INDOLE DERIVATIVES

XXX. The Polyalkylation of 1,2,3,4-Tetrahydropyrrolo[3,4-b]indoles*

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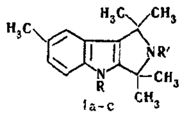
The Fischer condensation of arylhydrazones of 2,2,5,5-tetramethylpyrrolid-3-one has given 1,1,3,3-tetramethyl-7,8-benzo-1,2,3,4-tetrahydropyrrolo[3,4-b]indole and 1,1,3,3,7-pentamethyl-1,2,3,4-tetrahydropyrrolo[3,4-b]indole. On Clemmensen reduction of the latter, the pyrrole ring undergoes degradation.

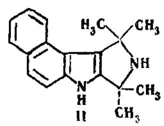
We have shown previously [1] that the Fischer cyclization of arylhydrazones of N-substituted pyrrolid-3-ones leads to the formation of 1,2,3,4-tetrahydropyrrolo[3,4-b]indoles only under strictly defined conditions. In the present work we have carried out an analogous investigation with 2,2,5,5-tetramethylpyrrolid-3-one, the cyclization of the arylhydrazones of which excluded the possibility of the formation of two series of isomers. It is known [2-4] that arylhydrazones of 2,2,6,6-tetramethylpiperid-4-one smoothly undergo cyclization to form tetrahydro-γ-carboline derivatives. The presence in 2,2,5,5-tetramethylpyrrolid-3-one of the same branching of the carbon radicals at the nitrogen atom as in the piperidone mentioned should have lowered the tendency of this ketone to undergo side reactions connected with the cleavage of the heterocycle. But, on the other hand, cyclopentanone, tetrahydrothiophen-3-one, and N-substituted pyrrolid-3-ones possess a considerably greater tendency to side reactions under the conditions of the Fischer reaction than the corresponding six-membered ketones. Consequently, no complete analogy between the cyclization of arylhydrazones of 2,2,5,5-tetramethylpyrrolid-3-one and the cyclization of arylhydrazones of 2,2,6,6-tetramethylpiperid-4-one was to be expected.

2,2,5,5-Tetramethylpyrrolid-3-one smoothly gave the corresponding arylhydrazones which, however, were unstable even in the form of the hydrochlorides and could not always be successfully analyzed, so that in a number of cases they were used in the subsequent reaction in the freshly-prepared, unrecrystallized, form.

In the cyclization of arylhydrazones of 2,2,5,5-tetramethylpyrrolid-3-one we encountered the difficulties noted previously in the case of N-substituted pyrrolid-3-ones [1]. Thus, when they were boiled with 5–20% ethanolic solutions of hydrogen chloride no separation of ammonium chloride was observed but decomposition took place with the formation of arylamines and the resinification of the reaction mixture. In the cyclization of the p-tolyl-, and p-ethoxycarbonylphenylhydrazones of 2,2,5,5-tetramethylpyrrolid-3-one, the corresponding arylamines were identified by means of thin-layer chromatography on alumina. We succeeded in performing the indolization reaction only in the case of the p-tolyl- and β-naphthylhydrazones of 2,2,5,5-tetramethylpyrrolid-3-one by boiling their hydrochlorides for 15 min with 33–35% solutions of hydrogen chloride in absolute ethanol. This gave the corresponding indoles, **Ia** and **II**, with yields of 61 and 75%, respectively:



Ia-c

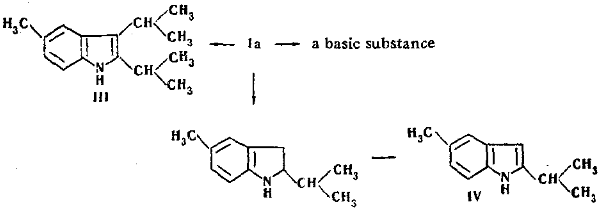


II

Ia $R = R' = H$; Ib $R = H$, $R' = CH_3$; Ic $R = CH_2C_6H_5$, $R' = H$

The pyrroloindoles **Ia** and **II** readily undergo alkylation both at the pyrrole and at the indole nitrogen atoms. For example, under the action of methyl iodide **Ia** gave **Ib**, and the alkylation of the sodium derivative of Ia with benzyl chloride in dimethylformamide gave compound **Ic**.

The Clemmensen reduction of 1,1,3,3,7-pentamethyl-1,2,3,4-tetrahydropyrrolo-[3,4-b]indole (Ia) presented independent interest, since reduction of the corresponding analogs of the tetrahydro-γ-carboline series takes place anomalously with the destruction of the piperidine ring and leads to substituted 2,3-dihydro-α-tryptamines [5]. After the Clemmensen reduction of Ia, four substances were found in the reaction product by gas-liquid chromatography. This mixture was dissolved in ether and after the extraction of the basic substances with dilute hydrochloric acid the ethereal extract yielded a compound corresponding, according to elementary analysis, to 2,3-diisopropyl-5-methylindole (III):



The hydrochloric acid solution was made alkaline and was extracted with ether. The oil remaining after the distillation of the ether was dehydrogenated by boiling in xylene over palladium black and the result-

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*For Part XXIX, see [1].

ing mixture of substances was again separated into basic and neutral fractions. The neutral fractions yielded 2-isopropyl-5-methylindole (IV), the structure of which was shown by a comparison with an authentic sample of the isomeric 3-isopropyl-5-methylindole obtained from isovaleraldehyde and p-tolylhydrazine. The basic fraction, according to gas-liquid chromatography, consisted of two substances, but these could not be separated and identified. Thus, it has been shown that the reduction of 1,1,3,3,7-pentamethyl-1,2,3,4-tetrahydropyrrolo[3,4-b]indole takes place with the destruction of the pyrrole ring.

EXPERIMENTAL

The gas-chromatographic analysis was carried out on a Khrom-2 chromatograph. The liquid phase was polyethyleneglycol 40,000 on Chromosorb W, the length of the column was 0.8 m, the carrier gas was nitrogen, and the temperature was 176° C.

Hydrochloride of the phenylhydrazone of 2,2,5,5-tetramethylpyrrolid-3-one. A mixture of 3 g (0.02 mole) of 2,2,5,5-tetramethylpyrrolid-3-one [6], 3 g (0.02 mole) of phenylhydrazine hydrochloride, and 15 ml of absolute ethanol was boiled for 30 min and, after cooling, the precipitate was filtered off and washed with absolute ether. This gave 4.7 g (83%) of the hydrazone hydrochloride with mp 242–243° C (from water). Found, %: Cl 13.10, 13.25; N 15.89, 15.97. Calculated for $C_{14}H_{21}N_3 \cdot HCl$, %: Cl 13.24; N 15.70. The base (mp 74–76° C) was unstable.

Hydrochloride of the p-ethoxycarbonylphenylhydrazone of 2,2,5,5-tetramethylpyrrolid-3-one. A mixture of 2 g (0.014 mole) of 2,2,5,5-tetramethylpyrrolid-3-one and 2.5 g (0.014 mole) of p-ethoxycarbonylphenylhydrazine in 10 ml of absolute ethanol containing 2 drops of glacial acetic acid was boiled for 30 min; after cooling it was diluted with ether and then a solution of hydrogen chloride in ethanol was added to precipitate the hydrazone hydrochloride; yield 3.6 g (77%), mp 232–234° C (decomp., from absolute ethanol with ether). Found, %: Cl 10.21, 10.28; N 12.46, 12.77. Calculated for $C_{16}H_{25}N_3 \cdot HCl$, %: Cl 10.81; N 12.82.

Hydrochloride of the p-tolylhydrazone of 2,2,5,5-tetramethylpyrrolid-3-one. Similarly, 10 g (0.071 mole) of 2,2,5,5-tetramethylpyrrolid-3-one and 10 g (0.063 mole) of p-tolylhydrazine hydrochloride in 40 ml of absolute ethanol yielded 11.7 g (66%) of the hydrazone hydrochloride; mp 223–223.5° C (decomp., from absolute ethanol). Found, %: Cl 12.59, 12.45; N 15.20, 14.98. Calculated for $C_{15}H_{23}N_3 \cdot HCl$, %: Cl 12.58; N 14.91.

Hydrochloride of the β-naphthylhydrazone of 2,2,5,5-tetramethylpyrrolid-3-one. A mixture of 1 g (0.007 mole) of 2,2,5,5-tetramethylpyrrolid-3-one and 1.38 g (0.007 mole) of β-naphthylhydrazine hydrochloride in 7 ml of absolute ethanol was boiled for 15 min and, after cooling, the precipitate was filtered off and washed with ether to give 1.2 g (87%) of the hydrazone hydrochloride with mp 226–227° C. Found, %: Cl 11.29, 11.23; N 13.11, 13.15. Calculated for $C_{18}H_{23}N_3 \cdot HCl$, %: Cl 11.16; N 13.22.

1,1,3,3,7-Pentamethyl-1,2,3,4-tetramethylpyrrolo[3,4-b]indole (Ia). A mixture of 10.5 g (0.037 mole) of the hydrochloride of the p-tolylhydrazone of 2,2,5,5-tetramethylpyrrolid-3-one and 30 ml of a 35% solution of hydrogen chloride in absolute ethanol was boiled for 10 min and then the hot solution was poured into water, the mixture was made alkaline with saturated potassium carbonate solution and after 1 hr the crystalline precipitate was filtered off. This gave 5.2 g (61.3%) of the indole Ia, mp 161–162° C (from cyclohexane). Found, %: C 78.85, 78.55; H 8.91, 9.00; N 12.88, 12.78. Calculated for $C_{15}H_{20}N_2$, %: C 78.91; H 8.83; N 12.28. Hydrochloride, mp 217–218° C (decomp., from absolute ethanol with ether). Found, %: Cl 13.02, 13.03; N 10.40, 10.47. Calculated for $C_{15}H_{20}N_2 \cdot HCl$, %: Cl 13.39; N 10.58.

1,1,3,3-Tetramethyl-7,8-benzo-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (II). A mixture of 1.2 g (3.8 mM) of the hydrochloride of the β-naphthylhydrazone of 2,2,5,5-tetramethylpyrrolid-3-one and 15 ml of 30% hydrogen chloride in absolute ethanol was boiled for 2 hr and poured into water, and the mixture was made alkaline with potassium carbonate solution. The precipitate that had deposited was filtered off, washed with water, and dried in the air to give 0.75 g (75%) of the indole II with mp 197–197.5° C (from aqueous ethanol). Found, %: C 81.25, 81.44; H 8.02, 8.12; N 10.82, 10.64. Calculated for $C_{18}H_{20}N_2$, %: C 81.77; H 7.63; N 10.59. Hydrochloride, mp 236–237° C (decomp.). Found, %: Cl 10.97, 11.14; N 9.09, 9.29. Calculated for $C_{18}H_{20}N_2 \cdot HCl$, %: Cl 11.79; N 9.30.

1,1,2,3,3,7-Hexamethyl-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (Ib). A mixture of 2 g (8.8 mM) of the pyrroloindole Ia, 8 ml of isopropanol, and 18 g (0.12 mole) of methyl iodide was kept at room temperature for 2 days. The precipitate that had deposited was filtered off and washed with cold ethanol and ether to give 2.3 g (71%) of the hydriodide of Ib, mp 196–198° C (from absolute ethanol). Found, %: I 34.48, 34.39; N 7.68, 7.60. Calculated for $C_{16}H_{22}N_2 \cdot HI$, %: I 34.28; N 7.56. 0.8 g (0.002 mole) of the hydriodide of Ib was dissolved with heating in 50 ml of water, the solution was made alkaline with potassium carbonate, and the precipitate that had deposited was filtered off, washed with water, and recrystallized from ethanol. This gave 0.4 g (77%) of the base Ib, mp 163–164° C. Found, %: C 79.13, 79.33; H 9.42, 9.30; N 11.72, 11.91. Calculated for $C_{16}H_{22}N_2$, %: C 79.29; H 9.15; N 11.56.

Hydrochloride of 1,1,3,3,7-pentamethyl-4-benzyl-1,2,3,4-tetrahydropyrrolo[3,4-b]indole (Ic). To 0.36 g (0.015 mole) of sodium hydride in 20 ml of dimethylformamide was added 2.3 g (0.01 mole) of the pyrroloindole Ia in 10 ml of dimethylformamide, the mixture was stirred at room temperature for 1 hr, and then 1.28 g (0.01 mole) of benzyl chloride was added and the mixture was heated at 60–70° C for 1.5 hr. On the following day the reaction mixture was poured into 150 ml of water and the mixture was acidified with dil (1 : 1) HCl and washed twice with ether. The acid solution was made alkaline with 20% caustic soda solution and extracted with ether. From the dried extract, a solution of hydrogen chloride in absolute ethanol precipitated the hydrochloride of Ic, yield 3.05 g (86%), mp 262–263° C, decomp., from absolute ethanol. Found, %: Cl 9.85, 10.00; N 7.96, 8.07. Calculated for $C_{22}H_{26}N_2 \cdot HCl$, %: Cl 9.99; N 7.89.

Reduction of 1,1,3,3,7-pentamethyl-1,2,3,4-tetrahydropyrrolo-[3,4-b]indole (Ia). In the presence of 0.1 g of mercuric chloride, 120 g of zinc dust, and 350 ml of conc HCl, 16 g (0.07 mole) of the pyrroloindole Ia in 80 ml of ethanol was reduced with boiling and stirring for 5 hr. The zinc dust was added at the rate of 25 g each hour, and the HCl was added dropwise at the rate of 70 ml/hr. With stirring and cooling, the mixture was made alkaline with 40% caustic soda solution until the zinc hydroxide formed had dissolved, and the oil liberated was repeatedly extracted with ether. Gas-liquid chromatography showed the presence in the ethereal extract of four substances with relative retention times (τ) of 1, 1.36, 2.9, and 4.3. The basic substances were extracted from the ethereal solution with dil HCl. The substance with τ 4.3 remained in the ethereal solution, which was then evaporated. The residue (2.9 g) crystallized on standing, mp 79–82° C (from heptane). Found, %: C 83.81, 83.82; H 9.88, 9.83; N 6.72, 6.75. Calculated for $C_{15}H_{21}N$, %: C 83.68; H 9.83; N 6.56. The elementary analysis of the substance corresponded to 2,3-diisopropyl-5-methylindole (III).

The hydrochloric acid solution was made alkaline with saturated potassium carbonate solution and extracted with ether. The ethereal extract was shown by gas chromatography to contain three substances with τ 1 (33.4%), 1.36 (26.5%), and 2.9 (8.6%). The ethereal extract was evaporated, giving 9.4 g of a viscous oil which did not crystallize on standing. This 9.4 g of basic substances was dehydrogenated by boiling in xylene over 1.2 g of palladium black for 9 hr, and the catalyst was filtered off. Gas-liquid chromatography showed the presence in the xylene solution of 3 substances with τ 1.36 (2.9%), 2.14 (34.4%), and 6.8 (62.5%). The basic substances were extracted from the xylene solution with dil (1 : 1) HCl and the xylene solution (τ 6.8) was evaporated; the residue (2.24 g) crystallized on standing, mp 76–77° C (from petroleum ether). Found, %: C 83.36, 83.06;

H 8.77, 8.88; N 8.33, 8.28. Calculated for $C_{12}H_{15}N$, %: C 83.22; H 8.70; N 8.09. The elementary analysis corresponds to 2-isopropyl-5-methylindole (IV).

The HCl solution was made alkaline with saturated potassium carbonate solution and the oil liberated was extracted with ether. After evaporation of the extract, 5.09 g of a viscous yellow oil was left which could not be fractionated on vacuum distillation. According to gas-liquid chromatography, this oil consisted of two substances (τ 1.36 and 2.14). The mixture was not studied further.

3-Isopropyl-5-methylindole. With stirring, 4.1 g (0.048 mole) of isovaleraldehyde was added to 8.5 g (0.054 mole) of p-tolylhydrazine hydrochloride in 30 ml of absolute ethanol, and the mixture was boiled for 30 min and poured into water, after which the oil that separated out was extracted with ether, and the extract was washed with 10% HCl, potassium carbonate solution, and water, and was dried and evaporated. The residue (5 g; 60%) was distilled twice. Light yellow oil with bp 110–112° C (2 mm); τ 8.2. Found, %: C 82.61, 82.58; H 9.10, 9.15; N 8.19, 8.32. Calculated for $C_{12}H_{15}N$, %: C 83.22; H 8.70; N 8.09.

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