Anal. Calcd for $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.5; H, 6.6.

Registry No.—**3**, 13395-89-6; **4**, 13395-90-9; **5**, 13395-91-0; **6**, 13395-92-1; **7**, 13428-04-1; **8**, 13428-05-2; **9**, 13395-93-2; **9**-d_1, 13395-94-3; **10**, 13395-95-4; **11**, 13391-20-3; **12**, 13396-00-4; 5,5a,6,11,11a,12-hexahydro-6,11-epoxy-5,12-dimethyl-5,12-*o*-benzenonaphthacene, 13395-96-5; 6-bromomethyl-5,12-dimethyl-5,12-*o*-benzeno-5,12-dihydronaphthacene, 13395-97-6; 2,5-dimethyltriptycene, 13395-98-7.

Acknowledgment.—We wish to thank Mr. R. L. Young for assistance in running nmr spectra, Dr. D. P. Maier and Mr. G. P. Happ for the mass spectrometric data, and Mrs. J. C. Dignan for synthesizing several compounds.

The Lithium-Ammonia Reduction of Benzofurans

STEPHEN D. DARLING AND KLAUS D. WILLS[1]

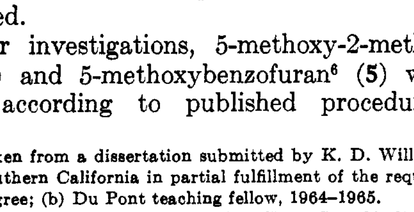
Department of Chemistry, University of Southern California, Los Angeles, California 90007

Received November 7, 1966

The reduction of 5-methoxy-2-methylbenzofuran (**4**), 5-methoxybenzofuran (**5**), 2,3-dihydro-5-methoxy-2-methylbenzofuran (**6**), and 2,3-dihydro-5-methoxybenzofuran (**7**) with lithium-liquid ammonia systems is described. Furan ring opening was observed in the reduction of **4** or **5** when a limited amount of alcohol was present in the ammonia solution. With excess alcohol, the corresponding 5-methoxy-2,3,4,7-tetrahydrobenzofuran was formed from each substrate. A side product from the reduction of **6** was 2,3,4,5,6,7-hexahydro-2-methylbenzofuran (**3**).

Metal-ammonia reductions of benzenoid systems often provide a key to unlock functional groups which have lain dormant during crucial stages of a synthetic study. In the course of our investigations into the synthesis of natural products, we sought to obtain a derivative of cyclohexane-1,4-dione which could be acted upon selectively. We believed this could be accomplished through tetrahydrobenzofuran derivatives. An obvious route to these compounds would be the metal-ammonia reduction of a benzofuran or of 2,3-dihydrobenzofuran.

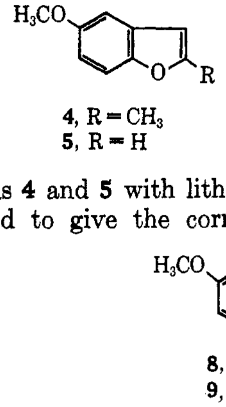
Treatment of 2-substituted benzofuran and 2,3-dihydro-2-methylbenzofuran (**1**) with sodium in liquid ammonia had been shown by Hurd to give products of furan ring cleavage.[2] More recently, Brust and Tarbell reported the reduction of **1** with lithium-ammonia and alcohol in which 2-methyl-2,3,4,7-tetrahydrofuran (**2**) and 2,3,4,5,6,7-hexahydro-2-methylbenzofuran (**3**) were formed.[3] While the latter conditions were undoubtedly vigorous enough to cause some isomerization of **2**, base cleavage[2] or electron cleavage[4] of the dihydrobenzofuran was averted.



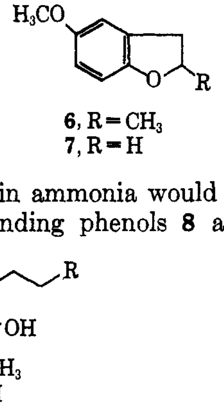
1

2 **3**

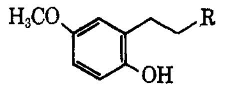
For our investigations, 5-methoxy-2-methylbenzofuran[5] (**4**) and 5-methoxybenzofuran[6] (**5**) were synthesized according to published procedures. The general method of acid-catalyzed ring closure of 2-allylphenols was used to prepare 2,3-dihydro-5-methoxy-2-methylbenzofuran (**6**).[7] Hydrogenation of **5** over 10% palladium on charcoal provided 2,3-dihydro-5-methoxybenzofuran (**7**). Reduction of the benzofurans **4** and **5** with lithium in ammonia would be expected to give the corresponding phenols **8** and **9**.[2]



4, R = CH_3
5, R = H



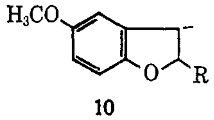
6, R = CH_3
7, R = H



8, R = CH_3
9, R = H

Thus the reduction of **5** with 2 equiv of lithium gave nearly equal amounts of **9** and **5**. The reaction appears to be much faster than previously[2] indicated, however.

Benzofuran cleavage may occur as a direct result of electron addition to give carbanion **10** and not as a subsequent amide-promoted β elimination. This may occur even though the benzyl carbanion is known to be protonated by ammonia.[2,8] β elimination of acetate ion has been reported during the lithium-ammonia reduction of an octalone[9] even though the tertiary carbanion formed in similar reductions has been shown to



10

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[1] (a) Taken from a dissertation submitted by K. D. Wills to the University of Southern California in partial fulfillment of the requirements for the Ph.D. degree; (b) Du Pont teaching fellow, 1964-1965.

[2] C. D. Hurd and G. L. Oliver, *J. Am. Chem. Soc.*, **81**, 2795 (1959).

[3] D. P. Brust and D. S. Tarbell, *J. Org. Chem.*, **31**, 1251 (1966).

[4] A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).

[5] E. Bernatek, *Acta Chem. Scand.*, **7**, 677 (1953); A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *Zh. Obshch. Khim.*, **27**, 1087 (1957) (see *Chem. Abstr.*, **52**, 3761 (1958)).

[6] S. Tanaka, *J. Am. Chem. Soc.*, **73**, 872 (1951).

[7] D. S. Tarbell, *Org. Reactions*, **2**, 1 (1944).

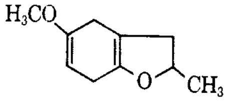
[8] C. B. Wooster and N. W. Mitchell, *J. Am. Chem. Soc.*, **52**, 688 (1930).

[9] T. A. Spencer, K. K. Schmiegel, and W. W. Schmiegel, *J. Org. Chem.*, **30**, 1626 (1965).

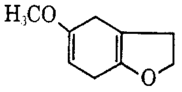
protonate rapidly in ammonia solution.[10] Although the tertiary carbanion exists only briefly, the benzyl carbanion exists long enough to be alkylated.[8] Thus the proportion of product resulting from the protonation of carbanion **10** should be greatly increased by using a protonating agent more acidic than ammonia.

From the reduction of **4** with 2 equiv each of *t*-butyl alcohol and lithium, a quantitative recovery of material was obtained. An analysis of the product nmr spectrum indicated the presence of 63% of **6**, 21% of starting material, and the remainder as phenol **8**. With an excess of the metal over the alcohol, the cleavage again takes precedence. As the usual metal–ammonia reductions employ a large excess of an alcohol, it seemed plausible that benzofurans could be reduced directly to tetrahydrobenzofurans.

When the benzofurans **4** and **5** and the 2,3-dihydrobenzofurans **6** and **7** were reduced with lithium in a solution of ammonia containing approximately 15% of absolute ethanol, the major product was the corresponding 5-methoxy-2,3,4,7-tetrahydrobenzofuran. Thus compounds **4** and **6** gave 5-methoxy-2-methyl-2,3,4,7-tetrahydrobenzofuran (**11**) in 70 and 80% yields. The structure was readily confirmed from the nmr spectrum. It showed a methyl doublet at 1.30 ppm, the absorption of the C_4 and C_7 protons as a broad singlet at 2.69 ppm, and the absorption of the C_2 proton overlapping with the C_6-vinyl proton at 4.6 ppm.[11] The remaining protons were also accounted for at their respective positions and with the intensities expected. Reduction of benzofuran derivatives **5** and **7** produced 88[12] and 98% yields of 5-methoxy-2,3,4,7-tetrahydrobenzofuran (**12**).



11



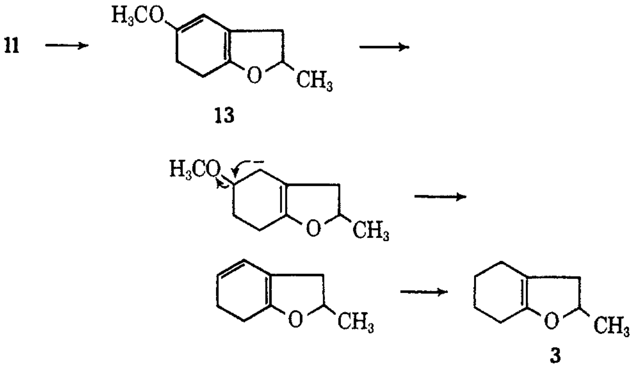
12

The presence of phenolic product from the benzofuran reductions, but the absence of such product from the reduction of the dihydrobenzofurans, was observed with interest. It is probable that the phenol represents the extent of the competing elimination under these conditions.

Although the products were quite pure, the reduction of **6** produced 3% of 2,3,4,5,6,7-hexahydro-2-methylbenzofuran (**3**). The elimination of methoxide ion has been observed during more vigorous metal–ammonia reductions.[13]

Two pathways to **3** from **6** may be envisioned, 1,2 reduction or conjugation followed by reduction. Although the 1,2 reduction of olefins is known,[14] such a reduction with concomitant β elimination of methoxide ion would form **2**. In the work of Brust and Tarbell,[5] **2** was shown to be only partially converted to **3**. In our work, **2** was not detected.

It has been demonstrated that 2,5-dihydrocumene can be isomerized slowly in a solution of ethanol, methyl amine, and lithium.[15] Conjugation of **11** to its isomer **13** would provide a facile route for elimination of methoxide ion. Since cyclic conjugated dienes which are unsymmetrically substituted tend to undergo 1,2 reduction,[16] further reduction of the least substituted double bond would lead to the product isolated, 2,3,4,5,6,7-hexahydro-2-methylbenzofuran (**3**). This mechanism would also predict a homogeneous product, rather than the mixture which might be obtained if additional equilibration were necessary.[17]



In summary, the metal–ammonia reduction of a benzofuran occurs rapidly in a stepwise manner. The cleavage reaction which had previously been observed[2] can be avoided by the use of excess alcohol in the reduction solution. Since the benzofurans described here are readily available, this reduction constitutes a convenient route to the corresponding 2,3,4,7-tetrahydrobenzofurans. The selective hydrolysis of these compounds is the subject of further study.

Experimental Section

Melting points and boiling points are uncorrected. The product solutions were dried over anhydrous sodium sulfate. Infrared spectra were determined neat on sodium chloride plates with a Perkin Elmer Model 337 spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer in carbon tetrachloride solution and chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. The signals are expressed as *x* s (singlet), *x* d (doublet), *x* t (triplet), *x* q (quartet), or *x* m (multiplet), where *x* refers to the number of protons indicated by integration. Microanalyses were performed by Elek Microanalytical Laboratories, Torrance, Calif. 90505.

2-Allyl-4-methoxyphenol.—Allyl 4-methoxyphenyl ether was prepared by a modification of the method of Goering and Jacobson.[18] A mixture of 500 g (4.03 moles) of 4-methoxyphenol, 340 ml (4.40 moles) of allyl chloride, 565 g (4.1 moles) of anhydrous potassium carbonate, 50 g of potassium iodide, and 1.2 l. of anhydrous acetone was refluxed overnight with continuous stirring.

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[10] (a) G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965); (b) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, **85**, 2091 (1963).

[11] A large chemical shift is characteristic for dihydrofuran protons: L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 88.

[12] When sodium was substituted for lithium in the reduction of **5**, an 88% yield of **12** was obtained.

[13] A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953).

[14] R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *ibid.*, **77**, 3230 (1955).

[15] R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963).

[16] H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., New York, N. Y., 1963, p 224.

[17] A similar overreduction product from **5** was not observed. This is no doubt due to the high yield of **12** and the relatively small reaction scale.

[18] H. L. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, **80**, 3277 (1958).

The yield of product was 520 g (93.7%), bp 134–135° (23 mm) (lit.[19] bp 119–120° (13 mm)). The nmr spectrum showed peaks at 3.60 (3 s, -OCH$_3$), 4.35 (2 m, -OCH$_2$-), 5.3 (2 m, C=CH$_2$), 5.65–6.3 (1 m, -CH=), and 6.68 ppm (4 s, aromatic *para*-substituted ring protons).

The allyl ether was rearranged by refluxing it for 2 hr in an equal weight of N,N-dimethylaniline.[19] The yield of product was 80%, bp 105–107° (0.3 mm) (lit.[19] bp 144–145° (13 mm)). The nmr spectrum showed peaks at 3.28 (2 m, Ar-CH$_2$-) and 6.0 ppm (1 s, Ar-OH) consistent with the expected product.

5-Methoxy-2-methylbenzofuran (4) was prepared according to published procedures.[5] The yield based on 2-allyl-4-methoxyphenol was 48.6%, bp 130–140° (24 mm) (lit.[5] bp 118–120° (10 mm)). The nmr spectrum showed peaks at 2.28 (3 d, J = 1.0 cps, -CH$_3$), 3.63 (3 s, -OCH$_3$), 6.10 (1 q, J = 1 cps, furan proton), and 6.8 ppm (3 m, aromatic protons).

5-Methoxybenzofuran (5) was prepared following the procedure of Tanaka.[6] After distillation of the product, bp 119–120° (25 mm) (lit.[6] bp 120–125° (30 mm)), it solidified, mp 33–34.5°. The identity of the product was verified by its nmr spectrum which showed peaks at 3.68 (3 s, -OCH$_3$), 6.55 (1 q, J = 1.0 cps, 3 proton), 7.46 (1 d, J = 2.0 cps, 2 proton), and 6.6–7.4 ppm (3 m, aromatic protons).

2,3-Dihydro-5-methoxy-2-methylbenzofuran (6).—Cyclization of 2-allyl-4-methoxyphenol by a general procedure[7] gave this dihydrofuran. A solution of the phenol (100 g) in 200 ml of glacial acetic acid containing 2 ml of concentrated sulfuric acid was refluxed under nitrogen for 18 hr. The solvent was removed on a flash evaporator and 50 g of sodium hydroxide pellets added. The dark liquid was decanted and distilled rapidly to give 59 g (59%) of colorless liquid, bp 68–70° (0.3 mm).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.39. Found: C, 73.11; H, 7.17.

The nmr of the product showed absorptions at 1.34 (3 d, J = 6 cps, -CH$_3$), 2.4–3.4 (2 m, two overlapping quartets, the AB portion of an ABX system, Ar-CH$_2$-), 3.60 (3 s, -OCH$_3$), 4.75 (1 m, the X portion of the ABX system split also by three additional α protons), and 6.5 ppm (3 m, aromatic protons).

2,3-Dihydro-5-methoxybenzofuran (7).—A solution of 21.34 g of 5-methoxybenzofuran and 100 ml of absolute alcohol was added to 2.0 g of 10% palladium on charcoal. This mixture was put under 41 psi initial hydrogen pressure on a Paar shaker and agitated for 3 hr at room temperature. Hydrogen (1 mole equiv) was taken up. The catalyst was filtered and the ethanol removed under reduced pressure. Distillation of the residue gave 20.7 g (95.6% yield) of product, bp 63–64° (0.2 mm) (lit.[20] 134° (20 mm)). The nmr spectrum showed peaks at 3.08 (2 t, J = 9 cps, Ar-CH$_2$-), 3.67 (3 s, -OCH$_3$), 4.43 (2 t, J = 9 cps, -OCH$_2$-), and 6.6 ppm (3 m, aromatic protons).

Lithium–Ammonia Reduction of 5-Methoxybenzofuran (5) with 2 equiv of Lithium.—Liquid ammonia (200 ml) was distilled into the reaction flask from sodium. The system was placed under nitrogen and 0.92 g (0.0062 mole) of 5-methoxybenzofuran was added. To the stirred solution was added 0.043 g (0.0062 mole) of lithium. After the lithium had dissolved and the solution became colorless, 0.460 g (0.0062 mole) of *t*-butyl alcohol in 5 ml of anhydrous ether was added rapidly, followed immediately by another 0.043 g of lithium. The solution was worked up by the addition of water and extraction with three portions of ether. The combined ether extracts were washed once with saturated sodium chloride solution and dried over sodium sulfate. The ether extract yielded 0.48 g of the starting material, 5-methoxybenzofuran. Acidification of the aqueous layer with 10% aqueous hydrochloric acid followed by a similar work-up gave 0.40 g of a liquid having an infrared spectrum with strong absorption at 3400 cm^{-1} (-OH). The nmr spectrum showed peaks at 1.13 (3 t, J = 7.5 cps, -CH$_3$), 2.62 (2 q, J = 7.5 cps, -CH$_2$O), 3.63 (3 s, -OCH$_3$), and 6.6 ppm (4 m, -OH and aromatic protons). These spectra are identical with those of an authentic sample of 2-ethyl-4-methoxyphenol.

Lithium–Ammonia Reduction of 5-Methoxy-2-methylbenzofuran (4) with 2 Equiv Each of Lithium and *t*-Butyl Alcohol.—A 100-ml three-neck flask fitted with a Dry Ice condenser, pressure-equalized dropping funnel, ammonia inlet tube, and magnetic stirrer was flamed and placed under nitrogen. A piece of lithium weighing 0.15 g (0.022 mole) was introduced and 50 ml of sodium dried liquid ammonia distilled into the flask. The dropping funnel was charged with a mixture of 1.62 g (0.01 mole) 5-methoxy-2-methylbenzofuran (4) and 1.63 g (0.022 mole) of *t*-butyl alcohol. A few milliliters of anhydrous ether was used to wash in the mixture. The contents of the funnel were added dropwise over 2 min to the stirred solution. With the last drops from the funnel, the blue color of the solution disappeared. The organic solution which contained a precipitate was acidified with ammonium chloride. Water was added cautiously and the reaction mixture extracted twice with ether. The ether solutions were combined, washed with 5% sodium hydroxide solution, water, and dried. Removal of the solvent left a clear crude oil, 1.43 g. An nmr spectrum of the product indicated two major fractions which corresponded to about 75% **6** and 25% **4**. This was obtained by comparing either the methyl absorptions at 1.32 ppm (doublet) and 2.45 ppm (singlet) or the methoxyl absorptions at 3.58 and 3.82 ppm.

The combined basic washing and reaction solution was acidified with concentrated hydrochloric acid and extracted with two portions of ether. After washing the combined ether extracts with water and drying it, the solvent was removed to yield 0.3 g of phenol **8**. This was also identified from its nmr spectrum which was identical with that obtained from an authentic sample of the phenol produced by catalytic reduction of 2-allyl-4-methoxyphenol.[21] The spectrum of the phenol shows absorption centered at 0.90 (3 t, J = 7 cps, -CH$_3$), 1.6 (sextet, J = 7 cps, -CH$_2$-), 2.5 (2 t, J = 8 cps, Ar-CH$_2$-), 3.62 (3 s, -OCH$_3$), 6.14 (1 s, -OH), and 6.5 ppm (3 m, aromatic protons).

Lithium–Ammonia Reduction of 5-Methoxy-2-methylbenzofuran (4) with Excess Lithium.—A solution of 5.0 g (0.031 mole) of 5-methoxy-2-methylbenzofuran (4), 3.0 ml (0.06 mole) of absolute ethyl alcohol, and 250 ml of anhydrous liquid ammonia was treated with 1.5 g (0.2 mole) of lithium. After the blue color had persisted for 10 min, 10 g of ammonium chloride was slowly added. The ammonia was allowed to evaporate. Water was added to dissolve the solids and the solution extracted with three portions of ether. The combined ether extracts were washed once with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The 4.5 g (90%) of dark liquid remaining after the solvent was removed was distilled, bp 154–160° (23 mm) (lit.[16] bp 145° (15 mm)). A colorless liquid was obtained which had infrared and nmr spectra identical with those of 4-methoxy-2-propylphenol prepared previously.

Lithium–Ammonia Reduction of 5-Methoxy-2-methylbenzofuran (4) in the Presence of Excess Alcohol.—To a solution of 1.0 g (0.0062 mole) of 5-methoxy-2-methylbenzofuran, 50 ml of liquid ammonia, and 7 ml of absolute ethanol in a 125-ml erlenmeyer flask was added approximately 0.5 g ofl ithium in small pieces until the solution remained blue for 10 min. Ammonium chloride was added to destroy the lithium and water was added cautiously to the solution. The aqueous mixture was extracted three times with ether. After washing the combined extracts with water, the solution was dried and concentrated. The yield of crude light-colored oil was 0.79 g. An nmr spectrum of the product showed the typical absorption of 5-methoxy-2-methyl-2,3,4,7-tetrahydrobenzofuran contaminated with about 12% of starting material. The analysis was made by comparing the methoxyl protons of the starting material at 3.82 ppm and those of the product at 3.63 ppm.

Lithium–Ammonia Reduction of 5-Methoxybenzofuran (5) in the Presence of Excess Alcohol.—To a solution of 9.8 g (0.066 mole) of 5-methoxybenzofuran (5), 35 ml of absolute ethanol, and 200 ml of anhydrous liquid ammonia was added 2.3 g (0.33 mole) of lithium in small pieces over 10 min. After the blue solution had persisted for a few minutes, the excess lithium was destroyed with ammonium chloride and the ammonia allowed to evaporate. Water was added to the residue and the mixture extracted three times with ether. The ether solutions were combined, washed once with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvent with a nitrogen stream left a residue which on distillation gave a colorless liquid, 9.0 g (88%), bp 65–67° (0.7 mm). The distillate partly solidified on standing. The infrared spectrum showed prominent bands at 1660 and 1220 cm^{-1} which are indicative of a vinyl ether. The nmr spectrum had peaks at 2.53 (2 t, J = 9 cps, -CH$_2$-), 2.70 (4 s, br, -CH$_2$- in six-membered ring), 3.50 (3 s, -OCH$_3$), 4.28 (2 t, J = 9 cps, -OCH$_2$-), and 4.50 ppm (1 s, br, C=CH).

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[19] F. Mauthner, *J. Prakt. Chem.*, **102**, 41 (1921).

[20] G. R. Ramage and C. V. Stead, *J. Chem. Soc.*, 3602 (1953).

[21] S. Marcinkiewicz, J. Green, and D. McHale, *J. Chromatog.*, **10**, 42 (1963).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.42; H, 8.09.

Lithium–Ammonia Reduction of 2,3-Dihydro-5-methoxy-2-methylbenzofuran (6).—To a magnetically stirred solution of 41 g (0.25 mole) of the dihydrobenzofuran in 50 ml of absolute alcohol and 400 ml of anhydrous liquid ammonia was added 6.5 g (0.94 mole) of lithium in 0.3-g pieces. The addition was carried out over 20 min. Ammonium chloride was added to destroy any excess lithium which still remained after 5 min. The ammonia was allowed to evaporate and the residue was treated with 300 ml of water. The aqueous mixture was extracted three times with ether and the combined extracts were washed once with saturated sodium chloride solution and dried. After concentrating the solution in a flash evaporator, the residue was distilled to give a colorless product, 33.0 g (80%), bp 68–70° (0.3 mm).

The infrared spectrum showed prominent bands at 1645 and 1230 cm^{-1} which are indicative of a vinyl ether. In the nmr spectrum, peaks were observed at 1.30 (3 d, J = 7 cps, $-CH_3$), 1.8–2.9 (6 m, br, $-CH_2-$), 3.45 (3 s, $-OCH_3$), and 4.6 ppm (2 m, one vinyl and one C_2 protons).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.48. Found: C, 72.49; H, 8.55.

Lithium–Ammonia Reduction of 2,3-Dihydro-5-methoxybenzofuran (7).—The reduction was carried out in the same manner as the reduction of 5-methoxybenzofuran (5) in excess alcohol. The yield from 12.4 g (0.083 mole) of the dihydrobenzofuran was 12.4 g (98%).

2,3,4,5,6,7-Hexahydro-2-methylbenzofuran (3) was formed in about 3% yield in the lithium–ammonia reduction of 2,3-dihydro-5-methoxy-2-methylbenzofuran (6). It was isolated from the forerun in the reduced-pressure distillation of the primary product: bp 74–75° (17 mm); ultraviolet (cyclohexane) 226 mμ (ε 3440) and 295 (ε 75); infrared peaks at 1710 and 1200 cm^{-1} (vinyl ether); nmr peaks at 1.23 (3 d, J = 6 cps, $-CH_3$), 1.5–2.9 (10 m, methylene protons), and 4.5 ppm (1 m, a symmetrical multiplet as in 2,3-dihydro-5-methoxy-2-methylbenzofuran).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.03; H, 9.94.

Registry No.—**3**, 10198-31-9; **4**, 13391-27-0; **5**, 13391-28-1; **6**, 13391-29-2; **7**, 13391-30-5; **8**, 13391-31-6; **9**, 13391-32-7; **11**, 13391-33-8; **12**, 13391-34-9; 2-allyl-4-methoxyphenol-, 584-82-7; allyl 4-methoxyphenyl ether, 13391-35-0.

Acknowledgment.—This investigation was supported in part by Grant GM 13452 from the U. S. Public Health Service.

The Resolution and Configuration of α-Substituted Phenylacetic Acids[1a]

COLIN AARON, DAVID DULL, JOEL LARKIN SCHMIEGEL,[1b] DAVID JAEGER, YOKO OHASHI, AND HARRY S. MOSHER

Department of Chemistry, Stanford University, Stanford, California 94305

Received March 3, 1967

Four new optically active substituted phenylacetic acids (α-isopropyl-, α-*t*-butyl-, and α-trifluoromethylphenylacetic acids and α-ethyl-*p*-methoxyphenylacetic acid) have been obtained by classical means and their relative configurations correlated with α-methylphenylacetic acid (hydratropic acid) whose absolute configuration is known. The N-methylthionamide derivatives from the positively rotating acids of this series all have a positive Cotton effect. Furthermore, there is a satisfactory correlation of the rotations of the amides, acids, and anilides within this series. Thus, based upon the positive Cotton effect and Freudenberg displacement rule, it is relatively certain that all of the dextrorotatory acids of this series have the absolute *S* configuration. An unexpected observation of racemization in the synthesis of the amide and anilide derivatives of the α-*t*-butyl- and α-trifluoromethylphenylacetic acids is being investigated further.

We required substantial amounts of α-substituted phenylacetic acids in connection with asymmetric Grignard reduction studies now in progress.[2] These studies, which were designed to determine the effect of increasing the bulk of a substituent group in certain Grignard reagents, required the synthesis, resolution, and determination of absolute configuration of several α-substituted phenylacetic acids. The resolutions were accomplished with reasonable facility by the fractional crystallization of the α-phenylethylamine salts according to the classical procedure.[3] Details for the resolutions are given in the Experimental Section. Properties of these resolved acids and their derivatives are given in Table I along with those of known homologs for comparison.

The amide and anilide were made for each acid, and the properties of these derivatives are listed in Tables I and II. Furthermore, the N-methylthionamide derivative was made in each case and the optical rotatory dispersion determined[4] as recorded in Table III.

The results clearly indicate that all of these (+)-α-alkylphenylacetic acids are configurationally related as evidenced by (1) the uniformly positive Cotton effect of their N-methylthionamide derivatives for the n → π* transition at approximately 340 mμ and (2) with the exception of the α-*t*-butyl case, which is not applicable as discussed below, by the uniform increase in the positive molecular rotations in going from the amide to the acid to the anilide according to the generalized concept of Freudenberg's displacement rule[5] for configurationally related compounds.

The α-*t*-butylphenylacetamide and anilide were not obtained enantiomorphically pure. They were prepared from enantiomorphically pure acid *via* the acid chloride by the same method used for the other members of the series but were found to be extensively racemized and in one experiment completely racemized. Furthermore, some racemization was observed in the preparation of α-trifluoromethylphenylacetamide using aqueous ammonia, although we obtained the pure isomer under anhydrous conditions. The reason for this unexpected racemization is being investigated further. One would expect that the bulky *t*-butyl group would inhibit racemization *via* enol anion formation, as is

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(1) (a) We acknowledge with gratitude support for these studies by the National Science Foundation (NSF GP 3888) and the U. S. Public Health Service (GM 05248); (b) National Science Foundation Predoctoral Fellow, 1963–1966.

(2) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964).

(3) K. Pettersson, *Arkiv Kemi*, **9**, 509 (1956); **10**, 283 (1956).

(4) J. Burakevich and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 51 (1965).

(5) K. Freudenberg, "Die Stereochemie," F. Deuticke Verlag, Leipzig, 1933, p 693.