(0.25 mole) was added over a period of fifteen minutes. A vigorous reaction occurred and ether was added to replace that lost through the condenser. The solution was still dark after eight hours of stirring. It was hydrolyzed, washed, and dried as in the other preparations. A fraction boiling at 120–135° (30 mm.) was redistilled, giving a 12% yield of slightly colored material having $n^{24.9}\text{D}$ 1.4567.

Tri-*t*-butylcarbinol. (a) From Hexamethylacetone.—To a well-stirred suspension of 16 g. of sodium sand (0.70 mole) in 40 g. of *t*-butyl chloride (0.435 mole) and 150 cc. of dry ether cooled to 0°, 25 g. (0.176 mole) of hexamethylacetone was added at once. After stirring for one hour at this temperature there was no evidence of reaction. However, warming to room temperature evoked a moderately vigorous reaction with the evolution of gas and the appearance of a black coloration. After stirring overnight, the mixture was treated with water and the organic layer dried over sodium sulfate. Distillation at 28–30 mm. yielded 20 g. of ketone and secondary carbinol, b. p. (30 mm.) 60–77°, and 3.00 g. of tri-*t*-butylcarbinol, b. p. (30 mm.) 135–144°, which solidified. The crude yield was 8.5%. After a recrystallization from low-boiling petroleum ether and three sublimations, 1.8 g. of the carbinol (5.1%) was obtained sintering at 83° and melting at 94–95°.

Anal. Calcd. for $C_{13}H_{28}O$: C, 77.93; H, 14.09. Found: C, 78.03; H, 14.02. Zerewitinoff determination: sample, 0.1373 g. Volume of gas at 25.3° and 766 mm., 15.39 cc.; at N. T. P., 14.21 cc. Active hydrogen, 93% of the calculated (15.36 cc.).

(b) From Methyl Pivalate.—Fraction 7, previously described under the reaction of methyl pivalate with *t*-butyl chloride and sodium, was found to be tri-*t*-butylcarbinol. By sublimation its melting point was raised to 85–90°.

The combustion of tri-*t*-butylcarbinol was carried out by Miss E. Werble in a tube specially packed with an extra quantity of platinized asbestos

When 0.5 g. of tri-*t*-butylcarbinol was dissolved in 5 cc. of *n*-pentane with 2 cc. of acetyl bromide, there was no evidence of reaction. The carbinol was recovered unchanged by the evaporation of the solvent and acetyl bromide.

1-*t*-Butylcyclohexanol-1.—To a stirred suspension of 13 g. (0.56 mole) of sodium sand in 50 cc. of *n*-pentane and 50 g. (0.54 mole) of *t*-butyl chloride was added 25 g. (0.25 mole) of cyclohexanone over a period of twenty minutes with no evidence of reaction. A sudden violent reaction began soon afterward and was controlled by cooling with ice-water. After refluxing for thirty minutes thereafter on the steam-bath, the mixture was stiff with white precipitate. Hydrolysis with 100 cc. of water yielded a yellow organic layer which was dried over potassium carbonate and distilled. The fraction of b. p. (30 mm.) 80–107° yielded, on redistillation, two solid fractions, 1.6 g., b. p. (30 mm.) 94–103°, and 1.1 g., b. p. (30 mm.) 103–104°, m. p. 46–48°. The former fraction was sublimed to yield long, diamond-shaped crystals melting at 46–49°; total yield, 6.8% based on cyclohexanone.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.09; H, 12.85. Zerewitinoff determination: sample, 0.0892 g. Volume of gas at 24.5° and 765 mm., 13.46 cc.; at N. T. P., 12.44 cc. Active hydrogen, 96% of the calculated (12.79 cc.).

Summary

The reaction of methyl pivalate with sodium and *t*-butyl chloride gives hexamethylacetone and di-*t*-butylcarbinol in nearly equal amounts, the combined yield being as high as 80%.

By the reaction of the corresponding ketones or esters, branched chlorides, and sodium, small yields have been obtained of triisopropylcarbinol, diisopropyl-*t*-butylcarbinol, isopropyl-di-*t*-butylcarbinol, tri-*t*-butylcarbinol, tricyclohexylcarbinol, and 1-*t*-butylcyclohexanol-1.

Tri-*t*-butylcarbinol reacts normally with Grignard reagents in the Zerewitinoff determination, is inert to acetyl bromide under conditions leading to vigorous reaction with other tertiary alcohols, and is readily destroyed by strong aqueous sulfuric acid.

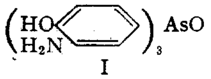
CAMBRIDGE, MASSACHUSETTS
RECEIVED SEPTEMBER 19, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Synthesis of Some Triarylarsines and Arsine Oxides

BY JAMES R. VAUGHAN, JR.,[1] AND D. STANLEY TARBELL

The observation that triarylarsines and arsine oxides can be condensed with derivatives of sulfanilamide to form arsinimines[2] of the type $Ar_3As(OH)NHSO_2C_6H_4NHR(R = H \text{ or } CH_3CO)$ suggested the synthesis and study of tri-(3-amino-4-hydroxyphenyl)-arsine oxide (I).



I

The present paper deals with the synthesis of derivatives of this compound.

The triarylarsines and arsine oxides previously condensed[2] with sulfanilamide included only triphenyl and tritolyl derivatives. Compound I has the same arrangement of amino and hydroxyl groups which is present in Mapharsen, arsphenamine and other important arsenical drugs, and hence should be of interest in itself, as well as on account of possible condensation products with sulfanilamide. There seems to be little on record on the chemotherapeutic activity of triarylarsine oxides, although it has been reported[3] that tetra-(3-amino-4-hydroxyphenyl)-diarsyl showed little trypanocidal activity.

The work of Voegtlin and others[4] has indicated that the organic arsenical drugs function by virtue of their ability to react with the sulfhydryl groups, which seem to be necessary for the life of the microörganisms. The arsenical is transformed into the arsine oxide, if it is originally present in

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[1] Present address: American Cyanamid Company, Stamford, Conn.

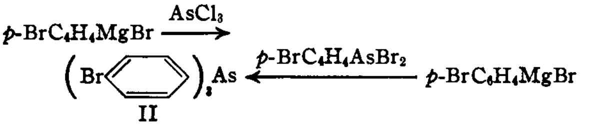
[2] Tarbell and Vaughan, THIS JOURNAL, **67**, 41 (1945)

[3] Blicke, Oneto and Webster, *ibid.*, **59**, 925 (1937).

[4] Voegtlin, Dyer and Leonard, *U. S. Pub. Health Rep.*, **38**, 1882 (1923), and later papers; Rosenthal, *ibid.*, **47**, 241 (1932); Eagles, *J. Pharmacol.*, **66**, 436 (1939).

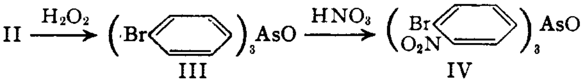
some other form, and reacts in that form with the sulfhydryl groups; primary arsine oxides are known to react with hydrogen sulfide and mercaptans to give compounds of the type RAsS or RAs(SR′)$_2$.[4] The triarylarsine oxides (or the dihydroxides) likewise react with hydrogen sulfide to form the corresponding sulfides, Ar$_3$AsS,[5] and hence presumably could react with sulfhydryl groups. On this basis, the tertiary arsine oxides should have a possibility of chemotherapeutic activity.

Tri-(4-bromophenyl)-arsine (II), which was the starting material in the projected synthesis of I, was prepared by the action of arsenic trichloride on 4-bromophenylmagnesium bromide, and was obtained as a crystalline solid, m. p. 95–96°.



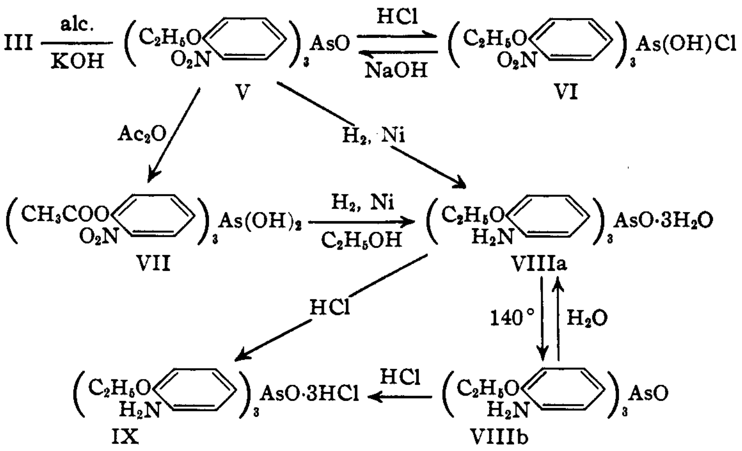
This product, prepared previously by the action of 4-bromophenylmagnesium bromide on 4-bromophenyldibromoarsine, was reported[6] to melt at 132–134° after recrystallization from isopropanol, but numerous experiments failed to yield a product of that m. p. from the material prepared by our method. A repetition of Blicke's method of synthesis yielded a sample of II identical with the one prepared from arsenic trichloride, and probably compound II is polymorphic, sinc derivatives prepared from our sample had essentially the same properties as those reported previously.[6] We also observed a sample melting at 101–102°, which may have been a third form, but it could not be obtained consistently, and it gave the same oxide as the 95–96° material. The product from the arsenic trichloride reaction is somewhat more difficult to obtain in pure crystalline form, but the method is nevertheless preferable to the alternative one, since the preparation of 4-bromophenyldibromoarsine involves two steps from 4-bromoaniline.

The tribromophenylarsine II was easily oxidized to the oxide III with hydrogen peroxide, which proved to be superior to other reagents for this purpose; it was not necessary to use crystalline arsine in this step, as the oxide was easily purified, even when it was prepared from impure arsine.



The oxide was nitrated to yield tri-(3-nitro-4-bromophenyl)-arsine oxide IV, which could be produced in much better yield by this method than by the nitration of II, which involves simultaneous nitration and oxidation.[7]

Attempts to replace the bromine atoms in IV by refluxing with potassium or silver acetate in acetic acid solution were unsuccessful, the starting material being recovered in high yield. Potassium hydroxide in aqueous dioxane also failed to effect the change satisfactorily, but treatment with alcoholic alkali under mild conditions gave tri-(3-nitro-4-ethoxyphenyl)-arsine oxide (V) in good yield. The ethoxyl group was not removed by heating with 20% hydrochloric acid, the result instead being the formation of the arsine hydroxychloride VI, from which the arsine oxide could be re-formed by heating with dilute alkali. Treatment of V with 48% hydrobromic acid likewise did not give cleavage of the ethoxyl group. When the ethoxyl compound V was treated with acetic anhydride in the presence of either sulfuric acid or pyridine, the ethoxyl group was replaced by an acetoxyl, with the formation of tri-(3-nitro-4-acetoxyphenyl)-arsine dihydroxide (VII). Evidently the acetolysis of the ether linkage is much more rapid than cleavage by mineral acid.



Reduction of the tri-(3-nitro-4-ethoxyphenyl)-arsine oxide (V) with hydrogen and Raney nickel at low temperature and pressure yielded the corresponding tri-(3-amino-4-ethoxyphenyl)-arsine oxide as a trihydrate (VIIIa), which was interconvertible with the anhydrous form VIIIb.[8] Both the hydrated and the anhydrous forms of VIII yielded the same trihydrochloride IX and the same picrate, neither of which contained water of crystallization. Compound VIIIa was further characterized by acetylation to a triacetamino compound, which also had no water of crystallization. When the acetoxy compound

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(5) Numerous examples are given by Raiziss and Gavron, "Organic Arsenical Compounds," Chemical Catalog Company, New York, N. Y., 1923, pp. 424–425.

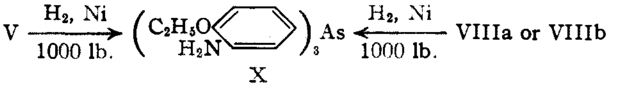
(6) Blicke and Safir, THIS JOURNAL, 63, 575 (1941).

(7) Compounds III and IV have been prepared previously[6] by different procedures not readily adapted to large-scale runs.

(8) Stevinson and Hamilton, THIS JOURNAL, 57, 1298 (1935), observed that the nitro group in nitroarylarsonic acids could be reduced with Raney nickel without affecting the arsono group.

VII was reduced catalytically in alcohol solution, the acetoxyl groups were replaced by ethoxyl, simultaneously with the reduction of the nitro group, so that VIIIa was obtained, instead of the expected acetoxyamino compound.

Catalytic reduction of tri-(3-nitro-4-ethoxyphenyl)-arsine oxide (V) under more vigorous conditions (1000 lb. of hydrogen at 80-100°) yielded tri-(3-amino-4-ethoxyphenyl)-arsine (X); both VIIIa and VIIIb could be reduced under the same conditions to the same compound. This seems to be the first catalytic reduction of a tertiary arsine oxide to the arsine.



X

Treatment of tri-(3-amino-4-ethoxyphenyl)-arsine oxide (VIII) with 48% hydrobromic acid, to remove the ethoxy group, gave an unsatisfactory result; the product obtained was unstable and good analytical values were not obtained. The amino group undoubtedly makes cleavage of the ether linkage more difficult, since it would form a positively charged ion in the acid solution. This would tend to prevent coördination of a proton with the ether oxygen, which is undoubtedly a necessary preliminary to cleavage. These considerations are supported by the observations of Ghaswalla and Donnan,[9] who found that substituted anisoles with an amino group ortho or para to the methoxyl were cleaved more slowly by acid than anisole itself.

The condensations of tri-(3-amino-4-ethoxyphenyl)-arsine oxide (VIII) and tri-(3-amino-4-ethoxyphenyl)-arsine (X), with sulfanilamide and N′-potassiochloro-N⁴-acetylsulfanilamide, respectively, by the methods previously developed,[2] have been so far unsuccessful; the corresponding arsinimines have not been obtained. In the latter case, treatment of X with the potassiochloro compound resulted in oxidation of the arsine to the oxide (VIIIa).

Tri-(3-amino-4-ethoxyphenyl)-arsine oxide trihydrate (VIIIa) was found to be virtually inactive against *T. pallida*, in tests carried out through the kindness of Dr. R. O. Roblin and Dr. H. J. White of the American Cyanamid Company.

Experimental[10]

Tri-(4-bromophenyl)-arsine (II) (a).—A solution of 4-bromophenylmagnesium bromide, prepared from 9.7 g. of magnesium, 95 g. of *p*-dibromobenzene and 250 cc. of ether, was stirred and 19.4 g. of arsenic trichloride, dissolved in 75 cc. of ether, was added dropwise. After twelve hours the mixture was treated with 175 cc. of 5% hydrochloric acid, extracted with ether, the extract washed with 20% sodium hydroxide solution, then with water, dried and the solvent removed. Upon distillation of the residue, a viscous yellow oil (28.3 g.) was obtained; b. p. 260-270° (3 mm.). The oil was dissolved in 100 cc. of hot purified petroleum ether (60-70°), the solution concentrated to 80 cc. and the colorless, slightly sticky, crystalline precipitate triturated with 15 cc. of ice-cold petroleum ether. The product, 7.4 g., melted at 88-91°. Concentration of the filtrates yielded an additional 4.8 g.; m. p. 84-89°. The filtrates contained about 15 g. of yellow oil, from which no crystalline product could be obtained. The combined crystalline material (12.2 g., 21%), after recrystallization from 35 cc. of petroleum ether, weighed 9 g.; m. p. 93-95°.

Anal. Calcd. for $C_{16}H_{12}AsBr_3$: C, 39.82; H, 2.23. Found: C, 39.90; H, 2.99.

(b) The required 4-bromophenyldibromoarsine has been reported[6] to be an oil. We obtained it in crystalline form; m. p. 35-36° after recrystallization from ligroin.

A solution of 4-bromophenylmagnesium bromide, obtained from 7.4 g. of magnesium, 63.5 g. of *p*-dibromobenzene and 350 cc. of ether, was allowed to react with 30 g. of 4-bromophenyldibromoarsine, dissolved in 100 cc. of ether according to the procedure described above. The product, which boiled at 260-270° (3 mm.) (24.5 g.), was dissolved in 100 cc. of petroleum ether, and a total of 13.8 g. (33%) of crystalline product, m. p. 87-92°, was obtained in three crops. Recrystallization from 40 cc. of petroleum ether yielded 11.0 g., m. p. 93-95°, which was raised to 95-96° by three more crystallizations; the mixed m. p. with sample made by procedure (a) was not depressed.

Tri-(4-bromophenyl)-arsine Oxide (III).—To 48.5 g. of the arsine (II) (non-crystalline, yellow oil) dissolved in 100 cc. of acetone was added dropwise 12.6 g. of 30% hydrogen peroxide (25% excess) with stirring and cooling in a water-bath. The solvent was then evaporated on a steam-bath, and the water removed by refluxing a benzene solution of the material through a water-trap. The benzene solution on cooling deposited the product as colorless crystals (47.2 g., 94%, m. p. 180-185°); these were removed, well washed with petroleum ether and dried overnight at room temperature. The product was recrystallized twice by extraction in a Soxhlet apparatus with 150 cc. portions of anhydrous ethyl acetate; the yield of colorless needle crystals was 25.0 g. (50%), m. p. 204-205°. This method of preparation is more convenient than the one previously reported, which yields material of m. p. 190-193°.[6]

Anal. Calcd. for $C_{18}H_{12}AsBr_3O$: C, 38.68; H, 2.16. Found: C, 38.79; H, 2.20.

Oxidation of both the crystalline forms of II (m. p. 95-96° and m. p. 101-102°) by the same method yielded the same oxide as above, m. p. 204-205°.

Tri-(3-nitro-4-bromophenyl)-arsine Oxide (IV).—To 10 g. of tri-(4-bromophenyl)-arsine oxide dissolved in 40 cc. of concentrated sulfuric acid was added dropwise and with stirring 20 cc. of concentrated nitric acid. The reaction mixture was heated on the steam-bath during the addition, and was then poured onto ice, which precipitated the nitrated product as a yellow, granular material. This was separated, washed with three 25-cc. portions of hot alcohol, and purified by extraction with 200 cc. of acetone in a Soxhlet, 7.6 g. (61%) of colorless crystals m. p. 252-254°, being obtained from the acetone. This is the reported[6] value for this compound prepared by another method. An additional 1.6 g. (13%) of product of the same m. p. was obtained by evaporating the acetone filtrate to about 50 cc. No improvement in yield was observed when this nitration was carried out using fuming sulfuric acid instead of concentrated acid.

Tri-(3-nitro-4-ethoxyphenyl)-arsine Oxide (V).—To 250 cc. of 1% alcoholic potassium hydroxide solution was added 10.0 g. of finely powdered tri-(3-nitro-4-bromophenyl)-arsine oxide (IV) and the mixture was heated on the steam-bath with stirring for one hour. The potassium bromide (4.15 g., 85%) which precipitated on cooling was filtered off, the filtrate was diluted with 500 cc. of water, made slightly acid with dilute sulfuric acid, and the precipitated product extracted with 175 cc. of hot benzene. The ben-

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[9] Ghaswalla and Donnan, *J. Chem. Soc.*, 1341 (1936).

[10] All melting points corrected; carbon and hydrogen analyses by Mr Carl Claus.

zene solution was separated, concentrated to 100 cc., and dried by refluxing through a water separator. Pale yellow crystals of the product separated from the hot solution; the yield, on cooling overnight, was 6.0 g. (71%), m. p. 205–208°. On extraction with 50 cc. of ethyl acetate in a Soxhlet, the product separated slowly from the solvent as very pale yellow needles, yield, 5.6 g. (67%), m. p. 215–216° after drying at 140° *in vacuo*.

Anal. Calcd. for $C_{24}H_{24}AsN_3O_{10}$: C, 48.92; H, 4.11. Found: C, 48.49; H, 4.09.

A sample of this compound was refluxed with sulfanilamide in dioxane solution for ten minutes, but there was no evidence of arsinimine formation, and the arsine oxide was recovered unchanged, as shown by a mixed m. p. determination.

Tri-(3-nitro-4-ethoxyphenyl)-arsine Hydroxychloride (VI).—A suspension of 0.70 g. of tri-(3-nitro-4-ethoxyphenyl)-arsine oxide in 20 cc. of 20% hydrochloric acid was heated for one hour on the steam-bath and then refluxed in five minutes with a free flame. The insoluble product was filtered from the hot acid solution, well washed with cold 5% hydrochloric acid, and dried at room temperature. The yield of pale yellow product was 0.70 g. (94%), m. p. 170–170.5° with dec.

Anal. Calcd. for $C_{24}H_{24}AsN_3O_{10}\cdot HCl$: C, 46.07; H, 4.03; As, 11.97. Found: C, 45.69; H, 4.07; As, 12.57.

A sample of this product was converted to the original arsine oxide by heating with 5% sodium hydroxide solution for fifteen minutes. The product gave no depression on mixed m. p. with the arsine oxide.

Tri-(3-nitro-4-acetoxyphenyl)-arsine Dihydroxide (VII).—A solution of 5.0 g. of tri-(3-nitro-4-ethoxyphenyl)-arsine oxide in 20 cc. of acetic anhydride containing 2–3 cc. of concentrated sulfuric acid as catalyst was heated for forty-five minutes on a steam-bath. The mixture was poured into 300 cc. of ice water, and the crude yellow product, which solidified after standing for several hours, was recrystallized from 25 cc. of alcohol; the product (3.25 g., 61%) melted at 117–120°. Recrystallization from alcohol (1 g. from 5 cc.) yielded 0.90 g. of pure material, m. p. 119–121°.

Anal. Calcd. for $C_{24}H_{20}AsN_3O_{14}$: C, 44.39; H, 3.11; As, 11.54. Found: C, 44.60; H, 3.84; As, 12.04.

Tri-(3-amino-4-ethoxyphenyl)-arsine Oxide Trihydrate (VIIIa).—A solution of 5.23 g. of tri-(3-nitro-4-ethoxyphenyl)-arsine oxide in 50 cc. of absolute alcohol was added to a suspension of 5–6 g. of Raney nickel, previously saturated with hydrogen under pressure, in a second 50-cc. portion of alcohol. The mixture was then shaken for about forty-five minutes at room temperature under 50 lb. of hydrogen pressure. The catalyst was removed by filtration, washed with 25 cc. of hot alcohol, and the combined filtrates concentrated to about 25 cc. on the steam-bath. The solution was diluted with 150 cc. of water, and the colloidal suspension which formed deposited, on standing overnight in the ice-box, 3.80 g. (78%) of colorless crystals, m. p. 105–107°. The product was purified by dissolving it in 100 cc. of 2–3% hydrochloric acid, decolorizing with charcoal, and reprecipitating with alkali. After twelve hours it separated practically quantitatively as colorless needles, m. p. 106–108°. Water content was determined by heating three hours at 140° *in vacuo*.

Anal. Calcd. for $C_{24}H_{30}AsN_3O_4\cdot 3H_2O$: C, 52.08; H, 6.56; H_2O, 9.76. Found: C, 52.08; H, 6.56; H_2O, 9.66.

The crystalline anhydrous monopicrate melts at 200–201° (dec.) and the trihydrochloride at 221–222° (dec.).

Anal. Calcd. for $C_{24}H_{30}AsN_3O_4\cdot C_6H_3O_7N_3$: neut. equiv., 728.6. Found: neut. equiv., 697. Calcd. for $C_{24}H_{30}AsN_3O_4\cdot 3HCl$: C, 47.35; H, 5.46. Found: C, 47.50; H, 5.56.

Reduction of Tri-(3-nitro-4-acetoxyphenyl)-arsine Dihydroxide (VII).—This substance (1.60 g.) was reduced with hydrogen and nickel in alcohol by the procedure described above. The alcohol remaining after removal of the catalyst was evaporated off, and the light yellow residue dissolved in 50 cc. of 1% hydrochloric acid and decolorized with charcoal. On adding alkali and allowing to stand overnight in the cold, 0.82 g. (59%) of tri-(3-amino-4-ethoxyphenyl)-arsine trihydrate (VIIIa) separated; mixed m. p. with an authentic sample 106–108°.

Tri-(3-amino-4-ethoxyphenyl)-arsine Oxide (VIIIb).—A suspension of 0.75 g. of the trihydrate (VIIIa) in 50 cc. of pure anhydrous xylene was heated under reflux through a water separator for three hours. On cooling, 0.61 g. (90%) of the insoluble product was recovered, m. p. 211–212°. The same compound was formed by heating the trihydrate at 140° (0.2 mm.) for three hours. The compound formed, under anhydrous conditions, a picrate and a hydrochloride, shown to be identical, by mixed m. p., with those obtained from the trihydrate. The anhydrous compound could be converted quantitatively into the trihydrate by dissolving in aqueous acid and precipitating with alkali.

Anal. Calcd. for $C_{24}H_{30}AsN_3O_4$: C, 57.72; H, 6.06. Found: C, 57.14; H, 6.29.

Tri-(3-acetamino-4-ethoxyphenyl)-arsine Oxide.—A solution of 0.8 g. of the trihydrate VIIIa in 20 cc. of acetic anhydride was refluxed for three hours, cooled, poured onto ice, the precipitate separated, dissolved in 50 cc. of alcohol, and the solution decolorized with charcoal. The filtrate was concentrated to 25 cc. and diluted with an equal volume of water. After standing overnight, pale brown needles, m. p. 178–180°, were obtained which, on recrystallization from 6 cc. of 35% alcohol, yielded 0.12 g. (13%) of product, m. p. 179–180°.

Anal. Calcd. for $C_{30}H_{36}AsN_3O_7$: C, 57.60; H, 5.80; As, 11.98. Found: C, 57.60; H, 5.87; As, 12.20.

Tri-(3-amino-4-ethoxyphenyl)-arsine (X).—A solution of 1.00 g. of tri-(3-amino-4-ethoxyphenyl)-arsine oxide trihydrate in 50 cc. of anhydrous alcohol was hydrogenated with 1 g. of Raney nickel for two hours at 80–100° under 1000 lb. of hydrogen. The catalyst was then removed by filtration, washed with two 20-cc. portions of hot alcohol, the combined filtrates concentrated to 15 cc. and cooled overnight in the ice-box. The product separated slowly as colorless cubic crystals, yield, 0.45 g. (52%), m. p. 198–199°. By diluting the filtrate with 75 cc. of water, 0.10 g. (10%) of starting material was recovered.

Anal. Calcd. for $C_{24}H_{30}AsN_3O_3$: C, 59.63; H, 6.26. Found: C, 59.59; H, 6.37.

The compound forms a tripicrate, m. p. 168–169° with dec., and a trihydrochloride, m. p. 196–198° with dec.

Anal. Calcd. for $C_{24}H_{30}AsN_3O_3\cdot 3C_6H_3N_3O_7$: neut. equiv., 390.2. Found: neut. equiv., 384.

Calcd. for $C_{24}H_{30}AsN_3O_4\cdot 3HCl$: neut. equiv., 197.6. Found: neut. equiv., 185.

Reaction of X with N′-Potassiochloro-N^4-acetylsulfanilamide.—A suspension of 0.3 g. of the arsine X and 0.18 g. of N^1-potassiochloro-N^4-acetylsulfanilamide in 3 cc. of pure dry dioxane was heated for one hour on the steam-bath. After filtering, the dark red solution was allowed to stand overnight; no crystallization occurred, and the solution was diluted with 5 cc. of anhydrous ethyl acetate, which precipitated a black tarry product. This was dissolved in 5 cc. of alcohol and the solution decolorized with charcoal; the addition of 20 cc. of water caused the slow crystallization of 0.06 g. (18%) of product, m. p. 98–102°, shown by mixed m. p. determination to be tri-(3-amino-4-ethoxyphenyl)-arsine oxide trihydrate (VIIIa).

Summary

1. Tri-(4-bromophenyl)-arsine, the corresponding oxide and tri-(3-nitro-4-bromophenyl)-arsine have been prepared by new methods. The usefulness of 30% hydrogen peroxide as a reagent for oxidizing a tertiary arsine to its oxide has been emphasized.

2. Tri-(3-amino-4-ethoxyphenyl)-arsine, its oxide and various related compounds have been prepared and characterized. Catalytic reduction

with nickel of a tertiary arsine oxide to the arsine has been carried out.

3. Attempts to prepare an arsinimine derived from sulfanilamide and tri-(3-amino-4-ethoxyphenyl)-arsine have not been successful.

ROCHESTER, NEW YORK RECEIVED OCTOBER 4, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Allylic Rearrangements. XVI. The Addition of the Butenyl Grignard Reagent to Some Simple Carbonyl Compounds[1]

BY JOHN D. ROBERTS[2] AND WILLIAM G. YOUNG

The nature of allylic Grignard reagents has been the subject of many investigations. Aside from those cases where the allylic double bond is included in an aromatic ring (as benzylmagnesium chloride) the structures of these substances are still open to question. For a simple primary–secondary allylic system it may be expected that the Grignard reagent will be primary (I), secondary (II) or a mixture of these forms.

$$\mathrm{RCH{=}CHCH_2MgX}\ \text{(I)} \qquad \mathrm{RCHMgXCH{=}CH_2}\ \text{(II)}$$

Assignment of the correct structure is complicated by at least three possibilities: (a) allylic rearrangement during the formation of the reagent; (b) the establishment of an allylic equilibrium between the forms (I and II) after the Grignard reagent has been formed; or (c) rearrangement during the course of the reaction with specific addends. In certain cases the possibility of rearrangement of the reaction products must not be overlooked.

The evidence obtained from the reactions of cinnamylmagnesium chloride offers a typical example of the prevailing confusion as to the nature of the allylic Grignard reagent. For this system it has been reported that the hydrolysis of the reagent gives a mixture of propenyl- and allylbenzene,[3] that treatment with chloroamine gives only the primary amine[4] and that with carbon dioxide[5a] and acetaldehyde[5b] only those products derived from structure II are obtained. This may appear surprising, since chloroamine, carbon dioxide and acetaldehyde may be classified as "normal"[6] reagents in the reactions of benzylmagnesium chloride.

In previous communications[7a,b] from this Laboratory it has been shown that the hydrolysis of butenylmagnesium halides results in a mixture of butenes and that the composition of this mixture is independent of the ratios of the possible allylic forms of the halide. This evidence, along with the results of Lespieau and Heitzmann[8] and Prevost and Richard[9] on the coupling reactions of allylic bromides with magnesium, has indicated that the Grignard reagent is formed with rearrangement but that no rearrangement occurs on hydrolysis. In order to test the validity of the conclusions derived from the previous work, a study is being made of the reactions of butenylmagnesium bromide with a variety of substances with detailed attention to those reactions which might be expected to give insight into the structure of the reagent and the mechanisms by which it reacts. The present report presents some preliminary results of this study.

The addition of butenylmagnesium bromide to carbonyl compounds has not been extensively studied. Ou Kiun-Houo[5b] reported that acetaldehyde, propionaldehyde, acrolein and benzaldehyde gave rise to products derived from the secondary form (II) of the Grignard reagent. However, the yields were uniformly below 25%. It is thus possible that considerable amounts of the isomeric products may have been overlooked, although the carbonation[10] of butenylmagnesium bromide has been shown to lead exclusively to the acid corresponding to the secondary form of the Grignard reagent.

From the reactions of butenylmagnesium bromide with acetone, acetaldehyde and formaldehyde we have substantiated the conclusions of Ou Kiun-Houo[5b] that only those products are obtained which may be considered to be derived from the secondary form of the Grignard reagent. No detectable amounts of the isomeric products corresponding to the primary Grignard reagent were isolated. The yields were excellent, and it may be pointed out that the 81% conversion of acetone to 2,3-dimethyl-4-pentenol-2 far exceeds the figures for the analogous conversion of *s*-butylmagnesium bromide to 2,3-dimethylpentanol-2. The structures of the products were established by ozonization and hydrogenation to the saturated alcohols.

Although the composition of the butene mixture produced by hydrolysis of the butenyl Grignard reagent has been shown[7a,b] to be independent of the nature and composition of the starting allylic

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[1] Presented before the Division of Organic Chemistry of the American Chemical Society at New York City, September, 1944.

[2] Abbott Laboratories Research Fellow, 1943–44.

[3] Young, Ballou and Nozaki, THIS JOURNAL, **61**, 12 (1939).

[4] Coleman and Forrester, *ibid.*, **58**, 27 (1936).

[5] (a) Gilman and Harris, *ibid.*, **49**, 1825 (1927); **53**, 3541 (1931); (b) Ou Kiun-Houo, *Ann. chim.*, [11] **13**, 175 (1940).

[6] Austin and Johnson, THIS JOURNAL, **54**, 647 (1932).

[7] (a) Young, Winstein and Prater, *ibid.*, **58**, 289 (1936); (b) Young and Eisner, *ibid.*, **63**, 2113 (1941).

[8] Lespieau and Heitzmann, *Compt. rend.*, **200**, 1077 (1935).

[9] Prevost and Richard, *Bull. soc. chim.*, [4] **49**, 1369 (1931).

[10] Lane, Roberts and Young, THIS JOURNAL, **66**, 543 (1944).