Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.25; H, 9.71.

The n.m.r. spectrum[16] of this compound in CCl_4 showed absorption at τ 6.47, 7.13, and 7.97 in ratios 1:1:2, corresponding to bridge hydrogen, hydroxyl hydrogen, and two bridgehead hydrogens. In addition, there were four complex bands centered at *ca.* τ 8.3 and 8.7 (total of four hydrogens), *ca.* 9.3 (three hydrogens), and 10.04 (one hydrogen). These correspond, respectively, to the four *exo/endo* hydrogens, three hydrogens of the cyclopropyl ring, and a fourth cyclopropyl hydrogen at highest field.[5]

The *p*-bromobenzenesulfonate ester of II, recrystallized from petroleum ether, melted at 83–83.5°.

Anal. Calcd. for $C_{14}H_{15}BrO_3S$: C, 48.98; H, 4.40. Found: C, 49.17; H, 4.50.

Reaction of CH_2N_2–CuCl with 7-Norbornadienyl Acetate.[15]—Reaction of diazomethane generated from 23.3 g. of N-methyl-N-nitrosurea with 9.0 g. of 7-norbornadienyl acetate over 8 hr. gave a product, separated by g.l.p.c. on a 5-ft. Ucon polar column at 110°, with analysis agreeing with addition of one methylene unit to the diolefin.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.40; H, 7.25.

The n.m.r. spectrum of this sample showed it to be *ca.* a 3:1 mixture of two compounds arising from addition to either of the double bonds of the diolefin. That is, there were triplets at τ 3.65 and 4.32 (area ratio 3:1) for olefinic hydrogens, singlets at 5.55 and 6.02 (ratio 1:3) for bridge hydrogens, multiplets centered at 7.10 and 7.65 (ratio *ca.* 3:1), peaks at 8.08 and 8.12 (ratio *ca.* 1:3) for acetate hydrogens, and a broad multiplex at *ca.* 9.0 for cyclopropyl hydrogens.

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(16) N.m.r. spectra were determined on a Varian A-60 spectrometer.

Trisarylmethanes. Synthesis of Diarylcarbinol Precursors by Controlled Catalytic Hydrogenation

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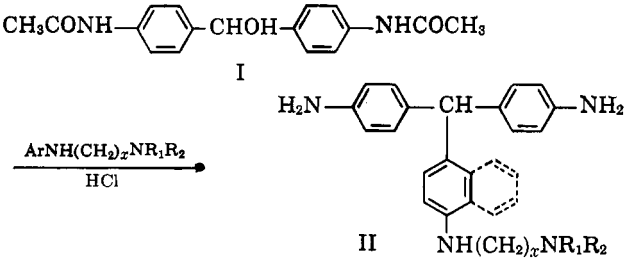
Previous studies in these laboratories[1] have demonstrated that pararosaniline pamoate and certain closely related compounds are effective in experimental schistosomiasis and paragonimiasis. Simple trisarylmethanes also have been reported to be effective against intestinal helminths, filariae, trichomonads, and trypanosomes.[2] It was, therefore, of interest to prepare various trisarylmethanes, including basically substituted compounds of structure II, for biological evaluation and for use as synthetic intermediates. The present communication describes a novel method for the preparation of selected diarylcarbinols, namely the controlled catalytic hydrogenation of the corresponding diaryl ketones, and their conversion to various trisarylmethanes.

The most attractive route to trisarylmethanes of structure II appeared to be condensation[3] of the corresponding aromatic amine[4,5] with 4,4′-diaminobenzhydrol. Wichelhaus[6] describes the conversion of 4,4′-diaminobenzophenone to the benzhydrol with sodium amalgam. This technique, however, is unattractive for large scale work. The erratic nature of this benzophenone–benzhydrol conversion with other reagents is evident from the literature. Treatment of 4,4′-diaminobenzophenone with tin and hydrochloric acid[7] or of 4-butyroylamino-4′-nitrobenzophenone with palladium and hydrogen[8] leaves the ketone function intact. Reduction of 4,4′-diaminobenzophenone with excess lithium aluminum hydride gives the hydrogenolysis product, 4,4′-methylenedianiline.[9] Numerous attempts in these laboratories to effect the reduction to the benzhydrol utilizing a variety of standard chemical and catalytic methods failed.

Efforts to convert 4′,4‴-carbonylbisacetanilide[10] to 4′,4‴-(hydroxymethylene)bisacetanilide (I) were more successful. Chemical reduction gave positive



but still unsatisfactory results, whereas catalytic hydrogenation under standard conditions gave primarily the hydrogenolysis product, 4′,4‴-methylenebisacetanilide. Fortunately, application of Kindler's procedure,[11] involving the use of a palladium catalyst, poisoned with nicotinamide or N,N-diethylnicotinamide, afforded I in 63% yield. Although the carbinol exhibited a variable melting point which was an unsatisfactory criterion of purity, the ultraviolet spectrum[12] (λ 254 mμ, E_1^1 1120, no absorption over 300 mμ) afforded an excellent method for detecting residual ketone (λ 231 mμ, E_1^1 614; λ 306 mμ, E_1^1 1060) during purification. The controlled catalytic hydrogenation technique also was used successfully for the preparation of 4′,4‴-(hydroxymethylene)bistrifluoroacetanilide (61%), 4-methylbenzhydrol[13] (80%), 4-chlorobenzhydrol[14] (35%), and 4-aminobenzhydrol[9] (59%), but failed with 4-bromobenzophenone, 4-hydroxybenzophenone, 4-(dimethylamino)benzophenone, 4-hydroxybenzophenone acetate ester, 2-benzoylbenzoic acid, and 4,4′-bis(dimethylamino)benzophenone. The moderate success achieved with 4-chlorobenzophenone is noteworthy in view of the known susceptibility of

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(2) For a brief review, see R. J. Schnitzer and F. Hawking, "Experimental Chemotherapy," Vol. I, Academic Press, New York, N. Y., 1963, pp. 200, 296, 789, 809, 906.

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(4) Farbenfabriken vorm. Friedr. Bayer and Co., British Patent 267,169 (March 7, 1927).

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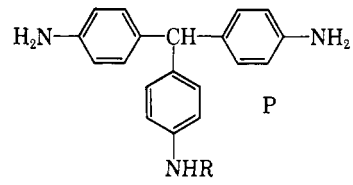
(11) K. Kindler, H. Helling, and E. Sussner, *Ann.*, **605**, 200 (1957).

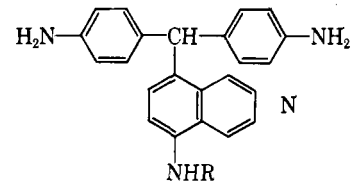
(12) Ultraviolet spectra were obtained in ethanol on a Cary 11 recording spectrophotometer.

(13) J. O. Halford and E. B. Reid, *J. Am. Chem. Soc.*, **63**, 1873 (1941).

(14) A. E. Chichibabin and A. A. Shesler, *J. Russ. Phys. Chem. Soc.*, **56**, 149 (1925); *Chem. Abstr.*, **19**, 3269 (1925).

TABLE I
TRISARYLMETHANES





Compd. no.	Structural type	R	M.p., °C.	Yield purified, %	Purification solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	P	H	245 dec.	32	A	$C_{19}H_{19}N_3 \cdot 3HCl$[b,c]	57.22	57.22	5.56	5.64	10.54	10.64
2	P	C_2H_5	233 dec.	30	A	$C_{21}H_{23}N_3 \cdot 3HCl \cdot 3H_2O$[d]	52.45	52.32	6.71	6.64	8.74	9.12
3	N	H	273–277	40	B	$C_{23}H_{21}N_3$	81.38	81.20	6.24	6.34	12.38	12.52
4	P	$(CH_2)_2N(C_2H_5)_2$	200 dec.	49	C	$C_{26}H_{32}N_4 \cdot 4HCl \cdot 0.75H_2O$[e]	54.80	55.05	6.90	7.18	10.23	10.16
5	P	$(CH_2)_3N(CH_2)_5$	219–229 dec.	55	D	$C_{27}H_{34}N_4 \cdot 4HCl \cdot 2H_2O$[f]	54.36	54.55	7.10	7.17	9.39	9.45
6	N	$(CH_2)_2N(C_2H_5)_2$	177–179	45	E	$C_{29}H_{34}N_4$	79.41	79.14	7.81	7.90	12.78	12.75

[a] A, dilute hydrochloric acid; B, not recrystallized; C, ethanol–methanol (9:1); D, crude product extracted with warm methanol; E, methanol. [b] E. Fischer and O. Fischer, *Ann.*, **194**, 272 (1878). [c] Contains 7.15% water by Karl Fischer water determination (analytical values reported are corrected for water). Cl: calcd., 26.67; found, 26.63. [d] Water: calcd., 11.24; found, 10.40. Cl: calcd., 22.11; found, 22.32. [e] Water: calcd., 2.47; found, 2.62. [f] Water: calcd., 6.04; found, 5.50. Cl: calcd., 23.78; found, 23.51.

aromatic halogen to hydrogenolysis in the presence of palladium.

The trisarylmethanes II (Table I) were obtained readily by refluxing an ethanol solution of the diarylcarbinol and the aromatic amine in the presence of concentrated hydrochloric acid. Primary or secondary naphthylamines and anilines gave comparable yields.

Experimental[15]

4',4'''-(Hydroxymethylene)bisacetanilide (I).—A solution of 200 g. (0.675 mole) of 4',4'''-carbonylbisacetanilide[10] in 1.5 l. of methanol was hydrogenated over 4.0 g. of 20% palladium-on-charcoal catalyst[16] poisoned with 0.01 g. of nicotinamide at 26° and an initial hydrogen pressure of 50 p.s.i.g. After 1 equivalent of hydrogen had been absorbed, the catalyst was collected by filtration, and the filtrate was evaporated to dryness *in vacuo*. Ultraviolet assay of the crude product (207 g.) indicated the presence of approximately 10% of the starting ketone. The crude hydrol was divided into two equal portions and each was crystallized from 2 l. of acetonitrile yielding a total first crop of 107 g. An additional 20 g. of product separated after the filtrates were allowed to stand at room temperature for 24 hr. The ratio of solvent to crude product (20 ml./g.) is crucial in the purification since the use of a lower ratio leads to coprecipitation of the starting material. The hot crystallization mixture should be allowed to cool slowly to room temperature and filtered promptly; it should not be refrigerated. The total yield of purified material was 63%; it melted at 174.5–176.5°, resolidified at 195°, and remelted at 258–266°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.46; H, 6.07; N, 9.44.

4',4'''-Carbonylbistrifluoroacetanilide.—To a solution of 226 g. (1.06 moles) of 4,4'-diaminobenzophenone in 800 ml. of dimethylformamide was added gradually a solution of 550 g. (2.62 moles) of trifluoroacetic anhydride in an equal amount of dimethylformamide. The mixture cautiously was heated to its boiling point and then boiled under reflux for 3 hr., cooled, and poured into iced water. The suspension was neutralized with ammonium hydroxide and filtered. Recrystallization of the crude product from 95% ethanol gave 315 g. (73%) of product, m.p. 235–236°.

Anal. Calcd. for $C_{17}H_{10}F_6N_2O_3$: C, 50.50; H, 2.49; N, 6.93. Found: C, 50.79; H, 2.70; N, 7.67.

4',4'''-(Hydroxymethylene)bistrifluoroacetanilide.—A mixture of 19 g. (0.047 mole) of 4',4'''-carbonylbistrifluoroacetanilide, 300 ml. of ethanol, and 2 drops of N,N-diethylnicotinamide was hydrogenated as described previously over 1.0 g. of 20% palladium on charcoal. The crude product recrystallized from dilute ethanol gave 12 g. (61%) of purified material, m.p. 213–214°.

Anal. Calcd. for $C_{17}H_{12}F_6N_2O_3$: C, 50.25; H, 2.98; N, 6.89. Found: C, 49.95; H, 3.18; N, 7.17.

4,4',4''-Methylidynetrianiline (Compound 1, Table I).—A solution of 60 g. (0.2 mole) of 4',4'''-(hydroxymethylene)bisacetanilide, 18.6 g. (0.2 mole) of aniline, and 20 ml. of concentrated hydrochloric acid in 600 ml. of 95% ethanol was heated under reflux for 4 hr. Concentrated hydrochloric acid (250 ml.) was added, and the mixture was heated under reflux for an additional 6 hr. Upon cooling, a yellow solid was deposited (32.6 g.). It was purified by dissolving in water, adding concentrated hydrochloric acid until a solid formed, warming to effect solution, and cooling to give 24.4 g. (32%) of the hydrated trihydrochloride salt. Conversion to the free base was effected by addition of ammonium hydroxide to an aqueous solution of the salt. Recrystallization of the base (ethanol) gave 4,4',4''-methylidynetrianiline, m.p. 207–210°.

The other trisarylmethanes (Table I) were prepared similarly. Because they did not precipitate directly from the reaction mixture, the solvent was removed *in vacuo;* compounds 2 and 5 were triturated with 2-propanol and crystallized as indicated, while compounds 3, 4, and 6 were dissolved in water, converted to the bases, and processed.

4-Methylbenzhydrol.—A solution of 19.6 g. (0.1 mole) of 4-methylbenzophenone in 150 ml. of methanol was hydrogenated over 0.5 g. 20% palladium on charcoal poisoned with 0.1 g. of nicotinamide. The mixture was filtered from the catalyst, concentrated to dryness, and recrystallized from petroleum ether (b.p. 30–60°) to give 15.7 g. (80%) of product, m.p. 53–55°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.74; H, 7.38.

When only 0.01 g. of nicotinamide was used, the hydrogenation proceeded rapidly to the diphenylmethane.

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(15) Melting points (corrected) were taken on a Thomas Hoover capillary melting point apparatus.

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General Base Catalysis for Imidazole-Catalyzed Hydration of *sym*-Dichloroacetone[1]

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Evidence implicating the imidazole side chain of a histidine residue as a constituent of the active site of several enzymes including trypsin, chymotrypsin, and