Inasmuch as the signal from the NH_2 protons has the greatest paramagnetic shift in the spectrum of aziridine I, it can be asserted that complexing with $Eu(DPM)_3$ occurs at the primary amino group.

The large paramagnetic shifts of the absorption signals from the protons in the 2 and 3-trans positions as compared with those for the 3-cis positions in aziridines II and III constitute unambiguous proof of the trans configuration of the larger.

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds (0.5 M) were obtained with a Perkin-Elmer R 12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. The chemical shifts were measured with an accuracy of ±0.5% of the scanning range.

Compounds I-II and III were obtained by the methods in [1-3], respectively. Their purity was verified by means of gas–liquid chromatography.

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CHEMISTRY OF INDOLE

XLIII.* NEW SYNTHESIS OF BENZ(AMINOMETHYL)INDOLES

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Indolines are amidomethylated in the 6 position in acidic media. N-Acetylation changes the orientation to give the 5-substituted isomers. Dehydrogenation of the reaction products and subsequent hydrolysis make it possible to obtain 5- or 6-aminomethylindoles.

Wooley and Shaw [2] have reported that some 5-aminomethyldimethylindoles have antiserotonin activity. However, these models must be synthesized by a roundabout method (for example, see [3, 4]), inasmuch as the pyrrole ring undergoes amidomethylation in the reaction of indole with N-methylolamides in alkaline media [5], whereas indole and 3-alkylindoles are polymerized in acidic media. We therefore used the indoline–indole method based on electrophilic substitution reactions in the benzene ring of indoline or its acyl derivatives and subsequent dehydrogenation. This method makes it possible to selectively obtain 5- or 6-substituted indoles. It was found that the reaction of both indoline and 1-acetylindolines with methylol derivatives of acetamide or chloroacetamide does not give good results (they form mixtures of substances that are difficult to separate and are, in part, easily hydrolyzed).

However, indoline (Ia) can be amidomethylated with N-methylolphthalimide in concentrated sulfuric acid at room temperature to give 6-phthalimidomethylindoline (IIa), from which, after removal of the phthalyl

*See [1] for communication XLII.

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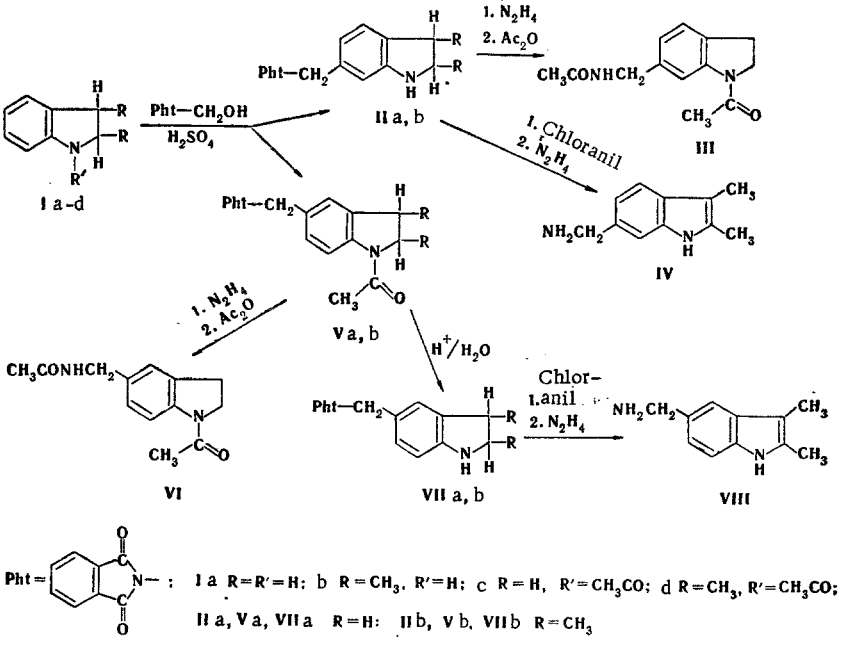
protective group, 6-aminomethylindoline is obtained as a viscous uncrystallizable oil, which is converted to an acetyl derivative (III); the structure of III was confirmed by its PMR spectrum, which contains two doublets (7.03 and 7.27 ppm, J = 7 Hz) characteristic for indoline 5-H and 4-H protons in the aromatic proton region. The signal of the 7-H proton is shifted to weak field (8.12 ppm) under the influence of the carbonyl group.

Similarly, from 2,3-dimethylindoline (Ib) we obtained 6-phthalimidomethyl-2,3-dimethylindoline (IIb), the dehydrogenation of which with chloranil gave the corresponding indole and, subsequently, the known [7] 6-aminomethyl-2,3-dimethylindole (IV).

The substituent enters the para position relative to the amide group in the amidomethylation of 1-acetylindoline (Ic) and 1-acetyl-2,3-dimethylindoline (Id) under similar conditions (at room temperature). The 1-acetyl-5-phthalimidomethylindoline (Va) obtained in this way loses its phthalyl protective group on treatment with hydrazine hydrate but retains its N-acetyl group.

On the other hand, refluxing Va or Vb in an alcohol solution of hydrochloric acid for many hours leads to splitting out only of the acetyl group, and this makes it possible to obtain 5-phthalimidomethylindoline (VIIa) and its 2,3-dimethyl derivative (VIIb).



We were able to obtain the known [4] 5-aminomethyl-2,3-dimethylindole by dehydrogenation of 5-phthalimidomethyl-2,3-dimethylindoline (VIIb) with chloranil and subsequent removal of the protective group; this confirms the structures of Vb and VIIb.

Two doublets (7.13 and 8.03 ppm, J = 7.5 Hz) characteristic for 6-H and 7-H protons are observed in the PMR spectrum of amide VI in the aromatic protein region. The singlet of the 4-H proton is found at 7.2 ppm. Thus the amidomethylation of indoline and its derivatives may serve as a convenient method for the synthesis of difficult-to-obtain 5- or 6-aminomethylindoles.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with IKS-22 and UR-20 spectrometers. The UV spectra of alcohol solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra of dimethyl sulfoxide (DMSO) solutions were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The course of the reaction was monitored by means of thin-layer chromatography (TLC) on activity II (Brockmann classification) aluminum oxide in benzene–methanol (9 : 1), benzene–ethyl acetate (9 : 1; 4 : 1), and benzene–ether–heptane (1 : 1 : 1) systems.

6-Phthalimidomethylindoline (IIa). A 5.3-g (0.04 mole) sample of indoline was dissolved in 10 ml of concentrated sulfuric acid with stirring and cooling with water. A solution of 9.3 g (0.052 mole) of N-methylolphthalimide in 20 ml of concentrated sulfuric acid was added dropwise in the course of 1 h to the resulting suspension of indoline sulfate in sulfuric acid, and the mixture was then stirred for 4 h. At the

end of the reaction (monitoring by means of TLC on aluminum oxide), the mixture was poured over ice, and the aqueous mixture was made alkaline with ammonia. The resulting yellow precipitate was removed by filtration and washed with water to give 6.6 g (53%) of 6-phthalimidomethylindoline with mp 143-144° (from benzene–heptane). Found: C 73.4; H 4.8%. $C_{17}H_{14}N_2O_2$. Calculated: C 73.4; H 5.0%. UV spectrum: λ_{max} 241 and 296 nm (log ε 4.15 and 3.57). IR spectrum: 1710 (C=O) and 3410 cm^{-1} (N–H).

1-Acetyl-5-phthalimidomethylindoline (Va). This compound, with mp 234-235° [benzene–heptane (9 : 1)], was similarly obtained in 97% yield from 4 g of 1-acetylindoline. Found: C 70.9; H 4.9%. $C_{19}H_{16}N_2O_3$. Calculated: C 71.2; H 5.0%. UV spectrum: λ_{max} 241, 257, and 286 nm (log ε 4.05, 4.25, and 3.65). IR spectrum: 1710 and 1660 cm^{-1} (C=O).

1-Acetyl-5-phthalimidomethyl-2,3-dimethylindoline (Vb). A solution of 3.5 g (0.02 mole) of N-methylolphthalimide in 20 ml of concentrated sulfuric acid was added dropwise in the course of 30 min to a solution of 3.8 g (0.02 mole) of 1-acetyl-2,3-dimethylindoline in 10 ml of concentrated sulfuric acid, after which the mixture was stirred at room temperature for ~2 days. At the end of the reaction (as monitored by TLC on aluminum oxide), the mixture was poured over ice, and the aqueous mixture was made alkaline with ammonia. The resulting precipitate was removed by filtration and washed with water to give 4.3 g (61%) of 1-acetyl-5-phthalimidomethyl-2,3-dimethylindoline with mp 155-156° [benzene–heptane (9 : 1)]. Found: C 72.6; H 5.7%. $C_{21}H_{20}N_2O_3$. Calculated: C 72.4; H 5.7%. UV spectrum: λ_{max} 217, 240, 256, 283, and 292 nm (log ε 4.81, 4.29, 3.89, and 3.86). IR spectrum: 1660 and 1720 cm^{-1} (C=O).

6-Phthalimidomethyl-2,3-dimethylindoline (IIb). This compound, with mp 128-129° [benzene–hexane (4 : 1)], was similarly obtained in 65% yield from 4 g of 2,3-dimethylindoline and N-methylolphthalimide. Found: C 74.4; H 6.0%. $C_{18}H_{18}N_2O_2$. Calculated: C 74.5; H 5.8%. UV spectrum: λ_{max} 206, 216, 240, and 295 nm (log ε 4.77, 4.82, 4.34, and 3.70). IR spectrum: 1710 (C=O) and 3370 cm^{-1} (N–H).

5-Phthalimidomethylindoline (VIIa). Concentrated hydrochloric acid (6 ml) was added to a suspension of 4 g (0.012 mole) of 1-acetyl-5-phthalimidomethylindoline in 120 ml of ethanol, and the mixture was refluxed for 9 h. At the end of the reaction (as monitored by TLC on aluminum oxide), the excess ethanol was removed by distillation, and the residue was diluted with water and made alkaline with ammonia. The resulting precipitate was removed by filtration and washed with water to give 2.2 g (78%) of 5-phthalimidomethylindoline with mp 187-188° (from isopropyl alcohol). Found: C 73.3; H 4.9%. $C_{14}H_{14}N_2O_2$. Calculated: C 73.3; H 5.0%. UV spectrum: λ_{max} 219, 233, and 294 nm (log ε 4.55, 4.27, 4.24, and 3.61). IR spectrum: 1710 (C=O) and 3400 cm^{-1} (N–H).

5-Phthalimidomethyl-2,3-dimethylindoline (VIIb). This compound, with mp 135-136° [benzene–heptane (4 : 1)], was similarly obtained in 62% yield from 5-phthalimidomethyl-2,3-dimethyl-1-acetylindoline. Found: C 74.3; H 5.6%. $C_{19}H_{18}N_2O_2$. Calculated: C 74.5; H 5.8%. UV spectrum: λ_{max} 218, 331, 240, and 293 nm (log ε 4.61, 4.28, 4.26, and 3.71). IR spectrum: 1710 (C=O) and 3410 cm^{-1} (N–H).

5-Phthalimidomethyl-2,3-dimethylindole. A mixture of 0.15 g (0.49 mmole) of 2,3-dimethyl-5-phthalimidomethylindoline and 0.12 g (0.42 mmole) of chloranil in 30 ml of dry xylene was refluxed at 150° for 45 min. At the end of the reaction, the mixture was poured into 20% sodium hydroxide solution, the xylene layer was separated, and the alkaline layer was extracted with ether. The xylene and ether extracts were combined, treated with hydrochloric acid (1 : 1), and washed with water. The solvents were then removed to give 0.07 g (48%) of 2,3-dimethyl-5-phthalimidomethylindole with mp 196-197° [benzene–heptane (6 : 3)]. The product was identical to the substance obtained in [4].

6-Phthalimidomethyl-2,3-dimethylindole. This compound, with mp 228-229° (from benzene), was similarly obtained in 60% yield by dehydrogenation of 1 g of 2,3-dimethyl-6-phthalimidomethylindoline with chloranil. Found: N 9.1%. $C_{19}H_{16}N_2O_2$. Calculated: N 9.3%. UV spectrum: λ_{max} 239 and 286 nm (log ε 4.80 and 4.02). IR spectrum: 1725 (C=O) and 3400 cm^{-1} (N–H).

6-Aminomethyl-2,3-dimethylindole (IV). A mixture of 0.4 g (2.3 mmole) of 6-phthalimidomethyl-2,3-dimethylindole and 0.5 ml of hydrazine hydrate in 25 ml of methanol was refluxed for 3 h. At the end of the reaction, the precipitate (phthalazinedione) was removed by filtration, and excess dilute (1 : 1) hydrochloric acid was added to the filtrate. The resulting precipitate was removed by filtration and washed with water. The excess methanol was removed by distillation, combined with the wash waters, made alkaline with ammonia, and extracted with ether. The ether extract was dried with fused potassium hydroxide, and the ether was removed to give 0.14 g (58%) of a product with mp 117-118° (from heptane) [7].

5-Aminomethyl-2,3-dimethylindole (VIII). This compound, with mp 153-154° (from heptane), was similarly obtained in 78% yield from 5-phthalimidomethyl-2,3-dimethylindole. Found: C 75.8; H 8.2%. $C_{11}H_{12}N_2$. Calculated: C 75.8; H 8.1%. UV spectrum: λ_{max} 233 and 286 nm (log ε 4.90 and 3.85).

1-Acetyl-5-acetamidomethylindoline (VI). A mixture of 2 g (6 mmole) of 1-acetyl-5-phthalimidomethylindoline and 2 ml of hydrazine hydrate in 60 ml of ethanol was refluxed for 3 h. At the end of the reaction (as monitored by TLC on aluminum oxide), the mixture was cooled and worked up as indicated above to give 0.4 g (36%) of 1-acetyl-5-aminomethylindoline. Excess (2 ml) acetic anhydride was added to the 0.4 g (2 mmole) of 5-aminomethylindoline, and the mixture was allowed to stand at room temperature for 1 h. Ether was then added to the mixture, and the resulting precipitate was removed by filtration to give 0.5 g (quantitative yield) of 1-acetyl-5-acetamidomethylindoline with mp 180° (from benzene). Found: C 67.2; H 6.9%. $C_{13}H_{16}N_2O_2$. Calculated: C 67.2; H 6.9%. UV spectrum: λ_{max} 256 and 285 nm (log ε 4.29 and 3.75). IR spectrum: 1650 (C=O) and 3300 cm^{-1} (N–H).

1-Acetyl-6-acetamidomethylindoline (III). This compound, with mp 123-124° (from benzene), was similarly obtained in 65% yield from 2 g of 6-phthalimidomethylindoline. Found: C 67.2; H 6.9%. $C_{13}H_{16}N_2O_2$. Calculated: C 67.2; H 6.9%. UV spectrum: λ_{max} 254 and 283 nm (log ε 4.17 and 3.64). IR spectrum: 1640 (C=O) and 3300 cm^{-1} (N–H).

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SYNTHESIS OF 2-INDOLYLACETIC ACID DERIVATIVES

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2-Indolylacetic acid derivatives were synthesized by condensation of diethyl acetonedicarboxylate with α-substituted arylhydrazines under the conditions of the Fischer reaction, and their transformations were studied.

Continuing our research on 2-indolylacetic acids [1], we have accomplished the Fischer synthesis of derivatives of ethyl 1-alkyl-3-carbethoxy-2-indolylacetates (I-VI, see Table 1) from diethyl acetonedicarboxylate and α-alkyl arylhydrazines. 2-(1,3-Dimethyl-2-indolyl)ethanol (VII) was obtained by reduction of ethyl-1-methyl-3-carbethoxy-2-indolylacetate with lithium aluminum hydride. Alkaline hydrolysis of esters I-IV at room temperature gives 3-carbethoxy-2-indolylacetic acids VIII-XI (see Table 1), whereas heating gives indolylcarboxylic acids XII-XIV (see Table 1).

Anhydrides XV-XVII were obtained by the usual method from acids XII-XIV, and amides (XVIII-XX) of substituted 2-indolylacetic acid were obtained from the anhydrides by the action of primary amines.

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