CARBOLINES.

14*. SYNTHESIS OF 5-AZAELLIPTICINE

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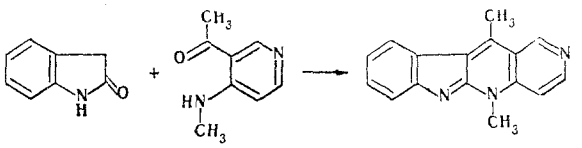
3-Acetyl-4-methylaminopyridine was obtained by cyanation of 3-acetylpyridine ethyleneketal N-oxide and subsequent chemical transformations of the nitrile group. Condensation of this product with oxindole led to the synthesis of 5H-5,11-dimethylindolo[3,2-j]-1,4-naphthyridine — the aza analog of the alkaloid ellipticine.

The alkaloid ellipticine (III) has been known since 1959 [2]. Since then, this compound has been of constant interest to synthetic chemists and specialists in the chemotherapy of malignant neoplasms. About three dozen methods for the total synthesis of ellipticine and its analogs have been described [3, 4]. The interest in alkaloid III is due both to its therapeutic properties and to the fact that it is a powerful intercalating agent. Substances of this type form complexes with DNA by intercalation (implantation) in the space between parallel layers of the bases in the double helix. The investigation of the principles of this sort of complexing is important for the development of some new directions in chemotherapy.

We have observed that cytotoxic 2-chloro-α-isocarbolines are also capable of forming intercalation complexes [1]. In this connection, we undertook the synthesis of the 5-aza analog of ellipticine with anhydronium structure II, in the molecule of which α-isocarboline and ellipticine fragments are combined.

Analog II was synthesized by condensation of oxindole with 3-acetyl-4-methylaminopyridine (I) by modifying the known method for the synthesis of quinindoline [5]:



I II

Derivative I was obtained starting from 3-acetylpyridine. The latter was treated with ethylene glycol in refluxing benzene containing p-toluenesulfonic acid [6]. The resulting cyclic ketal was converted to N-oxide IV by the action of hydrogen peroxide in acetic acid. Two isomeric nitriles V and X were formed by heating an aqueous solution of the O-methyl derivative of IV with potassium cyanide. The isomeric nitriles were separated by chromatography on silica gel, and their structures were established by means of PMR spectroscopy. Signals of two protons, viz., a singlet at 8.9 ppm and a doublet at 8.7 ppm with J = 6 Hz, were observed in the spectrum of isomer V at weak field. A signal of only one proton in the form of a doublet at 8.8 ppm with J = 3 Hz was observed in the weak-field part of the spectrum of X.

*See [1] for communication 13.

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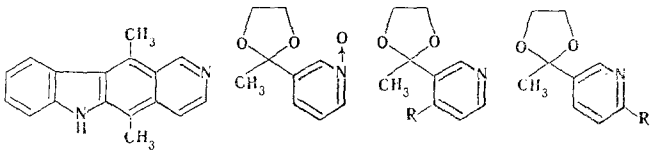
The required isomer V was treated with a solution of sodium hydroxide in the presence of hydrogen peroxide, and the resulting amide VI was subjected to the Hofmann rearrangement by the method in [7], which leads to the formation of urethane VIII. Similar transformations were realized with isomer X. When urethane VIII was heated with lithium aluminum hydride in ethylene glycol dimethyl ether, it was converted to reduction product IX, in which the keto group was unblocked by heating with dilute hydrochloric acid.



III IV V,VI,VIII,IX X–XII

V R=CN; VI R=$CONH_2$; VIII R=$NHCO_2CH_3$; IX R=$NHCH_3$; X R=CN; XI R=$CONH_2$; XII R=H

Compound I was condensed with oxindole by heating the components with piperidine in a sealed ampul at a high temperature. 5-Azaellipticine (II) was obtained as a bright-orange crystalline substance that forms a yellow hydrochloride. In the UV and visible regions II gives the spectrum that is typical for α-isocarboline compounds with a hypsochromic shift of the absorption maxima upon acidification. The data from PMR and mass spectroscopy confirm structure II.

With respect to its cytotoxic properties for tumor cells (NK/Ly, S-37, and Erlich and Fischer tumors) 5-azaellipticine is comparable to ellipticine. In *in vivo* tests 25 mg/kg doses of it retarded the growth of the NK/Ly tumor by 50%.

EXPERIMENTAL

The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. The UV spectra were recorded with an SF-4A spectrophotometer. The PMR spectra were recorded with a Tesla BS 487B spectrometer with hexamethyldisiloxane as the internal standard. The mass spectrum was obtained with an MKh-1303 spectrometer at an ionizing voltage of 30 eV.

3-Acetylpyridine Ethyleneketal (XII). A mixture of 10 g (0.08 mole) of 3-acetylpyridine, 17.3 g (0.09 mole) of p-toluenesulfonic acid, 15.6 ml (0.28 mole) of ethylene glycol, and 390 ml of benzene was refluxed with stirring in an apparatus fitted with a Dean–Stark adapter. After 3 h, 22.7 ml (0.41 mole) of ethylene glycol and 5.4 g (0.028 mole) of p-toluenesulfonic acid were added, and the mixture was refluxed until water separation ceased (10-12 h). The solution was cooled and poured into water, the aqueous mixture was made alkaline with 2 N sodium hydroxide solution, and the benzene layer was separated. The aqueous layer was extracted with benzene, and the combined benzene extracts were washed successively with 1 N sodium hydroxide solution and water, dried, and evaporated. The ketal was distilled *in vacuo* to give 9.5 g (70%) of a product with bp 93°C (3 mm).

3-Acetylpyridine Ethyleneketal N-Oxide (IV). A 10-ml sample of a 35% solution of hydrogen peroxide was added to a solution of 15.8 g (0.096 mole) of ketal XII in 54 ml of acetic acid, and the mixture was heated on a water bath at 70-80°C. After 3 h, an additional 5.7 ml of the hydrogen peroxide solution was added, and heating was continued for 7 h. The mixture was evaporated to a volume of 20 ml, 20 ml of water was added, and the acetic acid was removed as completely as possible by distillation. The residue was treated with dry sodium carbonate, shaken with chloroform, and allowed to stand. The solid residue was removed, and the filtrate was dried and evaporated. The yield of a viscous liquid, which solidified upon standing to give a product with mp 158-160°C (from benzene), was 13.7 g (79%). The results of elementary analysis were unsatisfactory.

3-Acetyl-4-cyanopyridine Ethyleneketal (V) and 3-Acetyl-6-cyanopyridine Ethyleneketal (X). A solution of 21 ml (0.22 mole) of dimethyl sulfate in 210 ml of dry benzene was added slowly to a solution of 25 g (0.14 mole) of N-oxide IV in 625 ml of dry benzene, and the mixture was stirred at room temperature for 12 h and allowed to stand overnight. The oil that separated was collected by decantation, and the organic layer was extracted with water. The oil and aqueous extracts were combined and diluted with 250 ml of ethanol. A solution of 21 g (0.32 mole) of potassium cyanide and 25 g (0.47 mole) of ammonium chloride in 50 ml of

water was added at 20-25°C in small portions to the resulting solution, and the mixture was stirred at the same temperature for 3 h. It was then extracted with chloroform, and the extract was washed with a saturated aqueous solution of sodium chloride, dried with potassium carbonate, and evaporated. The resulting mixture of isomeric nitriles was separated by chromatography on silica gel in a benzene–ethanol system (96:4).

The yield of V, with mp 65-67°C (from cyclohexane), was 10.8 g (42%). PMR spectrum (in CCl_4): 8.9 (1H, s, 2-H), 8.7 (1H, d, J = 6 Hz, 6-H), 7.5 (1H, d, J = 6 Hz, 5-H), 3.81 (4H, m, CH_2), and 1.67 ppm (3H, s, CH_3). IR spectrum: 2245 cm^{-1} (C≡N). Found: C 63.4, H 5.3, N 15.0%. $C_{10}H_{10}N_2O_2$. Calculated: C 63.2, H 5.3, N 14.7%. The yield of X, with mp 124-126°C (from hexane), was 3.1 g (12%). PMR spectrum (in CCl_4): 8.8 (1H, d, J = 3 Hz, 2-H), 7.87 (1H, q, J = 3 and 8 Hz, 4-H), 7.6 (1H, d, J = 8 Hz, 5-H), 3.8 (4H, m, CH_2), and 1.57 ppm (3H, s, CH_3). IR spectrum: 2240 cm^{-1} (C≡N). Found: C 63.4, H 5.6, N 14.9%. $C_{10}H_{10}N_2O_2$. Calculated: C 63.2, H 5.3, N 14.7%.

3-Acetyl-4-carboxamidopyridine Ethyleneketal (VI). A 4.1-ml sample of a 35% solution of hydrogen peroxide and 0.62 ml of a 6 N solution of sodium hydroxide were added to a solution of 0.5 g (2.6 mmole) of isomer V in 5 ml of ethanol, and the mixture was stirred at 50-55°C for 0.5 h. It was then cooled and poured into water, and the solution was saturated with sodium sulfate and extracted with ethyl acetate. The extract was dried with sodium sulfate and evaporated to give 0.49 g (90%) of a product with mp 137-139°C (from benzene). Found: C 57.5, H 5.8, N 13.5%. $C_{10}H_{12}N_2O_3$. Calculated: C 57.7, H 5.8, N 13.5%.

3-Acetyl-6-carboxamidopyridine Ethyleneketal (XI). This compound was obtained from isomer X by a method similar to that used to prepare VI. The yield of product with mp 142-143°C (from benzene) was 0.48 g (88%). Found: C 57.7, H 5.9, N 13.6%. $C_{10}H_{12}N_2O_3$. Calculated: C 57.7, H 5.8, N 13.5%.

3-Acetyl-4-(N-methoxycarbonyl)aminopyridine Ethyleneketal (VIII). A 0.2-g (0.9 mmole) sample of VI was dissolved with stirring and cooling in 3.7 ml of absolute methanol containing 0.037 g (1.6 mmole) of sodium, and the solution was cooled to 0°C and treated with 0.1295 g (0.8 mmole) of bromine. The mixture was stirred at 0°C for 1 h and refluxed for 1 h. The bulk of the methanol was evaporated, a solution of sodium bisulfite was added, and urethane VIII was extracted with ethyl acetate. The urethane was purified on silica gel (the substance–sorbent ratio was 1:30) by elution with an ether–acetone system (80:20) to give 0.14 g (61%) of urethane VIII with mp 154-156°C (from isopropyl alcohol). IR spectrum: 3320 (NH) and 1740 cm^{-1} (C=O). Found: C 55.5, H 5.9, N 11.7%. $C_{11}H_{14}N_2O_4$. Calculated: C 55.5, H 5.9, N 11.8%.

3-Acetyl-4-methylaminopyridine Ethyleneketal (IX). A 1.1-g (28 mmole) sample of lithium aluminum hydride was added to a solution of 3.45 g (14 mmole) of urethane VIII in 50 ml of ethylene glycol dimethyl ether, and the mixture was refluxed for 6 h. It was then cooled and poured into a solution of sodium potassium tartrate and extracted with ethyl acetate. The substance (2.5 g) was applied to activity III aluminum oxide (75 g) and eluted with a petroleum ether–benzene system (60:40) to give 1.5 g (53%) of IX with mp 82-84°C (from hexane). IR spectrum: 3380 cm^{-1} (NH). The monopicrate had mp 178-180° (from ethanol). Found: C 45.4, H 4.1, N 16.3%. $C_{10}H_{14}N_2O_2 \cdot C_6H_3N_3O_7$. Calculated: C 45.4, H 4.0, N 16.6%.

3-Acetyl-4-methylaminopyridine (I). A 1.5-g (7.7 mmole) sample of IX was dissolved in 15 ml of 10% hydrochloric acid, and the solution was refluxed for 30 min. The mixture was cooled, dry potassium carbonate was added, and the mixture was extracted with ethyl acetate. Evaporation was added, and the mixture was extracted with ethyl acetate. Evaporation of the solvent and recrystallization of the residue from cyclohexane with activated charcoal gave 1.1 g (94%) of 3-acetyl-4-methylaminopyridine with mp 95-97°C (from hexane). Found: C 64.0, H 6.6, N 18.7%. $C_8H_{10}N_2O$. Calculated: C 64.0, H 6.7, N 18.7%.

5H-5,11-Dimethylindolo[3,2-j]-1,4-naphthyridine (II). A mixture of 0.33 g (2 mmole) of I, 0.19 g (2 mmole) of piperidine, and 0.29 g (2 mmole) of oxindole was heated in a sealed ampul at 200°C for 11-12 h, after which it was cooled and dissolved in 5% hydrochloric acid solution, and the unchanged oxindole was extracted with ether. Alkalization gave 0.25 g (45%) of an orange precipitate of 5-azaellipticine with mp 213-215°C (from ethyl acetate). UV spectrum (in absolute ethanol), λ_{max} (log ε): 280 (4.69), 337 (4.51), and 355 nm (4.03). UV spectrum (in 0.1 N HCl in ethanol): 225 (4.27), 272 (4.63), 295 sh (4.34), and 350 nm (4.04). PMR spectrum (in deuteromethanol): 2.86 (3H, s, 11-CH_3), 3.98 (3H, s, CH_3–N), 9.14 (1H, s, 1-H), 8.55 (1H, d, J = 6 Hz, 3-H), 7.56 (1H, d, J = 6 Hz, 4-H), and 6.75-7.85

ppm (4H, m, aromatic protons). Mass spectrum, m/z (%): 247 [M^+] (100), 246 [M − 1] (17.1), 232 [M − 15] (21.3), 220 [M − 1 − C_2H_2] (8.5), and 206 [M − 15 − C_2H_2] (8.5). Found: C 77.6, H 5.7, N 17.2%. $C_{16}H_{13}N_3$. Calculated: C 77.7, H 5.3, N 17.0%.

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SYNTHESIS OF 2-CARBOXY-5,6-ETHYLENEDIOXYINDOLE AND ITS 3-, 4-, AND 7-HALO DERIVATIVES

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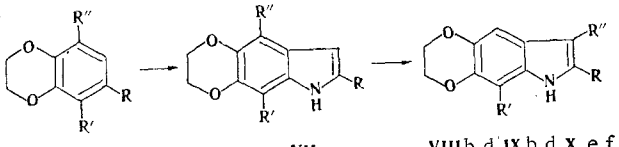
A method for the synthesis of 2-carboxy-5,6-ethylenedioxyindole and its 4- and 7-chloro derivatives from 3,4-ethylenedioxyaniline and, correspondingly, its 2- and 5-chloro derivatives via the Fischer reaction was developed. It was established that in the case of bromination or chlorination under mild conditions 2-carbethoxy-5,6-ethylenedioxyindole forms 3-halo derivatives, while 5,6-ethylenedioxyindole itself forms only 3,7-dihalo derivatives. The closeness in the reactivities of the 3 and 7 ring positions of 5,6-ethylenedioxyindole (as compared with indole) is in agreement with the results of calculations of the quantum-chemical reactivity indexes for electrophilic substitution.

Derivatives of acids of the ethylenedioxyindole series, particularly those that contain halogens, display anti-inflammatory activity [1, 2]. In connection with the manifestation of anti-inflammatory and analgesic activity by 2-carboxyindole derivatives [3], it therefore seems of interest to develop methods for the synthesis of ethylenedioxy-substituted 2-carboxyindolines and their halo derivatives.

We have developed the following scheme for the synthesis of the previously unknown 4- and 7-halo-2-carboxy-5,6-ethylenedioxyindoles in the preparation of chloro derivatives VIb,c:



I–IIIa–c, IV c V–VIa–c, VII a VIIIb, d, IX b, d, X e, f

I R=NO_2; II R=$NH_2 \cdot HCl$; III R=$NHNH_2 \cdot HCl$; IV R=NHN=$C(CH_3)COOC_2H_5$; V, VIII R=$COOC_2H_5$; VI, IX R=COOH; VII, X R=H; a R′=R″=H; b R′=H, R″=Cl; c R′=Cl, R″=H; d R′=H, R″=Br; e R′=R″=Br; f R′=R″=Cl

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