of alcohols or phenols to alkyl acrylates, or (b) alcoholysis of a lower alkyl ester of the appropriate ether-acid. The order of activity in (a) was phenol > primary alcohol > secondary alcohol. Tertiary alcohols did not react.

PHILADELPHIA 18, PA. RECEIVED OCTOBER 14, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Synthesis and Properties of 2,5-Diphenyl-1,4-dioxane[1,2]

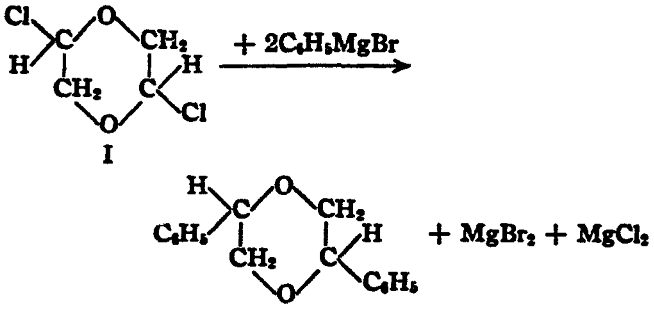
BY LOREN ALDRO BRYAN,[3] W. M. SMEDLEY[4] AND R. K. SUMMERBELL

Introduction

The first report of a synthesis of 2,5-diphenyl-1,4-dioxane was made by Breuer and Zincke,[5] who obtained a liquid having the correct analysis from the treatment of styrene glycol with hot dilute sulfuric acid. The molecular weight was shown to be correct by Auwers,[6] but Madelung and Oberwegner[7] pointed out the ease of hydrolysis in acid media of this and similar compounds and ascribed an acetal structure to them.

The compound was also reported by Lewis, Nierenstein and Rich[8] who claimed that 2,5-diphenyl-2,5-dibromo-1,4-dioxane was a product of the reaction of benzoyl bromide with diazomethane. This halogenated ether was reported to be reduced by formation of the Grignard reagent and hydrolysis to 2,5-diphenyl-1,4-dioxane. The structure of the latter was supposed to be indicated by the fact that an alcoholic solution turned deep red on the addition of hydrochloric acid, and the fact that it could be hydrolyzed to styrene glycol by mild treatment of a benzene solution with aqueous alkali. This synthesis is of some theoretical interest as it was used by Nierenstein[9] as an argument concerning the mechanism of the reactions of diazomethane with acid halides. The work has been criticized by Bradley and Robinson,[10] who were unable to repeat it and who questioned the probability of some of the reaction steps, and by Tellegen,[11] who questioned the proof of structure. It was accepted by Smith[12] who attempted to reconcile the views of Nierenstein and those of Robinson.

Preparation of 2,5-Diphenyl-1,4-dioxane.—In the present work we have obtained two compounds melting at 121–122° (IIb) and 173° (IIa) which we believe to be *cis* and *trans* forms of 2,5-diphenyl-1,4-dioxane by the reaction of phenylmagnesium bromide with 2,5-dichloro-1,4-dioxane. These compounds give no color reaction with alcoholic hydrochloric acid, but neither do pure samples of any dioxanes of proved structure. Commercial dioxane does sometimes give such a color test, but purified dioxane does not. When these compounds are subjected to the same alkaline hydrolytic conditions and to much more rigorous conditions than those described by Lewis, Nierenstein and Rich, they are recovered unchanged, as are a number of other substituted dioxanes of accepted structure. Thus the reactions used by Lewis, Nierenstein and Rich as a proof of the presence of a dioxane structure in their compound are actually an indication of its absence. We have not been able to repeat the work of Lewis, Nierenstein and Rich in that the alleged 2,5-dibromo-2,5-diphenyl-1,4-dioxane was never obtained by following their directions.



II (a and b)

A similar pair of isomers melting at 127° (IIIb) and 200–202° (IIIa) were isolated from the reaction of 2,5-dichloro-1,4-dioxane with *p*-tolylmagnesium bromide.

Evidence of Structure.—Although we have not been able to prove unequivocally the structure of our compounds, they do undergo a number of expected reactions, and the derivatives found are consistent with the suggested structures.

One mole of the 173° isomer reacts readily with two moles of bromine to form an unstable product (IVa) which is readily hydrolyzed to benzoylcarbinol. The simplest explanation of these reactions is that the bromination product is 2,5-diphenyl-2,5-dibromo-1,4-dioxane. The isomer (IIb) melting at 121–122° undergoes a similar series of reactions. Since it has been shown that mandelic aldehyde[13] is readily converted to benzoylcarbinol in acid solutions, the identification of

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[1] This work was supported in part by a grant from the Abbott Research Fund of Northwestern University.

[2] Abstracted from a Ph.D. thesis of Loren Aldro Bryan and an M.S. thesis by W. M. Smedley.

[3] Present address: U. S. Naval Academy, Annapolis, Maryland.

[4] Present address: Miner Laboratories, Chicago, Illinois.

[5] Breuer and Zincke, *Ann.*, 198, 141 (1879).

[6] Auwers, *Ber.*, 24, 1782 (1891).

[7] Madelung and Oberwegner, *Ann.*, 526, 195 (1936).

[8] Lewis, Nierenstein and Rich, THIS JOURNAL, 47, 1728 (1925).

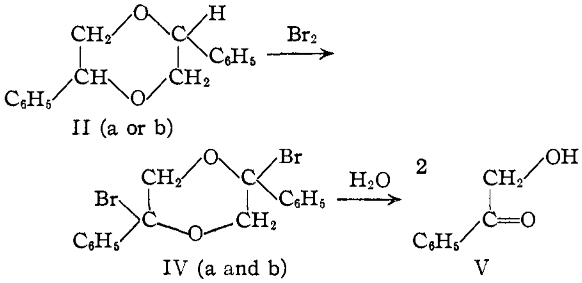
[9] Malkin and Nierenstein, *ibid.*, 52, 1504 (1930).

[10] Bradley and Robinson, *J. Chem. Soc.*, 1310 (1928).

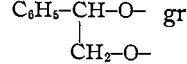
[11] Tellegen, "Dioxan en derivaten," University of Delft, 1934.

[12] Smith, *Chem. Revs.*, 23, 207 (1938).

[13] Evans and Parkinson, THIS JOURNAL, 35, 1770 (1913).



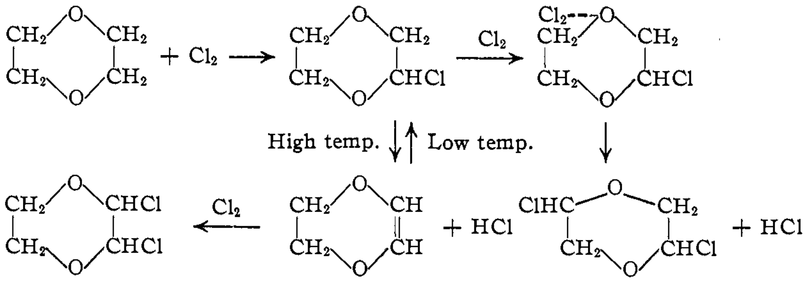
this product does not exclude the possibility that the bromination product was 2,5-diphenyl-3,6-dibromo-1,4-dioxane.

When 2,5-diphenyl-1,4-dioxane was refluxed with acetal chloride in the presence of zinc chloride, according to the method of Paul,[14] a chloroacetate was obtained. This was converted by heating with anhydrous potassium acetate to the diacetate and the latter on hydrolysis gave rise to styrene glycol. Since the over-all yield was less than fifty per cent., this experiment proves only that the  $C_6H_5–\underset{CH_2–O–}{CH}–O–$ group is present in our compound.

Because of the difficulty of isolating substantial quantities of the pure isomers, it was decided to use 2,3-diphenyl-1,4-dioxane as a model compound in some preliminary experiments. When dry hydrogen bromide was passed through molten 2,3-diphenyl-1,4-dioxane for several hours, *trans*-stilbene dibromide[15] was isolated. The use of glacial acetic acid as a solvent in the same reaction led to the production of stilbene. Tar was produced and unreacted material recovered in both cases. When 2,5-diphenyl-1,4-dioxane was treated with the same reagents as well as with hydrogen iodide, only tar resulted.

Neither the compound which melts at 121–122° (IIb) nor the one melting at 173° (IIa) was hydrolyzed by refluxing with aqueous sulfuric acid. This lack of sensitivity to acid hydrolysis would seem to minimize the possibility of an acetal or a ketal structure.

Preparation of 2,5-Dichloro-1,4-dioxane.—Small amounts of 2,5-dichloro-1,4-dioxane were obtained by Summerbell[16] and Umhoefer when hydrogen chloride was added to dioxadiene and this compound was also isolated by Rochen[17] from the reflux condenser when dioxane was chlorinated at reflux temperatures, but neither reaction is satisfactory as a method of obtaining working quantities. Conditions have now been found for the preparation of this compound in fair yield by carrying out the chlorination of dioxane at low temperatures with chloroform or carbon tetrachloride as a solvent. This is in sharp contrast to the high yields of 2,3-dichloro-1,4-dioxane obtained when dioxane is chlorinated near the refluxing temperature. A mechanism for the latter reaction was proposed by Bauer[18] and Summerbell, who postulated that the monochlorodioxane was formed first and that it dissociated to dioxene which subsequently added chlorine. In the current experiments, the temperature is much lower, and the dissociation tendency is diminished. Also, instead of escaping, much of the hydrogen chloride is held in the solution and would tend to react with any dioxene to reform monochlorodioxane. If one assumes that monochlorodioxane can still form addition compounds with chlorine on the oxygen more distant from the substituent chlorine, the formation of 2,5-dichloro-1,4-dioxane from this intermediate seems reasonable.



Thus the greater stability of the monochlorodioxane and the greater concentration of hydrogen chloride at the lower temperature may be used to account for the appreciable yield of 2,5-dichloro-1,4-dioxane under these conditions.

Experimental

Preparation of 2,5-Diphenyl-1,4-dioxane.—A Grignard reagent was prepared by the reaction of bromobenzene (86 g., 0.55 mole) with dry magnesium (12.2 g., 0.50 mole) turnings in 200 ml. of dry ether in a 500-ml. trident flask fitted with reflux condenser, mercury-sealed stirrer, dropping funnel, and cooling bath. The 2,5-dichloro-1,4-dioxane (27.5 g., 0.173 mole) was added portionwise and the mixture was stirred until there was no further reflux. The contents of the flask were poured into cracked ice and acidified. The white solid which formed at the ether–water interface was dissolved by the addition of ether. The ether layer was then separated and dried over calcium chloride. Distillation of the ether left a white solid residue, wt. 39.7 g., m. p. range 95–140°.

Separation of the Isomers of 2,5-Diphenyl-1,4-dioxane.—By fractional crystallization from acetone, 23.9 g. of the crude 2,5-diphenyl-1,4-dioxane was separated into a series of solid fractions. These fractions were recombined into two lots on the basis of the melting point range. When the higher melting mixture (m. p. 158–171°, 4.00 g.) was recrystallized from acetone, there was obtained 2.5 g. of glistening white platelets (IIa), m. p. 173–174°. *Anal.*[18a] Calcd. for $C_{16}H_{16}O_2$: C, 79.96; H, 6.71; mol. wt., 240. Found: C, 80.0; H, 6.86; mol. wt., 239. Similarly the lower melting mixture (m. p. 110–130°,

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[14] Paul, *Compt. rend.*, **211**, 645 (1940).

[15] Knoevenagel, *Ann.*, **402**, 133 (1914).

[16] Summerbell and Umhoefer, THIS JOURNAL, **61**, 3020 (1939).

[17] Rochen, Ph.D. Dissertation, Northwestern University, 1940.

[18] Summerbell and Bauer, THIS JOURNAL, **57**, 2364 (1935).

[18a] Analysis by T. S. Ma, University of Chicago.

11.45 g.) was fractionally recrystallized and there was obtained 1.20 g. of clear needles (IIb), m. p. 121–122°. *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 79.96; H, 6.71; mol. wt., 240. Found: C, 79.74; H, 6.74; mol. wt., 228.

Bromination of the Isomers of 2,5-Diphenyl-1,4-dioxane.—When 1.20 g. (0.005 mole) of (IIa) was dissolved in 10 ml. of dry carbon tetrachloride and treated with bromine (1.60 g., 0.01 mole) in sunlight, a vigorous reaction occurred with the evolution of much hydrogen bromide. The carbon tetrachloride was evaporated from the mixture under reduced pressure. The residue, 1.81 g. (91%) was a brownish-white solid (IVa) which could not be recrystallized from hot Skellysolve B and decomposed with the liberation of hydrogen bromide on standing. The material melted with decomposition at 115–120°. A sample of (IIb) was brominated under analogous conditions to form an unstable product (IVb) which melted with decomposition at 100–110°.

Hydrolysis of the Dibromo-2,5-diphenyl-1,4-dioxanes.—Product (IVa) was hydrolyzed by heating with 15 ml. of distilled water for three hours on a steam-bath. The product, a yellowish oil, was separated from the aqueous phase and treated with a hot saturated ethanol solution of 2,4-dinitrophenylhydrazine acidified with hydrochloric acid. An orange solid precipitated which was recrystallized from 95% ethanol and from Skellysolve B to give orange crystals, m. p. 289–290°. *Anal.*[18a] Calcd. for $C_{20}H_{14}O_8N_8$: N, 22.68. Found: N, 22.89. This product was the 2,4-dinitrophenylosazone of phenylglyoxal. It was also prepared from benzoylcarbinol, and this derivative, m. p. 287–288°, gave no depression in melting point when mixed with the analyzed sample.

Another sample of the hydrolysate of the brominated 2,5-diphenyl-1,4-dioxane (IVa) was treated with *p*-nitrophenylhydrazine to give the *p*-nitrophenylosazone of phenylglyoxal,[19] m. p. 308–310°. The melting point of a mixture of this derivative and a known sample of the osazone was not depressed.

The hydrolysis mixture did not produce a color change in Schiff reagent, but it did reduce Benedict reagent slowly. These observations indicate that the product of the hydrolysis contained no phenylglyoxyl.[20]

A sample of 0.5 g. of (IVb) was hydrolyzed in similar fashion. Treatment of an aqueous solution of the product with an alcoholic solution of 2,4-dinitrophenylhydrazine reagent yielded the 2,4-dinitrophenylosazone of phenylglyoxal, m. p. 287–288°. A similar hydrolysis mixture was neutralized with sodium hydroxide and treated for 0.5 hour on a steam-bath with phenylhydrazine in the presence of potassium acetate. The reaction mixture was then acidified and extracted with ether. The recrystallized residue, a yellow crystalline solid, m. p. 110–111°, was the phenylhydrazone of benzoylcarbinol.[21]

Styrene Glycol from 2,5-Diphenyl-1,4-dioxane.—This reaction was carried out essentially according to the method used by Paul.[14] A mixture consisting of 1.60 g. of 2,5-diphenyl-1,4-dioxane (IIa) and 5.52 g. of acetyl chloride was refluxed in the presence of a small sphere of freshly fused zinc chloride for two hours. Hydrogen chloride was evolved and some tar was formed. The excess acetyl chloride was distilled and the residue was then fractionated under reduced pressure. The distillate was a yellow oil, b. p. 120–122° at 24 mm., wt. 0.98 g. This material was believed to be the acetyl derivative of styrene chlorohydrin. It was heated for five hours at 150–170° with 1.10 g. of anhydrous potassium acetate, cooled and extracted three times with ether. Evaporation of the dried ether extracts left a brown oil believed to be the diacetate of styrene glycol. This oil was hydrolyzed by refluxing with 1.56 g. of barium hydroxide octahydrate for six and one-half hours. The mixture was cooled and extracted four times with ether. Evaporation of the ether left an oil which solidified on seeding with styrene glycol. The product, m. p. 65–66°, gave no depression of the melting point when mixed with an authentic sample of styrene glycol.

Stability of 2,5-Diphenyl-1,4-dioxane in Aqueous Sulfuric Acid.—When 1.00 g. of 2,5-diphenyl-1,4-dioxane (IIa) was refluxed for twelve hours in 25 ml. of 4% sulfuric acid, 98% of the starting material was recovered. The initial and final melting points were identical, 173–174°.

A sample of 0.30 g. of 2,5-diphenyl-1,4-dioxane (IIb) was refluxed for four hours with 15% sulfuric acid and 0.28 g. or 93% of the starting material was recovered. The melting point of the product was the same as that of the starting material, 121–122°.

Stilbene Dibromide from 2,3-Diphenyl-1,4-dioxane.—A sample of 4.8 g. (0.02 mole) of 2,3-diphenyl-1,4-dioxane was warmed to 50–70° and, over a period of three hours, 4.8 g. (0.29 mole) of dry hydrogen bromide was passed through the sample. At the end of the reaction period the contents of the reaction tube consisted of white crystals and tar. The tar was washed from the crystals with cold 95% ethanol. The crystals were recrystallized from a mixture of benzene and ether. The product, m. p. 237–238°, on the basis of melting point and mixed melting point with an authentic sample was *trans*-stilbene dibromide.[15]

Stilbene from 2,3-Diphenyl-1,4-dioxane.—A mixture consisting of 2.50 g. of 2,3-diphenyl-1,4-dioxane, 75 ml. of hydrobromic acid (sp. gr. 1.365), and 75 ml. of glacial acetic acid was refluxed for two hours and then cooled to −15°. After standing the mixture was filtered and the precipitate of white needle crystals was recrystallized from 95% ethanol. The product, 0.23 g., m. p. 123–125°, was identified as stilbene through preparation[22] of the *trans*-stilbene dibromide, m. p. 238–239°.

Stability of Some Aryl-1,4-dioxanes in Aqueous Alkali.—No hydrolysis resulted, and the starting dioxane derivative was recovered unchanged in high yield when each of the following was refluxed for eight to nine and one-half hours with a mixture of benzene and 20% aqueous potassium hydroxide solution: 2,3-diphenyl-1,4-dioxane, 2,5-diphenyl-1,4-dioxane (IIa), 2,3-dibenzyl-1,4-dioxane, 2-phenyl-1,4-dioxane.

Isomers of 2,5-Di-*p*-tolyl-1,4-dioxane.—By the reaction of an excess of *p*-tolylmagnesium bromide with 2,5-dichloro-1,4-dioxane (12.0 g., 0.057 mole) under the conditions used for the preparation of 2,5-diphenyl-1,4-dioxane, crude 2,5-di-*p*-tolyl-1,4-dioxane was obtained, m. p. 110–160°. The yield was 70% of the theoretical. After a series of seventeen recrystallizations two compounds (IIIa and b) were isolated. *Anal.*[18a] of (IIIa). Calcd. for $C_{18}H_{20}O_2$: C, 80.55; H, 7.52. Found: C, 80.80; H, 7.28; white crystals, m. p. 203–204°, wt. 0.84 g. *Anal.*[18a] of (IIIb). Calcd. for $C_{18}H_{20}O_2$: C, 80.55; H, 7.52. Found: C, 80.97; H, 7.36; white crystals, m. p. 126–127°, wt. 0.9 g.

Preparation of 2,5-Dichloro-1,4-dioxane.—In a trident flask fitted with a sealed stirrer, a reflux condenser and a sintered glass chlorine inlet tube and maintained at −5 to −10°, a mixture of 100 cc. of purified dioxane[23] and 100 cc. of dry carbon tetrachloride was chlorinated over a period of fifty-one hours during which stirring was continuous. After thirty hours of chlorination, white solid was visible in the reaction mixture. At the end of the reaction period, the solid was filtered from the reaction mixture in a Buchner funnel[23a] and recrystallized from hot carbon tetrachloride. The product, m. p. 118–120°, weighed 48.5 g. which was 23.9% of the theoretical yield. The structure of this compound was proved by converting

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(19) Straus, *Ann.*, **393**, 282 (1912).

(20) Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1938.

(21) Laubmann, *Ann.*, **243**, 245 (1888).

(22) Limpricht and Schwanert, *ibid.*, **145**, 336 (1916).

(23) Eigenberger, *J. prakt. Chem.*, **130**, 76 (1931).

(23a) It was found that the drying of the crude product on a clay plate before recrystallization was desirable. Recrystallization of the crude wet product generally resulted in decomposition and tar formation and the final product was not as easy to recover nor as pure as the product obtained from the dried crystals. The use of the drying step resulted in 2,5-dichloro-1,4-dioxane, m. p. 123–124°, which was stable for two weeks when kept in a dry condition at room temperature.

a small portion to 2,5-diacetoxy-1,4-dioxane in a manner similar to that used by Summerbell and Rochen[24] to convert 2,5-dibromo-1,4-dioxane to the same derivative.

Summary

1. The reported synthesis by Lewis, Nierenstein and Rich of 2,5-diphenyl-1,4-dioxane melting at 103° is questioned.

2. Aryl dioxanes are not hydrolyzed by refluxing with aqueous alkaline solutions as previously reported.

3. The reaction of phenylmagnesium bromide with 2,5-dichlorodioxane gives rise to a pair of isomers melting at 120–121° and 173°. Evidence is presented that these are *cis*- and *trans*-2,5-diphenyl-1,4-dioxane, respectively.

4. 2,3-Diphenyl-1,4-dioxane reacts with anhydrous hydrogen bromide to yield stilbene dibromide, and with an acetic acid solution of hydrogen bromide to yield stilbene.

5. A practical synthetic method is reported for obtaining 2,5-dichloro-1,4-dioxane. A mechanism for the reaction is postulated.

EVANSTON, ILLINOIS RECEIVED AUGUST 15, 1949

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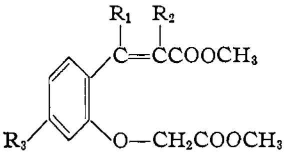
[24] Summerbell and Rochen, THIS JOURNAL, 63, 3241 (1941).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

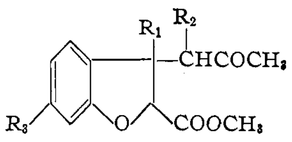
The Internal Michael Reaction. II. Formation of Arylated Coumarans, of an Indoline, a Dihydrothionaphthene and a Hydrocarbostyril[1]

BY C. F. KOELSCH AND C. R. STEPHENS, JR.

When ethyl coumarinate or a related ester (I) with an alkyl substituent on either or both the α- and β-carbons is treated with sodium alkoxide, an internal Michael reaction takes place, and a coumaran (II) is formed.[2]

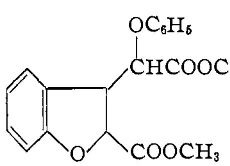


I

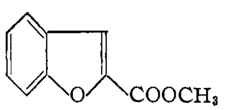


II

It has now been found that the same reaction can be effected with I when R_1 or R_2 is a phenyl. The first case (I, $R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$) is noteworthy because no example of the Michael reaction has been discovered previously in which the acceptor bears two aryl groups on its β-carbon. The second case ($R_1 = H$, $R_2 = C_6H_5$, $R_3 = H$) is of interest because the product of the reaction, III, tends to undergo a retrograde Michael reaction, in which it yields methyl phenylacetate and methyl coumarilate (IV).

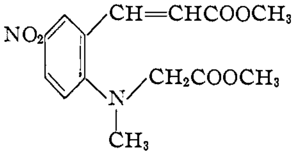


III

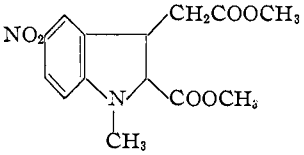


IV

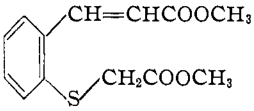
It has also been found that the internal Michael reaction can be brought about in methyl 2-methylamine-5-nitrocinnamate-N-acetate (V) and in methyl *o*-mercaptocinnamate-S-acetate (VII). From these compounds, the indoline VI and the dihydrothionaphthene VIII are formed.



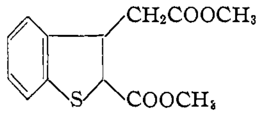
V



VI

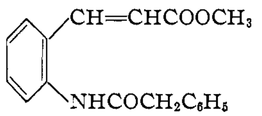


VII

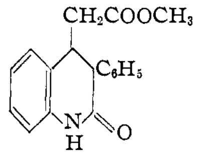


VIII

An internal Michael reaction takes place when methyl *o*-phenylacetylaminocinnamate (IX) is treated with sodium methoxide, and the hydrocarbostyril X is formed.



IX



X

Two substances in which an internal Michael reaction appeared possible have been investigated with negative results. One of them, methyl cinnamoylsarcosinate (XI), is recovered unchanged after it has been treated with sodium methoxide. The other, methyl *o*-acetyl-allocinnamate (XII), undergoes reaction, but the product is not homogeneous, and has furnished no methyl 1-hydrindone-3-acetate or other pure substance.

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[1] From the Ph.D. Thesis of Charles Robert Stephens, Jr., October, 1949.

[2] Koelsch, THIS JOURNAL, 67, 569 (1945).