INDOLE DERIVATIVES

XXVIII. Synthesis of Some New Polycondensed Indole Systems*

N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii

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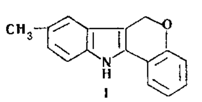
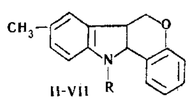
The Clemmensen reduction of 10-methylchromeno[4, 3-b]indole (I) and of 3-methyl-1, 2, 3, 4, 5, 6-hexahydroazepino[4, 5-b]indole has given 10-methyl-6b, 11b-dihydrochromano[4, 3-b]indole (II) and 3-methyl-1, 2, 3, 4, 5, 5a, 6, 10b-octahydroazepino[4, 5-b]indole, and some of their reactions have been studied. New polycyclic condensed systems have been synthesized from 6-amino-3-methyl-1, 2, 3, 4, 5, 5a, 6, 10b-octahydroazepino[4, 5-b]indole (X) and 9-amino-3-methyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XIII).

In view of the fact that the passage from condensed indole systems to the corresponding indolines considerably broadens synthetic possibilities, as has been shown, in particular, in our preceding papers [1–3], in the present work we have studied for the first time Clemmensen reduction in the pyranoindole and azepinoindole series using as examples 10-methylchromeno[4, 3-b]indole (I) and 3-methyl-1, 2, 3, 4, 5, 6-hexahydroazepino[4, 5-b]indole [4]. Substance I, obtained from p-tolylhydrazine and 4-chromanone by the Fischer reaction was converted in good yield under the action of amalgamated zinc dust and hydrochloric acid into 10-methyl-6b, 11b-dihydrochromano[4, 3-b] indole (II).

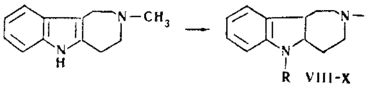

I


II-VII

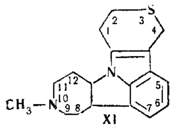
II R=H
III R=COCH$_3$
IV R=COCH$_2$CH$_2$Cl
V R=COCH$_2$CH$_2$N(C$_2$H$_5$)$_2$
VI R=NO
VII R=NH$_2$

From the indole II, the N-acyl derivatives III and IV were easily synthesized. The replacement of the halogen atom in compound IV by a diethylamino group gave the aminoacyl derivative V. The nitrosation of II in dilute sulfuric acid led to the nitrosoindoline VI, which was reduced in good yield with lithium aluminum hydride in the cold to the N-aminoindoline VII.

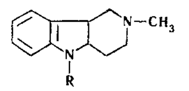
The reduction of 3-methyl-1, 2, 3, 4, 5, 6-hexahydroazepino[4, 5-b]indole took place smoothly with the formation of the indoline VIII which, in a similar manner to substance II, was nitrosated without complications to the N-nitroso derivative IX, which we then reduced with zinc in acetic acid at a low temperature to the N-amino-substituted indoline X.

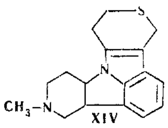

VIII R=H; IX R=NO; X R=NH$_2$

Compound X, as an arylhydrazine, was used in the Fischer reaction with tetrahydro-4-thiopyrone. Cyclization was carried out without the isolation of the corresponding hydrazone under the influence of an ethanolic solution of hydrogen chloride. This gave the five-ring condensed system XI.


XI

Similarly, from the known 3-methyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline [2], by nitrosation, reduction of the nitroso derivative (XII) and condensation of the hydrazine obtained (XIII) with tetrahydro-4-thiopyrone in ethylsulfuric acid solution, we synthesized compound XIV with a piperidine ring, which is a homolog of compound XI.


XII R=NO; XIII R=NH$_2$


XIV

Attempts to carry out the Fischer condensation with the amino derivative VII were unsuccessful.

EXPERIMENTAL

10-Methylchromeno[4, 3-b]indole (I). A mixture of 8 g (0.05 mole) of p-tolylhydrazine hydrochloride and 8 g (0.05 mole) of 4-chromanone in 15 ml of absolute ethanol was boiled for 7 min. It was poured into water, and the addition of a saturated solution of potassium carbonate liberated 5.5 g (50%) of the indole I with mp 157–158° C (from heptane). Found, %: C 81.86; H 5.60; N 6.18. Calculated for $C_{16}H_{13}NO$, %: C 81.68; H 5.56; N 5.98.

Hydrochloride of 10-methyl-6b, 11b-dihydrochromano[4, 3-b]indole (II). With stirring and boiling, 5 g (0.023 mole) of the indole I was reduced in the presence of 0.1 g of mercuric chloride in 30 ml of ethanol with 36 g of zinc dust and 84 ml of conc HCl. The zinc dust was added in 3 g portions and HCl in 7 ml portions. After the addition of all the zinc dust and HCl, the reaction mixture was made alkaline with a 50% solution of caustic potash until the zinc hydroxide formed initially had dissolved completely, the temperature during this process not being allowed to rise above 15° C. The oil that separated out was extracted with ether, and the ethereal solution was dried with anhydrous magnesium sulfate, after which the addition of a 10% solution of hydrogen chloride in absolute ethanol precipitated the hydrochloride of substance II. Yield 4 g (62.5%), mp 194–196° C (from absolute ethanol). Found, %: Cl 12.78; N 5.40. Calculated for $C_{16}H_{15}NO \cdot HCl$, %: Cl 12.94; N 5.12. **Base,** mp 89–90° C (from heptane.) Found, %: C 80.98, 81.02; H 6.31; 6.37. Calculated, for $C_{16}H_{15}NO$, %: C 80.98; H 6.37.

Hydrochloride of benzo[e]-6a, 13b-dihydrochromano[4, 3-b]indole (XVII). This was obtained in a similar manner to substance II from

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*For part XXVII, see [4].

4.5 g (0.0168 mole) of benzo[e]chromeno[4, 3-b]indole. The yield of the hydrochloride of **XVII** was 3.2 g (63%), mp 215–216.5° C (from absolute ethanol). Found, %: C 73.52, 73.54; H 5.33, 5.13; Cl 11.24, 11.18; N 4.65, 4.78. Calculated, %: $C_{19}H_{15}NO \cdot HCl$, %: C 73.86; H 5.26; Cl 11.44; N 4.52.

7-Acetyl-10-methyl-6b, 11b-dihydrochromano[4, 3-b]indole (III). A 3 ml quantity of acetic anhydride was added to 0.5 g (0.002 mole) of the chromanoindoline **II.** The temperature rose markedly, the indoline dissolved, and a new crystalline substance precipitated which was washed with water, dried, and recrystallized from absolute ethanol. Yield 0.6 g (~100%), mp 228–229° C. Found, %: C 77.53, 77.52; H 6.22, 6.32, N 5.35, 5.54. Calculated for $C_{18}H_{17}NO_2$, %: C 77.39; H 6.13; N 5.37.

7-(β-Chloropropionyl)-10-methyl-6b, 11b-dihydrochromano[4, 3-b]indole (IV). A solution of 1.18 g (0.005 mole) of the indoline **II** in 30 ml of benzene was added to a solution of 0.21 g (0.005 mole) of caustic soda in the minimum amount of water. Then, with vigorous stirring and cooling, 0.59 g (0.005 mole) of β-chloropropionyl chloride was added. The mixture was stirred for 1 hr, and then 50 ml of water was added and it was extracted with ether. The ethereal solution was dried with anhydrous magnesium sulfate and evaporated. The yield of substance **IV** was 1.3 g (86%), mp 189–189.5° C (from heptane). Found, %: Cl 10.74, 10.66; N 4.33, 4.35. Calculated for $C_{19}H_{18}ClNO_2$, %: Cl 10.81; N 4.27.

7-(β-Diethylaminopropionyl)-10-methyl-6b, 11b-dihydrochromano [4, 3-b]indole (V). A mixture of 1.1 g (0.003 mole) of substance **IV** and 2.5 ml of diethylamine in 25 ml of absolute toluene was boiled for 4 hr. The diethylamine hydrochloride that precipitated was filtered off and the toluene was distilled off to give 1.1 g (90%) of substance **V** with mp 110–112° C (from heptane). Found, %: C 75.76, 76.00, H 7.56, 7.70; N 7.65, 7.46. Calculated for $C_{23}H_{28}N_2O_2$, %: C 75.58; N 7.74 N 7.68.

10-Methyl-7-nitroso-6b, 11b-dihydrochromano[4, 3-b]indole (VI). A solution of 9 g (0.0039 mole) of the indoline **II** in 40 ml of ethanol was treated with 4.5 ml of concentrated sulfuric acid, and then, at a temperature of 0–2° C, 0.29 g (0.039 mole) of sodium nitrite in the minimum amount of water was added dropwise. The substance that separated out was filtered off and washed with water. Yield 5.5 g (57%) of the nitroso compound **VI** with mp 161–162° C (from absolute ethanol). Found, %: C 71.86; H 5.31; N 10.40. Calculated for $C_{16}H_{14}N_2O_2$, %: C 72.16; H 5.29; N 10.52.

7-Amino-10-ethyl-6b, 11b-dihydrochromano[4, 3-b]indole (VII). With stirring, a solution of 0.2 g (0.0056 mole) of lithium aluminum hydride in 30 ml of absolute ether at 10–15° C was added slowly in drops to 1.5 g (0.0056 mole) of the nitroso compound **VI** in 30 ml of absolute ether, and then the reaction mixture was stirred for 2 hr and decomposed with water. The ethereal solution was dried with anhydrous magnesium sulfate, and then the addition of a 10% solution of hydrogen chloride in absolute ethanol precipitated the hydrochloride of substance **VII.** Yield 1.35 g (83.5%), mp 162–163° C (from absolute ethanol). Found, %: Cl 12.27, 12.38; N 9.80, 9.85. Calculated for $C_{16}H_{16}N_2O \cdot HCl$, %: Cl 12.27; N 9.61. **Base,** mp 118–119° C (from heptane). Found, %: C 76.39, 76.06; H 6.56, 6.50; N 11.08, 11.14. Calculated for $C_{16}H_{16}N_2O$, %: C 76.16; H 6.39; N 11.13.

3-Methyl-1, 2, 3, 4, 5, 5a, 6, 10b-octahydroazepino[4, 5-b]indole (VIII). This was obtained in a similar manner to substance **II** from 3 g (0.015 mole) of 3-methyl-1, 2, 3, 4, 5, 6-hexahydroazepino[4, 5-b]indole. Yield 90%, mp 81–83° C (from heptane). Found, %: C 76.95, 77.27; H 9.00, 8.97; N 13.80, 13.69. Calculated for $C_{13}H_{18}N_2$, %: C 77.13; H 8.91; N 13.84.

3-Methyl-6-nitroso-1, 2, 3, 4, 5, 5a, 6, 10b-octahydroazepino[4, 5-b]indole (IX). To 2 g (0.01 mole) of the indole **VIII** were added 10 ml of water and 3 ml of conc HCl, and then, with stirring at a temperature of 0–2° C, a solution of 0.69 g (0.01 mole) of sodium nitrite in the minimum amount of water was added dropwise. The reaction mixture was stirred at 5–10° C for 1 hr and at 20° C for 2 hr. It was then poured into a saturated solution of potassium carbonate and extracted with ether. The ethereal solution was dried with anhydrous magnesium sulfate and evaporated to give 2 g (91%) of substance **IX** with mp 104–105.5° C (from cyclohexane). Found, %: N 18.14, 18.31. Calculated for $C_{13}H_{15}N_3O$, %: N 18.24.

6-Amino-3-methyl-1, 2, 3, 4, 5, 5a, 10b-octahydroazepino[4, 5-b] b]indole (X). At −7° to −12° C, g of zinc dust and 8.8 ml of acetic acid were added in small portions to a solution of 2.3 g (0.01 mole) of the nitroso compound **IX** in 17 ml of methanol. The reaction mixture was stirred for 1 hr 30 min at room temperature, decomposed with 40% of caustic potash solution with cooling, and extracted with ether. This gave 1.3 g (60%) of the amine **X**, mp 73–75° C (from heptane). Found, %: C 72.00; H 8.76; N 19.54. Calculated for $C_{13}H_{19}N_3$, %: C 71.84; H 8.83; N 19.33.

Hydrochloride of 4H, 10H-10-methyl-1, 2, 7b, 8, 9, 11, 12, 12a-octahydrothiopyrano[4', 3':4, 5]pyrrolo[3, 2, 1-h, i]azepino[4, 5-b]indole (XI). A mixture of 0.5 g (0.0023 mole) of the amine **X** and 0.27 g (0.0023 mole) of tetrahydro-4-thiopyrone in 5 ml of absolute ethanol was boiled for 15 min and was then evaporated to dryness in vacuum. The residue was treated with 7 ml of a 22.5% solution of hydrogen chloride in absolute ethanol, and the mixture was boiled for 10 min and cooled. The hydrochloride that deposited was filtered off and recrystallized twice from water. Yield 0.35 g (45.5%), mp 306–308° C (decomp.). Found, %: Cl 10.48, 10.25; N 8.52, 8.58; S 9.56, 9.37. Calculated for $C_{18}H_{22}N_2S \cdot HCl$, %: Cl 10.58; N 8.36; S 9.58. **Base,** mp 131–131.5° C (from heptane). Found, %: N 9.57, 9.52; S 10.67, 10.55. Calculated for $C_{18}H_{22}N_2S$, %: N 9.38; S 10.74.

6-(β-Diethylaminopropionyl)-1, 2, 3, 4, 5, 5a, 6, 10b-octahydroazepino[4, 5-b]indole. This was obtained in a similar manner to compound **V** from the indoline **VIII.** Mp 56–57° C (from petroleum ether). Found, %: C 72.69, 72.94; H 9.50, 9.68; N 12.59, 12.44. Calculated for $C_{21}H_{31}N_3O$, %: C 72.87; H 9.57; N 12.74.

3-Methyl-9-nitroso-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XV). This was obtained in a similar manner to the nitroso compound **IX** from 7 g (0.038 mole) of 3-methyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline. The yield was 6.5 g (78%), mp 104.5–105° C (from heptane). Found, %: C 66.12; H 7.11; N 19.35. Calculated for $C_{12}H_{15}N_3O$, %: C 66.31; H 6.95; N 19.33.

3-Amino-3-methyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XVI). This was obtained in a similar manner to the amine **VIII** from 2.1 g (0.055 mole) of the nitroso compound **XV** and 2.1 g (0.055 mole) of lithium aluminum hydride in absolute ether. Yield 11 g (98%), mp 114.5–115.5° C (from heptane). Found, %: C 70.87, 70.96; H 8.37, 8.38; N 20.66, 20.55. Calculated for $C_{12}H_{17}N_3$, %: C 70.89; H 8.43; N 20.67.

4H-9-Methyl-1, 2, 7b, 8, 9, 10, 11, 11a-octahydrothiopyrano[4', 3':4, 5]pyrrolo[3, 2, 1-h, i]pyrido[4, 3-b]indole (XIV). A mixture of 2 g (0.01 mole) of the amine **XVI** and 1.5 g (0.01 mole) of tetrahydro-4-thiopyrone was treated with 20 ml of methylsulfuric acid (60 ml of absolute ethanol and 3 ml of conc H_2SO_4). The reaction mixture was heated for 50 min, poured into water, and extracted with ether. The aqueous solution was made alkaline with potassium carbonate and the oil that separated out was extracted with ether. The ethereal extracts were dried with magnesium sulfate and evaporated. The yield of substance **XIV** was 1.7 g (61%) with mp 141–142° C (from ethanol). Found, %: N 9.85, 9.84; S 11.60, 11.50. Calculated for $C_{17}H_{20}N_2S$, %: N 9.85; S 11.27.

REFERENCES

1. N. K. Kochetkov, N. F. Kucherova, and I. G. Zhukova, ZhOKh, **31**, 924, 1961.

2. N. F. Kucherova, I. G. Zhukova, N. N. Komzolova, M. I. Petruchenko, N. M. Sharkova, and N. K. Kochetkov, ZhOKh, **31**, 930, 1961.

3. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, ZhOKh, **34**, 1614, 1964.

4. N. M. Sharkova, N. F. Kucherova, L. A. Aksanova, and V. A. Zagorevskii, KhGS [Chemistry of Heterocyclic Compounds], **5**, 81, 1969.

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Institute of Pharmacology and
Chemotherapy AMS USSR, Moscow