

SYNTHESIS OF CONDENSED DERIVATIVES OF INDOLO[2,3-c]PYRYLIUM SALTS
AND β -CARBOLINES

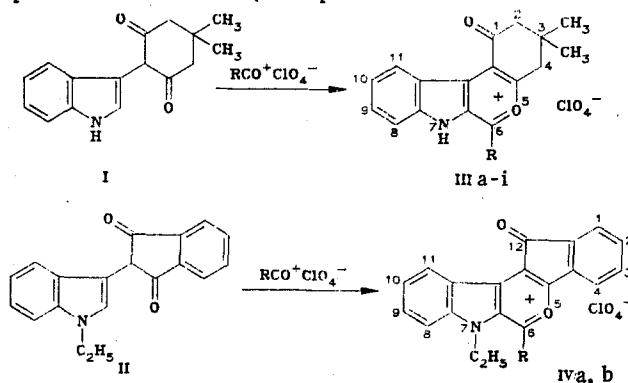
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UDC 547.753'821.3'833.9.07

Tetra- and pentacyclic indole[2,3-c]pyrylium salts were obtained by acylation of 2-(3-indolyl)dimedone and 2-(1-ethyl-3-indolyl)indan-1,3-dione. The latter salts by the action of ammonia are converted to the corresponding β -carboline derivatives of the natural alkaloid harman.

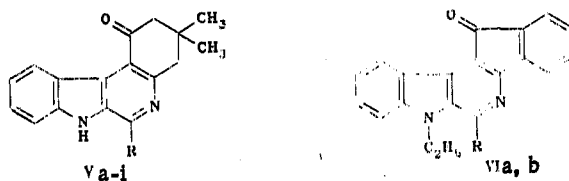
In the development of research with regard to indolopyrylium salts, which are convenient intermediates for the preparation of analogs of natural alkaloids [1, 2] we have accomplished the synthesis of new tetra- and pentacyclic compounds of this series. As starting compounds we used 2-(3-indolyl)dimedone (I) [3] and 2-(1-ethyl-3-indolyl)indan-1,3-dione (II), which was synthesized by the method described in [4].

3,3-Dimethyl-6-R-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]benzopyrylium perchlorates (IIIa-e) and 6-R-7-ethyl-12-oxoindolo[2,3-c]indeno(2,1-e)pyrylium perchlorates (IVa,b) were obtained by acylation of I and II with aliphatic carboxylic acid anhydrides in the presence of equimolar amounts of perchloric acid (the products were obtained in high yields).



III, IV.a R=CH₃; b R=C₂H₅; III c R=C₃H₇; d R=*i*-C₃H₇; e R=C₄H₉; f R=CH₂C₆H₅;
g R=C₆H₅; i R=CF₃

In order to obtain salts IIIf,g, as the acylating agents we used mixtures of phenylacetic and benzoic acid chlorides with perchloric acid. Perchlorate IIIi was synthesized by the reaction of indole I with trifluoroacetic anhydride in trifluoroacetic acid with subsequent treatment of the reaction mixture with perchloric acid.



The ability of pyrylium cations, under the influence of ammonia, to undergo conversion to pyridine bases was used to obtain, from salts III and IV, the previously unknown polycyclic β -carboline derivatives, viz., 3,3-dimethyl-6-R-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]quinoline (Va-i) and 6-R-6-ethyl-12-oxoindolo[2,3-c]indeno(2,1-e)pyridines (VIa,b).

*Deceased.

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TABLE 1. Characteristics of III-VI

Com- pound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
IIIa	245-246	57,0	4,7	9,5	3,6	C ₁₈ H ₁₈ ClNO ₆	56,9	4,7	9,4	3,7	89
IIIb	257-258	57,9	5,2	8,9	3,5	C ₁₉ H ₂₀ ClNO ₆	57,9	5,1	9,0	3,6	90
IIIc	240-242	59,2	5,5	8,9	3,4	C ₂₀ H ₂₂ ClNO ₆	58,9	5,4	8,7	3,4	91
IIId	265-267	59,0	5,3	8,7	3,4	C ₂₀ H ₂₂ ClNO ₆	58,9	5,4	8,7	3,4	87
IIIe	195-197	59,9	5,7	8,3	3,3	C ₂₁ H ₂₄ ClNO ₆	59,8	5,7	8,4	3,3	92
IIIf	175-176	62,9	5,0	7,7	3,0	C ₂₄ H ₂₂ ClNO ₆	63,2	4,9	7,8	3,1	75
IIIg	284-285	63,0	4,8	8,8	3,3	C ₂₃ H ₂₀ ClNO ₆	62,5	4,6	8,0	3,2	75
IIIi	220 (dec.)				3,3	C ₁₈ H ₁₅ ClF ₃ NO ₆				3,2	67
IVa	239-240	61,0	3,8	8,5	3,3	C ₂₁ H ₁₆ ClNO ₆	60,9	3,9	8,6	3,4	72
IVb	189-190	61,5	4,4	8,3	3,2	C ₂₂ H ₁₈ ClNO ₆	61,8	4,2	8,3	3,3	69
Va	176-177	77,9	6,5		10,0	C ₁₈ H ₁₈ N ₂ O	77,7	6,5		10,1	85
Va*	338-340	68,7	6,2	11,2	9,0	C ₁₈ H ₁₈ N ₂ O · HCl	68,7	6,1	11,3	8,9	80
Vb	140-142	78,3	6,9		9,4	C ₁₉ H ₂₀ N ₂ O	78,1	6,8		9,6	88
Vb*	246-248	69,6	6,4	10,6	8,5	C ₁₉ H ₂₀ N ₂ O · HCl	69,4	6,4	10,8	8,5	83
Vc	178-180	78,5	7,1		9,0	C ₂₀ H ₂₂ N ₂ O	78,4	7,2		9,2	85
Vc*	239-240	70,2	6,6	10,2	8,1	C ₂₀ H ₂₂ N ₂ O · HCl	70,1	6,7	10,4	8,2	85
Vd	168-170	78,5	7,1		9,0	C ₂₀ H ₂₂ N ₂ O	78,4	7,2		9,2	90
Vd*	206-208	70,0	6,7	10,4	8,1	C ₂₀ H ₂₂ N ₂ O · HCl	70,2	6,7	10,4	8,2	85
Ve	154-156	78,6	7,4		9,0	C ₂₁ H ₂₄ N ₂ O	78,8	7,5		8,8	84
Ve*	205-206	70,7	7,2	10,0	7,8	C ₂₁ H ₂₄ N ₂ O · HCl	70,7	7,0	10,0	7,9	80
Vf	140-142	81,3	6,3		7,9	C ₂₄ H ₂₂ N ₂ O	81,3	6,3		7,9	95
Vf*	179-180	73,5	6,0	8,9	7,0	C ₂₄ H ₂₂ N ₂ O · HCl	73,7	5,9	9,1	7,2	80
Vg	183-185	81,1	5,6		8,0	C ₂₃ H ₂₀ N ₂ O	81,2	5,9		8,2	95
Vg*	311-312	67,1	6,2	8,5	7,1	C ₂₃ H ₂₀ N ₂ O · HCl · 2H ₂ O	66,9	6,1	8,6	6,3	90
VI	157-158				8,7	C ₁₈ H ₁₅ F ₃ N ₂ O				8,4	95
VI*	226-227				7,3	C ₁₈ H ₁₅ F ₃ N ₂ O · HCl				7,5	95
VIa	185,5-187	80,5	5,2		8,9	C ₂₁ H ₁₈ N ₂ O	80,7	5,2		9,0	80
VIb	159-160	80,9	5,5		8,5	C ₂₂ H ₁₈ N ₂ O	81,0	5,6		8,6	53

*Hydrochlorides of the β -carbolines. The compounds were crystallized: IIIa-g from acetic acid, IIIi from acetic anhydride, IVi from acetone, Vg from cyclohexane, and the remaining compounds from alcohol.

Carbolines Va-f and VIa,b were synthesized by treatment of alcohol solutions of the corresponding indolopyrylium salts with gaseous ammonia, and bases Vg,i (R = C₆H₅ and CF₃) were synthesized by refluxing salts IIIg,i with ammonium acetate in acetic acid. Carboline hydrochlorides were obtained by the addition of hydrochloric acid to alcohol solutions of these substances. The characteristics of III-VI are presented in Table 1.

The IR spectra of indolopyrylium salts III and IV contain characteristic absorption bands of the pyrylium cation at 1605-1640 cm⁻¹ and of the ClO₄⁻ anion at 1100 cm⁻¹. The spectra of IIIf and Vf contain a broad absorption band at 1100-1200 cm⁻¹, which is characteristic for the vibrations of a trifluoromethyl group. The positions of the absorption bands of the carbonyl group in the spectra of III-VI are presented in Table 2.

A characteristic feature of the PMR spectra of all of the synthesized compounds (see Table 2) is the presence of a signal of an aromatic 11-H proton, which shows up in the form of a doublet at weaker field than the remaining aromatic protons of the indole fragment. This shift can be explained by the shielding influence of the closely situated oxygen atom of the carbonyl group in the 1 position for III and V and in the 12 position for IV and VI.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Tesla BS-467 spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard.

The characteristics of III-VI are presented in Table 1.

2-(1-Ethyl-3-indolyl)indan-1,3-dione. This compound was obtained by the method described in [4]. Workup gave a product with mp 168-170°C in 83% yield. Found: C 78.9; H 5.3; N 4.9%. C₁₉H₁₅NO₂. Calculated: C 78.9; H 5.2; N 4.8%.

Indolo[2,3-c]pyrylium Perchlorates (IIIa-e, IVa,b). A 0.01-mole sample of I or II was added with stirring at room temperature to a mixture of 25 ml of the carboxylic acid, 0.1 mole of a corresponding anhydride, and 0.01 mole of 70% perchloric acid. After 2 h, the resulting crystalline precipitate was removed by filtration, washed with ether, and dried.

TABLE 2. Spectral Characteristics of III-VI

Compound	PMR spectrum, δ , ppm (J, Hz)	IR spectrum, CO , cm^{-1}
IIIa	1,33 (6H, s, 3-CH ₃); 3,1 (2H, s, 2-CH ₂); 3,28 (3H, s, 6-CH ₃); 3,48 (2H, s, 4-CH ₂); 7,33—8,13 (4H, m, NH and arom. protons); 9,2 (1H, d, J=8, 11-H)	1705
IIIb	1,33 (6H, s, 3-CH ₃); 1,65 (3H, t, J=7; 6- β -CH ₂); 3,0 (2H, s, 2-CH ₂); 3,5 (2H, s, 4-CH ₂); 3,7 (2H, q, J=7, 6- α -CH ₂); 7,3—8,1 (4H, m, NH and arom. protons); 9,23 (1H, d, J=8; 11-H)	1705
IIIc	1,32 (6H, s, 3-CH ₃); 1,45 (3H, t, J=6; 6- γ -CH ₂); 1,67 (2H, m, 6- β -CH ₂); 3,0 (2H, s, 2-CH ₂); 3,45 (2H, s, 4-CH ₂); 3,73 (2H, t, J=8; 6- α -CH ₂); 7,3—8,15 (4H, m, 7-H and arom. protons); 9,25 (1H, d, J=8, 11-H)	1705
IIId	1,35 (6H, s, 3-CH ₃); 3,01 (2H, s, 2-CH ₂); 1,67 (6H, d, J=7; 6- β -CH ₂); 3,49 (2H, s, 4-CH ₂); 4,09 (1H, m, J=7; 6- α -CH); 7,4—8,1 (4H, m, NH and arom. protons); 9,19 (1H, d, J=8; 11-H)	1705
IIIe	1,01 (3H, t, J=6; 6- δ -CH ₃); 1,25—1,67 (4H, m, 6- β , γ -CH ₂); 1,35 (6H, s, 3-CH ₃); 3,1 (2H, s, 2-CH ₂); 3,5 (2H, s, 4-CH ₂); 3,75 (2H, t, J=8; 6- α -CH ₂); 7,25—8,1 (4H, m, N—H and arom. protons); 9,15 (1H, d, J=8, 11-H)	1705
IIIf	1,35 (6H, s, 3-CH ₃); 3,05 (2H, s, 2-CH ₂); 3,49 (2H, s, 4-CH ₂); 5,1 (2H, s, CH ₂); 7,2—8,1 (9H, m, N—H and arom. protons); 9,17 (1H, d, J=8, 11-H)	1705
IIIg	1,37 (6H, s, 3-CH ₃); 3,08 (2H, s, 2-CH ₂); 3,6 (2H, s, 4-CH ₂); 7,41—8,37 (9H, m, NH and arom. protons); 9,3 (1H, d, J=8; 11-H)	1715
IIIh	1,37 (6H, s, 3-CH ₃); 3,1 (2H, s, 2-CH ₂); 3,65 (2H, s, 4-CH ₂); 7,52—8,33 (4H, m, NH and arom. protons); 9,4 (1H, d, J=8, 11-H)	1718
IVa	1,6 (3H, t, J=7; 7- β -CH ₃); 3,46 (3H, s, 6-CH ₃); 4,73 (2H, q, J=7; 7- α -CH ₂); 7,4—8,16 (7H, m, and arom. protons); 9,0 (1H, d, J=8, 11-H)	1730
IVb	1,56 (3H, t, J=7; 6- β -CH ₃); 1,69 (3H, t, J=7; 7- β -CH ₃); 3,76 (2H, q, J=7; 6- α -CH ₂); 4,67 (2H, q, J=7; 7- α -CH ₂); 7,4—8,1 (7H, m, arom. protons); 9,0 (1H, d, J=8, 11-H)	1730
Va	1,3 (6H, s, 3-CH ₃); 2,97 (2H, s, 2-CH ₂); 3,17 (3H, s, 6-CH ₃); 3,37 (2H, s, 4-CH ₂); 7,33—7,9 (4H, m, NH and arom. protons); 9,27 (1H, d, J=8, 11-H)	1680, 1685*
Vb	1,3 (6H, s, 3-CH ₃); 1,61 (3H, t, J=7; 6- β -CH ₃); 3,0 (2H, s, 2-CH ₂); 3,45 (2H, s, 4-CH ₂); 3,56 (2H, q, J=7; 6- α -CH ₂); 7,3—8,0 (4H, m, NH and arom. protons); 9,2 (1H, d, J=8, 11-H)	1680, 1685*
Vc	1,21 (6H, s, 3-CH ₃); 1,4 (3H, t, J=6; 6- γ -CH ₃); 1,65 (2H, m, 6- β -CH ₂); 2,95 (2H, s, 2-CH ₂); 3,43 (2H, s, 4-CH ₂); 3,7 (2H, t, J=8, 6- α -CH ₂); 7,27—8,0 (4H, m, NH and arom. protons); 9,17 (1H, d, J=8, 11-H)	1680, 1685*
Vd	1,33 (6H, s, 3-CH ₃); 3,0 (2H, s, 2-CH ₂); 1,66 (6H, d, J=7; 6- β -CH ₃); 3,45 (2H, s, 4-CH ₂); 4,0 (1H, m, J=7; 6- α -CH); 7,4—8,1 (4H, m, NH and arom. protons); 9,17 (1H, d, J=8, 11-H)	1680, 1685*
Ve	1,0 (3H, t, J=6; 6- δ -CH ₃); 1,22—1,65 (4H, m, 6- β , α -CH ₂); 1,3 (6H, s, 3-CH ₃); 3,0 (2H, s, 2-CH ₂); 3,43 (2H, s, 4-CH ₂); 3,7 (2H, t, J=8; 6- α -CH ₂); 7,2—8,05 (4H, m, NH and arom. protons); 9,21 (1H, d, J=8; 11-H)	1680, 1685*
Vf	1,36 (6H, s, 3-CH ₃); 3,04 (2H, s, 2-CH ₂); 3,47 (2H, s, 4-CH ₂); 4,95 (2H, s, 6-CH ₂); 7,32—8,12 (9H, m, NH and arom. protons); 9,28 (1H, d, J=8; 11-H)	1680, 1685*
Vg	1,27 (6H, s, 3-CH ₃); 3,0 (2H, s, 2-CH ₂); 3,45 (2H, s, 4-CH ₂); 7,23—8,07 (9H, m, NH and arom. protons); 9,25 (1H, d, J=8, 11-H)	1680
Vi	1,33 (6H, s, 3-CH ₃); 3,0 (2H, s, 2-CH ₂); 3,5 (2H, s, 4-CH ₂); 7,4—8,2 (4H, m, NH and arom. protons); 9,3 (1H, d, J=8, 11-H)	1692, 1712*
VIa	1,58 (3H, t, J=7; 7- β -CH ₃); 3,44 (3H, s, 6-CH ₃); 4,73 (2H, q, J=7; 7- α -CH ₂); 7,4—8,16 (7H, m, arom. protons); 9,0 (1H, d, J=8, 11-H)	1712
VIb	1,55 (3H, t, J=7; 6- β -CH ₃); 1,67 (3H, t, J=7; 7- β -CH ₃); 3,75 (2H, q, J=7; 6- α -CH ₂); 4,65 (2H, q, J=7; 7- α -CH ₂); 7,4—8,1 (7H, m, arom. protons); 9,0 (1H, d, J=8, 11-H)	1712

*Hydrochlorides of the β -carbolines.

Indolo[2,3-c]pyrylium Perchlorates (III f, g). A 0.01-mole sample of indole I was added with stirring to a mixture of 0.05 mole of phenylacetic or benzoic acid chloride, 20 ml of nitromethane, and 0.01 mole of 70% perchloric acid, and the mixture was allowed to stand at room temperature for 3 h. During this time, the mixture turned dark and HCL was evolved, 100 ml of ether was added, and the resulting precipitate was removed by filtration and dried.

3,3-Dimethyl-6-trifluoromethyl-1-oxo-1,2,3,4-tetrahydroindolo[2,3-c]benzopyrylium Perchlorate (III i). A 2.55-g (0.01 mole) sample of indole I was added to a mixture of 7 ml (0.05 mole) of trifluoroacetic anhydride and 3 ml of trifluoroacetic acid, and the mixture was allowed to stand at room temperature for 24 h. A 0.8-ml (0.001 mole) sample of 70% perchloric acid and 100 ml of absolute ether were added successively with cooling to 5°C to

the resulting bright-red solution, and the crystalline precipitate was removed by filtration, washed with ether, and dried.

β -Carbolines (Va-f, VIa,b). Gaseous ammonia was passed into a suspension of 0.01 mole of perchlorates IIIa-f or IVa,b in 50 ml of alcohol in the course of 30 min, after which the solution was refluxed for 30 min, cooled, and diluted with 250 ml of water. The resulting precipitate was removed by filtration and dried.

β -Carbolines (Vg,i). A 0.01-mole sample of perchlorate IIIg or IIIi was added to a mixture of 3.8 g (0.05 mole) of ammonium acetate and 50 ml of acetic acid, and the resulting solution was refluxed for 30 min. It was then cooled and treated with 250 ml of water, and the precipitate was removed by filtration and dried.

Hydrochlorides of Va-i. These compounds were obtained by the addition of the calculated amount of concentrated hydrochloric acid to alcohol solutions of the β -carbolines.

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SYNTHESIS AND CONFIGURATION OF DIASTEREOMERIC 2,4-, 2,5-, AND 2,6-PIPERIDINEDICARBOXYLIC ACIDS AND THEIR DIMETHYL ESTERS

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UDC 547.823'826.2:541.67'634

The reduction in an acidic medium over a platinum catalysts of 2,4-, 2,5-, and 2,6-piperidinedicarboxylic acids gave cis-2,4-, -2,5-, and -2,6-piperidinedicarboxylic acids, heating of which in an alkaline medium led to thermodynamically equilibrium mixtures of diastereomers. Individual trans-2,5-piperidinedicarboxylic acid was isolated. The configurations of the 2,4-, 2,5-, and 2,6-piperidinedicarboxylic acids and their methyl esters were established by means of the PMR spectra.

Substituted 2-piperidinedicarboxylic acids are of interest as medicinals (dimecolin, mepivacin, etc.) [1], but little study has been devoted to the synthesis and stereoisomerism of piperidinedicarboxylic acids with a carboxy group in the 2 position of the piperidine ring. 2,3-Piperidinedicarboxylic acid was obtained at the end of the last century in the form of two diastereomers, which were assigned to the cis and trans series only on the basis of the difference in their melting points; the isomerization of the cis acid to the trans acid has been described [2, 3]. Later on, diethyl 2,3-piperidinedicarboxylate [4], 2,4-piperidinedicarboxylic acid, and its dimethyl ester [5] were synthesized; however, the configurations of the compounds were not established. Diethyl 2,5-piperidinedicarboxylate was obtained by hydrogenation of the corresponding pyridine ester, and a cis configuration was demonstrated for the isolated individual isomer.

The reduction of dipicolinic acid with platinum gives cis-2,6-piperidinedicarboxylic acid, whereas the reduction with sodium in alcohol or via an electrochemical method gave two forms of 2,6-piperidinedicarboxylic acid, the configurations of which were not estab-

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