**α-Amino-*p*-dichloroarsinoacetanilide Hydrochloride.**—Reduction of the corresponding arsonic acid[14] in hydrochloric acid gave this dichloroarsine. It could not be successfully hydrolyzed to the arsenoso derivative.

*Anal.* Calcd. for $C_8H_9AsCl_2N_2O\cdot HCl$: As, 22.6; N, 8.45. Found: As, 22.3; N, 8.45.

***p*'-Arsenoso-*p*-carbamylbenzanilide.**—By means of the Schotten–Baumann reaction *p*-toluyl chloride was condensed with atoxyl to give **N-*p*-toluylarsanilic acid.** This compound was oxidized with potassium permanganate in neutral solution, in the presence of magnesium sulfate. From the reaction mixture terephthalic acid was isolated in quantitative yield. According to German Patent 191,548[15] terephthalyl chloride condenses with arsanilic acid to give *p*-arsonoterephthalanilic acid. In several experiments, using various experimental conditions, we obtained a mixture of this compound and **N,N'-terephthaloyldiarsanilic acid.** It was found that the two compounds could be separated by the differential solubilities of their magnesium salts, as described for the separation of a similar mixture in the biphenyl series,[16] but the yield was poor. The desired compound was finally obtained by the following synthesis. *p*-Cyanobenzoic acid (14.7 g.) and 7.9 g. of pyridine were dissolved in 1 liter of absolute ether and the mixture treated with 11.9 g. of thionyl chloride according to the directions of Carré and Libermann.[17] While the resulting *p*-cyanobenzoyl chloride could not be readily separated from pyridine hydrochloride, this was found unnecessary. After removing the solvent the residue was triturated with 43 g. of arsanilic acid and then warmed on the water-bath for one hour. An excess of 10% hydrochloric acid was added and the mixture stirred for one hour to dissolve any unchanged arsanilic acid. The resulting **N-(*p*-cyanobenzoyl)-arsanilic acid** was purified through its magnesium salt. Oxidation with 30% hydrogen peroxide gave **N-(*p*-carbamylbenzoyl)-arsanilic acid,** which was reduced to the desired arsenoso derivative.

***p*-(*p*-Carbamylphenylsulfonyl)-benzenearsonic Acid.**—The Scheller–Bart reaction, applied to *p*-amino-*p*'-nitrodiphenyl sulfide,[18] gave **p-(*p*-nitrophenylthio)-benzenearsonic acid** which was reduced catalytically to ***p*-(*p*-aminophenylthio)-benzenearsonic acid.** The Sandmeyer reaction applied to this amine gave ***p*-(*p*-cyanophenylthio)-benzenearsonic acid.** This nitrile was then oxidized with an excess of 30% hydrogen peroxide in alkaline solution. ***p*-(*p*-Carbamylphenylsulfonyl)-benzenearsonic acid** precipitated when the alkaline solution was acidified. Unfortunately all attempts to reduce this compound to the corresponding arsenoso derivative resulted in partial hydrolysis of the amide group.

The table lists the arsonic acids and arsenoso compounds which are new compounds or are known compounds prepared by a new procedure. Under "description," the letters in parentheses refer to the solvent used for crystallizing: W = water, A = ethyl alcohol, M = methanol and AA = acetic acid. Melting points were taken by the procedure described in paper VI. All analytical results are the average of two or more determinations.

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

## Summary

A number of arsonic acids and arsenoso compounds containing amide groups have been prepared.

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[14] Jacobs and Heidelberger, THIS JOURNAL, **41** 1809 (1919).

[15] German Patent 191,548; *Chem. Zentr.*, **79**, I, 779 (1908).

[16] Doak, Eagle and Steinman, THIS JOURNAL, **64**, 1064 (1942).

[17] Carré and Libermann, *Compt. rend.*, **199**, 1422 (1934).

[18] Raiziss, Clemence, Severac and Moetsch, THIS JOURNAL, **61**, 2763 (1939).

BALTIMORE, MARYLAND RECEIVED OCTOBER 12, 1943

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[CONTRIBUTION FROM VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, UNITED STATES PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

# Arsonic Acids and Arsenoso Compounds Containing the Azo Linkage[1]

BY G. O. DOAK, H. G. STEINMAN AND HARRY EAGLE

The customary preparation of arsonic acids containing the azo linkage consists in the coupling of diazotized aminoarylarsonic acids with phenols and amines. We have also prepared such compounds by coupling diazo compounds with hydroxyarylarsonic acids and by the application of the Scheller–Bart reaction[2] to aminoazo compounds.

While it has been stated that *o*- and *m*-hydroxybenzenearsonic acids[3] and *m*-arsanilic acid[4] couple with diazo compounds, the only evidence for such a reaction was color formation. Benda[5] obtained only arsenic acid and the corresponding phenylazophenol from *p*-hydroxybenzenearsonic acid and diazo compounds. Lawrence and Hamilton,[6] however, have successfully coupled aminonaphthalenearsonic acids.

In this Laboratory it has been found that diazo compounds couple with *o*- and *m*-hydroxybenzenearsonic acids, the coupling occurring in *para* position to the hydroxy group. Where the para position is blocked, *e. g.*, *p*-hydroxybenzenearsonic acid, the arsonic acid group is partially replaced by the phenylazo group. In addition, however, some coupling occurs in *ortho* position to the hydroxy group. The resulting azoarsonic acid then reacts further with the diazo compound to give the *bis*-(phenylazo)-phenol. The extent to which each of these three reactions occurs depends not only upon the strength of the reactants as coupling agents but is also influenced by the *p*H of the reaction mixture. The results of a series of experiments are given in Table I.

## Experimental Part

**A. The Coupling of Diazo Compounds with Hydroxyarylarsonic Acids.**—The following description illustrates the general procedure that was followed.

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[1] Paper VIII in the Series Entitled "The Preparation of Phenylarsenoxides."

[2] Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 2229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).

[3] Jacobs and Heidelberger, *ibid.*, **41**, 1440 (1919).

[4] Bertheim, *Ber.*, **41**, 1655 (1908).

[5] Benda, *ibid.*, **44**, 3449 (1911).

[6] Personal communication from Dr. Hamilton.

TABLE I

THE COUPLING OF DIAZO COMPOUNDS WITH HYDROXYARYLARSONIC ACIDS IN RELATION TO *p*H

| Arsonic acid | Diazo compound from | *p*H | % Yield of products | | |
|---|---|---|---|---|---|
| | | | Phenylazophenol | Phenylazoaryl-arsonic acid | *bis*-(Phenylazo) phenol |
| *p*-$HOC_6H_4$- | Aniline | 5.8–6.6[a] | 36.9 | 0.5 | 4.6 |
| | | 7.3–7.4[b] | 39.4 | 5.9 | 12.2 |
| | | 8.5–9.5[c] | 9.4 | 0 | 27.8 |
| 4-$HOC_{10}H_6$-1- | Aniline | 7.1–7.4[b] | 34.4 | 20.0 | 33.8 |
| *p*-$HOC_6H_4$- | Sulfanilamide | 5.4–6.5[a] | [e] | 0 | |
| | | 7.1–7.5[b] | [e] | 0 | |
| *p*-$HOC_6H_4$- | *m*-Toluidine | 7.4–7.5[b] | No coupling | | |
| *m*-$HOC_6H_4$- | Aniline | 7.0–7.1[b] | 0 | 95 | 0 |
| | | 8.9–9.1[d] | 0 | 98 | 0 |
| *o*-$HOC_6H_4$- | Aniline | 8.9–9.1[d] | 0 | 88 | 0 |
| 2,4-$(HO)_2C_6H_3$- | Aniline | 7.6–7.9[b] | | 84[f] | |
| | | 8.5–9.5[c] | [g] | 5.6[f] | [g] |

[a] Phosphate buffer. [b] Sodium bicarbonate buffer. [c] In sodium carbonate solution. [d] In sodium hydroxide solution. [e] Analysis indicated that a mixture of phenylazophenols was obtained, which could not be readily separated. [f] This compound was 3,5-*bis*-(phenylazo)-2,4-dihydroxybenzenearsonic acid, obtained with an excess of the diazo solution. We were unable to obtain a phenylazo-2,4-dihydroxybenzenearsonic acid free from the *bis* compound. [g] A mixture was obtained from which only 2,4-*bis*-(phenylazo)-resorcinol could be obtained in a pure state.

**4-Hydroxy-3-phenylazobenzenearsonic Acid.**—The diazo solution, prepared from 0.93 g. (0.01 mole) of aniline and 0.03 mole of hydrochloric acid was added slowly to a solution of sodium *p*-hydroxyphenylarsonate (2.94 g. of the trihydrate, 0.01 mole) and 2.52 g. of sodium bicarbonate in 50 ml. of water, maintaining the temperature at 10°. The initial and final *p*H values were 7.4 and 7.3 (glass electrode). The reaction mixture was stirred for one hour, filtered and the residue washed with 100 ml. of warm 10% sodium carbonate solution. The insoluble fraction (0.37 g.) was recrystallized from alcohol. Analysis and melting point (131°) identified this substance as 2,4-*bis*-(phenylazo)-phenol. The combined filtrate and washings were acidified to congo red and cooled in the icebox for twenty-four hours. The mixture was filtered, the precipitate washed with 10 ml. of cold water and dried. Arsenic acid was determined in the filtrate as magnesium pyroarsenate. The dry precipitate was extracted with ether and the ether insoluble fraction (0.174 g.) recrystallized several times from water. This substance was identical with the 4-hydroxy-3-phenylazobenzenearsonic acid later prepared by the Scheller–Bart reaction. The ether soluble fraction gave *p*-phenylazophenol (0.78 g.) and 2,4-*bis*-(phenylazo)-phenol (0.15 g.) on fractional crystallization from alcohol. In subsequent reactions it was found advantageous to partially neutralize the diazo solution before coupling.

**4-Hydroxy-3-phenylazo-1-naphthalenearsonic Acid.**—4-Hydroxy-1-naphthalenearsonic acid has been previously described.[7] The yield has been increased considerably by the following modification. 4-Amino-1-naphthyl benzoate hydrochloride was treated with ammonia to give the free base. It was also obtained by reducing 4-nitro-1-naphthyl benzoate in alcohol, employing Raney catalyst. **4-Amino-1-naphthyl benzoate** crystallized from aqueous alcohol in plates, m. p. 107.2–107.6°. The yield was 95% by either procedure.

*Anal.* Calcd. for $C_{17}H_{13}NO_2$: N, 5.32. Found: N, 5.40.

The Scheller–Bart reaction applied to this amine gave **4-arsono-1-naphthyl benzoate** in 19% yield. It crystallized from aqueous alcohol in plates; m. p. 199.8–200°.

*Anal.* Calcd. for $C_{17}H_{13}AsO_5$: As, 20.1. Found: As, 19.8.

4-Hydroxy-1-naphthalenearsonic acid was prepared from this ester by hydrolyzing in methanol solution with dry hydrogen chloride in the cold. The solution was diluted with water, the methyl benzoate extracted with ether and the arsonic acid recrystallized from water. The yield was 57%.

*Anal.* Calcd. for $C_{10}H_9AsO_4$: As, 28.0. Found: As, 28.0.

The above arsonic acid (9 g.) was coupled with benzenediazonium chloride at *p*H 7.1–7.4. After standing for two hours at 10° the mixture was acidified to congo red. The precipitate which formed was dried and extracted with benzene. The benzene insoluble fraction was then extracted with boiling 10% sodium bicarbonate solution. This solution when cooled deposited a small amount of solid which was added to the bicarbonate insoluble fraction. When the bicarbonate solution was acidified to congo red 4-hydroxy-3-phenylazo-1-naphthalenearsonic acid precipitated (2.51 g.). It was recrystallized from aqueous alcohol.

The benzene soluble fraction (4.0 g.), after recrystallizing first from benzene and finally from amyl alcohol, was identified as 2,4-*bis*-(phenylazo)-1-naphthol by analysis and melting point (190–191°). The bicarbonate insoluble fraction (2.87 g.), after recrystallizing several times from amyl alcohol was similarly identified as 4-phenylazo-1-naphthol, m. p. 206°.

**3-Amino-4-hydroxy-1-naphthalenearsonic Acid.**—The preceding azoarsonic acid was converted to the monosodium salt and reduced catalytically, employing Raney nickel. The solution was filtered directly into dilute hydrochloric acid and the arsonic acid which precipitated purified by the method of Christiansen.[8] It was obtained as white needles which colored rapidly in the air and slowly when preserved in an atmosphere of hydrogen. It decomposed on heating. The yield was 52%.

*Anal.* Calcd. for $C_{10}H_{10}AsNO_4 \cdot H_2O$: As, 24.9. Found: As, 24.4.

**3-Hydroxy-1,4,α-naphthisoöxazine-6-arsonic Acid.**—This compound was prepared by the method of Newberry, Phillips and Stickings[9] for the corresponding benzene analog, employing chloroacetyl chloride. It crystallized from water in clusters of needles.

*Anal.* Calcd. for $C_{12}H_{10}AsNO_5$: As, 23.2. Found: As, 22.7.

The formation of the cyclic arsonic acid offers considerable evidence for the coupling of 4-hydroxy-1-naphthalenearsonic acid in the 3-position.

**2-Hydroxy-5-phenylazobenzenearsonic Acid.**—The crude product from the coupling of *o*-hydroxybenzenearsonic acid and benzenediazonium chloride was purified through the magnesium salt and finally by recrystallizing from water. It was reduced catalytically, employing

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[7] Doak, Steinman and Eagle, THIS JOURNAL, **64**, 1064 (1942).

[8] Christiansen, *ibid.*, **42**, 2402 (1920).

[9] Newberry, Phillips and Stickings, *J. Chem. Soc.*, 3051 (1928).

TABLE II

ARSONIC ACIDS AND ARSENOSO COMPOUNDS CONTAINING THE AZO LINKAGE

| Compound | Description | M. p., °C. | Yield, % | Formula | As analyses, % |  | N analyses, % |  |
|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  | Calcd. | Found | Calcd. | Found |
| R = Phenylazo, R' = Benzene-arsonic acid |  |  |  |  |  |  |  |  |
| 4-Hydroxy-3-R-R' | Orange needles | 290 | 40,[a] 5.9[b] | $C_{12}H_{11}AsN_2O_4$ | 23.2 | 22.9 | 8.70 | 8.70 |
| 2-Hydroxy-5-R-R' | Orange needles | 257.3 | 45 | $C_{12}C_{11}AsN_2O_4$ | 23.2 | 22.7 | 8.70 | 8.59 |
| 5-Hydroxy-2-R-R' | Golden plates | 237.5 | 65 | $C_{12}H_{11}AsN_2O_4$ | 23.2 | 23.0 | 8.70 | 8.64 |
| 4-Hydroxy-3-R-1-naphthalene arsonic acid | Red needles | 245 | 20 | $C_{16}H_{11}AsN_2O_4$ | 20.1 | 19.4 |  | [c] |
| 3,5-Bis-(R)-2,4-dihydroxy-R' | Orange powder | 268 | 84 | $C_{18}H_{15}AsN_4O_5$ | 17.0 | 16.2 | 12.7 | 12.5 |
| *p*-R-R' | Orange plates | 332.5–333.5 | 24 | $C_{12}H_{11}AsN_2O_3$ | 24.5 | 24.2 | 9.16 | 9.30 |
| *p*-(*p*-Tolylazo)-R' | Orange needles | > 360 | 41 | $C_{11}H_{13}AsN_2O_1$ | 23.4 | 23.5 | 8.76 | 8.25 |
| *p*-(*p*-Arsono-R)-benzoic acid | Orange needles | > 360 | 68 | $C_{13}H_{11}AsN_2O_5$ | 21.4 | 21.5 | 8.01 | 8.41 |
| *p*-(3-Acetamido-4-hydroxy-R)-R' | Red powder | 224.8–225.2 | 75 | $C_{14}H_{14}AsN_2O_5$ | 19.8 | 19.6 | 11.1 | 11.1 |
| *p*-(3-Amino-4-hydroxy-R)-R' hydrochloride | Red powder | Dec. | 70 | $C_{12}H_{11}AsClN_3O_4$ | 20.1 | 19.9 | 11.3 | 11.1 |
| R = Phenylazo, R' = Arsenoso |  |  |  |  |  |  |  |  |
| *p*-R'-R-benzene | Orange powder | 214–214.5 | 74 | $C_{12}H_9AsN_2O$ | 27.5 | 27.6 | 10.3 | 10.4 |
| *p*-(*p*-R'-R)-phenol[d] | Orange powder | > 360 | 100 | $C_{12}H_9AsN_2O_2$ | 26.0 | 26.0 | 9.73 | 9.73 |
| *p*-R'-2-R-phenol | Orange powder | 215 | 94 | $C_{12}H_9AsN_2O_2$ | 26.0 | 25.9 | 9.73 | 9.66 |
| *p*-(*p*-R'-R)-benzamide | Orange powder | Chars > 260 | 88 | $C_{11}H_{10}AsN_1O_2$ | 23.8 | 24.8 | 13.3 | 13.7 |
| *p*-(*p*-R'-R)-(N-2-hydroxyethyl)-benzamide | Orange powder | Chars > 275 | 74 | $C_{15}H_{14}AsN_3O_3 \cdot H_2O$ | 19.9 | 19.4 | 11.1 | 11.1 |
| 8-Amino-2-(*p*-R'-R)-1-naphthol-3,6-disulfonic acid[e] | Red powder | > 360 | 34 | $C_{16}H_{12}AsN_3O_8S_2 \cdot 2H_2O$ | 13.6 | 13.5 | 7.65 | 7.72 |

[a] By the Scheller–Bart reaction. [b] By coupling. [c] Doak, Eagle and Steinman, THIS JOURNAL, **64**, 1064 (1942), footnote[e] to Table I. [d] The corresponding arsonic acid was prepared by the method of Barrowcliff, Pyman and Remfry, *J. Chem. Soc.*, **93**, 1893 (1908). [e] The corresponding arsonic acid was prepared according to German Patent 212,018, Raiziss and Gavron, "Organic Arsenical Compounds," Chemical Catalog Co., 1923, p. 286.

Raney nickel, and the resulting 6-hydroxy-*m*-arsanilic acid reduced in hydrochloric acid solution to 4-amino-2-dichloroarsinophenol hydrochloride, m. p. 183–183.4°.

*Anal.* Calcd. for $C_6H_7AsCl_3NO \cdot H_2O$: As, 24.3; N, 4.54. Found: As, 24.3; N, 4.61.

This compound was identical with the compound prepared by the reduction of an authentic sample of 6-hydroxy-*m*-arsanilic acid, thus establishing that *o*-hydroxybenzenearsonic acid coupled in the 5-position.

**5-Hydroxy-2-phenylazobenzenearsonic Acid.**—The crude reaction product from the coupling of *m*-hydroxybenzenearsonic acid and benzenediazonium chloride was purified by dissolving in warm sodium bicarbonate solution and precipitating with acid. It was finally recrystallized several times from water. This was similarly reduced to 5-hydroxy-*o*-arsanilic acid which gave **5-amino-4-dichloroarsinophenol hydrochloride,** m. p. 128–128.2°, on reduction in hydrochloric acid.

*Anal.* Calcd. for $C_6H_7AsCl_3NO \cdot H_2O$: As, 24.3; N, 4.54. Found: As, 24.1; N, 4.73.

This compound depressed the melting points of authentic samples of 2-amino-3-dichloroarsino- and 4-amino-5-dichloroarsinophenol hydrochlorides.[10] The structure of the coupled product as 5-hydroxy-2-phenylazobenzenearsonic acid was thus established.

### B. The Scheller–Bart Reaction with Aminoazo Compounds

***p*-Phenylazobenzenearsonic Acid.**[11]—This compound was prepared by both the customary Bart reaction and the Scheller modification, but the latter method gave a somewhat larger yield. The compound was reduced catalytically, employing Raney nickel, to arsanilic acid and aniline which were identified by converting to *p*-dichloroarsinoaniline hydrochloride and acetanilide, respectively, and comparing with authentic samples of these two substances.

***p*-(*p*-Tolylazo)-benzenearsonic Acid.**—This was prepared from *p*-(*p*-tolylazo)-aniline which was obtained by a modification of the method of Nietzki.[12] *p*-(*p*-Tolylazo)-benzenearsonic acid, when oxidized with potassium permanganate gave ***p*-(*p*-arsonophenylazo)-benzoic acid.** The recrystallized compound, suspended in chloroform, was treated with phosphorus tri- and pentachlorides and the clear orange solution added to aqueous ammonia. ***p*-(*p*-Arsenosophenylazo)-benzamide** precipitated from this solution. No satisfactory means of purifying this compound was found.

***p*-(*p*-Arsenosophenylazo)-(N-2-hydroxyethyl)-benzamide** was obtained in a similar manner by using an aqueous solution of 2-aminoethanol instead of ammonia.

**4-Hydroxy-3-phenylazobenzenearsonic Acid.**[13]—This compound was prepared from the Scheller–Bart reaction applied to 4-amino-2-phenylazophenol. This latter compound was obtained by a slight modification of the method of Woroshzow.[14] The Scheller–Bart reaction was unsuccessful with the two following other amines which together with the two corresponding intermediate acetyl derivatives were prepared by the method of Woroshzow.[14]

***p*-(5-Amino-2-hydroxyphenylazo)-benzenesulfonic Acid.**—*Anal.* Calcd. for $C_{12}H_{11}N_3O_4S$: N, 14.3; S, 10.9. Found: N, 14.1; S, 11.5.

***p*-(5-Amino-2-hydroxyphenylazo)-benzenesulfonamide.**—*Anal.* Calcd. for $C_{12}H_{12}N_4O_3S$: N, 19.2. Found: N, 18.5.

**Sodium Salt of *p*-(5-Acetamido-2-hydroxyphenylazo)-benzenesulfonic Acid.**—*Anal.* Calcd. for $C_{14}H_{12}N_3NaO_5S$: N, 11.8; Na, 6.44. Found: N, 11.7; Na, 5.78.

***p*-(5-Acetamido-2-hydroxyphenylazo)-benzenesulfonamide.**—*Anal.* Calcd. for $C_{14}H_{14}N_4O_4S$: N, 16.8; S, 9.6. Found: N, 16.5; S, 10.1.

**2-Amino-4-(*p*-arsenosophenylazo)-phenol.**—*p*-Arsonobenzenediazonium chloride by coupling with *o*-acetamidophenol gave ***p*-(3-acetamido-4-hydroxyphenylazo)-benzenearsonic acid.** This was hydrolyzed with hydrogen chloride in methanol solution to give *p*-(**3-amino-4-hy-**

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(10) Doak, Steinman and Eagle, THIS JOURNAL, **63**, 99 (1941).

(11) Karrer, *Ber.*, **45**, 2359 (1912).

(12) Nietzki, *ibid.*, **10**, 662 (1877). *p,p*-Diazoaminotoluene. 10 g., 20 g. of aniline and 5 g. of aniline hydrochloride were heated at 36° for two hours, allowed to stand overnight and acidified with dilute acetic acid. The resulting compound was recrystallized twice from alcohol; yield 65%, m. p. 146–148°.

(13) Bart, *Ann.*, **429**, 55 (1922).

(14) Woroshzow, *J. Russ. Phys.-Chem. Soc.*, **43**, 787 (1911); *Chem. Zentr.*, **82**, II, 1218 (1911).

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

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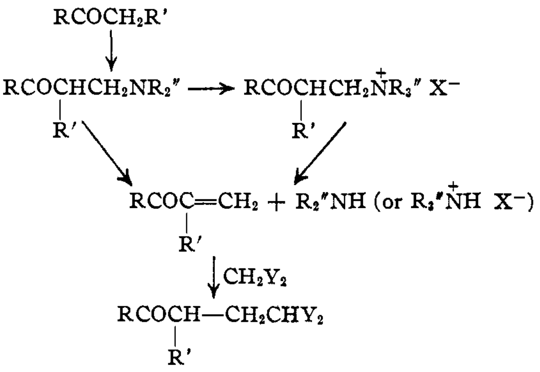
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# 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.