305. *Strychnine and Brucine. Part XLVIII. Degradation of the Strychnineacetic Acid prepared from Pseudostrychnine.*

By K. H. PAUSACKER and SIR ROBERT ROBINSON.

The alkaline degradation of strychnineacetic acid has been studied in the hope of supplying evidence in favour of one of the two structures discussed in Part XLII (Briggs, Openshaw, and Robinson, *J.*, 1946, 903). One of the products should be 3- or 4-methylcarbazole, and an unequivocal result would have been of great value. Actually the main constituent of the carbazole fraction was carbazole itself, but infra-red absorption analysis, carried out by Mr. R. E. Richards of the Physical Chemistry Laboratory, Oxford University, showed that 3-methylcarbazole, but no 4-methylcarbazole, was present in small relative amount.

The carbazole from strychnine was found to contain a trace of 3-methylcarbazole, and degradation of the product of interaction of oxodihydro*neo*strychnine and methylmagnesium iodide afforded a carbazole fraction containing 3-methylcarbazole and an unidentified substance.

For the study of the infra-red absorption 1-, 2-, and 3-methylcarbazoles were prepared by known methods.

4-Methylcarbazole does not appear to have been hitherto described and was synthesised without ambiguity from 4-chloro-*m*-tolylhydrazine by way of a related tetrahydrocarbazole.

CARBAZOLE was first obtained from strychnine by dry distillation and by heating with zinc dust (Lobisch and Schoop, *Monatsh.*, 1886, **7**, 614); by heating strychnine with soda-lime, Lobisch and Malfatti (*ibid.*, 1888, **9**, 626) obtained carbazole, skatole, and β-picoline. The formation of carbazole was confirmed by Clemo, Perkin, and Robinson (*J.*, 1927, 1625), who decomposed methylstrychnine at 150—200°. Such drastic degradations affording aromatic compounds of high intrinsic stability are admittedly of problematic value in constitutional studies, but it occurred to us that the survival of a group introduced into the strychnine molecule would be significant.

It is known that pseudostrychnine (hydroxystrychnine) contains $:\!N(b)\cdot C(OH)\!:$ (Blount and Robinson, *J.*, 1932, 2305), and Leuchs (*Ber.*, 1943, **76**, 1068) showed that this base condenses with malonic acid to strychnineacetic acid, $:\!N(b)\cdot\ddot{C}\cdot CH_2\cdot CO_2H$, which loses carbon dioxide with formation of methylstrychnine.

Degradation of a crude product obtained in this way gave a carbazole fraction which on examination by the usual methods was found to contain methylcarbazoles in considerable relative amount (up to 40%). At this point we were fortunate to receive the valuable co-operation of Mr. R. E. Richards to whom we express our gratitude. He examined the infra-red spectra of carbazole and the four *C*-methylcarbazoles and noted the presence of certain characteristic bands. He also studied our degradation products and synthetic mixtures of carbazole and the various isomerides. The degradation product was found to contain from 5 to 12% of 3-methylcarbazole, and 4-methylcarbazole was absent.

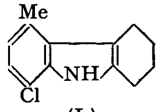
As a control we degraded strychnine by the same method, and the infra-red analysis of the product showed that it was carbazole containing a little (<1%) 3-methylcarbazole. As the 3-position is *para* to the imino-group it would not be surprising if a small amount of the homologue were synthesised by condensation reactions in the course of the process. It was also shown that a mixture of 4-methylcarbazole and carbazole afford no 3-methylcarbazole under the conditions employed, although naturally it would never be feasible to eliminate the possibility of migration of groups at an earlier stage.

Up to this point it seemed safe to conclude that N(b) is attached to position 3 of a partly reduced carbazole nucleus in the strychnine molecule. We hoped to clinch the matter by introducing a methyl group in a different position, and for this purpose selected oxodihydro*neo*strychnine (see the preceding paper) as the starting point. This base probably contains $:\!N(b)\cdot\dot{\underset{\cdot}{C}}\cdot CO\cdot$, and reaction with methylmagnesium iodide should result in attachment of methyl to the β-carbon with respect to N(b). Hence the result of degradation was expected to be 4-methylcarbazole (or 2-methylcarbazole). The outcome was surprising since the carbazole fraction of the degradation product contained about 10% of 3-methylcarbazole as found by infra-red absorption analysis. Unidentified substances were also present. Now whatever the constitution of strychnine may be, it is anomalous that these two degradations should have given the same result. It is inescapable that migration must have occurred in one of the cases unless, indeed, the methyl group of 3-methylcarbazole does not arise from that introduced into the strychnine molecule. It will be seen that the clarity of an argument that could be developed is obscured by the necessity to exercise judgment in the interpretation of the results.

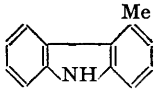
Synthesis of 4-*Methylcarbazole.*—According to Plancher and Carrasco [*Roy. Acad. Lincei*, 1904, (V), **13**, (i), 632, cited by Hollins, " Synthesis of Nitrogen Ring Compounds," p. 168] the

Fischer reaction applied to 3-methyl*cyclo*hexanone phenylhydrazone affords a mixture of 2- and 4-methyltetrahydrocarbazole; Borsche, Bothe, and Witte (*Annalen*, 1908, **359**, 61) found only the 2-methyl derivative. (Owing to a special numbering system this is described as the 4-methyl derivative, but it gives 2-methylcarbazole on dehydrogenation.) To effect an unambiguous synthesis it was preferable to start with a *m*-tolylhydrazine, and we blocked the 4-position by a chlorine atom.

4-Chloro-*m*-toluidine (Gattermann and Kaiser, *Ber.*, 1885, **18**, 1600) was converted in the usual manner into the *hydrazine* and then into *8-chloro-5-methyl-*1 : 2 : 3 : *4-tetrahydrocarbazole*



(I.)



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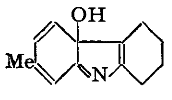

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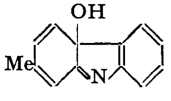

(IV.)

(I) by heating with dilute sulphuric acid; a by-product is discussed below. (I) was dehydrogenated by chloranil with formation of *1-chloro-4-methylcarbazole* and converted into *4-methylcarbazole* (II) by heating with palladised charcoal in a stream of hydrogen.

The by-product mentioned above contained a trace of chlorine and hence gave low results for carbon. It appears, however, to be $C_{13}H_{15}ON$. It was dehydrogenated by palladised charcoal to a substance $C_{13}H_{11}ON$ which gave sharp results on analysis. These curious compounds are devoid of phenolic character and do not form picrates. The constitutions (III) and (IV) are suggested provisionally. It is hoped that an opportunity to make a further examination of these substances will be found.

Added in Proof (*November* 9*th*, 1947).—We now know that oxodihydro*neo*strychnine is a derivative of *allo*strychnine and is an aldehyde. The methyl introduced by the Grignard reagent is remote from the carbazole nucleus. Therefore the formation of 3-methylcarbazole is probably due to rearrangement or synthesis in the course of the degradation process.

EXPERIMENTAL.

Degradation of Strychnineacetic Acid.—Pseudostrychnine was prepared by the elegant method of Leuchs (*Ber.*, 1940, **73**, 734) who states that strychnine (100 g.) yields crude pseudostrychnine (41—43 g.), neutral product (10—15 g.), and unchanged strychnine (30—33 g.). Our experience of several runs is that the respective average figures are 54, 20, and 4.

This crude pseudostrychnine (43 g.) was converted into strychnineacetic acid (Leuchs, *loc. cit.*) by condensation with malonic acid. The isolated perchlorate was powdered with animal charcoal and extracted with water in a Soxhlet apparatus (39 g.). On treatment with N-sodium bicarbonate solution (69 c.c.) and continuous extraction with chloroform, strychnineacetic acid (30 g.) was obtained. This was then heated in batches (6 g.) for 0·5 hour at 280—300°; a brown powder (25 g.) was obtained. Leuchs (*Ber.*, 1943, **76**, 1069) claims that methylstrychnine can be obtained in 17—25% yield by this method. This was powdered in 5 g. lots with soda-lime (30 g.) and heated in a metal-bath at 380—400° for 1 hour. The distillate, a brown tar, was extracted with benzene, washed with acid and alkali and steam-distilled. After about 10 l. had distilled, no further volatile substances came over. The distillate was extracted with benzene, concentrated, and passed through an alumina column. The first washings were found to be light yellow and fluorescent in ultra-violet light. These were concentrated and the resultant crystals were recrystallised from light petroleum (b. p. 60—80°). After sublimation in a high vacuum at 160°, a white solid (30 mg.) was obtained. It had a faint indolaceous odour, m. p. 203—207° after shrinking at 199° (Found: C, 86·0; H, 5·9; *C*-Me, 3·7%). On being kept in the air it became light brown. When this substance (3 mg.) was treated with picric acid (3·6 mg.) in benzene, a red-brown picrate, m. p. 156—162°, was obtained. The white solid dissolved in concentrated sulphuric acid to a very pale yellow solution which became ultramarine blue on the addition of a drop of concentrated nitric acid. When it was dissolved in alcohol and an acid solution of *p*-nitrobenzenediazonium chloride added, a bright yellow coloration developed. Infra-red measurements indicate that the mixture contains about 8—12% of 3-methylcarbazole along with carbazole. None of the other methylcarbazoles were detected but a small amount of some impurity was also found to be present.

The following experiments were made for comparative purposes.

Carbazole. When recrystallised from benzene the specimen employed had m. p. 238° (Found : *C*-Me, 0·85. Calc.: C, 86·2; H, 5·4; *C*-Me, 0·0%). The yellow solution in concentrated sulphuric acid became ultramarine blue on the addition of a drop of concentrated nitric acid. Its solution in alcohol became pale pink on the addition of an acidified solution of *p*-nitrobenzenediazonium chloride. The picrate (bright red) had m. p. 183—184°; mixed m. p. with the unknown picrate, 157—160°. The melting points of mixtures of carbazole and 3-methylcarbazole, and of carbazole and 4-methylcarbazole are shown below :

Carbazole and 3-methylcarbazole.

Carbazole, %	4	16	27	38	52	62	79	89	95
Softening pt.	200°	198°	198°	203°	210°	213°	220°	228°	234°
M. p.	200—202°	199—201°	201—203°	205—207°	212—214°	214—217°	224—227°	231—233°	237—238°

Carbazole and 4-*methylcarbazole.*

Carbazole, %	4	13	24	36	53	62·5	75	87·5	94·5
Softening pt.	110°	110°	107°	117°	130°	175°	190°	224°	230°
M. p.	112—117°	113—117°	115—150°	140—174°	168—196°	198—220°	214—224°	228—232°	235—236°

A mixture of the unknown with an equal quantity of a 3-methylcarbazole–carbazole mixture (60 : 40) softened at 198° and had m. p. 202—205°.

3-*Methylcarbazole.* The specimen had m. p. 202° (Found : *C*-Me, 6·0. Calc.: C, 86·2; H, 6·1; *C*-Me, 8·3%). It gave a colourless solution in concentrated sulphuric acid which turned emerald green upon the addition of a drop of concentrated nitric acid. Its alcoholic solution became faintly yellow upon the addition of *p*-nitrobenzenediazonium chloride. The dark red picrate had m. p. 178—179°; mixed m. p. with the unknown picrate, 155—158°; mixed m. ps. with carbazole picrate were 158—162° (33%, carbazole picrate), 160—164° (50%), 160—164° (66%).

A mixture of carbazole (20 mg.) and 3-methylcarbazole (20 mg.) could not be separated by chromatography under the conditions employed.

4-*Methylcarbazole* (Found: *C*-Me, 5·7%). The colourless solution in sulphuric acid became ultramarine blue on the addition of nitric acid. Its alcoholic solution gave a yellow–brown coloration with *p*-nitrobenzenediazonium chloride.

From these results it appears that the degradation product contains a compound, affording acetic acid in the Kuhn–Roth estimation of side-chain methyl, other than the 10% of 3-methylcarbazole indicated by the infra-red analysis. The faint indolaceous odour and the colour reactions suggest that this may be an indole derivative, but the possibility of the presence of higher homologous carbazoles cannot be dismissed.

The residue in the flask from the degradation reaction was found to contain a fluorescent acid substance. It gave the carbazole reaction with sulphuric–nitric acid but was obtained in such small quantity that further examination was precluded. When strychnine was distilled over soda-lime at 400°, carbazole, m. p. 229—232°, could be isolated in the manner described above. The specimen had the usual faint indolaceous odour and became light brown in colour on being kept for a few days. The infra-red spectrum showed strong carbazole bands at 845 cm.$^{-1}$ and 857 cm.$^{-1}$, a weak band at 810 cm.$^{-1}$ (3-methylcarbazole, $<1\%$), and a very weak band at 787 cm.$^{-1}$, which was not found with carbazole or any of the four *C*-methylcarbazoles. A mixture of carbazole (60 mg.) and 4-methylcarbazole (40 mg.) was heated with soda-lime (30 g.) for an hour at 380—400°. The distillate was collected by means of acetone and sublimed, m. p. 192—217°; carbazole–4-methylcarbazole (62·5 : 37·5), m. p. 198—220°. Infra-red examination showed the presence of carbazole and 4-methylcarbazole, but the absence of 3-methylcarbazole could not be categorically affirmed because 4-methycarbazole has a band at 812 cm.$^{-1}$ in the vicinity of that of 3-methylcarbazole at 808 cm.$^{-1}$. However in the graph obtained there was no appreciable broadening of the 812 band towards 808.

ββ-N(b)-*Hydroxymethyldihydro*neo*strychnine.*—A Grignard solution was prepared from magnesium (13 g.), methyl iodide (23·5 c.c.), and ether (300 c.c.); after the addition of anisole (200 c.c.), the ether was distilled (bath at 100°). A solution of oxodihydro*neo*strychnine (28·5 g. of the base, 1 MeOH) in anisole (350 c.c.) was added and the whole heated for 5 hours at 100°. After being poured on ice, the product was extracted by dilute hydrochloric acid and the solution basified with ammonia (dried as a light yellow solid, 27·5 g.). A portion was crystallised from alcohol (charcoal) and from benzene–light petroleum (b. p. 80—100°) and obtained as prismatic needles, which shrank at 130°, m. p. 160° (decomp.) (Found : C, 72·5; H, 7·2. $C_{22}H_{26}O_3N_2$ requires C, 72·1; H, 7·1%). This *base* (5 g., crude) was ground with soda-lime (25 g.) and distilled at 400°, and the product from five such batches was worked up in the manner already described. The carbazole fraction had m. p. 116—200°. The infra-red spectrum showed strong bands at 810 cm.$^{-1}$ (3-methylcarbazole, *ca.* 10%), the carbazole bands at 845 cm.$^{-1}$ and 857 cm.$^{-1}$, and a very weak band at 787 cm.$^{-1}$ (see above). The absence of 4-methylcarbazole is not established owing to the possible swamping of its relatively weak characteristic bands by stronger neighbouring absorption due to carbazole and 3-methylcarbazole. The low m. p. suggests the presence of 4-methylcarbazole or of some other unidentified constituent.

4-*Chloro*-m-*tolylhydrazine.*—A hot solution of 4-chloro-*m*-toluidine (5·8 g.) in dilute hydrochloric acid (67 c.c. containing 11 c.c. of concentrated acid) was added to concentrated hydrochloric acid (107 c.c.), cooled to 0°, and diazotised by addition of sodium nitrite (3·2 g.) dissolved in a little water. The diazo-solution was poured into an ice-cold solution of stannous chloride (21 g.) in concentrated hydrochloric acid (26 c.c.). After an hour at 0° the mixture was kept for 12 hours at the room temperature, the solid collected, washed with saturated brine, and triturated with a solution of sodium hydroxide (17 g.) in water (50 c.c.). The base was collected, washed with water, and dried (3·8 g. or 59%). The *substance* crystallised from water in needles, m. p. 61° (Found : C, 53·5; H, 5·6. $C_7H_9N_2Cl$ requires C, 53·7; H, 5·8%). A mixture of *cyclo*hexanone (2·4 g.), 4-chloro-*m*-tolylhydrazine (3·6 g.), and ethanol (10 c.c.) was refluxed for an hour and added to water. The product was isolated by means of ether (yield, 4·8 g.), and it crystallised from alcohol in plates, m. p. 58°.

The crude *cyclo*hexanone 4-chloro-*m*-tolylhydrazone (from 5·7 g. of chlorotolylhydrazine) was boiled with a mixture of concentrated sulphuric acid (10 c.c.) and water (90 c.c.) for 5 minutes; chloride ion was detected in the aqueous solution. The red oil was extracted with ether leaving a pink solid (0·35 g.) which crystallised from alcohol in dark red needles, m. p. 195—197° (decomp.), and contained nitrogen and chlorine (Found : C, 66·0; H, 4·9; N, 6·1%). The nature of this compound has not been discovered. The oil from the ethereal extract was distilled, b. p. 222—223°/20 mm. (5·7 g.), and treated with light petroleum (b. p. 40—60°). An insoluble white solid residue (0·7 g.) crystallised from aqueous alcohol (charcoal) in white needles, m. p. 199—201° (decomp.) [Found : C, 76·8; H, 7·4; N, 6·9; *M* (Rast in camphor), 220. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%; *M*, 201]. The low percentage of carbon found is due to a trace of chlorine the presence of which was shown by the Beilstein test. This *compound*

(A) will be further examined. The light petroleum solution was concentrated and afforded 5·0 g. of a pale yellow solid. Recrystallisation from aqueous ethanol gave colourless needles, m. p. 64·5° (Found : C, 70·4; H, 6·5. $C_{13}H_{14}NCl$ requires C, 71·0; H, 6·4%). When the specimens of this 8-*chloro*-5-*methyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (I) were examined after a lapse of months, in order to repeat the analysis, it was found that they had decomposed with formation of dark resins.

4-*Methylcarbazole* (II).—Chloromethyltetrahydrocarbazole (0·5 g.) and palladised charcoal (0·15 g.) were heated (bath at 280—300°) in a stream of hydrogen; evolution of hydrogen chloride ceased after 2 hours.

The mass was extracted with acetone and the methylcarbazole precipitated by addition of water (0·38 g.). The *compound* crystallised from aqueous ethanol as small white needles, m. p. 115—116° (Found : C, 85·8; H 6·2. $C_{13}H_{11}N$ requires C, 86·1; H, 6·1%). The *picrate*, m. p. 160·5°, separated from benzene in red needles (Found : C, 56·0; H, 3·6. $C_{19}H_{14}O_7N_4$ requires C, 55·6; H, 3·4%). Other properties of 4-methylcarbazole are mentioned above.

When the compound (A), $C_{13}H_{15}ON$, was similarly dehydrogenated, 0·33 g. gave 0·25 g. of solid material. This crystallised from aqueous ethanol as white needles, m. p. 262° (decomp.) [Found : C, 79·2; H, 5·8; N, 7·2; *M* (Rast in camphor), 195. $C_{13}H_{11}ON$ requires C, 79·2; H, 5·6; N, 7·1%; *M*, 197]. This *substance* is isomeric with a methylphenoxazine, but phenoxazine has m. p. 156° and 2-methylphenoxazine has m. p. 123—125°, so that it is unlikely to be 3-methylphenoxazine. The only alternative we can suggest is (IV) whence the tetrahydro-derivative (A) should be (III). The stability of these substances is noteworthy.

1-*Chloro*-4-*methylcarbazole*.—Chloromethyltetrahydrocarbazole (1·5 g.) was oxidised by chloranil in xylene according to the method of Barclay and Campbell (*J.*, 1945, 530). The resultant dark oil afforded a *picrate* (2·1 g.) which crystallised from benzene in dark red needles, m. p. 154·5° (Found : C, 51·7; H, 3·3. $C_{19}H_{13}O_7N_4Cl$ requires C, 51·3; H, 2·9%). The *chloromethylcarbazole* crystallised from aqueous ethanol in slender, white needles, m. p. 70° (Found : C, 71·6; H, 4·4. $C_{13}H_{10}NCl$ requires C, 72·4; H, 4·7%).

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