droxyphenylazo)benzenearsonic acid hydrochloride. The last traces of methanol were removed *in vacuo* at 100°. The compound showed the typical properties of an *o*-aminophenol. When this was reduced with sulfur dioxide a red insoluble product was obtained, the structure of which could not be determined.

Table II lists the arsonic acids and arsenoso compounds which were prepared. Melting points were taken by the procedure described in paper VI. All analytical results are the average of two or more determinations. The crystalline arsonic acids were recrystallized from either water or alcohol. The yields given are for the purified compounds.

Acknowledgment.—The authors wish to acknowledge the assistance given by Leon D. Freedman throughout the course of the work.

Summary

Arsonic acids containing the azo linkage have been prepared by coupling diazo compounds with hydroxyarylarsonic acids and by the Scheller–Bart reaction applied to aminoazo compounds. A number of these arsonic acids have been reduced to the corresponding arsenoso derivatives.

BALTIMORE, MD. RECEIVED OCTOBER 12, 1943

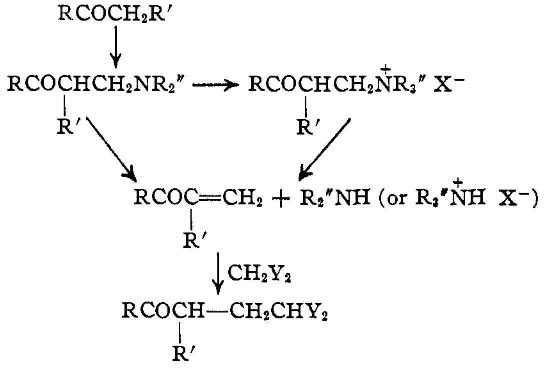
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Carbon-Alkylation with Quaternary Ammonium Salts. A New Approach to the Synthesis of Compounds Containing the β-Indolemethylene Group

BY H. R. SNYDER, CURTIS W. SMITH AND JOHN M. STEWART

Although simple quaternary ammonium salts have been used as alkylating agents in the preparation of numerous sulfur-,[1] oxygen-[2,3,4,5] and nitrogen-[6,7] alkylated substances, they have not appeared promising as reagents for the preparation of carbon-alkyl derivatives. For example, benzyldimethylphenylammonium chloride has been found not to yield phenacetonitrile by reaction with sodium cyanide in water,[1] and certain salts containing allyl groups attached to the nitrogen atom have been found not to produce allylphenols by reaction with phenolic substances.[3]

Successful reactions of quaternary salts derived from Mannich bases with active methylene compounds have been reported,[8,9] but these reactions have been interpreted as consisting not in simple alkylation but in Michael condensations of the active methylene compounds with vinyl ketones formed by decomposition of the quaternary salts of the Mannich bases.[10] The Mannich bases themselves react similarly in the presence of catalytic amounts of sodium, presumably also by decomposition to the vinyl ketones and the amines. The reactions are summarized in the following scheme.



In a study of the action of quaternary ammonium salts containing a benzyl group on sodium derivatives of acetoacetic ester and malonic ester it now has been found that carbon-alkylation occurs. Sodio acetoacetic ester reacts with benzyldimethylphenylammonium chloride in boiling ethanol to produce about 60% yields of crude ethyl α-benzylacetoacetate. Under the same conditions the sodium derivative of malonic ester reacts with the salt to give a yield of about 40% of diethyl benzylmalonate. The reactions probably proceed by an ionic path.

$$C_6H_5CH_2N^+(CH_3)_2C_6H_5 \longrightarrow$$
$$C_6H_5N(CH_3)_2 + [C_6H_5CH_2^+] \xrightarrow{CH(CO_2C_2H_5)_2^-} C_6H_5CH_2CH(CO_2C_2H_5)_2$$

There is no possibility of decomposition of this quaternary salt to an olefinic substance, according to the mechanism indicated above for reactions of the salts obtained from Mannich bases. As might have been expected, the amine, benzylmethylaniline, was found ineffective in these alkylations.

When benzylmethylpiperidinium chloride was allowed to react with the sodium derivative of malonic ester in ethanol solution the yield of diethyl benzylmalonate was only 5%. When the reaction was carried out in boiling 1-butanol the yield of crude ester (*ca.* 50%) was much improved, but the product apparently consisted of a mixture of ethyl and *n*-butyl esters. In order to effect the reaction at temperatures

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[1] Snyder and Speck, THIS JOURNAL, **61**, 668, 2895 (1939).

[2] Hla Baw, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926).

[3] Tarbell and Vaughan, THIS JOURNAL, **65**, 231 (1943).

[4] Willstätter, *Ber.*, **35**, 584 (1902).

[5] Griess, *ibid.*, **6**, 585 (1873); **13**, 246 (1880).

[6] Rodionov, *Bull. soc. chim.*, **39**, 305 (1926); **45**, 109 (1929).

[7] *Frdl.*, **10**, 1215 (1910–1912); German Patent 247,180.

[8] Du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).

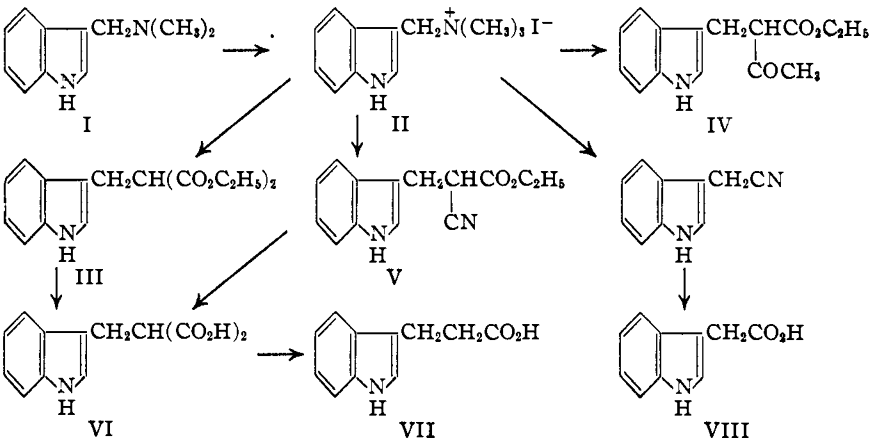
[9] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 239, 288 (1938); **73**, 233 (1939).

[10] Blicke, "The Mannich Reaction," in "Organic Reactions," John Wiley and Sons, Inc., New York, 1942, Vol. I, pp. 320–322.

above the boiling point of ethanol, but without the risk of transesterification of the product, the reaction mixture in ethanol was heated in an autoclave at temperatures between 110 and 130°. The best yield obtained by this procedure was about 35%. The residue from the distillation of diethyl benzylmalonate was shown to contain diethyl dibenzylmalonate.

The occurrence of the ester of dibenzylmalonic acid is not surprising. Other side-reactions which might be expected in alkylations with benzylmethylpiperidinium chloride are the decomposition of the salt to an olefin, and the reaction with the alcohol used as solvent to form benzyl ethyl ether.[10a] That olefin formation is impossible with benzyldimethylphenylammonium chloride may account for the higher yields of diethyl benzylmalonate obtained with this salt.

Experimental conditions chosen with the view to the suppression of dialkylation and ether formation have resulted in further improvement of the yield of diethyl benzylmalonate. For example, when an ethanol solution of equivalent amounts of benzyldimethylphenylammonium ethoxide and malonic ester was added dropwise to an equivalent quantity of hot malonic ester with provision for removal of ethanol by distillation as rapidly as it entered the reaction mixture, the yield of diethyl benzylmalonate was slightly above 50%. When the chloride was added to a mixture of the sodium derivative of malonic ester and excess malonic ester, prepared by adding sodium ethoxide to an excess of malonic ester and removing most of the ethanol by distillation under diminished pressure, the yield was a little over 70%. When the reaction was carried out by adding the salt to the sodium derivative prepared from metallic sodium and excess malonic ester the yield was about 80%. These are the best conditions so far discovered. Substitution of benzylmethylpiperidinium iodide and benzyltriethylammonium iodide for the benzyldimethylphenylammonium chloride resulted in yields of 43 and 62%, respectively.



Alkylations of the type studied will be most useful in synthesis when the quaternary ammonium salts are more accessible than the alkyl halides. Gramine [3-dimethylaminomethylindole, (I)] can be prepared readily from indole[11] and it is converted easily to quaternary ammonium salts, such as the methiodide (II), which contain a radical of the benzyl type.

In a preliminary study of the use of gramine methiodide as an alkylating agent it has been found that this salt is more reactive than those containing a simple benzyl group. Reaction of II with the sodium derivative of malonic ester produced the substituted malonic ester (III) in 85% yields. Condensations with acetoacetic ester and cyanoacetic ester also were successful, although the products (IV and V) were oils which were not purified. The malonic ester condensation product was saponified and the malonic acid (VI) was decarboxylated to β-indolepropionic acid (VII). Hydrolysis of the crude cyanoacetic ester condensation product (V) gave the same malonic acid (VI). β-Indoleacetic acid (VIII) was prepared from the salt (II) and potassium cyanide in water solution, but in better yields from the salt (II) and potassium silver cyanide; the intermediate nitrile was not isolated in the pure state.

The greater reactivity of gramine methiodide, as compared to benzyltrimethylammonium salts, suggested that the possibility of alkylation with the free tertiary amine be reëxamined. Reaction occurred when gramine was heated with malonic ester containing a trace of the sodium derivative. The reaction, which could be followed by noting the evolution of dimethylamine, was very slow, however; the yield of ethyl α-carbethoxy-β-(3-indole)-propionate (III) obtained from a reaction carried out for fifty-three hours at temperatures between 120 and 150° was only about 40%.

Further studies of the application of these and similar reactions in the synthesis of indole derivatives are in progress.

Experimental

1. **Benzyldimethylphenylammonium Chloride and the Sodium Derivative of Acetoacetic Ester in Ethanol.**—To a solution of 1.15 g. (0.05 mole) of sodium in 100 cc. of absolute ethanol were added 7.15 g. (0.055 mole) of acetoacetic ester and 10.6 g. (0.05 mole) of benzyldimethylphenylammonium chloride. The mixture was heated under

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(10a) Ingold and Patel [*J. Chem. Soc.*, 68 (1933)] obtained 65% yield of the ether from benzyltrimethylammonium iodide and sodium ethoxide in ethanol.

(11) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

reflux for a total of three and one-half hours (heating was interrupted after the first half hour to permit the removal of sodium chloride by filtration). About half of the ethanol was removed by evaporation and the residual solution was poured into a cold solution of 15 cc. of concentrated hydrochloric acid and 250 cc. of water. The aqueous phase was separated and extracted with three 50-cc. portions of ether. The ether extracts were combined with the organic layer and dried over sodium sulfate. Distillation yielded 6.6 g. (60%) of ethyl α-benzylacetoacetate boiling at 140–150 (2–3 mm.). The dinitrophenylhydrazone melted at 71.5°.

Anal. Calcd. for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.04. Found: C, 57.19; H, 5.04.

2. **Benzyldimethylphenylammoniuum Chloride and the Sodium Derivative of Malonic Ester in Ethanol.**—To a solution of 2.3 g. (0.10 mole) of sodium in 80 cc. of absolute ethanol were added 17 g. (0.11 mole) of malonic ester and 28 g. (0.12 mole) of the quaternary chloride. The mixture was refluxed for ten hours. The ethanol was removed by evaporation and the residue was worked up in a manner similar to that described in 1. The diethyl benzylmalonate, b. p. 128–133° (6 mm.), weighed 9.4 g. (37.6%). The diamide[12] melted at 225°.

3. **Benzylmethylpiperidinium Chloride and the Sodium Derivative of Malonic Ester in Ethanol and in Butanol.**—The reaction in ethanol, run as in (2) gave a 5% yield of diethyl benzylmalonate. From the reaction in boiling *n*-butanol 52% yield of an oil boiling at 163–173 (4 mm.) was obtained. This product reacted very slowly with concentrated aqueous ammonia to give benzylmalonamide, m. p. 225°. The oil was probably a mixture of the ethyl butyl and dibutyl esters.

4. **Various Quaternary Ammonium Salts and the Sodium Derivative of Malonic Ester.**—The procedure used in the following experiments differed from that of (2) only in that reactions were carried out in an autoclave. A considerable residue remained after the distillation of the product in each of these experiments. The residue from the first run contained an oil, b. p. 170–183 (3 mm.), which was shown to contain diethyl dibenzylmalonate by saponification and decarboxylation to yield dibenzylacetic acid,[12] m. p. 88–89°.

Organic residues other than $C_6H_5CH_2$ in $C_6H_5CH_2NR_3{}^+X^-$	Anion	Solvent	Temp., °C.	Time, hr.	Yield, %
C_6H_5-, CH_3-, CH_3-	Cl^-	C_2H_5OH	115	12	32
C_6H_5-, CH_3-, CH_3-	Cl^-	C_2H_5OH	130	4	36
CH_3-, -$(CH_2)_5$-	I^-	C_2H_5OH	120	6	22
CH_3-, -$(CH_2)_5$-	I^-	C_2H_5OH	135	9	36
CH_3-, -$(CH_2)_5$-	Cl^-	C_2H_5OH	135	10	20
CH_3-, -$(CH_2)_5$-	Cl^-	C_2H_5OH	130	12	26

When benzylmethylaniline was substituted for the quaternary salt in the second experiment, no diethyl benzylmalonate was obtained.

5. **Benzyldimethylphenylammonium Ethoxide and the Sodium Derivative of Malonic Ester, with Removal of ethanal by Distillation.**—The quaternary ethoxide was prepared by adding 25 g. (0.10 mole) of the quaternary chloride to 2.3 g. (0.10 mole) of sodium in 165 cc. of absolute ethanol and filtering from precipitated sodium chloride. The resulting solution was mixed with 16 g. (0.10 mole) of malonic ester and added over a period of about one hour to 16 g. (0.10 mole) of malonic ester in a distilling apparatus. During this period, and for two hours after the addition was complete, the oil-bath surrounding the flask containing the malonic ester was maintained at 150°. The bath temperature was then reduced to 110° for ten hours. The diethyl benzylmalonate, isolated essentially as described in (2), weighed 12.8 g. (51.3%).

6. **Benzyldimethylphenylammonium Chloride and the Sodium Derivative of Malonic Ester without Solvent.**—(a) A mixture of the sodium derivative of malonic ester and free malonic ester was prepared from 2.3 g. (0.10 mole) of sodium dissolved in 40 cc. of ethanol and 40 g. (0.25 mole) of malonic ester and removal of the ethanol by heating the mixture under 30 mm. pressure in an oil-bath at 50°. To the residue was added 27 g. (0.12 mole) of the quaternary chloride and the stirred mixture was suspended in an oil-bath which was heated to 110° over a period of two hours and then maintained at this temperature for six hours. The diethyl benzylmalonate, isolated essentially as in (2), weighed 18.2 g. (73%).

(b) The sodium derivative of malonic ester was prepared from 2.3 g. (0.10 mole) of powdered sodium and 40 g. (0.25 mole) of malonic ester in the presence of 100 cc. of anhydrous ether by stirring the mixture for six hours. To this mixture was added 27 g. (0.12 mole) of the finely ground quaternary chloride. The ether was removed by raising the temperature of the oil-bath to 110° over a period of about two hours. The stirred mixture was then heated at 140° for three hours. The yield of diethyl benzylmalonate was 19.7 g. (79%).

7. **Other Quaternary Ammonium Salts Under the Approximate Conditions of Experiment 6-b.**—In these experiments dibutyl ether (*ca.* 50 cc.) was added to facilitate stirring. N-Benzylmethylpiperidinium iodide gave a 43% yield of diethyl benzylmalonate, although the period of heating was extended by two hours. Benzyltriethylammonium iodide gave a 62.5% yield of the ester. With benzyltrimethylammonium bromide, evolution of trimethylamine began at 90°, continued for two hours with the oil-bath at 110–120°, and was completed after an additional half-hour at 140°. The yield of the ester was 77%.

8. **3-Dimethylaminomethylindole (Gramine).**—The procedure was a modification of that of Kuhn and Stein.[11] To 135 g. of 35% dimethylamine (equivalent to 1.05 mole) at 5° was added 140 g. (2.33 moles) of glacial acetic acid. The mixture was cooled to 5° and 76 g. of 40% formalin (equivalent to 1.0 mole of formaldehyde) at 5° was added. The mixture was agitated mildly and poured into a flask containing 117.2 g. (1 mole) of indole. The flask was shaken occasionally until the indole had dissolved. The temperature of the mixture rose to 56° during this period. The mixture was allowed to stand for ten hours and was added slowly to a stirred solution of 140 g. of sodium hydroxide in 1 liter of water. The resulting suspension was cooled in an ice-bath for two hours. The gramine was collected by filtration, pressed dry, washed with three 100-cc. portions of water and dried in an oven at 50° overnight; m. p. 127–128°.

9. **Methiodide of 3-Dimethylaminomethylindole.**—To a solution of the base from the previous experiment in 750 cc. of absolute ethanol was added 156 g. of methyl iodide over a period of about one hour. The mixture was allowed to stand at room temperature for twelve hours and was then stored at 0° for six hours. The product was collected by filtration and was washed with three 100-cc. portions of absolute ethanol and three 100-cc. portions of dry ether. The dried product weighed 248.4 g. (80%, based on indole).

10. **Ethyl α-Carbethoxy-β-(3-indole)-propionate.**—The sodium derivative of malonic ester was prepared by stirring for twelve hours a mixture of 1.15 g. (0.05 mole) of powdered sodium, 75 cc. of butyl ether and 20 g. (0.125 mole) of malonic ester. To the resulting paste was added 17.5 g. of gramine methiodide. This mixture was heated, with stirring, for two hours with the oil-bath at 110° and for four hours with the oil-bath at 145°. The cooled mixture was stirred with three 100-cc. portions of water. The combined aqueous washings were extracted with three 100-cc. portions of ether and the ether extracts were added to the organic layer from the first extractions. The solution was dried and the solvents and excess malonic ester were removed by distillation, first from a steam-bath and finally at 5 mm. pressure with an oil-bath at 90°. The residual red liquid was poured slowly into 75 cc. of high-boiling petroleum ether, with cooling and stirring. The solid which soon formed was triturated with the cold solvent and collected by filtration; it weighed 16 g. (calcd. 14.5 g.) and melted at 60°.

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[12] Bischoff and Siebert, *Ann.*, **239**, 96 (1888).

The crude material was recrystallized by dissolving 13 g. in 30 cc. of hot ethanol and 15 cc. of hot water. After decolorization of the hot solution the filtrate was cooled to 50° and an additional 5 cc. of water was added. Crystallization was induced by careful cooling and stirring. After drying in a vacuum desiccator the product weighed 10 g. (85%, based on sodium) and melted at 61°. The analytical sample, prepared by a second recrystallization, melted at 62°. Ethyl α-carbethoxy-β-(3-indole)-propionate is soluble in benzene, toluene, chloroform and ethanol, and substantially insoluble in water, petroleum ether and carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 65.93; H, 6.53.

11. **α-Carboxy-β-(3-indole)-propionic Acid.**—The ester was saponified by heating under reflux with 30% aqueous sodium hydroxide for six hours. The acid, after recrystallization from water, was obtained in 87% yield; m. p. 178° (dec.). The acid is very soluble in ethanol, and quite insoluble in chloroform and benzene.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.77; H, 4.75. Found: C, 61.51; H, 4.88.

The diamide, prepared by allowing a mixture of the ester with ten times its weight of concentrated aqueous ammonia to stand for two weeks, crystallized from aqueous ethanol or acetone; m. p. 206°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.66. Found: C, 62.53; H, 5.59.

12. β-(3-**Indole)-propionic** acid was prepared by heating the dibasic acid in an oil-bath at 180–190° for about fifteen minutes (until frothing stopped). The crude material, obtained by decolorizing a solution in 5% aqueous sodium hydroxide and reprecipitation by treatment with acid, melted at 120–123° (yield 75%). One recrystallization from water raised the melting point to 132–133°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86. Found: C, 68.96; H, 6.06.

The nitroso derivative melted at 135° (lit.,[13] 135°).

13. **Ethyl α-cyano-β-(3-indole)-propionate** was prepared by a procedure similar to that of (10). The crude material, obtained in 87% yield, was an oil which could not be crystallized. However, saponification with alcoholic potassium hydroxide gave α-carboxy-β-(3-indole)-propionic acid, m. p. 176°, which was shown by mixed melting point to be identical with the acid obtained in (11).

14. **Ethyl α-Aceto-β-(3-indole)-propionate** was obtained as an oil when acetoacetic ester was used in the procedure of (10). The dinitrophenylhydrazone prepared from the oil melted at 133.5°.

Anal. Calcd. for $C_{21}H_{21}N_5O_6$: C, 57.39; H, 4.82. Found: C, 57.51; H, 5.02.

15. **3-Indoleacetic Acid.**—To a solution of potassium silver cyanide, prepared from 4.25 g. (0.025 mole) of silver nitrate and 3.2 g. (0.05 mole) of potassium cyanide in 28 cc. of water, was added 8 g. (0.025 mole) of gramine methiodide. The solution was heated under reflux for one and one-half hours, during which period trimethylamine was steadily evolved. The cooled solution was extracted with three 30-cc. portions of ether. Removal of the ether from the dried extracts gave a light red oil (4.8 g.). This oil was added to 75 cc. of 20% aqueous potassium hydroxide and the mixture was heated under reflux for ten hours. The acid, recovered by acidification of the cold mixture, was dissolved in 75 cc. of hot water and, after decolorization, was allowed to crystallize. The pure acid weighed 2 g. (46%), m. p. 164.5–165.5°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.57; H, 5.20.

In an experiment in which gramine methiodide was treated with twice the theoretical amount of potassium cyanide in boiling water for four hours, 3-indoleacetic acid was obtained in only 11.4% yield.

16. **3-Dimethylaminomethylindole and Malonic Ester.**—A mixture of 17.4 g. (0.1 mole) of 3-dimethylaminomethylindole and 49 g. (0.3 mole) of malonic ester was warmed until complete solution resulted and then approximately 0.05 g. (0.002 mole) of sodium was added. This mixture was heated in an oil-bath at 120° for five hours, during which time a slow evolution of dimethylamine occurred. At the end of five hours another 0.05 g. of sodium was added and the mixture was heated at 130° for nineteen hours. Another 0.05 g. of sodium was added and the mixture was heated at 150° for seventeen hours. The evolution of amine had become almost imperceptible. After the addition of another 0.05 g. of sodium and heating at 150° for twelve hours, heating of the now slightly amber solution was discontinued.

The reaction mixture was poured into 100 cc. of water containing 10 cc. of concentrated hydrochloric acid and extracted with three 150-cc. portions of ether. The combined ether extracts were washed with two 150-cc. portions of 10% sodium bicarbonate solution and dried over anhydrous sodium sulfate. After removal of the ether on a steam-cone the residue was heated under reduced pressure (140° (3 mm.)) to remove the excess malonic ester. The residue, 22 g. (76%) of a red viscous oil, did not crystallize on standing in the icebox overnight. About 0.5 cc. of this oil was extracted with low-boiling petroleum ether and allowed to stand for two days. This partly crystalline mixture was transferred to a clay plate which absorbed the oil; the solid melted at 59–61.5°. After two recrystallizations from ethanol and water the ethyl α-carbethoxy-β-(3-indole)-propionate melted at 62°; a mixture with a known sample also melted at 62°.

The remaining oil (about 21.5 g.) was extracted with 50 cc. of low-boiling petroleum ether and added to a solution of 22 g. of potassium hydroxide in 220 cc. of 90% ethanol. The solution was refluxed for three hours. Most of the ethanol was removed by distillation from the steam-bath and steam was passed into the residue until about 500 cc. of distillate had collected. The residual solution (volume, 250 cc.) was separated from a small amount of insoluble material, cooled, and acidified with 60 cc. of concentrated hydrochloric acid. The red solid which separated when the acidified mixture was stored in an icebox for twenty-four hours was collected and dissolved in 100 cc. of water containing 3 g. of sodium hydroxide and about 0.01 g. of sodium hydrosulfite. The solution was decolorized with charcoal and acidified. The crude α-carboxy-β-(3-indole)-propionic acid, m. p. 172–175° (dec.), weighed 9.6 g. (41%). A sample recrystallized from water melted at 178° (dec.) and a mixed melting point with a known sample showed no depression.

Summary

Benzyldimethylphenylammonium chloride and other quaternary ammonium salts containing a benzyl group are shown to react with the sodium derivatives of malonic ester and acetoacetic ester to yield C-benzyl derivatives. Diethyl benzylmalonate is obtained in approximately 80% yields by this method.

The method of C-alkylation is applied to the synthesis of a number of substances containing the β-indolemethylene group; the methiodide of gramine (β-dimethylaminomethylindole), easily prepared from indole, formaldehyde, dimethylamine and methyl iodide, is used as the alkylating agent. Malonic, acetoacetic and cyanoacetic esters are alkylated in this way. The products from malonic and cyanoacetic esters, by hydrolysis and decarboxylation, are converted to β-indolepropionic acid. β-Indoleacetic acid is prepared by hydrolysis of the nitrile obtained

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(13) Beilstein, "Handbuch der organische Chemie," Julius Springer, Berlin, 1935, ed. 4, Vol. XXII, p. 69.

from gramine methiodide and potassium silver cyanide.

The tertiary amine (gramine) reacts with malonic ester in the presence of a small amount of the sodium derivative of the ester to yield ethyl α-carbethoxy-β-(3-indole)-propionate. However, the yield of alkylation product obtained from the amine is inferior to that obtained from the amine methiodide.

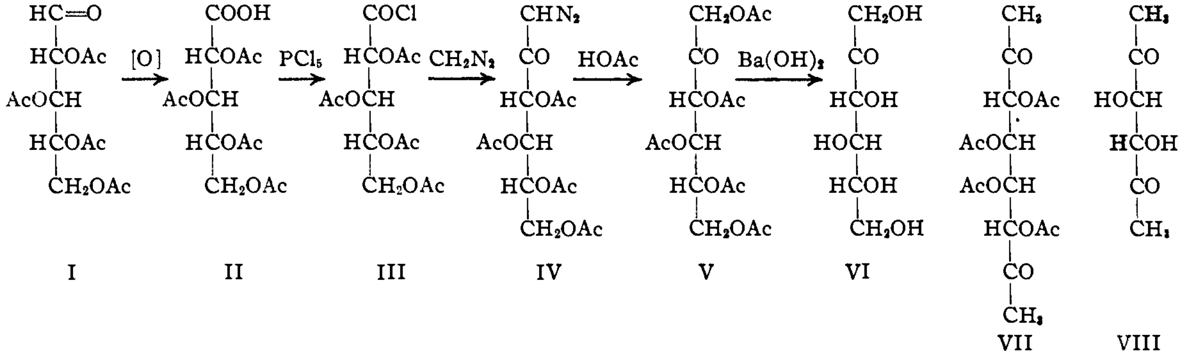
URBANA, ILLINOIS RECEIVED OCTOBER 2, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Action of Diazomethane upon Acyclic Sugar Derivatives. VI.[1] D-Sorbose[2]

BY M. L. WOLFROM, S. M. OLIN AND EVAN F. EVANS[3]

In continuation of our work upon the action of diazomethane upon acyclic sugar derivatives, we have synthesized 1-desoxy-1-diazo-*keto*-D-sorbose tetraacetate (IV) from D-xylonyl chloride tetraacetate (III). D-Xylonic acid tetraacetate (II) was prepared by the oxidation of *aldehydo*-D-xylose tetraacetate (I) according to the procedure reported by Major and Cook.[4] We describe an improved preparation of *aldehydo*-D-xylose tetraacetate[5] from D-xylose diethyl mercaptal tetraacetate, utilizing the general techniques of Wolfrom and Konigsberg.[6] The constants of Major and Cook[4] for I (m. p. 90–91°, spec. rot. +22.5° in absolute chloroform, for the L-form) have been verified. The rotation value differs appreciably from that previously reported[5] (m. p. 87–89°, spec. rot. −16° in chloroform, for the D-form). D-Xylonyl chloride tetraacetate has apparently not been recorded, although Major and Cook[7] described the D,L form.



Treatment of the diazomethyl ketone IV with acetic acid yielded *keto*-D-sorbose pentaacetate, enantiomorphic with the substance prepared by Arragon[8] and, nearly simultaneously, by Schlubach and Vorwerk[9] through the direct acetylation of L-sorbose. The acyclic nature of *keto*-L-sorbose pentaacetate was demonstrated by Cramer and Pacsu[10] and shortly later by Arragon.[11] We report herein a crystalline oxime of *keto*-L-sorbose pentaacetate. To our knowledge, this is the first nitrogen condensation product obtained for an acyclic or *keto* form of a ketohexose pentaacetate, previous attempts[10,12] having been unsuccessful. We record also the D,L form of *keto*-sorbose pentaacetate.

Careful saponification of *keto*-D-sorbose pentaacetate led to the synthesis of D-sorbose. Previous saponifications of the enantiomorphic derivative have been recorded by Schlubach and Vorwerk[9] and by Arragon.[11] This synthesis of D-sorbose from D-xylose compares with the synthesis of L-sorbose reported by Gätzi and Reichstein.[13] These workers oxidized diethylidene-(*levo*)-sorbitol to diethylidene-L-xylonic acid. From the crystalline acid chloride of the latter substance a sirupy diazomethyl ketone was obtained which on acid hydrolysis yielded crystalline L-sorbose. D-Sorbose (earlier psuedo-tagatose, *l*-sorbose) was first synthesized by Lobry de Bruyn and Alberda van Ekenstein[14] by the action of dilute aqueous alkali upon D-galactose. It was later formed from D-gulose and D-idose

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[1] Previous publication in this series: M. L. Wolfrom and Robert L. Brown, THIS JOURNAL, **65**, 1516 (1943).

[2] Presented before the Division of Sugar Chemistry and Technology at the 106th meeting of the American Chemical Society, Pittsburgh, Pennsylvania, September 7, 1943.

[3] Allied Chemical and Dye Corporation Fellow, 1942–1943.

[4] R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2474 (1936).

[5] M. L. Wolfrom and Mildred R. Newlin, *ibid.*, **53**, 4379 (1931).

[6] M. L. Wolfrom and M. Konigsberg, *ibid.*, **61**, 574 (1939).

[7] R. T. Major and E. W. Cook, *ibid.*, **58**, 2477 (1936).

[8] G. Arragon, *Compt. rend.*, **196**, 1733 (1933).

[9] H. H. Schlubach and J. Vorwerk, *Ber.*, **66B**, 1251 (1933).

[10] F. B. Cramer and E. Pacsu, THIS JOURNAL, **59**, 1467 (1937).

[11] G. Arragon, *Compt. rend.*, **205**, 735 (1937).

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[13] K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).

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