SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES. 6.* ADDUCTS OF DIALKYLPHOSPHITES WITH 1,3,3-TRIMETHYL-2-METHYLENEINDOLINE. REAGENTS FOR SYNTHESIZING 5-SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES

A. A. Tolmachev, A. Yu. Mitrokhin, V. S. Tolmacheva, and A. V. Kharchenko

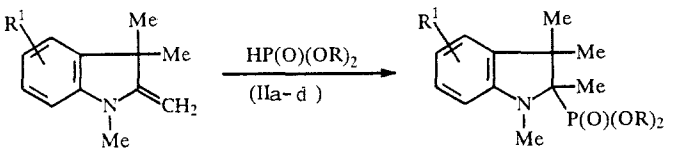
The readily formed addition products of dialkylphosphites and 1,3,3-trimethyl-2-methyleneindoline have been used to synthesize 1,2,3,3-tetramethyl-3H-indolium salts and their derivatives substituted in the benzene ring. In most cases the protecting phosphorus group can be readily removed by adding mineral acids.

1,2,3,3-Tetramethyl-3H-indolium salts and their free bases (1,3,3-trimethyl-2-methyleneindolines I, Fischer bases) are widely used for synthesis of different dyes [2]. For this reason a huge number of these indolines with substituents in the benzene ring are now known and their synthesis continues to attract the attention of investigators [3].

In those cases where the phenyl-substituted hydrazones are unavailable, the synthesis of the corresponding 2-methyleneindolines using the classical Fischer cyclization [4] is difficult.

In order to synthesize 1,3,3-trimethyl-2-methyleneindolines substituted in the benzene ring we have used 1,2,3,3-tetramethylindolines [5]. The 1,2,3,3-tetramethylindolines substituted in the benzene ring were subjected to electrophilic substitution reaction and then oxidized to the 2-methyleneindolines. Some of the 2-methyleneindolines thus synthesized could not be prepared by a conventional method [6]. However, this method could not be used to introduce powerfully acceptor groups or those prone to oxidation.

We have used another route in this work for protecting the methylene group in the 1,3,3-trimethyl-2-methyleneindole I. Thus, acid phosphites II readily add to the double bond of I to form the reasonably stable 2-phosphorylated tetramethylindolines III. The addition is achieved by simply holding an equimolar mixture of I and II at room temperature or with short heating at 80°C. The possibility of such a ready addition of acid phosphites to enamines was reported in 1963 [7] and subsequently studied in [8, 9]. All of the products, however, could also be obtained by the well known Kabachnik–Fields reaction.



I,VIf,e IIIa-e, IVe,f

I R^1 = H; II,III R^1 = H; a R = Me; b R = Et; c R = Bu; d R = *i*-Pr; e R = CMe_2CMe_2; IVe R = Et, R^1 = 6-NO_2; IVf R = Et, R^1 = 5-NH_2; VIf R^1 = 5-NH_2; VIe R^1 = 6-NO_2

*For Communication 5, see [1].

Chemico-Technological Institute, Dnepropetrovsk 320640. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1049-1054, August, 1993. Original article submitted April 27, 1993.

0009-3122/93/2908-0892$12.50

TABLE 1. ^{13}C NMR Spectra of IIIa-c, IVa-d

Compound	Chemical shift, δ, ppm, (J, Hz)											
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	N—CH_3	2-CH_3	3-CH_3	3-CH_3
IIIa[*1]	73,3 (152,2)	47,0 (1,9)	120,7	117,9	127,5	106,4	137,7 (7,5)	149,1 (7,9)	30,8	13,6 (7,3)	25,3 (4,8)	23,8 (6,9)
IIIb[*2]	72,8 (152,6)	46,8 (1,8)	120,5	117,6	127,2	106,0	137,8 (7,4)	149,2 (7,1)	30,6	13,5 (7,4)	25,1 (4,9)	23,9 (7,1)
IIIc[*3]	71,9 (150,5)	45,8 (1,8)	119,5	116,7	126,3	104,9	136,9 (6,8)	148,3 (6,4)	29,7	12,7 (7,8)	23,9 (5,0)	23,3 (8,0)
IVa [*4]	72,9 (149,6)	46,8 (2,0)	125,5	133,8	120,5	106,4	140,6 (5,6)	151,4 (4,1)	30,2	13,6 (8,0)	25,0 (4,0)	23,7 (4,3)
IVb [*5]	73,1 (149,4)	46,3 (—)	122,3	145,8	124,5	104,7	139,9 (—)	156,7 (2,0)	30,2	13,9 (6,3)	25,8 (6,3)	25,7 (5,0)
IVc [*6]	74,4 (150,9)	47,2 (1,9)	121,9	135,8	120,0	106,7	141,6 (2,6)	156,8 (3,7)	30,8	14,3 (5,5)	27,2 (10,8)	22,9 (4,6)
IVd [*7]	71,8 (154,5)	45,9 (3,6)	122,1	108,8	133,4	100,7	143,4 (3,9)	144,5 (—)	32,2	13,7 (4,8)	25,6 (12,0)	22,0 (4,5)

Other C atoms, δ, ppm (J_{med}, Hz):

[*1]OCH_3: 52.3 dd (8.4).

[*2]OEt: 61.4 dd (7.6); 16.2 d (5.7).

[*3]OBu: 64.1 dd (8.2); 31.6 d (2.2); 31.5 d (2.3); 17.8 d (3.3).

[*4]OEt: 61.8 dd (7.8); 16.2 d (5.8); SCN: 129.8 s.

[*5]OEt: 61.9 dd (7.8); 16.3 d; Ar: 147.1 s (C_i); 112.6 s (C_o); 131.5 s (C_m); 153.6 s (C_n).

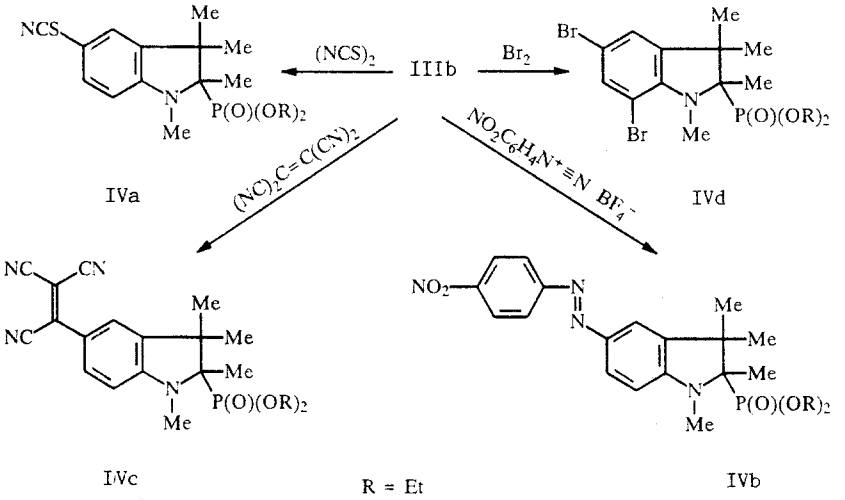
[*6]OEt: 63.0 dd (7.8); 16.8 d (5.5); CN: 115.1 s; 114.8 s; 114.4 s; Cα: 137.5 s; Cβ: 127.4 s.

[*7]OEt: 61.3 dd (7.9); 15.4 (5.6).

Compounds IIIa-d are oils which decompose to starting materials when distillation is attempted. Decomposition of structurally similar materials on distillation in vacuum has been reported. Analytically pure phosphonates IIIa-d were isolated after shaking their hexane solutions with 10% solutions of sodium hydroxide and removal of the solvent.

The speed of addition of the phosphines decreases markedly with growth of the radical in the order MeO > EtO > BuO > i-PrO > CMe_2CMe_2. The reactions were monitored using ^{31}P NMR spectral data. Addition of pyridine to the mixture markedly slows the reaction and an even stronger base (e.g., triethylamine) virtually stops it.

The formed 2-phosphorylated indolines are readily decomposed by addition of mineral acids to give 1,2,3,3-tetramethyl-3H-indolium salts and acid phosphites. Decomposition occurs even with acetic acid and, in this instance, the reaction can be followed by ^{31}P NMR spectroscopy. The rate of the reaction changes with the bulk of the radical in the sequence: MeO > EtO > BuO > i-PrO > CMe_2CMe_2. We have studied the reaction with diethylphosphite not only with the unsubstituted 2-methyleneindoline I but also with the indolines VIf and VIe which contain donor 5-amino and acceptor 5-nitro groups, respectively. At room temperature, the reaction with 5-amino-2-methyleneindoline occurs virtually instantaneously whereas completion of the reaction with the unsubstituted 2-methyleneindoline needs about 1 day. For the 5-nitro indoline the reaction is still not complete after 10 h at 110°C and the addition product cannot be separated. For the reaction of the 6-nitro-substituted analog, where the nitro group shows a weaker acceptor character, the addition of the phosphite acid is complete after 10 h at 80°C.



The 2-phosphorylated tetramethylindolines III took part in an electrophilic substitution to give 1,2,3,3-tetramethylindolines substituted in the ring. The reactions were carried out by methods analogous to those used previously for introduction of a substituent into dialkylanilines [10, 11]. However, a necessary modification is the presence of a base which inhibits fission of the C–P bond by the evolved acid.

Even in the presence of base, we were unable to apply this reaction to other electrophiles having acidic character, such as phosphorus tribromide or the Vilsmeier–Haack complex [5]. Conversion of IVa, d to the corresponding 1,2,3,3-tetramethyl-3H-indolium salts (Va, d) was easily achieved by addition of mineral acid. Even on prolonged refluxing in HBr solution, IVb, c could not be converted to the indolium salts. This is probably due to the strong decrease in the basicity of the indoline nitrogen atom when the tricyanoethylene- or p-nitrodiazo-groups are present.

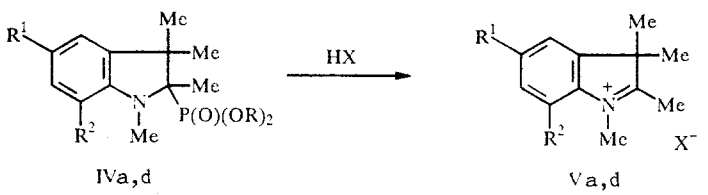


TABLE 2. PMR Spectra of IIIa-c, e; IVa-e; Va (δ, ppm)

Compound	1-CH_3,	2-CH_3,	2-R		3-CH_3, s	4-H, d	5-H (5-R)	6-H	7-H, d
			CH_2	CH_3					
IIIa	2,88	1,40	—	3,59 q 3,68 d	1,37; 1,26	7,67 (J_{45} = 7,1)	6,69 m	7,07 m (J_{57} = 7,6)	6,59
IIIb	2,87	1,38	3,82 m; 4,08 m ($^3J_{CH_2CH_3}$ = 7,2)	1,12 m; 1,21 m	1,26; 1,34	6,89 (J_{45} = 7,6)	6,63 m	7,01 m (J_{57} = 7,1)	6,33
IIIc	2,90	1,36	3,75 m, 3,82 m ($J_{CH_2CH_2}$ = 4,6); 3,90...4,10 m ($^3J_{CH_2CH_3}$ = 7,2)	0,87 m, 0,91 m	1,35; 1,34	6,94 (J_{45} = 7,6)	6,68 m	7,07 m (J_{57} = 7,4)	6,34
IIId	2,90	1,55	—	1,37 s; 1,43 s	1,18; 1,30	6,97 (J_{76} = 7,4)	6,71 m	7,08 m (J_{75} = 7,8)	6,39
IVa	2,91	1,46	3,85 m; 4,05 m ($J_{CH_2CH_3}$ = 7,0)	1,13 m; 1,20 m	1,26; 1,37	7,09 (J_{67} = 8,2)	—	7,30 d (J_{46} = 1,8)	6,33
IVb	3,08	1,60	3,85 m; 4,05 m ($J_{CH_2CH_3}$ = 7,1)	1,18 m; 1,25 m	1,35; 1,50	7,64 (J_{46} = 1,8)	7,93 d (2H, H_A; $J_{H_AH_B}$ = 8,4); 8,33 d (2H, H_B; $J_{H_AH_B}$ = 7,0)	7,83 d (J_{67} = 8,4)	6,47
IVc	3,14	1,54	3,90 m, 4,08 m ($J_{CH_2CH_3}$ = 7,0)	1,13 m, 1,26 m	1,18; 1,26	7,28 (J_{46} = 1,8)	—	7,98 d (J_{67} = 8,8)	6,52
IVd	2,81	1,30	3,81 m; 4,03 m ($J_{CH_2CH_3}$ = 7,15)	1,12 m; 1,20 m	1,18; 1,25	6,88	—	6,97 d (J_{46} = 7,4)	—
IVe	2,95	1,45	3,90 m; 4,10 m ($J_{CH_2CH_3}$ = 7,1)	1,15 m; 1,20 m	1,22; 1,32	7,58 (J_{57} = 2,4)	7,09 d	— (J_{45} = 7,8)	6,97
Va	3, 04	3,92 (H_A); 6,38 (H_B)	—	—	1,32	7,24 (J_{46} = 1,8)	—	7,35 d (J_{67} = 8,0)	6,52

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ solvent using TMS internal standard. Elemental analysis for P and N agreed with that calculated.

2-Diethoxyphosphonyl-1,2,3,3-tetramethylindoline (IIIb). Diethylphosphite (IIb, 0.37 mole) was added in small portions and with stirring and cooling in an ice-water bath to freshly distilled 1,3,3-trimethyl-2-methyleneindoline I (0.25 mole). After standing at room temperature for 2 days, the mixture was washed with a small amount of water, extracted with pentane (3 × 15 ml), and the organic layer dried (sodium sulfate) and the solvent removed. The pinkish, viscous oily product was obtained in 94% yield.

The following were obtained similarly: **2-dimethoxyphosphonyl-1,2,3,3-tetramethylindoline (IIIa)** as a pinkish, viscous oil (92%); **2-dibutoxyphosphonyl-1,2,3,3-tetramethylindoline (IIIc)** as a viscous red oil by heating for 10 h at 50°C (88%); **2-diisopropoxyphosphonyl-1,2,3,3-tetramethylindoline (IIId, 85%).**

2-Tetramethylethyleneoxyphosphonyl-1,2,3,3-tetramethylindoline (IIIe). Tetramethylethylenephosphite (0.27 mole) was added to freshly distilled 1,3,3-trimethyl-2-methyleneindole (I, 0.35 mole). The mixture was heated to 60°C until the phosphite melted and held at this temperature for 10 h. It was then washed with a little water, extracted with chloroform (3 × 15 ml), and the organic layer dried (sodium sulfate), and the solvent evaporated. The residue was treated with hexane and crystallized from pentane to give white crystals (85%, mp 95°C).

2-Diethoxyphosphonyl-6-nitro-1,2,3,3-tetramethylindoline (IVe). Diethylphosphite (0.27 mole) was added to 1,3,3-trimethyl-2-methylene-6-nitroindoline (VIe, 0.25 mole). The product was held at 80°C for 10 h, separated, and crystallized as for IIIe to give orange crystals (94%) with mp 142°C.

2-Diethoxyphosphonyl-5-thiocyanato-1,2,3,3-tetramethylindoline (IVa). Bromine (0.06 mole) in methanol (15 ml) was added dropwise with stirring to a solution of 1,2,3,3-tetramethylindolinediethylphosphite (IIIb, 0.06 mole), ammonium thiocyanate (0.06 mole), and triethylamine (0.1 mole) in methanol (50 ml) which was cooled to −10°C. The product was stirred for a further 2 h and the precipitate of triethylamine hydrobromide was filtered off and the solvent evaporated. The residue was washed with a little water and extracted with chloroform (3 × 15 ml). The chloroform extracts were dried (sodium sulfate), the chloroform evaporated, and the residue dissolved in hexane. The solution was filtered through a fluted filter and the solvent evaporated to give the product (86%) as a viscous red oil.

2-Diethoxyphosphonyl-5-p-nitrophenylazo-1,2,3, 3-tetramethylindoline (IVb). A suspension of p-nitrophenyldiazonium tetrafluoroborate (0.06 mole) in acetone (10 ml) was added in small portions to a solution of 1,2,3,3-tetramethylindolinediethylphosphite (0.06 mole) in pyridine (15 ml) with cooling in an ice-water bath. The product was held at room temperature for 2 days, the precipitate filtered, and the solution evaporated. The residue was treated with hexane and crystallized from pentane to give red crystals (80%) with mp 152°C.

2-Diethoxyphosphonyl-5-tricyanovinyl-1,2,3,3 -tetramethylindoline (IVc). A solution of tetracyanoethylene (0.06 mole) in pyridine (5 ml) was added to a solution of 1,2,3,3-tetramethylindolinediethylphosphite (IIIb, 0.06 mole) in pyridine (5 ml). The product was held at room temperature for 2 days, the precipitate filtered off, and the solvent evaporated. The residue was treated with hexane and crystallized from decane to give black crystals (80%) with mp 158°C.

2-Diethoxyphosphonyl-5,7-dibromo-1,2,3,3-tetramethylindoline (IVd). A solution of bromine (0.12 mole) in chloroform (15 ml) was added dropwise with stirring to a solution of 1,2,3,3-tetramethylindolinediethylphosphite (IIIb, 0.06 mole) and triethylamine (0.2 mole) in chloroform (30 ml) heated to 60°C. The product was stirred for a further 2 h at this temperature, cooled, and the triethylamine hydrobromide filtered off. After evaporation of solvent the product was treated with pentane and crystallized from octane to give IVd (80%) with mp 144°C.

1,3,3-Trimethyl-5-thiocyanato-2-methyleneindoline (Va). Dry HCl was passed through a stirred solution of IVa (0.1 mole) in dry diethyl ether (50 ml) to saturation. The precipitated 1,2,3,3-tetramethyl-5-thiocyano-3H-indolium hydrochloride was filtered off and treated with aqueous ammonia. The organic layer was extracted with chloroform (3 × 20 ml) and the chloroform extracts dried (sodium sulfate). Evaporation of solvent gave a viscous red oil in 85% yield.

1,3,3-Trimethyl-5,7-dibromo-2-methyleneindoline (Vd). This was obtained similarly to Va. After separation of solvent the residue was treated with hexane and crystallized from octane to give red crystals (85%) with mp 123°C.

REFERENCES

1. A. A. Tolmachev, A. V. Kropachev, V. S. Tolmacheva, L. I. Shevchuk, A. Ya. Il'chenko, and F. S. Babichev, Khim. Geterotsikl. Soedin., No. 12, 1614 (1992).
2. R. Kühlhau and A. Bauer, German Patent 3213966.
3. Yu. M. Chunaev and R. M. Przhnyalgovskaya, Summaries in Science and Technology. Organic Chemistry. 2-Methyleneindoline Bases. Synthesis and Properties, Moscow (1990), Vol. 14.
4. B. Robinson, The Fischer Indole Synthesis, Wiley (1982).
5. A. A. Tolmachev and V. S. Tolmacheva, Khim. Geterotsikl. Soedin., No. 11, 1474 (1965).
6. A. A. Tolmachev, L. N. Babichenko, T. N. Chmilenko, A. K. Sheikman, and V. S. Tolmacheva, Khim. Geterotsikl. Soedin., No. 8, 1050 (1990).
7. G. Opits, A. Grissinder, and H. W. Schubert, Annalen, **665**, 91 (1963).
8. I. I. Krasavtsev, E. D. Basalkevich, and M. O. Lozinskii, Zh. Org. Khim., **20**, 1167 (1984).
9. Yu. G. Safina and R. A. Cherkasov, Zh. Obshch. Khim., **62**, 945 (1992).
10. A. E. Agronomov and Yu. S. Shabarov, Laboratory Studies in an Organic Practical Course, Khimiya, Moscow (1974), p. 160.
11. Organic Synthesis, Vol. 33, New York–London (1953), p. 27.