The dibenzoate caused irritation of the eye. The dicinnamate caused a milky film to appear over the cornea, sloughing of the tissue, and about twelve hours later, marked conjunctival irritation and swelling of the eyelids. The difuroate and the difuranacrylate seemed to have a lachrymatory effect, but caused very little, if any, irritation of the eyes. There was considerable difficulty in obtaining a solution of the dicinnamate. A few drops of hydrochloric acid were used to produce the 1% suspension for testing on the cornea, and a 25% solution of propylene glycol was required to produce the 1% solution for testing on the sciatic nerve of the frog.

It will be seen that the dibenzoate was more active than the difuroate, which agrees with the findings of Gilman and Pickens.[3] However, introduction of a double bond appears to reverse this order, the difuranacrylate being more active than the dicinnamate. In the furan series, the introduction of the double bond gave an expected increase in activity, the furanacrylate being twice as active as the furoate. A similar increase in activity is not found on comparing the dicinnamate with the dibenzoate, but this may have been due to the low solubility of the dicinnamate and the precipitation on application to the eye. The dicinnamate showed rapid penetration when applied to the nerve. As was expected, the diacetate was inactive. The furan compounds have the advantage over the benzene analogs of being more soluble and less irritating.

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Summary

The diacetate, dibenzoate, difuroate, dicinnamate, and difuranacrylate of piperidinopropanediol were prepared. The results of the pharmacological tests indicate that the furan ring has a favorable effect on anesthetic action. It apparently increases the solubility and decreases the irritation in this series of compounds.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

Addition Reactions of Unsaturated Alpha-Ketonic Acids. V

BY MARIE REIMER AND ELIZABETH CHASE

Earlier papers in this series[1] have shown that the behavior of the unsaturated side-chain of benzalpyruvic acid is influenced strongly by methoxyl groups in different positions in the benzene ring: the stability of the dibromo addition products, the tendency to formation and the stability of hydrates, the color of the compounds alone and in solution in concentrated sulfuric acid show decided variation in the different compounds. Most striking is the fact that a methoxyl group in the para position entirely inhibits the photochemical reaction so conspicuous a characteristic of benzalpyruvic acid and its esters[2] and noticeable to a less degree with the *o*- and the *m*-methoxy-substituted acids. Because of the prevalence of methoxyl groups in natural products and because of differences in activity noticed when methoxyl replaces hydrogen in several different classes of compounds,[3] it becomes of interest to determine whether the blocking of the sunlight reaction is a function of the *p*-methoxyl group, as such, or whether and to what extent other groups in the para position in the benzene ring have the same effect. Such studies are now under way in this Laboratory.

The present paper deals with benzalpyruvic acid in which there is a methyl group in the para position. The methyl group was chosen because of certain well-known similarities in the influence of methyl and methoxyl: the effect on orientation in the benzene ring, on ease of substitution and on the coupling reaction,[4] for example. These, however, are influences of these groups on hydrogen of the ring. In reactions involving a side-chain wide differences have been described, not-

(1) No. IV, Reimer, Tobin and Schaffner, THIS JOURNAL, **57**, 211 (1935).

(2) Reimer, *ibid.*, **46**, 783 (1924).

(3) *Cf.* Reimer, *ibid.*, **48**, 2454 (1926).

(4) V. Auwers and Borsche, *Ber.*, **48**, 1716 (1915).

ably the greater effect of the methoxyl over that of the methyl group on dissociation into free radicals of hexaarylethanes[5] and of phenylated hydrazines[6] and the increased "migration aptitude" of the anisyl group.[7] In the case here studied differences have been noted. The *p*-methylbenzalpyruvic acid adds bromine readily to form a dibromide more stable than that of the *p*-methoxy compound but less so than that of the unsubstituted acid. It forms an unstable hydrate: that of benzalpyruvic acid is stable while the *p*-methoxy acid forms no hydrate. The methyl substituted acid is slowly affected by sunlight. The color changes with sulfuric acid are not so marked as with the methoxy acid. In all these reactions the effect of the methyl group is seen to be intermediate between that of methoxyl and of hydrogen in the para position.

Experimental Part

4-Methylbenzalpyruvic acid was prepared by mixing 17.6 g. (0.2 mole) of pyruvic acid with 24 g. (0.2 mole) of toluic aldehyde and adding slowly, with stirring, 55 cc. (0.23 mole) of a 25% solution of potassium hydroxide in methyl alcohol. The temperature was kept at about 10°. Toward the end of the reaction a yellow color developed and the yellow condensation product crystallized out. After standing overnight, this was filtered and washed with methyl alcohol and with ether; yield of pure product, 95%. From a cooled, saturated aqueous solution of this potassium salt, hydrochloric acid precipitated an acid which crystallized from boiling benzene in bright canary yellow plates melting at 127°. The acid is fairly soluble in boiling water, more soluble in the usual organic solvents.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.86; H, 5.37.

If the acid is allowed to crystallize slowly from dilute aqueous solution it separates in long shining yellow needles which soften about 80° and melt 100–110°. The needles rapidly become opaque and then melt at 127°. This loss of water is so rapid that no significant analyses could be obtained.

On exposure of the pure acid to the sunlight, the odor of *p*-tolualdehyde is at once apparent showing oxidation of the acid at the ethylenic linkage. The yellow color of the acid fades slowly. After several weeks' exposure the pale tan amorphous product was dissolved in benzene, the sirupy solution filtered and allowed to evaporate at room temperature. From the dark shellac-like mass which resulted none of the original acid nor any other crystalline product could be separated. It is undoubtedly a mixture of oxidation and polymerization products. The acid is perfectly stable in the dark.

The methyl ester of *p*-methylbenzalpyruvic acid, prepared readily by dissolving the acid in a small volume of cold methyl alcohol saturated with hydrochloric acid, crystallized from boiling methyl alcohol in slender pale yellow needles melting at 81°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.56; H, 5.88. Found: C, 70.70; H, 6.16.

After long exposure of the ester to bright sunlight about one-half was regained unchanged. The residue was a heavy reddish oil, evidently a mixture of products like that obtained from the acid.

The ethyl ester, prepared in the same way, did not crystallize from the alcohol–acid mixture. When the reaction mixture was poured into iced sodium carbonate solution an oil separated which quickly solidified. The solid separates from a slightly warmed concentrated solution of ethyl alcohol to which a few drops of water have been added in light yellow shining plates melting at 44–46°. From a more dilute solution it crystallizes slowly in stiff yellow needles of the same melting point.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.22; H, 6.53.

Reactions with Bromine

4-Methylbenzalpyruvic Acid Dibromide, $CH_3C_6H_4CHBr$-$CHBrCOCOOH$.—To the pyruvic acid dissolved in iced, dry chloroform, one molecular proportion of bromine was added drop by drop. The decolorization was rapid. Toward the end of the reaction the dibromo addition product separated out as a nearly white, granular solid, which, after washing with cold chloroform, melted at 145–147°. A further quantity was obtained from the filtrates; yield 84%. The compound can be crystallized from benzene but a purer product is obtained by adding an equal volume of low boiling ligroin to the warm benzene solution.

Anal. Calcd. for $C_{11}H_{10}O_3Br_2$: C, 37.71; H, 2.86. Found: C, 37.76; H, 3.73.

The methyl ester of the dibromo acid may be prepared by dissolving the acid in the smallest possible quantity of methyl alcohol, saturated with hydrogen chloride or with an ethereal solution of diazomethane. It separates from methyl alcohol in shining plates melting at 86–87°.

Anal. Calcd. for $C_{12}H_{12}O_3Br_2$: C, 39.56; H, 3.29. Found: C, 39.64; H, 3.53.

β-Bromo-4-methylbenzalpyruvic Acid, $CH_3C_6H_4CH{=}$ $CBrCOCOOH$.—On boiling the dibromo acid for a few minutes with water and allowing the filtered solution to cool, crystals of the unsaturated acid separated in colorless needles. The compound does not crystallize with water as do the corresponding bromo-*p*-methoxyl- and the unsubstituted bromobenzalpyruvic acids. It separates from boiling benzene in fine, colorless needles melting at 182°.

Anal. Calcd. for $C_{11}H_9O_3Br$: C, 49.07; H, 3.34. Found: C, 48.90; H, 3.28.

The methyl ester cannot be prepared by action of methyl alcohol and hydrogen chloride. This is also the case with all other β-bromobenzalpyruvic acids so far studied. It is obtained readily by action of diazomethane in ethereal solution. It separates from boiling methyl alcohol in colorless crystals melting at 77°.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.88; H, 3.88. Found: C, 50.91; H, 3.75.

(5) Gomberg and Buchler, THIS JOURNAL, **45**, 207 (1923).

(6) Wieland and Lecher, *Ann.*, **381**, 206 (1911); *Ber.*, **45**, 2600 (1912).

(7) Bachmann and Moser, THIS JOURNAL, **54**, 1124 (1932).

Oxidation of β-bromo-4-methylbenzalpyruvic acid in dilute alkaline solution with a slight excess of hydrogen peroxide gave in good yield the corresponding bromomethylcinnamic acid. The acid separates from hot ethyl alcohol or from benzene in long, fine, shining needles with a characteristic asbestos-like texture. After repeated crystallization the substance melts at 192°. This is the melting point of the bromo-4-methylcinnamic acid described by Gattermann[8] and listed in Beilstein[9] as α- or β-bromo-4-methylcinnamic acid. The acid prepared as just described from the β-bromo ketonic acid must be α-bromo-4-methylcinnamic acid. In order to test its identity with Gattermann's acid the latter was prepared from *p*-methylcinnamic acid.

4-Methylcinnamic acid was obtained readily by hydrogen peroxide oxidation of 4-methylbenzalpyruvic acid dissolved in a 1% solution of sodium carbonate. After standing overnight the yellow color of the ketonic acid had disappeared and dilute acid precipitated from the solution an almost quantitative yield of the methylcinnamic acid. It crystallized from methyl alcohol in colorless, stocky crystals melting at 198–199° and readily formed a methyl ester melting at 58°. When bromination was carried out in boiling carbon bisulfide solution, as described by Gattermann, a dibromo addition product separated on cooling. This melted with decomposition at 192°, and, on treatment with a 25% solution of potassium hydroxide in methyl alcohol, yielded an unsaturated bromo acid melting also at 192°, all as described by Gattermann. This acid crystallized from benzene in shining silky needles with an asbestos-like texture. A mixed melting point determination proved the acid identical with that obtained by oxidation of β-bromo-4-methylbenzalpyruvic acid. This acid, therefore, described in Beilstein as α- or β-bromo-4-methylcinnamic acid, is the α-bromo acid.

Its methyl ester, prepared by use of diazomethane, separates slowly from ether in large flat plates melting at 36–37°.

Anal. Calcd. for $C_{11}H_{11}O_2Br$: C, 51.76; H, 4.31. Found: C, 51.66; H, 4.54.

The methyl ester of the 4-methylcinnamic acid dibromide (192°) separates from methyl alcohol in shining prisms melting at 101°.

Anal. Calcd. for $C_{11}H_{12}O_2Br_2$: C, 39.28; H, 3.57. Found: C, 39.62; H, 3.88.

When the bromination of 4-methylcinnamic acid was carried out slowly in iced chloroform in the usual way, about one-third of the product had crystallized out by the time the last drops of bromine were added. This product, after washing with cold chloroform, consisted of fine shining crystals melting with slow decomposition at 180–182°. Repeated analyses of samples from different preparations showed the substance to contain a little more than one-half the amount of bromine for the dibromo addition compound so that it was thought to be impure α-bromo-4-methylcinnamic acid. Heating the substance with potassium acetate in methyl alcohol, however, yielded an oil with a strong odor of bromostyrene, and, as the only acid product, the original unbrominated 4-methylcinnamic acid. The substance, melting 180–182°, is then a mixture of 4-methylcinnamic acid and a dibromo addition product which is decomposed completely by treatment with potassium acetate. As Gattermann's 4-methylcinnamic acid dibromide, melting at 192°, gives a quantitative yield of α-bromo-4-methylcinnamic acid under the same treatment and even when warmed with a 25% solution of potassium hydroxide, this substance formed by reaction of bromine in cold chloroform must be an isomeric dibromide. Such a compound was postulated by Gattermann to account for his poor yield of dibromide. We have been no more successful than he in obtaining the substance in pure condition.

The chloroform filtrates from this reaction deposited about a 50% yield of the 192° dibromo addition product.

Reactions with Excess of Bromine

When *p*-methoxybenzalpyruvic acid[3] was treated with bromine in methyl alcoholic solution for the purpose of forming the methyl hypobromite addition product, no such reaction took place. The products were found to be β-bromoanisalpyruvic acid accompanied by its methyl ester brominated in the ring. For purposes of comparison this experiment was repeated with 4-methylbenzalpyruvic acid. The products were in large yield β-bromo-4-methylbenzalpyruvic acid. A small amount of impure residues on oxidation in hot solution of potassium permanganate gave terephthalic acid. There had been, then, no bromination in the ring.

By direct action of excess of bromine in boiling carbon bisulfide solution or on long standing at room temperature, there was also no ring substitution. These experiments show a very definite resistance to bromination in the ring when methyl instead of methoxyl is present in the para position to the unsaturated side-chain.

Reaction with Concentrated Sulfuric Acid.—The yellow color of 4-methylbenzalpyruvic acid and of its methyl and ethyl esters changes rapidly in solution in concentrated sulfuric acid to a reddish-orange then to deep red and finally to a dark brown color. The bromine compounds, all colorless, change to a greenish-yellow and finally to a faint violet. None of the colored products compare in brilliancy with those of the methoxy-substituted compounds.

Summary

For purposes of comparison with other para-substituted benzalpyruvic acids, the para methylbenzalpyruvic acid has been studied.

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(8) Gattermann, *Ann.*, **347**, 358 (1906).

(9) Beilstein, (ed. IV), Vol. IX, p. 617.