3. Cystamine is converted into the diurea by treatment with nitrourea.
4. This diurea when condensed with malonic acid, in the presence of acetic anhydride, yields the corresponding barbituric acid, as well as malonuric acid derivatives of cystamine and acetylation products.
5. From the disulfide barbituric acid, there have been obtained the corresponding violuric acid, uramil, and uric acid.
6. The latter is to be used as initial material for the preparation of *beta*-mercaptoethyl and thiazolidino uric acids.

NEW YORK, N. Y. RECEIVED FEBRUARY 24, 1940

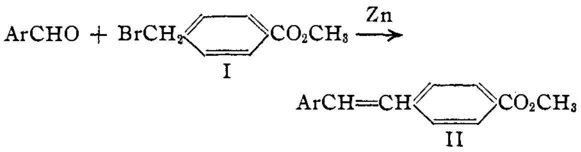
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Certain Carbalkoxystilbenes

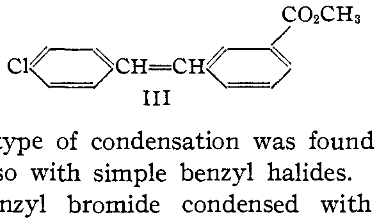
BY REYNOLD C. FUSON AND H. G. COOKE, JR.

Carbalkoxystilbenes of the type $ArCH{=}CHC_6H_4CO_2R$, needed for certain studies on the reversibility of the Friedel–Crafts condensation, could not be found in the literature. It was necessary, therefore, to devise ways for synthesizing them. The present paper reports three such methods.

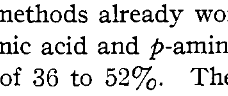
The first to be studied was the condensation of aromatic aldehydes with methyl α-bromo-*p*-toluate (I) by an adaptation of the Reformatsky reaction. This method was suggested by the vinylogous relationship between the α-bromo-*p*-toluates and bromoacetic esters. Experiments showed that the method could be used. Benzaldehyde, *p*-chlorobenzaldehyde and *p*-bromobenzaldehyde were condensed with methyl α-bromo-*p*-toluate to give the corresponding *p*-carbomethoxystilbenes (II).



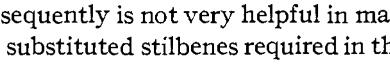
The activation of the bromine atom by the carbomethoxy group proved, however, not to be essential. Similar results were obtained with the *meta* isomer of the bromotoluate. *p*-Chlorobenzaldehyde condensed with methyl α-bromo-*m*-toluate to give 4-chloro-3′-carbomethoxystilbene (III).



This type of condensation was found to take place also with simple benzyl halides. Thus *p*-chlorobenzyl bromide condensed with methyl terephthalaldehydate (IV) to give 4-chloro-4′-carbomethoxystilbene, the product (V) being identical with that from methyl α-bromo-*p*-toluate and *p*-chlorobenzaldehyde. These two methods give about the same yields: approximately 20% of the theoretical. The former is preferable because the starting materials are less difficult to obtain.



IV



V

The preparation of the α-bromotoluates[1] was accomplished by the method of Davis and Perkin.[2] The terephthalaldehydate was much more difficult to prepare. It was found that Mayer and Sieglitz's method[3] for α-naphthaldehyde could be applied successfully to methyl α-bromo-*p*-toluate to give methyl terephthalaldehydate.

After this work was completed Meerwein, Büchner and Emster[4] reported a new method for making substituted stilbenes from cinnamic acids and primary aromatic amines. For certain carbalkoxystilbenes this procedure proved to be superior to the methods already worked out. Applied to cinnamic acid and *p*-aminobenzoic esters it gave yields of 36 to 52%. The method gives low yields when applied to chlorocinnamic acids and consequently is not very helpful in making the halogen substituted stilbenes required in this work.

Experimental

Methyl α-Bromo-*p*-toluate.—Eighty-three grams of bromine was added slowly, with stirring, to 80 g. of *p*-

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[1] Zal'kind, *J. Russ. Phys.-Chem. Soc.*, **46**, 508 (1914).

[2] Davis and Perkin, *J. Chem. Soc.*, **121**, 2202 (1922).

[3] Mayer and Sieglitz, *Ber.*, **55**, 1835 (1922).

[4] Meerwein, Büchner and Emster, *J. prakt. Chem.*, **152**, 237 (1939).

toluyl chloride heated to approximately 180°.[2] The bromination mixture was allowed to cool and 50 cc. of methanol was added dropwise. Distillation of this reaction mixture under reduced pressure gave 72 g. of methyl α-bromo-*p*-toluate; b. p. 115–117 (3 mm.). After crystallization from methanol or low-boiling petroleum ether the ester melted at 54–55°. This melting point agrees with that reported by Zal'kind,[1] who made the ester by direct esterification of α-bromo-*p*-toluic acid.

Methyl α-Iodo-*p*-toluate.—To a solution of 50 g. of methyl α-bromo-*p*-toluate in 100 cc. of acetone was added a solution of 33 g. of sodium iodide in 150 cc. of acetone, and the mixture was refluxed for fifteen minutes. The sodium bromide was removed by filtration, the acetone was distilled and the residue was taken up in ether. The ether solution was washed with 1% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. The ether was distilled, and the iodo ester was crystallized from methanol; m. p. 76–77°, yield 51 g.

Anal. Calcd. for $C_9H_9O_2I$: C, 39.13; H, 3.29. Found: C, 39.12; H, 3.35.

Methyl α-Bromo-*m*-toluate.—The method of synthesis was similar to that outlined for the para isomer. Distillation of the reaction mixture under reduced pressure gave 68 g. of the methyl α-bromo-*m*-toluate; b. p. 112–114° (3 mm.). After recrystallization from methanol or low-boiling petroleum ether the ester melted at 46–47°.

Anal. Calcd. for $C_9H_9O_2Br$: C, 47.16; H, 3.93; Br, 35.02. Found: C, 47.37; H, 4.09; Br, 35.08.

Methyl α-Iodo-*m*-toluate.—The conversion of the bromo ester to the corresponding iodo ester was found to proceed in the manner described for the para isomer. The iodo ester was recrystallized from methanol and low-boiling petroleum ether; m. p. 52–53°; yield 78%.

Anal. Calcd. for $C_9H_9O_2I$: C, 39.13; H, 3.29. Found: C, 39.38; H, 3.44.

The Condensation of Methyl α-Bromo-*p*-toluate with *p*-Chlorobenzaldehyde.—Twenty-five grams of methyl α-bromo-*p*-toluate in 100 cc. of dry benzene was added dropwise to a refluxing mixture of 21 g. of *p*-chlorobenzaldehyde, 50 cc. of dry benzene and 8 g. of zinc dust. The mixture was refluxed with stirring for eighteen hours, then decomposed with 100 cc. of dilute hydrochloric acid. The solid was removed by filtration, and the benzene layer was separated, washed with a 5% solution of sodium carbonate, and dried over anhydrous magnesium sulfate. The dry benzene solution was refluxed for two hours with 15 cc. of acetic anhydride. The solution was then concentrated under reduced pressure to a thick sirup. The 4-chloro-4'-carbomethoxystilbene solidified on cooling and was recrystallized from methanol.

Numerous attempts were made to increase the yield by using such solvents as toluene, ethyl ether and butyl ether in place of benzene. The iodo ester was used in place of the bromo ester and magnesium was substituted for zinc, but the above conditions were the most successful.

4-Chloro-4'-carbomethoxystilbene Bromide.—An excess of a 5% solution of bromine in carbon tetrachloride was added to a solution of 1 g. of 4-chloro-4'-carbomethoxystilbene in 25 cc. of carbon tetrachloride. The reaction mixture was heated to a temperature of 70° for twenty minutes. The carbon tetrachloride was removed by distillation and the 4-chloro-4'-carbomethoxystilbene bromide was recrystallized from methanol.

Debromination of 4-Chloro-4'-carbomethoxystilbene Bromide.—A solution of 1 g. of sodium iodide in 30 cc. of acetone was added to a solution of 1 g. of 4-chloro-4'-carbomethoxystilbene bromide in 30 cc. of acetone. This mixture was refluxed for fifteen minutes, the precipitate of sodium bromide removed by filtration and the acetone distilled. The residue was dissolved in ether and washed with a 1% solution of sodium thiosulfate. After the ether solution had been dried over anhydrous calcium chloride, the ether was distilled, and the 4-chloro-4'-carbomethoxystilbene crystallized from methanol; m. p. 161–162°, yield 95%. There was no depression of melting point when this product was mixed with the parent stilbene.

The condensation of other aromatic aldehydes and benzyl halides was carried out in the manner given for the synthesis of 4-chloro-4'-carbomethoxystilbene. The stilbene in each case was transformed into the corresponding dibromide which in turn was reconverted to the parent stilbene by treatment with sodium iodide in acetone. The results of these syntheses are collected in Table I. The yields in the debromination reactions varied from 86 to 92%. Purification of the stilbenes and their bromides was carried out in each case by recrystallization from methanol.

Attempted Condensation of Methyl α-Iodotoluates with Acetone.—When the meta and para α-iodotoluates were treated with zinc and acetone the only products were the corresponding methyl toluates and the bibenzyls produced by coupling. The 4,4'-dicarbomethoxybibenzyl melted at 118–119°.[5] The 3,3'-dicarbomethoxybibenzyl was a new compound. It was recrystallized from methanol, m. p. 84–85°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.51; H, 6.05. Found: C, 72.79; H, 5.86.

The Condensation of Benzyl Chloride with Benzaldehyde.—A solution of 45 g. of benzyl chloride in 200 cc. of dry benzene was added dropwise to a refluxing mixture of 38 g. of benzaldehyde, 100 cc. of dry benzene and 25 g. of zinc dust. The mixture was refluxed for twenty-four hours and decomposed with dilute hydrochloric acid. The solid was removed by filtration and the benzene layer was separated, washed and dried. The dry benzene solution was fractionally distilled to give 12 g. of diphenylmethane, b. p. 260–265°, and 16 g. of stilbene, b. p. 300–310°. Diphenylmethane is known to form when benzyl chloride is heated in the presence of zinc[6]; the structure of this hydrocarbon was proved by its oxidation to benzophenone. By the method of mixed melting points the high-boiling compound was shown to be *trans*-stilbene, m. p. 123–124° (from methanol); yield, 24%.

Preparation of Methyl Terephthalaldehyde.—This aldehyde was prepared by the same method that Mayer and Sieglitz[3] used for the preparation of α-naphthaldehyde. A solution of 28 g. of hexamethylenetetramine in 300 cc. of water was added to 44 g. of methyl α-bromo-*p*-toluate dissolved in 500 cc. of methanol. The solution was refluxed for seven hours, and the methanol was distilled.

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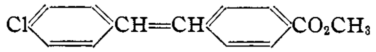
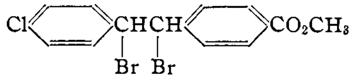
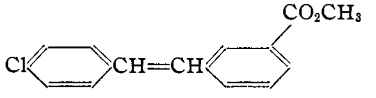
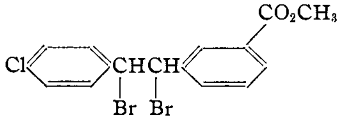
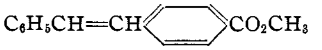
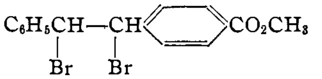
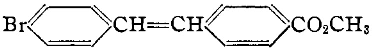
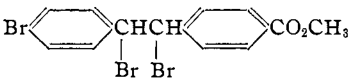
[5] Fischer and Wolfenstein, *Ber.*, **37**, 3215 (1904).

[6] Zincke, *Ann.*, **159**, 367 (1871).

TABLE I

	M. p., °C.	Yield, %	Formula and calcd. for	Analyses, % C	H
	161–162	22	$C_{16}H_{13}O_2Cl$	70.46	4.81
			Found	70.62	4.79
	202–203 (dec.)	90	$C_{16}H_{13}O_2ClBr_2$	44.41	3.01
			Found	44.52	3.29
	110–111	18	$C_{16}H_{13}O_2Cl$	70.46	4.81
			Found	70.42	4.71
	175–176	90	$C_{16}H_{13}O_2ClBr_2$	44.41	3.01
			Found	44.03	3.22
	158–159	21	$C_{16}H_{14}O_2$	80.67	5.93
			Found	80.63	6.16
	192–193	91	$C_{16}H_{14}O_2Br_2$	48.24	3.55
			Found	48.31	3.71
	179–180	20	$C_{16}H_{13}O_2Br$	60.57	4.13
			Found	60.64	4.34
	211–213	87	$C_{16}H_{13}O_2Br_3$	40.27	2.75
			Found	40.78	2.95

The aqueous residue was extracted with 1000 cc. of ether, and the ether solution was washed with a dilute solution of sodium bicarbonate and dried over anhydrous calcium chloride. The ether was removed by distillation and the residue distilled under diminished pressure in an atmosphere of nitrogen. Eighteen grams of methyl terephthalaldehydate was obtained, b. p. 95–97° (2 mm.), m. p. 61–62° (from low-boiling petroleum ether). This melting point agrees with that observed by Simonis,[7] who prepared the ester by direct esterification of terephthalaldehydic acid.

The Condensation of *p*-Chlorobenzyl Bromide with Methyl Terephthalaldehydate.—A solution of 14 g. of *p*-chlorobenzyl bromide in 75 cc. of dry benzene was added dropwise to a refluxing mixture of 10 g. of methyl terephthalaldehydate, 50 cc. of dry benzene and 6 g. of zinc dust. The mixture was refluxed for ten hours and decomposed with dilute hydrochloric acid. The solid was removed by filtration, and the benzene layer was washed and dried over anhydrous magnesium sulfate. The dry benzene solution was refluxed for two hours with 15 cc. of acetic anhydride. The solution was concentrated to a thick sirup under reduced pressure, and the residue was allowed to cool. The partially solidified residue was washed with methanol, and the solid was crystallized from methanol to give 3.2 g. of 4-chloro-4′-carbomethoxystilbene melting at 158–160°. By the method of mixed melting points this compound was shown to be identical with the stilbene obtained from methyl α-bromo-*p*-toluate and *p*-chlorobenzaldehyde. A bromide was prepared from this product which was shown by the method of mixed melting points to be identical with the 4-chloro-4′-carbomethoxystilbene bromide which had been previously prepared.

Distillation of the oil gave a compound which distilled at 160–170° (2 mm.) and melted at 100° (from methanol). Its composition corresponded to that of *p*,*p*′-dichlorobibenzyl.

Anal. Calcd. for $C_{14}H_{12}Cl_2$: C, 66.91; H, 4.82. Found: C, 66.71; H, 5.01.

Preparation of 4-Carbomethoxystilbene from Cinnamic Acid and Methyl *p*-Aminobenzoate.—The general directions used by Meerwein[4] for the preparation of substituted stilbenes were used in this synthesis of 4-carbomethoxystilbene. The diazonium salt of methyl *p*-aminobenzoate was made by adding a solution of 9 g. of sodium nitrite in 15 cc. of water to a mixture of 50 cc. of 25% hydrochloric acid, 19 g. of methyl *p*-aminobenzoate and 50 g. of ice. Throughout this experiment the reaction mixture was well stirred. An ice-bath was placed around the reaction flask and 27.5 g. of sodium acetate was added. A solution of 18.5 g. of cinnamic acid in 150 cc. of acetone was added and the ice-bath was removed. Five minutes later a solution of 5.3 g. of cupric chloride in 15 cc. of water was added and the mixture was stirred for one hour at room temperature. The 4-carbomethoxystilbene was removed, washed with methanol and crystallized from methanol, m. p. 158–159°; yield, 52%.

By the method of mixed melting points this compound was shown to be identical with the stilbene prepared from methyl α-bromo-*p*-toluate and benzaldehyde. The bromide prepared from this stilbene was shown to be identical with the previously prepared 4-carbomethoxystilbene bromide.

4-Carbethoxystilbene.—By use of the foregoing procedure a 36% yield of 4-carbethoxystilbene was obtained from ethyl *p*-aminobenzoate. It was crystallized from ethanol, m. p. 105–106°.

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[7] Simonis, *Ber.*, **45**, 1585 (1912).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.38. Found: C, 80.77; H, 6.43.

The **bromide** was recrystallized from absolute ethanol, m. p. 180–181°; yield 90%.

Anal. Calcd. for $C_{17}H_{16}O_2Br_2$: C, 49.51; H, 3.91. Found: C, 49.89; H, 4.07.

Treatment of the bromide with sodium iodide in acetone gave an 85% yield of the parent stilbene.

Summary

Carbomethoxystilbenes of the type ArCH=$CHC_6H_4CO_2CH_3$ have been prepared from aromatic aldehydes and the appropriate methyl α-bromotoluates by the action of zinc.

Similar results have been obtained by condensing benzyl halides with methyl terephthalaldehydate.

For the unsubstituted carbalkoxystilbenes the method of Meerwein, Büchner and Emster was found to be excellent.

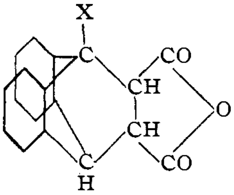
URBANA, ILLINOIS RECEIVED FEBRUARY 23, 1940

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Bicyclic Structures Prohibiting the Walden Inversion. Some Bicyclo[2,2,2]octane Derivatives with Substituents at the Bridge-Head[1]

BY PAUL D. BARTLETT AND SAUL G. COHEN

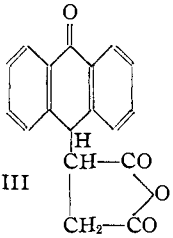
It has been shown in the laboratories of Barnett[2] and of Bachmann[3] that maleic anhydride readily undergoes addition to 9-substitution products of anthracene, yielding dibenzobicyclooctadiene derivatives such as I with substituents at the bridge-head position. These are among the few compounds known which are structurally incapable of replacement reactions with Walden inversion. In connection with our study of such compounds in the apocamphane series[4] the substances I, II and III, in which X is Br, NH_2 and OH are of special interest.



I X = Br
Ia X = H
II X = NH_2
III X = OH
IV X = $OOCCH_3$
V X = NO_2
VI X = $NHCOCH_3$
VII X = $NHCOOC_2H_5$

These compounds have three principal features not found in the apocamphanes. The bridge-head carbon atom is directly bound to two phenyl groups, which in the acyclic analogs means an enhanced reactivity of the group X. The presence of two potential acid groups provides water-solubility in the salts, making these compounds quite different in manipulation from the apocamphanes. Finally, the dibasic acids show geometrical isomerism.

Barnett and his co-workers[2] observed that the addition product from 9-bromoanthracene (I) withstood treatment with alcoholic alkali for forty minutes without any replacement of the bromine. They also obtained only decomposition products from attempts to hydrolyze the corresponding acetate (IV). The direct reaction of maleic anhydride with anthranol or anthrone occurred only in the sense of a Michael condensation with the latter, yielding an uncyclized addition product (VIII).



VIII

From these results Barnett concluded that the compound III must be incapable of existence.

Where our experiments have duplicated those of Barnett and his co-workers, there is complete agreement. We subjected the bromo compound, I, in different experiments, to treatment for fifteen to eighteen hours with boiling 15 to 30% potassium hydroxide, with no other effect than to open the anhydride ring and isomerize the *cis*- into the *trans*-dibasic acid. The aqueous extract of the product, after acidification and shaking with ether, gave no precipitate with silver nitrate. As the nearest analogous compound without the bridged ring structure we

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[1] Presented before the Organic Division of the American Chemical Society at its Boston meeting, September, 1939.

[2] Barnett, Goodway, Higgins and Lawrence, *J. Chem. Soc.*, 1224 (1934).

[3] Bachmann and Kloetzel, *J. Org. Chem.*, **3**, 55 (1938).

[4] Bartlett and Knox, THIS JOURNAL, **61**, 3184 (1939).