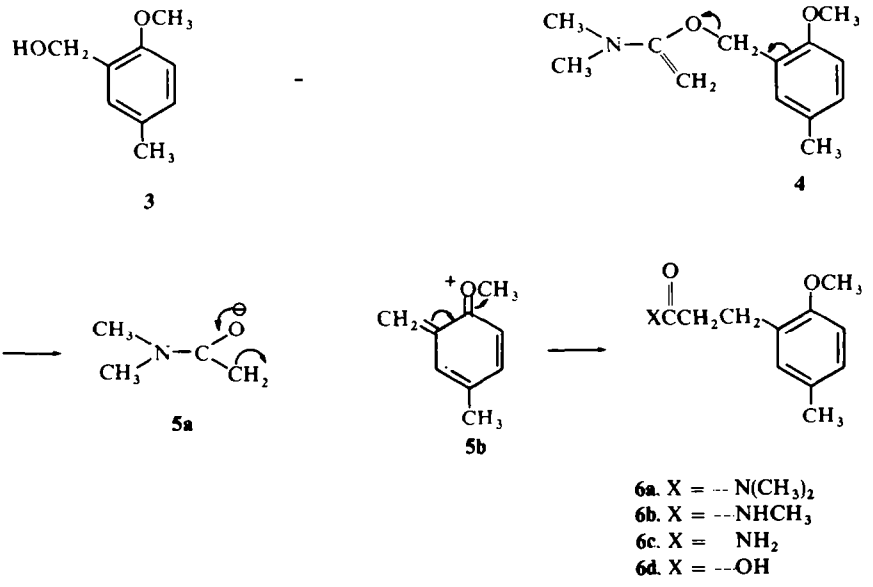


The effect of an *ortho* (or *para*) methoxyl group on the course of this reaction is satisfactorily accounted for by dissociation of intermediate **4** into an ion pair (**5a–5b**) followed by internal return as indicated. or by external attack of either the leaving group **5a** or of dimethylaminoethoxyethylene on positively charged species **5b**.

The structure assigned to **6a** was established by conversion of this substance into the known methylamide **6b** and amide **6c**.[6]

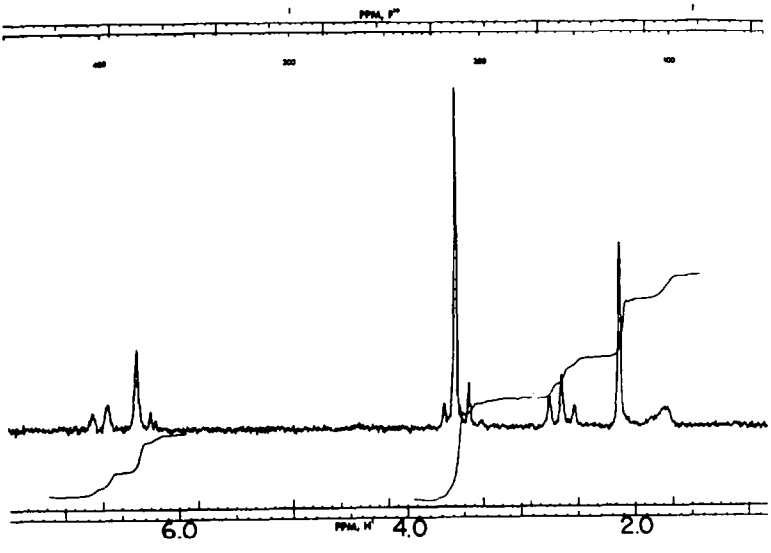
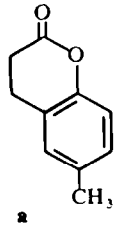


FIG 1. NMR spectrum of 3-methoxy-6-methylphenethyl alcohol **11**

The melting point of 157–158° reported by these authors[6] for **6b** is in error. An authentic sample obtained by reaction of dihydrocoumarin **a** with methyl amine

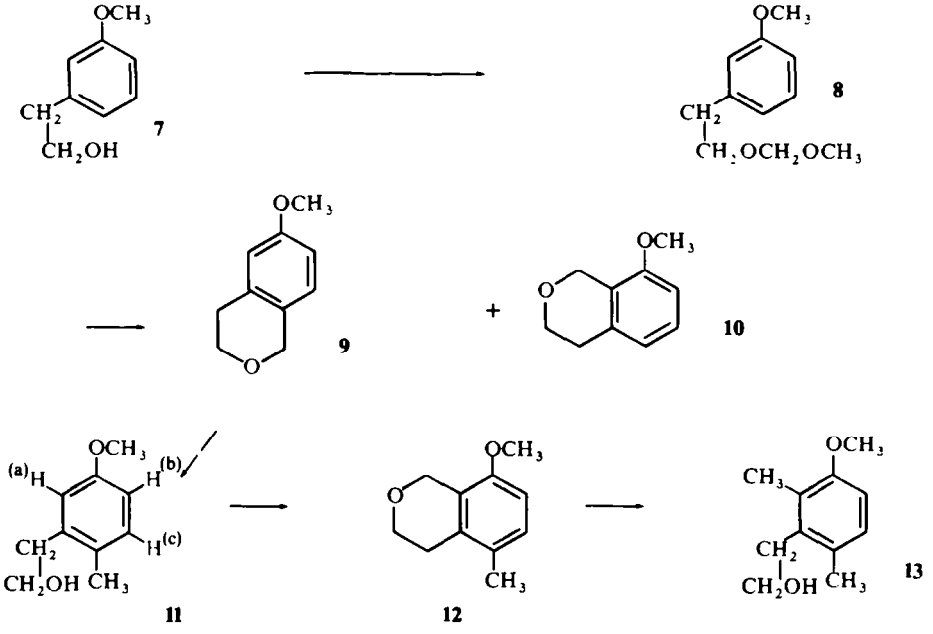


a

followed by methylation of the resulting phenol with dimethylsulfate melts at 83–84° and is identical in all respects with **6b** obtained as described above.

The procedure which was ultimately developed for synthesis of **13** employs 3-methoxyphenethyl alcohol **7**[7] as starting material and involves introduction of the required Me substituents by an internal methylation procedure which circumvents the steric difficulties encountered in other more routine approaches.

3-Methoxyphenethyl alcohol **7** is readily obtainable by LAH reduction of *m*-methoxyphenylacetic acid methyl ester. On consecutive treatment with NaH and chloromethyl methyl ether it yields the mixed acetal **8**. The latter substance was not



normally isolated but was cyclized directly with *p*-toluenesulfonic acid in C_6H_6 to a mixture of isochromans **9** and **10**[8] including also some starting alcohol **7**. Alcohol **7** was readily removed by filtration of the mixture through silica gel. The isomeric products **9** and **10** could be separated by silica gel chromatography, but since **10** was present in the isochroman fraction to the extent of only about 3% its separation was

unnecessary for preparative scale work. The overall yield of **9** from **7** was 70% based upon one pass, or 95% based upon a 74% conversion of **7**.

Catalytic hydrogenolysis of compound **9** proved to be extremely slow.[9] but cleavage to 3-methoxy-6-methylphenethyl alcohol **11** was smoothly accomplished in 96% yield by the use of LAH and $AlCl_3$.[10]

The structures which are assigned to compounds **9** and **11** were established by examination of the aromatic region of the 60 MHz NMR spectrum* of compound **11** in the presence and absence of tris(dipivalomethanato)europium.[11]

Although only limited information could be obtained from the unperturbed spectrum (Fig 1), addition of the "shift" reagent permitted unambiguous assignment of lines to the three aromatic protons of **11** (Fig 2). Thus H_a appears as a doublet

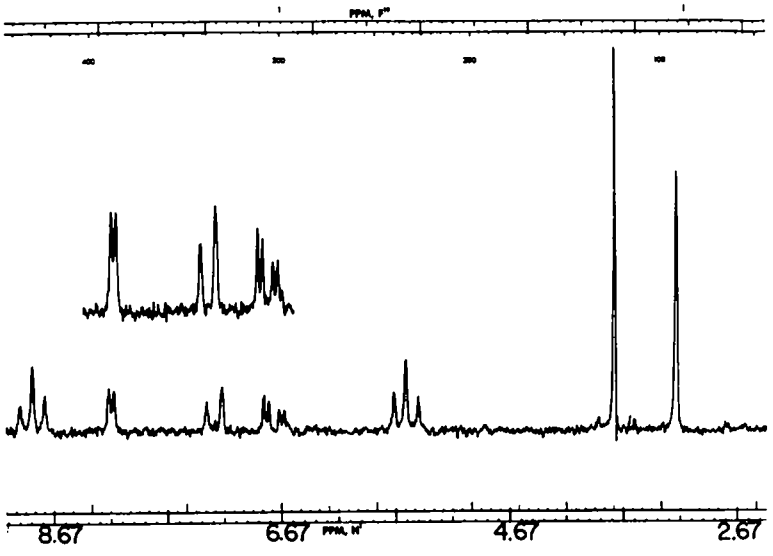


FIG 2. NMR spectrum of 3-methoxy-6-methylphenethyl alcohol **11** with added tris(dipivalomethanato)europium offset 100 Hz

(J = 2·5 Hz, *meta* coupling) centered at about 8·1 δ, H_c as a doublet (J = 8·0 Hz, *ortho* coupling) at 7·3 δ, and H_b as a doublet (J = 8·0 Hz) of doublets (J = 2·5 Hz) at 6·7 and 6·8 δ. The remaining features of the spectrum are entirely consistent with the assigned structure.

Repetition of the NaH-chloromethyl methyl ether-*p*-toluene-sulfonic acid sequence with **11** afforded isochroman **12** in 83% yield (97% based upon recovered starting material). Reductive cleavage of this material with LAH–$AlCl_3$ gave somewhat erratic results, and the final step in the synthesis was therefore carried out with Li in liquid NH_3. The desired product **13** was thereby obtained in 67% yield.

Crystallization of **13** from hexane afforded rhombohedral plates melting at 58–60° (lit.[1] 58–59°). Further recrystallization, however, gave needles, m.p. 68–68·5°. Since

* We are indebted to the National Science Foundation for funds which assisted in the purchase of this instrument.

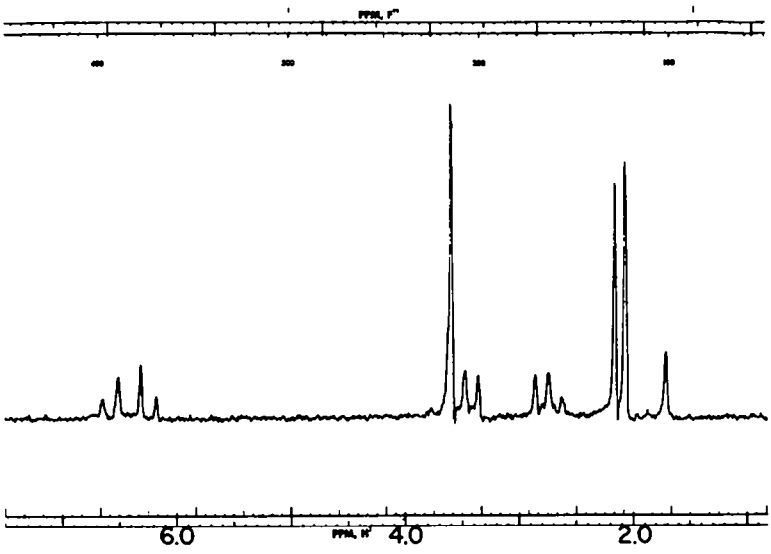


FIG 3. NMR spectrum of 3-methoxy-2,6-dimethylphenethyl alcohol **13**

the solution IR spectra of the two samples were identical, we assume that the substance is dimorphic. NMR spectra with and without tris(dipivalomethanato)europium are shown in Figs 3 and 4. Oxidation of **13** with the Jones reagent[12] furnished the known 3-methoxy-2,6-dimethylphenylacetic acid, m.p. 126–128° (lit.[1] 123–125°).

Synthesis of 3-methoxy-2,6-dimethylphenethyl alcohol **13** can thus be accomplished from *m*-methoxyphenethyl alcohol in four operations with an ultimate yield exceeding 50%.

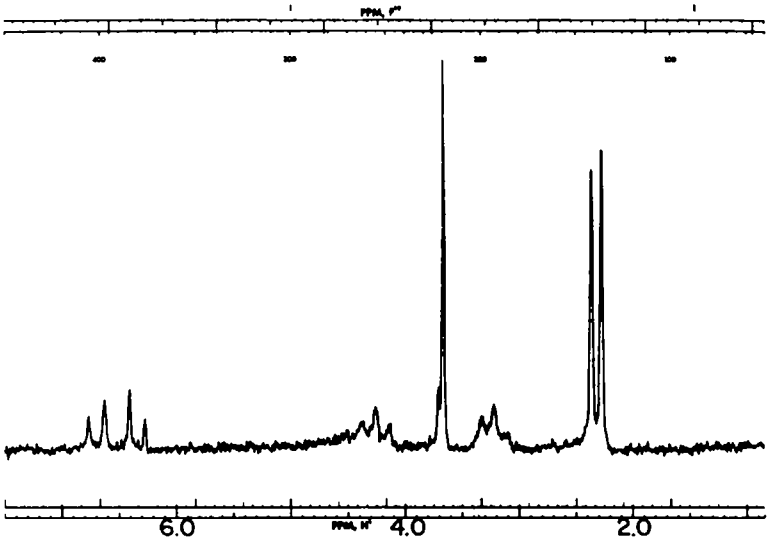


FIG 4. NMR spectrum of 3-methoxy-2,6-dimethylphenethyl alcohol **13** with sufficient added tris(dipivalomethanato)europium to resolve the 4·0 δ region

EXPERIMENTAL

Preparation of N,N-dimethyl-3-(2-methoxy-5-methylphenyl)-propionamide 6a. A solution of 1-dimethylamino-1-ethoxyethylene[5] (1·71 g) and 2-hydroxymethyl-5-methylanisole (1·30 g) **3** in 10 ml of anhydrous DMF was heated under reflux in a N_2 atmosphere for 20 hr. After this time the mixture was cooled, diluted with ether, and washed successively with an AcOH–NaOAc buffer (pH 5) and with saturated NaCl aq. The organic layer was dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The dark residue was chromatographed on silica gel and afforded oil (388 mg) which was distilled in a Hickman tube; 290 mg, 120–130°/0·1 mm 120–130.

Prep. TLC of this material on silica gel furnished **6a** as an oil (160 mg). *m/e* 221. $\lambda_{max}^{CS_2}$ 6·06 μ.

Hydrolysis of **6a** was accomplished by heating a sample overnight in aqueous dioxane solution containing NaOH. The resulting oily acid was converted via the acid chloride into N-methyl-3-(2-methoxy-5-methylphenyl)-propionamide **6b**, m.p. 84·5–85°, and into the corresponding unsubstituted amide, m.p. 165–165·5° (lit.[6] 158–159°). The IR and NMR spectra of the former substance (**6b**) were identical with those of an authentic specimen prepared as described below. A m.m.p. of the two samples was undepressed.

Preparation of N-methyl-3-(2-methoxy-5-methylphenyl)-propionamide 6b *from 3,4-dihydro-6-methylcoumarin.* A solution of 3,4-dihydro-6-methylcoumarin[13] (65 mg) in THF (1 ml) and 40% aqueous methylamine (0·5 ml) was treated with a catalytic amount of *p*-toluenesulfonic acid and stirred overnight at room temperature. The solvents were removed under reduced pressure and the residue taken up in ether. The ethereal solution was washed with dilute HCl, H_2O, and saturated NaCl aq. After drying over anhydrous Na_2SO_4, the ether was evaporated, and the residue crystallized from ether–petroleum ether; m.p. 154–155°.

This phenolic product was dissolved in 1N NaOH (0·6 ml), and H_2O (2 ml) was added followed by 0·15 g of dimethyl sulfate. The mixture was stirred at room temperature for 20 min and heated on a steam bath for 10 min. The product was isolated by extraction with hexane. Recrystallization from hexane afforded a pure sample, m.p. 83–84°. $\nu_{max}^{CS_2}$ 1655 cm^{-1}. (Calcd. for $C_{12}H_{17}NO_2$; C, 69·56; H, 8·27. Found: C, 69·48; H, 8·28%).

Preparation of 6-methoxyisochroman 9. Sodium hydride (3·70 g, 0·154 mol) was placed in a 500 ml, 3-neck flask (nitrogen atmosphere) and covered with anhydrous THF. A solution of 23·0 g (0·152 mol) of *m*-methoxyphenethyl alcohol **7**, obtained by LAH reduction of *m*-methoxyphenylacetic acid methyl ester,[14] in dry THF (350 ml) was then added slowly with stirring. After H_2 evolution ceased, chloromethyl methyl ether (14 g) was added and stirring was continued at room temperature for 2 hr. The reaction was completed by heating under reflux for 30 min.

The solvent was removed under reduced pressure, and the residue taken up in ether and H_2O. The H_2O layer was extracted several times with ether, and the combined ether fractions finally back-washed with saturated NaCl aq and evaporated. The crude product was dissolved in dry C_6H_6 containing a catalytic amount of anhydrous *p*-toluenesulfonic acid and was heated under reflux for 12 hr. Routine processing of the reaction mixture followed by filtration of the material through silica gel furnished starting alcohol (6·50 g) **7** and isochroman **9** (17·8 g) of sufficient purity for further transformation.

Careful silica gel chromatography of the product of a separate run yielded, in addition to recovered starting material, two isochromans in a ratio of 32·8 to 1. The major product **9**, 65–67°/0·15 mm, showed IR absorption (CS_2) at 2990, 2840, 2820, 1270, 1245, 1240, 1100, 1040, 990, 808, 795, and 750 cm^{-1}. The NMR spectrum (CCl_4 solution) exhibited a 3 H multiplet at 6·90–6·45 δ, a 2 H singlet (broad) at 4·55 δ, a triplet at 3·83 δ and a singlet at 3·70 δ consisting together of 5 protons, and a 2 H triplet at 2·72 δ. (Calcd. for $C_{10}H_{12}O_2$: C, 73·15; H, 7·37. Found: C, 73·44; H, 7·61%). The minor product **10** showed IR absorption (CS_2) at 2990, 2840, 2820, 1250, 1110, 1100, 1050, 970, 750, and 740 cm^{-1}. The NMR spectrum of the substance (CCl_4 solution) showed a 3 H multiplet at 7·14–6·38 δ, a 2 H singlet at 4·60 δ, a 5 H composite triplet (3·75 δ) and singlet (3·69 δ), and a 2 H triplet at 2·69 δ. The mass spectrum revealed a parent ion peak at *m/e* 164.[11]

Preparation of 3-methoxy-6-methylphenethyl alcohol 11. LAH (790 mg) was placed in a 3-neck flask equipped with a mechanical stirrer, reflux condenser, and addition funnel. Anhydrous ether (100 ml) was added, and the mixture was cooled to 0°. Anhydrous $AlCl_3$ (3·51 g) was then introduced in portions, and stirring was continued in the cold for 20 min. A solution of 4·02 g of isochroman **9** in dry ether (50 ml) was finally added, and the resulting mixture then heated under reflux for 24 hr. After this time the reaction mixture was cooled to room temperature, and a saturated solution of NaK tartarate added. After stirring for 30 min, the organic layer was separated, and the aqueous phase extracted with ether. The combined ether fractions were dried over Na_2SO_4, and the solvent removed.

The residue was taken up in C_6H_6, filtered through a column of silica gel, and the product finally isolated by distillation; yield, 3·91 g (96%), 93–94°/0·3 mm. $\nu_{max}^{CS_2}$ 3610, 3590, 1250, 1045, 1030, 810, 797 cm^{-1}. NMR data are shown in Figs 1 and 2. (Calcd. for $C_{10}H_{14}O_2$: C, 72·26; H, 8·49. Found: C, 71·88; H, 8·55%).

Preparation of 8-*methoxy*-5-*methylisochroman* 12. NaH (735 mg of a 50% dispersion in mineral oil) was treated with a solution of compound **11** (2·21 g) in dry THF under N_2 atmosphere. The mixture was stirred at room temperature, and when evolution of hydrogen had ceased, chloromethyl methyl ether (2·18 g) was added. Stirring was continued for 1 hr, and the reaction mixture then heated to reflux for 30 min. The resulting mixed acetal was isolated by water dilution and ether extraction, and was heated for 24 hr in refluxing C_6H_6 containing anhydrous *p*-TsOH (242 mg).

The C_6H_6 solution was washed with diluted base, dried, and filtered through a column of silica gel, to give starting alcohol **11** (310 mg), and isochroman **12** (1·98 g), m.p. 55–57° (needles from hexane). $\nu_{max}^{CS_2}$ 2980, 2850, 1255, 1245, 1220, 1120, 1105, 1065, 980, 985, 800, and 720 cm^{-1}. The NMR spectrum showed an AB quartet centered at 6·67 δ (2 H), a broad singlet at 4·50 δ (2 H), an overlapping triplet and singlet at 3·90–3·55 δ (5 H), a triplet at 2·45 δ (2 H), and a singlet at 2·03 δ (3 H). The parent ion peak appeared in the mass spectrum at *m/e* 178.

Preparation of 3-*methoxy*-2,6-*dimethylphenethyl alcohol* 13. A 1·30 g sample of 8-methoxy-5-methylisochroman **12** in dry dimethoxyethane (20 ml) and 40 ml of liquid NH_3 was treated with 215 mg of Li added in small pieces at −33°. After stirring in the cold for 2 hr, 95% EtOH was added, and the NH_3 allowed to evaporate. The mixture was diluted with H_2O and ether extracted. The combined organic layers were dried over Na_2SO_4 and evaporated. Chromatography of the crude material in silica gel afforded 880 mg (67%), m.p. 58–60° (plates from hexane). Further recrystallization from hexane yielded needles m.p. 68·68·5°. The IR spectra (CS_2) of the plates and needles were identical: $\nu_{max}^{CS_2}$ 3605, 3595, 2930, 1240, 1090, 1030, 1010, and 780 cm^{-1}. The parent peak in the mass spectrum appeared at *m/e* 180. NMR data are shown in Figs 3 and 4. (Calcd. for $C_{11}H_{16}O_2$: C, 73·30; H, 8·95. Found: C, 73·20; H, 8·96%). Oxidation of a sample with the Jones reagent[12] afforded 3-methoxy-2,6-dimethylphenylacetic acid, m.p. 126–128 (lit.[2] 123–125°).

REFERENCES

1 L. Mandell, D. Caine and G. E. Kilpatrick, *J. Am. Chem. Soc.* **83**, 4457 (1961)
2 G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *Ibid.* **85**, 207 (1963)
3 D. Felix, K. Gschwend-Steen, A. E. Wick and A. Eschenmoser, *Helv. Chim. Acta* **52**, 1030 (1969)
4 M. Quelet, J. Allard, J. Ducasse and Y. Germain, *Bull. Soc. Chim.* **4**, 1092 (1937)
5 H. Bredereck, F. Effenberger and H. P. Beyerlin, *Ber. Dtsch. Chem. Ges.* **97**, 3081 (1964)
6 B. M. Shieman, A. H. Kost, L. Ya. Denisova and V. E. Zhvirblis, *Vestn. Mosk. U. Khim.* Ser. II, **20**, 42 (1965)
7 S. Natelson and S. P. Gottfried, *J. Am. Chem. Soc.* **61**, 1001 (1939)
8 R. Leipins, *Diss. Abs.* **21**, 461 (1960)
9 P. Maitte, *Ann. Chim. Paris* **9**, 431 (1954)
10 B. R. Brown and G. A. Somerfield, *Proc. Chem. Soc.* 7 (1958)
11 J. K. M. Sanders and D. H. Williams, *Chem. Comm.* 422 (1970); C. C. Hinckley, *J. Am. Chem. Soc.* **91**, 5160 (1969)
12 K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946)
13 A. H. Kost and B. N. Shieman, *Vestn. Mosk. U. Khim.* Ser. II, **15**, 65 (1960)
14 J. F. Collins and H. Smith, *J. Chem. Soc.* 4308 (1956)