[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Derivatives of 5-Methoxyhydrindene and 6-Methoxytetralin. Synthesis of β-(2-Carboxy-5-methoxyphenyl)-propionic Acid[1]

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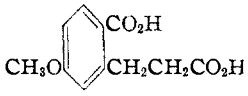
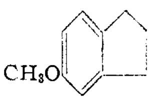
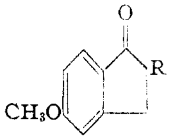
For the synthesis of β-(2-carboxy-5-methoxyphenyl)-propionic acid (I) which was desired as an intermediate in some projected syntheses of steroid types, the readily available[2] 5-methoxyhydrindene (II) and the similarly accessible[3] 6-methoxytetralin (VI) were chosen as promising starting materials.



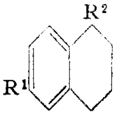
I



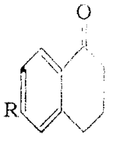
II



III (R = H)
IV (R = Br)
V (R = CN)



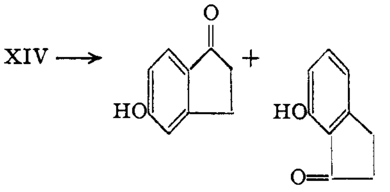
VI (R^1 = OCH_3, R^2 = H)
VII (R^1 = H, R^2 = $OCOCH_3$)
VIII (R^1 = OCH_3, R^2 = $OCOCH_3$)
IX (R^1 = OCH_3, R^2 = OH)



X (R = OCH_3)
XI (R = H)

Since it has been shown[4] that 6-methoxytetralin (VI) is converted by oxidation with chromic oxide into 6-methoxytetralone-1 (X) in yields up to 70%,[3b] it was hoped that a similar selective oxidation would take place in the case of the five-membered ring homolog II to produce 5-methoxyhydrindone-1 (III). This indeed was realized, and conditions were found whereby the pure ketone (III) was obtained in 75–80% yields. The identity of the substance was confirmed by comparison with material prepared by a conventional synthesis involving no new compounds, but describing a new series of reactions[5]

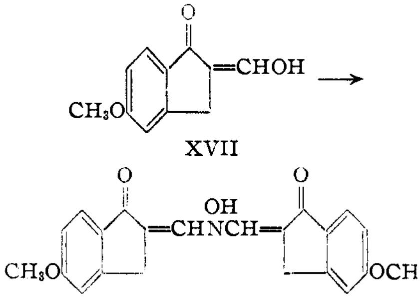
$$m\text{-}HOC_6H_4CHO\ (XII) \longrightarrow m\text{-}HOC_6H_4CH{=}CHCO_2H\ (XIII) \longrightarrow m\text{-}HOC_6H_4CH_2CH_2CO_2H\ (XIV)$$



XV (85%) XVI (13%)

The cyclization of *m*-hydroxyhydrocinnamic acid (XIV) with hydrogen fluoride[6] gave a 98% yield of a mixture of isomeric ketones easily and quantitatively separated by steam distillation. The non-volatile 5-hydroxyhydrindone-1 (XV) was formed in preponderance (yield 85%), and methylation afforded the ether III, identical with the oxidation product of II described above.

It was planned to degrade 5-methoxyhydrindone-1 to the desired acid (I) by a series of reactions employed by Lapworth[7] to open the ketonic ring of camphor to obtain homocamphoric acid. This method has been used also by Bardhan[8] to open ring D of estrone, and by Robinson and Rydon[9] to cleave the analogous ring of a synthetic product related to equilenin. The Claisen condensation of III with ethyl formate gave 2-hydroxymethylene-5-methoxyhydrindone-1 (XVII) in 98% yield. This in glacial acetic acid



XVII

XVIII

condensed with hydroxylamine to give—instead of the expected[7,8,9] nitrile (V)—a 90% yield of an insoluble orange compound, $C_{22}H_{19}O_5N$, probably bis-(5-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (XVIII).[10] The condensation product has an acidic hydrogen, and on

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(1) This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

(2) A. H. Cook and Linstead, *J. Chem. Soc.*, 946 (1934).

(3) (a) Schroeter, *Ann.*, **426**, 83 (1922); (b) Burnop, Elliott and Linstead, *J. Chem. Soc.*, 727 (1940).

(4) Goertz, Dissertation, Berlin, p. 17 (1924): German Patent 397,150 [*Chem. Zentr.*, **95**, II, 1404 (1924)].

(5) *Cf.* the syntheses of (a) Ingold and Piggott, *J. Chem. Soc.*, 1469 (1923), and (b) Brand and Horn, *J. prakt. Chem.*, [2] **115**, 351 (1927).

(6) Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939).

(7) Lapworth, *J. Chem. Soc.*, 1053 (1900).

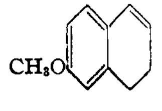
(8) Bardhan, *ibid.*, 1848 (1936).

(9) Robinson and Rydon, *ibid.*, 1394 (1939).

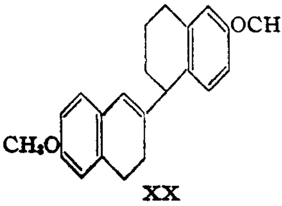
(10) During a study of the condensation of hydroxylamine with a number of hydroxymethylene ketones under various conditions we have come to the conclusion that the product obtained by Robinson and Rydon (reference 9) and presumed by them to be a nitrile, probably was a dimolecular condensation product like XVIII. The formation and alkaline cleavage of compounds of this type will be considered in a subsequent communication.

dissolving in alkali gives an intense purple color which is gradually dispelled on warming. Prolonged heating of XVIII with one equivalent of hydroxylamine in alkaline solution was accompanied by the evolution of ammonia and the formation of β-(2-carboxy-5-methoxyphenyl)-propionic acid (I) in 61% yield. Lower yields were obtained in the absence of hydroxylamine. The structure of the acid was confirmed by distillation with barium oxide to regenerate 5-methoxyhydrindone-1. The mechanism of the degradation of XVIII to the dicarboxylic acid (I) may involve the nitrile (V) as an intermediate,[10] although we have not yet been able to prepare V from either XVIII or the hydroxymethylene derivative XVII. The nitrile could be obtained, however, in 73% yield from 2-bromo-5-methoxyhydrindone-1 (IV), and on alkaline hydrolysis afforded an 88% yield of the acid (I).

Preliminary attempts to prepare β-(2-carboxy-5-methoxyphenyl)-propionic acid by direct oxidation of 6-methoxytetralin (VI) or of the tetralone derivative X using acid permanganate[11] or chromic acid were so unpromising that this method of attack was abandoned. A more favorable approach was found in the oxidation of VI with lead tetraacetate. Since it has been shown[12] that this reagent reacts with tetralin to give 1-acetoxytetralin (VII), it was expected that the 6-methoxy derivative (VI) also would be acetoxylated. This indeed was realized, the reaction proceeding at room temperature, and a monoacetoxy derivative was obtained in 62% yield. Since the methoxyl group of VI activates the hydrogen atoms on the carbon atom in the *para* position toward chromic acid oxidation,[4] it was presumed that lead tetraacetate had attacked the same position to produce 1-acetoxy-6-methoxytetralin (VIII). This substance exhibited a remarkable tendency to lose acetic acid, also probably due to the activating effect of the *p*-methoxyl substituent. The decomposition was catalyzed by mineral acid, and 7-methoxy-1,2-dihydronaphthalene (XIX) was thus obtained in 87% yield as a liquid, b. p. 95° (2–3 mm.). A solid, m. p. 73–74°, presumed to have the structure XIX has been described by Long and Burger.[13] Their substance was prepared by the action of hydrobromic acid on 1-hydroxy-6-methoxytetralin (IX).[14] The structural similarity between XIX and anethole, which is known to dimerize in the presence of mineral acids,[15] suggested that XIX would not be stable in such a medium. Indeed when our liquid compound was treated with hydrobromic acid it was converted into a solid dimer, m. p. 75.5–76.5°, apparently identical with the previously reported substance. By analogy to the anethole dimer of known structure, the present substance may be formulated tentatively as XX.



XIX



XX

Oxidation of XIX with cold permanganate in acetone solution gave β-(2-carboxy-5-methoxyphenyl)-propionic acid (I) in 40% yield. The identity of this product established the structure of XIX and, in turn, that of the acetoxylation product VII.

Experimental Part[15a]

5-Methoxyhydrindone-1 (III). (a) **By the Oxidation of 5-Methoxyhydrindene (II).**—A solution of chromic anhydride (28 g.) in 14 cc. of water and 80 cc. of glacial acetic acid was added slowly with mechanical stirring to a chilled solution of 26.2 g. of 5-methoxyhydrindene (prepared[16] from hydrindene according to A. H. Cook and Linstead[2]) in 160 cc. of glacial acetic acid. The temperature was maintained between 5 and 10° during the addition (one hour). The mixture was kept cool for five hours and then allowed to come to room temperature. After standing overnight most of the acetic acid was removed at 40° under diminished pressure, water was added, and the oil extracted with ether. The combined extracts were washed cautiously with 10% potassium carbonate solution until all of the acid was removed, then with concentrated sodium chloride solution, and finally dried over anhydrous potassium carbonate. The product on evaporation of the ether distilled at 130-132° (2-3 mm.), giving a yellowish oil which presently solidified, m. p. 95–108°; yield 22.3 g. (78%). A single crystallization from dilute methanol gave 20.0 g. of long colorless prismatic rods, m. p. 108–110°. A sample was recrystallized from benzene to a constant m. p. 109.8–110.5° (literature m. p. 110°[5a] and 108°[5b]). This material as well as the semicarbazone, m. p. 240–241° (dec.) (literature m. p. 239°[5a]) showed no depression of m. p. on mixing with the specimens prepared as described below.

(b) **By the Cyclization of *m*-Hydroxyhydrocinnamic Acid (XIV).**—*m*-Hydroxycinnamic acid (XIII) was prepared in 91% yield from *m*-hydroxybenzaldehyde by heating the latter (20.9 g.) with malonic acid (31.2 g.) in pyridine (32 cc.) and piperidine (8 drops) for four and one-half hours on the steam-bath. Acidification with dilute hydrochloric acid yielded 25.5 g. of XIII, m. p. 192–194°. Material once recrystallized from dilute methanol solution had the m. p. 194–195° (literature m. p. 191°[5a,17] and 193°[18]). This was reduced in methanol solution with platinum oxide to give a quantitative yield of *m*-hydroxy-

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[11] The permanganate oxidation of tetralin to *o*-carboxyhydrocinnamic acid was reported by Bamberger and Kitschelt, *Ber.*, **23**, 1561 (1890). Later, however, v. Braun and Deutsch, *ibid.*, **45**, 1267 (1912), produced evidence indicating that the previous work had been carried out on impure tetralin containing some dihydronaphthalene which was actually the principal source of the dicarboxylic acid.

[12] Criegee, *Ann.*, **481**, 263 (1930).

[13] Long and Burger, *J. Org. Chem.*, **6**, 852 (1941).

[14] Salzer, *Z. physiol. Chem.*, **274**, 39 (1942), reported material b. p. 103° (1 mm.) from the dehydration of 1X. The reactions of this material indicated that it was, at least in part, 7-methoxy-1,2-dihydronaphthalene, but no analytical data were given. Compare German Patent 708.114 [*Chem. Abs.*, **37**, 2748 (1943)] and U. S. Patent 2,223,664 [*Chem. Abs.*, **35**, 1808 (1941).]

[15] Goodall and Haworth, *J. Chem. Soc.*, 2482 (1930).

[15a] All melting points are corrected.

[16] The preparation of 5-methoxyhydrindene was carried out by Mr. E. Goldstein who also performed some of the preliminary oxidation experiments.

[17] Tiemann and Ludwig, *Ber.*, **15**, 2043 (1882).

[18] Posner, *J. prakt. Chem.*, [2] **82**, 425 (1910).

hydrocinnamic acid (XIV), m. p. about 99°. The pure acid, m. p. 111.8–112.5° (literature m. p. 111°[17]) was obtained by distillation under diminished pressure and crystallization from benzene.

For the cyclization 3.31 g. of pure XIV was treated in a platinum vessel with approximately 100 g. of anhydrous hydrogen fluoride.[6] On standing overnight the yellow solution evaporated, leaving a colorless crystalline mass which was submitted to steam distillation. 7-Hydroxyhydrindone-1 (XVI) crystallized from the distillate which was saturated with sodium chloride and extracted with ether. This extract after drying over anhydrous sodium sulfate and evaporation yielded 0.40 g. (13%) of almost colorless material, m. p. 109–111°. Recrystallized from methanol–petroleum ether, it formed colorless prisms, m. p. 110.5–111.5° (literature m. p. 111°[19,5]) and gave an intense violet color with ferric chloride.[19,5] Practically pure crystalline 5-hydroxyhydrindone-1 (XV) remained in the distilling flask from the steam distillation, and amounted to 2.50 g. (85% yield), m. p. 184–185°. Recrystallized from dilute alcohol (Norit) it formed almost colorless prisms, m. p. 184–185.5° (literature m. p. 182°[5a] and 183°[19]); semicarbazone, m. p. 222–222.5° (dec.) (introduced in bath at 215°) (literature m. p. 223°[19]). The **acetate** of XV crystallized from ether–petroleum ether in colorless plates, m. p. 92.8–93.2°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.66; H, 5.55.

When the cyclization was performed on distilled but unrecrystallized *m*-hydroxyhydrocinnamic acid (yield 90–95%) the total yield of ketones was 94% instead of 98%.

Crude 5-hydroxyhydrindone-1 (11 g.) prepared as above was converted into the methyl ether III by the action of dimethyl sulfate in alkaline solution. The yield of crude III was 11.6 g. (97%), m. p. about 110° with previous softening. Recrystallized from benzene it melted at 110–110.5°; semicarbazone m. p. 240–241° (dec.) (*cf.* the product prepared in (a) above). The **2,4-dinitrophenylhydrazone** formed red needles from chloroform, m. p. 282–284° (dec.) (uncor.).

Anal. Calcd. for $C_{16}H_{14}O_5N_4$: N, 16.37. Found: N, 16.45.

The ***p*-nitrophenylhydrazone** crystallized from dilute alcohol in small orange needles, m. p. 209–211.5° (dec.) (introduced in bath at 200°).

Anal. Calcd. for $C_{16}H_{15}O_3N_3$: N, 14.14. Found: N, 14.25, 14.31.

2-Hydroxymethylene-5-methoxyhydrindone-1 (XVII).[20] —A solution of sodium methoxide prepared from 0.74 g. (0.032 mole) of sodium and 10 cc. of methanol was evaporated to dryness at 200° under reduced pressure. The colorless cake was broken up, and a solution of 2.38 g. (0.032 mole) of ethyl formate in 16 cc. of dry benzene was added, and the system evacuated and filled with nitrogen. To the cooled mixture was added with swirling, a solution of 2.60 g. (0.016 mole) of 5-methoxyhydrindone-1 in 20 cc. of dry benzene. A precipitate having a pink tinge gradually formed, and after four to five hours slightly below room temperature it was hydrolyzed with cold water, and a few cc. of ether was added to minimize emulsion formation. The organic layer was washed once with water and with dilute sodium hydroxide. The aqueous portions were combined, washed with ether, and acidified with ice and hydrochloric acid. Almost pure 2-hydroxymethylene-5-methoxyhydrindone-1 precipitated; yield 2.98 g. (98%), m. p. 136.5–138°. Recrystallized from benzene it formed almost colorless plates, m. p. 138–138.5° (dec.), which gave an intense purple color with ferric chloride.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.65; H, 5.53.

The **bis-(2,4-dinitrophenylhydrazone)** of XVII **crystallized** from bromobenzene in short, orange needles, m. p. 223–226° (dec.) (introduced in bath at 220°).

Anal. Calcd. for $C_{23}H_{18}O_9N_8$: N, 20.36. Found: N, 20.40.

2-Hydroxymethylene-5-methoxyhydrindone-1, on melting, turns dark red and slowly gives off a gas. This decomposition represents the elimination of formic acid between two molecules of XVII to form a condensation product of the type described by Ruhemann and Levy.[21] The product, probably **2-(5-methoxy-1-keto-2-hydrindylidenemethyl)-5-methoxyhydrindone-1**, was obtained after heating for one hour at 140–150°. It crystallized from benzene–petroleum ether or from glacial acetic acid in orange prisms, m. p. 213–215° (dec.) (introduced in bath at 205°).

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.82; H, 5.51.

Bis-(5-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (XVIII).—A solution of 1.42 g. (0.0075 mole) of 2-hydroxymethylene-5-methoxyhydrindone-1 in 20 cc. of glacial acetic acid was treated with 0.59 g. (0.0085 mole) of powdered hydroxylamine hydrochloride. Although the latter is sparingly soluble, the reaction started presently as indicated by coloring of the solution followed by the formation of a red precipitate. The mixture was stirred or shaken mechanically for twenty-four hours, and the product filtered and triturated with water which caused the color to change from red to orange. The yield of dry material amounted to 1.27 g. (90%), m. p. 190–204° (dec.) (introduced in bath at 180°). It crystallized from pyridine in the form of orange needles, m. p. 216–218° (dec.) (introduced in bath at 214°). The same m. p. was observed in an evacuated tube.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.93; H, 5.14; N, 3.62.

The condensation product XVIII is sparingly soluble in the common organic solvents. It dissolves in dilute alkali to give an intense violet color like that of permanganate solution.

2-Bromo-5-methoxyhydrindone-1 (IV).—A solution of 5-methoxyhydrindone-1 (1.68 g.) in 200 cc. of anhydrous ether was treated with 0.60 cc. of bromine according to the procedure of Wilds[22] for the bromination of 1-keto-1,2,3,4-tetrahydrophenanthrene. A purer product was obtained when the reaction mixture was allowed to stand overnight after the addition of the bromine. The crude material amounted to 2.38 g. (95% yield), m. p. 102–105°. A sample recrystallized for analysis from benzene formed colorless prisms, m. p. 107.8–108.5°.

Anal. Calcd. for $C_{10}H_9O_2Br$: C, 49.81; H, 3.77. Found: C, 49.93; H, 3.77.

2-Bromo-5-methoxyhydrindone-1 2,4-dinitrophenylhydrazone formed red needles from chloroform, m. p. 202.5–204.5° (dec.) (introduced in bath at 195°).

Anal. Calcd. for $C_{16}H_{13}O_5N_4Br$: C, 45.62; H, 3.12; N, 13.30. Found: C, 45.58; H, 3.11; N, 13.48.

2-Cyano-5-methoxyhydrindone-1 (V).—A solution of 2.38 g. of crude 2-bromo-5-methoxyhydrindone-1 (m. p. 102–105°) and 4.76 g. of sodium cyanide in 70 cc. of alcohol and just enough water to dissolve the salt, was allowed to reflux on the steam-bath for twenty-five minutes. After cooling, the solution was diluted with water, extracted twice with ether to remove neutral material, and the chilled aqueous portion was acidified with cold hydrochloric acid. The oily cyano ketone which separated was extracted with chloroform, and this solution was clarified with Norit, then extracted with small portions of 5% potassium hydroxide solution until a test portion no longer gave a precipitate on acidification. Acidification of the combined cold aqueous layers gave 1.34 g. (73%) of 2-cyano-5-methoxyhydrindone-1 which soon solidified, m. p. 90–92.5°. The pure material crystallized from alcohol in tan plates, m. p. 96–96.5°; ferric chloride test negative.

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(19) v. Auwers and Hilliger, *Ber.*, **49**, 2410 (1916).

(20) An adaptation of the procedure of Bachmann and Thomas, THIS JOURNAL, **63**, 598 (1941), for the condensation of tetralone-1 with dimethyl oxalate.

(21) Ruhemann and Levy, *J. Chem. Soc.*, 2542 (1912).

(22) Wilds, THIS JOURNAL, **64**, 1421 (1942).

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.57; H, 4.86; N, 7.48. Found: C, 70.70; H, 4.78; N, 7.50.

The **2,4-dinitrophenylhydrazone** of V formed small red crystals from glacial acetic acid, m. p. 217.5–219.5° (dec.) (introduced in bath at 214°).

Anal. Calcd. for $C_{17}H_{13}O_5N_5$: N, 19.07. Found: N, 19.02.

The **semicarbazone** of V formed buff-colored microscopic prisms from dilute alcohol, m. p. 219.5–220° (dec.) (introduced in bath at 215°).

Anal. Calcd. for $C_{12}H_{12}O_2N_4$: N, 22.94. Found: N, 22.99, 23.01.

1-Acetoxy-6-methoxytetralin (VIII).—A suspension of 100 g. of lead tetraacetate[23] in 150 cc. of glacial acetic acid (previously distilled from permanganate) containing 33 g. of 6-methoxytetralin[3] was stirred at room temperature for sixteen hours. The reaction, at first slightly exothermic, was controlled by external cooling. The excess oxidizing agent was decomposed with a small amount of glycerol[24] (using the starch-iodide test) and most of the solvent removed under reduced pressure. The oil obtained on dilution with water was extracted with ether, washed with water followed by successive portions of 10% sodium carbonate solution to remove the acetic acid. Two washings with 2% sodium hydroxide solution removed a small amount of dark material (phenolic ?). The ether solution was then washed with water, saturated sodium chloride solution, and dried over anhydrous potassium carbonate. The oil obtained on evaporation was roughly fractionated through a short Vigreux column, and the pale yellow portion, b. p. 132–139° (1–2 mm.), was 1-acetoxy-6-methoxytetralin; yield 27.9 g. (62%). The analytical sample boiled at 118.5° (0.5 mm.); n^{25}_{D} 1.5348.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.21; H, 7.19.

This ester is quite unstable, having a pronounced tendency to lose acetic acid to form 7-methoxy-1,2-dihydronaphthalene (XIX). Even on standing, the substance gradually darkens and develops the odor of acetic acid. Since the decomposition is catalyzed by mineral acid, all glassware to come in contact with the ester must be freed of traces of acid by washing with alkali.

7-Methoxy-1,2-dihydronaphthalene (XIX).—When 1-acetoxy-6-methoxytetralin (9.4 g.) was heated at 120° (22 mm.) with a crystal of potassium acid sulfate the elimination of acetic acid was complete in a few minutes. The remaining product distilled at 85–86° (about 1 mm.); yield 5.9 g. (87%). Redistilled material had the b. p. 94–95° (2–3 mm.); 75–76° (0.3–0.4 mm.), $n^{26.5}_{D}$ 1.5837, $d_4^{26.5}$ 1.0561, M_D (found) 50.75, M_D (calcd.) 48.37.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.48; H, 7.48.

The exaltation of the molecular refractivity of XIX is in close agreement with that predicted from data on similar compounds.[25] The exaltation for 1,2-dihydronaphthalene is 1.47. The additional influence of the methoxyl group *para* to the olefinic bond may be estimated from the increase (0.60) in the exaltation produced in the case of styrene by introduction of a *p*-methoxyl group. The expected exaltation for 7-methoxy-1,2-dihydronaphthalene therefore would be 2.07. The observed value is 2.38.

Dimeric 7-Methoxy-1,2-dihydronaphthalene (possibly formula XX).—Four g. of XIX was treated with 40 cc. of 48% hydrobromic acid as described by Long and Burger[13] for 1-hydroxy-6-methoxytetralin. The fraction b. p. about 230° (0.5–1 mm.) amounted to 3.3 g. Recrystallization from 40–60° petroleum ether gave 2.8 g. (70% yield) of material, m. p. 73–76°. A sample purified by recrystallization from methanol formed colorless needles, m. p. 75.5–76.5°. Long and Burger give the m. p. 73–74°.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55; mol. wt., 320. Found: C, 82.30; H, 7.53; mol. wt., 333 (Rast).

β-(2-Carboxy-5-methoxyphenyl)-propionic Acid (I). (a) From bis-(5-Methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (XVIII).—A solution of 0.500 g. (0.0013 mole) of uncrystallized XVIII and 0.092 g. (0.0013 mole) of hydroxylamine hydrochloride in 85 cc. of 2% aqueous sodium hydroxide was boiled under reflux. The deep purple color gradually faded, and usually within forty minutes the solution was light-red. Ammonia was slowly evolved as the heating was continued for four days. The filtered solution was acidified and the precipitated acid extracted with ether from which it was recovered by extraction with 5% sodium bicarbonate solution. Acidification of the combined aqueous extracts yielded 0.360 g. (61%) of yellowish β-(2-carboxy-5-methoxyphenyl)-propionic acid, m. p. 194–199° with previous softening. A pure sample of the acid was obtained by sublimation under reduced pressure and crystallization from alcohol. It formed colorless needles, m. p. 203.5–204°.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.94; H, 5.44.

(b) **By Hydrolysis of 2-Cyano-5-methoxyhydrindone-1 (V).**—A solution of 1.07 g. (0.006 mole) of the crude nitrile in 170 cc. of 5% aqueous potassium hydroxide was boiled under reflux until ammonia was no longer evolved (forty-eight hours). The dibasic acid was isolated from the alkaline solution just as described in (a). The yield of colorless material was 1.13 g. (88%), m. p. 201–202.5°; after sublimation under reduced pressure and recrystallization from water it formed colorless needles, m. p. 201.5–203.7°.

(c) **By Oxidation of 7-Methoxy-1,2-dihydronaphthalene (XIX).**—Powdered potassium permanganate (3.62 g.) was added in portions with stirring to a solution of 1.38 g. of XIX in 30 cc. of acetone. During the addition (twenty minutes) the temperature was maintained between 0 and 3°, then the mixture was stirred at room temperature for about forty minutes. The acetone was removed, dilute sulfuric acid added followed by sodium sulfite to dissolve the manganese dioxide, and the residue extracted with ether. This solution was extracted with 5% sodium bicarbonate solution which on acidification yielded 0.78 g. (40%) of the dibasic acid (I), m. p. 195–199° with previous softening. A sample purified by clarification of a solution of the sodium salt with Norit, followed by recrystallization from alcohol had the m. p. 201–203.5°.

The samples of β-(2-carboxy-5-methoxyphenyl)-propionic acid prepared by the three methods above showed no melting point depressions on mixing.

Cyclization of β-(2-Carboxy-5-methoxyphenyl)-propionic Acid.—Each of the products obtained by the three methods described above was submitted to the following treatment: about 0.2 g. of the acid mixed with a few mg. of barium oxide was distilled slowly in a two-bulb flask. The distillate was dissolved in warm dilute alcohol containing about 2% of sodium bicarbonate. On cooling, crystals of 5-methoxyhydrindone-1 separated, m. p. 108–110°, no depression on mixing with an authentic sample.

Summary

During a search for methods of obtaining β-(2-carboxy-5-methoxyphenyl)-propionic acid several transformations in the 6-methoxytetralin and 5-methoxyhydrindene series have been correlated.

5-Methoxyhydrindone-1 is obtained in good yield by oxidation of 5-methoxyhydrindene. The structure of the ketone was confirmed by com-

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[23] A slight modification in the procedure (Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 2nd ed., 1941, p. 436) for the preparation of lead tetraacetate seemed to be advantageous. When the reaction temperature was kept lower (between 40 and 50°) very little darkening occurred, and the crude product was pale yellow. A single recrystallization without the use of Norit gave an excellent yield of colorless material.

[24] Fieser, "Experiments in Organic Chemistry," 1941, p. 438.

[25] v. Auwers, *Ann.*, **413**, 284 (1917); *Ber.*, **46**, 2988 (1913).

parison with material prepared by a conventional synthesis involving the cyclization of *m*-hydroxyhydrocinnamic acid. Condensation of 2-hydroxymethylene-5-methoxyhydrindone-1 with hydroxylamine hydrochloride in acetic acid yields, instead of the expected nitrile, a dimolecular condensation product which is probably bis-(5-methoxy - 1 - keto - 2 - hydrindylidenemethyl) - hydroxylamine. Alkaline hydrolysis of the latter in the presence of hydroxylamine gives β-(2-carboxy-5-methoxyphenyl)-propionic acid. This acid is also obtained on alkaline cleavage of 2-cyano-5-methoxyhydrindone-1 which can be prepared from 5-methoxyhydrindone-1 through the 2-bromo derivative.

Oxidation of 6-methoxytetralin with lead tetraacetate gives the 1-acetoxy derivative in 62% yield. The latter readily loses the elements of acetic acid to form 7-methoxy-1,2-dihydronaphthalene which forms a crystalline dimer in the presence of hydrobromic acid. Oxidation of the monomeric substance gives β-(2-carboxy-5-methoxyphenyl)-propionic acid.

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Morpholinomethyl Derivatives of Urea and Substituted Ureas[1]

BY WELCOME I. WEAVER,[2] J. K. SIMONS[2] AND WILMER E. BALDWIN

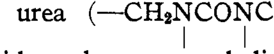
The aminomethylation of active hydrogen compounds by primary or secondary amines and formaldehyde has received considerable attention. The work with active methylene compounds, the Mannich reaction, has been reviewed recently,[3] while that with nitrogen compounds has been reported in a number of investigations of amines,[4] imides,[5] amides[6] and thiourea.[7] Einhorn and Spröngerts[8] described the reaction products of diethylaminomethanol and piperidinomethanol with urea. Later Einhorn[9] patented the reaction products of these alcohols with isovalerylurea. More recently there has appeared a patent[10] on the use of several bis-(dialkylaminomethyl)-ureas including bis-(morpholinomethyl)-urea.

The object of the present work was to prepare morpholinomethyl derivatives of urea and a number of substituted ureas and to investigate their behavior under conditions which would bring about cleavage, *e. g.*, reduction, treatment with acid anhydrides, picric acid or alkali.

Monomorpholinomethyl- and bis-(morpholinomethyl)-urea were prepared in yields of 85–95% by the reaction of urea with one or two equivalents of morpholinomethanol in aqueous solution or with paraformaldehyde and morpholine in dioxane. The reaction of dimethylol urea and morpholine gave the bis derivative in a yield of 60%. Methylene-bis-morpholine and urea produced monomorpholinomethylurea in a yield of 33%.

Hydrolysis of these compounds in hot alkaline solution yielded morpholine quantitatively. Zinc and hydrochloric acid reduction of either compound produced N-methylmorpholine. Catalytic reduction of monomorpholinomethylurea under non-hydrolyzing conditions described in the experimental part yielded urea and the calculated anount of N-methylmorpholine.

Monomorpholinomethylurea treated with an excess of acetic anhydride yielded N-acetylmorpholine and a white solid which was provisionally identified by analysis as polymeric dimethylene urea $(\text{—CH}_2\text{NCONCH}_2\text{—})_x$. Butyric anhydride and monomorpholinomethylurea produced a similar product.



The reaction of picric acid and the morpholinomethylureas in ethanol or water solution formed impure products. Recrystallization progressively changed the melting points until they were near that of morpholine picrate. The hydrolysis indicated by this result is similar to the reported behavior of the morpholinomethyl derivatives of ketones and phenylacetonitrile.[11] It was found that the picrates of both mono- and bis-(morpholino-methyl)-urea could be prepared in glacial acetic acid.

Monomorpholinomethyl derivatives of 18 different substituted ureas were prepared. The N-morpholinomethyl-N′-acetylurea was more stable to hydrolysis than any other urea derivative studied. It formed a picrate stable in water, ethanol and glacial acetic acid, which could be recrystallized without decomposition. Acetic or butyric anhydrides reacted to form N-acetoxymethyl-N′-acetylurea and N-butyroxymethyl-N′-acetylurea, respectively. The acylmorpholine was formed simultaneously.

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[1] From a thesis submitted by Welcome I. Weaver in partial fulfillment of requirements for the degree of Doctor of Philosophy, University of Pittsburgh, 1943.

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[3] Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303–341.

[4] Henry, *Bull. soc. chim.*, **13**, 157 (1895).

[5] (a) Sach, *Ber.*, **31**, 1230 (1898); (b) Cherbuliez and Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925); (c) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

[6] Einhorn, *Ann.*, **342**, 269 (1905).

[7] Morgan and Wells, German Patent 575,114; *C. A.*, **27**, 3483 (1933).

[8] Einhorn and Spröngerts, *Ann.*, **361**, 113 (1908).

[9] Einhorn, German Patent 248,440; *Frdl.*, **12**, 702 (1915).

[10] Burke and Peters, U. S. Patent 2,281,410.

[11] Zief and Mason, *J. Org. Chem.*, **8**, 1 (1943).