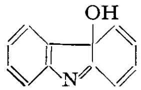
269. *The Formation of Osazones. Part I. The Reaction of 2-Hydroxy*cyclo*hexanone with Arylhydrazines.*

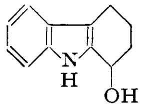
By G. J. Bloink and K. H. Pausacker.

The reaction between 2-hydroxy*cyclo*hexanone and various arylhydrazines has been studied. In aqueous-alcoholic sulphuric acid, the corresponding 1-ketotetrahydrocarbazole only is formed, whereas in alcohol alone (with phenylhydrazine) a mixture of 1-ketotetrahydrocarbazole and the bisphenylhydrazone of *cyclo*hexane-1 : 2-dione was obtained. In glacial acetic acid, osazone formation only occurred, except that when *p*-methoxyphenylhydrazine was used, the 1-ketotetrahydrocarbazole was alone formed.

In order to prepare the compound formulated as 11-hydroxy-11-*iso*carbazole (I) by Barnes, Pausacker, and Schubert (*J.*, **1949**, **1381**), it was decided to proceed as follows. Cyclisation of the phenylhydrazone of 2-hydroxy*cyclo*hexanone should yield a mixture of the neutral 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole (II) and the basic 11-hydroxy-1 : 2 : 3 : 4-tetrahydro-11-*iso*carbazole (III). Dehydrogenation of the latter product should then yield (I), which would thus be prepared by an unambiguous synthesis.



(I.)



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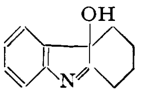

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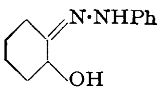
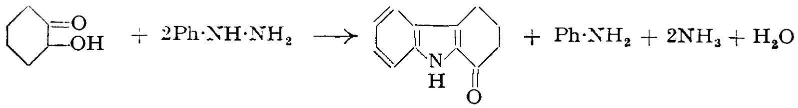


(IV.)

Bergmann and Gierth (*Annalen*, 1926, **448**, 72) described the preparation of the phenylhydrazone (IV) (m. p. 121°) of 2-hydroxy*cyclo*hexanone by condensation of phenylhydrazine with 2-hydroxy*cyclo*hexanone (V) in aqueous acetic acid. Attempts to repeat this work proved abortive, the only pure product isolated being the bisphenylhydrazone (VI) of *cyclo*hexane-1 : 2-dione (an osazone) (m. p. 153°). However, when equimolecular amounts of phenylhydrazine and (V) were heated, in a boiling water-bath, under reduced pressure, a loss in weight corresponding to one mole of water was noted. The resulting red, viscous oil did not contain any (VI) and could not be induced to crystallise. This oil was then heated with aqueous-alcoholic sulphuric acid, but neither (II) nor (III) was isolated. Instead, the neutral fraction yielded 1-ketotetrahydrocarbazole (VII), and the basic fraction was identified as aniline. (VII) was found to be identical (mixed m. p.) with the product obtained from the cyclisation of the monophenylhydrazone of *cyclo*hexane-1 : 2-dione (Coffey, *Rec. Trav. chim.*, 1923, **42**, 528). Similar results were obtained when the reagents were heated with aqueous-alcoholic sulphuric acid without prior condensation.

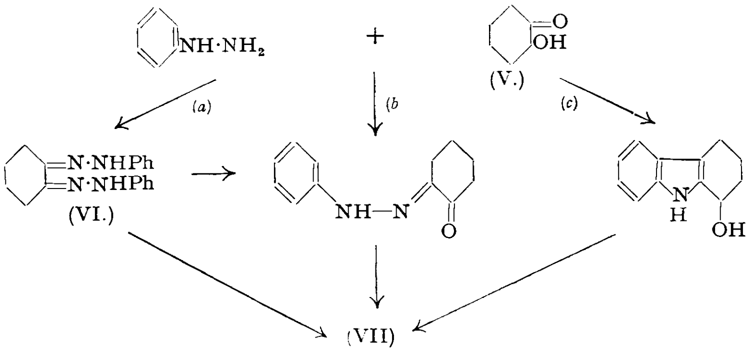
It thus seems probable that, in these reactions in sulphuric acid, phenylhydrazine is acting as an oxidising agent, as in the preparation of osazones. This hypothesis was verified by the observation that the yield of (VII) was doubled when two moles of phenylhydrazine were heated with one mole of (V) in aqueous-alcoholic sulphuric acid under the same conditions, thus :



(V.) (VII.)

As far as the authors are aware, this is the first recorded example of the simultaneous oxidation and cyclisation of an α-hydroxy-ketone. It is therefore of interest to determine the course of the reaction.

It is unlikely that the reaction would follow course (*a*) for, as Semple (*J. Amer. Chem. Soc.*, 1934, **56**, 1352) has pointed out, osazone formation (for glucose) is inhibited in the presence of dilute mineral acid, although hydrazone formation can take place. In order to verify that the osazone (VI) is not involved as an intermediate in the reaction, (VI) was treated under the same conditions. A surprising result was obtained, namely, a 21% conversion of (VI) into (VII). It is still considered that (VI) is not an intermediate, however, for a much greater yield (46%) of (VII) was obtained by starting with phenylhydrazine and (V). It is nevertheless interesting that (VI) may be converted into (VII), as osazones are generally resistant to cyclisation. This ready ring closure may be correlated with the ready formation of tetrahydrocarbazoles by the Fischer method. It thus appears that the reaction follows either course (*b*) or course (*c*), and at present no distinction can be made between these two possibilities except to say that mechanism (*b*) is perhaps more analogous to osazone formation. It should also be noted that both these reactions imply a direct oxidation of –CH·OH– to –CO–. Similar reactions were noted when *p*-tolyl-, *p*-methoxyphenyl-, and *p*-ethoxyphenylhydrazine were used in place of phenylhydrazine.



When a mixture of phenylhydrazine and (V) was refluxed, in ethyl-alcoholic solution, without an acid catalyst, a copious evolution of ammonia took place and both (VI) and (VII) were isolated from the reaction mixture. This shows that osazone formation can take place in an alkaline medium and provides an example of the Fischer indole synthesis occurring without the addition of an acid catalyst.

Finally, the condensation of phenylhydrazine and (V) in glacial acetic acid at 0° resulted in rapid formation of (VI) (cf. Bergmann and Gierth, *loc. cit.*), the product being precipitated almost quantitatively. (VII) could not be isolated from the reaction mixture. With three moles of various substituted phenylhydrazine per mole of (V) in glacial acetic acid at 0°, the yields of osazone, after one hour, were 88, 72, 70, 16, and 0% when the substituents were *p*-nitro, *p*-chloro, unsubstituted, *p*-methyl, and *p*-methoxy, respectively. As all these osazones were sparingly soluble in glacial acetic acid, the yields probably give an approximate measure of the relative reaction rates. It is thus seen that osazone formation takes place most readily when the substituent has an overall effect ($-I$ or $-T$) and occurs very slowly indeed when *p*-methyl ($+I$) is the substituent and not at all when the substituent is *p*-methoxy ($+T > -I$). When the various hydrazines were set aside for a long time with (V) in glacial acetic acid it was found that, except when *p*-methoxyphenylhydrazine was used, the corresponding osazone was the only product isolated even though the sparing solubility of the osazones in most solvents allows their ready separation from any 1-ketotetrahydrocarbazole formed simultaneously. When *p*-methoxyphenylhydrazine was used, however, it was impossible to isolate any osazone, but instead an 89% yield of 1-*keto*-6-*methoxytetrahydrocarbazole* was obtained.

It is thus seen that in glacial acetic acid both tetrahydrocarbazole and osazone formation are possible. When *p*-nitro-, *p*-chloro-, unsubstituted, and *p*-methyl-phenylhydrazines were used, the rate of osazone formation decreased in this order but must be much greater than the rate of tetrahydrocarbazole formation. This inference is in accord with the statement of Pigman and Geopp (" Chemistry of the Carbohydrates," Academic Press, 1948, p. 404) that " osazone formation is favoured by the presence of electron-attracting groups attached to the hydrazine radical." However, when *p*-methoxyphenylhydrazine was used, the rate of tetrahydrocarbazole formation must have been much greater than that of osazone formation. This result is in accord with the above statement, and in addition we have recently found (unpublished results) that the *p*-methoxyphenylhydrazone of *cyclo*hexanone is converted into the corresponding tetrahydrocarbazole (in glacial acetic acid) much more rapidly than the *p*-nitro-, unsubstituted, or *p*-methyl-phenylhydrazones of *cyclo*hexanone (in that order).

It is interesting that, when Adkins and Rossow (*J. Amer. Chem. Soc.*, 1949, **71**, 3836) treated 2-methoxy*cyclo*hexanone with 2 : 4-dinitrophenylhydrazine in the presence of alcoholic hydrochloric acid, the corresponding osazone was the only product isolated. Although our results indicate that mineral acid should favour the formation of a 1-ketotetrahydrocarbazole, it is well known that dinitrophenylhydrazones are particularly resistant to Fischer cyclisation, and so the alternative osazone formation, favoured by the presence of nitro-groups, takes place after hydrolysis of the methoxyl group.

Finally, it may be noted that 2-chloro*cyclo*hexanone also condenses with phenylhydrazine in glacial acetic acid to form (VI).

A kinetic investigation of osazone formation is now proceeding.

EXPERIMENTAL.

*2-Hydroxy*cyclo*hexanone* (V).—The method of Bergmann and Gierth (*loc. cit.*) was slightly modified. 2-Chloro*cyclo*hexanone (100 g.) was shaken (5 hours) with a solution of potassium carbonate (400 g.) in water (750 ml.). The solid obtained was washed, first with water (until chloride free) and then with three 50-ml. portions of ice-cold ether. After drying in a vacuum desiccator, pure (V) (69 g., 81%) was obtained, m. p. 112° (Bergmann and Gierth give m. p. 112—113°, Bouveault and Chereau, *Compt. rend.*, 1906, **142**, 1086, give m. p. 113°, and Kötz and Grethe, *J. pr. Chem.*, 1909, [ii], **80**, 488, give m. p. 92—92·5°). Difficulty is encountered if an attempt is made to crystallise the product from alcohol as suggested by some of the above authors.

Condensations in the Presence of Dilute Sulphuric Acid.—The ketone (V) (4 g.) was dissolved in ethyl alcohol (50 ml.) along with the appropriate hydrazine (1 mole), and the solution added to 2·5N-sulphuric acid (150 ml.). After refluxing (1 hour), the alcohol was distilled off and the product extracted with ether and crystallised from benzene. The yields are based on the amount of the phenylhydrazine used.

1-*Ketotetrahydrocarbazole.* Yield 71%. Colourless plates from benzene. M. p. and mixed m. p. with a sample prepared by the method of Coffey (*loc. cit.*) 168—169° (Found: C, 78·3; H, 6·0; N, 7·4. Calc. for $C_{12}H_{11}ON$: C, 77·9; H, 5·95; N, 7·6%). *Picrate*: light orange needles (from benzene), m. p. 167° (Found: C, 60·3; H, 4·1; N, 11·6. $2C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 60·1; H, 4·2; N, 11·1%). *Semicarbazone*: colourless plates (from benzene), m. p. 228—230° (Found: C, 64·5; H, 6·0; N, 23·0. Calc. for $C_{13}H_{14}ON_4$: C, 64·5; H, 6·0; N, 23·1%). Coffey (*loc. cit.*) reports m. p. 228—230°. p-*Nitrophenylhydrazone*: dark red needles (from glacial acetic acid), m. p. 228—230° (Found: N, 12·5. $C_{18}H_{16}O_2N_4$ requires N, 12·5%).

1-*Keto*-6-*methyltetrahydrocarbazole.* Yield 71%. Colourless prisms, m. p. 194—195°, from benzene (lit., m. p. 195°, 195—196°) (Found: C, 78·3; H, 6·5; N, 7·3. Calc. for $C_{13}H_{13}ON$: C, 78·3; H, 6·5; N, 7·0%).

1-*Keto*-6-*methoxytetrahydrocarbazole.* Yield 89%. Colourless plates [from benzene–light petroleum (b. p. 40—60°)], m. p. 180—182° (decomp.) (Found: N, 5·9; OMe, 12·5. $C_{13}H_{13}O_2N,0{\cdot}5C_6H_6$ requires N, 5·6; OMe, 12·3%).

1-*Keto*-6-*ethoxytetrahydrocarbazole.* Yield 74%. Colourless needles (from aqueous alcohol), m. p. 185—186° (Found: N, 6·05. $C_{14}H_{15}O_2N$ requires N, 6·1%).

Condensation in Ethyl Alcohol.—(V) (3 g.) was dissolved in ethyl alcohol (35 ml.), and phenylhydrazine (2·85 g., 1 mole) was added. After refluxing (15 hours), during which ammonia was evolved, the cooled solution deposited fine yellow needles of (VI) (1·30 g.; m. p. 153°). When the solution was concentrated (to *ca.* 8—10 ml.), a further quantity of (VI) (0·14 g.) was obtained. The filtrate was added to 2·5N-sulphuric acid (150 ml.) and extracted with ether. The ethereal extract was dissolved in a small volume of benzene and slowly added to light petroleum (b. p. 60—90°). The resultant amorphous precipitate was crystallised from benzene, yielding pure 1-ketotetrahydrocarbazole (0·45 g.; m. p. 169°). When the acidic solution was basified and extracted with ether, aniline (0·61 g.) [identified as its picrate, m. p. and mixed m. p. 163—165° (decomp.)] was obtained.

Condensation in the Presence of Glacial Acetic Acid.—(V) (3 g.) was dissolved in glacial acetic acid (25 ml.) and cooled to 0°. The appropriate phenylhydrazine was added and the mixture set aside for various times. The resultant osazone was filtered off. Only a very small amount of osazone was obtained from the filtrate. The table summarises the results obtained. The percentage yields are based on the weight of (V) used.

Substituted phenyl-hydrazine.	No. of moles per mole of (V).	Time.	Temp.	Yield of osazone, %.
(Unsubstituted)	1	1 hr.	0°	10
	2	,,	,,	42
	3	,,	,,	70
p-Tolyl	1 & 2	,,	,,	0
	3	,,	,,	16
	3	24 hrs.	20°	68
p-Chloro	1	1 hr.	0°	16
	3	,,	,,	72
p-Nitro	3	,,	,,	88
p-Methoxy ...	3	15 hrs.	20°	0 *

* Although no precipitate was formed, it was found that, when the glacial acetic acid was evaporated under reduced pressure and the residue treated with dilute sulphuric acid and extracted with ether, an 89% yield of 1-keto-6-methoxytetrahydrocarbazole (identical with the product from the dilute sulphuric acid condensation) was obtained.

The *cyclo*hexane-1 : 2-dione bisphenylhydrazone formed yellow needles, m. p. 153°, from ethyl alcohol (Kötz, Blendermann, Rosenblusch, and Sirringhaus, *Annalen*, 1913, **400**, 67, report m. p. 150—151°, and Bergmann and Gierth, *loc. cit.*, report m. p. 153°) (Found: N, 19·1. Calc. for $C_{18}H_{20}N_4$: N, 19·1%). It gave a *picrate*, light orange needles (from benzene), m. p. 149° (Found: N, 19·0. $C_{18}H_{20}N_4,C_6H_3O_7N_3$ requires N, 18·8%), and *styphnate*, orange needles (from ethyl alcohol), m. p. 163° (decomp.) (Found: N, 18·0. $C_{18}H_{20}N_4,C_6H_3O_8N_3$ requires N, 18·2%).

The cyclo*hexane*-1 : 2-*dione bis*-p-*tolylhydrazone* formed yellow prisms, m. p. 136°, from ethyl alcohol (Found: N, 17·2. $C_{20}H_{24}N_4$ requires N, 17·4%).

The cyclo*hexane*-1 : 2-*dione bis*-p-*chlorophenylhydrazone* formed yellow needles (from ethyl alcohol), m. p. 196—197° (decomp.) (Found : N, 15·5. $C_{18}H_{18}N_4Cl_2$ requires N, 15·5%).

The cyclo*hexane*-1 : 2-*dione bis*-p-*nitrophenylhydrazone* formed bright red needles (from ethyl alcohol), m. p. 231° (decomp.) (Found : N, 21·4. $C_{18}H_{18}O_4N_6$ requires N, 22·0%).

When 2-chloro*cyclo*hexanone (3 g.) was shaken in glacial acetic acid (25 ml.) at 0° for 1 hour with phenylhydrazine (1, 2, or 3 moles), (VI) was produced in yields of 0, 15, and 34% respectively. (The percentage yields are based on the weight of 2-chloro*cyclo*hexanone used.)

Analyses are by Drs. Strauss and Weiler and Messrs. N. L. Lottkowitz and N. W. Gamble.

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