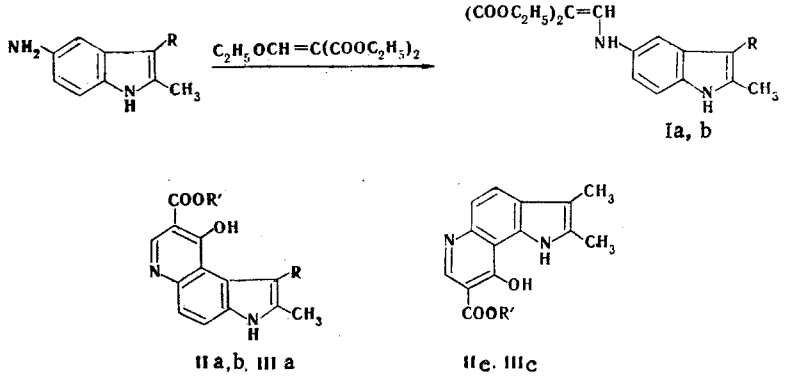
SYNTHESIS OF PYRROLOQUINOLINES FROM AMINOINDOLES AND ETHOXYMETHYLENEMALONIC ESTER

V. P. Chetverikov, S. A. Yamashkin,
A. N. Kost, and L. G. Yudin

UDC 547.836.3.07

Intensive researches have recently been carried out in the series of pyrroloquinolines. They are synthesized by enlarging the pyrrole ring to quinolines [1-3] or the pyridine ring to indoles [4,5]. However, existing methods do not make it possible to obtain compounds with functional groups in the pyridine part of the molecule, although by analogy with a series of known biologically active compounds, interesting pharmacological characteristics can be expected in such structures. In this connection we investigated the cyclization of indolylaminomethylenemalonic esters (Ia-c), which are easy to obtain by condensation of 5- or 6-aminoindoles with ethoxymethylenemalonic esters.



Ia-IIIa R=CH_3; Ib, IIb R=H; IIa,b,c R′=C_2H_5; IIIa, c R′=H

Ia R=CH_3; b R=H; IIa R=CH_3, R′=C_2H_5; b R=H, R′=C_2H_5; c R′=C_2H_5; III a R=CH_3, R′=H; c R′=H

It was found that when heated in boiling diphenyl ether, compound (Ia) forms a pyrroloquinoline with an angular structure, i.e., 1,2-dimethyl-8-ethoxycarbonyl-9-hydroxypyrrolo[3,2-f]quinoline (IIa), as shown by the PMR spectrum, where the signals of an AB system of aromatic protons are seen (Table 1). The ester (Ib) is converted similarly into compounds (IIb), the UV and PMR spectra of which are similar to the spectra of compound (IIa) (Table 1). Alkaline hydrolysis of the ester (IIa) leads to the acid (IIIa). In contrast to the examples of the synthesis of pyrroloquinolines by the Combes condensation described above [4, 5], the process is regiospecific, since in both cases it was not possible to detect the linear isomer as impurity by thin-layer chromatography of the reaction mass. If we start from N-(2,3-dimethyl-6-indolyl)aminomethylenemalonic ester (Ib), the drastic conditions of high-temperature condensation here overcome the steric hindrances, and the main reaction product is the angular 2,3-dimethyl-8-ethoxycarbonyl-9-hydroxypyrrolo[2,3-f]quinoline (IIc) on account of intramolecular acylation with attack at the $C_{(7)}$ atom.

According to data obtained by V. M. Kurilenko (Novokuznetsk Scientific-Research Chemical-Pharmaceutical Institute), the esters (Ia) and (IIa, c) and also the acid (IIIc) have low toxicity when administered intraabdominally to white mice (LD_{50} more than 1000 mg/kg). The pyrroloquinolines (IIc) and (IIIc) have a general depressing action on the central nervous system; they reduce the body temperature, disrupt the coordination of movement, depress orientation reactions, and prolong chloral hydrate sleep. Hypothermic action is most clearly

M. V. Lomonosov Moscow State University, Moscow 117234. Mordovian State University, Saransk 430000. Novokuznetsk Scientific-Research Chemical-Pharmaceutical Institute, Novokuznetsk 654034. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1084-1086, August, 1979. Original article submitted December 22, 1978.

 0009-3122/79/1508-0888$07.50

TABLE 1. Pyrroloquinolines

Compound	mp, °C	Found, %			Molecular formula	Calculated, %			UV spectrum, λ_{max}, nm (log ε)	Yield, %
		C	H	N		C	H	N		
IIa	269—270[a]	67,5	5,6	9,4	$C_{16}H_{16}N_2O_2$	67,6	5,6	9,8	224 (4,60), 260 (4,16), 303 (4,41), 352 (4,17)	68
IIb	268—270[b]	67,0	5,6	—	$C_{15}H_{14}N_2O_3$	66,7	5,2	—	222 (4,55), 255 (4,10), 295 (4,44), 349 (4,20)	56
IIc	287—288[c]	67,7	5,7	10,0	$C_{26}H_{16}N_2O_3$	67,6	5,6	9,8	213 (4,48), 240 (4,01) (sh), 296 (4,46), 339 (3,99)	70
IIIa	247—248	65,6	4,9	10,4	$C_{14}H_{12}N_2O_3$	65,6	4,7	11,0	—	90
IIIc	261—262	65,2	5,1	10,1	$C_{14}H_{12}N_2O_3$	65,6	4,7	11,0	—	82

a From DMFA. PMR spectrum: 7.08 (d, 4-H; J_{45} = 9 Hz), 7.53 (d, 5-H), 8.23 (bs, 7-H), 11.20 (s, 3-H), 11.93 ppm (bs, 6-H).
b From DMSO. PMR spectrum: 7.22 (d, 4-H ; J_{45} = 9 Hz), 7.25 (s, 1-H), 7.62 (d, 5-H), 8.40 (s, 7-H), 11.40 ppm (s, 3-H).
c From DMCO. PMR spectrum: 7.14 (d, 4-H; J_{45} = 9 Hz), 7.71 (d, 5-H), 8.40 (s, 7-H), 11.42 ppm (s, 1-H).

defined in the ester (IIc), which reduces the body temperature by 5.5-7.0°C. Compound (IIa) has a stimulating action, reducing the threshold convulsive dose of Corazol, whereas compound (Ia) has tranquillizing properties. At a dose equal to 1/5 of the LD_{50} it reduces the body temperature, impedes orientation reaction, prolongs chloral hydrate sleep, and increases the threshold of Corazol convulsions. Analgesic activity (in mice and rats) was found in compounds (IIa, c) and (IIIa). Compound (IIc) only increases the threshold of pain sensitivity during electric stimulation. The other two compounds exhibit analgesic action comparable with Analgin during electric, mechanical, or thermal stimulation. Compound (IIa) possesses antiserotonin characteristics and, in particular, reduces the peripheral effect of serotonin.

EXPERIMENTAL

The PMR spectra were recorded on a Varian S-100X instrument in DMSO with TMS as internal standard. The electronic spectra were recorded on a Cary-15 instrument in ethanol. The individualities of the compounds were determined by TLC on Silufol.

Diethyl N-(2,3-Dimethyl-5-indolyl)aminomethylenemalonate (Ia). To a solution of 11 mmole of 5-amino-2,3-dimethylindole [4] in 20 ml of alcohol we added 11 mmole of ethoxymethylenemalonic ester. The mixture was boiled for 1 h, and the crystals which separated on cooling were filtered off and washed with alcohol. The yield of the ester (Ia) was 64%; mp 146-147°C. UV spectrum, λ_{max} (log ε): 230 (4,33), 297 (4.37), 336 nm (4.40). Found, %: C 65.5; H 7.0; N 8.5. $C_{18}H_{22}N_2O_4$. Calculated, %: C 65.4; H 6.7; N 8.5. The following compounds were obtained similarly.

Diethyl N-(2-Methyl-5-indolyl)aminomethylenemalonate (Ib). The yield was 65%; mp 141-142°C. UV spectrum, λ_{max} (log ε): 255 (4.29), 285 (4.31), 334 nm (4.42). Found, %: C 64.5; H 6.3. $C_{17}H_{20}N_2O_4$. Calculated, %: C 64.5; H 6.3.

Diethyl N-(2,3-Dimethyl-6-indolyl)aminomethylenemalonate (Ic). The yield was 73%; mp 159-160°C. UV spectrum, λ_{max} (log ε): 225 (4.20), 286 (3.97), 350 nm (4.22). Found, %: C 65.4; H 6.8; N 8.4. $C_{18}H_{22}N_2O_4$. Calculated, %: C 65.4; H 6.7; N 8.5.

Pyrroloquinolines (IIa-c) (Table 1). To 45 ml of boiling diphenyl ether we added 9 mmole of the respective ester (I). The mixture was boiled for 20-40 min. After cooling, it was diluted with hexane (50 ml). The precipitate was filtered off, washed with hexane, and crystallized from DMFA or DMSO.

Pyrroloquinolinecarboxylic Acids (IIIa, c) (Table 1). A 0.7-mmole sample of the ester (II) was dissolved in 10 ml of a saturated alcohol solution of sodium hydroxide and heated at 95°C for 1 h 30 min. On cooling, the acid was precipitated by acidification with hydrochloric acid and by dilution with water. The precipitate was filtered off and crystallized from alcohol.

LITERATURE CITED

1. H. Wieland and L. Horner, Ann., 536, 89 (1938).
2. Zh. F. Sergeeva, R. N. Akhvlediani, V. P. Shabunova, B. A. Korolev, A. M. Vasil'ev, T. N. Babushkina, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 12, 1639 (1975).
3. N. N. Suvorov, Zh. F. Sergeeva, A. P. Gryaznov, V. P. Shabunova, L. G. Tret'yakova, T. K. Efimova, T. A. Volodina, I. A. Morozova, R. N. Akhvlediani, A. M. Vasil'ev, and T. K. Trubitsina, "Physiologically active compounds," Mosk. Khim.-Tekhnol. Inst. im D. I. Mendeleeva, No. 94, 23 (1977).
4. A. N. Kost, S. A. Yamashkin, and L. G. Yudin, Khim. Geterotsikl. Soedin., No. 6, 770 (1977).
5. S. A. Yamashkin, A. N. Kost, L. G. Yudin, P. B. Terent'ev, and O. A. Solov'ev, Khim. Geterotsikl. Soedin., No. 10 (1979) (in press).

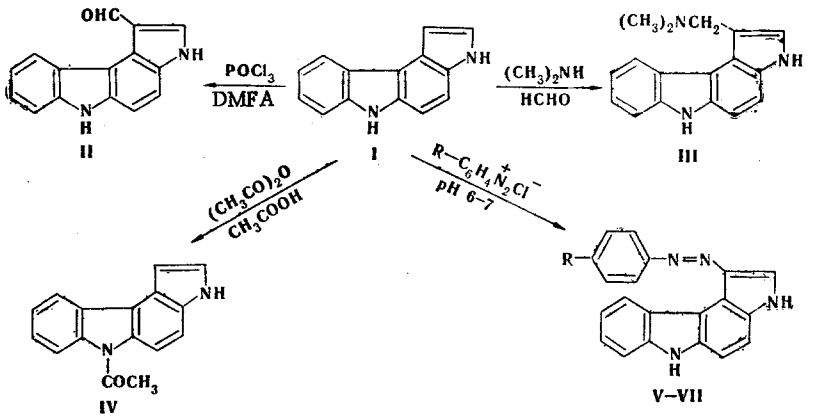
PYRROLOCARBAZOLES 2.*

SOME DERIVATIVES OF 3H-PYRROLO[2,3-c]CARBAZOLE

M. I. Sikharulidze, T. E. Khoshtariya, L. N. Kurkovskaya, and N. N. Suvorov

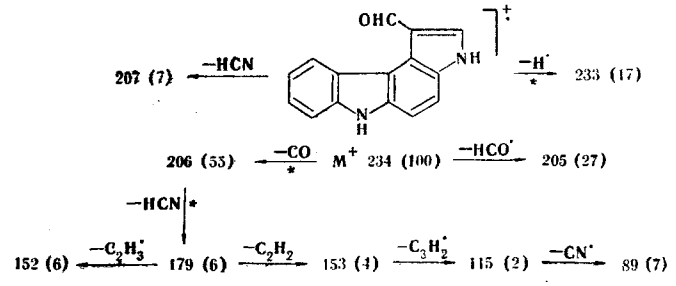
UDC 547.759.52.07

In the previous communication we described the synthesis of 3H-pyrrolo[2,3-c]carbazole [1]. In the present work, in order to investigate its reactivity, we studied certain electrophilic substitution reactions typical of the indole series (the Vilsmeier, Mannich, azo coupling, and acylation reactions).



V R=H; VI R=Cl; VII R=NO_2

In view of a certain structural similarity between pyrrolocarbazole and indole, the above-mentioned reactions were carried out with certain modifications under the conditions described for indole itself [2-5].



*For Communication 1, see [1].

D. I. Mendeleev Moscow Chemical Technology Institute, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1087-1091, August, 1979. Original article submitted December 5, 1978.

 0009-3122/79/1508-0890$07.50