[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

Some α-Alkoxyarylacetic Acids

BY WILKINS REEVE AND PAUL E. PICKERT

RECEIVED JANUARY 11, 1957

The preparations of some substituted α-methoxyphenylacetic acids and related compounds are described together with a brief summary of their physiological activity in plants.

α-Methoxyphenylacetic acid has been demonstrated to have pronounced physiological activity in many dicotyledonous plants, and it is unusual in its ability to be translocated downward through the stem and out through the root system of bean plants.[1] It is also an unusual acid in that it forms a difficultly soluble sodium acid salt corresponding to the formula $C_6H_5CH(OCH_3)COOH·C_6H_5CH(OCH_3)COONa$.[2] In view of these unusual properties, a series of related compounds has been prepared to determine the effects of structural modifications. All of the alkoxy acids have been synthesized by the same general procedure involving the conversion of an aldehyde into its cyanohydrin, hydrolysis with warm concentrated hydrochloric acid to the hydroxy acid and methylation of the hydroxyl group with a dialkyl sulfate and alkali.

Experimental

All melting points are corrected. Analyses are by Mrs. Mary Aldridge and Miss Kathryn Gerdeman of this Laboratory.

2,4-Dichloromandelic acid was prepared by the hydrolysis of **2,4-dichloromandelonitrile**. This was prepared by treating 31 g. of 2,4-dichlorobenzaldehyde, dissolved in 200 ml. of ether, with 42 g. of sodium bisulfite dissolved in 60 ml. of water. The mixture was cooled, shaken well, filtered and the solid bisulfite addition product triturated with isopropyl alcohol and filtered. There was obtained 64 g. which was dissolved in 1 l. of water, and to the cloudy solution was added 25 g. of sodium cyanide dissolved in 100 ml. of water. The solid nitrile precipitated immediately in practically quantitative yield. It was filtered off and the damp filter cake warmed to 80° with 200 ml. of concentrated hydrochloric acid for several hours and then evaporated to dryness under reduced pressure. The residue was refluxed with 200 ml. of benzene, some water present being removed with a water trap, filtered hot, the filtrate allowed to stand overnight and the crystals (25 g.) of the 2,4-dichloromandelic acid filtered off. Concentration of the benzene mother liquor yielded 3 g. more. After recrystallizing from ten times its weight of benzene, the acid melted at 120–121°.

Anal. Calcd. for $C_8H_6O_3Cl_2$: C, 43.46; H, 2.74; neut. equiv., 221. Found: C, 43.54; H, 2.74; neut. equiv., 223.

2,4-Dichloro-α-methoxyphenylacetic acid was prepared by the methylation of the 2,4-dichloromandelic acid with dimethyl sulfate as in the case of mandelic acid itself.[2] From 22 g. of the 2,4-dichloromandelic acid was obtained 30 g. of a mixture of the sodium salts of the methylated and unmethylated acids. This was dissolved in ten times its weight of water, acidified to expel carbon dioxide, sodium hydroxide added to a *p*H of 6 to 7 and four times the theoretical amount of hydrated barium chloride dissolved in ten times its weight of water. The precipitated barium salt of the methoxy acid was heated on the steam-bath with a 1 *N* barium chloride solution to dissolve traces of the soluble barium 2,4-dichloromandelate, cooled and filtered; 22 g. was obtained. The **barium 2,4-dichloro-α-methoxyphenylacetate** can be recrystallized from thirty times its weight of hot water.

Anal. Calcd. for $C_{18}H_{14}O_6Cl_4Ba$: $-OCH_3$, 10.24. Found: $-OCH_3$ 10.01.

In the case of the magnesium salts, the relative solubilities are reversed, the magnesium 2,4-dichloromandelate being the less soluble.

2,4-Dichloro-α-methoxyphenylacetic acid was prepared from its barium salt by treatment with 3 *N* hydrochloric acid. Extracted with ether and recrystallized from cyclohexane, it melted at 115°.

Anal. Calcd. for $C_9H_8O_3Cl_2$: C, 45.98; H, 3.43; Cl, 30.16; $-OCH_3$, 13.20; neut. equiv., 235. Found: C, 46.17; H, 3.45; Cl, 30.02; $-OCH_3$, 13.12; neut. equiv., 236.

3,4-Dichloro-α-methoxyphenylacetic acid was prepared from 3,4-dichlorobenzaldehyde by the same method used in the preparation of 2,4-dichloro-α-methoxyphenylacetic acid. From 31 g. of 3,4-dichlorobenzaldehyde was obtained the **3,4-dichloromandelonitrile** as an oil which was hydrolyzed with 250 ml. of concentrated hydrochloric acid in a flask at steam-bath temperature for 10 hr. with mechanical stirring. After evaporating off the hydrochloric acid, the residual oil was treated with excess sodium bicarbonate solution, and this solution was then acidified and extracted with ether. On evaporating the ether there was obtained 29 g. of the **3,4-dichloromandelic acid** as an oil. This was methylated as before; the crude sodium 3,4-dichloro-α-methoxyphenylacetate was insoluble in the reaction mixture and filtered off. This was converted to the crude acid with 6 *N* hydrochloric acid. The acid was purified by converting it into its sodium salt again and treating a 0.5 *M* solution of this with an equal volume of 20% sodium hydroxide solution. The precipitated sodium salt of the methoxy acid was filtered off, dissolved in water and the water solution acidified with 6 *N* hydrochloric acid and extracted with ether; 10 g. of the 3,4-dichloro-α-methoxyphenylacetic acid was obtained as an oil. After being crystallized from 400 ml. of 60–80° petroleum ether, the material (7 g.) melted at 89°.

Anal. Calcd. for $C_9H_8Cl_2O_3$: C, 45.98; H, 3.43; Cl, 30.16; $-OCH_3$, 13.20. Found: C, 45.82; H, 3.24; Cl, 29.97; $-OCH_3$, 13.19.

This acid could be demonstrated to form a sodium acid salt by titrating a 5% solution in isopropyl alcohol with 0.5 *N* aqueous sodium hydroxide solution to the phenolphthalein end-point and then back titrating half way with 0.5 *N* hydrochloric acid. After standing ten minutes and scratching the walls of the flask with a stirring rod, crystals of the sodium acid salt began to precipitate. Unlike the sodium acid salt of α-methoxyphenylacetic acid, the material could not be crystallized from water; it dissociated into the free acid which remained insoluble in the aqueous solution and the normal sodium salt which stayed in solution.

N-Carbethoxy-O-methyl-3-chlorophenylhydroxylamine.—*m*-Chlorophenylhydroxylamine was prepared from *m*-chloronitrobenzene in 30% yield (19% after recrystallization from petroleum ether) by a zinc dust reduction under the same conditions as used for phenylhydroxylamine.[3] It melted at 47–49° as reported.[4] This was converted to **N-carbethoxy-3-chlorophenylhydroxylamine** by the same procedure used by Bamberger and Tschirner[5] in the case of phenylhydroxylamine. From 20 g. was obtained 15 g. of the crude solid product. This was recrystallized from 60–80° petroleum ether giving 12 g., m.p. 43–44° (yield 80%).

---

[1] John W. Mitchell and William H. Preston, Jr., *Science*, **118**, 518 (1953); W. H. Preston, Jr., John W. Mitchell and Wilkins Reeve, *ibid.*, **119**, 437 (1954).

[2] Wilkins Reeve and Ivan Christoffel, THIS JOURNAL, **72**, 1480 (1950); *Anal. Chem.*, **29**, 102 (1957).

[3] O. Kamm and C. S. Marvel in "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 445.

[4] R. D. Haworth and A. Lapworth, *J. Chem. Soc.*, **119**, 773 (1921).

[5] E. Bamberger and F. Tschirner, *Ber.*, **52**, 1121 (1919).

Anal. Calcd. for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.68. Found: C, 50.20; H, 4.71.

The N-carbethoxy-3-chlorophenylhydroxylamine was methylated with methyl iodide and potassium hydroxide by the procedure of Bamberger and Tschirner.[5] From 13 g. there was obtained 4.9 g. (42% yield) of **N-carbethoxy-O-methyl-3-chlorophenylhydroxylamine** as an orange-red oil, b.p. 128–130° at 3 mm.

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.29; H, 5.27; alkoxyl calcd. as $-OCH_3$, 25.40. Found: C, 52.52; H, 5.16; $-OCH_3$, 24.39.

α-**Ethoxyphenylacetic acid** was prepared by the diethyl sulfate alkylation of 100 g. of mandelic acid under the same conditions as employed in preparing α-methoxyphenylacetic acid except the reaction was carried out at 90° and the crude product was isolated by acidifying the cold reaction mixture to a *p*H of 1 and extracting with benzene. On removing the benzene by distillation at water-pump pressure, a light yellow oil was obtained. This was dissolved in 5% sodium hydroxide solution and the solution extracted with ether to remove non-acidic material. The aqueous solution was acidified and extracted with ether. On removing the ether, 20 g. of a light yellow oil remained. This was dissolved in 4% sodium hydroxide solution. On adding twice its volume of 50% sodium hydroxide solution, the sodium salt of the desired acid precipitated, and any sodium mandelate present remained dissolved. After repeating the precipitation, a solution of the sodium salt was acidified, extracted with ether and the ether removed by distillation. Nine grams (7% yield) of the α-ethoxyphenylacetic acid was obtained as a light yellow oil, $d^{25}{}_4$ 1.121, n^{25}D 1.5120.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72; $-OC_2H_5$, 25.01. Found: C, 66.77; H, 6.68; $-OC_2H_5$, 25.03.

On attempting to distil the material under reduced pressure, it decomposed to phenyl ethyl ether.[6]

α-**Methyoxydiphenylacetic acid** was prepared by methylating benzylic acid with a fivefold excess of dimethyl sulfate in a sodium hydroxide solution at 50° as in the previous cases. Sodium α-methoxydiphenylacetate was precipitated by adding two volumes of 25% sodium hydroxide solution to 0.25 *M* solution of the crude sodium salt. Sodium benzylate remained in solution under these conditions. The sodium α-methoxyldiphenylacetate was dissolved in fifteen parts of water and converted to the free acid with 6 *N* hydrochloric acid. An oil was obtained which soon solidified to the solid acid melting at 105°. Recrystallization from 60–80° petroleum ether gave pure α-methoxydiphenylacetic acid melting at 106.5–107°. Reported values range from 99 to 112°, but Ziegler and Thielmann report 107° using another method of preparation.[7]

Methyl α-**methoxyphenylacetate** was prepared by slowly adding the free acid to excess diazomethane in methylene dichloride. The boiling point was 96–97° at 6 mm., n^{25}D 1.5010. McKenzie and Wren report a boiling point at 118° at 8 mm.[8]

2,4-Dichlorophenylacetic acid was prepared by refluxing 2,4-dichlorobenzyl chloride with twice the theoretical amount of sodium cyanide for 20 hr. in a 2:1 alcohol–water solution. **The 2,4-dichlorophenylacetonitrile** was obtained in 75% yield as a white solid, b.p. 145 at 13 mm., m.p. 62–62.5° after two recrystallizations from cyclohexane.

Anal. Calcd. for $C_8H_5NCl_2$: C, 51.65; H, 2.71; N, 7.53; Cl, 38.12. Found: C, 51.76; H, 2.76; N, 7.41; Cl, 37.96.

The nitrile was hydrolyzed to the acid in about 70% yield by refluxing 6 hr. with three times the theoretical amount of a 25% sodium hydroxide solution. The acid was recrystallized twice from benzene. It was a white solid, m.p. 132–133°.

Anal. Calcd. for $C_8H_6O_2Cl_2$: C, 46.85; H, 2.95; Cl, 34.58; neut. equiv., 205. Found: C 47.13; H 2.97; Cl, 34.36; neut. equiv., 206.1.

This acid has been examined by other investigators as a plant growth regulator and for its effect on glucose fermentation, but its method of preparation and physical properties have not been reported.

3,4-Dichlorophenylacetic acid was prepared as previously described.[9] This is essentially the same method as given above for the isomeric 2,4-dichlorophenylacetic acid, except that in the case of the 3,4-dichloro compounds the rate of nitrile formation and hydrolysis proceeds two to three times more rapidly. After recrystallizing twice from benzene, once from water and once more from benzene, the acid melted at 90.5–91.5°. The reported value[9] is 82–82.5°.

Anal. Calcd. for $C_8H_6O_2Cl_2$: C, 46.85; H, 2.95; Cl, 34.58; neut. equiv., 205. Found: C, 46.97; H, 3.00; Cl, 34.78; neut. equiv., 205.

Discussion

All of the acids prepared were examined to determine if they would form sodium salts sufficiently insoluble to be of interest in analytical chemistry and were examined for physiological activity in plants by J. W. Mitchell and W. H. Preston, Jr., of the U. S. Department of Agriculture. Only the 3,4-dichloro-α-methoxyphenylacetic acid showed any tendency to form an insoluble sodium acid salt, and in this case the acid salt was decomposed by boiling water.

The physiological activity of the compounds in plants will be presented in detail elsewhere. In general, these compounds affect dicotyledonous plants in somewhat the same way as 2,4-dichlorophenoxyacetic acid. The following briefly summarizes the conclusions that have been drawn so far about the effect of structure modifications on activity. In this series, physiological activity is relatively marked when the basic skeleton is a substituted aryl acetic acid. Without the α-methoxy group, the compound does not appear to be translocated as readily through the plant. This group increases water solubility, and α-methoxy acids are not metabolized in the plant as readily or in the same way as α-hydroxy acids. An α-ethoxy group is slightly less effective. Replacing the aryl group of the α-methoxyphenylacetic acid with either methyl or hydrogen practically eliminates activity. Likewise, replacing the hydrogen on the α-carbon with a phenyl group gives an inactive product; replacing the carboxylic acid group by hydrogen or an hydroxymethyl group leads to inactivity. The methyl ester of α-methoxyphenylacetic acid is almost as active as the free acid itself. Chlorine substituents in the 2,4- and the 3,4-positions of the ring increase activity. Replacing the α-carbon atom of the ethyl α-methoxyphenylacetate by a nitrogen atom gives N-carbethoxy-O-methylphenylhydroxylamine. The *m*-

---

(6) This ethoxy acid has been prepared by other methods, but it is poorly characterized in the literature. A. McKenzie (*J. Chem. Soc.*, **75**, 755 (1899)) prepared the acid as an oil and satisfactorily analyzed its barium, silver and zinc salts but gave no analytical data on the acid. A. Findlay and W. E. S. Turner (*ibid.*, **87**, 755 (1905)) prepared the free acid as an oil but gave no physical properties of their product or analytical data. A. Findlay, W. E. S. Turner and G. E. Owen (*ibid.*, **95**, 939 (1909)) stated that the acid could be distilled under reduced pressure, and K. Hess and K. Dorner (*Ber.*, **50**, 393 (1917)) gave a b.p. of 172–173° at 17–18 mm., but neither gave any analytical data to show that decarboxylation had not occurred. P. Hebert (*Bull. soc. chim. France*, **27**, 50 (1920)) also obtained the acid as an oil, and his material gave a satisfactory carbon–hydrogen analysis. E. D. Bergmann, D. Ginsburg and D. Lavie (THIS JOURNAL, **72**, 5012 (1950)) prepared the acid by essentially the same method used by Hebert. Their product was distilled at 3 mm. pressure and was satisfactorily analyzed. Our α-ethoxyphenylacetic acid would not distil without decarboxylation even at an initial pressure of 1 mm.

(7) K. Ziegler and F. Thielmann, *Ber.*, **56**, 1741 (1923).

(8) A. McKenzie and H. Wren, *J. Chem. Soc.*, **97**, 483 (1910).

(9) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 631 (1946).

chloro derivative of this is inactive, but the hydroxylamine without the methyl group, N-carbethoxy-*m*-chlorophenylhydroxylamine, affected the growth of grasses but was inactive when applied to dicotyledonous plants.

COLLEGE PARK, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Base-Catalyzed Condensations of Aldehydes with α,β-Unsaturated Ketones[1]

BY SARGENT G. POWELL AND WILLIAM J. WASSERMAN[2]

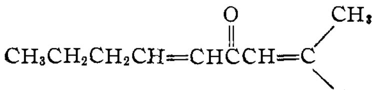
RECEIVED JUNE 19, 1956

Condensations of α,β-unsaturated ketones with aldehydes were studied in an attempt to determine the site of condensation in the ketones. Butyraldehyde condensed with mesityl oxide to give 2-methyl-2,5-nonadien-4-one, the result of condensation with the α-methyl group. The condensation of benzaldehyde with 2,2-dimethyl-4-hexen-3-one gave 2,2-dimethyl-7-phenyl-4,6-heptadien-3-one, the product resulting from condensation in the vinylogous γ-position.

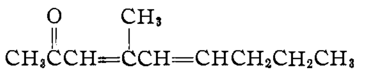
In the past 75 years since Claisen and Claparede[3] first studied the condensation of benzaldehyde with mesityl oxide many condensations of aldehydes and ketones with α,β-unsaturated carbonyl compounds have been observed, but very few have been investigated sufficiently to elucidate the nature of the condensation products. Where condensation was possible on both the vinylogous γ-carbon and on the α-methyl or methylene group of the α,β-unsaturated ketone (1-acetyl-2-methylcyclohexene,[4] 3,5-dimethyl-2-cyclohexen-1-one[5] and 3,4,5,6-tetrahydroacetophenone),[6] investigation of the condensation product showed the condensation to have occurred on the α-methyl or methylene group.

Butyraldehyde was condensed with mesityl oxide in dioxane using potassium hydroxide as the catalyst. Besides the 2-ethyl-2-hexenal resulting from self condensation of butyraldehyde, two products were isolated.

The lower boiling product (I) was found to have a molecular weight of 151 corresponding to either Ia or Ib.


$CH_3CH_2CH_2CH{=}CH\overset{\overset{O}{\|}}{C}CH{=}C\begin{smallmatrix}CH_3\\ CH_3\end{smallmatrix}$

Ia


$CH_3\overset{\overset{O}{\|}}{C}CH{=}\overset{\overset{CH_3}{|}}{C}CH{=}CHCH_2CH_2CH_3$

Ib

Hydrogenation of I gave II which was identical with a sample of 2-methyl-4-nonanone prepared by an authentic method, and did not agree in properties with a sample of 4-methyl-2-nonanone prepared by an authentic method. In this case, therefore, the condensation had occurred with the α-methyl group in preference to the vinylogous carbon.

The other product, b.p. 125–127° (5 mm.), was not satisfactorily identified. Cryoscopic determination of its molecular weight gave a value of 178 as compared to an expected value of 180 for 2,4-diethyl-2,4-octadienal[7] ($C_{12}H_{20}O$, arising from a condensation of 2-ethyl-2-hexenal and butyraldehyde). Analysis of a 2,4-dinitrophenylsemicarbazone supported the presumed structure. Hydrogenation data seemed to indicate the presence of impurities. The product of the platinum-catalyzed hydrogenation gave a 2,4-dinitrophenylsemicarbazone which analyzed correctly for 2,4-diethyloctanal 2,4-dinitrophenylsemicarbazone.

Since only a small sample of the highest boiling product had been obtained, it seemed profitable to examine the contents of the residue of the distillation of the C.P. butyraldehyde used in the condensation. The lower boiling constituents of the residue were identified as 2-ethyl-2-hexenal, butyric acid and butyraldol. Another fraction, b.p. 97–100° (0.5 mm.), was identified as 2-ethyl-3-hydroxy-1-hexyl butyrate.[8] The hydroxyester was conclusively identified by saponification and identification of the butyric acid and 2-ethyl-1,3-hexanediol produced. The presence of the hydroxyester in the butyraldehyde residues is difficult to explain since the ordinary Tischenko reaction is promoted by basic catalysts.[9] Since the formation of the hydroxyester probably occurred in an acid medium (assuming the auto-oxidation of butyraldehyde to butyric acid to be the initial reaction) it is most likely that the hydroxyester was formed by some type of acid-catalyzed Tischenko reaction from butyraldehyde and butyraldol.

After determining that the methyl group in the α-position is preferred as a condensation site to the vinylogous position, it seemed desirable to extend the comparison to other groups placed in the α-po-

---

[1] Abstracted from a dissertation submitted by William J. Wasserman to the University of Washington in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Division of Natural Sciences, Humboldt State College, Arcata, Calif. Please address all inquiries to this author.

[3] L. Claisen and A. Claparede, *Ber.*, **14**, 349 (1881).

[4] R. B. Turner and D. M. Voitle, THIS JOURNAL, **72**, 4166 (1950); W. S. Johnson, J. Szmuszkovicz and M. Miller, *ibid.*, **72**, 3726 (1950).

[5] E. Knoevenagel, *Ann.*, **281**, 117 (1894).

[6] R. E. Christ and R. C. Fuson, THIS JOURNAL, **59**, 893 (1937).

[7] Similar products had reportedly been isolated from butyraldehyde self-condensations. F. Bauer (*Monatsh.*, **25**, 1 (1904)) obtained $C_{12}H_{20}O$, b.p. 200° (20 mm.). A. Gorhan (*ibid.*, **26**, 73 (1905)) and C. Weizmann and S. F. Garrard (*J. Chem. Soc.*, **117**, 324 (1920)) obtained $C_{12}H_{22}O_2$, b.p. 160–162° (12 mm.) which the latter believed to be 2,4-diethyl-3-hydroxy-4-octenal.

[8] This compound had previously been observed by V. Grignard and M. Fluchaire (*Ann. chim.*, [10] **9**, 18 (1928)) and F. J. Villani and F. F. Nord (THIS JOURNAL, **69**, 2605 (1947)), to be among the base-catalyzed self-condensation products of butyraldehyde. It had also been identified by J. von Braun and G. Manz (*Ber.*, **67**, 1696 (1934)) among the products resulting from the heating of butyraldehyde in an inert atmosphere.

[9] T. A. Geissman, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 102; W. A. Waters, "Organic Chemistry," H. Gilman, editor, Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 1244.