TABLE I

ESTERS OF TRIMETHYLACETIC ACID AND BROMOPHENYLPHENOLS

Phenol used	Yield, %[a]	Solvent, ligroin	Crystal form	M. p., °C.	Formula	Analyses, % Br Calcd.	Analyses, % Br Found
2-Bromo-4-phenyl-[b]	40.2	30–60°	Large prisms	60.5–62	$C_{17}H_{17}O_2Br$	23.95	23.91
4-(4-Bromophenyl)-[c,d]	35.3	70–90°	Plates	119.5–121	$C_{17}H_{17}O_2Br$	23.95	23.99
2,6-Dibromo-4-phenyl-[b]	43.6	70–90°	Prisms	86–87	$C_{17}H_{16}O_2Br_2$	38.78	38.57
2-Bromo-4-(4-bromophenyl)-[e]	36.7	70–90°	Heavy plates	93.5–94	$C_{17}H_{16}O_2Br_2$	38.78	38.62

[a] Purified products. [b] Ref. 2. [c] Bell and Robinson, *J. Chem. Soc.*, 1127 (1927). [d] Ref. 3.

Trimethylacetyl Chloride.—Trimethylacetic acid was treated with thionyl chloride as directed by Helferich and Schaefer[9] for the preparation of *n*-butyryl chloride; yields of between 50 and 60% were obtained.

4-Phenylphenyl Trimethylacetate.—Twenty-eight grams of 4-phenylphenol was dissolved in 12 ml. of dry pyridine and 24 ml. of dry 1,4-dioxane. The solution was cooled to 8°, and 18 g. of trimethylacetyl chloride was added in small portions with stirring and cooling. After the reaction mixture had been allowed to stand at room temperature for ninety minutes, it was warmed on a steam-bath for an equal period of time; finally, it was placed in an oil-bath at 100°, gradually heated to 140°, and then permitted to cool slowly. The colorless reaction mixture was extracted three times with 50-ml. portions of hot benzene; the residue was treated with water, and again it was extracted with benzene. The extracts were combined, washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide, and water and dried over sodium sulfate. The residue obtained by filtration and removal of the solvent was crystallized from 30–60° ligroin; large crystals resulted, m. p. 66.5–67.5°, 28.5 g. (75%).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.14. Found: C, 80.28; H, 7.23.

Trimethylacetates of the Bromophenylphenols.—These esters were prepared by treating the appropriate phenol in the presence of 1,4-dioxane as diluent with 1.1 to 1.2 molecular proportions of trimethylacetyl chloride in an equivalent quantity of dry pyridine. The colorless esters were extracted from the reaction mixtures with boiling benzene and recrystallized from suitable solvents, *cf.* Table I.

Bromination of 4-Phenylphenyl Trimethylacetate.—Eight grams of 4-phenylphenyl trimethylacetate was dissolved in 60 ml. of carbon tetrachloride, and the solution was warmed to 70° in an oil-bath. At this temperature, 1.7 ml. of bromine in 20 ml. of carbon tetrachloride was added drop by drop with stirring over a period of thirty minutes in the presence of a trace of powdered iron. The stirring was continued for five hours, and the mixture was kept at 80–85°. The red solution was treated with Norite and filtered, and the solvent was distilled off on a steam-bath. The oily residue was dissolved in benzene, and this solution was washed with water, 5% sodium hydroxide solution, and water and set to dry over anhydrous sodium sulfate. (From the alkaline extract, 0.2 g. of unidentified material was isolated.) From the benzene solution an oily residue was obtained; it was dissolved in warm 30–60° ligroin, and colorless crystals appeared upon cooling the solution in a refrigerator. Three recrystallizations from the same solvent raised the melting point to 114–117°, 0.2 g. (1.9%). A mixed melting point determination was made with authentic 4-(4-bromophenyl)-phenyl trimethylacetate; observed, 119–119.5°.

Summary

1. The bromination of 4-phenylphenyl trimethylacetate in carbon tetrachloride resulted in the formation of 4-(4-bromophenyl)-phenyl trimethylacetate.
2. The results somewhat confirm the suggestion that steric factors may function, in part, in determining the orienting effect of an acyloxy group present in a molecule.
3. Several related compounds were prepared, and some of their properties are reported.

PULLMAN, WASHINGTON RECEIVED JULY 21, 1944

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[9] *Ibid.*, p. 147.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Tri-*t*-butylcarbinol and Other Highly Branched Alcohols by Means of Sodium

BY PAUL D. BARTLETT AND ABRAHAM SCHNEIDER

This is a report of some work, interrupted by the war, which it seems desirable to publish in view of a recent paper by Young and Roberts[1] which extends the list of available highly branched alcohols by the use of organolithium compounds. An unsuccessful attempt was made in this Laboratory in 1941[2] to prepare tri-*t*-butyl-carbinol by the reaction of *t*-butyllithium with hexamethylacetone. Thereafter we turned our attention to the possible use of sodium and alkyl halides in the synthesis of highly branched compounds. This reaction, which has been used many times to achieve results parallel to those of the Grignard reaction,[3] is now found capable of yielding compounds so highly branched as to be inaccessible by other means hitherto reported.

Coarse sodium sand can be stirred for hours with *t*-butyl chloride in ether or pentane without any evidence of reaction. Upon addition of methyl pivalate, however, the sodium and the solution turn black and a vigorous evolution of an unsaturated gas occurs. The products identified

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[1] Young and Roberts, THIS JOURNAL, **66**, 1444 (1944).

[2] Bartlett, Swain and Woodward, *ibid.*, **63**, 3229 (1941).

[3] Kekulé, *Ann.*, **137**, 181 (1866); Frey, *Ber.*, **28**, 2514 (1895); Schorigin, *ibid.*, **40**, 3111 (1907); **41**, 2711, 2717 (1908); Morton and Stevens, THIS JOURNAL, **53**, 2244 (1931).

from this reaction include hexamethylacetone and di-*t*-butylcarbinol (in about equal amounts, totaling in the most favorable cases 80%), hexamethylethane, pivaloin, and a small amount of tri-*t*-butylcarbinol, identified by comparison with another product to be described later. The proportions of these products are highly dependent upon the conditions of the reaction. High yields of di-*t*-butyl compounds are favored by a reaction temperature not over 35°, sodium sand of average particle diameter about 2 mm., excess of *t*-butyl chloride, and as rapid addition of the ester as will permit control of the reaction. For the purpose of preparing hexamethylacetone, the mixture of it with its reduction product can be oxidized with chromic or nitric acid. We have found this a more convenient preparation of pure hexamethylacetone than the difficult methylation of isobutyrone and pentamethylacetone which has long been the chief method of preparation in quantity.

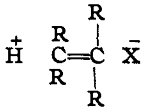
By appropriate choice of halide and ketone or ester, the highly branched tertiary alcohols listed in Table I have been prepared. Tricyclohexylcarbinol, the only trisecondary carbinol previously known at the time of this work,[4] was prepared as a check upon the method. The yield of pure material (19.3%) was higher than that obtained previously by the use of the Grignard reaction (7%). The same is doubtless generally true of the carbinols in the table, several of which have been diligently sought but not found among the products of the Grignard reaction. The chief competing reaction in the sodium synthesis as in the Grignard synthesis is reduction of the ketone to a secondary carbinol.

TABLE I

CARBINOLS PREPARED FROM HALIDES, SODIUM AND KETONES

Carbinol	Yield, %	Boiling point		Refractive index
		°C.	Mm.	
Triisopropyl	2.7	105	50	1.4478 (20°)
Diisopropyl-*t*-butyl	5.7	103–104	27	1.4559 (20.7°)
Isopropyl-di-*t*-butyl	15.3	120–122	30	1.4623 (25.5°)
Tri-*t*-butyl	5.1	138–140	28	M. p. 94–95°
t-Butylcyclohexanol-1	6.8	103–104	30	M.p. 46–49°
Tricyclohexyl	19.3			M. p. 92–93°

Tri-*t*-butylcarbinol is especially worthy of careful study, and we look forward to further work upon it at the earliest opportunity. This alcohol is the logical starting point for the preparation of the free radical tri-*t*-butylmethyl, to which the greatest interest has been attached ever since the observation by Conant and Bigelow[4a] that diphenyl-*t*-butylmethyl can exist as a stable free radical similar to triphenylmethyl. Thermochemical measurements on tri-*t*-butylcarbinol would be interesting, inasmuch as a Stuart model[5] allows none of the nine methyl groups to rotate and this would surely be reflected in an unusual entropy. Tri-*t*-butylcarbinol is also of interest to the theory of hyperconjugation or "no-bond" resonance,[6] since it is the first tertiary alcohol whose hydroxyl group cannot be activated by any such structures as



$$\overset{+}{\mathrm{H}}\ \ \underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{C}}}{=}\underset{|\atop\mathrm{R}}{\overset{\mathrm{R}\atop|}{\mathrm{C}}}\ \ \overset{-}{\mathrm{X}}$$

of which *t*-butyl alcohol, for instance, has nine. To these questions we have as yet no answers, but only three orienting observations. (1) Tri-*t*-butylcarbinol shows normally active hydrogen toward the Grignard reagent in the Zerewitinoff determination. (2) It is inert toward acetyl bromide under conditions which convert other tertiary alcohols rapidly into bromides. (3) It is readily destroyed by strong aqueous sulfuric acid, yielding a poorly characterized product which may prove to be an isomeric alcohol.

One of the difficulties encountered was in achieving quantitative combustion of these highly branched compounds in the carbon and hydrogen analysis. It was found necessary to use a long combustion tube with an extra quantity of platinized asbestos.

It is possible to formulate the condensation as proceeding through an initial reaction of the sodium with either the halide or the carbonyl compound. The fact that no reaction occurs until the carbonyl compound is introduced may point to the latter interpretation, or it may merely indicate an action of the ketone or ester in loosening or removing a thin coating of sodium chloride on the metallic surface.[6a]

From some of the evidence presented by Kharasch, Sternfeld and Mayo,[7] it seems a possible interpretation that the halide reacts metathetically with the di-sodium derivative of the carbonyl compound

$$\mathrm{RCl} + \mathrm{Na{-}}\underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{C}}}\mathrm{{-}O{-}Na} \longrightarrow \mathrm{NaCl} + \mathrm{R}\underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{C}}}\mathrm{ONa}$$

whose existence has been definitely established both for esters and for ketones. The strong tendency of any strong base to eliminate hydrogen chloride from *t*-butyl chloride to the exclusion of other reactions casts doubt upon this mechanism, although this may be the way in which the large amount of isobutylene and reduction product arises. It is equally conceivable that the monosodium addition product of the carbonyl compound, a ketyl, may serve as an intermediary

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[4] Neunhoeffer, *Ann.*, **509**, 115 (1934).

[4a] Conant and Bigelow, THIS JOURNAL, **50**, 2041 (1928).

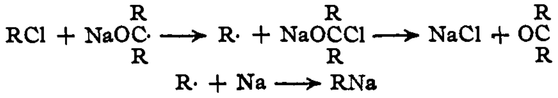
[5] Stuart, *Z. physik. Chem.*, **27B**, 354 (1934).

[6] Wheland, *J. Chem. Phys.*, **2**, 478 (1934); Baker and Nathan, *J. Chem. Soc.*, 1844 (1935); Mulliken, Rieke and Brown, THIS JOURNAL, **63**, 41 (1941).

[6a] We are indebted to one of the Referees for calling our attention to this point. Compare Morton, Davidson and Newey, THIS JOURNAL, **64**, 2241 (1942).

[7] Kharasch, Sternfeld and Mayo, *J. Org. Chem.*, **5**, 362 (1940).

free radical to initiate the conversion of *t*-butyl chloride into *t*-butylsodium. This organosodium compound may then attack the ester or ketone, showing a greater power of addition than the lithium compound, just as many organolithium compounds show a greater power of addition than the related Grignard reagents.



$$\mathrm{RCl} + \mathrm{NaO}\overset{\mathrm{R}}{\underset{\mathrm{R}}{\mathrm{C}}}\cdot \longrightarrow \mathrm{R}\cdot + \mathrm{NaO}\overset{\mathrm{R}}{\underset{\mathrm{R}}{\mathrm{C}}}\mathrm{Cl} \longrightarrow \mathrm{NaCl} + \mathrm{O}\overset{\mathrm{R}}{\underset{\mathrm{R}}{\mathrm{C}}}$$

$$\mathrm{R}\cdot + \mathrm{Na} \longrightarrow \mathrm{RNa}$$

Experimental

Reaction of Methyl Pivalate with *t*-Butyl Chloride and Sodium.—In a three-liter, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and wide-bore condenser, 65 g. (2.82 moles) of coarse sodium sand (average particle size about 2 mm.) was prepared by melting sodium under toluene and stirring until cooled to solidification. The toluene was decanted and the sodium washed three times with *n*-pentane; then 150 cc. of *n*-pentane and 150 g. (1.63 moles) of *t*-butyl chloride were introduced and stirring commenced. Methyl pivalate (75 g., 0.646 mole) was dropped in over a period of one hour. After 10 cc. had been added the sodium became covered with black spots and the solution turned black. Spontaneous refluxing occurred with a steady stream of gas escaping from the condenser. This gas decolorized a solution of bromine in carbon tetrachloride. After the ester had been added the mixture began to turn green and refluxing continued for some time after the addition. After standing overnight the flask contained a bright, yellow-green solid mass which was then treated with 200 cc. of water. The light yellow organic layer was dried over potassium carbonate and distilled through a 7 mm. × 60 cm. partial condensation Podbielniak column with a nichrome spiral. After removal of the ether and *t*-butyl chloride the following fractions were obtained:

Fraction	Boiling point, °C.	Weight, g.	
1	95–100	2.2	Semi-solid
2	105	3.5	Solid
3	105–150	0.5	
4	150–160	36.7	
5	160–165	28.0	
	Residue	10.0	

The residue was distilled at 27 mm. from a small Claisen flask:

Fraction	Boiling point, °C.	Weight, g.	
6	74–120	6.9	
7	120–134	0.9	Semi-solid
8	134–143	0.4	
Residue		1.0	

Fractions 4 and 5 represented a mixture of hexamethylacetone and di-*t*-butylcarbinol, amounting to a combined yield of 71%. In a similar run using one mole of methyl pivalate and ether as the solvent, the yield of di-*t*-butyl compounds was 67.5%. The di-*t*-butylcarbinol melted at 50° and yielded a phenylurethan melting at 121–122°.[8] Of the fractions of the residue, Fraction 6 was identified as pivaloin and Fraction 7 as impure tri-*t*-butylcarbinol.

Oxidation of Di-*t*-butylcarbinol to Hexamethylacetone.—Di-*t*-butylcarbinol (64.7 g.) was mixed with 180 cc. of concentrated nitric acid. After the vigorous reaction had subsided the mixture was refluxed for twenty minutes. The organic layer was washed with water, shaken well with a strong sodium hydroxide solution, and distilled. The yield was 81% of hexamethylacetone boiling at 153.0–153.6°, $n^{22.4}\mathrm{D}$ 1.4188.

Reaction of Ethyl Hexahydrobenzoate with Cyclohexyl Chloride and Sodium.—To a well-stirred suspension of 17.2 g. of sodium sand (0.75 mole) in 45 g. (0.38 mole) of cyclohexyl chloride and 100 cc. of *n*-pentane, 25 g. of ethyl hexahydrobenzoate (0.16 mole) was added dropwise. A violent reaction set in after about half of the ester had been added, and the reaction was cooled with ice during its latter half. The mixture was stirred for ten hours and hydrolyzed with 200 cc. of water. The organic layer was dried over potassium carbonate, stripped, and separated roughly by distillation into three fractions. The portion boiling from 50 to 80° weighed 13 g., and was largely cyclohexene. There was 20.84 g. boiling up to 200° under 27 mm. pressure, evidently dicyclohexyl ketone and the dicyclohexylcarbinol. A fraction boiling from 160 to 195° at 3 mm. solidified and was recrystallized from isopropanol to yield 10.5 g. (19.3%) of thick, transparent prisms melting at 92–93°.[4]

Triisopropylcarbinol.—To 40 g. (0.5 mole) of isopropyl chloride and 12 g. (0.52 mole) of sodium sand in 200 cc. of dry ether, a solution of 28.6 g. (0.25 mole) of isobutyrone in 50 cc. of ether was added during twenty minutes. The mixture turned black immediately and refluxed slowly. After ten hours there was a thick white precipitate in a blue supernatant solution. Hydrolysis was effected with 53.5 g. (1 mole) of ammonium chloride in 160 cc. of water. The ether layer was washed with sodium carbonate solution, dried over sodium sulfate, and distilled. After the removal of isobutyrone at 124° and diisopropylcarbinol at 140°, there was obtained 3.52 g. having b. p. 84–85° (30 mm.) and $n^{23.5}\mathrm{D}$ 1.4444. This is a 7.2% yield of triisopropylcarbinol. Although its analysis was satisfactory (below), its refractive index differed from that of Young and Roberts. Later redistillation at 50 mm. yielded 0.25 g., b. p. 101–104°, $n^{26}\mathrm{D}$ 1.4424; 0.73 g., b. p. 104–105°, $n^{26}\mathrm{D}$ 1.4446, $n^{20}\mathrm{D}$ 1.4465; and 0.60 g., b. p. 105°, $n^{26}\mathrm{D}$ 1.4458, $n^{20}\mathrm{D}$ 1.4478. The material of Young and Roberts had $n^{20}\mathrm{D}$ 1.4476–1.4480.

Anal. Calcd. for $C_{10}H_{22}O$: C, 75.87; H, 14.01. Found: C, 76.03; H, 14.13.

Diisopropyl-*t*-butylcarbinol.—Over a period of twelve minutes 25 g. (0.218 mole) of isobutyrone was added to a suspension of 12 g. of sodium sand (0.52 mole) in 40 g. of *t*-butyl chloride (0.435 mole) and 100 cc. of dry ether. After ten hours of stirring the mixture was worked up as in the preceding preparation and distilled. On redistillation, a yield of 2.2 g. (6.4%) was obtained of material boiling at 103–104° (27 mm.), $n^{20.7}\mathrm{D}$ 1.4559.

Anal. Calcd. for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 77.17; H, 14.27.

Another preparation gave a 6.6% yield of carbinol with $n^{23.2}\mathrm{D}$ 1.4550. Redistillation yielded 5.7%, $n^{20.7}\mathrm{D}$ 1.4559, b. p. 103–104° (27 mm.).

Isopropyl-di-*t*-butylcarbinol. (*a*) ***From Pentamethylacetone.***—Pentamethylacetone (kindly supplied by Dr. R. Altschul) was distilled through the Podbielniak column and material boiling at 132–136° was collected for use. Of this, 25 g. (0.195 mole) was added to a suspension of 18 g. of sodium sand (0.78 mole) in 40 g. of *t*-butyl chloride (0.435 mole) and 100 cc. of dry ether over thirteen minutes. After fifteen hours the mixture was still intensely black. Working up as usual and distillation yielded, beside much ketone and secondary carbinol, a 5.8-g. cut boiling from 118 to 125° (30 mm.). This is a crude yield of 15.9%. On redistillation 5.6 g. (15.3%) of the carbinol was obtained boiling at 120–122°, $n^{25.5}\mathrm{D}$ 1.4623.

Anal. Calcd. for $C_{12}H_{26}O$: C, 77.35; H, 14.07. Found: C, 77.44; H, 14.34. Zerewitinoff determination: sample, 0.1287 g. Volume of gas at 26° and 765.5 mm., 16.36 cc.; at N.T.P., 15.05 cc. Active hydrogen, 97.4% of calculated (15.48 cc.).

(b) **From Methyl Isobutyrate.**—To a suspension of 27.6 g. (1.2 moles) of sodium in 70 g. (0.76 mole) of *t*-butyl chloride and 100 cc. of ether 25.5 g. of methyl isobutyrate

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(8) Compare Haller and Bauer, *Ann. chim.*, [8] **29**, 213 (1913).

(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.

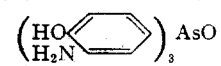
CAMBRIDGE, MASSACHUSETTS
RECEIVED SEPTEMBER 19, 1944

[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 $Ar_2As(OH)NHSO_2C_6H_4NHR(R = H \text{ or } CH_3CO)$ 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).