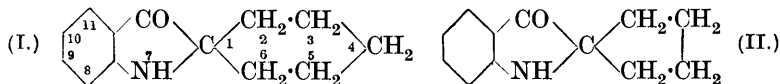


CCLXX.—*Derivatives of ψ -Indoxylspirocyclohexane.*

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It has recently been shown that ψ -indoxylspirocyclohexane (I) and ψ -indoxylspirocyclopentane (II), although having many reactions in common, differ in some respects (Betts, Muspratt, and Plant, J., 1927, 1310), and it became clear that a study of some of the derivatives of the former would be interesting. By methods similar to those used in the synthesis of (I) we have now prepared 10-*methyl*-



8-*methyl*-, 4-*methyl*-, and 8 : 10-*dimethyl- ψ -indoxylspirocyclohexane*, and have examined their reactions. The compounds (I) and (II) are each nitrated, even by dilute nitric acid, with remarkable ease to give a nitro-derivative, which, in the case of (I), is believed to be 10-nitro- ψ -indoxylspirocyclohexane. The methyl derivatives here described can all be nitrated with dilute nitric acid: the nitro-compounds form characteristic sodium derivatives in aqueous sodium hydroxide which are only sparingly soluble in cold water. The positions occupied by these nitro-groups are uncertain, but it seems probable that the 10-position is taken if possible, and the 8- if the former is not vacant. Attempts were made to reduce the nitro-group in some of these compounds with a view ultimately of introducing another substituent to give a substance which might be synthesised by methods similar to those used for making ψ -indoxylspirocyclohexane, but the isolation of the corresponding amino-compounds has not been brought about. There can, however, be little doubt that these nitro-groups are in the benzenoid part of the molecule, and this view is supported by the fact that the reactions

of these compounds, especially with aqueous sodium hydroxide, are similar to those of 1-nitro- and 3-nitro-tetrahydroacridone (Perkin and Sedgwick, J., 1924, **125**, 2438).

Although 10-methyl- and 4-methyl- ψ -indoxyldispirocyclohexane can be readily converted by acetic anhydride into the corresponding 7-acetyl compounds, acetylation of the 8-methyl and 8 : 10-dimethyl derivatives by this reagent is much more difficult and requires the presence of a little concentrated sulphuric acid. This reluctance can be ascribed to the steric effect of the methyl group in the 8-position.

The alkylated 1-anilino- ψ -cyclohexane-1-carboxylic acids, from which the ψ -indoxyldispirocyclohexane derivatives described in this paper were obtained by fusion with potassium hydroxide, all dissociate, on distillation, to yield the corresponding alkylated aniline and Δ^1 -cyclohexene-1-carboxylic acid, or, in the case of 1-anilino-4-methylcyclohexane-1-carboxylic acid, aniline and Δ^1 -tetrahydro-*p*-toluic acid. This behaviour is similar to that of 1-anilino- ψ -cyclohexane-1-carboxylic acid itself, but differs completely from that of the analogous 1-anilino- ψ -cyclopentane-1-carboxylic acid (Plant and Facer, J., 1925, **127**, 2037).

EXPERIMENTAL.

10-Methyl- ψ -indoxyldispirocyclohexane.—When a cooled solution of *p*-toluidine (24 g.) and cyclohexanone (20 g.) in glacial acetic acid (100 c.c.) was treated with a concentrated aqueous solution of potassium cyanide (16 g.), 1-*p*-toluidino-1-cyanocyclohexane separated in good yield; it was obtained from dilute alcohol in colourless needles, m. p. 76°. A solution of this nitrile (5 g.) in concentrated sulphuric acid (40 c.c.) was kept for 2 days at room temperature, then poured on ice and made alkaline with ammonia; 1-*p*-toluidino- ψ -cyclohexane-1-carboxamide separated quantitatively. It crystallised from alcohol in colourless prisms, m. p. 156°. A mixture of the amide (5 g.) and concentrated hydrochloric acid (100 c.c.) was boiled under reflux for 8 hours and then evaporated to dryness. The residue was treated with hot aqueous sodium hydroxide (8%), the solution was filtered, and then acidified with glacial acetic acid. 1-*p*-Toluidinocyclohexane-1-carboxylic acid separated in good yield and was obtained from dilute alcohol in colourless needles, m. p. 172° (Found: N, 5.8. $C_{14}H_{19}O_2N$ requires N, 6.0%). When the liquid obtained by distilling this acid from a distillation flask was treated with an excess of dilute hydrochloric acid, Δ^1 -cyclohexene-1-carboxylic acid, m. p. 29–31°, remained undissolved; the acid solution, on the addition of ammonia, yielded *p*-toluidine.

A mixture of 1-*p*-toluidinocyclohexane-1-carboxylic acid (25 g.)

and potassium hydroxide (65 g.) was heated at 350—360° for $\frac{1}{2}$ hour, allowed to cool, and then treated with an excess of water. The insoluble residue was dried over sulphuric acid in a desiccator and distilled, and the distillate crystallised from petroleum; 10-methyl- ψ -indoxylspirocyclohexane was obtained in colourless prisms, m. p. 164° (Found: N, 6.4. $C_{14}H_{17}ON$ requires N, 6.5%). On boiling its solution in an excess of acetic anhydride for an hour and shaking the cooled product with water, 7-acetyl-10-methyl- ψ -indoxylspirocyclohexane was obtained; it crystallised from methyl alcohol in colourless prisms, m. p. 144° (Found: C, 74.6; H, 7.5. $C_{16}H_{19}O_2N$ requires C, 74.7; H, 7.4%). This acetyl derivative is readily hydrolysed to the parent substance by boiling its solution in aqueous-alcoholic potassium hydroxide.

When a mixture of 10-methyl- ψ -indoxylspirocyclohexane (2 g.), water (40 c.c.), and nitric acid (10 c.c. of *d* 1.4) was boiled for 4 minutes, the solid gradually melted and a red oil appeared. The solution became yellow and, on cooling, the product appeared as a yellow solid. It was crystallised from alcohol, from which (?)8-nitro-10-methyl- ψ -indoxylspirocyclohexane separated in yellow prisms, m. p. 158° (Found: N, 10.8. $C_{14}H_{16}O_3N_2$ requires N, 10.8%).

8-Methyl- ψ -indoxylspirocyclohexane.—The preparation of this substance followed the course outlined above for the 10-methyl derivative. 1-*o*-Toluidino-1-cyanocyclohexane separated from alcohol in colourless prisms, m. p. 72°, and 1-*o*-toluidinocyclohexane-1-carboxamide from dilute alcohol in colourless prisms, m. p. 143°. It was found advantageous to boil the solution of crude 1-*o*-toluidinocyclohexane-1-carboxylic acid in very dilute aqueous sodium hydroxide for $\frac{1}{2}$ hour with charcoal and then to acidify the filtered solution gradually by adding dilute acetic acid with constant stirring. The acid separated from dilute alcohol in colourless prisms, m. p. 117° (Found: N, 6.0. $C_{14}H_{19}O_2N$ requires N, 6.0%), and, on distillation, it dissociated into *o*-toluidine, identified as aceto-*o*-toluidide, and Δ^1 -cyclohexene-1-carboxylic acid. 8-Methyl- ψ -indoxylspirocyclohexane was obtained from petroleum in colourless prisms, m. p. 197°. On boiling its solution in acetic anhydride, containing a few drops of concentrated sulphuric acid, for several hours and shaking the product with water, 7-acetyl-8-methyl- ψ -indoxylspirocyclohexane was obtained as an oily mass, which solidified on being rubbed with ether; after being distilled under reduced pressure, the solid crystallised from methyl alcohol in colourless prisms, m. p. 226° (Found: N, 5.5. $C_{16}H_{19}O_2N$ requires N, 5.4%). (?)10-Nitro-8-methyl- ψ -indoxylspirocyclohexane can be obtained by boiling 8-methyl- ψ -indoxylspirocyclohexane with dilute nitric acid, but a more convenient method is to dissolve the substance in cold, con-

centrated nitric acid and, after 5 minutes, dilute the solution with water. It separates from alcohol in pale yellow prisms, m. p. 273—274° (Found: N, 10.7. $C_{14}H_{16}O_3N_2$ requires N, 10.8%).

8 : 10-Dimethyl- ψ -indoxyldispirocyclohexane.—By methods similar to those described for the 8-methyl derivative the following products were isolated: 1-2' : 4'-Dimethylanilino-1-cyanocyclohexane from alcohol in colourless prisms, m. p. 115—116°, 1-2' : 4'-dimethylanilinocyclohexane-1-carboxamide from dilute alcohol in colourless prisms, m. p. 133°, 1-2' : 4'-dimethylanilinocyclohexane-1-carboxylic acid (which dissociated into 2 : 4-dimethylaniline and Δ^1 -cyclohexene-1-carboxylic acid on distillation) from dilute alcohol in colourless prisms, m. p. 125° (Found: N, 5.7. $C_{15}H_{21}O_2N$ requires N, 5.7%), 8 : 10-dimethyl- ψ -indoxyldispirocyclohexane from petroleum in colourless prisms, m. p. 190°, and 7-acetyl-8 : 10-dimethyl- ψ -indoxyldispirocyclohexane from methyl alcohol in colourless plates, m. p. 96° (Found: N, 5.2. $C_{17}H_{21}O_2N$ requires N, 5.2%). When a mixture of 8 : 10-dimethyl- ψ -indoxyldispirocyclohexane and dilute nitric acid was boiled for $\frac{1}{2}$ hour, a mononitro-derivative was produced and this separated from alcohol in pale yellow prisms, m. p. 183—184° (decomp.) (Found: N, 9.9. $C_{15}H_{18}O_3N_2$ requires N, 10.2%).

4-Methyl- ψ -indoxyldispirocyclohexane.—From 4-methylcyclohexanone and aniline by methods similar to those described under 10-methyl- ψ -indoxyldispirocyclohexane the following substances were obtained: 1-Anilino-1-cyano-4-methylcyclohexane from dilute alcohol in colourless needles, m. p. 107°, 1-anilino-4-methylcyclohexane-1-carboxamide from alcohol in colourless prisms, m. p. 161°, 1-anilino-4-methylcyclohexane-1-carboxylic acid from dilute alcohol in colourless prisms, m. p. 179° (Found: N, 6.2. $C_{14}H_{19}O_2N$ requires N, 6.0%), 4-methyl- ψ -indoxyldispirocyclohexane from petroleum in colourless plates, m. p. 189° (Found: N, 6.5. $C_{14}H_{17}ON$ requires N, 6.5%), 7-acetyl-4-methyl- ψ -indoxyldispirocyclohexane from methyl alcohol in colourless prisms, m. p. 102°, (?) 10-nitro-4-methyl- ψ -indoxyldispirocyclohexane from dilute alcohol in pale yellow prisms, m. p. 198° (Found: N, 10.9. $C_{14}H_{16}O_3N_2$ requires N, 10.8%), and (?) 10-nitro-4 : 7-dimethyl- ψ -indoxyldispirocyclohexane from dilute alcohol in pale yellow prisms, m. p. 141° (Found: N, 10.3. $C_{15}H_{18}O_3N_2$ requires N, 10.2%). The mixture obtained by distilling 1-anilino-4-methylcyclohexane-1-carboxylic acid, on treatment with dilute hydrochloric acid, yielded a solid which was readily soluble in aqueous sodium carbonate. This is clearly identical with the Δ^1 -tetrahydro-*p*-toluic acid of Einhorn and Willstätter (*Annalen*, 1894, **280**, 163) and of Perkin and Pickles (*J.*, 1905, **87**, 645), since it was obtained from dilute acetic acid in colourless needles, m. p.

134° (Found : C, 68.1; H, 8.4. Calc. : C, 68.6; H, 8.6%). The hydrochloric acid solution yielded aniline, identified as acetanilide, on being made alkaline with ammonia.

1-p-Aminoanilinocyclohexane-1-carboxylic Acid.—A mixture of *p*-nitroaniline (14 g.), cyclohexanone (12 g.), glacial acetic acid (200 c.c.), and potassium cyanide (10 g. in concentrated aqueous solution) was kept at 40—45° for 2 days, and then poured into dilute hydrochloric acid. *1-p-Nitroanilino-1-cyanocyclohexane*, which separated, was obtained from alcohol in pale yellow prisms, m. p. 134° (Found : N, 17.2. $C_{13}H_{15}O_2N_3$ requires N, 17.1%), and was hydrolysed in the usual way to *1-p-nitroanilinocyclohexane-1-carboxamide*, isolated from alcohol in yellow prisms, m. p. 217° (Found : N, 16.0. $C_{13}H_{17}O_3N_3$ requires N, 16.0%), and then to *1-p-nitroanilinocyclohexane-1-carboxylic acid*, which separated from dilute alcohol in yellow plates, m. p. 201° (Found : N, 10.3. $C_{13}H_{16}O_4N_2$ requires N, 10.6%). The acid (3 g.), dissolved in dilute aqueous ammonia, was added to a mixture of ferrous sulphate (28 g. in concentrated aqueous solution) and ammonia (25 c.c. of *d* 0.880) at 90—95°, and, after being shaken at that temperature for $\frac{1}{2}$ hour, the solution was filtered and just neutralised with glacial acetic acid. The *1-p-aminoanilinocyclohexane-1-carboxylic acid* which separated was obtained from aqueous pyridine in colourless needles, m. p. 216—217° (Found : N, 12.0. $C_{13}H_{18}O_2N_2$ requires N, 12.0%). The amino-acid decomposed completely on heating with potassium hydroxide alone or admixed with sodium ethoxide.

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