A Reexamination of Phthalide Precursors[1]

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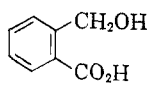
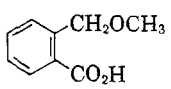
Received March 14, 1958

In the course of a study of the comparative ease of lactonization of various phthalide precursors, it was desired to contrast the chemical properties of *o*-hydroxymethylbenzoic acid (I) and *o*-methoxymethylbenzoic acid (II). While I has long been known,[2] there has been considerable confusion over the physical properties of the ethereal acid II.



I



II

Both McGeoch and Stevens[3] and von Braun, Anton, and Weiszbach[4] have reported the preparation of II by treatment of phthalide with alkaline dimethyl sulfate. The recorded melting points of the products, however, were 116–118° and 93–94°, respectively. A melting point of 92–93° was reported by Clemo and Swan[5] for the acid II, which they prepared by an independent route from ethyl *o*-toluate. In another instance[6] a product from metalation and subsequent carbonation of benzyl methyl ether was assigned the structure of *o*-methoxymethylbenzoic acid on the basis of its melting point, 94–95°.

Since the only evidence offered by McGeoch and Stevens for structure II was a neutralization equivalent, it seemed necessary to repeat their work and reexamine the acid product. From combustion analysis, mixture melting point, and a comparison of infrared spectra, it was shown to be *o*-hydroxymethylbenzoic acid (I), which is also formed easily from phthalide by saponification. *o*-Methoxymethylbenzoic acid (II), m.p. 95–96°, prepared for comparison by the method of Clemo and Swan, exhibits a distinctly different infrared spectrum.

The most likely spectral band associated with alcohol or ether C–O stretching is at 1032 cm.$^{-1}$ for I and at 1114 cm.$^{-1}$ for II. While the value for I is considerably higher than that for benzyl alcohol,[7] it is consistent with a similar band at 1032–1033 cm.$^{-1}$ in both *o*-mesitoyl- and *o*-duroylbenzyl alcohol[8]; thus it appears that the bathochromic shift, ordinarily observed as a result of conjugation,[7] is partially counterbalanced by an acyl or carboxy group in the *ortho* position. Analogies for the corresponding assignment in II are to be found in the spectra of ethyl *o*-methoxymethylbenzoate(1115 cm.$^{-1}$) and *o*-duroylbenzyl methyl ether (1110 cm.$^{-1}$).[8]

Chemical evidence for the structure of McGeoch and Stevens' product is the fact that I has been found to be stable under their conditions of alkylation. While it is unusual that dimethyl sulfate is sometimes ineffective as an alkylating agent, it is now clear that their acid should be reassigned structure I.

EXPERIMENTAL[9]

o-Hydroxymethylbenzoic acid (I). Phthalide (10 g.) was heated with 19 g. of sodium hydroxide and 200 ml. of water at 60° for 90 min. After acidification at 5° with dilute hydrochloric acid, the white solid (22 g.) was collected and dried. It was recrystallized from chloroform: ethanol (20:1) in the form of fine needles; m.p. 111–112°.

The infrared spectrum (Nujol mull) contains bands attributable to a primary alcohol (3200 cm.$^{-1}$ broad, 1032 cm.$^{-1}$), to a carboxylic acid group (1670 cm.$^{-1}$ broad), and to *ortho*-disubstituted benzene (740 cm.$^{-1}$).

Attempted methylation of o-hydroxymethylbenzoic acid with dimethyl sulfate. A mixture of 20 g. of the above acid (unrecrystallized), 15 g. of sodium hydroxide, 200 ml. of water, and 25 g. of dimethyl sulfate was heated, with stirring, at 50° for 2 hr. and then stirred an additional 2 hr. By acidification and recrystallization as described above, there was obtained 6 g. (59% based on phthalide) of colorless needles, m.p. 111–112°. A mixture melting point with I showed no depression; and the infrared spectra (Nujol mulls) of the two samples are superimposable.

Attempted direct preparation of o-methoxymethylbenzoic acid (II) *from phthalide.* The procedure, similar to that previously described,[4] was carried out with 10 g. of phthalide, 100 ml. of water, 57 g. of dimethyl sulfate, and 360 ml. of 10% sodium hydroxide. After being washed with ether, the mixture was acidified and the product extracted once with ether and twice with ethyl acetate. By removal of the solvent there was obtained 5.5 g. (48%) of a white solid, m.p. 107–109°. After three recrystallizations from chloroform: ethanol (20:1) the melting point of the *o*-hydroxymethylbenzoic acid (I) was 111.5–112.5°.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.17; H, 5.49.

From the filtrate there was recovered 2.2 g. (22%) of phthalide.

o-Methoxymethylbenzoic acid (II). The acid was prepared essentially by the method previously described[5] from 33 g. of ethyl *o*-toluate in an over-all yield of 21%. Intermediates were ethyl *o*-bromomethylbenzoate (not purified) and ethyl *o*-methoxymethylbenzoate (b.p. 246–248°/740 mm.; infrared bands (smear) at 1725, 1267, 1140, 1114, and 742 cm.$^{-1}$). The major modification was the use of *N*-bromosuccinimide in carbon tetrachloride rather than molecular bromine for

(1) This work was supported by a Frederick Gardner Cotrell Grant from the Research Corp. of New York and in part by a grant from the University Research Fund of the University of New Hampshire.

(2) J. Hessert, *Ber.*, 10, 1445 (1877); E. Hjelt, *Ber.*, 25, 524 (1892).

(3) S. N. McGeoch and T. S. Stevens, *J. Chem. Soc.*, 1465 (1934).

(4) J. von Braun, E. Anton, and K. Weiszbach, *Ber.*, 63, 2847 (1930).

(5) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946).

(6) H. Gilman, G. E. Brown, F. J. Webb, and S. M. Spatz, *J. Am. Chem. Soc.*, 62, 977 (1940).

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, N. Y., 1954, p. 95.

(8) R. C. Fuson, W. C. Hammann, and P. R. Jones, *J. Am. Chem. Soc.*, 79, 928 (1957).

(9) Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn.

bromination of the side chain. The acid, after two recrystallizations from benzene, was in the form of white prisms, m.p. 95.0–96.0°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.33; H, 6.27.

The infrared spectrum (10% chloroform) of *o*-methoxymethylbenzoic acid contains the typical, broad bands attributable to a carboxylic acid function (3525, 1693 cm.$^{-1}$), as well as a strong band at 1114 cm.$^{-1}$

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An Improved Synthesis of *N*-Phenethylnormorphine and Analogs

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Received March 14, 1958

N-Phenethylnormorphine (Ia) has been prepared[2] by direct phenylethylation of normorphine and exhibits six to ten times the analgesic potency[3] of morphine. We have had occasion to prepare this compound for addiction studies and wish to report an improved method of synthesis.

In this method normorphine was converted to the *N*-phenylacetyl derivative which, without purification, was reduced to the tertiary amine (Ia) with ethereal lithium aluminum hydride.[4] The isolation of Ia from the reduction mixture (in 90% yield based on normorphine) was rendered simple by reason of the low water solubility of its hydrobromide salt.[5] By a similar sequence, norcodeine and dihydrodesoxynorcodeine-D (the latter prepared by cyanogen bromide *N*-demethylation of dihydrodesoxycodeine-D) were transformed into the corresponding *N*-phenethyl derivatives Ib and IIb. There was no complication in isolation of the bases from the reduction mixture since the phenolic hydroxyl is protected in these instances. Hydrobromic acid demethylation of *N*-phenethyldihydrodesoxynorcodeine-D (IIb) gave the phenolic congener (IIa).

The analgesic potency of IIa is five times that of dihydrodesoxymorphine-D (desomorphine), while the effectiveness of Ib and *N*-phenethylnorheterocodeine is twice that of the parent compounds. The duration of action of Ia and the corresponding heterocodiene derivative is about the same as seen in the parent compounds, while Ib and IIb are analgesic twice as long as the *N*-methyl counterparts. In all cases testing was done in mice.

EXPERIMENTAL

Microanalyses and most of the rotations were performed by the Institutes service analytical laboratory, Dr. William C. Alford, director.

N-Phenethylnormorphine (Ia). Normorphine hydrochloride (5 g.),[6] 8 g. of K_2CO_3, 30 ml. of water, and 80 ml. of methanol were treated (stirring) with 6 ml. (2.8 molar equivalents) of phenylacetyl chloride during 0.4 hr. After stirring for an additional 3 hr., the mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were washed with a little dilute HCl, dried and evaporated to thorough dryness *in vacuo*. The residue and 50 ml. of dry ether were treated (stirring) with 100 ml. of 1.5*M* ethereal $LiAlH_4$ at such a rate as to cause gentle refluxing (10–15 min.). The mixture was refluxed for 15 hr. and treated gradually (vigorous stirring) with 75 ml. of 48% HBr in 130 ml. of water. All inorganic material gradually dissolved leaving a viscous, ball-like mass which, on cooling, crystallized and was easily pulverized. Filtration gave the gummy hydrobromide which, in warm methanol, was converted to the base (Ia) by addition of dilute NH_4OH; yield 5.5 g. (90%), m.p. 250–253° (dec.); thin prisms from absolute ethanol, $[\alpha]_D^{20}$ −117° (c 0.84 in 2:1 $CHCl_3$-MeOH).

Anal. Calcd. for $C_{24}H_{25}NO_3$: C, 76.76; H, 6.71. Found: C, 76.95; H, 6.54.

The tartrate,[1] prepared from the base in refluxing 95% ethanol, melted at 144–147° (froth) alone or in mixture with authentic material[7] and had $[\alpha]_D^{20}$ −68.9° (c 0.99 in 50% by vol. ethanol); reported[1] $[\alpha]_D^{20}$ −67° (solvent not specified).

N-Phenethylnorcodeine hydrobromide (Ib). The reaction of phenylacetyl chloride (1.2 g.) with norcodeine hydrochloride (2 g.) was carried out as described for normorphine above. Reduction of the resultant amide (1.8 g.) with 20 ml. of 1.5*M* ethereal $LiAlH_4$ gave, after addition of 5–10 ml. of water and drying the ethereal filtrate, 1.5 g. of Ib. Acidification of an ether solution of this base with 33% HBr-AcOH yielded an amorphous hydrobromide which crystallized from acetone in prisms; yield 1.5 g., m.p. 273–275°. It was further purified by dissolving it in 225 ml. of boiling 95% ethanol, concentrating the solution to 50–75 ml. and cooling to 0°; m.p. 290–293° (dec.), $[\alpha]_D^{20}$ −97.0° (c 0.58 in MeOH-H_2O, 3:2).

Anal. Calcd. for $C_{25}H_{28}BrNO_3$: C, 63.83; H, 6.00. Found: C, 63.52, 63.46; H, 5.81, 5.95.

N-Phenethyldihydrodesoxynorcodeine-D hydrobromide (IIb). To 2.0 g. of cyanogen bromide (Eastman) in 13 ml. of dry chloroform was added (stirring) during 1 hr. 5.0 g. of dihydrodesoxycodeine-D[8] in 20 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residue and 100 ml. of 6% HCl were refluxed overnight. Cooling and basification gave 4.5 g. of crude secondary base which was phenylacetylated as described for normorphine except that 2 molar equivalents of chloride was used. The amide in 50 ml. of dry ether was treated with 50 ml. of 1.5*M* ethereal $LiAlH_4$ during 10–15 min. and the mixture was refluxed overnight. After addition of 20 ml. of water (stirring)

(1) Deceased, June 1957.

(2) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **75**, 4963 (1953).

(3) C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. intern. pharmacodynamie*, **110**, 186 (1957); N. B. Eddy, unpublished.

(4) This procedure has been used successfully in preparing *N*-phenethyl analogs of synthetic analgesics, phenyl- and benzomorphans [E. L. May, *J. Org. Chem.*, **21**, 899 (1956); J. H. Ager and E. L. May, unpublished].

(5) In another set of experiments in which norheterocodeine was used, almost equally good yields of the *N*-phenethylnorheterocodeine could be obtained in the same fashion.

(6) Supplied by Merck & Co., Inc., *via* Dr. H. F. Fraser, PHS Hospital, Lexington, Ky.

(7) Supplied by Merck & Co., Inc. *via* Dr. Joseph Cochin of this Institute.

(8) L. F. Small and F. L. Cohen, *J. Am. Chem. Soc.*, **53**, 2227 (1931); H. Rapoport and R. M. Bonner, *J. Am. Chem. Soc.*, **73**, 2872 (1951).