67. *The Action of Halogens on Polycyclic Indole Derivatives. Part IV. Some Reactions of* 1-*Keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole.*

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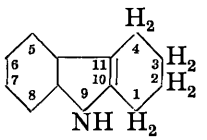
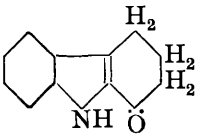
The double linkage in tetrahydrocarbazole (I) and many of its derivatives is characterised by the extreme readiness with which it combines additively with various reagents. For example, when such substances are treated with an equimolecular quantity of bromine no

(I.) 

 (II.)

substitution occurs, but the products isolated are derived exclusively from the primary addition of the halogen at the 10 : 11-position (Plant and Tomlinson, J., 1931, 3324; 1933,

298). In 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (II; named in this paper "1-ketotetrahydrocarbazole") the position of the carbonyl group in relation to the double linkage is such that it would be expected to modify considerably the reactions referred to above. This substance has been prepared by Coffey (*Rec. trav. chim.*, 1923, **42**, 528) by an application of Fischer's indole synthesis to *cyclo*hexane-1 : 2-dione monophenylhydrazone, which was obtained from 2-hydroxymethylene*cyclo*hexanone and benzenediazonium chloride in neutral solution. These reactions have now been extended, by the use of other diazonium salts, to the synthesis of several derivatives required in the present investigations.

When 1-ketotetrahydrocarbazole was treated with an equimolecular quantity of bromine in acetic acid, *6-bromo-1-ketotetrahydrocarbazole* separated in good yield as a hydrobromide which was readily hydrolysed; its identity was established by synthesis from *p*-bromoaniline. For the purposes of comparison, Coffey's process has been applied to *m*-bromoaniline, and, since it is impossible to identify the two products completely, one of them (m. p. 233—235°) has been named 5(or 7)- and the other (m. p. 163°) 7(or 5)-bromo-1-ketotetrahydrocarbazole in accordance with established procedure in analogous cases. Attempts to apply Fischer's reaction to cyclo*hexane*-1 : 2-*dione mono*-o-*bromophenylhydrazone* were unsuccessful.

Under similar conditions, 1-*keto*-8-*methyltetrahydrocarbazole* readily yielded its 6-*bromo*-derivative, and 1-keto-6-methyltetrahydrocarbazole also gave a monosubstitution product. The latter was different from synthetic 8-*bromo*-1-*keto*-6-*methyltetrahydrocarbazole*, but identical with one of the two compounds obtained by eliminating ammonia from *cyclo*hexane-1 : 2-dione mono-2-bromo-*p*-tolylhydrazone. The bromine has therefore entered the 5- or 7-position and the substance has been named 7(or 5)-*bromo*-1-*keto*-6-*methyltetrahydrocarbazole*. It is apparent from these results that the additive properties of tetrahydrocarbazole are enormously diminished in the 1-keto-compound. It cannot be said that they are entirely absent, since, although the yields of the substitution products were substantial, it was not possible to obtain the whole of the product in a pure crystalline condition. These additive reactions are also very well developed in the *N*-acyl derivatives of tetrahydrocarbazole and it was accordingly hoped that an investigation might be made of the 9-acyl-1-ketotetrahydrocarbazoles. The >NH group in the keto-compound is, however, extremely unreactive and conditions for the ready formation of the acyl derivatives have not been found.

The problem of orientation is of interest in the above experiments, and in this connexion the nitration of 1-ketotetrahydrocarbazole and its 8-methyl and 6-methyl derivatives has been studied. In sulphuric acid solution the first two gave their 6-*nitro*-derivatives, and the last yielded 7(or 5)-*nitro*-1-*keto*-6-*methyltetrahydrocarbazole*.

Experimental.

1-Ketotetrahydrocarbazole was obtained by Coffey's method (*loc. cit.*), but ethyl formate was used instead of amyl formate in the preparation of *cyclo*hexane-1 : 2-dione monophenylhydrazone. It was also found more satisfactory to purify the crude product by crystallisation first from carbon tetrachloride (with charcoal) and then from alcohol.

By a similar process cyclo*hexane*-1 : 2-*dione mono*-p-*bromophenylhydrazone*, red needles, m. p. 176°, from alcohol, was obtained from *p*-bromoaniline (Found : N, 10·1. $C_{12}H_{13}ON_2Br$ requires N, 10·0%). A solution of this hydrazone (4 g.) in acetic acid (50 c.c.) and concentrated hydrochloric acid (8 c.c.) was boiled for ½ hour, cooled, and poured into water, with stirring; the precipitated *6-bromo-1-ketotetrahydrocarbazole*, practically colourless needles, m. p. 222—224°, was crystallised from alcohol and then benzene (Found : N, 5·3. $C_{12}H_{10}ONBr$ requires N, 5·3%). The latter compound (0·2 g.) in hot acetone (15 c.c.) was shaken with aqueous potassium hydroxide (1·5 g. of 66%) and acetyl chloride (1 c.c.), and the product was recovered by precipitation with water. After this had been again submitted to the same treatment, *6-bromo-1-keto-9-acetyltetrahydrocarbazole*, orange needles, m. p. 154—155°, from alcohol, was obtained (Found : C, 54·9; H, 4·0. $C_{14}H_{12}O_2NBr$ requires C, 54·9; H, 3·9%).

Prepared in a similar manner, cyclo*hexane*-1 : 2-*dione mono*-o-*bromophenylhydrazone*, dark red needles, m. p. 172—174°, from alcohol, solidified only after the reaction mixture had been carefully neutralised and kept for several hours (Found : N, 10·1%).

*cyclo*Hexane-1 : 2-dione mono-*m*-bromophenylhydrazone (4 g.), red plates, m. p. 165°, from

alcohol, was prepared as before and boiled for ½ hour with acetic acid (65 c.c.) and concentrated hydrochloric acid (13 c.c.). The cooled solution was poured into water, and the precipitate, on crystallisation from alcohol, yielded 5(or 7)-bromo-1-ketotetrahydrocarbazole, nearly colourless needles, m. p. 233—235°, after further crystallisation from alcohol; this was converted as for the corresponding 6-bromo-compound, into 5(or 7)-*bromo*-1-*keto*-9-*acetyltetrahydrocarbazole*, orange needles, m. p. 135°, from alcohol (Found: Br, 26·1. $C_{14}H_{12}O_2NBr$ requires Br, 26·1%). When the first alcoholic mother-liquor was evaporated and the residue crystallised from acetic acid, a further small quantity of the 5(or 7)-bromo-compound was obtained. The substance which was then isolated by dilution of the acetic acid mother-liquor with water could not be crystallised, but it was acetylated by the usual procedure, and, after repeated crystallisation of the product from alcohol, 7(or 5)-*bromo*-1-*keto*-9-*acetyltetrahydrocarbazole*, nearly colourless prisms, m. p. 186—188°, was obtained (Found: Br, 26·2%). 7(or 5)-Bromo-1-ketotetrahydrocarbazole, obtained by boiling the latter with aqueous alcoholic potassium hydroxide for ½ hour and diluting the product with water, separated from benzene in colourless needles, m. p. 163°.

*cyclo*Hexane-1 : 2-dione mono-*p*-nitrophenylhydrazone (3 g.), prepared as above from *p*-nitroaniline, yellow prisms, m. p. 230—240° (decomp.), from *cyclo*hexanone, was refluxed for 2 hours with acetic acid (50 c.c.) and concentrated hydrochloric acid (10 c.c.). The resulting solution was diluted with much water, and the product extracted with ether; after the extract had been shaken with a small amount of aqueous sodium carbonate, dried, and evaporated, 6-nitro-1-ketotetrahydrocarbazole, yellow prisms, m. p. 259°, from alcohol or acetic acid, remained (Found: N, 12·5. Calc.: N, 12·2%). Sen and Ghosh (*J. Indian Chem. Soc.*, 1927, **4**, 477) have described the synthesis of this compound, but the m. p. is stated to be 212°.

Bromination of 1-*Ketotetrahydrocarbazole*.—When a solution of 1-ketotetrahydrocarbazole in acetic acid at 40° was treated with bromine (1 mol.), cooled, and stirred, 6-bromo-1-ketotetrahydrocarbazole separated as its yellow hydrobromide. This was collected and washed with acetic acid, water, and aqueous ammonia, and the free 6-bromo-compound so produced was found, after crystallisation from alcohol and benzene, to be identical (mixed m. p.) with the synthetical compound described above. The same yellow hydrobromide was obtained by treating the 6-bromo-compound in acetic acid with hydrogen bromide; it readily lost its hydrogen bromide on heating or by treatment with water, alcohol, or aqueous ammonia. An analogous hydrobromide separated slowly when 1-ketotetrahydrocarbazole was treated with hydrogen bromide in acetic acid.

Nitration of 1-*Ketotetrahydrocarbazole*.—Potassium nitrate (1·12 g.) was added gradually with continuous stirring to the keto-compound (2 g.) dissolved in concentrated sulphuric acid (25 c.c.) at − 5°. The solution was poured on ice, and the product extracted with ether. When the extract had been shaken with a limited amount of aqueous sodium carbonate, dried, and evaporated, the residue, after crystallisation from alcohol or acetic acid, was found to be identical (mixed m. p.) with the synthetical 6-nitro-1-ketotetrahydrocarbazole mentioned above.

1-*Keto*-8-*methyltetrahydrocarbazole and its Derivatives*.—Prepared by the usual procedure from *o*-toluidine, cyclo*hexane*-1 : 2-*dione mono*-o-*tolylhydrazone*, red prisms, m. p. 95—96°, from alcohol, solidified gradually after the reaction mixture had been carefully neutralised (Found: N, 13·2. $C_{13}H_{16}ON_2$ requires N, 13·0%). After its solution in acetic acid (30 g. in 180 c.c.) containing concentrated hydrochloric acid (30 c.c.) had been boiled for ½ hour, 1-*keto*-8-*methyltetrahydrocarbazole*, colourless needles, m. p. 167°, from alcohol, separated on cooling (Found: N, 7·2. $C_{13}H_{13}ON$ requires N, 7·0%).

cyclo*Hexane*-1 : 2-*dionemono*-5-*bromo*-o-*tolylhydrazone*, brownish-yellow plates, m. p. 95—97°, from alcohol, was obtained similarly from 5-bromo-*o*-toluidine (Found: N, 9·6. $C_{13}H_{15}ON_2Br$ requires N, 9·5%), and was converted into 6-*bromo*-1-*keto*-8-*methyltetrahydrocarbazole*, colourless needles, m. p. 229—230°, from alcohol (Found: N, 5·2. $C_{13}H_{12}ONBr$ requires N, 5·0%). An analogous procedure with 5-nitro-*o*-toluidine led first to cyclo*hexane*-1 : 2-*dione mono*-5-*nitro*-o-*tolylhydrazone*, brown plates, m. p. 155—157°, from alcohol (Found: N, 16·0. $C_{13}H_{15}O_3N_3$ requires N, 16·1%), and then to 6-*nitro*-1-*keto*-8-*methyltetrahydrocarbazole*, yellow needles, m. p. 294°, from acetic acid (Found: N, 11·6. $C_{13}H_{12}O_3N_2$ requires N, 11·5%).

When 1-keto-8-methyltetrahydrocarbazole was treated in acetic acid with bromine (1 mol.), and the resulting red solution diluted with water, 6-bromo-1-keto-8-methyltetrahydrocarbazole, m. p. 226° after crystallisation from alcohol and then benzene, was obtained; it was identified by mixed m. p. with the synthetical compound.

When nitrated by the procedure given above for 1-ketotetrahydrocarbazole, the 8-methyl

compound gave its 6-nitro-derivative, yellow needles, m. p. 294°, from acetic acid, identified by mixed m. p. with the synthetical product.

1-*Keto*-6-*methyltetrahydrocarbazole and its Derivatives.*—*cyclo*Hexane-1 : 2-dione mono-*p*-tolylhydrazone, red plates, m. p. 188—190°, from alcohol (Found : N, 13·0%), was obtained from *p*-toluidine, and was transformed, as for the 8-methyl compound, into 1-keto-6-methyltetrahydrocarbazole, colourless needles, m. p. 195—196°, from alcohol (Found : N, 7·0%). The preparation of the latter compound by analogous methods has been described by Sen and Ghosh (*loc. cit.*) and by Lions (*J. Proc. Roy. Soc. New South Wales*, **1933**, **66**, 516).

cyclo*Hexane*-1 : 2-*dione mono*-3-*bromo*-p-*tolylhydrazone*, red prisms, m. p. 79—82°, from alcohol (Found : N, 9·4%), was converted by the usual procedure into 8-*bromo*-1-*keto*-6-*methyltetrahydrocarbazole*, colourless prisms, m. p. 164°, from petroleum and then alcohol (Found : C, 55·7; H, 4·3; N, 5·2. $C_{13}H_{12}ONBr$ requires C, 56·1; H, 4·3; N, 5·0%), the crude product being extracted with ether from the acetic acid solution after dilution with water.

The corresponding mono-2-bromo-*p*-tolylhydrazone (7 g.), red prisms, m. p. 177—178° after crystallisation from acetic acid and then *cyclo*hexanone, was prepared from 2-bromo-*p*-toluidine, and was refluxed for 20 minutes with acetic acid (70 c.c.) and concentrated hydrochloric acid (13 c.c.). The solid mixture, m. p. 175—225°, which separated after several hours was crystallised from acetic acid, and the product washed by decantation with acetic acid. It was then possible to separate by hand considerable quantities of clusters of very dark brown prisms and of light brown plates. The former, on crystallisation from acetic acid (charcoal), gave 5(or 7)-*bromo*-1-*keto*-6-*methyltetrahydrocarbazole* in colourless prisms, m. p. 253—254° (Found : C, 56·1; H, 4·4%), and the latter, after being twice recrystallised from benzene, gave 7(or 5)-*bromo*-1-*keto*-6-*methyltetrahydrocarbazole* in colourless plates, m. p. 197° (Found : Br, 29·0. $C_{13}H_{12}ONBr$ requires Br, 28·8%).

*cyclo*Hexane-1 : 2-dione mono-3-nitro-*p*-tolylhydrazone, orange plates, m. p. 114—118°, from alcohol, prepared from 3-nitro-*p*-toluidine, solidified when the reaction mixture had been carefully neutralised. It was converted into 8-*nitro*-1-*keto*-6-*methyltetrahydrocarbazole*, brown plates, m. p. 199—201°, from alcohol (Found : N, 11·7%), by a process analogous to that used for 6-nitro-1-ketotetrahydrocarbazole.

The corresponding *mono*-2-*nitro*-p-*tolylhydrazone* (6 g.), red prisms, m. p. 141—142°, from alcohol (Found : N, 15·7%), was refluxed for 40 minutes with acetic acid (70 c.c.) and concentrated hydrochloric acid (15 c.c.), and the resulting solution poured into water. When the product had been extracted with ether, washed with a small amount of aqueous sodium carbonate, and dried (sodium sulphate), the residue, after evaporation, gave a mixture, m. p. 175—215°, on crystallisation from acetic acid. When this was again crystallised from a somewhat larger volume of acetic acid, 5(or 7)-*nitro*-1-*keto*-6-*methyltetrahydrocarbazole*, yellow needles, m. p. 253—255°, after a further crystallisation from acetic acid, separated (Found : N, 11·7%). The acetic acid mother-liquor, after 2 days, deposited 7(or 5)-*nitro*-1-*keto*-6-*methyltetrahydrocarbazole*, brown plates, m. p. 207—208°, from alcohol (Found : N, 11·6%).

Treatment of 1-keto-6-methyltetrahydrocarbazole in acetic acid with bromine (1 mol.) led to the separation of a red solid, which dissolved, on warming, with the evolution of hydrogen bromide. The product obtained on dilution with water gave the 7(or 5)-bromo-compound, m. p. 196—197° (identified by mixed m. p. with the synthetical derivative), after being twice recrystallised from alcohol and then from benzene.

When 1-keto-6-methyltetrahydrocarbazole was nitrated by the procedure described for 1-ketotetrahydrocarbazole, the product, after crystallisation from acetic acid and then alcohol, yielded the 7(or 5)-nitro-derivative, brown plates, m. p. 204—206°, which was identical (mixed m. p.) with the synthetical compound described above.

Reduction of 1-*Ketotetrahydrocarbazole.*—(a) After the keto-compound (2 g.) had been heated on the steam-bath for 4 hours with red phosphorus (3·5 g.) and hydriodic acid (25 c.c. of *d* 1·9), the cooled mixture was made alkaline with aqueous caustic soda and extracted with chloroform. When the extract had been washed with water, dried (potassium carbonate), and evaporated, tetrahydrocarbazole, colourless plates, m. p. 114—116° (after crystallisation from aqueous alcohol), remained; it was identified by a mixed m. p. with an authentic specimen.

(*b*) A mixture of the keto-compound (2 g.), granulated tin (12 g.), alcohol (12 c.c.), and concentrated hydrochloric acid (12 c.c.) was refluxed for 7 hours, and the alcohol was then removed by distillation in steam. After the residue had been made alkaline with aqueous caustic soda, the product was extracted with ether, and the extract was shaken with an excess of dilute hydrochloric acid. Evaporation of the ether then yielded no residue, but aqueous caustic soda precipitated *cis*-hexahydrocarbazole (Gurney, Perkin, and Plant, J., 1927, 2676), m. p. 97—98°

(after crystallisation from aqueous alcohol), identified by a mixed m. p. with an authentic specimen, from the aqueous solution. The use of restricted quantities of the reducing agent resulted in the isolation of unchanged 1-ketotetrahydrocarbazole from the ethereal layer, and *cis*-hexahydrocarbazole from the acid solution.

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