INTRODUCTION OF SUBSTITUENTS INTO THE BENZENE NUCLEUS OF INDOLE

XII*. CONSTRUCTION OF HETEROCYCLIC SYSTEMS FROM 5,6-SUBSTITUTED INDOLINES

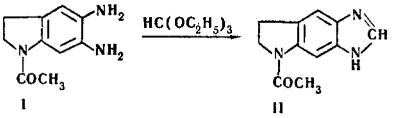
A. P. Terent'ev, E. V. Vinogradova,
V. P. Chetverikov, and S. N. Dashkevich

UDC 547.751.547.785.5.07

A number of derivatives of 6,7-dihydroimidazolo[4,5-f]indole, imidazolo[4,5-f]indole, 6,7-dihydroimidazolo[4,5-f]indol-2(3H)-one, and 6,7-dihydrotriazolo[4,5-f]indole has been synthesized from 1-acetyl-5,6-diaminoindoline and 5,6-dinitroindoline.

In preceding communications [1, 2] we have proposed methods for obtaining new heterocyclic compounds from 5,6-diaminoindole. The present paper broadens the synthesis of imidazoloindolines and also gives methods for obtaining imidazoloindoles and triazoloindoline.

It is known that the synthesis of benzimidazoles can be performed by the reaction of o-phenylenediamine both with carboxylic acids themselves and with their esters and the corresponding aldehydes [3] (in the latter case, in the presence of an oxidizing agent). The reaction of 1-acetyl-5,6-diaminoindoline (1) with acetic acid [1] and that with orthoformic ester take place with yields of about 90%.

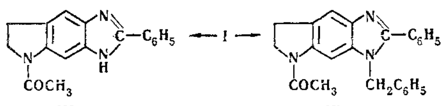


With aromatic acids, as in the synthesis of 2-aryl-substituted benzimidazoles, the reaction takes place with difficulty, under severe conditions, and with very low yields. In Weidenhagen's method [4], the reaction of benzaldehyde with o-phenylenediamine is carried out in the presence of copper acetate as oxidizing agent. However, when the copper salt formed is decomposed with hydrogen sulfide, the copper sulfide precipitating in the finely dispersed state adsorbs the reaction product, which leads to a fall in the yields. In our case, we were able to obtain only 34% of 5-acetyl-2-phenyl-6,7-dihydroimidazolo[4,5-f]-indole (III). Consequently, we have attempted to use nitrobenzene, which has been employed successfully in the synthesis of benzimidazoles [5]; this simultaneously plays the parts of oxidizing agent and solvent, and in this case it was possible to raise the yield of III to 43%. The latter method has its advantages not only because of the increase in yield, but also because of the simplicity of the isolation of the imidazole formed. Raising the temperature by 10-15°C leads to the formation of 5-acetyl-3-benzyl-2-phenyl-6,7-dihydroimidazolo[4,5-f]indole (IX).

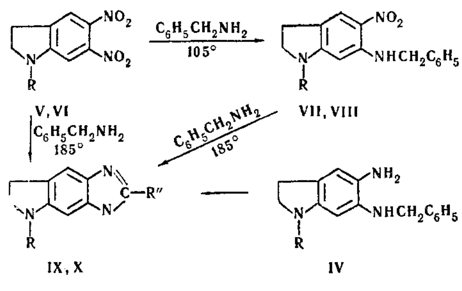
---

* For Communication XI, see [7].

Lomonosov State University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 6, pp. 770-774, June, 1970. Original article submitted September 27, 1967.



Compound IX, and also X (see below), can be obtained by a far simpler method: by boiling dinitroindoline or its acetyl derivative in benzylamine solution. First one nitro group is replaced by a benzylamine residue [7] and the remaining nitro group then plays the role of oxidizing agent. This is confirmed by the fact that compound X is also formed when 6-benzylamino-5-nitroindoline (VIII) is boiled in benzylamine solution.



IV, V, VII, IX R=COCH₃; VI, VIII, X R=H

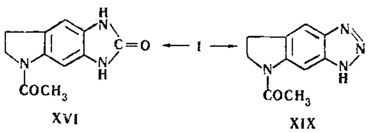
It may be assumed that the nitro group oxidizes the benzylamine to benzaldehyde and is itself reduced. The yield for compound X is about 95% and for IX only 55%, which is explained by the deacylation of IX by the more basic benzylamine. The possibility of the replacement of one nitro group of dinitroindoline by an alkylamino group enables compounds to be obtained with a strictly fixed position of the substituent from appropriately substituted aminonitroindolines [7]. As the compound to be studied we took 1-acetyl-6-benzylamino-5-nitroindoline (VII) [7]. Its reduction with hydrazine hydrate in the presence of Raney nickel in an ethanolic medium gave the aminobenzylamino derivative (IV). When IV was condensed with orthoformic ester, acetic acid, and benzaldehyde (in the presence of an oxidizing agent), we obtained the corresponding imidazole derivatives (XI, XII, and IX). The reaction with benzaldehyde took place through the intermediate formation of the benzylidene derivative (XIII), which was synthesized by the reaction of the components in an ethanolic medium in the absence of an oxidizing agent with 87% yield. When it was heated with nitrobenzene, compound IX was again obtained.

It is known that the dehydrogenation of N-acetylated indolines to indole derivatives takes place with difficulty and requires special conditions. Consequently, we performed the hydrolysis of the N-acetylated indolinoimidazoles. The hydrolysis of 5-acetyl-6,7-dihydroimidazolo[4,5-f]indole (II) took place readily, but the precipitate obtained could not be purified to the analytical state, and it was identified in the form of the dipicrate (XVIII). We studied the dehydrogenation reaction on 2-methyl-6,7-dihydroimidazolo[4,5-f]indole, the purification of which presented no difficulties. The best dehydrogenation conditions were found to be 8 h boiling in diethyleneglycol in the presence of palladium black. This gave a 57% yield of 2-methylimidazolo[4,5-f]indole (XV), the formation of which was confirmed by analytical results and by a comparison of the UV spectrum with the spectrum of the corresponding indole derivative.

In comparing the spectra it was observed that the short-wave absorption band corresponding to the $A_{1q} \rightarrow B_{2u}$ benzene transition was shifted somewhat, and the long-wave band had undergone a hypsochromic shift and its intensity had risen.

Like o-phenylenediamines, 1-acetyl-5,6-diaminoindoline reacts with urea and nitric acid with the formation of 5-acetyl-6,7-dihydroimidazolo[4,5-f]indol-2(3H)-one (XVI) and 5-acetyl-6,7-dihydrotriazalo-[4,5-f]indole (XIX).

All the tricyclic compounds obtained fluoresce in solutions in incident UV light.



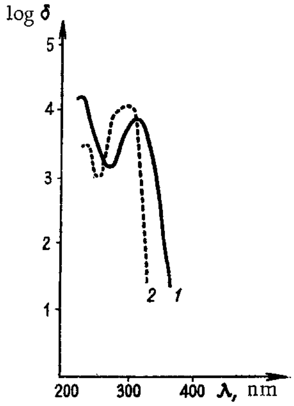


Fig. 1. UV spectra: 1) 2-methyl-6,7-dihydroimidazolo-[4,5-f]indole (XIV); 2) 2-methylimidazolo[4,5-f]-indole (XV).

EXPERIMENTAL

5-Acetyl-6,7-dihydroimidazolo[4,5-f]indole (II). A mixture of 6.3 g (0.33 mole) of 1-acetyl-5,6-diaminoindoline (I) and 32 ml (0.193 mole) of orthoformic ester was heated in the boiling water bath for 4 h, the ethanol formed being distilled off, and was then cooled and filtered, and the residue was washed with ether. Yield 5.9 g (89%). Light yellow almost white crystals with mp 232-233.5°C (from methanol), insoluble in ether, benzene, and acetone; sparingly soluble in water and methanol (better in the hot), readily soluble in dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 272 (3.75), 305-314 (4.00) (in dimethylformamide). Found, %: C 65.4; 65.5; H 5.6; 5.6. $C_{11}H_{11}N_3O$. Calculated, %: C 65.7; H 5.5.

5-Acetyl-2-phenyl-6,7-dihydroimidazolo[4,5-f]indole (III). a) A solution of 5.44 g (0.03 mole) of copper acetate in 88 ml of 50% aqueous methanol was treated with 2.6 g (0.0136 mole) of I and 2.2 ml (0.02 mole) of benzaldehyde in 16 ml of methanol, and the mixture was boiled for 3 h, poured into 200 ml of water, and left overnight. The precipitate was separated off in the centrifuge, washed with water, and suspended in 75 ml of methanol, and then hydrogen sulfide was passed through the suspension for 3 h, after which it was purged with air. The copper sulfide was filtered off and washed several times with hot dimethylformamide. The filtrates were combined and evaporated to small volume. The precipitate was filtered off and washed with a small amount of ether. This gave 1.1 g (34.6%) of white crystals with mp 299.5-301.5°C (from methanol). Insoluble in ether, benzene, and acetone. Sparingly soluble in methanol, soluble in dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 337 (4.41) (in dimethylformamide). Found, %: N 14.9; 15.0. $C_{17}H_{15}N_3O$. Calculated, %: N 15.2.

b) A solution of 1.8 ml (0.017 mole) of benzaldehyde in 15 ml of methanol was slowly added to a suspension of 3.2 g (0.0167 mole) of I in 45 ml of methanol cooled to −10°C, and then 7 ml of nitrobenzene was added and the mixture was boiled for 8-10 h. On cooling, a precipitate deposited, and this was filtered off and washed with a small amount of methanol. Yield 1.85 g (43%), mp 299.5-301.5°C (from methanol).

1-Acetyl-5-amino-6-benzylaminoindoline (IV). A suspension of 3.1 g (0.0097 mole) of 1-acetyl-6-benzylamino-5-nitroindoline [7] in 180 ml of methanol was treated with 1.5 g of a paste of Raney nickel, and the mixture was heated to 40°C, treated with 11.6 ml (0.2 mole) of hydrazine hydrate, and boiled for 2 h. Then the hot solution was treated with activated carbon, the filtrate was evaporated in vacuum almost to dryness, the residue was cooled, and the precipitate was filtered off. This gave 2.3 g (81.5%) of a product with mp 191-193°C (from methanol, in a sealed capillary). White crystals, insoluble in ether and acetone, sparingly soluble in cold methanol, soluble in dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 272-280 (4.07), 330-336 (3.93) (in dimethylformamide). Found, %: C 72.4; 72.6; H 6.8; 6.7. $C_{17}H_{19}N_3O$. Calculated, %: C 72.6; H 6.8.

5-Acetyl-3-benzyl-2-phenyl-6,7-dihydroimidazolo[4,5-f]indole (IX). a) Solution of 2 g (0.01 mole) of copper acetate in 70 ml of 5% aqueous methanol was treated with 1.8 g (0.0064 mole) of I and 1.3 ml (0.0128 mole) of benzaldehyde in 6 ml of methanol. The reaction and the isolation of the IX were carried out as for III (method "a"). This gave 1.35 g (76.6%) of IX, with mp 257-258.5°C (from dimethylformamide, using activated carbon and a small amount of alumina). White crystals, insoluble in ether, benzene, acetone, and methanol, sparingly soluble in cold dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 279 (4.08); 325-329 (4.55) (in dimethylformamide). Found, %: C 78.1; 78.2; H 6.0; 6.0. $C_{24}H_{21}N_3O$. Calculated, %: C 78.4; H 5.8.

b) A mixture of 1.12 g (0.004 mole) of IV and 6 ml of methanol was cooled to 0°C, and 0.435 g (0.004 mole) of benzaldehyde in 2 ml of methanol was slowly added. The reaction mixture was kept at 0°C for 5 min, and then 12 ml of nitrobenzene was slowly added and it was boiled in the water bath for 4 h 30 min. After cooling, the yellowish precipitate that had deposited was filtered off and washed with ether. This gave 0.959 g (65%) of a product with mp 257.5-259°C.

c) A mixture of 0.289 g (0.78 mmole) of 1-acetyl-6-benzylamino-5-benzylideneiminoindoline (XIII) and 4 ml of nitrobenzene was heated in the boiling water bath for 4 h 30 min. After cooling, 0.237 g (82.6%) of IX with mp 257-258.5°C was obtained.

d) A suspension of 6.5 g (0.034 mole) of I in 30 ml of methanol was cooled to 0°C, and, with stirring, 7 ml (0.068 mole) of benzaldehyde and then 15 ml of nitrobenzene were added. The mixture was carefully heated to the boil and kept for 20 min. After cooling, 6.25 g (50%) of IX with mp 257-258.5°C was obtained.

e) A mixture of 3 g (0.0119 mole) of 1-acetyl-5,6-dinitroindoline and 8 ml (0.075 mole) of benzylamine was boiled for 1 h-1 h 30 min and cooled, and then 10 ml of ether was added and the precipitate was filtered off. This gave 2.45 g (55%) of IX, with mp 257-258°C.

3-Benzyl-2-phenyl-6,7-dihydroimidazolo[4,5-f]indole (X). a) A mixture of 1 g (0.0048 mole) of 5,6-dinitroindoline [1] and 8 ml (0.075 mole) of benzylamine was boiled for 3 h and cooled, and 50 ml of ether was added to the dark red, almost black, mass. On trituration, white crystals separated out. Yield 1.23 g (94.5%) mp 219-220°C (from ethanol). White needles, insoluble in water, sparingly soluble in alcohols and ether. The substance can be recrystallized from dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 328 (3.89) (in methanol). Found, %: C 81.1; 81.3; H 6.1; 6.0; N 13.0; 12.8. $C_{22}H_{19}N_3$. Calculated, %: C 81.2; H 6.1; N 12.9.

b) A solution of 1 g (2.13 mmoles) of IX in 10 ml of conc. HCl was boiled for 1 h 30 min. Then it was cooled and neutralized with 30% caustic soda solution, and the precipitate that had deposited was filtered off. This gave 0.91 g (quantitative yield) mp 219-220°C.

5-Acetyl-3-benzyl-6,7-dihydroimidazolo[4,5-f]indole (XI). This was obtained from 0.58 g (0.002 mole) of IV and 15 ml (0.09 mole) of orthoformic ester in a similar manner to II. Yield 0.4 g (72.4%), mp 203-204°C (from methanol). Almost colorless crystals, insoluble in ether, benzene and acetone, and sparingly soluble in cold methanol. UV spectrum, λ_{max}, nm (log ε): 276 (4.00), 315 (4.01) (in dimethylformamide). Found, %: C 73.8; 74.0; H 5.9; 6.0; N 14.7; 14.5. $C_{18}H_{17}N_3O$. Calculated, %: C 74.2; H 5.9; N 14.4.

5-Acetyl-3-benzyl-2-methyl-6,7-dihydroimidazolo[4,5-f]indole (XII). A solution of 1.5 g (0.0053 mole) of IV in 13.6 ml of glacial acetic acid was boiled for 5h, treated with activated carbon, and, with ice cooling, neutralized with aqueous ammonia. The precipitate that deposited was filtered off and was washed with 35 ml of water. This gave 1.5 g (92%) of product with mp 222-223.5°C (from dimethylformamide). White crystals insoluble in ether, benzene, and acetone, sparingly soluble in methanol, and soluble in acetic acid and dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 276 (3.90), 310-315 (4.18) (in dimethylformamide). Found, %: C 74.2; 72.3; H 6.4; 6.4; N 13.6. $C_{19}H_{19}N_3O$. Calculated, %: C 74.7; H 3.3; N 13.8.

1-Acetyl-6-benzylamino-5-benzylideneiminoindoline (XIII). A suspension of 1.12 g (0.004 mole) of IV in 6 ml of methanol was cooled to 0°C, and 0.435 g (0.004 mole) of benzaldehyde in 2 ml of methanol was added slowly. The mixture was kept for 5 min, and was then boiled for 10 min, and, after cooling, the precipitate was filtered off and washed with ether. This gave 1.28 g (87%) of XIII, mp 200-202°C (from dimethylformamide, in a sealed capillary); bright yellow needles soluble in ether and acetone, and sparingly soluble in dimethylformamide. UV spectrum, λ_{max}, nm (log ε): 270 (4.56), 425-440 (4.05) (in dimethylformamide). Found, %: C 77.8; 77.9; H 6.2; 6.3. $C_{24}H_{23}N_3O$. Calculated, %: C 78.0; H 6.3.

2-Methyl-6,7-dihydroimidazolo[4,5-f]indole (XIV). A solution of 1.72 g (0.008 mole) of 5-acetyl-2-methyl-6,7-dihydroimidazolo[4,5-f]indole [1] in 14 ml of conc. HCl was heated in the boiling water bath for 1 h, treated with activated carbon, and, with ice cooling, neutralized with caustic soda solution. The white precipitate that deposited was filtered off and washed with 3 ml of water. This gave 1.25 g (91.7%) of XIV, mp 238-239.5°C (from water, in a sealed capillary). White crystals soluble in alcohols and dimethylformamide, insoluble in ether, hydrocarbons, and benzene. UV spectrum, λ_{max}, nm (log ε): 237 (3.62), 280 (3.91), 307 (2.35) (in 0.01 N HCl). Found, %: C 69.0; 68.9; H 6.1; 6.2. $C_{10}H_{11}N_3$. Calculated, %: C 69.3; H 6.4.

2-Methylimidazolo[4,5-f]indole (XV). A solution of 1 g (0.0058 mole) of XIV in 2.5 ml of diethyleneglycol was boiled with 50 mg of palladium black for 9 h and cooled, 20 ml of water was added, and it was extracted with ether. The extract was dried with calcium chloride and evaporated to dryness. Yield 0.56 g (57%), mp 247.5-249°C (from aqueous ethanol, in a sealed capillary). Light grey crystals, sparingly soluble in water and ether, readily soluble in alcohols. UV spectrum, λ_{max}, nm (log ε): 299 (4.14) (in ethanol). Found, %: C 70.6; 70.4; H 5.6; 5.6. $C_{10}H_9N_3$. Calculated, %: C 70.2; H 5.3.

6,7-Dihydroimidazolo[4,5-f]indol-2(3H)-one (XVI). A mixture of 3.1 g (0.0162 mole) of I and 1.17 g (0.019 mole) of urea was heated in an atmosphere of nitrogen at 180-190°C for 15 h. After cooling, 50 ml of ethanol was added to the reaction mixture and it was then heated to the boil and filtered hot. Yield 3.1 g (83.5%). Light grey crystals insoluble in ether and ethanol, sparingly soluble in dimethylformamide, mp above 380°C (from dimethylformamide). UV spectrum, λ_{max}, nm (log ε): 271 (4.05), 318 (4.13) (in dimethylformamide). Found, %: C 60.4; 60.6; H 5.0; 5.1. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.8; H 5.1.

6,7-Dihydroimidazolo[4,5-f]indole (XVII). This was obtained in a similar manner to XIV from II. Yield 87.5%, mp 176.5-178.5°C. Light grey crystals soluble in water, acetone, alcohols, and dimethylformamide, and insoluble in ether, hydrocarbons, and benzene.

Dipicrate of XVII – yellow crystals, very sparingly soluble in hot methanol, mp 200-201°C (in a sealed capillary). Found, %: C 40.8; 40.9; H 2.9; 2.8. $C_9H_9N_3 \cdot 2C_6H_3N_3O_7$. Calculated, %: C 40.8; H 2.44.

5-Acetyl-6,7-dihydrotriazolo[4,5-f]indole (XIX). A suspension of 3 g (0.0157 mole) of I in 1.8 ml of acetic acid and 4.7 ml of water was cooled to −5°C, and a solution of 1.8 g (0.017 mole) of sodium nitrite in 1.88 ml of water was slowly added. The temperatures of the reaction mixture rose spontaneously to 75°C. It was heated to 80°C for 1 h and cooled, and the light yellow crystalline precipitate was filtered off. Insoluble in boiling toluene and ether; it dissolves in methanol on heating but reprecipitates only on dilution with water. Yield 2.85 g (90%), mp 241-242.5°C (from water). UV spectrum, λ_{max}, nm (log ε): 303 (4.04), 315 (4.03) (in methanol). Found, %: C 59.7; 59.5; H 5.2; 5.2. $C_{10}H_{10}N_4O$. Calculated, %: C 59.9; H 5.0.

The UV spectra were recorded on an SF-4A instrument.

LITERATURE CITED

1. A. P. Terent'ev, E. V. Vinogradova, V. P. Chetverikov, and V. S. Lenenko, KhGS [Chemistry of Heterocyclic Compounds], 5, 258, 1969.
2. A. P. Terent'ev, E. V. Vinogradova, V. P. Chetverikov, and V. S. Lenenko, KhGS [Chemistry of Heterocyclic Compounds], 5, 262, 1969.
3. I. W. Wright, Chem. Rev., 48, 466, 1951.
4. R. Weidenhagen, Ber., 69, 2263, 1936.
5. D. Jerchel, H. Fischer, and M. Kracht, Ann., 575, 162, 1951.
6. N. Rao and C. Ratman, J. Ind. Chem. Soc., 38, 631, 1961.
7. A. P. Terent'ev, E. V. Vinogradava, V. P. Chetverikov, and S. N. Dashkevich, KhGS [Chemistry of Heterocyclic Compounds], 6, 161, 1970.