151. *The Chemistry of the Carbazoles.* 1 : 2 : 3 : 4-*Tetrahydro*-4-*ketocarbazoles.*

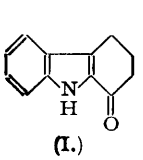
By G. R. Clemo and D. G. I. Felton.

The monophenylhydrazones of *cyclo*hexane-1 : 3-diones undergo the Fischer indole reaction to yield 1 : 2 : 3 : 4-tetrahydro-4-ketocarbazoles. The position of the keto-group has been established completely. 1 : 2 : 3 : 4 : 10 : 11-Hexahydro-2-methylcarbazole exists in two diastereoisomeric forms (α and β), both assumed to be *cis*-hexahydrocarbazoles.

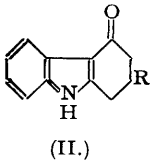
1 : 2 : 3 : 4-Tetrahydro-1-ketocarbazole (I) was long since prepared by Coffey (*Rec. Trav. chim.*, 1923, **42**, 528) who boiled *cyclo*hexane-1 : 2-dione monophenylhydrazone (prepared by the action of benzenediazonium chloride on 2-hydroxymethylene*cyclo*hexanone) with hydrochloric acid in acetic acid. Since then a number of homologues and substituted tetrahydro-1-ketocarbazoles have been recorded (Sen and Ghosh, *J. Indian Chem. Soc.*, 1927, **4**, 477; Lions, *J. Proc. Roy. Soc. N.S.W.*, 1933, **66**, 516) and the action of halogens on this class of compound has been studied (Mears, Oakeshott, and Plant, *J.*, 1934, 272). Recently interest in such compounds has re-awakened in connection with the complex reactions involved in the action of bromine followed by water on 9-benzoyltetrahydrocarbazole whereby 1 : 2 : 3 : 4-tetrahydro-1-hydroxycarbazole is formed (Plant, Robinson, and Tomlinson, *Nature*, 1950, **165**, 928). This hydroxy-compound can be obtained by the reduction with sodium and alcohol of 1 : 2 : 3 : 4-tetrahydro-1-ketocarbazole (Moore, reported by Plant, Robinson, and Tomlinson, *loc. cit.*).

There is, however, no record of tetrahydroketocarbazoles with the keto-group in a position other than 1. In connection with another topic, we were interested in the possibility of preparing 1 : 2 : 3 : 4-tetrahydro-4-ketocarbazole (II; R = H) but, since this work is at present in abeyance, we are placing some of our observations on record.

From the first, the most attractive route lay in achieving the ring-closure, under the conditions of the Fischer indole synthesis, of the monophenylhydrazone of *cyclo*hexane-1 : 3-dione, which is readily available (Merling, *Annalen*, 1894, **278**, 39; Felton and King, *J.*, 1948, 1371). It was found that a compound giving analyses correct for the required product could be obtained in 50—60% yield by the action of approximately 40% sulphuric acid at 100°.



(I.)



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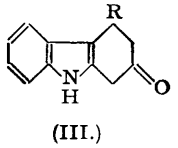


(III.)

The compound was *N*-acetylated with difficulty by an application of the method used by Mears, Oakeshott, and Plant (*loc. cit.*), and the presence of a keto-group was shown by the formation of a deep maroon-coloured 2 : 4-dinitrophenylhydrazone.

It is clear that ring closure to a tetrahydroketocarbazole can yield (II) or (III) (R = H). The maroon colour of the dinitrophenylhydrazone suggested the conjugation of an olefinic link with the keto-group and therefore indicated structure (II; R = H), although the position was complicated by the likelihood that the intense colour was perhaps due to the polynitro-nucleus since the tetrahydroketocarbazole yielded a bright red picric acid complex. This complex is interesting in that the ratio of the two components was 1 : 1, in contrast to that obtaining with tetrahydro-1-ketocarbazole, 2 molecules of which unite with 1 molecule of the polynitro-compound (Kent, *J.*, 1935, 976; Kent and McNeil, *J.*, 1938, 8).

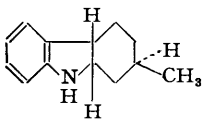
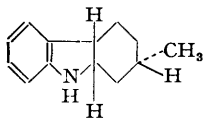
The first attempt at orientation consisted in an attempted dehydrogenation, using chloranil (Barclay and Campbell, *J.*, 1945, 530), to yield a hydroxy-carbazole, the 1-, 2-, and 3-hydroxy-carbazoles being known. After 40 hours' reflux, a test portion still showed the presence of chloranil, and after attempted purification by chromatography, when no clear-cut fractions were obtained, the product was still an inseparable mixture which could not be crystallised. Accordingly, the properties of the tetrahydroketocarbazole were further studied.

Reduction by tin and hydrochloric acid and also electrolytically yielded *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole, identified by comparison with an authentic sample. While reduction of a keto-group by chemical means is well known, electrolytic reduction of a

carbonyl group is, as far as we are aware, restricted to amides. This is a further indication that (II; R = H) is the structure in question, since this contains the group $-NH-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$, the vinylogue of an amide group. Electrolytic reduction of the 10 : 11-double bond of tetrahydrocarbazoles has been often observed previously.

These reduction processes, by which the carbonyl group is eliminated, offered a means of orientation if some other position in the hydrogenated portion of the molecule could be unequivocally marked relative to the carbonyl group. Thus starting from 5-methyl*cyclo*hexane-1 : 3-dione monophenylhydrazone, ring closure may yield either (II) or (III) (R = Me). Reduction will remove the carbonyl group to give 1 : 2 : 3 : 4 : 10 : 11-hexahydro-2-methylcarbazole from (II; R = Me) or 1 : 2 : 3 : 4 : 10 : 11-hexahydro-4-methylcarbazole from (III; R = Me). All four methylcarbazoles are known and the hexahydromethylcarbazoles will readily yield the dehydrogenated product (Barclay and Campbell, *loc. cit.*).

Accordingly 5-methyl*cyclo*hexane-1 : 3-dione (Vorländer and Kalkow, *Ber.*, 1897, **30**, 1802) was converted into the previously unknown monophenylhydrazone and this on treatment with *ca.* 40% sulphuric acid at 100° yielded a tetrahydroketomethylcarbazole, which gave a *N*-acetyl compound under the same conditions as above and readily formed a 2 : 4-dinitrophenylhydrazone of an identical shade of maroon, thus indicating a high probability that ring closure had occurred in the same direction as with the unmethylated compound. Reduction of the keto-compound either with tin and hydrochloric acid or electrolytically yielded a mixture of isomeric hexahydromethylcarbazoles, which gave isomeric *N*-acetyl derivatives. These were shown to be hexahydro-2-methylcarbazoles by direct comparison with the corresponding isomeric substances produced by either chemical or electrolytic reduction of 1 : 2 : 3 : 4-tetrahydro-2-methylcarbazole, when in each case an α- and a β-form were isolated. The comparison was extended to the *N*-acetyl derivatives of the hexahydro-2-methylcarbazoles in each case and completed by chloranil dehydrogenation of the hexahydrocarbazoles (α- and β-forms) to 2-methylcarbazole, identical with a sample obtained by chloranil dehydrogenation of tetrahydro-2-methylcarbazole. The orientation of the methyl group in the tetrahydromethylcarbazole and in the parent methylcarbazole had been previously established by Borsche, Witte, and Bothe (*Annalen*, 1908, **359**, 52).

(IV.)   (V.)

The yields of α- and β-forms, if losses on recrystallisation are neglected, were approximately 60% and 40% Hexahydrocarbazoles are known to give *cis*- and *trans*-isomers, but the strain in the unsubstituted *trans*-isomer is such that it is only formed to the extent of 1—2% (Gurney, Perkin, and Plant, *J.*, 1927, 2676). In the case of the unsubstituted hexahydrocarbazole, we were unable to isolate any *trans*-form when using small quantities. Consequently, we believe that the α- and β-forms are both *cis*-diastereoisomers, owing to the methyl group being *cis* or *trans* in relation to the *cis*-hydrogen atoms (cf. IV and V).

Experimental.

(All m. p.s are uncorrected.)

1 : 2 : 3 : 4-*Tetrahydro*-4-*ketocarbazole.*—*cyclo*Hexane-1 : 3-dione monophenylhydrazone (m. p. 189—192°; Merling, *loc. cit.*, gives m. p. 176—177°) (2·7 g.) was treated with sulphuric acid (10 ml.) in water (25 ml.), a dark blue-violet colour developing. The solution was warmed on the steam-bath for 1½ hours, the hot solution decanted rapidly from some tar which was produced, and then slowly diluted with water (110 ml.). A grey precipitate was obtained, which was collected, washed thoroughly with water, and dried (1·3 g.). Three recrystallisations from ethanol afforded the *carbazole* as colourless refracting rhombs, m. p. 223° (Found : C, 77·5; H, 6·2. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·95%). A solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid was added to an ethanolic solution of the tetrahydroketocarbazole. Slow precipitation of dark-red needles occurred and, after crystallisation from glacial acetic acid, the 2 : 4-*dinitrophenylhydrazone* formed dark maroon-coloured needles, m. p. 288° (decomp.) (Found : C, 58·9; H, 4·2. $C_{18}H_{15}O_4N_5$ requires C, 59·2; H, 4·1%). Equivalent quantities of the tetrahydroketocarbazole and picric acid were crystallised together from a little alcohol. Recrystallisation afforded the picric acid *complex* as bright red rhombs, m. p. 167° (Found : C, 52·6; H, 3·6. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%). The tetrahydrocarbazole (0·4 g.) in boiling acetone was treated with shaking with acetyl chloride (2 ml.) and 66% potassium hydroxide solution (3 ml.), and the product precipitated by the addition of water. It was redissolved in boiling acetone and the process repeated. The final product, crystallised from aqueous ethanol, gave the 9-*acetyl* derivative as colourless needles, m. p. 136° (Found : C, 74·2; H, 5·65. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7%).

Reduction.—(i) *Electrolytic reduction.* 1 : 2 : 3 : 4-Tetrahydro-4-ketocarbazole (1 g.) in 50% sulphuric acid was reduced in the cathode compartment of an electrolytic cell for 18 hours at 4—5 amps. The cathode liquor was then diluted with an equal volume of water and by addition of aqueous ammonia the base was liberated as a white precipitate. Crystallisation from aqueous ethanol afforded colourless rods, m. p. 96°, undepressed on admixture with *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole. The acetyl derivative was prepared by heating the base with acetic anhydride at 105—110° for ½ hour. Recrystallisation from aqueous ethanol gave needles, m. p. 97—98°, undepressed by an authentic sample of 9-acetylhexahydrocarbazole.

(ii) *Chemical reduction.* 1 : 2 : 3 : 4-Tetrahydro-4-ketocarbazole (2 g.) was added to a mixture of granulated tin (10 g.), concentrated hydrochloric acid (12 c.c.), and ethanol (12 c.c.). The mixture was refluxed for 9 hours with small additions of concentrated hydrochloric acid from time to time. The ethanol was steam-distilled from the mixture and, after cooling and basification with sodium hydroxide until the solution was strongly alkaline, the steam-distillation was continued. A white solid, practically insoluble in water was obtained, which was collected, dried, and crystallised from aqueous ethanol, yielding *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole, m. p. 96° undepressed by an authentic specimen of the product obtained in (i).

In neither (i) nor (ii) was any trace of isomers detected.

5-*Methyl*cyclo*hexane*-1 : 3-*dione Monophenylhydrazone.*—5-Methyl*cyclo*hexane-1 : 3-dione (1·26 g.) in dilute acetic acid was treated with phenylhydrazine (1·0 ml.) in dilute acetic acid, and the mixture warmed on the water-bath for 5 minutes. Scratching the cooled solution produced a pale yellow crystalline precipitate which on crystallisation from aqueous ethanol (charcoal) afforded the *monophenylhydrazone* as colourless rhombs, m. p. 206° (decomp.) (Found : C, 72·2; H, 7·3. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*keto*-2-*methylcarbazole.*—The above monophenylhydrazone (5 g.) was added to a mixture of sulphuric acid (20 ml.) and water (50 ml.), and the resulting brownish solution gently warmed on the steam-bath for 2 hours. Cautious dilution with water (100 ml.) produced a brownish precipitate, which after crystallisation from ethanol yielded the *tetrahydroketomethylcarbazole* as colourless needles, m. p. 259—260° (Found : C, 78·4; H, 6·8; N, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5; N, 7·0%). The 2 : 4-*dinitrophenylhydrazone* formed very fine, iridescent, maroon needles (from glacial acetic acid), m. p. 291° (decomp.) (Found : C, 57·8; H, 4·8. $C_{19}H_{17}O_4N_5,CH_3{\cdot}CO_2H$ requires C, 57·4; H, 4·8. Found, on a sample dried at 140° in a high vacuum : C, 59·9; H, 4·3. $C_{19}H_{17}O_4N_5$ requires C, 60·2; H, 4·5%). The 9-*acetyl* derivative of the ketone, prepared as described above, formed colourless needles, m. p. 125°, from aqueous methanol (Found : C, 74·5; H, 6·3. $C_{15}H_{15}O_2N$ requires C, 74·7; 6·2%).

Reduction. 1 : 2 : 3 : 4-Tetrahydro-4-keto-2-methylcarbazole (4 g.) was added to a mixture of granulated tin (26 g.), concentrated hydrochloric acid (26 ml.), and ethanol (26 ml.). A further addition of concentrated hydrochloric acid (10 ml.) was made midway through the 9-hour period of reflux. The ethanol was removed by steam-distillation; after cooling and addition of sodium hydroxide, the passage of steam was continued, a white solid (2·2 g.) slowly distilling. Crystallisation from aqueous ethanol yielded long needles, m. p. 68—74°. These were dissolved in methanol, and water was added dropwise; addition was stopped before turbidity was reached. The solution, in the refrigerator, deposited long prisms, which were rapidly collected and recrystallised from aqueous methanol to afford *cis*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-2-*methylcarbazole*-α (1·0 g.) as long colourless prisms, m. p. 81·5° (Found : C, 83·5; H, 9·4. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1%). Acetylation at 105—110° for ½ hour with acetic anhydride gave the 9-*acetyl* derivative, colourless small prisms, m. p. 92—93° (from aqueous ethanol) (Found : C, 78·8; H, 8·4. $C_{15}H_{19}ON$ requires C, 78·6; H, 8·3%). The mother-liquors from the crystallisation of the hexahydro-compound were concentrated and allowed to cool, colourless crystals being deposited. Recrystallised from aqueous ethanol, these yielded *cis*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-2-*methylcarbazole*-β (0·7 g.) as long felted needles, m. p. 84—85° (mixed m. p. with the α-*cis*-compound, 63—70°) (Found : C, 83·3; H, 9·3%). Acetylation of the β-form yielded the β-9-*acetyl* derivative as colourless needles, m. p. 97° (mixed m. p. with the α-compound, 78—83°) (Found : C, 78·4; H, 8·1%).

Reduction of 1 : 2 : 3 : 4-*Tetrahydro*-2-*methylcarbazole.*—(i) 1 : 2 : 3 : 4-Tetrahydro-2-methylcarbazole (Borsche, Witte, and Bothe, *loc. cit.*) (7 g.) was refluxed for 10 hours with granulated tin (14 g.), ethanol (14 ml.), and concentrated hydrochloric acid (14 ml.). The product was isolated by steam-distillation in the usual way and was crystallised from aqueous ethanol, yielding α-*cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-2-methylcarbazole, m. p. 81·5° undepressed on admixture with the specimen obtained above (acetyl derivative, m. p. and mixed m. p. 92—93°). On concentration of the mother-liquors, the β-*cis*-compound was obtained, m. p. and mixed m. p. 84—85° (acetyl derivative, m. p. 97° alone or mixed with the specimen described above).

(ii) *Electrolytic reduction.* The tetrahydrocarbazole (5 g.) was reduced electrolytically and isolated as above. Fractional crystallisation of the product from aqueous ethanol afforded both the α- (m. p. 81·5°) and the β-*cis*-form (m. p. 84—85°).

Dehydrogenation of cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-2-*methylcarbazole*-α.—(i) The α-*cis*-form from the corresponding tetrahydro-keto-compound) (0·33 g.) was dissolved in xylene, chloranil (0·915 g., 2 mols.) was added, and the mixture refluxed until a test portion gave no pink colour with sodium hydroxide solution (2 hours). The solution was then cooled and filtered from the precipitated tetrachloroquinol, and the filtrate processed in the usual way. Crystallisation of the product from ethanol yielded 2-methylcarbazole as silvery glistening leaflets, m. p. 259°, alone or mixed with an authentic sample obtained from tetrahydromethylcarbazole (Barclay and Campbell, *loc. cit.*). The picrate formed orange-red prisms, m. p. and mixed m. p. 168° (Borsche *et al.*, *loc. cit.*, give m. p. 167°).

(ii) The *β-cis*-form (0·1 g.) was dehydrogenated by means of chloranil (0·3 g.) in xylene. The product on crystallisation from ethanol formed colourless leaflets of 2-methylcarbazole, m. p. 259°, undepressed by an authentic sample (picrate, m. p. and mixed m. p. 168°).

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UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-ON-TYNE, 1.

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