CLXXXIV.—*Substitution in Hexahydrocarbazole Derivatives.*

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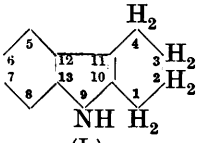
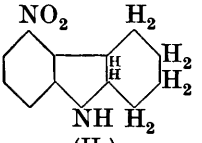
THE action of nitric acid on tetrahydrocarbazole (I) and its 9-acyl derivatives was found to give rise, among other products, to nitro-compounds which appeared at first sight to be formed by a reversal of the ordinary rules of substitution (Perkin and Plant, J., 1921, **119**, 1825; 1923, **123**, 676). The double linking in tetrahydrocarbazole has been shown to be a very active one, and the formation of these compounds can be explained, as was pointed out by Professor Robinson, by taking the view that the orienting influence is transmitted through this linking. In hexahydrocarbazole, this double bond is absent, and the introduction of substituents into this molecule ought to give results which are different from those observed with tetrahydrocarbazole. We have now investigated this problem and established the constitutions of the products with respect to those of the corresponding tetrahydrocarbazole derivatives.

The structures assigned to the nitro-compounds obtained from hexahydrocarbazole and its 9-acyl derivatives depend upon the configurations of the four isomeric mononitrotetrahydrocarbazoles. Three of these are obtained synthetically from *cyclo*hexanone-*o*-, -*m*-, and -*p*-nitrophenylhydrazone, respectively, by Fischer's indole synthesis (Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 53), whilst the fourth is prepared from 9-acetyltetrahydrocarbazole (Perkin and Plant, *loc. cit.*). There is no doubt at all about the configurations of 6-nitro- and 8-nitro-tetrahydrocarbazole. The sole product obtained when ring closure takes place by loss of ammonia from *cyclo*hexanone-*m*-nitrophenylhydrazone has been assumed by Borsche, Witte, and Bothe to be 7-nitrotetrahydrocarbazole, but it may possibly be the 5-nitro-compound, whilst the fourth isomeride, assumed in consequence by Perkin and Plant to be 5-nitrotetrahydrocarbazole, may be the 7-nitro-derivative. Ring closure in the case of the corresponding *cyclo*hexanone-*m*-carboxyphenylhydrazone does, in fact, give both of the two alternative

products (Collar and Plant, J., 1926, 808). Both the 5- and the 7-position are, however, meta with respect to the >NH group.



(I.)



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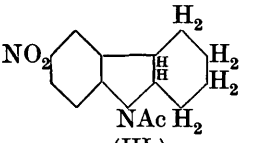

(III.)

The nitration of hexahydrocarbazole in concentrated sulphuric acid solution gives a single product, which has been identified as 5-*nitrohexahydrocarbazole* (II). Its structure has been established by reducing it to the corresponding 5-*aminohexahydrocarbazole*, which has also been prepared by the reduction of 5-aminotetrahydrocarbazole. The nitration of 9-methylhexahydrocarbazole under the same conditions gives a product which must be 5-*nitro*-9-*methylhexahydrocarbazole*, since it is identical with the substance obtained by methylating 5-nitrohexahydrocarbazole. Von Braun and Ritter (*Ber.*, 1922, **55**, 3802) nitrated 9-ethylhexahydrocarbazole in concentrated sulphuric acid and obtained a compound, m. p. 142°, which they assumed, without proof, to be 7-nitro-9-ethylhexahydrocarbazole. If the structures assigned to the nitrotetrahydrocarbazoles are correct, this substance is 5-nitro-9-ethylhexahydrocarbazole, since it can also be obtained by ethylation of 5-nitrohexahydrocarbazole. In any case, the statement of von Braun and Ritter that the nitro-group takes up a position which is meta with respect to the >NH group is correct.

The action of nitric acid on 9-acetylhexahydrocarbazole in glacial acetic acid gave unexpected products. From the reaction mixture, 6-*nitro*-9-*acetylhexahydrocarbazole* (III) was isolated. The structure of this compound was established by hydrolysing it to 6-*nitrohexahydrocarbazole* and reducing the latter to the corresponding *amine*, which gave a *diacetyl* derivative on treatment with acetic anhydride. The same diacetyl derivative was obtained when 6-aminotetrahydrocarbazole was reduced electrolytically, and the product treated in the same way with acetic anhydride. In addition to 6-nitro-9-acetylhexahydrocarbazole, 5-nitro-9-acetyltetrahydrocarbazole and 9-acetyl-10 : 11-dihydroxyhexahydrocarbazole were isolated in considerable quantities from the product. The latter two substances are the compounds formed when nitric acid acts under the same conditions on 9-acetyltetrahydrocarbazole (Perkin and Plant, *loc. cit.*). It thus appears that only a portion of the 9-acetylhexahydrocarbazole undergoes nitration under these conditions, the remainder being oxidised to 9-acetyltetrahydrocarbazole, which is then acted on by more nitric acid in the way previously

established. In concentrated sulphuric acid, nitration of 9-acetylhexahydrocarbazole to the 6-nitro-derivative proceeds without any appreciable side reactions.

When nitric acid was allowed to react with 9-benzoylhexahydrocarbazole in glacial acetic acid, some oxidation to 9-benzoyltetrahydrocarbazole again first took place. The isolation of all the products of this reaction in a pure state was not achieved on account of their great solubility in acetic acid, but on using a small quantity of solvent and seeding the solution with a crystal of 11-nitro-9-benzoyl-10-hydroxyhexahydrocarbazole, there separated a considerable quantity of that substance, which is one of the two products obtained when nitric acid acts on 9-benzoyltetrahydrocarbazole (Perkin and Plant, *loc. cit.*; 9-benzoyltetrahydrocarbazole and 9-acetyltetrahydrocarbazole react in different ways with nitric acid). Direct nitration of 9-benzoylhexahydrocarbazole was accomplished in concentrated sulphuric acid, the product being 6-*nitro*-9-*benzoylhexahydrocarbazole*, its structure being established by the fact that it gave 6-nitrohexahydrocarbazole, identical with the substance obtained from 9-acetylhexahydrocarbazole, on hydrolysis.

Bromination of hexahydrocarbazole in glacial acetic acid gave 6-*bromohexahydrocarbazole*, the structure of which is established by the fact that it is identical with 6-bromohexahydrocarbazole prepared by the reduction of 6-bromotetrahydrocarbazole. The bromination of 9-acetyl- and 9-benzoyl-hexahydrocarbazole proceeded in the same way to give 6-*bromo*-9-*acetylhexahydrocarbazole* and 6-*bromo*-9-*benzoylhexahydrocarbazole* respectively, both of which gave 6-bromohexahydrocarbazole on hydrolysis.

It is clear from these results that substitution in hexahydrocarbazole takes quite a different course from that observed with tetrahydrocarbazole, and that the compound may be considered for this purpose as a simple benzene derivative.

EXPERIMENTAL.

The Nitration of Hexahydrocarbazole and 9-Methylhexahydrocarbazole.

The hexahydrocarbazole used in these experiments was prepared by the electrolytic reduction of tetrahydrocarbazole (see Perkin and Plant, J., 1924, **125**, 1512).

5-*Nitrohexahydrocarbazole*.—A solution of hexahydrocarbazole (30 g.) in concentrated sulphuric acid (300 c.c.) was treated gradually with powdered potassium nitrate (17·5 g.), the temperature being kept at 3°, allowed to remain for 15 minutes, and then poured on ice. The solution was kept at 0° by the addition of ice, and made alkaline with ammonia; the oily product then soon solidified (m. p. 68°).

After crystallisation from alcohol, 5-*nitrohexahydrocarbazole* was obtained in lemon-yellow needles, m. p. 69° (Found : N, 12·8. $C_{12}H_{14}O_2N_2$ requires N, 12·8%). 5-*Nitro*-9-*acetylhexahydrocarbazole* was obtained when a mixture of 5-nitrohexahydrocarbazole (5 g.) and acetic anhydride (10 g.) was kept at 110° for 3 hours, cooled, and shaken with an excess of water. It separated from alcohol in pale yellow, square plates, m. p. 142° (Found : N, 10·5. $C_{14}H_{16}O_3N_2$ requires N, 10·8%).

5-*Aminohexahydrocarbazole*.—A solution of 5-nitrohexahydrocarbazole (10 g.) in sulphuric acid (150 c.c. of 60%) was reduced for 10 hours in the cathode compartment of an electrolytic cell, lead electrodes and a current of 4·1 amps. (0·02 amp. per sq. cm. of cathode) being used, and the cell being kept in cold water. After dilution with an equal volume of water and filtering, the mixture was made alkaline with ammonia, crushed ice also being added. The solid product was crystallised from alcohol, from which 5-*aminohexahydrocarbazole* separated in colourless prisms, m. p. 111° (Found : N, 14·9. $C_{12}H_{16}N_2$ requires N, 14·9%). Yield, 55% of the theoretical.

5-Aminohexahydrocarbazole was also obtained by reducing a solution of 5-aminotetrahydrocarbazole hydrochloride (3 g., prepared as described by Edwards and Plant, J., 1923, **123**, 2395) in sulphuric acid (100 c.c. of 60%) in the electrolytic cell as before, but keeping it immersed in boiling water for 16 hours. The solution was then filtered and made alkaline at 0° with ammonia, and the product was extracted with ether. After the extract had been dried over potassium carbonate and the solvent removed, the residue solidified on rubbing, and, after recrystallisation from alcohol, 5-aminohexahydrocarbazole (0·4 g.) was obtained in colourless prisms; these, alone or mixed with the 5-aminohexahydrocarbazole described above, melted at 111°.

Both products gave the same diacetyl derivative on being heated with an excess of acetic anhydride at 100° for 15 minutes. After the solution had been cooled, and shaken with an excess of water, the solid obtained was crystallised from acetone, 5-*acetamido*-9-*acetylhexahydrocarbazole* separating in colourless prisms, m. p. 163° (Found : N, 10·1. $C_{16}H_{20}O_2N_2$ requires N, 10·3%).

5 - *Nitro* - 9 - *methylhexahydrocarbazole*.— 9- Methylhexahydrocarbazole was prepared by the reduction of 9-methyltetrahydrocarbazole (Perkin and Plant, *loc. cit.*). This substance shows a marked tendency to remain in a supercooled condition (a specimen is still completely liquid after 3 years) and has hitherto been described as a colourless oil (see also von Braun and Ritter, *loc. cit.*), but it can be crystallised from alcohol, from which it separates in colourless prisms,

m. p. 50° (Found : N, 7·4. Calc. : N, 7·5%). A solution of 9-methylhexahydrocarbazole (1 g.) in concentrated sulphuric acid (30 c.c.) was treated below 3° with potassium nitrate (0·55 g.), allowed to remain for 5 minutes, poured on ice, made alkaline with ammonia, and saturated with sodium chloride. The solid produced (m. p. 49—50°) was crystallised from alcohol, from which *5-nitro-9-methylhexahydrocarbazole* (0·6 g.) separated in bright yellow needles, m. p. 52° (Found : N, 12·2. $C_{13}H_{16}O_2N_2$ requires N, 12·1%).

5-Nitro-9-methylhexahydrocarbazole was also prepared by heating 5-nitrohexahydrocarbazole (1 g.) with methyl iodide (3·5 g.) in a sealed tube at 100° for 2 hours, removing the excess of methyl iodide, treating the residue with dilute aqueous sodium hydroxide and extracting the solution with ether. After the ether had been removed, the residue was recrystallised from alcohol, from which the product separated in yellow needles; these, alone or mixed with the 5-nitro-9-methylhexahydrocarbazole described above, melted at 50°.

5-*Nitro*-9-*ethylhexahydrocarbazole*.—5-Nitrohexahydrocarbazole was ethylated by a process similar to that described for the methylation, but the reaction was much slower and heating was continued for 18 hours. The product was recrystallised from alcohol, from which 5-nitro-9-ethylhexahydrocarbazole separated in bright yellow prisms, m. p. 143° (Found : N, 11·5. Calc. : N, 11·4%). This product is evidently identical with that described by von Braun and Ritter (*loc. cit.*).

Action of Nitric Acid on 9-Acetylhexahydrocarbazole.

A solution of 9-acetylhexahydrocarbazole (50 g., prepared by the direct acetylation of hexahydrocarbazole; Graebe and Adlerskron, *Annalen*, 1880, **202**, 25) in glacial acetic acid (50 c.c.) was treated gradually at 23—25° with a mixture of nitric acid (26·5 g. of *d* 1·4) and glacial acetic acid (75 c.c.). After 2 hours, the mixture was poured into water; the product then gradually solidified to a yellow mass, from which three substances were isolated in a pure condition. After repeated crystallisation from acetone, a small quantity (0·2 g.) of glistening, colourless plates, m. p. 204°, was obtained. An analysis (Found : N, 6·0. Calc. : N, 5·7%) and a mixed m.-p. determination showed that this substance was 9-acetyl-10 : 11-dihydroxyhexahydrocarbazole, one of the products obtained when nitric acid acts on 9-acetyltetrahydrocarbazole in glacial acetic acid. The mixture in the acetone mother-liquor, on repeated crystallisation from glacial acetic acid, yielded yellow needles (5 g.), m. p. 175°, which an analysis (Found : N, 10·8. Calc. : N, 10·9%) and

a mixed m.-p. determination proved to be 5-nitro-9-acetyltetrahydrocarbazole, the other of the two products from 9-acetyltetrahydrocarbazole. Further proof of the structure of this compound was obtained on boiling it for a short time with aqueous-alcoholic sodium hydroxide, diluting the solution with water, and recrystallising the product from alcohol, from which 5-nitrotetrahydrocarbazole separated in yellow prisms, m. p. 172°. From the acetone and glacial acetic acid mother-liquors there was isolated by repeated fractional crystallisation a product which ultimately separated from acetone in lemon-yellow prisms (5 g.), m. p. 150°, and was shown to be 6-*nitro*-9-*acetylhexahydrocarbazole* (Found : N, 10·7. $C_{14}H_{16}O_3N_2$ requires N, 10·8%). The solution of this product (1 g.) in a mixture of alcohol (15 c.c.) and aqueous sodium hydroxide (15 c.c. of 30%) was boiled for 20 minutes and then poured into water. After crystallisation from alcohol, 6-*nitrohexahydrocarbazole* was obtained in bright yellow prisms, m. p. 84° (Found : N, 12·6. $C_{12}H_{14}O_2N_2$ requires N, 12·8%).

6-Nitro-9-acetylhexahydrocarbazole is more easily obtained by nitration in concentrated sulphuric acid solution. 9-Acetylhexahydrocarbazole (5 g.), dissolved in sulphuric acid (40 c.c.), was treated with potassium nitrate (2·3 g.) at 5—7°, the solution poured, after a short time, on ice, and the product crystallised from acetone, from which 6-nitro-9-acetylhexahydrocarbazole separated in yellow prisms, m. p. 150°. The m. p. of the mixture with the 6-nitro-9-acetylhexahydrocarbazole described above showed no depression. The hydrolysis of this product was also carried out by heating it for an hour on the steam-bath with concentrated hydrochloric acid, and, on cooling, the *hydrochloride* of 6-nitrohexahydrocarbazole separated. After recrystallisation from alcohol, it was obtained in pale yellow plates, m. p. 199° (Found : N, 11·2. $C_{12}H_{15}O_2N_2Cl$ requires N, 11·0%). This hydrochloride readily yielded 6-nitrohexahydrocarbazole, m. p. 84°, on treatment with dilute aqueous sodium hydroxide.

6-*Aminohexahydrocarbazole*.—A solution of 6-nitrohexahydrocarbazole (5 g.) in sulphuric acid (140 c.c. of 60%) was reduced electrolytically for 15 hours by the method described above, the cell being kept immersed in cold water. After the solution had been diluted with an equal volume of water, filtered, and made alkaline at 0° with concentrated ammonia, the mixture was extracted with ether, and the ethereal solution dried over potassium carbonate. The viscous, oily 6-*aminohexahydrocarbazole* remaining after removal of the ether could not readily be made to crystallise, so it was treated with an excess of acetic anhydride at room temperature. The

product separated on rubbing, and, after the whole had been shaken with an excess of water and then crystallised from alcohol, 6-*acetamido*-9-*acetylhexahydrocarbazole* was obtained in colourless needles (1·2 g.), m. p. 213° (Found: N, 10·3. $C_{16}H_{20}O_2N_2$ requires N, 10·3%).

6-Aminohexahydrocarbazole was also obtained by the electrolytic reduction of a solution of 6-aminotetrahydrocarbazole (4 g., prepared as described by Edwards and Plant, *loc. cit.*) in sulphuric acid (120 c.c. of 60%), a current of 5 amps. being used for 22 hours at room temperature. After the solution had been diluted with water (60 c.c.), filtered, and made alkaline with concentrated ammonia at 0°, a colourless solid separated. This (0·5 g.), after crystallisation from toluene, proved to be unchanged 6-aminotetrahydrocarbazole. The aqueous solution was extracted with ether, and from the ethereal solution the oily 6-aminohexahydrocarbazole was obtained as before. On treatment with acetic anhydride as described above, 6-acetamido-9-acetylhexahydrocarbazole (0·5 g.), m. p. 212°, was formed. A mixture of the two products, prepared by different methods, also melted at 212°.

7-*Acetamido*-9-*acetylhexahydrocarbazole*.—This derivative was prepared during the course of the present work, although it has not been required in order to establish the structure of any compound obtained directly from hexahydrocarbazole. A solution of 7-aminotetrahydrocarbazole hydrochloride (4 g., prepared as described by Edwards and Plant, *loc. cit.*) in sulphuric acid (140 c.c. of 60%) was reduced electrolytically by a current of 5 amps. for 36 hours at 100°; it was then diluted with water, made alkaline with ammonia, and shaken with ether. After being dried with potassium carbonate, the ether was removed and 7-*aminohexahydrocarbazole* remained as a brown oil; this was warmed with an excess of acetic anhydride at 100° for a minute and shaken with an excess of water, and the product was crystallised from alcohol, 7-*acetamido*-9-*acetylhexahydrocarbazole* being obtained in colourless prisms, m. p. 233° (Found: N, 10·4. $C_{16}H_{20}O_2N_2$ requires N, 10·3%).

Action of Nitric Acid on 9-*Benzoylhexahydrocarbazole.*

9-Benzoylhexahydrocarbazole was prepared by shaking a suspension of hexahydrocarbazole in an excess of a 10% aqueous solution of potassium hydroxide with benzoyl chloride (1¼ mols.). The product separated from alcohol in colourless needles, m. p. 106° (compare von Braun, *Ber.*, 1910, **43**, 2880, who describes it as an oil, b. p. 270°/10 mm.) (Found: N, 4·9. Calc.: N, 5·1%). A solution of 9-benzoylhexahydrocarbazole (5 g.) in glacial acetic

acid (15 c.c.) was treated at 60—67° with a mixture of nitric acid (1·9 g. of *d* 1·4) and glacial acetic acid (1 c.c.). The product was cooled, a crystal of 11-nitro-9-benzoyl-10-hydroxyhexahydrocarbazole (prepared from 9-benzoyltetrahydrocarbazole) added, and the whole stirred for 3 hours. The colourless prisms (0·1 g.), m. p. 146°, that separated were shown by a mixed m.-p. determination to be 11-nitro-9-benzoyl-10-hydroxyhexahydrocarbazole. When the acetic acid mother-liquor was poured into water, a thick, pale yellow oil separated, but attempts to obtain crystalline substances from this were unsuccessful.

6-*Nitro*-9-*benzoylhexahydrocarbazole*.—A solution of 9-benzoylhexahydrocarbazole (25 g.) in concentrated sulphuric acid (200 c.c., was treated gradually at 10—12° with potassium nitrate (9·1 g.), kept for 30 minutes, and then poured on ice. The yellow solid which separated was recrystallised from alcohol, from which 6-*nitro*-9-*benzoylhexahydrocarbazole* separated slowly in clusters of yellow prisms, m. p. 106—107° (Found : N, 8·7. $C_{19}H_{18}O_3N_2$ requires N, 8·7%). When a solution of this nitro-compound (6 g.) in a mixture of alcohol (100 c.c.) and aqueous sodium hydroxide (75 c.c. of 30%) was boiled for 20 minutes and then poured into cold water, 6-nitrohexahydrocarbazole, which separated from alcohol in yellow prisms, m. p. 84°, was precipitated. The m. p. of a mixture of this product and 6-nitrohexahydrocarbazole obtained from the corresponding acetyl derivative showed no depression.

Bromination of Hexahydrocarbazole Derivatives.

6-*Bromohexahydrocarbazole*.—A solution of hexahydrocarbazole (5 g.) in glacial acetic acid (50 c.c.) was treated gradually at room temperature with bromine (1·8 c.c.). An oily product separated, and, after the addition of all the bromine, the mixture was heated for a minute on the steam-bath; a clear solution was then obtained. On cooling, colourless crystals of the *hydrobromide* (6·3 g.), m. p. 203° (decomp.), separated, and this product, when treated with dilute aqueous sodium hydroxide, yielded 6-*bromohexahydrocarbazole*, which separated from alcohol in colourless, pentagonal plates, m. p. 75° (Found : N, 5·8. $C_{12}H_{14}NBr$ requires N, 5·6%).

The preparation of 6-bromohexahydrocarbazole by the electrolytic reduction of 6-bromotetrahydrocarbazole (prepared as described by Borsche, Witte, and Bothe, *loc. cit.*) had previously been carried out by Miss E. I. Postgate. A suspension of 6-bromotetrahydrocarbazole (4 g.) in sulphuric acid (100 c.c. of 60%) was reduced by a current of 5 amps. (0·02 amp. per sq. cm. of cathode) during 7 hours,

the cell being immersed in boiling water. After being diluted to 200 c.c. and filtered from any unchanged 6-bromotetrahydrocarbazole, the solution was made alkaline at 0° with concentrated ammonia; the 6-bromohexahydrocarbazole which separated was crystallised from alcohol and obtained in colourless, pentagonal plates, m. p. 75°. The mixture of these two specimens of 6-bromohexahydrocarbazole also melted at 75°.

6-*Bromo*-9-*acetylhexahydrocarbazole*.—A solution of 9-acetylhexahydrocarbazole (15 g.) in glacial acetic acid (24 c.c.) was treated gradually with bromine (3·6 c.c.), the mixture being kept cool in ice-water. When the reaction had finished, the yellow oil which had separated was dissolved by warming the mixture to 60°, and, on cooling and rubbing, a bright yellow, crystalline product, m. p. 132—134° (decomp.), was obtained. This appeared to be a *hydrobromide* of 6-bromo-9-acetylhexahydrocarbazole, since, on warming it with water or, more readily, by treating it with dilute aqueous potassium hydroxide and then recrystallising the product from alcohol, 6-*bromo*-9-*acetylhexahydrocarbazole* was obtained in long, colourless prisms, m. p. 104° (Found : N, 4·8. $C_{14}H_{16}ONBr$ requires N, 4·8%). After a solution of 6-bromo-9-acetylhexahydrocarbazole in aqueous-alcoholic sodium hydroxide had been boiled for 8 hours, it was poured into water, and the product recrystallised from alcohol; 6-bromohexahydrocarbazole, identical in every way with the specimens described above, separated.

6-*Bromo*-9-*benzoylhexahydrocarbazole*.—A solution of 9-benzoylhexahydrocarbazole (5 g.) in glacial acetic acid (20 c.c.) was treated gradually at room temperature with bromine (1 c.c.), then warmed to 60°, diluted with water, and made alkaline with ammonia. The oily product solidified on standing, and, after crystallisation from alcohol, 6-*bromo*-9-*benzoylhexahydrocarbazole* was obtained in colourless needles (4·2 g.), m. p. 125° (Found : N, 3·8. $C_{19}H_{18}ONBr$ requires N, 3·9%). This product was hydrolysed by boiling it with aqueous-alcoholic potassium hydroxide for 10 hours; the mixture was poured into water, and on recrystallising the precipitate from alcohol, 6-bromohexahydrocarbazole, identical with the specimens described above, was obtained.

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