S 35. *Products from the Condensation of Tolylene-2:4-diamine with the Cyanohydrins of* cyclo*Pentanone and* cyclo*Hexanone.*

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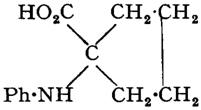
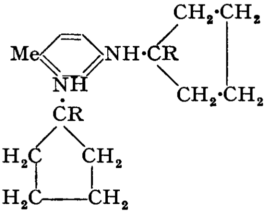
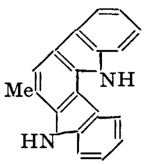
NN′-*Bis*-(1-*cyano*cyclo*pentyl*)*tolylene*-2 : 4-*diamine* and 1-o-*amino*-p-*toluidino*-1-*cyano*cyclo*pentane* have been obtained from the interaction of tolylene-2 : 4-diamine and *cyclo*pentanone cyanohydrin under different conditions. Several derivatives and substances related to these cyanides have been prepared and investigated in an attempt to synthesise a methylindolocarbazole. A study of the reaction between tolylene-2 : 4-diamine and *cyclo*hexanone cyanohydrin has given results which do not agree with earlier recorded statements.

Carbazole and its 1-methyl and 3-methyl derivatives have been obtained from 1-anilino-*cyclo*pentane-1-carboxylic acid (I) and the corresponding toluidino-compounds by fusion with potassium hydroxide, with or without the addition of sodium ethoxide (Plant and Facer, *J.*, 1925, **127**, 2037; Oakeshott and Plant, *J.*, 1926, 1210; 1927, 484). During the course of investigations directed towards the synthesis of indolocarbazoles and their simple derivatives it seemed possible that an application of this reaction to the dibasic acid (II; R = CO_2H) would lead to the compound (III).

NN′-*Bis*-(1-*cyano*cyclo*pentyl*)*tolylene*-2 : 4-*diamine* (II; R = CN) has been obtained by adding potassium cyanide to an acetic acid solution of tolylene-2 : 4-diamine and *cyclo*pentanone, but attempts to hydrolyse it directly to the acid failed, partly owing to the ease with which it is split, *e.g.*, by boiling hydrochloric acid, to give tolylene-2 : 4-diamine. The corresponding *diamide* (II; R = $CO{\cdot}NH_2$) was readily obtained from it, however, by the sulphuric acid method, but this also could not be converted into the acid. Furthermore, when the diamide was heated with potassium hydroxide in an attempt to get (III), a relatively large amount of tolylene-2 : 4-diamine distilled over, and there was no trace of an alkali-insoluble carbazole derivative in the residue.

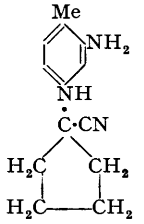

(I.)

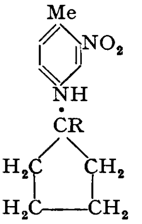

(II.)


(III.)

When a mixture of tolylene-2 : 4-diamine and *cyclo*pentanone cyanohydrin in the molecular proportions of 1 : 2 was left at room temperature, the condensation proceeded only as far as the half-way stage, and the product was shown to be 1-o-*amino*-p-*toluidino*-1-*cyano*cyclo*pentane* (IV) by synthesis from *o*-nitro-*p*-toluidine *via* 1-o-*nitro*-p-*toluidino*-1-*cyano*cyclo*pentane* (V; R = CN), which was hydrogenated catalytically.

1-o-*Nitro*-p-*toluidino*cyclo*pentane*-1-*carboxyamide* (V; R = $CO{\cdot}NH_2$), from the nitrile, could not be hydrolysed further, but 1-o-*nitro*-p-*toluidino*cyclo*pentane*-1-*carboxylic acid* (V; R = CO_2H) was readily obtained by the nitration of 1-*p*-toluidino*cyclo*pentane-1-carboxylic acid in sulphuric acid, and its structure confirmed by pyrolysis with the formation of *o*-nitro-*p*-toluidine. The acid (V; R = CO_2H) was reduced to 1-o-*amino*-p-*toluidino*cyclo*pentane*-1-*carboxylic acid.* The isomeric 1-p-*amino*-o-*toluidino*cyclo*pentane*-1-*carboxylic acid* (VI) was prepared from *p*-nitro-*o*-toluidine *via* 1-p-*nitro*-o-*toluidino*-1-*cyano*cyclo*pentane* and the corresponding *amide,* which, unlike its isomer, was readily hydrolysed to the *nitro-acid* before reduction. The acid (VI) was also very conveniently made from *p*-acetamido-*o*-toluidine through 1-p-*acetamido*-o-*toluidino*-1-*cyano*cyclo*pentane* and the corresponding *amide,* which was directly converted into the amino-acid by hydrolysis with hydrochloric acid. It was thought that these isomeric amino-acids might give aminomethylcarbazoles on fusion with potassium hydroxide, whence by a sequence of reactions similar to those outlined above the compound (III) might ultimately be obtained, but fission of the substances with the formation of tolylene-2 : 4-diamine again ensued and no appreciable quantity of a carbazole derivative was formed.


(IV.)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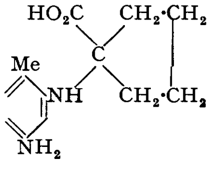
(VI.)

The reaction between tolylene-2 : 4-diamine and *cyclo*hexanone cyanohydrin has been investigated by Bucherer and Fischbeck (*J. pr. Chem.*, 1934, **140**, 69) who claim that 1-*p*-amino-*o*-toluidino-1-cyano*cyclo*hexane, m. p. 130°, was obtained by heating a mixture of the reactants in equimolecular proportions for a day on the steam-bath. There is no proof of the structure of the product other than a nitrogen analysis and such an orientation of the substituents in the benzene ring would be extremely improbable in view of the results described above. *NN'*-Bis-(1-cyano*cyclo*hexyl)tolylene-2 : 4-diamine is said to result from keeping a mixture of the diamine and cyanohydrin in the molecular proportions of 1 : 2 at room temperature for three weeks. No analysis is given for the product, m. p. 116°, but it was hydrolysed to a diamide, m. p. 207°. We have found that *NN'*-bis-(1-cyano*cyclo*hexyl)tolylene-2 : 4-diamine, which melts at 124°, can be readily prepared by treating the diamine and *cyclo*hexanone in acetic acid solution with potassium cyanide, and have transformed it into the corresponding diamide, m. p. 232—233°. A study of the reaction between the diamine and the cyanohydrin under various conditions similar to those described by Bucherer and Fischbeck has failed to give a homogeneous monocyanide, the only pure material obtained being the dicyanide, m. p. 124°.

NN'-Bis-(1-carbamyl*cyclo*hexyl)tolylene-2 : 4-diamine behaved like the analogous *cyclo*pentane derivative on fusion with potassium hydroxide and gave tolylene-2 : 4-diamine, and attempts to get the corresponding dicarboxylic acid were unsuccessful.

EXPERIMENTAL.

NN'-*Bis*-(1-*cyano*cyclo*pentyl*)*tolylene*-2 : 4-*diamine*.—Potassium cyanide (40 g.) in water (100 c.c.) was gradually added to tolylene-2 : 4-diamine (24 g.) dissolved in glacial acetic acid (280 c.c.) containing *cyclo*pentanone (40 g.), and the whole left at room temperature for 24 hours. When the product (55 g.), which separated as an oil and slowly solidified, was crystallised from acetic acid or alcohol, NN'-*bis*-(1-*cyano*cyclo*pentyl*)*tolylene*-2 : 4-*diamine* was obtained in colourless prisms, m. p. 112° (Found : C, 73·9; H, 7·8. $C_{19}H_{24}N_4$ requires C, 74·0; H, 7·8%). It was insoluble in dilute hydrochloric acid, but a salt (decomposed by water) separated when hydrogen chloride was passed into its solution in dry ether. When recrystallised from dioxan, it was obtained in colourless needles, m. p. 88—94°, containing solvent of crystallisation (Found : C, 71·3; H, 8·1; N, 16·1. $2C_{19}H_{24}N_4,C_4H_8O_2$ requires C, 71·6; H, 8·0; N, 15·9%).

After a solution of the dicyanide (2 g.) in concentrated hydrochloric acid (20 c.c.) had been refluxed for 2 hours and evaporated to dryness, the residue was dissolved in aqueous sodium hydroxide, and the whole acidified with acetic acid and shaken with acetic anhydride. A copious precipitate of *NN'*-diacetyltolylene-2 : 4-diamine, m. p. and mixed m. p. 224°, soon separated.

NN'-*Bis*-(1-*carbamyl*cyclo*pentyl*)*tolylene*-2 : 4-*diamine*.—A solution of the above dicyanide (15 g.) in concentrated sulphuric acid (150 c.c.) was left for 2 days at room temperature, poured on ice, and made alkaline with ice–concentrated ammonia. The solid (12·3 g.) was crystallised from aqueous alcohol and NN′-*bis*-(1-*carbamyl*cyclo*pentyl*)*tolylene*-2 : 4-*diamine* obtained in colourless prisms, m. p. 209° (Found : C, 66·2; H, 8·1; N, 16·2. $C_{19}H_{28}O_2N_4$ requires C, 66·3; H, 8·1; N, 16·3%). It was readily dissolved by dilute hydrochloric acid.

A mixture of the diamide (10 g.) and powdered potassium hydroxide (30 g.) was heated in a copper tube for 20 minutes at 270—300°, and the volatile products were condensed and collected. When the distillate was dissolved in dilute acetic acid, the whole shaken with ether, and the aqueous solution shaken with acetic anhydride, *NN′*-diacetyltolylene-2 : 4-diamine (2 g.), identified by mixed m. p., rapidly separated. No insoluble material remained when the alkali residue was dissolved in water.

1-o-*Amino*-p-*toluidino*-1-*cyano*cyclo*pentane*.—(*a*) When a mixture of *cyclo*pentanone cyanohydrin (6·6 g.) and tolylene-2 : 4-diamine (3·6 g.) was left at room temperature for 4 days, it partly solidified, and treatment with alcohol gave 1-o-*amino*-p-*toluidino*-1-*cyano*cyclo*pentane* (5·8 g.), which separated from alcohol in colourless prisms, m. p. 133—134° (Found : C, 72·7; H, 7·8; N, 19·1. $C_{13}H_{17}N_3$ requires C, 72·6; H, 7·9; N, 19·5%), readily soluble in dilute hydrochloric acid. The amine was ground with acetic anhydride, the mixture shaken with water for 15 minutes, and the product crystallised from alcohol; 1-o-*acetamido*-p-*toluidino*-1-*cyano*cyclo*pentane* was obtained in colourless prisms, m. p. 164° (Found : C, 70·3; H, 7·4. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·4%). When the cyanohydrin (15 g.) and diamine (7·2 g.) in dioxan (36 g.) had been kept at 40° for 10 days, and some of the solvent removed, the above amine (4 g.) again separated. After filtration and removal of all the solvent from the filtrate, treatment of the residue with dilute hydrochloric acid extracted more amine (2 g.) and left *NN′*-bis-(1-cyano*cyclo*pentyl)tolylene-2 : 4-diamine (5 g.).

(*b*) A solution of *o*-nitro-*p*-toluidine (4·5 g.) and *cyclo*pentanone (3 g.) in glacial acetic acid (30 c.c.) was treated with potassium cyanide (3 g.) in water (6 c.c.), and left for a day. The 1-o-*nitro*-p-*toluidino*-1-*cyano*cyclo*pentane* (6·5 g.), golden yellow needles, m. p. 131°, from alcohol, which gradually separated was collected after dilution with water (Found : N, 17·4. $C_{13}H_{15}O_2N_3$ requires N, 17·1%). The nitro-compound was reduced in methyl-alcoholic solution (only partly soluble) by hydrogen and Raney nickel (about 3 atmospheres) at room temperature (about an hour), and, after the filtered solution had been evaporated under reduced pressure, 1-*o*-amino-*p*-toluidino-1-cyano*cyclo*pentane remained. It was dissolved in dilute hydrochloric acid, the solution filtered and made alkaline, and the product (yield : 76%), colourless prisms, m. p. 131—132°, from alcohol, shown to be identical with the above amine by mixed m. p., and by conversion into the acetamido-compound, also identified by mixed m. p.

1-o-*Nitro*-p-*toluidino*cyclo*pentane*-1-*carboxyamide*.—Prepared from 1-*o*-nitro-*p*-toluidino-1-cyano*cyclo*pentane by a process similar to that described for *NN′*-bis-(1-carbamyl*cyclo*pentyl)tolylene-2 : 4-diamine, this *amide* separated from *iso*amyl alcohol in orange prisms, m. p. 162° (Found : N, 15·8. $C_{13}H_{17}O_3N_3$ requires N, 16·0%).

1-o-*Nitro*-p-*toluidino*cyclo*pentane*-1-*carboxylic Acid*.—Powdered potassium nitrate (15 g.) was gradually added with stirring to a solution of 1-*p*-toluidino*cyclo*pentane-1-carboxylic acid (30 g.; Oakeshott and Plant, *J.*, 1926, 1210) in concentrated sulphuric acid (300 c.c.) at room temperature. After the whole had been poured on ice, partial neutralisation of the solution with ammonia precipitated 1-o-*nitro*-p-*toluidino*cyclo*pentane*-1-*carboxylic acid*, which separated from benzene in yellow prisms (24 g.), m. p. 132° (Found : N, 10·6. $C_{13}H_{16}O_4N_2$ requires N, 10·6%). When the acid was heated for a short time at 200°, the product distilled under reduced pressure, and the distillate crystallised from water, *o*-nitro-*p*-toluidine, identified by mixed m. p., was obtained in yellow needles, m. p. 78°.

The *nitrosoamine*, precipitated when sodium nitrite was added to a solution of the nitro-acid in dilute hydrochloric acid, crystallised from aqueous alcohol in almost colourless plates, m. p. 133° (decomp.) (Found : N, 14·5. $C_{13}H_{15}O_5N_3$ requires N, 14·3%).

When the nitro-acid (1 g.) was treated in pyridine with acetyl chloride (0·5 c.c.), and dilute hydrochloric acid added after a few minutes, the *acetyl* derivative was precipitated as a gum which gradually solidified. It was obtained from alcohol in colourless plates (0·8 g.), m. p. 162° (Found : N, 9·2. $C_{15}H_{18}O_5N_2$ requires N, 9·2%).

The *methyl* ester of the nitro-acid, prepared by refluxing the acid for 4 hours with methyl-alcoholic hydrogen chloride and pouring the mixture into ammonia, crystallised from methyl alcohol in golden yellow prisms, m. p. 111° (Found : N, 10·4. $C_{14}H_{18}O_4N_2$ requires N, 10·1%).

1-o-*Amino*-p-*toluidino*cyclo*pentane*-1-*carboxylic Acid*.—A solution of 1-*o*-nitro-*p*-toluidino*cyclo*pentane-1-carboxylic acid (10 g.) in dilute ammonia was gradually added to a hot mixture obtained by adding excess of ammonia (*d* 0·88) to a boiling solution of ferrous sulphate (90 g.) in water. The whole was boiled for 15 minutes and filtered, and the filtrate evaporated under reduced pressure in an atmosphere of nitrogen. 1-o-*Amino*-p-*toluidino*cyclo*pentane*-1-*carboxylic acid* remained when the residue was washed with water, and, after crystallisation from alcohol, it was obtained in colourless needles, m. p. 163—164° (Found : N, 11·7. $C_{13}H_{18}O_2N_2$ requires N, 12·0%).

When the acid was heated with potassium hydroxide at 270—330° in a manner similar to that described in the case of *NN′*-bis-(1-carbamyl*cyclo*pentyl)tolylene-2 : 4-diamine, a substantial amount of *NN′*-diacetyltolylene-2 : 4-diamine was obtained from the distillate, while no insoluble material remained after the alkali residue had been dissolved in water.

1-p-*Nitro*-o-*toluidino*cyclo*pentane*-1-*carboxylic Acid*.—After a mixture of *p*-nitro-*o*-toluidine (20 g.), *cyclo*pentanone (12 g.), glacial acetic acid (200 c.c.), and potassium cyanide (12·8 g. in 30 c.c. of water) had been kept at 40° for 48 hours, addition of water precipitated 1-p-*nitro*-o-*toluidino*-1-*cyano*cyclo*pentane* (22 g.), which crystallised from alcohol in yellow needles, m. p. 121—122° (Found : N, 16·9%). 1-p-*Nitro*-o-*toluidino*cyclo*pentane*-1-*carboxyamide*, prepared like its isomer, separated from alcohol in yellow prisms, m. p. 153° (Found : N, 15·8%). After a solution of the amide (16 g.) in concentrated hydrochloric acid (400 c.c.) had been refluxed for an hour and evaporated to dryness on a steam-bath, the residue was treated with warm aqueous sodium hydroxide, the solution filtered, and the cold filtrate acidified with acetic acid. The precipitated 1-p-*nitro*-o-*toluidino*cyclo*pentane*-1-*carboxylic acid* (12·6 g.) crystallised from aqueous acetic acid in yellow plates, m. p. 190—193° (Found : N, 10·6%).

1-p-*Amino*-o-*toluidino*cyclo*pentane*-1-*carboxylic Acid*.—(*a*) When *p*-acetamido-*o*-toluidine (1·6 g., prepared as described by Wallach, *Annalen*, 1886, **234**, 350) and *cyclo*pentanone (1 g.) in glacial acetic acid (25 c.c.) were treated with potassium cyanide (0·75 g. in 3 c.c. of water), and the whole left at room temperature for 36 hours, 1-p-*acetamido*-o-*toluidino*-1-*cyano*cyclo*pentane* gradually separated. After addition of water, the product (yield : 75%) was crystallised from acetic acid or alcohol and obtained in colourless prisms, m. p. 180° (decomp., after sintering from 165°) (Found : C, 70·3; H, 7·6; N, 16·4. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·4; N, 16·3%). The cyanide was hydrolysed by sulphuric acid as described above to 1-p-*acetamido*-o-*toluidino*cyclo*pentane*-1-*carboxyamide* which separated from alcohol in colourless prisms (yield : 80%), m. p. 202—203° (Found : C, 65·5; H, 7·5. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·6%). When a solution of the amide in concentrated hydrochloric acid was evaporated on the steam-bath, the residue dissolved in hot aqueous sodium hydroxide, and the cold filtered solution carefully neutralised with acetic acid, 1-p-*amino*-o-*toluidino*cyclo*pentane*-1-*carboxylic acid*, colourless needles, m. p. 202° (decomp., after sintering from 180°), from alcohol, was precipitated (yield, 70%) (Found : C, 66·9; H, 8·0; N, 12·1. $C_{13}H_{18}O_2N_2$ requires C, 66·7; H, 7·7%).

(*b*) 1-*p*-Nitro-*o*-toluidino*cyclo*pentane-1-carboxylic acid was reduced by the ferrous sulphate and ammonia method described above for the isomeric acid, and the resulting amino-acid, m. p. 202° (decomp.) (Found : N, 12·3%), proved to be identical with that obtained by method (*a*).

The acid (6 g.) was heated with potassium hydroxide (21 g.) at 320—340° for 15 minutes as previously described, and *NN*′-diacetyltolylene-2 : 4-diamine (1·8 g.) was obtained from the distillate. When the alkali melt was dissolved in water, there was some insoluble material (1 g.), but this could not be obtained crystalline, and it is unlikely that it contained any appreciable quantity of 4-amino-1-methylcarbazole because it was practically insoluble in hot dilute hydrochloric acid.

NN′-*Bis*-(1-*cyano*cyclo*hexyl*)*tolylene*-2 : 4-*diamine*.—(*a*) Conditions similar to those described above for *NN*′-bis-(1-cyano*cyclo*pentyl)tolylene-2 : 4-diamine, but with *cyclo*hexanone, gave a good yield of NN′-*bis*-(1-*cyano*cyclo*hexyl*)*tolylene*-2 : 4-*diamine*, which separated from alcohol in colourless prisms, m. p. 124° (Found : C, 75·3; H, 8·4; N, 16·6. $C_{21}H_{28}N_4$ requires C, 75·0; H, 8·3; N, 16·7%). It was not dissolved by dilute hydrochloric acid.

(*b*) After a mixture of tolylene-2 : 4-diamine (6·1 g.) and *cyclo*hexanone cyanohydrin (12·5 g.) had been left at room temperature for 3 weeks with occasional shaking, a little *cyclo*hexanone was added and the whole heated for 7 hours on a steam-bath. When cold, the mixture was stirred with dilute hydrochloric acid, the aqueous solution removed by decantation, and the residue crystallised from alcohol. *NN*′-Bis-(1-cyano*cyclo*hexyl)tolylene-2 : 4-diamine (6·7 g.), m. p. 124°, identical (mixed m. p.) with the above material, was obtained.

(*c*) A mixture of tolylene-2 : 4-diamine (2·4 g.) and *cyclo*hexanone cyanohydrin (2·5 g.) was heated at 100° for 11 hours, cooled, and stirred with dilute hydrochloric acid. The insoluble product was crystallised from alcohol, and *NN*′-bis-(1-cyano*cyclo*hexyl)tolylene-2 : 4-diamine (0·3 g.), m. p. 123°, identified by mixed m. p., obtained. When the acid solution was made alkaline with ammonia, a gummy precipitate was formed, but it was not possible to isolate a homogeneous product from it. Exactly similar results were obtained after the reaction mixture had been heated for 24 hours at 100°.

NN′-*Bis*-(1-*carbamyl*cyclo*hexyl*)*tolylene*-2 : 4-*diamine*.—Prepared from the corresponding dicyanide like the other amides, this compound crystallised from aqueous alcohol in colourless needles (yield, 90%), m. p. 232—233° (Found : C, 67·4; H, 8·5; N, 14·9. Calc. for $C_{21}H_{32}O_2N_4$: C, 67 7; H, 8·6; N, 15·1%).

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