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

The Synthesis of α-Methoxyarylacetic Acids from the Base-catalyzed Condensation of Arylaldehydes with Haloforms and Methanol

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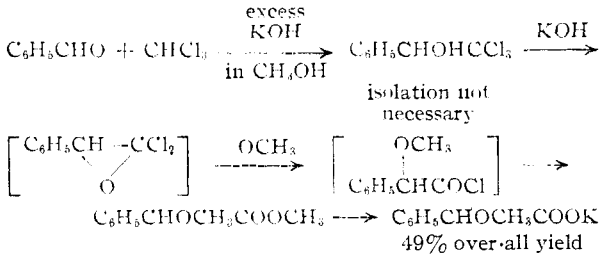
A one-step synthesis of salts or esters of α-methoxyarylacetic acids has been developed starting with arylaldehydes, chloroform or bromoform, and sodium methoxide or potassium hydroxide in methanol. Eight arylaldehydes have been studied. The mechanism of the reaction and nature of the by-products are discussed. The α-methoxyarylacetic acids are unusual in that most of them form sodium *acid* salts, and these have been found to be ideal intermediates for isolating and purifying the acids. The acids are also plant growth regulators, and the influence of structure on this characteristic property is discussed.

α-Methoxyarylacetic acids are of interest because many of them are plant growth regulators,[2,3] and also because many members of this series have the unusual property of forming sodium acid salts, of which one has been demonstrated to be useful in analytical chemistry.[4] Of the several methods described in the literature for synthesizing these compounds, the best is the one which involves converting the aromatic aldehyde to the cyanohydrin, hydrolyzing this with concentrated hydrochloric acid, and methylating the arylglycolic acid with a large excess of dimethyl sulfate in a strongly alkaline solution.[5] This sequence of reaction fails with compounds which contain other functional groups which are sensitive to acid or base or which can be methylated.

The object of this work was to develop further an alternative synthesis of the α-methoxyarylacetic acids involving the condensation of an arylaldehyde with chloroform to form an aryltrichloromethylcarbinol, and the conversion of the latter to the methoxy acid by reaction with methoxide ion in methanol. By this method, acid-sensitive compounds such as α-methoxy-2-furylacetic acid can be synthesized. Of even more importance, the reaction from the aldehyde to the ester or salt of the methoxy acid can often be carried out in good yield in one step, thus providing an attractive synthetic method for preparing α-alkoxy acids.



There are several instances in the literature where others have treated nucleophilic reagents with trichloromethylcarbinols to form α-substituted acids, but the one-step procedure for preparing the salts or esters of α-methoxy acids directly from arylaldehydes appears to be new. The closest approach has been with a ketone, namely the synthesis of α-aryloxyisobutyric acids from acetone, chloroform, various phenols and potassium hydroxide. This was first described by Link, and others have used it more recently.[6] Trichloromethylphenylcarbinol has been converted into α-chlorophenylacetic acid by aqueous potassium hydroxide in 26% yield,[7] into α-methoxyphenylacetic acid by potassium hydroxide in methanol in 72% yield, and into α-ethoxyphenylacetic acid by sodium ethoxide in ethanol in 33% yield.[8]

An alternative mechanism for the one-step reaction would involve a dichlorocarbene as an intermediate, but the fact that the trichloromethylcarbinols can be isolated and that these react in high yield to give the final methoxy acids causes us to favor the trichloromethylcarbinols as intermediates. Part of the mechanism outlined in the above equation is similar to the mechanism previously proposed by McElvain.[9]

Results and Discussion

A series of eight arylaldehydes was converted to the corresponding α-methoxyarylacetic acids, or easily isolated salts, by reaction with chloroform or bromoform and a base in methanol solution. The results are given in Table I.

The general procedure for carrying out the reaction involved dissolving one mole of the aldehyde and 1.2 to 1.5 moles of the haloform in methanol, and adding a methanol solution of 4.5 to 5 moles of base over a 3-hour period. The preferred reaction temperature was around 5° for bromoform and 45° for chloroform. The use of bromoform is advantageous with some aldehydes, but with others chloroform works as well or better. At temperatures 10 to 20 degrees above those recommended, an uncontrollable reaction occurs between the base and the haloform, and the reaction mixture foams out of the flask. Potassium hydroxide was found to be

(1) Eastman Kodak Fellow, 1956–1957.

(2) (a) J. W. Mitchell and W. H. Preston, Jr., *Science*, **118**, 518 (1953); (b) W. H. Preston, Jr., J. W. Mitchell and W. Reeve, *ibid.*, **119**, 437 (1954).

(3) W. Reeve and P. E. Pickert, THIS JOURNAL, **79**, 1932 (1957).

(4) W. Reeve and I. Christoffel, *Anal. Chem.*, **29**, 102 (1957); W. Reeve, *ibid.*, **31**, 1066 (1959).

(5) (a) J. von Braun, E. Anton and K. Weissbach, *Ber.*, **63**, 2847 (1930); (b) W. Reeve and I. Christoffel, THIS JOURNAL, **72**, 1480 (1950).

(6) (a) G. Link, German Patent 80,986 (July 14, 1894), from *Chem. Zentr.*, **66** (II), 70 (1895); (b) P. Galimberti and A. Defranceshi, *Gazz. chim. ital.*, **77**, 431 (1947), from *C. A.*, **42**, 3362 (1948); (c) H. Gilman and G. R. Wilder, THIS JOURNAL, **77**, 6644 (1955).

(7) J. Joclcz, *Zhur. Russ. Fiz.-Khim. Obshch.*, **29**, 97 (1897), from *Chem. Zentr.*, **68** (I), 1013 (1897).

(8) (a) Ch. Weizmann, M. Sulzbacher and E. Bergmann, THIS JOURNAL, **70**, 1153 (1948); (b) E. D. Bergmann, D. Ginsburg and D. Lavie, *ibid.*, **72**, 5012 (1950); (c) P. Hebert, *Bull. soc. chim. France*, **27**, 45 (1920).

(9) S. M. McElvain and C. L. Stevens, THIS JOURNAL, **69**, 2667 (1947).

TABLE I

PERCENTAGE YIELDS OF α-METHOXYARYLACETATE SALTS FROM ARYL ALDEHYDE, HALOFORM AND BASE IN METHANOL SOLUTION

Arylaldehyde	Haloform	Yield, %, with the bases: CH_3ONa	NaOH	KOH
Benzaldehyde	$CHCl_3$	38	32	49
Benzaldehyde	$CHBr_3$	32		40
3,4-Dichloro-	$CHCl_3$			18
3,4-Dichloro-	$CHBr_3$			46
o-Methoxy-	$CHCl_3$	29		
o-Ethoxy-	$CHCl_3$	32		
2,3-Dimethoxy-	$CHCl_3$	28		
3,4-Dimethoxy-	$CHCl_3$	0		
3,4-Dimethoxy-	$CHBr_3$	19		
3,4-Diethoxy-	$CHBr_3$	24		
p-Isopropyl-	$CHCl_3$	32		

superior to sodium hydroxide as a condensing agent. This is reminiscent of the Perkin reaction where potassium salts are likewise more effective than sodium salts.[10] The fact that sodium hydroxide in an eightfold molar excess of methanol gives nearly as good a yield as sodium methoxide in methanol demonstrates that strictly anhydrous solutions are not necessary. This is a consequence of methanol being a stronger acid than water,[11] and also a strong nucleophile. However, if it is desired to isolate the ester, then the reaction mixture obviously must be anhydrous, and the base must be sodium or potassium methoxide.

By-products.—The fact that the yield of the desired α-methoxy acid never exceeded 50% of the theoretical amount prompted a study of the condensation of benzaldehyde, chloroform and sodium methoxide on a large scale (8 moles of benzaldehyde) in an effort to determine what other products were formed. These are listed in Table II; the percentage figures refer to the per cent. of benzaldehyde accounted for by the weight of the material isolated.

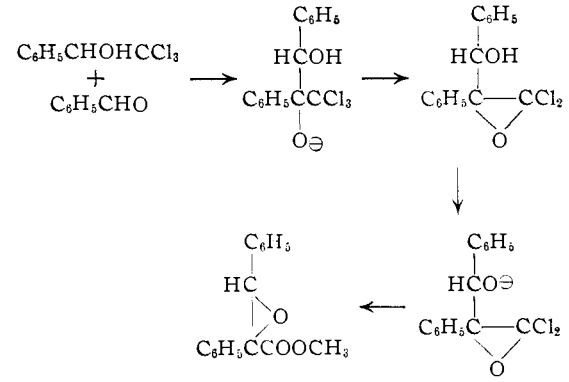
TABLE II

MATERIAL RECOVERED FROM THE REACTION OF BENZALDEHYDE, CHLOROFORM, AND SODIUM METHOXIDE IN DRY METHANOL[a]

Volatile forerun (mostly benzaldehyde and methyl benzoate)	10%
Methyl α-methoxyphenylacetate	41
Methyl α,β-diphenylglycidate	6
Sodium α,β-diphenylglycidate	3
Non-volatile residue, assumed to be polymerized glycidate	18
Total accounted for	78

[a] Eight moles of benzaldehyde, 12 moles of chloroform and 35 moles of sodium methoxide were allowed to react in anhydrous methanol at 40 to 50° over a 6-hour period.

The α,β-diphenylglycidate is believed to result from the sodium methoxide-catalyzed condensation of the trichloromethylphenylcarbinol with benzaldehyde followed by the formation and rupture of epoxide rings in a manner analogous to the sequence of reactions previously given to account for the formation of the main product.



In support of the above reaction path, it was found that trichloromethylphenylcarbinol and benzaldehyde in equimolecular amounts reacted with 3.5 moles of sodium methoxide in excess methanol at 30–50° for four hours to give an 11% yield of the methyl α,β-diphenylglycidate whereas no glycidate resulted from a similar reaction using methyl α-methoxyphenylacetate instead of the trichloromethylphenylcarbinol.

Formation of Acid Salts.—The usefulness of the haloform–arylaldehyde route to the α-methoxy acids is greatly enhanced by taking advantage of the fact that many of the latter form insoluble sodium acid salts.[3,5b] These are easily isolated, and since they are also insoluble in acetone, the unreacted materials and by-products can be separated from the acid salt by washing with this solvent. A typical example is sodium hydrogen di-(α-methoxyphenylacetate); this can be written, $C_6H_5CH(OCH_3)COOH \cdot C_6H_5CH(OCH_3)COONa$, in a manner analogous to the way double salts are represented. This acid salt is precipitated almost quantitatively from an aqueous alcoholic solution of the acid at *p*H 3.3 when sodium chloride is present.

The formation of sodium acid salts is an unusual property which only certain of the monobasic carboxylic acids possess. Thus, benzoic acid, phenylacetic acid, α-methylmercaptophenylacetic acid, α-chlorophenylacetic acid, *p*-isopropyl-α-methoxyphenylacetic acid, α-ethoxyphenylacetic acid, α,β-diphenylglycidic acid, and many other carboxylic acids will not form sodium acid salts. On the other hand, formic and acetic acids are known to form a series of sodium and potassium acid salts which are water soluble,[12] and mandelic acid forms a difficultly soluble sodium acid salt.[13] 2,4-Dichloro-α-methoxyphenylacetic acid will not form a sodium acid salt, whereas the isomeric 3,4-dichloro acid forms an insoluble one.[3] Of the nine α-methoxyphenylacetic acids studied here, all but two could be made to form sodium acid salts. In the more difficult cases, the sodium acid salt was prepared by mixing the crude oily acid with the theoretical amount of 20% aqueous sodium hydroxide solution, allowing the mixture to stand for an hour, and then washing

(10) J. R. Johnson in "Organic Reactions," Vol. I, edited by R. Adams, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 238–240.

(11) J. Hine and M. Hine, THIS JOURNAL, **74**, 5266 (1952); W. C. Woodland, R. B. Carlin and J. C. Warner, *ibid.*, **75**, 5835 (1953).

(12) J. Kendall and H. Alder, *ibid.*, **43**, 1470 (1921).

(13) A. McKenzie and N. Walker, *J. Chem. Soc.*, **121**, 356 (1922); B. F. Duesel and S. Gister, U. S. Patent 2,562,861 (July 31, 1951), *C. A.*, **46**, 1591 (1952).

the powdered, solid material with acetone to remove impurities.

The solubilities in water of the seven sodium acid salts are given in Table III.

TABLE III

SOLUBILITY IN WATER OF SODIUM ACID SALTS

Parent acid of sodium acid salt	Solubility in water at 26 ± 1°, g./100 ml.
α-Methoxyphenylacetic	2.2
3,4-Dichloro-α-methoxyphenylacetic	0.43
α,2-Dimethoxyphenylacetic	4.7
2-Ethoxy-α-methoxyphenylacetic	8.3
α,3,4-Trimethoxyphenylacetic	17
3,4-Diethoxy-α-methoxyphenylacetic	5.1
4-Bromo-α-methoxyphenylacetic	0.79

As expected, alkoxy substituents increase the water solubility of the acid salt, and halogen substituents have the opposite effect. Further work will be necessary to determine whether any of the latter are useful in analytical chemistry.

The 4-bromo-α-methoxyphenylacetic acid was also observed to form a difficultly soluble normal lithium salt, soluble in water to the extent of 1.04 g./100 ml. of water at 28°, but preliminary attempts to prepare a useful reagent from this acid for precipitating lithium were unsuccessful.

Syntheses of Some Related Compounds.—α-Methoxy-2-furanacetic acid was prepared by condensing chloroform with furfural, isolating the trichloromethylfurylcarbinol and treating this with sodium methoxide in methanol to form the methyl ester of the desired acid. Oddly enough, the free acid, obtained from the ester, did not form an insoluble sodium acid salt and exhibited no growth-regulating properties in plants.

The *p*-bromo-α-methoxyphenylacetic acid was likewise made from trichloromethyl-*p*-bromophenylcarbinol, but this intermediate was prepared from *p*-bromophenylmagnesium bromide and chloral. This method of preparing trichloromethylcarbinols has been previously used and found to work well in the aromatic series; an oxidation–reduction side reaction occurs with most aliphatic Grignard reagents.[14]

It was thought that α-methylmercaptophenylacetic acid is so closely related to the α-methoxyphenylacetic acid that their properties should be alike. The material was prepared from methyl α-bromophenylacetate and methyl mercaptan, but it did not form a sodium acid salt nor have any plant growth-regulating properties.

Physiological Activity in Plants.—All of the acids prepared were examined for physiological activity in plants by J. W. Mitchell, B. C. Smale and W. H. Preston of the U. S. Department of Agriculture, and their results have been presented in detail elsewhere.[15] In general, these α-methoxyarylacetic acids affect dicotyledonous plants in much the same way as 2,4-dichlorophenoxyacetic acid, and the following conclusions have been drawn about the effect of structural modifications on activity in the α-methoxy acid series. Replacing the α-methoxy group with amino, methyl, ethyl or methylmercapto groups results in compounds having little or no activity. Relative to α-methoxyphenylacetic acid, all alkoxy substituted α-methoxyphenylacetic acids are much less active except α,2,3-trimethoxyphenylacetic acid, which is essentially as effective as the α-methoxyphenylacetic acid, but differs in that it does not have the property of being exuded from roots in detectable amounts. Substituting an isopropyl group into the *p*-position gives an inactive material. Placing a bromine atom in the *p*-position gives a material that has essentially the same activity as the unsubstituted α-methoxyphenylacetic acid. The activity of halogen substituted α-methoxyphenylacetic acids has been observed before in the case of the 2,4- and 3,4-dichloro-α-methoxyphenylacetic acids; in these cases increased activity was observed.[5,15]

(14) See ref. 8c for references to early work. More recent work includes that of: V. W. Floutz, THIS JOURNAL, **65**, 2255 (1943); H. Gilman and R. K. Abbott, *J. Org. Chem.*, **8**, 224 (1943).

(15) J. W. Mitchell, B. C. Smale and W. H. Preston, *J. Agr. Food Chem.*, **7**, 841 (1959).

Experimental

All melting points are corrected. Analyses are by Mrs. Mary Aldridge, Miss Kathryn Gerdeman and Miss Jane Swan.

α-Methoxyphenylacetic Acid.—This preparation illustrates the general procedure for condensing a benzaldehyde with chloroform and methanol using potassium hydroxide.

A 1-liter 3-necked flask was arranged so that an external bath containing either hot or cold water could be applied. In the flask were placed 53.5 g. (0.5 mole) of benzaldehyde, 89.5 g. (0.75 mole) of chloroform and 100 ml. of methanol. The mixture was stirred and a solution of 165 g. (2.5 moles) of potassium hydroxide in 400 ml. of methanol was added dropwise over a 3-hour period. The reaction mixture was maintained at 44 to 45°; the reaction is exothermic and will get completely out of control if the temperature gets in the upper fifties. For this reason, one neck of the flask should be unstoppered. The reaction was stirred at 45° for an additional hour, and allowed to stand overnight in a water-bath at this temperature initially.

The next day, the reaction mixture was filtered and the potassium chloride filter cake stirred in a beaker three times with 50 ml. of water each time. The combined filtrates in a beaker were acidified by adding from a buret sufficient 6 *N* hydrochloric acid so that a milliliter sample when diluted with four parts of water had a *p*H of 3.3. Three hundred milliliters of a half-saturated aqueous sodium chloride solution was added, the mixture stirred for half an hour, the *p*H of the supernatant liquid checked, the beaker placed in an ice–salt-bath, the mixture stirred mechanically for an additional hour at 0° and then filtered. The filter cake was washed on the filter with 50 ml. of cold acetone, and then with 50 ml. of water at 0°. The moist filter cake was then stirred in a beaker for a few minutes with another 50 ml. of water at 0°, filtered, and washed on the filter with a final 50 ml. of cold acetone. The air-dried filter cake weighed 48 g. and was shown to be 91% pure **sodium hydrogen di-(α-methoxyphenylacetate)** by titration with standard sodium hydroxide. The yield was 49%. One recrystallization from ten times its weight of water yields a pure sample.[5b] From 50 g. of the crude sodium acid salt, there was obtained 34.5 g. (76% recovery) of the pure material, titrating 100.0% pure, without working up the filtrate.

The recrystallized acid salt was converted to the free acid by dissolving in dilute sodium or potassium hydroxide and acidifying the warm aqueous solution with an excess of 25% sulfuric acid. Most of the α-methoxyphenylacetic acid separated as an oil and was removed. The aqueous solution was extracted four times with benzene and the extracts combined with the oily acid. The benzene solution was washed with water until the aqueous washes gave no test for sulfate. The benzene solution was then distilled from a steam-bath until the temperature reached 81° and there was about 40 g. of benzene present for each 50 g. of acid theoretically present. The hot solution was filtered, and on cooling to 5° for half an hour, the pure α-methoxyphenylacetic acid crystallized out and was washed first with a little cold benzene and then with

small amounts of cold cyclohexane. It melted at 72.5–74°.[5b]

Methyl α-Methoxyphenylacetate, the Glycidates and Other By-products.—This preparation illustrates the general procedure for preparing the methyl ester of the methoxy acids; also how the by-products were isolated.

A reaction similar to the preceding one was carried out in a 12-liter 3-necked flask with 7.8 moles of benzaldehyde, 11.7 moles of chloroform and an anhydrous methanol solution of sodium methoxide prepared by dissolving 35 g. atoms of sodium in 8 l. of dried methanol. The temperature was maintained between 35 and 40° for 3 hours during the addition of the base, raised to 55° for 3 hours afterward, and allowed to cool to room temperature overnight. The excess base was neutralized by saturating the solution with carbon dioxide, and the precipitated sodium chloride and sodium methyl carbonate were filtered off. The methanol was removed by distillation under reduced pressure, and the solid material which separated during this process was twice filtered off. The clear, liquid residue amounted to 760 g. Most of this was fractionally distilled and an amount of **methyl α-methoxyphenylacetate** equivalent to 64% of the residue was obtained, b.p. 72–74° (0.6 mm.). If the residue is not promptly distilled after removing the methanol, further condensation may occur. The two solid fractions which separated during the concentration of the reaction mixture were washed with ether, and 150 g. more of the methyl ester was obtained on fractionating the ether washings.

The foreruns from the distillation of the main residue yielded benzaldehyde 2,4-dinitrophenylhydrazone on treatment with dinitrophenylhydrazine reagent, and also methyl benzoate which was identified by saponification to benzoic acid.

From the material which distilled after the methyl α-methoxyphenylacetate, and from the residue which was not distilled, 64 g. of a solid material, m.p. 82–82.5°, was obtained which was readily recrystallized from methanol. This was identified as **methyl α,β-diphenylglycidate** on the basis of its saponification equivalent, molecular weight, elemental and methoxyl analyses, and m.p. and mixed m.p. with an authentic sample, m.p. 82–83.5° from methanol, prepared from methyl α-bromophenylacetate and benzaldehyde by the general method of Johnson.[16] The literature m.p. is 80°.[17]

The gelatinous material which precipitated during the concentration of the reaction mixture weighed 75 g. after being washed with ether. It was recrystallized three times from water and 20 g. of crystalline material was obtained. On acidification of this sodium salt and recrystallization of the resulting acid from cyclohexane, α,β-diphenylglycidic acid, m.p. 115–116°, was obtained. It was identified by neutral equivalent, elemental analysis, and m.p. and mixed m.p. comparisons with the acid obtained by hydrolysis of the glycidic ester obtained from the benzaldehyde–chloroform condensation. The reported melting point is 121°.[17] The material balance in Table II was calculated from these data, allowance being made for intermediate fractions.

3,4-Dichloro-α-methoxyphenylacetic acid was prepared by the same general procedure as that first given but using bromoform instead of chloroform. To 87 g. (0.5 mole) of 3,4-dichlorobenzaldehyde, 58 ml. (0.67 mole) of bromoform and 50 ml. of methanol was added at 5 to 15° a solution of 150 g. (2.5 moles) of potassium hydroxide in 400 ml. of methanol over a period of 2 hours. After the addition was complete, the mixture was stirred for an additional 5 hours while the ice-bath slowly warmed up to room temperature, and was then allowed to stand overnight. To the mixture was added 150 ml. of water, dilute hydrochloric acid to a *p*H of 3.2, and finally 500 ml. of a half-saturated sodium chloride solution. In this case, the mixture had to stand overnight for the sodium acid salt to precipitate, and it then came out in the form of amorphous lumps. The aqueous phase was decanted, the lumps thoroughly masticated with 150 ml. of acetone, and the solid (65 g.) filtered off. After another treatment with acetone, and two washings with water, 57 g. (46% yield) of **sodium hydrogen di-(3,4-dichloro-α-methoxyphenylacetate)**, was obtained. *Anal.* Calcd. for $C_{18}H_{15}O_6Cl_4Na$: $-OCH_3$, 12.61; neut. equiv., 492. Found: $-OCH_3$, 12.99; neut. equiv., 490. The acid salt is soluble in dilute sodium or potassium hydroxide, and on acidification the acid is obtained as previously described.[3]

α,2-Dimethoxyphenylacetic Acid.—This illustrates the method by which most of the compounds were prepared prior to the discovery that potassium hydroxide was more effective as a condensing agent than sodium methoxide. The procedure was quite similar to that described above for α-methoxyphenylacetic acid. Twenty-five grams (0.18 mole) of *o*-methoxybenzaldehyde and 33 g. (0.28 mole) of chloroform were treated with a sodium methoxide solution prepared by dissolving 19 g. (0.82 g. atom) of sodium in 200 ml. of dry methanol. After the addition of the sodium methoxide solution was complete and the reaction mixture had stood for an hour, it was heated at reflux temperature for an additional hour, 35 ml. of a 20% sodium hydroxide solution was then added to hydrolyze the ester, and the reaction mixture was refluxed for another half-hour. The bulk of the methanol was removed by distillation, water was added and the solution was acidified. The crude, oily methoxy acid which separated was partially purified by dissolving in ether, extracting the acid with dilute sodium hydroxide, and reacidifying. A light colored oil was obtained which could not be made to crystallize.

The sodium hydrogen di-(α,2-dimethoxyphenylacetate) was prepared by adding to this oily acid an amount of 20% sodium hydroxide solution sufficient to half neutralize the acid. The solid sodium acid salt formed over a period of an hour. It was washed with acetone, filtered, and recrystallized from ethanol. It had a melting point of 186–189°, and a neutralization equivalent of 417 compared to the theoretical value of 414.

Some of the crude, oily acid recovered from the acetone washings of the sodium acid salt was finally made to crystallize by cooling in Dry Ice. After recrystallizing from cyclohexane, the **free acid** melted at 98–99.5°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.19; H, 6.17; $-OCH_3$, 31.66; neut. equiv., 196. Found: C, 61.13; H, 6.25; $-OCH_3$, 31.67; neut. equiv., 197. The total yield of acid and acid salt was 29%.

2-Ethoxy-α-methoxyphenylacetic acid was prepared from *o*-ethoxybenzaldehyde by the same procedure used in the preparation of the α,2-dimethoxyphenylacetic acid. The acid was obtained as a light colored oil which could not be made to crystallize. It was half neutralized with 20% sodium hydroxide, and the sodium acid salt which formed was washed with acetone and recrystallized from ethanol. The **sodium hydrogen di-(2-ethoxy-α-methoxyphenylacetate** melted at 162–165° and was obtained in 32% yield. *Anal.* Calcd. for $C_{22}H_{27}O_8Na$: C, 59.69; H, 6.15; $-OCH_3$ and $-OC_2H_5$ calcd. as $-OCH_3$, 28.04; neut. equiv., 443. Found: C, 59.61; H, 6.24; $-OCH_3$, 28.04; neut. equiv., 443.

The free acid obtained by acidifying the sodium acid salt was an oil which could be made to crystallize from petroleum ether at −70°, but the crystals melted on warming to room temperature.

α,2,3-Trimethoxyphenylacetic acid was prepared from 2,3-dimethoxybenzaldehyde by the same procedure used in the preparation of α,2-dimethoxyphenylacetic acid. The acid was an oil and it would not form a sodium acid salt. **Ammonium α,2,3-trimethoxyphenylacetate** was prepared by treating the acid with concentrated ammonium hydroxide, evaporating to dryness, and recrystallizing from ethanol. This melted at 151–155° and was obtained in 28% yield from the aldehyde. *Anal.* Calcd. for $C_{11}H_{17}O_5N$: C, 54.30; H, 7.05; $-OCH_3$, 38.27; N, 5.77. Found: C, 54.03; H, 6.95; $-OCH_3$, 38.18; N, 5.68.

α,3,4-Trimethoxyphenylacetic acid could not be prepared by the above procedure with chloroform. With bromoform and a reaction temperature of 3°, the crude trimethoxyphenylacetic acid was obtained as an oil in 55% yield. This was converted to **sodium hydrogen di-(α,3,4-trimethoxyphenylacetate)**, m.p. 191–194°, by half neutralizing with 20% sodium hydroxide, and the acid salt was recrystallized from ethanol. The over-all yield from the aldehyde to the recrystallized acid salt was 19%. *Anal.* Calcd. for $C_{22}H_{27}O_{10}Na$: neut. equiv., 474. Found: neut. equiv., 476.

The free acid was obtained by acidifying the sodium acid salt. It melted at 96–97.5° after recrystallization from *n*-butyl ether. *Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24; $-OCH_3$, 41.16. Found: C, 58.10; H, 6.09; $-OCH_3$, 40.88.

(16) W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt, THIS JOURNAL, **75**, 4995 (1953).

(17) E. P. Kohler and F. W. Brown, *ibid.*, **55**, 4299 (1933).

3,4-Diethoxy-α-methoxyphenylacetic acid was prepared from 3,4-diethoxybenzaldehyde and bromoform by the same procedure used in the preparation of the α,3,4-trimethoxyphenylacetic acid. The oily acid was converted into its acid salt by half neutralization with 20% sodium hydroxide. **The sodium hydrogen di-(3,4-diethoxy-α-methoxyphenylacetate)**, m.p. 156–157.5° after crystallization from ethanol, was obtained in 24% yield from the aldehyde. *Anal.* Calcd. for $C_{26}H_{33}O_{10}Na$: C, 58.87; H, 6.65; $-OCH_3$ and $-OC_2H_5$ calcd. as $-OCH_3$, 35.10; neut. equiv., 531. Found: C, 58.95; H, 6.74; $-OCH_3$, 34.83; neut equiv., 535.

A solid free acid was obtained by acidifying the acid salt, but attempts to recrystallize it from various solvents gave only an oil.

4-Isopropyl-α-methoxyphenylacetic acid was prepared from *p*-isopropylbenzaldehyde by the same procedure used in the preparation of α,2-dimethoxyphenylacetic acid. After distilling off most of the methanol, water was added to the reaction mixture to dissolve the sodium chloride, and the insoluble **normal sodium salt** was filtered off; the yield was 32%. The sodium salt was shaken with ether and dilute hydrochloric acid until the solid had dissolved. Evaporation of the ether yielded the oily acid which was converted to the ammonium salt by evaporating to near dryness with an excess of concentrated ammonium hydroxide. Recrystallization of the wet solid from an ethanol–water mixture containing a few drops of ammonium hydroxide gave the pure **ammonium salt**, m.p. 200–201°. *Anal.* Calcd. for $C_{12}H_{19}O_3N$: C, 63.96; H, 8.50; $-OCH_3$, 13.77; N, 6.22. Found: C, 64.26; H, 8.33; $-OCH_3$, 14.10; N, 5.79.

Acidifying the ammonium salt gave the crystalline **free acid**, m.p. 51–53.5°. The reported m.p. is 52–53°.[18]

α-Methoxy-2-furanacetic Acid.—To 200 g. (2 moles) of freshly distilled furfural and 470 g. (4 moles) of chloroform at 0° and under a nitrogen atmosphere was added 140 g. (2 moles) of dried powdered potassium hydroxide in small portions at 1-minute intervals over a 2-hour period with vigorous stirring. Stirring was continued for 2 more hours, and the temperarure was allowed to rise slowly to 20°. Then, 150 ml. of water was added, the mixture was acidified to *p*H 6 with 6 *N* sulfuric acid, 100 ml. of chloroform was added, and the mixture was filtered to remove a large quantity of potassium sulfate. The two layers were separated, the aqueous layer extracted with more chloroform, and the combined chloroform extracts were thoroughly washed with sodium carbonate solution, water, and dried. Distillation at 3 mm. pressure gave 125 g. (29% yield) of the **α-(trichloromethyl)-furfuryl alcohol**, b.p. 94–105°.

This material was treated with a sodium methoxide solution prepared by dissolving 35 g. (1.5 g. atoms) of sodium in 500 ml. of anhydrous methanol. After standing overnight at room temperature, it was heated at reflux temperature for 6 hours. The alcoholic solution was decanted from the sodium chloride, the alcohol distilled off under reduced pressure, and the residue distilled at 5 mm. pressure. The fraction distilling between 85 and 120° was refractionated through a glass helices packed column and 10 g. (10% yield based on the trichlorocarbinol) of **methyl α-methoxy-2-furanacetate** was obtained, b.p. 77–81° at 2 mm. *Anal.* Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92; $-OCH_3$, 36.45. Found: C, 56.16; H, 5.67; $-OCH_3$, 36.41.

The normal sodium salt was prepared by mixing 0.006 mole of the ester with 0.004 mole of water and 0.004 mole of sodium methoxide in 2 ml. of anhydrous methanol. After standing half an hour at room temperature, crystals of the **sodium salt** precipitated. These were filtered off, and were recrystallized from an ethanol–water mixture. *Anal.* Calcd. for $C_7H_7O_4Na$: $-OCH_3$, 17.40. Found: $-OCH_3$, 17.50.

The free acid was prepared by treating the sodium salt with an exactly equivalent amount of dilute sulfuric acid, extracting with ether, washing the ether with small portions of water until free of sulfate, and evaporating the ether to yield brown crystals. Recrystallizing these from petroleum ether gave white crystals of the **free acid**, m.p. 42–45°. The free acid was not stable and decomposed after standing for several months. *Anal.* Calcd. for $C_7H_8O_4$: C, 53.84; H, 5.16; $-OCH_3$, 19.85. Found: C, 53.57; H, 5.35; $-OCH_3$, 19.92.

4-Bromo-α-methoxyphenylacetic Acid.—*p*-Bromophenylmagnesium bromide was prepared in the usual way from *p*-dibromobenzene. To this Grignard reagent was added an equivalent amount of anhydrous chloral in ether, the reaction mixture worked up in the usual way, and the 4-bromo-α-(trichloromethyl)-benzyl alcohol obtained as a light yellow viscous liquid distilling at 18 mm. The yield of crude material was 49% (62 g.). Hebert reports a 29% yield of material by this method of preparation.[8c] This material was treated with four equivalents of potassium hydroxide in methanol, first at room temperature and then for half an hour at reflux temperature. The reaction mixture was worked up in the usual way and the crude free acid obtained as an oil. This was converted into the sodium acid salt by treatment with half an equivalent of 20% sodium hydroxide solution, and the acid salt which formed was washed thoroughly with acetone. Two recrystallizations from 1:1 aqueous methanol gave the pure **sodium hydrogen di-(*p*-bromo-α-methoxyphenylacetate)**, m.p. 234.5–238.5°, in 51% yield, based on the trichloromethylcarbinol. *Anal.* Calcd. for $C_{18}H_{17}O_6Br_2Na$: neut equiv., 512. Found: neut. equiv., 514.

Acidifying the sodium acid salt gave the crystalline **free acid**, m.p. 95.5–97° after recrystallization from petroleum ether. *Anal.* Calcd. for $C_9H_9O_3Br$: C, 44.10; H, 3.70; $-OCH_3$, 12.66. Found: C, 44.31; H, 3.62; $-OCH_3$, 12.42.

***o*-Methylmercaptophenylacetic acid** was prepared by treating 25 g. (0.11 mole) of methyl α-bromophenylacetate[19] at 0° with a solution containing 0.11 mole of sodium methyl mercaptide in 30 ml. of methanol. After standing overnight the solution was heated on the steam-bath for 2 hours, excess sodium hydroxide solution then added to hydrolyze the ester, the methanol evaporated off, the neutral material removed by an ether extraction, and the acid isolated by acidifying and again extracting with ether. On evaporating the ether, the oily acid readily solidified. After recrystallizing four times from 60-ml. portions of cyclohexane, 15 g. (76% of theory) of the free acid was obtained, m.p. 79–80.5°.

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.59; H, 5.65; S, 17.29.

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