21. *Experiments on the Preparation of Indolocarbazoles. Part V.* The Synthesis of Indolo*(3′ : 2′-1 : 2)*carbazole and its* 3-*Methyl Derivative.*

By J. A. Hall and S. G. P. Plant.

Indolo(3′ : 2′-1 : 2)carbazole and its 3-methyl derivative have been synthesised through their octahydro-compounds by heatng 2-chloro*cyclo*hexanone with 5-amino- and 5-amino-8-methyl-tetrahydrocarbazole respectively. The preparation of certain derivatives of 5- and 8-anilinotetrahydrocarbazole which might serve for the unambiguous synthesis of substituted indolocarbazoles has been studied.

The well-known reaction by which indoles are obtained from aromatic amines and 2-halogeno-ketones (see, *e.g.*, Möhlau, *Ber.*, 1881, **14**, 173; 1882, **15**, 2480; Bischler, *Ber.*, 1892, **25**, 2860) has been extended to the preparation of tetrahydrocarbazole ("tetrahydrocarbazole" throughout this communication signifies 1 : 2 : 3 : 4-tetrahydrocarbazole) from aniline and 2-chloro*cyclo*hexanone (D.R.-P. 374,098; *Chem. Zentr.*, 1923, IV, 724). Several substituted tetrahydrocarbazoles have been prepared in this way by Campbell and McCall (*J.*, 1950, 2870) in yields which were generally 30—60%. It seemed possible therefore that this reaction might be applied to the aminotetrahydrocarbazoles with the formation of octahydroindolocarbazoles from which the parent substances would be formed on dehydrogenation. The only one of the five isomeric indolocarbazoles so far prepared is the substance obtained by Tomlinson (*J.*, 1951, 809) by dehydrogenation of the product obtained by applying the Fischer indole synthesis to bis*cyclo*hexanone *m*-phenylenedihydrazone, and regarded as indolo(3′ : 2′-1 : 2)carbazole (I; R = H), although two structural interpretations are possible.

The material obtained by heating 5-aminotetrahydrocarbazole with 2-chloro*cyclo*hexanone has yielded a small quantity of 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-octahydroindolo(3′ : 2′-1 : 2)carbazole which gave, on dehydrogenation, indolo(3′ : 2′-1 : 2)carbazole, identical with Tomlinson's substance, the structure of which is thus unambiguously established. Similar treatment of 5-aminotetrahydro-8-methylcarbazole has given a compound which, in view of its ultra-violet absorption spectrum (see Figure), must be 3-methylindolo(3′ : 2′-1 : 2)carbazole (I; R = Me). The yields of these indolocarbazoles were very small, and attempts to obtain isomers of the former from 6-, 7-, and 8-aminotetrahydrocarbazole failed. When 2-arylamino-ketones are heated with aromatic amines, indoles derived from the amine are formed with elimination of the arylamino-group (Bischler, *loc. cit.*), and Campbell and McCall (*loc. cit.*) have observed that 2-*p*-bromoanilino*cyclo*hexanone gives tetrahydrocarbazole (in unstated yield) when heated with aniline hydrochloride. It seemed possible that by heating the last-named ketone with 5-aminotetrahydrocarbazole

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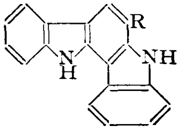
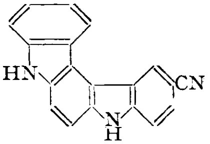
* Part IV, *J.*, 1951, 809.

hydrochloride better yields of the indolocarbazole would be obtained, but nothing crystalline was isolated from the product.



(I)



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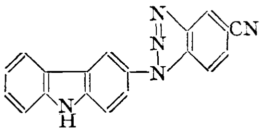

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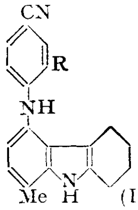
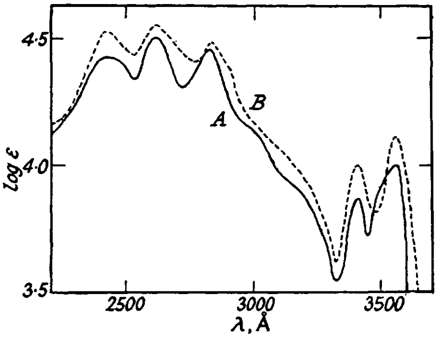


(IV)

Clifton and Plant (*J.*, 1951, 461) obtained a substance regarded as 6-cyanoindolo(2′ : 3′-3 : 4)carbazole (II) by applying the Graebe–Ullmann reaction to the triazole (III), prepared from 3-aminocarbazole. This suggests that indolocarbazole derivatives of unambiguous structure might be obtained fairly readily from 5- and 8-aminotetrahydrocarbazole and some of their substitution products through suitable triazoles. These amines are more easily accessible than the corresponding aminocarbazoles. So the condensation of 5- and 8-amino-, 5-amino-8-chloro-, and 5-amino-8-methyl-tetrahydrocarbazole with 1-chloro-2 : 4-dinitrobenzene, 4-chloro-3-nitrobenzonitrile, and/or 4-bromo-3-nitroacetophenone was studied under a variety of conditions. The yields of the substituted anilinotetrahydrocarbazoles were generally disappointing and the products difficult to purify, owing mainly to the relative instability of the initial amines under the reaction conditions. Of the derivatives examined, 5-(4-cyano-2-nitroanilino)tetrahydro-8-methylcarbazole (IV; R = NO_2) was obtained most readily in reasonable amount; it was reduced to the amine (IV; R = NH_2), but attempts to make the corresponding triazole failed. Clifton and Plant (*loc. cit.*) found it necessary to use a carefully controlled amount of nitrous acid in preparing the triazole (III) in order to avoid other reactions, and the possibilities of such complications are even greater with the compound (IV; R = NH_2) owing to the presence of a reactive double bond.



A, ———————, *Indolo*(3′ : 2′-1 : 2)*carbazole.*
B, – – – – – –, 3-*Methylindolo*(3′ : 2′-1 : 2)*carbazole.*
(*Both in methanol solution.*)

EXPERIMENTAL

8-*Chlorotetrahydro*-5-*nitrocarbazole*.—The following method for the preparation of this substance gave a better yield than that of Perkin and Plant (*J.*, 1921, **119**, 1825). After a mixture of 2-chloro-5-nitrophenylhydrazine (15 g.), *cyclo*hexanone (8 c.c.), and a little ethanol had been boiled for a few minutes, acetic acid (80 c.c.) and concentrated hydrochloric acid (20 c.c.) were added, and the whole was refluxed for 2 hours. The product which separated on cooling was obtained from acetic acid in orange-yellow needles (12 g.), m. p. 214°.

5-*Aminotetrahydrocarbazole*.—Reduction of 8-chlorotetrahydro-5-nitrocarbazole to a mixture of 5-aminotetrahydro- and 5-aminohexahydro-carbazole has been described by Plant (*J.*, 1936, 899). The following modified procedure has worked well for the preparation of the tetrahydro-base. After a mixture of 8-chlorotetrahydro-5-nitrocarbazole (30 g.), granulated tin (125 g.), ethanol (250 c.c.), and concentrated hydrochloric acid (250 c.c.) had been refluxed for 1½ hours, the solution was filtered, the ethanol distilled off, and the residue made strongly alkaline with aqueous sodium hydroxide. The precipitated solid was dried and extracted with hot benzene.

When the extract was concentrated, 5-aminotetrahydrocarbazole (13·2 g.) separated, on cooling, in colourless prisms, m. p. 162—164°.

Indolo(3′ : 2′-1 : 2)*carbazole*.—After a mixture of 5-aminotetrahydrocarbazole (2·25 g.) and 2-chloro*cyclo*hexanone (0·75 g.) had been heated at 160° for ¼ hour, the cold material was powdered and extracted with dilute hydrochloric acid. The residue was dried and extracted with boiling benzene, the solvent being then removed from the filtered extract by distillation under reduced pressure. 5 : 6 : 7 : 8: 4′ : 5′ : 6′ : 7′-Octahydroindolo(3′ : 2′-1 : 2)carbazole was obtained in nearly colourless prisms (0·05 g.), m. p. 225—227° (from acetic acid) (Tomlinson, *loc. cit.*, gives m. p. 228°). This substance was heated with half its bulk of palladium–charcoal, first at 240° for 20 minutes and then at 320° for ½ hour, under nitrogen. Indolo(3′ : 2′-1 : 2)carbazole sublimed as colourless plates, m. p. 299—300°, not depressed by admixture with a specimen obtained from bis*cyclo*hexanone *m*-phenylenedihydrazone and kindly supplied by Dr. M. L. Tomlinson. A further quantity was obtained by extraction from the residue with acetic acid, precipitation with water, and sublimation in nitrogen.

5-*Aminotetrahydro*-8-*methylcarbazole*.—Prepared from diazotised 4-nitro-*o*-toluidine by stannous chloride in hydrochloric acid, 4-*nitro*-o-*tolylhydrazine* (yield, 50%) crystallised from methanol in yellow needles, m. p. 154° (Found : C, 50·2; H, 5·4. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4%). It was converted into *tetrahydro*-8-*methyl*-5-*nitrocarbazole* (yield, 60%), orange prisms, m. p. 215° (from acetic acid), as described above for the analogous 8-chloro-compound except that the cyclisation was effected at 100° (Found : C, 67·9; H, 6·2; N, 11·9. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). Sodium hydrosulphite (dithionite) was gradually added to a solution of the nitro-compound (10 g.) in the minimum amount of boiling aqueous ethanol (75% v/v) until the colour became very pale yellow. The ethanol was distilled off, water added, and the solid 5-*aminotetrahydro*-8-*methylcarbazole* (6·5 g.) crystallised from benzene, from which it separated in colourless plates, m. p. 202—204° (rapid heating) (Found : C, 77·6; H, 7·8. $C_{13}H_{16}N_2$ requires C, 78·0; H, 8·0%).

3-*Methylindolo*(3′ : 2′-1 : 2)*carbazole*.—5-Aminotetrahydro-8-methylcarbazole (2·1 g.) was heated with 2-chloro*cyclo*hexanone (0·75 g.) for 5 minutes at 160°, cooled, and ground with dilute hydrochloric acid. The insoluble material was dried, and extracted with hot benzene, the solvent being distilled from the extract under reduced pressure. The residue was heated with its own volume of palladium–charcoal in nitrogen at 240° for 20 minutes. The temperature was then gradually raised to 320° and kept there for 2½ hours. When the solid which sublimed was resublimed in nitrogen at 270°, 3-*methylindolo*(3′ : 2′-1 : 2)*carbazole* was obtained in colourless needles (0·01 g.), m. p. 261—262° (Found : C, 85·3; H, 5·2. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2%).

5-*Amino*-8-*chlorotetrahydrocarbazole*.—8-Chlorotetrahydro-5-nitrocarbazole was reduced as described above for the analogous 8-methyl compound, and the *amine* (yield, 65%) isolated from light petroleum (b. p. 60—80°) in colourless prisms, decomp. above 160° without melting (Found : C, 65·0; H, 5·7. $C_{12}H_{13}N_2Cl$ requires C, 65·3; H, 5·9%). 5-*Acetamido*-8-*chlorotetrahydrocarbazole*, colourless needles, m. p. 236° (from benzene), separated after the amine had been boiled with a slight excess of acetic anhydride in benzene (Found : N, 10·6. $C_{14}H_{15}ON_2Cl$ requires N, 10·7%).

Derivatives of 5-*Anilinotetrahydrocarbazole*.—(*a*) After a mixture of 5-aminotetrahydrocarbazole (0·2 g.), 1-chloro-2 : 4-dinitrobenzene (0·3 g.), and anhydrous sodium acetate (0·2 g.) had been heated on a steam-bath for an hour, cooled, and extracted with hot acetic acid, the addition of water to the filtered extract precipitated 5-(2 : 4-*dinitroanilino*)*tetrahydrocarbazole*, red prisms (0·06 g.), m. p. 224° (from ethanol) (Found : C, 61·0; H, 4·9. $C_{18}H_{16}O_4N_4$ requires C, 61·4; H, 4·5%). (*b*) The amine (0·65 g.), 4-chloro-3-nitrobenzonitrile (0·65 g.), and anhydrous sodium acetate (0·5 g.) were heated at 160° for ½ hour, and the product extracted with hot benzene. After the extract had been concentrated, the solute was adsorbed on alumina and then thrice recrystallised from ethanol; 5-(4-*cyano*-2-*nitroanilino*)*tetrahydrocarbazole* was obtained in red prisms (0·1 g.), m. p. 214—216° (Found : C, 68·1; H, 4·8. $C_{19}H_{16}O_2N_4$ requires C, 68·7; H, 4·8%). (*c*) Prepared from 4-bromo-3-nitroacetophenone as described for the analogous cyano-compound, 5-(4-*acetyl*-2-*nitroanilino*)*tetrahydrocarbazole* (yield, 30%) crystallised from ethanol in red prisms, m. p. 181° (Found : C, 68·8; H, 5·6. $C_{20}H_{19}O_3N_3$ requires C, 68·8; H, 5·4%).

Derivatives of 5-*Anilino*-8-*chlorotetrahydrocarbazole*.—(*a*) After 5-amino-8-chlorotetrahydrocarbazole (0·45 g.) had been heated with 1-chloro-2 : 4-dinitrobenzene (0·45 g.) and anhydrous sodium acetate (0·2 g.) at 130—135° for ¾ hour, and the product extracted with boiling ethanol (5 × 50 c.c.), the material obtained by pouring the extracts into water was dried and purified by adsorption from benzene on alumina. 8-*Chloro*-5-(2 : 4-*dinitroanilino*)*tetrahydrocarbazole* was obtained in red needles (0·01 g.), m. p. 282° (from benzene) (Found : C, 56·2; H, 3·8. $C_{18}H_{15}O_4N_4Cl$ requires C, 55·9; H, 3·9%). (*b*) An intimate mixture of 5-amino-8-chlorotetrahydrocarbazole hydrochloride (1 g.; prepared by passing hydrogen chloride through the base in ether), 4-chloro-3-nitrobenzonitrile (0·75 g.), and sodium acetate (2 g.) was refluxed in amyl alcohol for 2½ hours, the solvent removed under reduced pressure, and the product extracted from the residue with boiling benzene. After purification by adsorption on alumina, 8-*chloro*-5-(4-*cyano*-2-*nitroanilino*)*tetrahydrocarbazole* crystallised from acetic acid in red needles (0·1 g.), m. p. 292° (Found : C, 62·6; H, 4·1. $C_{19}H_{15}O_2N_4Cl$ requires C, 62·2; H, 4·1%).

Derivatives of 5-*Anilinotetrahydro*-8-*methylcarbazole*.—(*a*) 5-Aminotetrahydro-8-methylcarbazole (0·5 g.), 1-chloro-2 : 4-dinitrobenzene (0·5 g.), and anhydrous sodium acetate (0·3 g.) were heated on a steam-bath for 2 hours, cooled, and ground with a little ethanol. 5-(2 : 4-*Dinitroanilino*)*tetrahydro*-8-*methylcarbazole*, red needles (0·45 g.; from ethanol), m. p. 258°, remained (Found : C, 62·2; H, 5·2. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·9%).

(*b*) Prepared similarly from 4-chloro-3-nitrobenzonitrile, 5-(4-*cyano*-2-*nitroanilino*)*tetrahydro*-8-*methylcarbazole* crystallised from ethanol in red needles (yield, 60%), m. p. 267° (Found : C, 69·2; H, 5·2. $C_{20}H_{18}O_2N_4$ requires C, 69·4; H, 5·2%). After its solution in dioxan–water (3 : 2 by volume) had been treated on the steam-bath with sodium dithionite until almost colourless, water precipitated 5-(2-*amino*-4-*cyanoanilino*)*tetrahydro*-8-*methylcarbazole* (33%), pale brown needles (from aqueous methanol), m. p. 187—189° (Found : C, 75·8; H, 6·3. $C_{20}H_{20}N_4$ requires C, 75·9; H, 6·3%).

8-(2 : 4-*Dinitroanilino*)*tetrahydrocarbazole*.—Prepared like the isomeric 5-(2 : 4-dinitroanilino)-compound described above, this *compound* was extracted from the reaction mixture with boiling benzene, purified on alumina, and twice recrystallised from ethanol; it formed red prisms (yield, 20%), m. p. 191—193° (Found : C, 61·4; H, 4·6%).

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