The Chemistry of Carbazole. VI. On the Formation of *N*-Ethylcarbazoles in the Cadogan Reaction

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Reaction of 2',6-dimethyl-2-nitrobiphenyl with triethyl phosphite gave 4,5-dimethyl-9-ethylcarbazole besides 4,5-dimethylcarbazole. In this reaction, 4,5-dimethylcarbazole was ethylated by triethyl *N*-(2',6-dimethylbiphenyl-2-yl)phosphorimidate and diethyl *N*-(2',6-dimethylbiphenyl-2-yl)phosphoramidate, which arose from a nitrene-intermediate and triethyl phosphite. Analogous ethylations of carbazole with other phosphorimidate and phosphoramidates were investigated.

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The reductive cyclization of 2-nitro- and 2-nitrosobiphenyls with trialkyl phosphite has been found to be a valuable method for the preparation of carbazole derivatives (1,2). Although this reaction, which has been referred as the Cadogan reaction, has a wide range of applicability, some unexpected results were reported. Puskas, *et al.* (3), obtained 9-ethylated hexamethylcarbazoles in the reactions of the corresponding 2-nitro-hexamethylbiphenyls with triethyl phosphite. The formation of *NH*-carbazoles was strongly restricted. Analogous *N*-ethylations were reported by Kurihara (4), Sundberg (5) and Tanaka (6).

In continuing our study of methylcarbazoles, we also encountered similar case. The reaction of 2',6-dimethyl-2-nitrobiphenyl and triethyl phosphite gave mainly 4,5-dimethyl-9-ethylcarbazole, and the yield of 4,5-dimethylcarbazole was unexpectedly low. Difficulty of ring closure can be attributed to the limited coplanality of two benzene rings caused by the steric hindrance of two methyl groups. However, the introduction of ethyl group at 9-position can not be elucidated. These results prompted us to investigate the reaction sequence concerned with *N*-ethylation.

Results and Discussion.

2',6-dimethyl-2-nitrobiphenyl **1** was heated with triethyl phosphite **2** under nitrogen for 14 hours. After removal of the excess **2** and triethyl phosphate **3** *in vacuo*, the residue was chromatographed on alumina column. The elution with benzene gave 6.4% of 4,5-dimethyl-9-ethylcarbazole **5** and a small amount of 4,5-dimethylcarbazole **4**. In the sequence of the reaction, gas chromatography showed that three intermediates were increasing temporarily, and they disappeared at final stage. In order to isolate these intermediates, the reaction was discontinued at early stage and the reaction mixture was chromatographed on alumina with benzene. After elution of **4** and **5**, the third component was eluted with acetone. This material was comfirmed as diethyl *N*-(2',6-dimethylbiphenyl-2-yl)phosphoramidate **7a** by comparison with an authentic sample. Another component was identified as triethyl *N*-(2',6-dimethylbiphenyl-2-yl)phosphorimidate **6** by gas chromatography but it could not be isolated either by chromatography or by fractional distillation. Phosphorimidates are known to be unstable and easily converted to phosphoramidates by heating or in contact with alumina or silica gel (1,7-11).

When the phosphoramidate was heated alone, 2-amino- **8a**, 2-(*N*-ethylamino)- **8b**, 2-(*N,N*-diethylamino-2',6-dimethylbiphenyl **8c** and ethylene were obtained in accordance with the results reported by Puskas (3) and Cadogan (12). However, any formation of the carbazoles **4** and **5** was not detected, therefore, the phosphoramidate **7a** is not a precursor of carbazoles. The phosphorimidate **6** also gave no carbazoles on heating. These results led to an idea that **6** or **7a** would ethylate 4,5-dimethylcarbazole **4**. In addition, there may be a possibility that triethyl phosphate **3** is an ethylating agent. Puskas (3), Kurihara (4), Sundberg (5) and Tanaka (6) considered that **3** ethylates carbazoles and other *N*-heterocyclic compounds. Yamauchi (13) found that indole could not be alkylated by alkylphosphates, although other heterocycles, such as imidazole, pyrazole and triazole, were easily alkylated.

Thus, we tested the ability of *N*-ethylation for **6**, **7a** and **3**. Either **6** or **7a** reacted with **4** to give the 9-ethyl compound **5** as expected. On the contrary, the phosphate **3** ethylated **4** difficultly. The yield of the *N*-ethylated product was only 0.3% after 22 hours at 210°.

In the reaction of **4** with triethyl *N*-(2',6-dimethylbiphenyl-2-yl)phosphorimidate **6** at 170°, as shown in Figure 1, the decrease in chromatographic peak area for **6** was in accord with the increase in those for **5** and **7**. This observation indicates that **6** ethylates **4** and this reaction is accompanied by simaltaneous decomposition to the phosphoramidate **7a**. An unidentified intermediate is thought

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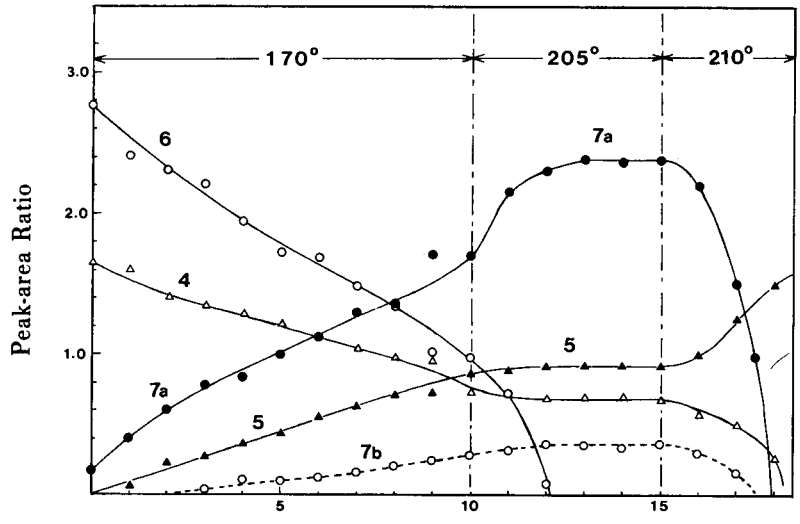


Fig. 1 Gas chromatographic peak-area changes for **5**, **7a** and **7b** with elapse of reaction time in the reaction of **4** with **6**. (internal standard: 9-ethylcarbazole).

to be diethyl *N*-ethyl-*N*-(2',6-dimethylbiphenyl-2-yl)phosphoramidate **7b**. In the analogous ethylation by triethyl *N*-(*o*-tolyl)phosphorimidate **9**, a product was diethyl *N*-ethyl-*N*-(*o*-tolyl)phosphoramidate **10b**, which also showed ethylating ability, as described later. After 10 hours **5** increased scarcely, which was consistent with the decrease of **6**. When the temperature was raised to 205°, **6** was consumed completely and amounts of **5** and **7** did not change any more. At 210°, **7a** and **7b** disappeared rapidly and yield of **5** was increased again. These results indicate that **6** ethylates **4** at temperature below 170°, and **7a** and probably **7b** ethylate **4** above 210°.

Similar tendency was observed in the reaction of carbazole **11** with triethyl *N*-(*o*-tolyl)phosphorimidate **9**, diethyl *N*-(*o*-tolyl)phosphoramidate **10a** and diethyl *N*-ethyl-*N*-(*o*-tolyl)phosphoramidate **10b** as illustrated by Scheme 1. And the results are shown in Table 1.

Scheme 1

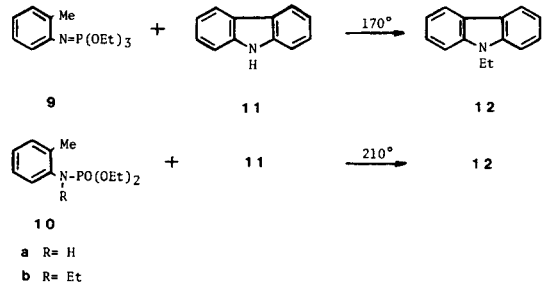
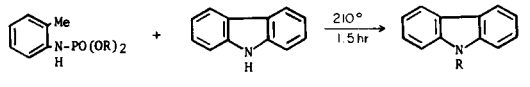


Table I
Ethylation of Carbazole **11** with **9**, **10** and **3**

Compound No.	Mole	Reaction Time (hours)	Temperature (°C)	Yield of **12** (%)
9	2.5	15	170	17
10a	2.5	15	170	0.0
	2.6	1.5	210	12
	6.0	1.5	210	30
10b	1.7	5	170	0.0
	1.7	5	210	21
3	4.0	16	170	0.0
	5.0	22	210	0.4

These reactions were extended to methylation of carbazole **11** with dimethyl *N*-(*o*-tolyl)phosphoramidate **13** as illustrated by Scheme 2. The ethylation proceeded more readily than the methylation in contrast to alkylations of indole with trialkyl phosphates, where triethyl phosphate was unreactive (8).

Scheme 2



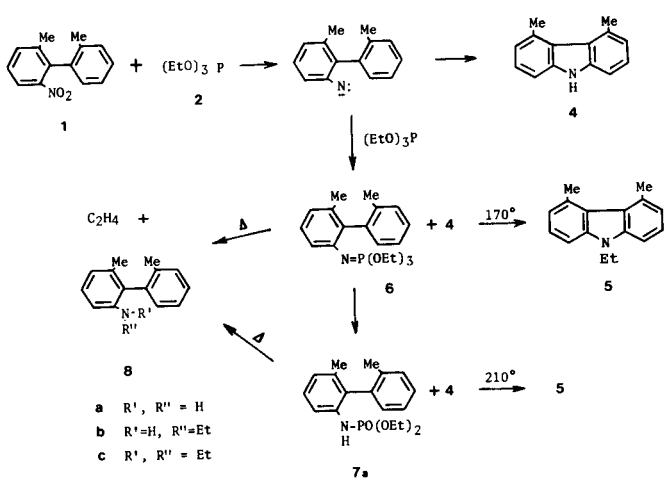
10a R = Et **11** **12** R = Et (30% Y.)

13 R = Me **11** **14** R = Me (7% Y.)

The Pathway of 4,5-Dimethyl-9-ethylcarbazole Formation in the Cadogan Reaction.

On the basis of our findings, it is obvious that ethylation of **4** is done by at least two organophosphoric intermediates **6** and **7** as shown in Scheme 3. Thus, 2',6-dimethyl-2-nitrobiphenyl **1** is deoxygenated by triethyl phosphate **2** to give a nitrene. The nitrene gives 4,5-dimethylcarbazole **4** and the phosphoramidate **6**. In two competing reactions of nitrene, *i.e.*, ring closure and addition of triethyl phosphite, the carbazole ring formation will be restricted in some extent by non-coplaner configuration of two benzene rings and this situation is favorable to the addition reaction. Analogous cases are the reactions of 2,4,6-trimethyl-2'-nitrobiphenyl (14) and *o*-alkylnitrobenzenes (7,8) with triethyl phosphite which produce phosphorimidates on account of prohibited ring closure. The phosphorimidate **6** ethylates **4** subsequently, and then the phosphoramidate **7a** and presumably also **7b**, both of which arise from **6**, undergo ethylation again above 210°.

Scheme 3



Although Puskas (3), Kurihara (4), Sundberg (5) and Tanaka (6) considered that triethyl phosphate involved in *N*-ethylation, there was no conclusive evidence for participation of the phosphate in this work.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra of liquids were determined as neat films and solids as potassium bromide pellets with a Jasco IRA-1 spectrophotometer. Nmr spectra were recorded on a Jeol-PS-100 (100 MHz, deuteriochloroform, tetramethylsilane as internal standard). Mass spectra were taken on a Hitachi RMU-7M spectrometer at 70 eV. Uv spectra were obtained using a Hitachi EPS-3T spectrophotometer. Gas liquid chromatography analysis was carried out on a Shimadzu GC-4C (FID) with a capillary column (30 m, 0.28 mm) coated with Silicone OV-17. Peak areas were evaluated by a digital integrator, and 9-ethylcarbazole or pyrene were used as internal standards.

Triethyl phosphite, triethyl phosphate and trimethyl phosphite were obtained from a commercial source (Tokyo Kasei Kogyo Co.) and were used without further purification.

Triethyl *N*-(*o*-tolyl)phosphorimidate (**9**).

This compound was prepared from *o*-tolyl azide by the method of Kabachnik (9), b.p. 115-124° (2.5 mm) (64.2%). Redistillation through a spinning band column gave the nearly pure phosphorimidate **9**, b.p. 92-98° (0.1 mm) [lit. b.p. 90-93° (0.12 mm) (8)]; ir: 1380, 1360 (N=P), 1025, 970 cm^{-1} (POC).

Diethyl *N*-(*o*-tolyl)phosphoramidate (**10a**).

This compound was prepared from **9** by the method as described below in the preparation of **7a**, m.p. 93-94° [lit. m.p. 92-94° (8), 93-94° (10), 95° (15)].

Dimethyl *N*-(*o*-tolyl)phosphoramidate (**13**).

This compound was prepared from *o*-tolyl azide and trimethyl phosphite by the same method of **7a** and **10a**, m.p. 115-116° [lit. m.p. 110° (14)].

Reaction of 2',6-Dimethyl-2-nitrobiphenyl **1** with Triethyl Phosphite **2**.

(A)

A mixture of **1** (3.2 g., 0.014 mole) and **2** (9.3 g., 0.056 mole) was refluxed (170-200°) for 14 hours under nitrogen. After removal of low boiling point liquid by distillation under reduced pressure, the residue was chromatographed on alumina with benzene to give the two compounds **4** and **5**. 4,5-Dimethylcarbazole **4**, needles of m.p. 176-177° (cyclohexane), 10 mg. (0.2%). This was identical with an authentic specimen which was prepared by thermolysis of 2-azido-2',6-dimethylbiphenyl. 9-Ethyl-4,5-dimethylcarbazole **5** was obtained as needles of m.p. 115-116° (cyclohexane), 0.2 g. (6.4%); ir: 1440, 1315, 1150 cm^{-1}; nmr: δ 1.38 (3H, t, NC-CH_3), 3.0 (6H, s, 4, 5-CH_3), 4.3 (2H, q, N-CH_2-), 6.9-7.3 (6H, m, Ar-H); uv (cyclohexane): λ max nm, log ε 227.6 (4.37), 242.8 (4.54), 249.3 (4.65), 257.3 (4.49), 266.2 (4.25), 285.7 (3.95), 295.3 (4.26), 323.5 sh (3.30), 334.9 (3.63), 344.3 (3.52), 351.4 (3.88).

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.12; H, 7.67; N, 6.24.

(B).

In another run, 5.4 g. of **1** and 16.0 g. of **2** were heated at 170° for 5 hours. After triethyl phosphate **3** and excess of **2** were distilled off, the reddish brown oil was distilled at 100-140° (1 mm). From the distillate, **5** deposited as white crystals. The filtrate was placed on an alumina column and benzene eluate gave additional **5** (8.2% total yield). The residual part on the column was eluted with acetone and the eluate was purified by preparative thin layer chromatography on silica gel to give diethyl *N*-(2',6-dimethylbiphenyl-2-yl)phosphoramidate **7a**, m.p. 51-52°; ir: 3400 (NH), 1265 (P=O), 1225, 970 cm^{-1} (P-O-C); nmr: δ 1.30 (6H, t, OC-CH_3), 1.91 (3H, s, 2'-CH_3), 2.02 (3H, s, 6-CH_3), 3.9-4.3 (4H, overlap q, PO-CH_2-), 4.58 (1H, d, NH), 6.8-7.3 (7H, m, Ar-H); ms: 333 (M^+).

Anal. Calcd. for $C_{16}H_{24}O_3NP$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.82; H, 7.32; N, 4.16.

The distillation residue was also chromatographed on alumina and the elution with benzene afforded **4**, 0.32 g. (6.9%), m.p. 174-176°.

2',6-Dimethyl-2-nitrobiphenyl (**1**).

Copper bronze (20 g.) was added to the mixture of 2-bromo-3-nitrotoluene (21.6 g., 0.10 mole) and *o*-iodotoluene (27.0 g., 0.12 mole) at 175° in a period of an hour, and heated at 230° for an hour. The reaction mixture was extracted by chloroform. The yellow oil was distilled at 123-125° (1.5 mm), which was solidified on cooling giving 12.4 g. (54.5%), m.p. 41-41.5° (ethanol) [lit. m.p. 45° (16)].

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.76; N, 6.16. Found: C, 74.42; H, 5.76; N, 6.34.

2-Azido-2',6-dimethylbiphenyl (**15**).

The nitro biphenyl **1** (9.0 g.) in ethanol (100 ml.) was hydrogenated at ambient temperatures and pressures using platinum dioxide (0.18 g.) as a catalyst. After the mixture was filtered, the filtrate was evaporated to give an essentially quantitative yield of the corresponding amine 7.5 g. (95.2%); ir: 3460, 3370 cm^{-1} (NH). The amine was converted to the azide **15** using procedure A of Smith and Brown (17) with Smolinsky's modification (18) giving 7.55 g. (89.4%) of an orange liquid, n_D^{25} = 1.5955; ir: 2120 cm^{-1} (N_3); nmr: δ 1.97 (3H, s, CH_3), 2.01 (3H, s, CH_3), 7.0-7.35 (7H, m, Ar-H).

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.17; H, 6.13; N, 17.76.

4,5-Dimethylcarbazole **4** from **15**.

The azide **15** (4.9 g.) was dropped into 200 ml. of decaline at 190-210° within an hour and heated at same temperature for 3 hours. The removal of the solvent left oil, which was placed on a column of alumina. After elution with hexane, the exhaustive extraction with benzene gave a white needles 0.6 g. (14%), m.p. 177-177.5° (cyclohexane); ir: 3380 cm^{-1} (NH), nmr: δ 3.01 (6H, s, 4, 5-CH_3), 6.9-7.3 (6H, m, Ar-H); uv (cyclohexane): λ max nm, log ε 218.2 (4.44), 239.9 (4.59), 246.0 (4.66), 253.2 (4.42), 274.0 sh (3.72), 282.4 (4.07), 292.2 (4.34), 315.4 sh (3.49), 326.3 (3.70), 333.0 (3.55), 339.7 (3.82).

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.11; H, 6.71; N, 7.17. Found: C, 86.22; H, 6.86; N, 7.05.

Triethyl *N*-(2',6-Dimethylbiphenyl-2-yl)phosphorimidate (**6**).

Triethyl phosphite **2** (9.0 g.) was dissolved in ether (100 ml.). This solution was added to an ice-cold solution of **15** (10 g.) in ether (100 ml.). The solution was kept at room temperature for an hour and then distilled, giving crude phosphorimidate **6** (9.8 g., 60.6%), b.p. 135-140° (0.005 mm). The redistillation repeated several times gave the nearly pure **6**; ir: 1390, 1370 cm^{-1} (N=P); nmr: δ 1.15 (9H, t, OC-CH_3), 1.95 (3H, s, 2'-CH_3), 2.05 (3H, s, 6-CH_3), 3.75 (6H, q, O-CH_2-), 6.8-7.3 (7H, m, Ar-H).

Anal. Calcd. for $C_{20}H_{28}NO_3P$: C, 66.47; H, 7.81; N, 3.88. Found: C, 66.19; H, 7.60; N, 3.61.

Diethyl *N*-(2',6-Dimethylbiphenyl-2-yl)phosphoramidate (**7a**).

This compound was obtained by the Cadogan reaction mentioned before. The same compound was prepared as follows. The phosphorimidate **6** and alumina were mixed in hexane. After stirring for several hours, the alumina was filtered off and **7a** was obtained as needles, m.p. 51-52°, (86%). This method is similar to those of Cadogan (1) and Sundberg (7,8).

Anal. Calcd. for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.78; H, 7.20; N, 4.16.

Diethyl *N*-Ethyl-*N*-(*o*-tolyl)phosphoramidate (**10b**).

The phosphorimidate **9** was heated at 170° (upper limit) to generate two kinds of phosphoramidates **10a** and **10b**, which were redistillated through a spinning band column. The distillate at 80-92° (0.01 mm) was the phosphoramidate **10b** (99.8% purity by glc), [lit. b.p. 110-115° (0.01 mm) (10)]; ir: 1260 cm^{-1} (P=O); nmr: δ 1.05 (3H, t, NC-CH_3), 1.25 (6H, t, OC-CH_3), 2.31 (3H, s, Ar-CH_3), 3.1-3.5 (2H, overlap q, N-CH_2-), 3.75-4.1 (4H, q, O-CH_2-), 7.0-7.3 (4H, m, Ar-H).

Anal. Calcd. for $C_{13}H_{22}NO_3P$: C, 57.55; H, 8.18; N, 5.16. Found: C, 57.81; H, 8.21; N, 5.02.

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