TRIARYLMETHANE COMPOUNDS AS REDOX INDICATORS IN THE SCHOENEMANN REACTION

II. SYNTHESES OF THE TRIARYLMETHANES[1]

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ABSTRACT

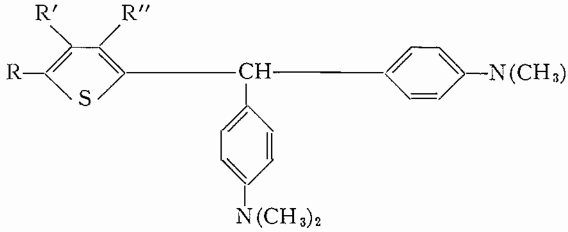
The syntheses and properties of a series of 4,4′-thenylidene bis[N,N-dimethylaniline] compounds, variously substituted in the thiophene ring, are reported. These compounds were tested as redox indicators in the Schoenemann reaction for the detection of phosphonofluoridate esters in solution. The most effective indicator was 4,4′(5-methyl-4-propyl-2-thenylidene)bis[N,N-dimethylaniline].

INTRODUCTION

The previous paper of this series (9) dealt with the mechanism of the Schoenemann reaction when a triarylmethane compound was used as the redox indicator. It was suggested that the perphosphonate formed from the interaction of the phosphonofluoridate esters and alkaline peroxide liberated hypochlorous acid from chloride ion upon acidification. The hypochlorous acid then oxidized some of the leuco compound to the violet dye.

It was proposed to employ this modified Schoenemann reaction to determine very low concentrations of the phosphonofluoridate ester. The compound most suitable for this purpose would have, in the dye form, the highest extinction coefficient under the optimum conditions for the reaction. It would also have a redox potential between −0.7 and −1.0 volts.

To determine the most suitable triarylmethane compound for this reaction, variously substituted triarylmethanes were synthesized within a restricted range of substitution. The compounds tested in the preliminary screening were modifications of leucomalachite green with the unsubstituted benzene ring replaced by the furan or thiophene nucleus. Leucomalachite green itself and the furan analogue prepared by the usual method (7) were found to be ineffective as indicators in this reaction sequence as they were oxidized by the peroxide employed to react with the phosphonofluoridate esters.



[I]

However, "thiophene malachite green" (I: R = R′ = R″ = H) showed promise, and the compounds made for testing in this reaction were therefore all of type I with various R groups. Alkyl substituents proved particularly effective; thus mainly compounds of this type were investigated.

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EXPERIMENTAL

The general method of preparation consisted of the synthesis of various substituted thiophenealdehydes and their condensation with dimethylaniline by the use of anhydrous zinc chloride. In all cases the condensation reaction described by Mason and Nord (16) was employed to form the leuco base.

I(a) 4,4′-Thenylidene bis[N,N-dimethylaniline] (I: R = R′ = H)

The 2-thiophenealdehyde was prepared on a large scale by a method reported by Hartough (10 (pp. 310 and 510), 11, 12) and Angyal *et al.* (2).

I(b) 4,4′-5-Methyl-2-thenylidene)bis[N,N-dimethylaniline] (I: R = CH_3, R′ = R″ = H)

The 5-methyl-2-thiophenealdehyde was prepared by the formylation of 2-methylthiophene employing the Weston and Michaels method (23).

The 2-methylthiophene was prepared by Huang-Minlon's modification of the Wolff-Kishner reduction (17).

An alternative route to 2-methylthiophene was the reaction of levulinic acid with "phosphorus heptasulphide" (P_4S_7). The procedure given in Organic Syntheses (19) was modified as follows. A mixture of the monosodium salt of the alkyl succinic or levulinic acid (0.2 mole), sea sand or pumice (40 g.), and phosphorus heptasulphide (110 g.) was dry distilled from a 1 liter flask in a current of oxygen-free nitrogen. The reaction flask was heated gradually to 300° C. or higher. The liquid distillate was collected in an ice-cooled receiver and the gaseous distillate washed by being bubbled through chilled ether using a wash bottle fitted with a fritted glass gas dispersion disk. Two consecutive runs were made and the products from the condenser, receiver, and wash bottle were transferred to a separatory funnel and washed three times with 10% sodium hydroxide. The ethereal solution was dried over sodium sulphate and the ether removed by distillation. The product was then distilled at atmospheric pressure. The yield, using levulinic acid, was below 20% of the theoretical.

I(c) 4,4′-(5-Ethyl-2-thenylidene)bis[N,N-dimethylaniline] (I: R = C_2H_5, R′ = R″ = H)

The 5-ethyl-2-thiophenealdehyde was prepared by applying to 2-ethylthiophene the Vilsmeier modifications of the formylation (23, 15). This latter compound was prepared by the reduction of 2-acetothienone using a modified Wolff-Kishner reaction (17), and the 2-acetothienone was made by acetylation of thiophene with acetyl chloride using stannic chloride as catalyst (14).

I(d) 4,4′-(5-Propyl-2-thenylidene)bis[N,N-dimethylaniline] (I: R = CH, R′ = R″ = H)

This leuco compound was synthesized exactly as described for the ethyl substituted compound (I(*c*)) (16, 23, 15, 17) except that propionyl chloride was used to give 2-propiothienone in the Friedel-Crafts acylation (14).

I(e) 4,4′-(5-Phenyl-2-thenylidene)bis[N,N-dimethylaniline] (I: R = C_6H_5, R′ = R″ = H)

The 5-phenyl-2-thiophenealdehyde was prepared by the application of the Vilsmeier formylation to 5-phenylthiophene. The product was not distilled, however, but was crystallized from ethyl alcohol – water; melting point 92° to 93° C. The 5-phenylthiophene was synthesized as described by Gomberg (8).

I(f) 4,4′-(5-Chloro-2-thenylidene)bis[N,N-dimethylaniline] (I: R = Cl, R′ = R″ = H)

The 5-chloro-2-thiophenealdehyde formylation (23, 15) of 5-chlorothiophene, which is available commercially.

I(g) 4,4′-(5-Bromo-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = Br$, $R' = R'' = H$)

The 5-bromo-2-thiophenealdehyde was prepared by the modified formylation (23, 15). Phosphorus oxybromide had to be used to catalyze the formylation of bromothiophene, since the use of phosphorus oxychloride led to a halogen interchange between the thiophene and the catalyst and gave a mixture of products.

I(h) 4,4′-(5-Acetamido-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = CH_3CONH$, $R' = R'' = H$)

5-Acetamido-2-thiophenealdehyde was prepared from 2-acetamidothiophene by the modification of the Vilsmeier reaction introduced by Campaigne and Archer (5).

The acetamidothiophene was made from thiophene by nitration using the procedure of Steinkopf (20), reduction with tin according to the directions in Hartough (10, p. 513), and acetylation of the tin salt by the method of Steinkopf (21).

I(i) 4,4′-(3-Methyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = R' = R'' = CH_3$)

This leuco compound was synthesized in the regular manner. The 3-methyl-2-thiophenealdehyde was the product of the modified Vilsmeier reaction (23, 15) using 3-methylthiophene.

The 3-methylthiophene was obtained by reacting phosphorus heptasulphide and sodium pyrotartrate (19). The yield in this case was from 33 to 38% of the theoretical amount of 3-methylthiophene. The sodium pyrotartrate (monosodium salt of α-methyl succinic acid) was made by the procedure described in Organic Syntheses (3).

I(j) 4,4′-(3,4-Dimethyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = H$, $R' = CH_3$)

This material was prepared from the 3,4-dimethyl-2-thiophenealdehyde, which was produced by the modified formylation (23, 15) of 3,4-dimethylthiophene.

This dialkylthiophene was obtained by a new application of the Hinsberg condensation of dicarbonyl compounds with thiodiglycolic ester (13). For this series of reactions, 0.2 mole of thiodiglycolic ester, prepared according to the method of Overberger and co-workers (18), in 200 ml. of absolute methanol was added to a solution of 0.2 mole of diacetyl in 200 ml. of absolute methanol. The solution was cooled to −20° C. with vigorous stirring and to it was added a solution of 12 g. of sodium metal in 120 ml. of methanol. The reaction mixture was allowed to reach room temperature gradually and was stirred for 4 hours. Water was then added and the organic solvent was removed by distillation on a steam bath. This process saponified the ester to the acid. The aqueous residue was then cooled, acidified, and filtered. The plaster-like material was dried in air. The yield was about 50%. The acid so obtained, 3,4-dimethylthiophene-2,5-dicarboxylic acid, was decarboxylated to 3,4-dimethylthiophene in 20% yield by dry distillation of three parts of acid with one part of precipitated copper powder.

I(k) 4,4′-(4,5-Dimethyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = R' = CH_3$, $R'' = H$)

The 4,5-dimethyl-2-thiophenealdehyde was prepared from 4,5-dimethylthiophene by the formylation method previously described (23, 15).

The alkylthiophene was the product of the Huang-Minlon modification of the Wolff-Kishner reduction of 3-methyl-2-thiophenealdehyde, the latter compound being the product of the formylation (23, 15) of 3-methylthiophene.

A second method used for obtaining the 4,5-dimethylthiophene was by cyclizing sodium β-methyllevulinate with phosphorus heptasulphide. This was carried out using the procedure recorded under compound I(*b*) but the yields were from 5 to 10%. The sodium salt was obtained from β-methyllevulinic acid, according to the directions of Steinkopf (22). The ester was prepared by the alkylation of ethyl acetosuccinate with methyl iodide following the method of Bruhl (4), the ethyl acetosuccinate having been synthesized as in Organic Syntheses (1).

I(l) 4,4'-(5-Ethyl-4-methyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = C_2H_5$, $R' = CH_3$, $R'' = H$)

This compound was prepared employing procedures outlined for compound I(*k*) (15, 16, 17, 23). The 5-ethyl-4-methylthiophene was synthesized from 3-methylthiophene and the 3-methylthiophene was obtained by cyclizing pyrotartrate with phosphorus heptasulphide.

I(m) 4,4'-(4-Ethyl-5-methyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = CH_3$, $R' = C_2H_5$, $R'' = H$)

This compound was produced by the usual chain of reactions from 2-methyl-3-ethylthiophene to the aldehyde (23, 15) and then to the leuco compound (16).

The 2-methyl-3-ethylthiophene was produced in 10 to 20% yield by the ring closure of sodium β-ethyllevulinate with phosphorus heptasulphide described under compound I(*b*). The sodium β-ethyllevulinate was obtained exactly as described earlier for β-methyllevulinate (compound I(*k*), second method) using ethyl iodide instead of methyl iodide for the alkylation (1, 4, 22).

I(n) 4,4'-(4-Methyl-5-propyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = CH$, $R' = CH_3$, $R'' = H$)

This material was prepared like compound I(*l*), using propionyl chloride instead of acetyl chloride in the original Friedel-Crafts acylation of 3-methylthiophene.

I(o) 4,4'-(3,4-Diphenyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = H$, $R' = R'' = C_6H_5$)

The 3,4-diphenyl-2-thiophenealdehyde was obtained by the modified Vilsmeier formylation (23, 15) of 3,4-diphenylthiophene.

The 3,4-diphenylthiophene was produced by decarboxylating 3,4-diphenylthiophene-2,5-dicarboxylic acid with copper chromite catalyst in quinoline. A mixture of the diacid (three parts) and copper chromite (one part) was refluxed for 1 hour in quinoline. The reaction mixture was then cooled and the quinoline was precipitated with the theoretical quantity of zinc chloride dissolved in 6 *N* hydrochloric acid. The insoluble quinoline – zinc chloride – hydrochloride salt was then extracted six times by being ground in a mortar with portions of benzene, and filtered. The benzene extracts were dried and concentrated. The organic residue was recrystallized from ethanol. The yield was 35%.

The above diacid was synthesized by the Hinsberg condensation of benzil with thiodiglycolic acid (13). This procedure was modified by using 200 ml. of ether as solvent for the benzil and carrying out the reaction at 10° C.

I(p) 4,4'-(5-Bromo-4-methyl-2-thenylidene)bis[N,N-dimethylaniline] (I: $R = Br$, $R' = CH_3$, $R'' = H$)

The 5-bromo-4-methyl-2-thiophenealdehyde was the produce of the modified Vilsmeier reaction (23, 15), using phosphorus oxybromide. The bromomethylthiophene was synthesized by peroxide-free bromination of 3-methylthiophene with one molar equivalent of N-bromosuccinimide. This gave a mixture similar to that obtained by Dittmer and coworkers (6) which was separated by fractional distillation.

Purification of Leuco Compounds

Most of the substances were crystallized several times from ethanol–water, and some from benzene–ethanol; in some cases the compounds were dissolved in chloroform and chromatographed through an alumina column. After compounds I(*e*) and I(*m*) were tested, there was insufficient pure sample left for melting point determination and analysis. The melting points were determined on a Kofler block.

Procedure for Testing the Leuco Compounds as Redox Indicators in the Schoenemann Reaction Sequence

The procedure mentioned in the first paper of this series (9) was followed. One milliliter of a 4% aqueous solution of sodium pyrophosphate peroxide ($Na_2P_2O_7 . 2H_2O_2$) was added to 10 ml. of an aqueous solution of sarin, the isopropyl ester of methyl phosphonofluoridic acid, whose concentration of from 5 to 10 p.p.m. had been accurately determined. The solutions of sarin and sodium pyrophosphate peroxide were mixed and, within 30 seconds, 1 ml. of a 1:16 hydrochloric acid solution of the leuco compound was added. The blank was made up in the same fashion, using distilled water in place of the sarin solution. Optical density readings were taken in 1 cm. Corex cells using the Beckman Model DU spectrophotometer. Measurements were made at the absorption maximum, 7 minutes after the mixing of the acidified indicator and perphosphonate solutions. Previous experience justified the use of Beer's law to calculate the optical densities for all samples at a sarin concentration of 5 p.p.m.

RESULTS AND DISCUSSION

The melting points and analyses for the compounds prepared are given in Table I.

Although great care was taken to purify the compounds, melting point ranges up to 7° C. were noted. The agreement between the calculated and observed values for the

TABLE I

PROPERTIES OF THE LEUCO COMPOUNDS

Compound No.	M.p., ° C.	Formula	Analyses							
			Calculated, %				Found, %			
			C	H	N	S	C	H	N	S
I(*a*)	93–95	$C_{21}H_{24}N_2S$	74.95	7.19	—	9.53	74.98	7.17	—	9.69
I(*b*)	131–133	$C_{22}H_{26}N_2S$	75.38	7.48	—	9.15	75.53	7.37	—	9.26
I(*c*)	119–122	$C_{23}H_{28}N_2S$	75.78	7.74	—	8.79	75.45	7.50	—	8.66
I(*d*)	130.5–132.5	$C_{24}H_{30}N_2S$	76.14	7.99	—	8.47	76.52	8.11	—	8.44
I(*f*)	133–135	$C_{21}H_{23}N_2SCl$	67.99	6.25	7.55	8.64	67.55	6.11	8.12	8.76
I(*g*)	150–152	$C_{21}H_{23}N_2SBr$	60.72	5.58	6.86	7.72	60.53	5.45	6.75	—
I(*h*)	219–226	$C_{23}H_{27}N_3SO$	70.19	6.92	10.68	8.14	70.31	6.87	10.86	8.26
I(*i*)	115.5–118.5	$C_{22}H_{26}N_2S$	75.38	7.48	—	9.15	75.27	7.60	—	9.27
I(*j*)	128–134	$C_{23}H_{28}N_2S$	75.78	7.74	—	8.79	75.72	7.76	—	9.11
I(*k*)	129–132	$C_{23}H_{28}N_2S$	75.78	7.74	—	8.79	75.66	7.36	—	8.44
I(*l*)	129–131	$C_{24}H_{30}N_2S$	76.14	7.99	—	8.47	—	7.83	—	8.44
I(*n*)	104–106	$C_{25}H_{32}N_2S$	76.48	8.22	—	8.17	76.47	8.33	—	8.40
I(*o*)	188–195	$C_{33}H_{32}N_2S$	81.10	6.66	—	6.56	80.93	6.29	—	6.76
I(*p*)	146–149	$C_{22}H_{25}N_2SBr$	61.53	5.87	6.53	7.47	61.34	5.84	6.70	7.90

elemental analyses suggested that the correct compounds had been synthesized and were more than 95% pure.

Substitution in the thiophene ring of these leuco dyes appeared to have an influence upon their effectiveness as redox indicators in the Schoenemann reaction. This effectiveness is expressed quantitatively in Table II. A given type of substitution may affect the following parameters: the redox potential; the extinction coefficient of the dye formed; the efficiency of the oxidation of the leuco compound by the hypochlorous acid; the stability of the dye, once formed, to the bleaching action of the medium (probably related to the potential at which destructive oxidation of the dye would occur); and the solubility of the leuco compound.

TABLE II

COLOR DEVELOPED IN THE SCHOENEMANN REACTION SEQUENCE

Leuco compound used as redox indicator					
	Formula I with:			Absorption maximum	
Compound No.	R (5)	R′ (4)	R″ (3)	Wavelength, mμ	Optical density*
I(*n*)	C_3H_7	CH_3	H	610	0.846
I(*l*)	C_2H_5	CH	H	614	0.782
I(*k*)	CH_3	CH_3	H	614	0.597
I(*m*)	CH_3	C_2H_5	H	614	0.495
I(*o*)	H	C_6H_5	C_6H_5	620	0.062
I(*d*)	C_3H_7	H	H	615	0.053
I(*c*)	C_2H_5	H	H	616	0.051
I(*b*)	CH_3	H	H	616	0.050
I(*p*)	Br	CH_3	H	624	0.025
I(*g*)	Br	H	H	476	0.020
I(*j*)	H	CH_3	CH_3	610	0.012
I(*a*)	H	H	H	625	0.010
I(*e*)	C_6H_5	H	H	632	0.010
I(*f*)	Cl	H	H	634	0.010
I(*i*)	H	H	CH_3	620	0.003

**Intensities converted to 3 p.p.m. aqueous sarin.*

Although it is not certain which, if any, of these parameters is involved, some trends have been observed. Monosubstituted compounds with phenyl or halogen in the 5-position of the thiophene ring (compounds I(*e*), I(*f*), and I(*g*)) gave about the same absorption intensity on reaction as the parent leuco thiophene malachite green. Alkyl substitution in the 3-position had an adverse effect (compound I(*i*)) also apparent in the 3,4-dimethyl compound (I(*j*)). The intensity values were of a much higher order with 4,5-dialkyl substitution (compounds I(*k*), I(*l*), I(*m*), I(*n*)). A synergistic effect was observed when the 4,5-substituents were both alkyl, which was not observed when the 5-substituent was halogen (compound I(*p*)). The most effective members of this class had a long aliphatic side chain in position 5 and a methyl group (the shortest possible side chain) in position 4 (compounds I(*k*), I(*l*), and I(*n*)). Further comments on the effect of substitution on the dye spectra will be given in a later paper.

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