

Formic Acid Reduction. XXI.¹⁾ Reductive Cleavage Reaction of *p*-Dimethylamino-substituted Triphenylmethanes induced by Formate

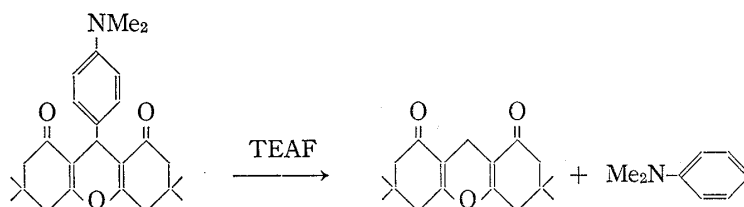
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On heating with the formate, triethylammonium formate, known as the distillable liquid given by $5\text{HCO}_2\text{H}\cdot 2\text{NEt}_3$, several triphenylmethanes possessing dimethylamino group on their benzene rings have been shown to suffer reductive cleavage at the carbon bond bound to the dimethylaminophenyl carbon to give *N,N*-dimethylaniline and diphenylmethanes. The reaction is controlled by the structure and the substituent effect. Isotopic experiments using a deuterated formate has revealed that formyl hydrogen of formic acid is transferred to the methylene carbon of the diphenylmethane product. From the assembled data, a possible mechanism is proposed.

In the paper dealing with the formic acid reaction upon triarylcarbinol, reported by Guyot, *et al.*³⁾ in 1913, there was exhibited the conversion of *p,p',p''*-tris(dimethylamino)-triphenylmethane (leucocrystal violet) into *p,p'*-bis(dimethylamino)diphenylmethane. In addition, the formic acid reduction of 1,8-dioxo-3,3,6,6-tetramethyl-9-(*p*-dimethylamino-phenyl)-1,2,3,4,5,6,7,8-octahydroxanthene converting into 1,8-dioxo-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene and *N,N*-dimethylaniline reported⁴⁾ from this laboratory appeared to be of a mode similar to the above reaction. When presumed from these two reac-

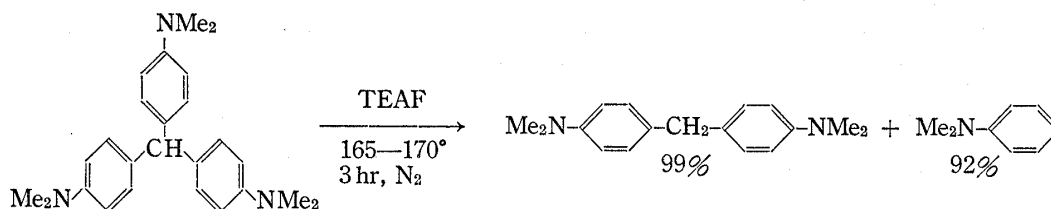


tions, reductive cleavage appeared to occur by action of formic acid at the specific carbon bond bound to the carbon like *p*-dimethylaminophenyl carbon, but no authentic work aimed at such a reaction had been reported in literature. Our interest in such a reductive cleavage, which may be induced by formic acid, prompted us to seek its scope and to elucidate its mechanistic feature. We have initiated this program by the use of *p*-dimethylamino-substituted triphenylmethane derivatives as substrates.

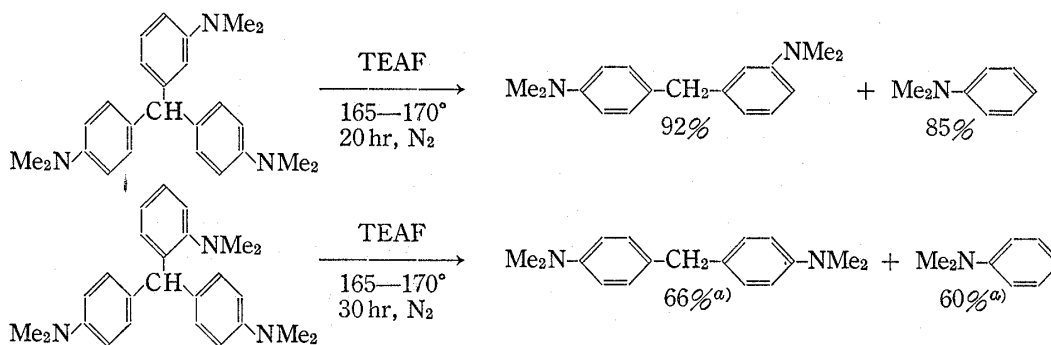
In the previous report³⁾ describing the formic acid reaction of leucocrystal violet, a mixture of formic acid and sodium formate was used as reagent, although without any description about the detail of the reaction. A test to carry out the reaction with this reagent under refluxing condition required much longer reaction period (above 16 hr) and resulted in 52% yield of *p,p'*-bis(dimethylamino)diphenylmethane together with a formation of a resinous product. A sufficient result was obtained by the use of the formate reagent, triethylammonium formate (TEAF), which has been known⁵⁾ as the constant boiling liquid given by

- 1) Part XX: T. Okugawa, K. Suzuki, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **22**, 448 (1974).
- 2) Location: 2-2-1, Oshika, Shizuoka.
- 3) A. Guyot and A. Kovache, *Compt. Rend.*, **156**, 1324 (1913) [*Beilstein*, **13-1**, p. 71].
- 4) M. Sekiya and K. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1540 (1971).
- 5) K. Ito, *Yakugaku Zasshi*, **86**, 1166 (1966).

$5\text{HCO}_2\text{H}\cdot 2\text{NEt}_3$. When leucocrystal violet was heated with TEAF at $165\text{--}170^\circ$ under a stream of nitrogen, *p,p'*-bis(dimethylamino)diphenylmethane and *N,N*-dimethylaniline were obtained almost quantitatively for shorter reaction period. This TEAF reaction indicates a reductive cleavage at the *p*-dimethylaminophenyl carbon bond bound to the methine carbon of leucocrystal violet. From extensive study, triphenylmethane and *p,p',p''*-trihydroxytriphenylmethane were shown to be inert under the same condition.



Comparative experiments were conducted to know how the reaction is influenced by the use of the substrates which possess *m*- and *o*-dimethylamino group instead of *p*-substituent. Results are shown in the following. Whenever the *m*-substituent is present, the reductive



a) recovery of the substrate: 30%

cleavage proceeds at *p*-dimethylaminophenyl carbon bond but with slower velocity. When the *o*-substituent is present, the reductive cleavage proceeds at the *o*-dimethylaminophenyl carbon bond, but much more suppressed.

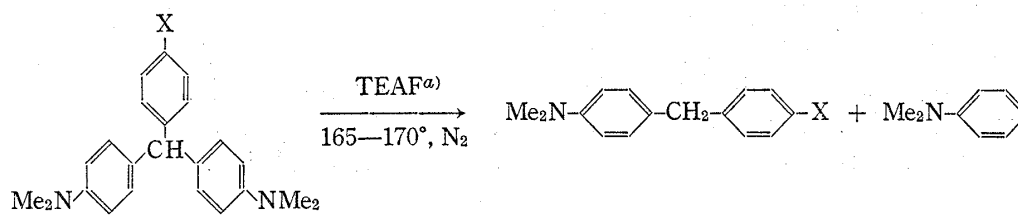
Effect of several other *p*-substituents such as HO-, MeO-, H_2N -, H- and Cl- in place of one of the *p*-dimethylamino group of leucocrystal violet on the reaction was then examined. Results are shown in Table I, where the cleavage reaction of the triphenylmethanes proceeds with rapidity varying with substrate, without any side reaction. These data are sufficient to give relative rates, qualitatively, which are deduced to be in the order $\text{Me}_2\text{N}->\text{HO}->\text{MeO}->\text{Me}->\text{H}->\text{Cl}-$. Except for a particular substituent $-\text{NH}_2$, which is capable of the conversion into $-\text{NHCHO}$ by action of formic acid in the reaction, the reaction is facilitated by electron-releasing substituent.

In our interest to speculate on a mechanism of this cleavage reaction, incorporation mode of the two different hydrogens of formic acid into the product was then investigated by the use of the deuterated formate reagent.⁶⁾ Selected leucocrystal violet as a model substrate, the reaction of this compound with deuterated TEAF composed of formic-*d* acid ($5\text{DCO}_2\text{H}\cdot 2\text{NEt}_3$) was carried out and incorporation of deuterium in the product was then inspected.

Since in the nuclear magnetic resonance (NMR) spectrum of *p,p'*-bis(dimethylamino)diphenylmethane the methylene protons appeared as a singlet at $\tau=6.28$ in carbon tetrachloride, content of the protons of the cleaved product at this position was measured in comparison of its peak area with the aromatic (8H) and *N*-methyl (12H) proton peak areas which appeared as two doublets at $\tau=3.08$ and 3.48 ($J=6.0$ Hz) and as a singlet at $\tau=7.20$, respec-

6) K. Ito, H. Oba, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 2112 (1972).

TABLE I. Substituent Effect on the Reductive Cleavage Reaction



X	Reaction time (hr)	Percentage of the cleavage ^{b)}
Me ₂ N-	3	99
HO-	11	99
MeO-	22	97
Me-	30	90 (8) ^{c)}
H ₂ N-	30	87
H-	30	81 (18) ^{c)}
Cl-	30	52 (38) ^{c)}

a) molar ratio: substrate/TEAF=1/20 (based on HCO₂H)

b) based on yield of the product, *p,p'*-disubstituted diphenylmethane actually isolated

c) percentage of recovery of the substrate

tively. The product obtained by the reaction with TEAF composed of formic-*d* acid showed 55% absence of the methylene proton peak area in comparison with that of non-deuterated *p,p'*-bis(dimethylamino)diphenylmethane. This result shows transference of the formyl deuterium of formic-*d* acid in TEAF into the methylene carbon.

In order to obtain more reliable quantitative data, mass spectral method was employed for determination of the deuterium contents in the two cleaved products. On inspection of the mass spectra of the two products corresponding to *p,p'*-bis(dimethylamino)diphenylmethane and N,N-dimethylaniline, the mass spectrum of the latter was completely consistent with that of the non-deuterated one and that of the former was shown to be one deuterated in most part. The mass spectra of an authentic *p,p'*-bis(dimethylamino)diphenylmethane

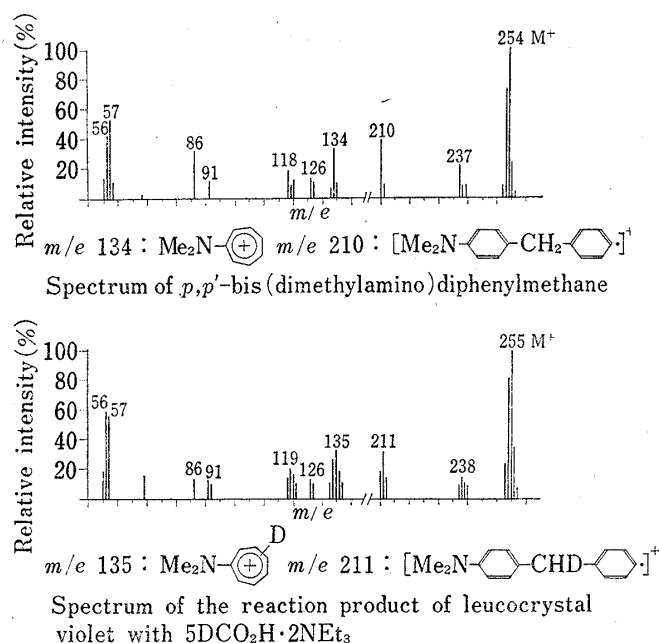


Fig. 1

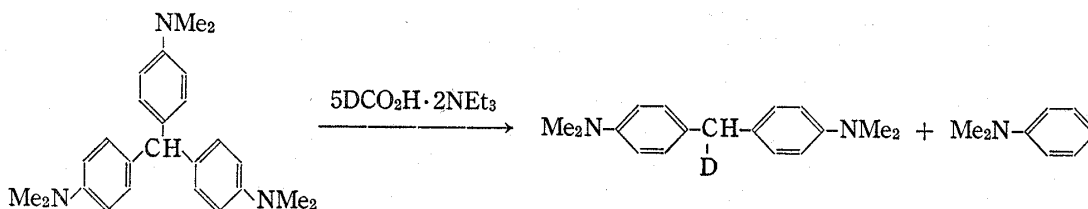
and the corresponding product obtained by the reaction with TEAF composed of formic-*d* acid are represented in Fig. 1. That the parent ion fragment peak at *m/e* 254 shifts to the peak of one unit higher *m/e* 255 in the product shows existence of mono-deuterium-substituted product in major. This mono-deuterated product is presumed to be *p,p'*-bis(dimethylamino)-diphenylmethane-*α-d* from the result of the foregoing NMR measurement. When compared the intensities of the parent ion peak groups of the two spectra, it is seen that the product is not pure but contaminated with nondeuterated one. Content of mono-deuterated one is calculated from the heights of the peaks to be about 84% (see Table II). The existence of the non-deuterated one in the product is presumed to be attributed to replacement of deuterium of the initially formed deuterated product by proton of the formic-*d* acid in TEAF. This was confirmed by treatment of non-deuterated *p,p'*-bis(dimethylamino)diphenylmethane with TEAF composed of formic acid-*d* (5HCO₂D·2NEt₃). After a mixture of TEAF

TABLE II. Mass Spectral Data of Authentic *p,p'*-Bis(dimethylamino)-diphenylmethane and Deuterated Ones obtained

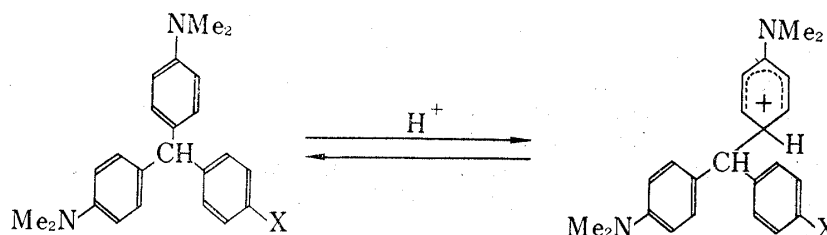
<i>m/e</i>	Non-deuterated authentic sample	Intensity of parent ion peak group of deuterated <i>p,p'</i> -bis(dimethylamino)-diphenylmethane obtained			
		Product A ^{a)}		Product B ^{b)}	
		Found	Calcd. ^{c)}	Found	Calcd. ^{d)}
252	6.0	—	1.1	5.4	5.3
253	72.3	23.7	18.8	70.4	64.6
254	100.0	81.7	87.4	100.0	100.0
255	22.3	100.0	100.0	26.9	31.9
256	2.7	34.9	21.9	4.7	6.4
257	—	6.9	2.6	2.6	0.6
258	—	—	—	1.0	0.04

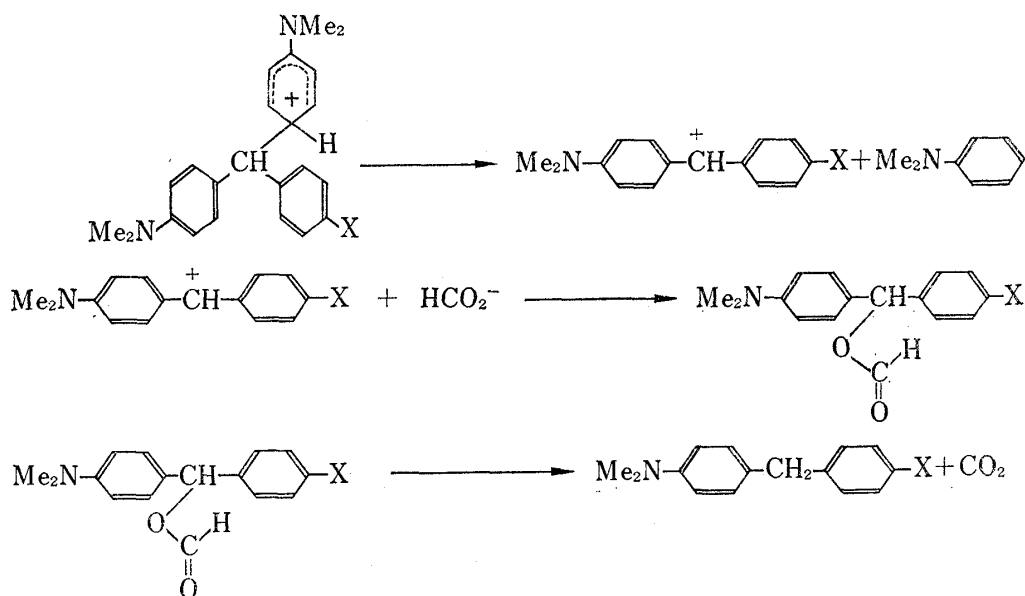
- a) product A: obtained by heating leucocrystal violet with 5DCO₂H·2NEt₃ [molar proportion of 1:10 (based on DCO₂H)] at 165–170° for 3.5 hr
 b) product B: obtained by heating *p,p'*-bis(dimethylamino)diphenylmethane with 5HCO₂D·2NEt₃ [molar proportion of 1:10 (based on HCO₂D)] at 165–170° for 3.5 hr
 c) intensity calculated as a mixture of non-deuterated and α -mono-deuterated *p,p'*-bis(dimethylamino)diphenylmethane in 16:84 proportion
 d) intensity calculated as a mixture of non-deuterated, α -mono-deuterated and α,α -dideuterated *p,p'*-bis(dimethylamino)diphenylmethanes in 83:15:2 proportion

composed of formic acid-*d* and *p,p'*-bis(dimethylamino)diphenylmethane in 10 molar ratio (based on HCO₂D) was heated at 165–170° for 3.5 hr (these conditions are the same as those of the reductive cleavage reaction), a recovered substrate was subjected to mass spectral measurement. Proportion of the deuterium substitution of methylene proton was measured by the same manner as described in the foregoing. Thus, 17% of deuterium substitution was shown as represented in detail in Table II. This value agrees with the foresaid proportion of the non-deuterated one in the product obtained by the reaction of leucocrystal violet with TEAF composed of formic-*d* acid. From the above result it is clarified that in the reaction with TEAF composed of formic-*d* acid *p,p'*-bis(dimethylamino)diphenylmethane which possesses one deuterium at methylene position is formed and deuterium of this product is in part replaced by proton of formic-*d* acid in TEAF. Therefore, in the TEAF reaction of leucocrystal violet formyl hydrogen of formic acid is transferred to the methylene carbon of *p,p'*-bis(dimethylamino)diphenylmethane.

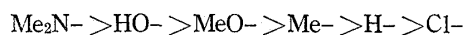


When we speculate on a mechanism of the TEAF reaction of *p*-dimethylamino-substituted triphenylmethane, the following scheme may be adequate, which is comprehensible to the above determined reaction mode and to the substituent effect described in the foregoing.





Effect of the substituent X:



Possibly, the formate initially induces a transformation of *p*-dimethylamino-substituted triphenylmethane into the corresponding diphenylmethyl cation with an elimination of *N,N*-dimethylaniline through a protonated σ -complex intermediate. The known formation⁷⁾ of triphenylmethane derivatives from benzaldehydes and *N,N*-dimethylaniline in acidic medium presumably involves a reverse of the above transformation. The initial stage may endothermic and slow but an attack of the formate anion may more rapidly lead to the corresponding diphenylmethane with an elimination of carbon dioxide. This stage is presumable from the known formation⁸⁾ of diphenylmethane from benzohydrol by formic acid reduction.

Experimental⁹⁾

Preparation of *p*-Dimethylamino-substituted Triphenylmethanes—The following nine *p*-dimethylamino-substituted triphenylmethanes shown with their melting points were prepared and used as substrates for the TEAF reaction. Leucocrystal violet, mp 177—178° (lit.¹⁰⁾ mp 175°); *p,p'*-bis(dimethylamino)-*p''*-methoxytriphenylmethane, mp 103—104° (lit.¹⁰⁾ mp 105°); *p,p'*-bis(dimethylamino)-*p''*-methyltriphenylmethane, mp 97—98° (lit.¹⁰⁾ mp 100°); *p,p'*-bis(dimethylamino)triphenylmethane (leucomalachite green), mp 98—99° (lit.¹⁰⁾ mp 99°); *p,p'*-bis(dimethylamino)-*p''*-chlorotriphenylmethane, mp 95—96° (lit.¹⁰⁾ mp 97°); *m,p',p''*-tris(dimethylamino)triphenylmethane, mp 145—146° (lit.¹¹⁾ mp 153—154°); *o,p',p''*-tris(dimethylamino)triphenylmethane, mp 121—122°; *p,p'*-bis(dimethylamino)-*p''*-hydroxytriphenylmethane, mp 163—164° (lit.¹²⁾ mp 163°); *p,p'*-bis(dimethylamino)-*p''*-aminotriphenylmethane, mp 150—152° (lit.¹²⁾ mp 151—152°). These compounds except *p,p'*-bis(dimethylamino)-*p''*-aminotriphenylmethane were prepared by the usual means of heating the corresponding benzaldehydes and *N,N*-dimethylaniline in hydrochloric acid.⁷⁾ *p,p'*-Bis(dimethylamino)-*p''*-aminotriphenylmethane was prepared by catalytic reduction of *p,p'*-bis(dimethylamino)-*p''*-nitrotriphenylmethane over Raney nickel catalyst at high hydrogen pressure at 80—85°. Among these nine compounds thus prepared the following has not been known.

7) P. Boessneck, *Ber.*, **19**, 366 (1886).

8) A. Kovache, *Ann. Chim. Phys.*, [9] **10**, 242 (1918) [*C.A.*, **13**, 441 (1919)].

9) All melting points are uncorrected. Ultraviolet (UV) spectra were recorded with a Hitachi EPS-2U spectrophotometer. NMR spectra were taken with a JEOL-C-60-H spectrometer (at 60 MHz) in CCl_4 solution using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, b=broad, m=multiplet.

10) C.D. Ritchie, W.F. Sager, and E.S. Lewis, *J. Am. Chem. Soc.*, **84**, 2349 (1962).

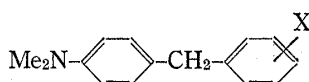
11) A. Baeyer, *Ann. Chem.*, **354**, 152 (1907) [*Beilstein*, **13**, 312].

12) O. Fisher, *Ber.*, **14**, 2523 (1881).

o,p',p''-Tris(dimethylamino)triphenylmethane: Prisms (from BuOH). *Anal.* Calcd. for C₂₅H₃₁N₃: C, 80.37; H, 8.37; N, 11.25. Found: C, 80.24; H, 8.25; N, 11.36. UV $\lambda_{\max}^{\text{hexane}}$ nm(log ϵ): 262 (4.60), 303 (3.71). NMR τ : 7.48 (6H, s, *o*-NMe₂), 7.15 (12H, s, *p*-NMe₂), 4.00 (1H, s, >CH-), 3.55—2.80 (12H, m, aromatic protons).

Reaction of *p*-Dimethylamino-substituted Triphenylmethanes with TEAF General Procedure—In a flask provided with an air condenser tube and an inlet tube, were placed 0.03 mole of triphenylmethane derivative and 51.9 g (0.60 mole based on HCO₂H) of TEAF. A constant stream of nitrogen was passed through the reaction mixture and the mixture was heated at 165—170° with stirring until no starting material was detected by TLC (silica gel, benzene–chloroform). In several runs in which more than 30 hr was required the reaction was suspended after 30 hr. As the reaction proceeded the reaction temperature be-

TABLE III. Analytical, Physical and Spectral Data of Diphenylmethanes



X	bp[°C(mmHg)]	mp (°C) [lit. mp (°C)]	Appearance (recryst. solvt.)	UV $\lambda_{\max}^{\text{hexane}}$ (log ϵ)
<i>p</i> -NMe ₂	176—183(0.2)	90—91 [89—90.5 ^a]	plates (petr. ether)	262(4.44) 303(3.58)
<i>m</i> -NMe ₂	170—175(0.05)	43—45	needles (petr. ether)	258(4.50) 302(3.71)
<i>p</i> -OH	—	101—103 [107—108 ^b]	prisms (petr. ether)	259(4.30) 305(3.37)
<i>p</i> -OMe	150—153(0.08)	47—48	prisms (petr. ether)	259(4.30) 305(3.35)
<i>p</i> -Me	145—146(0.1)	43—47	prisms (petr. ether)	259(4.29) 305(3.36)
<i>p</i> -NHCHO	221—223(0.05)	125—127	powders (MeOH)	257(4.41) ^c 310(3.24) ^e
H	125—127(0.25)	31 [30—31 ^d]	needles (petr. ether)	259(4.29) 305(3.35)
<i>p</i> -Cl	150—154(0.08)	68—69	prisms (petr. ether)	261(4.29) 305(3.37)

X	NMR τ				<i>Anal.</i> Calcd. (Found)			
	NMe ₂	-CH ₂ -	X	aromatics	C	H	N	Cl
<i>p</i> -NMe ₂	7.20(s)	6.27(s)		3.08(d, <i>J</i> =6.0 Hz) 3.48(d, <i>J</i> =6.0 Hz)	80.27 (80.53)	8.72 (8.70)	11.01 (10.85)	
<i>m</i> -NMe ₂	7.15(s)	6.23(s)	7.15(s, <i>m</i> -NMe ₂)	3.68—2.82(m)	80.27 (80.05)	8.72 (8.51)	11.01 (11.07)	
<i>p</i> -OH	7.13(s)	6.20(s)	4.10(b, OH)	3.45—2.80(m)	79.26 (79.13)	7.54 (7.56)	6.16 (5.85)	
<i>p</i> -OMe	7.13(s)	6.21(s)	6.28(s, OMe)	3.50—2.90(m)	79.63 (79.89)	7.94 (7.63)	5.80 (5.80)	
<i>p</i> -Me	7.13(s)	6.23(s)	7.78(s, Me)	3.53—2.85(m)	85.28 (85.23)	8.50 (8.31)	6.22 (6.45)	
<i>p</i> -NHCHO	7.09(s)	6.13(s)	2.45(b, NH) 1.66(d, <i>J</i> =1.5 Hz, -CHO)	3.37—2.40(m)	75.56 (75.89)	7.13 (7.16)	11.02 (11.16)	
H	7.13(s)	6.12(s)		3.42—2.82(m)	85.31 (85.37)	8.06 (8.12)	6.63 (6.58)	
<i>p</i> -Cl	7.11(s)	6.20(s)		3.50—2.85(m)	73.31 (73.41)	6.56 (6.46)	5.70 (5.57)	14.43 (14.38)

a) J.I.G. Cadgon, D.H. Hey, and W.A. Sanderson, *J. Chem. Soc.*, **1960**, 3202; Y. Ogata and M. Okano, *J. Am. Chem. Soc.*, **72**, 1459 (1950); W.L. Borkowski and E.C. Wagner, *J. Org. Chem.*, **17**, 1128 (1942).

b) L.H. Smith and K.N. Welch, *J. Chem. Soc.*, **1934**, 1136; G. Sunagawa, T. Ichii, and N. Yoshida, *Pharm. Bull.* (Japan), **3**, 116 (1955).

c) Methanol was used as a solvent.

d) A. Mangani and R. Passerini, *J. Chem. Soc.*, **1956**, 4954.

came lower because of the consumption of formic acid and the partial decomposition of formic acid. Accordingly, the low boiling liquid containing water, triethylamine and *N,N*-dimethylaniline was topped from the end of the condenser tube and collected in an ice-cooling receiver. After the reaction, the reaction solution was concentrated under reduced pressure and excess TEAF was removed. The resulting residue was subjected to distillation under reduced pressure to give the product, diphenylmethane derivative as a nearly pure solid distillate which was weighed. Recrystallization from an appropriate solvent gave an analytical sample. From the residue undistilled, when present, a recovered substrate was obtained by trituration with petr. ether followed by recrystallization.

The foregoing TEAF distillate combined with the topping liquid was diluted with water and excess KOH was added on cool. The liberated triethylamine layer was separated and aqueous layer was once extracted with ether. The triethylamine layer combined with the ethereal layer was dried over anhydrous K_2CO_3 . Evaporation of ether and triethylamine followed by distillation of the resulting residue under reduced pressure gave *N,N*-dimethylaniline.

The run with *p,p'*-bis(dimethylamino)-*p''*-hydroxytriphenylmethane is an exception of the above isolation procedure. The reaction solution was concentrated under reduced pressure and excess TEAF was removed. The resulting residue was dissolved in 10% HCl solution. The clear solution was neutralized with $NaHCO_3$ and crystals deposited were collected by filtration and washed with water, which were shown to be *p*-dimethylamino-*p'*-hydroxydiphenylmethane.

In each run yield of the product, diphenylmethane derivative, can be seen in Table I with recovery of the substrate, and *N,N*-dimethylaniline was obtained in the yield corresponding to diphenylmethane. Analytical, physical and spectral data of diphenylmethanes obtained are listed in Table III.

Reaction of Leucocrystal Violet with Formic Acid-Sodium Formate—A mixture of 11.2 g (0.03 mole) of leucocrystal violet, 28 g of 99% formic acid and 4 g of sodium formate was refluxed in a stream of nitrogen for 16 hr. After removal of formic acid the residue was treated with aqueous KOH. A liberated material was extracted with isopropyl ether and the solution was dried over anhydrous K_2CO_3 . Removal of isopropyl ether and distillation of the resulting residue under reduced pressure gave an oily distillate, bp 85–90° (30 mmHg), a solid distillate, bp 173–181° (0.04 mmHg) and a resinous residue. The former two were shown to be *N,N*-dimethylaniline and *p,p'*-bis(dimethylamino)diphenylmethane, yields of which were 26% and 52%, respectively, after purification.

Reaction of Leucocrystal Violet with TEAF Composed of Formic-*d* Acid ($5DCO_2H \cdot 2NEt_3$)—A mixture of 3.7 g (0.01 mole) of leucocrystal violet and 8.7 g (0.1 mole based on DCO_2H) of TEAF composed of formic-*d* acid was heated at 165–170° with constant stirring in a stream of nitrogen. After 3.5 hr's heating, the reaction solution was concentrated under reduced pressure and excess TEAF was removed. Distillation of the resulting residue under reduced pressure gave a solid distillate, bp 155–156° (0.1 mmHg). Prisms (from dry petr. ether), mp 84–85.5°. This was shown to be *p,p'*-bis(dimethylamino)diphenylmethane- α -*d* in major by NMR and mass spectral measurements. In a NMR spectrum the methylene protons appeared as a singlet at $\tau=6.28$ and the peak area of this signal showed 45% content of proton owing to the deuterium substitution. By mass spectral measurement this was shown to contain *p,p'*-bis(dimethylamino)diphenylmethane- α -*d* and non-deuterated one in about 84:16 proportion.

Reaction of *p,p'*-Bis(dimethylamino)diphenylmethane with TEAF Composed of Formic Acid-*d* ($5HCO_2D \cdot 2NEt_3$)—A mixture of 1.27 g (0.005 mole) of *p,p'*-bis(dimethylamino)diphenylmethane and 4.4 g (0.05 mole based on HCO_2D) of TEAF composed of formic acid-*d* was heated at 165–170° for 3.5 hr with stirring. The reaction solution was concentrated under reduced pressure to remove excess TEAF. The resulting residue was subjected to distillation under reduced pressure to give a solid distillate, bp 162–165° (0.3 mmHg). Prisms (from dry petr. ether), mp 88–89°. This product was shown to contain non-deuterated *p,p'*-bis(dimethylamino)diphenylmethane, α -monodeuterated and α,α -dideuterated ones in about 83:15:2 proportion by mass spectral measurement.

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