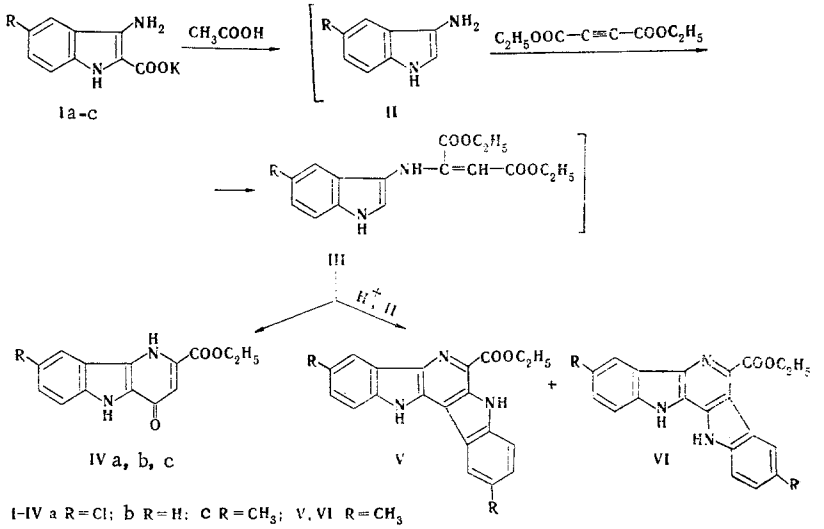
REACTION OF 3-AMINOINDOLE-2-CARBOXYLIC ACIDS WITH DIETHYL ACETYLENEDICARBOXYLATE

O. N. Boyarintseva, G. N. Kurilo,
O. S. Anisimova, and A. N. Grinev

UDC 547.759.3:542.953.7

δ-Carboline and indolo-δ-carboline derivatives were obtained by reaction of the potassium salts of 3-aminoindole-2-carboxylic acids with diethyl acetylenedicarboxylate. A difference in the behavior of 3-aminoindole derivatives in the Michael reaction due to the nature of the substituent in the 5 position of the indole ring was established.

The reaction of aromatic and heteroaromatic amines with diethyl acetylenedicarboxylate is widely used for the construction of α- and γ-pyridone fragments in the synthesis of condensed heterocycles [1-3]. The reaction of some heteroaromatic amines with diethyl acetylenedicarboxylate proceeds in a more complex manner and is accompanied by ring expansion [4]. In order to synthesize δ-carboline (pyrido[3,2-b]indole) derivatives, we studied the behavior of 3-aminoindole-2-carboxylic acids in the Michael reaction. It was established that the only product of the reaction of 3-amino-5-chloroindole-2-carboxylic acid (Ia) with diethyl acetylenedicarboxylate is 4-oxo-1,4-dihydro-δ-carboline (IVa). However, when R = H, CH_3, two isomeric indolo-δ-carbolines (V, VI) are formed as side products, in addition to 4-oxo-1,4-dihydro-δ-carbolines (IVb, c). When R = H, we were unable to separate isomeric indolo-δ-carboline.

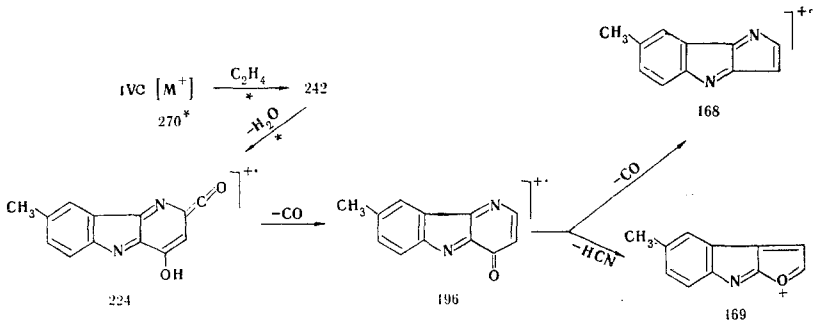


3-Aminoindole (II), which is formed from the potassium salt of the amino acid (Ia-c) by acidification as a result of facile decarboxylation, undergoes Michael reaction at the amino group to give adduct III. Intramolecular cyclization of the latter leads to 4-oxo-1,4-dihydro-δ-carbolines (IVa-c). A competitive process due to protonation of the indolenine form of adduct III and subsequent reaction with a second molecule of aminoindole II, leads to two isomeric indolo-δ-carbolines (V, VI).

The presence of a γ-pyridone fragment in IVa-c was confirmed by the similarity in the mass spectra of these compounds and the mass spectra of γ-pyridones formed by fragmentation of the furan cation [5]. A charac-

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119815.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 82-84, January, 1977. Original article submitted February 16, 1976.

teristic feature of the fragmentation of IVa-c is elimination of ethanol from the molecular ion due to the ortho orientation of the carbethoxy group with respect to the NH group of the γ-pyridone ring.



The mass spectra of isomeric indolo-δ-carbolines V and VI have molecular ions with an identical mass number (357).* The chief pathway of fragmentation of V and VI is stepwise elimination of a carbethoxy group to give ions with m/e 329, 311, and 283. A distinctive feature of the fragmentation of VI is elimination of a molecule of ethanol, on the basis of which the indolo[3,2-c]-δ-carboline structure was assigned to it.

The assignment of the isomeric indolo-δ-carbolines to the corresponding structures V and VI was additionally made on the basis of the PMR spectra.

A doubled number of protons corresponds to each signal in the PMR spectrum of VI; this indicates the magnetic equivalence of the two indole rings. The imino groups in V are not equivalent because of the closeness of the carbethoxy group to one of them; this is responsible for the difference in the chemical shifts of the protons of the NH groups and the remaining protons of both of the indole rings.

The higher melting point of V than that of isomer VI is evidently due to intramolecular hydrogen bonding.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in deuterodimethyl sulfoxide–CCl_4 were recorded with a C-60HL (JEOL) spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 30 eV and an ionization chamber temperature of 125°. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer.

1H,5H-2-Carbethoxy-8-chloro-4-oxo-1,4-dihydro-δ-carboline (IVa). A 5-ml sample of 50% potassium hydroxide solution was added to a solution of 1.19 g (0.005 mole) of 2-carbethoxy-3-amino-5-chloroindole in 10 ml of alcohol, and the mixture was refluxed for 20 min, after which it was cooled. The precipitated potassium salt of 3-amino-5-chloroindole-2-carboxylic acid (Ia) was removed by filtration and treated with a solution of 0.7 ml (0.0059 mole) of diethyl acetylenedicarboxylate in 10 ml of glacial acetic acid, after which the mixture was refluxed for 20 min. It was then cooled, and the precipitate was removed by filtration and washed with acetic acid to give 0.6 g (46.4%) of a product with mp 317-318° [from dimethylformamide (DMF)]. Found: C 58.2; H 3.8; Cl 12.4; N 9.7%. $C_{14}H_{11}ClN_2O_3$. Calculated: C 57.8; H 3.8; Cl 12.2; N 9.6%. IR spectrum: 3420, 2700, 1715, 1680 cm^{-1}.

1H,5H-2-Carbethoxy-4-oxo-1,4-dihydro-δ-carboline (IVb). This compound was similarly obtained, except that the reaction with diethyl acetylenedicarboxylate was carried out at room temperature for 1 h. Workup gave the product, with mp 278-279° (from DMF), in 25.4% yield. Found: C 65.9; H 4.6; N 11.1%. $C_{14}H_{12}N_2O_3$. Calculated: C 65.6; N 4.7; N 10.9%. IR spectrum: 3420, 2700, 1700, 1660 cm^{-1}.

7H,8H-2-Carbethoxy-4,11-dimethylindolo[3,2-c]-δ-carboline (VI). This compound, with mp 257-258° (from isopropyl alcohol), was obtained in 24.9% yield by the method used to prepare IVb. Found: C 73.7; H 5.4; N 11.7%. $C_{22}H_{19}N_3O_2$. Calculated: C 73.9; H 5.4; N 11.8%. IR spectrum: 3450, 3300, 1695 cm^{-1}. PMR spectrum, δ, ppm: 1.53 (2-$COOCH_2\mathbf{CH_3}$, 3H, m); 2.52 (4, 11-CH_3, 6H, s); 4.64 (2-$COOCH_2CH_3$, q); 7.21 (6,9-CH, 2H, d); 7.47 (5,10-CH, 2H, d); 8.05 (3,12-CH, 2H, d); 10.83 (7,8-NH, 2H, s).

3H,8H-2-Carbethoxy-6,11-dimethylindolo[2,3-c]-δ-carboline (V). The filtrate obtained after separation of VI was allowed to stand overnight, and the resulting precipitate was removed by filtration and washed with

*Here and subsequently, the m/e values are presented for the mass spectra.

alcohol-hexane (2 : 8) to give a product with mp 318-319° (from acetone) in 1.4% yield. Found: C 74.0; H 5.3; N 12.2%. $C_{22}H_{19}N_3O_2$. Calculated: C 73.9; H 5.4; N 11.8%. IR spectrum: 3420, 3140, 1690 cm^{-1}. PMR spectrum, δ, ppm: 1.49 (2-$COOCH_2CH_3$, m); 2.51 (11-CH_3, s); 2.55 (6-CH_3, s); 4.51 (2-$COOCH_2CH_3$, q); 7.12-7.72 (aromatic protons, 4-H, 5-H, 9-H, 10-H, m); 8.07 (12-CH, s); 8.44 (7-CH, s); 11.6 (8-NH, s); 12.12 (3-NH, s).

1H,5H-2-Carbethoxy-4-oxo-8-methyl-1,4-dihydro-δ-carboline (IVc). The filtrate obtained after separation of VI was vacuum evaporated, and the residue was suspended in acetone. The resulting crystals were removed by filtration and recrystallized from 125 ml of acetone to give a product with mp 289-290° (from acetone) in 26.8% yield. Found: C 66.6; H 5.2; N 10.2%. $C_{15}H_{14}N_2O_3$. Calculated: C 66.6; H 5.2; N 10.4%. IR spectrum: 3480, 2700, 1710, 1680 cm^{-1}. PMR spectrum, δ, ppm: 1.36 (2-$COOCH_2CH_3$, m); 2.39 (8-CH_3, s); 4.42 (2-$COOCH_2CH_3$, q); 6.33 (3-CH, s); 7.11 and 7.20 (6-CH, d); 7.43 and 7.52 (7-CH, d); 7.76 (9-CH, s); 10.92 (5-NH, s); 11.75 (1-NH, s).

LITERATURE CITED

1. N. D. Heindel, I. S. Bechara, P. D. Kennewell, J. Molnar, C. J. Ohnmacht, S. M. Lemke, and T. F. Lemke, J. Med. Chem., 11, 1218 (1968).
2. A. Shafiee and I. Zalesari, J. Heterocycl. Chem., 4, 675 (1975).
3. F. Troxler and H. P. Weber, Helv. Chim. Acta, 57, 2356 (1974).
4. Zin Mei-Sie and V. Snieckus, J. Org. Chem., 36, 645 (1971).
5. H. Budzikiewicz, C. Djerassi, and D. Williams, Interpretation of the Mass Spectra of Organic Compounds, Holden-Day, San Francisco (1964).

PORPHYRINS

IV.* SYNTHESIS AND PROPERTIES OF SCHIFF BASES OF meso-FORMYLETIOPORPHYRIN I

G. V. Ponomarev and G. B. Maravin

UDC 547.749.07:541.49

The reaction of salts of meso-dimethylformaldiminoetioporphyrin I and its copper complex with ammonia, hydrazine, aliphatic and alicyclic amines, and amino acids was investigated, and the corresponding azomethine derivatives were obtained.

It has recently been demonstrated [2] that meso-dimethylaminomethyletioporphyrin I, obtained from the phosphorus complex (I), facilitates the postradiation revivification of a culture of heart cells from the ape, cynomolgus. A number of compounds containing, in the meso position of the porphyrin ring, an effective, within a radiobiological framework, aminomethyl group with diverse substituents attached to the nitrogen atom, seem of interest for the study of the effect of porphyrins on the organs and tissues in the case of radiation sickness. Compounds of this type might have been synthesized by reduction of the corresponding Schiff bases.

Several examples of the preparation of Schiff bases of meso-formylporphyrins with aromatic amines [3], as well as a single communication regarding the synthesis of a Schiff base of meso-formyloctaethylporphyrin with β-alanine [4], are presently known. All of these reactions proceed at high temperatures because of the low reactivity of the meso-formyl group. This is probably why our attempts to obtain Schiff bases by the classical method [starting from meso-formyletioporphyrin I (II) with lower aliphatic amines] were unsuccessful.

* For Communication III, see [1].

Institute of Biophysics, Ministry of Public Health of the USSR, Moscow 123182.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 85-89, January, 1977. Original article submitted January 23, 1976; revision submitted May 6, 1976.