INDOLE DERIVATIVES

XCI.* 3-INDOLYLPHENYLACETIC ACID

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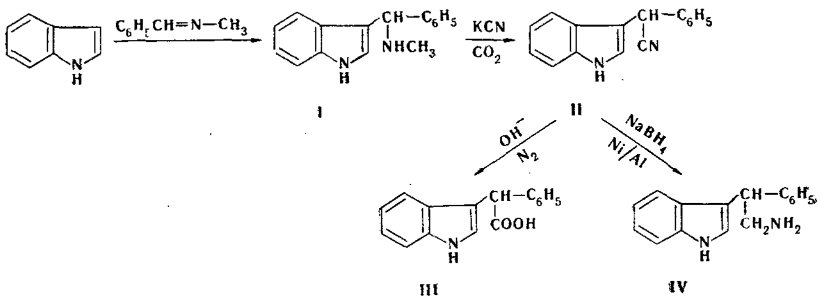
Reaction of 3-(α-methylaminobenzyl)indole (I) with potassium cyanide in a stream of carbon dioxide gave 3-indolylphenylacetonitrile (II), which was converted to 3-indolylphenylacetic acid (III) by alkaline hydrolysis. The acid has herbicidal action but does not have an antibacterial effect.

Replacement of one of the phenyl groups by a heteroaromatic group in diphenylacetic acid derivatives may lead to favorable changes in the spectrum of pharmacological action [2]. In this connection, we have carried out the synthesis of 3-indolylphenylacetic acid (III).



As we have previously shown, amine I reacts with KCN in the presence of air oxygen to give only insignificant amounts of nitrile II [3, 4]. Carrying out the reaction in a stream of carbon dioxide made it possible to exclude contact with oxygen and reduce the alkalinity of the medium; this enabled us to obtain II in quantitative yield [5]. (The use of the adipate rather than the free base and carrying out the reaction in a stream of nitrogen or argon raised the yield of II only to 41%.) Nitrile II was characterized by spectral data and reduction to the known β-phenyltryptamine (IV) [6] by the action of sodium borohydride in methanol in the presence of Raney nickel [7]. Alkaline hydrolysis of II in ethylene glycol leads to acid III in 90% yield (in a stream of an inert gas to exclude the formation of oxidation products [4]). Acid III was characterized by the preparation of derivatives.

Tests showed that the sodium salt of acid III does not stimulate the growth of plants but has herbicidal activity. According to the data of T. N. Zykova and T. A. Gus'kova (Department of Chemotherapy of the S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute), acid III in concentrations of 1000 μg/ml does not inhibit the growth of tubercular bacilli (H-37 RV strain) and does not have fungicidal action.

β-Phenyltryptamine IV does not have radiation-protection properties.

EXPERIMENTAL

The IR spectra of mineral oil suspensions or chloroform solutions were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions were recorded with an SF-4A spectrophotometer.

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*See [1] for communication XC.

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3-Indolylphenylacetonitrile (II). A 9.6 g (0.04 mole) sample of amine I [3] was dissolved in 100 ml of ethanol and 5 ml of water, and the solution was saturated at 70-80° with carbon dioxide. A solution of 6.5 g (0.1 mole) of potassium cyanide in 20 ml of water was added, and the mixture was stirred in a gentle stream of carbon dioxide for 4 h and then allowed to stand for 12 h. The inorganic precipitate was removed by filtration and washed with alcohol. Nitrile II was precipitated by adding water to the alcohol filtrate. The yield of product with mp 113-114° (ether–cyclohexane) was quantitative. Found, %: C 82.8; H 5.2; N 12.0. $C_{16}H_{12}N_2$. Calculated, %: C 82.7; H 5.2; N 12.16. UV spectrum, λ_{max}, nm ($\log \varepsilon$): 272 (4.084), 278 (4.092), 288 (4.020). IR spectrum: 3390 (N–H), 2270 ($C \equiv N$) cm^{-1}.

2-(3'-Indolyl)-2-phenylethylamine (IV). A solution of 0.59 g of $NaBH_4$ in 2.23 ml of 8 N NaOH was added in the course of 10 min at 40-45° to a mixture of 3 g (0.013 mole) of nitrile II, 1.01 g of Raney nickel, and 11.4 ml of methanol, after which the mixture was stirred for another 30 min, and the catalyst was removed by filtration and washed with methanol. The filtrate was evaporated to dryness, and the residue was extracted with methylene chloride until the extract gave a negative test with Erlich's reagent. The solvent was removed by distillation, and the residue was crystallized from benzene to give 2.15 g (70%) of amine IV with mp 131-132° (mp 130.5-131.5° [6]). Found, %: C 81.4; H 6.8; N 11.5. $C_{16}H_{16}N_2$. Calculated, %: C 81.3; H 6.8; N 11.9. UV spectrum, λ_{max}, nm ($\log \varepsilon$): 222 (4.52), 280 (3.745), 290 (3.680). The hydrochloride of amine IV was obtained by the action of a 5% alcohol solution of HCl on a solution of amine IV in anhydrous benzene (pH 6.5-7.0). The yield of hydrochloride with mp 225-226° (dec.) was quantitative. Found, %: C 70.5; H 6.3; N 10.5; Cl 13.01. $C_{16}H_{16}N_2 \cdot HCl$. Calculated, %: C 70.5; H 6.3; N 10.2; Cl 13.0.

3-Indolylphenylacetic Acid (III). A. A 2.5 g sample of potassium hydroxide and 5 g of nitrile II were dissoled in 80 ml of ethylene glycol, and the solution was heated at 150-160° in a stream of nitrogen until ammonia evolution ceased (18-20 h). It was then diluted with a double volume of water and extracted with ether to remove the oily products. The aqueous solution was cooled and acidified with hydrochloric acid, and the precipitated acid was removed by filtration, washed with water, dried, and recrystallized from benzene–ethyl acetate to give 4.8 g (90%) of acid III with mp 175-176.5°. Found, %: C 76.3; H 5.3; N 5.7. $C_{16}H_{13}NO_2$. Calculated, %: C 76.5; H 5.2; N 5.6. IR spectrum: 1710 (COOH), 3450 (N–H) cm^{-1}.

B. A solution of 0.5 g of KOH in 3 ml of water was added to a solution of 0.25 g of II in 10 ml of ethanol, and the mixture was refluxed until ammonia evolution ceased (33 h). The solvent was removed by distillation, 10 ml of water was added to the residue, and the aqueous mixture was extracted with ether. The aqueous solution was acidified with hydrochloric acid, and the precipitate was removed by filtration and treated with sodium bicarbonate solution. Acidification with hydrochloric acid gave 0.23 g (85%) of acid III. The solid [0.03 g (10.5%)] that was isoluble in sodium bicarbonate solution was found to be 2-ethoxy-3-benzoylindole [4]. The ether solution yielded 0.01 g (4.2%) of 3-benzoylindole.

Methyl 3-Indolylphenylacetate (V). A 2.5 g (10 mmole) sample of acid III was added in portions with stirring and cooling to an ether solution containing 15-20 mmole of diazomethane. The mixture was then stirred for another hour, after which petroleum ether was added. The precipitate was removed by filtration and recrystallized from ether–petroleum ether to give 2.2 g (83%) of methyl ester V with mp 69-70°. Found, %: C 77.2; H 5.9; N 5.3. $C_{17}H_{15}NO_2$. Calculated, %: C 77.0; H 5.7; N 5.3. IR spectrum ($CHCl_3$, concentration 0.5%, d = 1.0 mm): 1740 (C=O), 3490 (N–H) cm^{-1}.

Ethyl 3-Indolylphenylacetate (VI). A solution of 1 g of III in 25 ml of ethanol was refluxed with stirring for 19 h with 0.5 g of KU-2 resin in the H form. The reaction was monitored by chromatography in a thin layer of aluminum oxide. At the end of the reaction, the KU-2 resin was separated by filtration, the solvent was removed by distillation, and the residue was recrystallized from ether–cyclohexane to give 0.77 g (69%) of VI with mp 92-93°. Found, %: C 77.6; H 6.2; N 5.1. $C_{18}H_{17}NO_2$. Calculated, %: C 77.6; H 6.1; N 5.0. IR spectrum: 1715 (C=O), 3370 (N–H) cm^{-1}.

3-Indolylphenylacetic Acid Diethylamide (VIII). A 0.7 ml (5 mmole) sample of triethylamine was added with stirring at 0° to a solution of 1.25 g (5 mmole) of III in 20 ml of absolute tetrahydrofuran (THF), after which the mixture was stirred for 10 min, and 5 ml of a 1 M solution of ethyl chlorocarbonate in absolute tetrahydrofuran was added at this temperature. The mixture was then stirred for 15-20 min, after which 0.6 ml (5 mmole) of diethylamine in 3 ml of absolute THF was added. This mixture was stirred at room temperature for 1 h, after which the precipitated triethylamine hydrochloride was removed by filtration and the solvent was removed by distillation. The residue was treated with 15 ml of methylene chloride. The methylene chloride solution was washed with sodium bicarbonate solution and water and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was recrystallized from benzene to give 0.54 g of amide VIII with mp 160-162°. Found, %: C 78.8; H 7.2; N 8.9. $C_{20}H_{22}N_2O$. Calculated, %: C 78.5; H 7.2; N 9.2. IR spectrum: 1630 (C=O, amide band), 3290 (N–H) cm^{-1}.

LITERATURE CITED

1. G. P. Petrova, V. F. Shner, L. M. Alekseeva, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 208 (1974).
2. S. S. Liberman and L. N. Yakhontov, Khim.-Farmats. Zh., 5, 7 (1971).
3. V. N. Rusinova, Yu. I. Smushkevich, and N. N. Suvorov, Trudy MKhTI imeni D. I. Mendeleeva, 66, 125 (1970).
4. V. N. Rusinova, Yu. I. Smushkevich, T. A. Kozik, and N. N. Suvorov, Zh. Organ. Khim., 8, 1735 (1972).
5. N. N. Suvorov, Yu. I. Smushkevich, and V. N. Rusinova, USSR Author's Certificate No. 355,164; Byul. Izobr., No. 31, 79 (1972).
6. W. E. Noland, G. M. Christensen, G. E. Sauer, and G. S. Dutton, J. Am. Chem. Soc., 77, 456 (1955).
7. R. A. Egli, Helv. Chim. Acta, 53, 47 (1970).