INDOLE DERIVATIVES

VII.* REACTION OF INDOLE WITH AZIRIDINES

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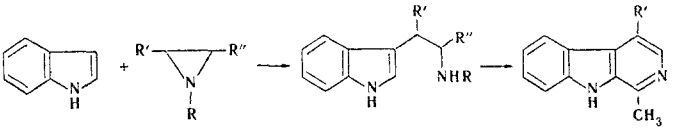
The reaction of substituted aziridines with indole was studied. It is shown that the presence of electron-donor substituents attached to the carbon atom or of bulky substituents attached to the nitrogen atom in aziridines favors cleavage of the aziridine ring by indole to give derivatives of tryptamine and tryptophan.

It is known that aziridine reacts with indole or indolylmagnesium bromide to give tryptamine [2, 3]. In addition, we have previously established that 3-phenylaziridine-2-carboxylic acid ester is cleaved by indole to give β-phenyltryptophan ester [4]. In the present communication we describe experiments undertaken in order to determine the range of application of this reaction for the synthesis of tryptamines and tryptophans substituted in the side chain. In doing so we established that neither mono- and 2,3-dialkylaziridines themselves nor their tetrafluoroborates react with indole or indolylmagnesium halides. We were also unable to introduce unsubstituted or 1- and 3-alkyl-substituted esters of aziridinecarboxylic acid into this reaction. In all of these cases, polymerization of the ethyleneimines predominated. However, 2-phenylaziridine (I) reacted with indole under the influence of boron trifluoride etherate and particularly readily when it was heated with tetracetyl diborate. According to the results of thin-layer chromatography (TLC), the amine portion of the reaction products consisted of one substance, for which it was shown that it was identical to β-phenyltryptamine. The facilitation of the reaction of this case is probably associated with an electronic factor – stabilization of the positively charged $C_{(2)}$ carbon atom of the aziridine ring by conjugation with the π electrons of the benzene ring. Heterocyclic substituents manifest a similar effect. When aziridine Ib† was heated with indole and tetracetyldiborate in nitromethane, glassy tryptophan ester IIb, which we were unable to prepare in analytically pure form, was formed. It was saponified with alkali, and β-carboline IIIb was obtained after treatment with acetaldehyde and dichromate by the method in [4].



I a-c II a-d III b

I—III a R=R″=H, R′=C_6H_5; b R=H, R′=1-benzimidazol-2-yl, R″=CO_2—i-C_3H_7; c R=$C(CH_3)_3$, R′=H, R″=CO_2—i-C_3H_7; I, d R=$C(CH_3)_3$, R′=CO_2—i-C_3H_7, R″=H.

Steric factors also affect the reaction under consideration. A bulky substituent, by hindering polymerization, favors reaction with indole. However, structural specificity in this case is probably lost.

* For Communication VI see [1].

† For the synthesis of Ib, 1-benzyl-2-formylimidazole was condensed with isopropoxycarbonylbromoethylenetriphenylphosphorane [5] to give (1-benzyl-2-imidazolyl)-α-bromoacrylic acid ester, which was cyclized to Ib by treatment with ammonia in dimethyl sulfoxide. The similarly obtained indole bromoacrylate did not undergo the cyclization reaction.

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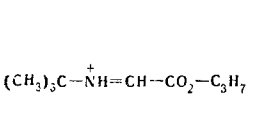
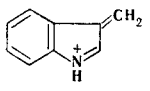
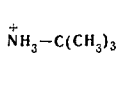
Thus, treatment of 1-tert-butylaziridinecarboxylic acid ester Ic and indole with boron trifluoride etherate gave two isomers, which we were able to separate by chromatography on silica gel. Intense peaks with m/e 172, 130, and 74, which correspond to ions *a*, b, and c, were recorded in the mass spectrum of the higher-melting product. One cannot exclude the possibility that the peak with m/e 130 is a composite peak containing a contribution from the $(CH_3)_3C-\overset{+}{N}H=CH-COOH$ fragment ion, which is formed from ion *a* after loss of a propylene molecule with hydrogen migration. The presence of ion *a* attests to the fact that the isopropoxycarbonyl residue is in the α-position with respect to the amine nitrogen, and the high-melting product, consequently, has structure IIc.



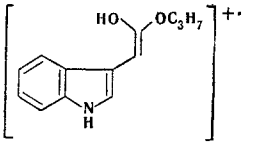
a *m/e* 172



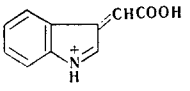
b *m/e* 130



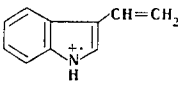
c *m/e* 74



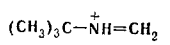
d *m/e* 217



e *m/e* 171



f *m/e* 143



g *m/e* 86

The mass spectrum of the low-melting product contains intense peaks with m/e 217, 174, 143, and 86, which correspond to ions d, e, f, and g. The ester function is, consequently, in the β-position with respect to the amine nitrogen, and isomeric structure IId should be assigned to the low-melting product.

The other peaks in the mass spectra confirm the proposed formulas. The stability of the molecular ions with respect to electron impact (W_M) and the selectivity ($S_{1/2}$) proved to be greater for the high-melting product.

EXPERIMENTAL

The melting points were determined with a Koffler block and were not corrected. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions of the compounds were obtained with a Specord UV VIS spectrophotometer. The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing-chamber temperature of 150° and an ionizing voltage of 70 eV.

Isopropyl 2-Bromo-3-(1-benzyl-2-imidazolyl)acrylate. A 7.5-g (0.04 mole) sample of 2-formylimidazole [6] was added cautiously to a solution of 20 g (0.04 mole) of isopropoxycarbonylbromomethylenetriphenylphosphorane in 75 ml of pure methylene chloride, and the mixture was allowed to stand at room temperature for 20 h. It was then extracted with 5% HCl, and the precipitated hydrochloride was removed by filtration and stirred with a saturated sodium bicarbonate solution. The solution was then extracted with ether. The extract was dried, and the ether was evaporated to give white crystals, which were crystallized from benzene to give a product with mp 128-130° in 68% yield. IR spectrum, cm^{-1}: 530 (C–Br), 1620 (C=C), and 1670 (C=O). Found: C 55.4; H 5.4; Br 22.9; N 8.0%. $C_{16}H_{12}BrN_2O_2$. Calculated: C 55.0; H 4.9; Br 23.1; N 8.0%.

Isopropyl 3-(1-Benzyl-3-indolyl)-2-bromoacrylate. A solution of 4.61 g (0.0105 mole) of isopropoxycarbonylbromomethylenetriphenylphosphorane and 2.35 g (0.01 mole) of 1-benzyl-3-formylindole in 24 ml of benzene was refluxed for 8 h, after which the solvent was removed by distillation, and the residue was extracted thoroughly with boiling petroleum ether. The petroleum ether was removed, and the residue was chromatographed on 120 g of activity III aluminum oxide with benzene–petroleum ether (1:9) to give 1.5 g (40%) of colorless crystals. Crystallization from cyclohexane gave an analytically pure sample with mp 87.5-89°. IR spectrum, cm^{-1}: 700 (C–Br), 1620 (C=C), and 1715 (C=O). Found: C 63.5; H 5.1; Br 20.1; N 3.3%. $C_{21}H_{20}BrNO_2$. Calculated: C 63.3; H 5.0; Br 20.1; N 3.5%.

2-(3-Indolyl)-2-phenylethylamine (IIa). A mixture of 344 mg (2.9 mmole) of indole and 950 mg (3.5 mmole) of tetraacetyl diborate in 1.8ml of nitromethane was maintained at 20° for 15 min, after which 294 mg of phenylhydrazine [7] in 1.5 ml of nitromethane was added. The mixture was stirred from 3 h, after which dilute hydrochloric acid was added, and the mixture was extracted with ether. The aqueous layer was made alkaline with potassium carbonate and extracted with methylene chloride. The extract was dried with

sodium sulfate and evaporated, and the residue was crystallized from benzene to give 300 mg (65%) of IIa with mp 127-130°. No melting-point depression was observed for a mixture of this product with a sample of known structure [4].

Tetraacetyl diborate was obtained by heating a suspension of 20 g of boric acid with 130 ml of acetic anhydride until a vigorous reaction developed. The hot solution was then filtered, and the product was crystallized by cooling the filtrate.

1-Methyl-4-(1-benzyl-2-imidazolyl)-β-carboline (IIIb). A 10.0-g (0.035 mole) sample of aziridine Ib was added with water cooling to a stirred solution of 19.2 g (0.07 mole) of tetraacetyl diborate and 6.2 g (0.053 mole) of indole in 50 ml of nitromethane, and the mixture was maintained at 25° for 20 h. It was then poured into dilute hydrochloric acid, and the acidic mixture was extracted with ether. The aqueous layer was made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was cooled in a refrigerator, the precipitated crystals were separated, and the filtrate was dried with sodium sulfate and evaporated to dryness to give 8.5 g of crude tryptophan ester IIb. A 7-g sample of this product was dissolved in 17.5 ml of 2 N aqueous alcoholic sodium hydroxide, and the solution was maintained at room temperature for 26-30 h. It was then neutralized with 35 ml of 1 N sulfuric acid, and the resulting oil was separated and dissolved in 70 ml of 50% formic acid. The formic acid solution was mixed with 7 ml of acetaldehyde, and the mixture was allowed to stand at 17° for 48 h. The acid and water were removed by vacuum distillation to give 5.2 g of crude residue; 4.2 g of this residue was dissolved in 440 ml of water, and the solution was heated to the boiling point and mixed with 122 ml of 12% potassium dichromate and 26 ml of acetic acid. The mixture was refluxed for 5 min, after which it was cooled and treated with sodium sulfite and neutralized with potassium carbonate. The resulting suspension was extracted with chloroform, and the substance that passed into the chloroform phase was purified by chromatography on activity III aluminum oxide. Benzene–petroleum ether eluted a first fraction, which was discarded. Benzene eluted 0.76 g of solid colorless β-carboline IIIb. UV spectrum, λ_{max}, nm (log ε): 212 (4.44), 241 (4.45), 254 (4.46), 285 (3.98), 294 (4.13), 349 (3.79), and 357 (3.90). The dihydrochloride of IIIb had mp 360° (from methanol, in a sealed capillary). Found: C 64.1; H 5.2; Cl 16.9; N 13.7%. $C_{22}H_{18}N_4 \cdot 2HCl$. Calculated: C 64.0; H 4.9; Cl 17.1; N 13.7%.

Isopropyl 2-tert-Butylamino-3-(3-indolyl)propionate (IIc) and Isopropyl 3-tert-Butylamino-2-(3-indolyl)propionate (IId). A solution of 0.50 g (2.7 mmole) of aziridinecarboxylic acid ester Ic [8] and 0.48 g (4.1 mmole) of indole in 4 ml of tetrahydrofuran (THF) was added to a cooled solution of 0.35 g (2.5 mmole) of boron trifluoride etherate in anhydrous THF. The solvent was then removed rapidly in vacuo, and the residue was heated at 100° for 3 h. The glassy reaction mixture was shaken with 5% hydrochloric acid and ether, and the aqueous layer was separated and made alkaline with sodium bicarbonate. The alkaline mixture was extracted with ether to give 0.5 g of an oil, which crystallized on trituration with cyclohexane. According to TLC, these crystals constituted a mixture of two substances. They were spearated by chromatography with a column filled with silica gel and elution with benzene–petroleum ether (4:1) saturated with ammonium hydroxide. The first fractions contained 0.14 g of tryptophan derivative IIc with mp 120° (from carbon tetrachloride). IR spectrum, cm^{-1}: 1740 (CO), 3300 (NH), and 3420 (indole NH). Mass spectrum, m/e (%): 302 (6), 287 (0.4), 245 (0.5), 230 (16), 215 (12), 188 (0.8), 172 (74), 159 (15), 130 (77), 116 (59), 74 (100), 57 (48), 43 (12), 41 (25). Found: C 66.9; H 7.9; N 8.6%. $C_{18}H_{26}N_2O_2 \cdot H_2O$. Calculated: C 67.5; H 8.1; N 8.7%.

Workup of the subsequent fractions gave 0.1 g of IId with mp 101-103° (from carbon tetrachloride). IR spectrum: 1740 (CO), 3310 (NH), and 3400 (indole NH). Mass spectrum, m/e (%): 302 (12), 287 (3), 245 (1), 230 (2), 217 (24), 175 (20), 174 (33), 159 (8), 157 (11), 143 (32), 130 (44), 86 (100), 57 (66), 44 (40), 43 (45), 41 (71).

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