7-AZAINDOLE DERIVATIVES

# XIX. Synthesis and Some Transformations of 2-Phenyl-4-(1'-Phenyl-4'-Methyl-7'-Azaindolyl-3'-Methylene)-1,3-Oxazol-4-One*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 1, pp. 141–144, 1967

UDC 547.78+547.836+543.422

A study is made of new synthetic routes, based on accessible 3-formyl-7-azaindoles, to 3-substituted 7-azaindole. 2-Phenyl-4-(1'-phenyl-4'-methyl-7-azaindolyl-3'-methylene)-1, 3-oxazol-5-one is synthesized, and it is converted to 1-phenyl-4-methyl-7-azatryptophane, 1-phenyl-4-methyl-7-azaindolyl-3-acetic acid, 1-phenyl-3-(β, γ-dihydroxypropyl)-4-methyl-7-azaindole, and 1-phenyl-4-methyl-7-azaindolyl-3-pyrotartaric acid.

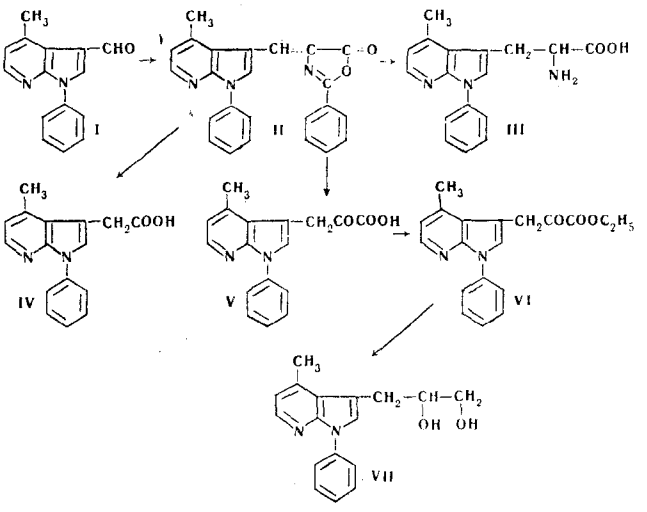
The previously developed general method [2, 3] for introducing the formyl group at position 3 in the 7-azaindole ring, revealed new possibilities of synthesizing 3-substituted 7-azaindoles. The accessibility of 3-formyl-7-azaindoles was of particular interest in connection with the feebler alkylating properties of 7-azagramines as compared with the analogous indole derivatives [4]. The reaction of 3-formyl-7-azaindoles with nitroalkanes, malonic ester, and diethyl ethoxycarbonylmethylphosphonate followed by transformations of the resultant products, provided routes to various 3-aminoalkyl-7-azaindoles [4–6], to derivatives of 7-azaindolyl-3-propionic and acrylic acids [3], as well as to other aza-analogs of indole-series biologically active compounds.

The present paper deals with further synthetical researches based on 1-phenyl-3-formyl-4-methyl-7-azaindole (I) [3].

Study of the condensation of I with the acid group showed that 2-phenyl-4-(1'-phenyl-4'-methyl-7'-azaindolyl-3'-methylene)-1,3-oxazol-5-one (II) is formed in 54% yield by 6 hours refluxing of the reactants in acetic anhydride in the presence of fused sodium acetate. Both cutting the reaction time and leaving out the sodium acetate cut the yield of II.

The azalactone II synthesized was used to prepare a series of 3-substituted 1-phenyl-4-methyl-7-azaindoles. Reduction of II with hydriodic acid and red phosphorus gave 1-phenyl-4-methyl-7-azatryptophane (III), isolated in 80% yield as its dihydroiodide. The free amino acid and its dihydrochloride were prepared from III dihydriodide.

Acid or alkaline hydrolysis of II gives 1-phenyl-4-methyl-7- azaindolyl-3-pyrotartaric acid (V). The highest yield of keto-acid V (76%) was observed in acid hydrolysis. Keto-acid V was converted via its acid chloride into ethyl 1-phenyl-4-methyl-7-azaindolyl-3-pyrotartrate (VI). Simultaneous lithium aluminum hydride reduction of ester and keto groups in the ketoester VI



made it possible to pass to a 7-azaindole derivative of propylene glycol, 1-phenyl-3-(β, γ-dihydroxypropyl)-4-methyl-7-azaindole (VII).

Azalactone II also proved to be a convenient intermediate for the synthesis of 1-phenyl-4-methyl-7-azaindolyl-3-acetic acid (IV). The yield of IV obtained by alkaline hydrolysis of the azalactone II followed by hydrogen peroxide oxidation of the reaction products was 76.5%. Acid IV was identified as being identical with the compound previously synthesized [4] from 1-phenyl-3-chloromethyl-4-methyl-7-azaindole by reacting it with acetone cyanohydrin, followed by saponification of the resultant nitrile with concentrated hydrochloric acid.

## EXPERIMENTAL

**2-Phenyl-4-(1'-phenyl-4'-methyl-7'-azaindolyl-3'-methylene)-1, 3-oxazol-5-one (II).** 7.1 g (0.003 mole) 1-Phenyl-3-formyl-4-methyl-7-azaindole (I) [3], 4.9 g hippuric acid, 2.4 g fused NaOAc, and 20 ml distilled $Ac_2O$ were refluxed together for 6 hr. The mixture became homogeneous and turned red. On cooling crystals of II separated, they were filtered off, and washed with benzene, EtOH, and water. Yield 6.2 g (54%). Orange-red crystals, mp 222°. The compound was only very slightly soluble in ether, benzene, alcohols, EtOAc, and water, but was readily soluble in $CHCl_3$. Found: C 75.78; H 4.61; N 11.17%. Calculated for $C_{24}H_{17}N_3O_2$. C 75.99; H 4.48; N 11.08%. The mother liquor remaining after removing II was vacuum-evaporated to dryness. The residue was washed with ether, then with 8% $NaHCO_3$ solution, and finally with water, to give 1.2 g (17%) I, mp 126–128°. Cutting reaction time to 4 hr cut the yield of II to 50.5%, and omitting the NaOAc (4 hr) cut it to 38.5%.

*For Part XVIII see [1].

**1-Phenyl-4-methyl-7-azaindolyl-3-pyrotartaric acid (V).** a) A mixture of 0.8 g (0.002 mole) azalactone II, 8 ml glacial AcOH, and 2 ml concentrated HCl was refluxed for 3 hr, and the products vacuum-evaporated to dryness. The residue was extracted with ethanol, and recrystallized from HCl, to give 0.58 g (76%) hydrochloride of V, forming colorless crystals, mp 218–220° (decomp.). The compound was insoluble in ether, acetone EtOAc, benzene $CHCl_3$, and water, slightly soluble in alcohols. Found: C 61.83; H 4.67; Cl 10.78; 11.11; N 8.49; 8.60%. Calculated for $C_{17}H_{14}N_2O_3 \cdot C$ 61.72; H 4.53; Cl 10.75; N 8.47%.

Recrystallization of V hydrochloride from EtOH gave the free keto-acid V, mp 238–239° (decomp.). Found: C 69.31; 69.29; H 4.99; 4.90; N 9.49; 9.46%. Calculated for $C_{17}H_{14}N_2O_3$. C 69.38; H 4.76; N 9.53%. b) 8 ml 10% aqueous KOH was added to 0.8 g (0.002 mole) azalactone II, and the mixture refluxed for 3 hr. The resultant solution was washed with benzene, and then made acid to Congo red with AcOH. The precipitate of V was filtered off, and washed with EtOH, yield 0.39 g (63%), mp 238–239° (decomp., ex EtOH). IR spectrum*: 3390, 1692, 1646 $cm^{-1}$ (–COCOOH), UV spectrum: $\lambda_{max}$, mμ (lg ε): 226 (4.11), 265 (4.17), 317 (4.11), 336 (4.06). Found: C 69.33, 69,20; H 5.00, 5.18; N 9.42%. Calculated for $C_{17}H_{14}N_2O_3$. C 69.38; H 4.76; N 9.53%.

**Ethyl 1-phenyl-4-methyl-7-azaindolyl-3-pyrotartrate (VI).** 0.33 g (0.001 mole) V hydrochloride was heated with 3 ml purified $SOCl_2$ for 5 hr at 60° (in bath). Gradually the solid acid V dissolved and was converted to acid chloride. The solution was then vacuum-evaporated, and traces of $SOCl_2$ removed by adding 5 ml dry benzene and vacuum-distilling it off three times. 3 ml dry EtOH was added to the resultant V acid chloride, the whole refluxed for 6 hr, the products vacuum-evaporated to dryness, the residue made alkaline with 25% $K_2CO_3$ solution, and VI extracted with ether. The ether solution was dried over $K_2CO_3$, and vacuum-evaporated, to give 0.23 g (72%) VI. VI hydrochloride formed colorless crystals, mp 184–185° (ex ETOAc). Readily soluble in water, alcohols, and acetone, slightly soluble in EtOAc, insoluble in ether. IR spectrum: 1648, 1739 $cm^{-1}$ (–$COCOOC_2H_5$). Found: C 63.34; H 5.05; Cl 10.01; N 8.02%. Calculated for $C_{19}H_{18}N_2O_3 \cdot HCl$. C 63.60; H 5.30; Cl 9.90; N 7.81%.

1-Phenyl-3-(β, γ-dihydroxypropyl)-4-methyl-7-azaindole (VII). A solution of 1.7 g (0.005 mole) ketoester VI in 50 ml dry ether was added to 1 g (0.03 mole) $LiAlH_4$, and the whole refluxed for 4 hr. The products were decomposed with 1 ml water, extracted with ether, the ether extracts dried over $K_2CO_3$, and vacuum-evaporated, to give 0.98 g (66%) VII, colorless crystals, mp 75–76° (ex heptane). Readily soluble in the usual organic solvents, slightly soluble in water and heptane. The IR spectrum has a band at 3300–3400 $cm^{-1}$ region. Found: C 71.98; H 6.56; N 10.09%. Calculated for $C_{17}H_{18}N_2O_2$. C 72.34; H 6.38; N 9.93%.

**1-Phenyl-4-methyl-7-azaindolyl-3-acetic acid (IV).** 0.8 g (0.002 mole) azalactone II and 8 ml 10% aqueous NaOH was refluxed for 2 hr, the products cooled to room temperature, and 25 ml 10% $H_2O_2$ added. Foaming took place. The mixture was left overnight at room temperature, then made acid to Congo red with acetic acid. The precipitate of IV was filtered off, washed with water, dried, dissolved in acetone, and IV hydrochloride precipitated by adding ethanolic HCl. Yield 0.49 g (76.5%) IV hydrochloride, mp 203–204° [4], undepressed mixed mp with IV hydrochloride prepared from 1-phenyl-3-chloromethyl-4-methyl-7-azaindole by reacting it with acetone cyanohydrin, with subsequent saponification of the resultant 1-phenyl-4-methyl-7-azaindolyl-3-acetonitrile with conc TiCl [4]. The IR spectra of the two specimens of IV hydrochloride were identical.

**1-Phenyl-4-methyl-7-azatryptophane (III).** 10 ml freshly distilled 48% HI was added to a mixture of 0.38 g (0.001 mole) azalactone II, 0.1 g red P, and 2 ml $Ac_2O$, when there was marked evolution of heat, and frothing. The mixture was refluxed for 6 hr, cooled to room temperature, the phosphorus filtered off, washed with 2 ml 48% HI, the filtrate vacuum-evaporated, to give 0.44 g (80%) III dihydriodide, as pale yellow crystals, mp 244–245° (decomp.). Soluble in alcohols and water, insoluble in ether, acetone, EtOAc, benzene and $CHCo_3$. Found: C 36.98; 36.88; H 3.45; 3.60; N 7.54; 7.80; I 46.13%. Calculated for $C_{17}H_{17}N_3O_2 \cdot 2HI$: C 37.02; H 3.45; N 7.62; I 46.10%.

0.27 g III dihydriodide was dissolved in 5 ml water, to give a solution pH 1, which was brought to pH 5 with 6% $NaHCO_3$ solution. The precipitate of III was filtered off, washed with water and acetone, yield 0.12 g (81%) free amino acid III, colorless crystals, mp 238° (decomp.). Readily soluble in benzene, slightly soluble in EtOH and dioxane, insoluble in water, ether, acetone, EtOAc, and $CHCl_3$. For analysis the compound was dried in a vacuum-pistol ($P_2O_5$, 100°, 5 mm, 12 hr). Found: N 14.12, 14.07%. Calculated for $C_{17}H_{17}N_3O_2$. N 14.24%.

**III Dihydrochloride,** colorless crystals, mp 265° (decomp.), readily soluble in water, slightly soluble in alcohols, insoluble in ether, EtOAc, benzene, $CHCl_3$, and acetone. Found: N 10.18, 10.13; Cl 17.79; 17.64%. Calculated for $C_{17}H_{17}N_3O_2 \cdot 2HCl \cdot 2H_2O$. N 10.39; Cl 17.57%.

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*All IR spectra were measured with a UR-10 spectrophotometer, using vaseline mulls. UV spectra were measured with a SF-4 instrument, in ethanol.

11 April 1965

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