SYNTHESIS OF INDOLO-α-PYRONES, INDOLO-α-PYRIDONES, AND INDOLOPYRYLIUM SALTS

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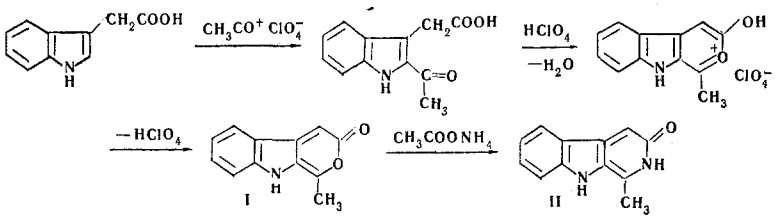
A method has been developed for obtaining indolo-α-pyrones by acylation of 3-indolylacetic acid and its N-methyl derivatives. Indolo-α-pyrones form indolo-α-pyridones by refluxing with ammonium acetate in acetic acid. Indolo[2,3-c]pyrylium salts were obtained by acylation of 4-methoxy- and 3,4-dimethoxy-3-phenacylindoles.

Indolopyrones can be obtained from 2-indolylcarboxylic acids [1] or by acylation of 3-indolylacetic acid with aliphatic acid anhydrides in the presence of boron trichloride [2]. We have shown that the acylation of 1-methyl-3-indolylacetic acid with acetic anhydride in the presence of 70% perchloric acid gives high yields of an unstable 1,2-dimethyl-3-hydroxyindolo[2,3-c]pyrylium perchlorate, which is readily converted to 1,2-dimethylindolo[2,3-c]-6-pyrone by treatment with ammonia [3].

As shown in this study, 3-indolylacetic acid (I, R = H) also readily forms an unstable 1-ethylindolo-[2,3-c]pyrylium salt by the action of acetyl perchlorate; the salt is converted to 2-methylindolo[2,3-c]-6-pyrone (I):



The heterocyclic oxygen is readily exchanged for nitrogen by refluxing I with ammonium acetate in glacial acetic acid to form 3-keto-1-methyl-2,3-dihydro-β-carboline (II).

Our proposed method for the synthesis of substituted indolo[2,3-c]-6-pyridones is considerably simpler than alkaline cyclization of amides of (2-acyl-3-indolyl)acetic acids [2].

The acylation of 3-indolylacetic acid and (1-methyl-3-indolyl)acetic acid with aromatic (benzoic and veratric), aliphatic-aromatic (phenylacetic and homoveratric), and heterocyclic (pyromucic and 3-indolylacetic) acids in the presence of polyphosphoric acid (PPA) proceeds similarly.

Under the influence of PPA an electrophilic substituent is initially directed to the 2-position of the indole ring to form keto acid III, which is cyclized with closing of the pyrone ring with subsequent formation in high yields (85-88%) of the previously undescribed indolo-α-pyrones (IV), which are brightly colored substances which fluoresce intensely in solutions.

Attempts to convert indolo-α-pyrones to indolo[2,3-c]pyrylium salts by alkylation of the lactone oxygen with ethyl orthoformate or by the action of a Grignard reagent [4] did not give positive results.

The IR spectra of indolopyrones IV, obtained as mineral oil pastes with an IKS-14 spectrophotometer (NaCl prism), contain an intense absorption band at 1670-1700 cm^{-1} ($\nu_{C=O}$) which is bathochromically

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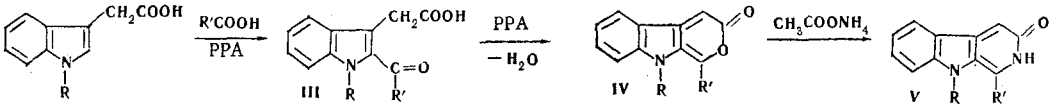
TABLE 1. Substituted Indolo-α-pyrones (IV)

R	R′	mp	IR spectrum, ν_{max}, cm^{-1}	Empirical formula	Found, %		Calc., %		Yield, %
					C	H	C	H	
CH_3	C_6H_5	165	1675; 1660; 1616; 1530	$C_{18}H_{13}NO_2$	78,3	4,9	78,5	4,7	95
CH_3	3,4-$(CH_3O)_2C_6H_3$	186	1690; 1595; 1512; 1275; 1060; 1010	$C_{20}H_{17}NO_4$	71,3	5,2	71,6	5,1	98
CH_3	$C_6H_5CH_2$	235	1680; 1665; 1654; 1560; 1540	$C_{19}H_{15}NO_2$	79,1	5,2	71,9	5,2	98
CH_3	3,4-$(CH_3O)_2C_6H_3CH_2$	187	1696; 1648; 1595; 1512; 1275; 1010	$C_{21}H_{19}NO_4$	72,6	4,8	72,8	4,6	97
H	3,4-$(CH_3O)_2C_6H_3$	204	1680; 1630; 1610; 1516; 1266; 1024	$C_{19}H_{15}NO_4$	70,7	4,9	71,0	4,7	86
H	$C_6H_5CH_2$	211	1690; 1650; 1610; 1540	$C_{18}H_{13}NO_2$	78,7	4,9	78,5	4,7	93
H	3,4-$(CH_3O)_2C_6H_3CH_2$	215	1692; 1620; 1616; 1560; 1512; 1258; 1230; 1065; 1018	$C_{20}H_{17}NO_4$	71,3	5,2	71,6	5,1	85
H	α-C_4H_3O	190	1713; 1692; 1650; 1618; 1512; 1273; 1230	$C_{15}H_9NO_3$	71,5	3,6	71,7	3,6	87

TABLE 2. Substituted 3-Keto-2,3-dihydro-β-carbolines

R′	mp	IR spectrum, ν_{max}, cm^{-1}	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
3,4-$(CH_3O)_2C_6H_3$	261	1650; 1620; 1546; 1512; 1258; 1135; 1018	$C_{19}H_{16}N_2O_3$	71,1	4,9	8,2	71,5	4,7	8,8	95
$C_6H_5CH_2$	255	1650; 1610; 1546; 1500	$C_{18}H_{14}N_2O$	78,8	5,0	10,2	79,1	4,8	10,2	91
3,4-$(CH_3O)_2C_6H_3CH_2$	253	1650; 1618; 1539; 1512; 1238; 1010	$C_{20}H_{18}N_2O_3$	71,7	5,3	8,6	72,0	5,1	8,4	85
α-C_4H_3O	231	1700; 1650; 1620; 1560	$C_{15}H_{10}N_2O_2$	71,9	4,0	11,1	72,3	4,0	11,2	97

shifted as compared with the position of this band in the spectra of α-pyrones [5] and isocoumarins [6] as well as an absorption band for the pyrone ring [5] at 1630-1650 cm^{-1}. The absorption bands at 1600-1610 cm^{-1} and 1500-1520 cm^{-1} are characteristic for the aromatic ring, while those at 1250-1280 and 1000-1050 cm^{-1} correspond to vibrations of the methoxy groups.



R = H, CH_3; R′ = C_6H_5, 3,4-$(CH_3O)_2C_6H_3$, $C_6H_5CH_2$, α-C_4H_3O, 3,4-$(CH_3O)_2C_6H_3CH_2$

Refluxing of indolo-α-pyrones in glacial acetic acid with a four- to fivefold excess of ammonium acetate yielded 92-97% of 3-keto-1-aryl(arylalkyl)-2,3-dihydro-β-carbolines (V), which are yellow or orange and fluoresce in solutions.

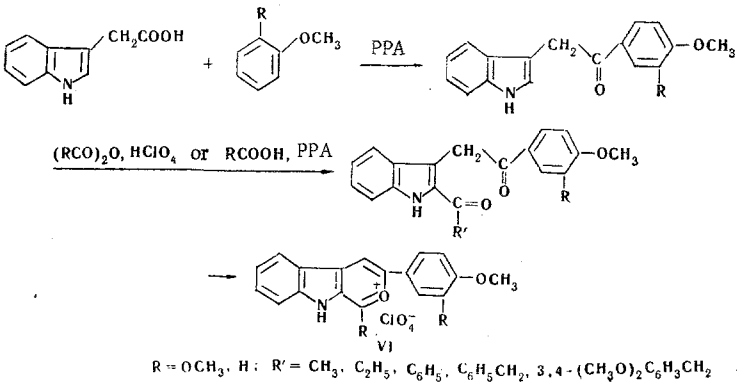
Like the spectrum of 3-isoquinolone [7], the IR spectra of indolopyridones V have a characteristic absorption band for the C=O group at 1650 cm^{-1} and absorption bands of the aromatic ring (1600-1620 cm^{-1} and 1500-1510 cm^{-1}) and of the methoxy groups (1250-1280 cm^{-1} and 1050-1100 cm^{-1}).

Pyrylium salts condensed with heterocyclic rings [8] and particularly with an indole ring are worthy of attention since the transition to β-carbolines [9] can be accomplished from indolo[2,3-c]pyrylium salts.

To obtain indolo[2,3-c]pyrylium salts which do not contain substituents attached to the nitrogen atom of the indole ring, we used the synthesis through the corresponding pyrylium compounds [8, 9] and obtained 86-88% yields of substituted 3-phenacylindoles by acylation of anisole or veratrole with 3-indolylacetic acid in the presence of PPA:

TABLE 3. Indolo[2,3-c]pyrylium Perchlorates (VI)

R	R′	mp	IR spectrum, ν max, cm^{-1}	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	Cl	C	H	Cl	
H	C_2H_5	300	1634; 1585; 1250; 1195; 1080	$C_{20}H_{18}ClNO_6$	60,0	4,6	8,5	59,5	4,5	8,8	47
H	$C_6H_5CH_2$	205	1662; 1625; 1609; 1250; 1178; 1092	$C_{25}H_{20}ClNO_6$	64,0	4,5	7,4	64,4	4,3	7,6	53
H	3,4-$(CH_3O)_2C_6H_3CH_2$	above 360	1624; 1520; 1275; 1232; 1088	$C_{26}H_{24}ClNO_8$	61,2	4,5	6,2	61,6	4,6	6,7	47
OCH_3	CH_3	285	1625; 1570; 1265; 1092	$C_{20}H_{18}ClNO_7$	57,5	4,6	8,8	57,2	4,3	8,5	50
OCH_3	C_2H_5	286	1662; 1626; 1560; 1275; 1090	$C_{21}H_{20}ClNO_7$	57,8	4,6	7,8	58,1	4,6	8,2	40
OCH_3	C_6H_5	265	1662; 1624; 1512; 1260; 1072	$C_{25}H_{20}ClNO_7$	62,0	4,3	7,1	62,3	4,1	7,4	47
OCH_3	$C_6H_5CH_2$	245	1660; 1625; 1560; 1275; 1095	$C_{26}H_{22}ClNO_7$	62,7	4,4	6,7	63,0	4,4	7,2	37
OCH_3	3,4-$(CH_3O)_2C_6H_3CH_2$	above 360	1625; 1515; 1275; 1230; 1090	$C_{28}H_{26}ClNO_9$	61,0	4,7	6,6	60,5	4,7	6,4	55



VI

R = OCH_3, H; R′ = CH_3, C_2H_5, C_6H_5, $C_6H_5CH_2$, 3,4-$(CH_3O)_2C_6H_3CH_2$

Acylation of these ketones with acetic or propionic anhydrides in the presence of 70% $HClO_4$ leads to 2-alkyl-4-arylindolo[2,3-c]pyrylium perchlorate (VI) in yields of about 50%.

Acylation with benzoic, phenylacetic, or homoveratric acids in the presence of a tenfold amount of PPA yields 80-90% of 2,4-diarylindolo-[2,3-c]pyrylium phosphates, which were converted to crystalline perchlorates VI in glacial acetic acid with an equimolecular amount of perchloric acid.

The IR spectra of all of the pyrylium salts obtained contain an intense absorption band at 1640-1650 cm^{-1} which corresponds to the symmetrical valence vibrations of the pyrylium cations [10, 11]. The band at 1600 cm^{-1} (aromatic ring absorption) in several cases is overlapped by the stronger absorption band of the pyrylium cation. The absorption at 1260-1270 cm^{-1} indicates the presence of methoxy groups. There is also an intense absorption band at 1090-1100 cm^{-1} which is characteristic for the ClO_4^- anion.

In an attempt to convert 2-methyl-3-(p-anisyl)indolo[2,3-c]pyrylium perchlorate to the corresponding β-carboline by the action of ammonium hydroxide or by refluxing with ammonium acetate in glacial acetic acid we isolated a ring opening product – 2-acetyl-3-(p-methoxyphenacyl)indole – which was also obtained by the reaction of this salt with an alcohol solution of sodium acetate. The identical character of the two preparations was proved by chromatography in a thin layer of aluminum oxide and also by IR spectroscopy.

2-Methyl-3-(p-methoxyphenacyl)indolo[2,3-c]pyrylium perchlorate is formed from 2-acetyl-3-(p-methoxyphenacyl)indole by the addition of acetyl perchlorate.

EXPERIMENTAL

2-Methyl-3-hydroxyindolo[2,3-c]pyrylium Perchlorate. Glacial acetic acid (7 ml) and a solution of acetyl perchlorate, prepared with cooling from 6.5 ml of acetic anhydride and 1 ml of 70% perchloric acid, were added dropwise to 1.61 g (9.2 mmole) of 3-indolylacetic acid. The solution was diluted with ether, and the reaction product was recrystallized from glacial acetic acid to give 2.4 g (80%) of a perchlorate which decomposed on heating. IR spectrum (ν max, cm^{-1}): 1660 strong, 1626 weak, 1583 weak, 1546 medium, 1100 strong, 1529 strong. Found %: Cl 11.4. $C_{12}H_{10}ClNO_6$. Calculated %: Cl 11.8.

2-Methylindolo[2,3-c]-6-pyrone. A total of 10 ml of a 25% ammonium hydroxide solution was added to 1 g (3 mmole) of 2-methyl-3-hydroxyindolo[2,3-c]pyrylium perchlorate to give 0.47 g (71%) of bright-yellow crystals with mp 263° (from ethanol) (mp 260° [2]). IR spectrum (ν_{max}, cm^{-1}): 1700 strong; 1646 medium, 1600 medium, 1550 medium, 1520 medium. Found %: C 71.9; H 4.5; N 7.3. $C_{12}H_9NO_2$. Calculated %: C 72.2; H 4.5; N 7.0.

3-Keto-1-methyl-2,3-dihydro-β-carboline. A mixture of 1 g (5 mmole) of 2-methylindolo[2,3-c]-6-pyrone, 5 g of ammonium acetate, and 10 ml of glacial acetic acid was refluxed for 1.5 h. The mixture was cooled and diluted with water to give 0.85 g (86%) of a precipitate with mp 300° (decomp., from ethanol) (mp 300° (decomp.) [2]). IR spectrum (ν_{max}, cm^{-1}): 1640 strong, 1612 strong, 1550 weak, 1528 medium. Found %: C 73.0; H 5.2; N 13.8. $C_{12}H_{10}N_2O$. Calculated %: C 72.7; H 5.0; N 14.1.

2-Phenylindolo[2,3-c]-6-pyrone. Hot PPA (10 g), prepared from 10 g of H_3PO_4 and 15 g of P_2O_5 (100° for 2 h) [12], was added to a mixture of 0.87 g (5 mmole) of 3-indolylacetic acid and 1 g (8 mmole) of benzoic acid. The mixture was stirred thoroughly and heated on a water bath (95-100°) for 30 min. The mixture became dark red. The hot solution was poured into 150 ml of cold water. The resulting precipitate was triturated thoroughly and filtered and washed on the filter successively with water, 10% sodium carbonate, and again with water to give 1.3 g (97%) of an orange, crystalline substance with mp 231° (from ethanol). IR spectrum (ν_{max}, cm^{-1}): 1690 strong, 1640 medium, 1610 strong, 1250 weak. Found %: C 77.9; H 4.4. $C_{17}H_{11}NO_2$. Calculated %: C 78.2; H 4.2.

The remaining indolo-α-pyrones were similarly obtained (Table 1).

3-Keto-2-phenyl-2,3-dihydro-β-carboline. A mixture of 1.08 g (4.1 mmole) of indolo-α-pyrone, a four- to fivefold excess of ammonium acetate, and 5 ml of glacial acetic acid was refluxed for 10 h. The mixture was poured into ice water (150 ml), and the precipitate was thoroughly ground, filtered, and washed with water to give 1.05 g (96%) of a light-yellow, crystalline product with mp 290° (from xylene). IR spectrum (ν_{max}, cm^{-1}): 1650 strong, 1610 strong, 1546 strong, 1500 medium. Found %: C 78.6; H 4.4; N 10.7. $C_{17}H_{12}N_2O$. Calculated %: C 78.8; H 4.2; N 10.8.

The other β-carbolines were similarly obtained (Table 2).

3-(3,4-Dimethoxyphenacyl)indole. A mixture of 1.6 g (9.2 mmole) of 3-indolylacetic acid, 3 ml of veratrole, and 20 g of PPA was heated on a water bath (70-75°) for 30 min and poured into ice water. The resulting precipitate was filtered and washed on the filter with water, 10% sodium carbonate, and water; and the substance was dried to give 2.5 g (96%) of red crystals with mp 243° (from alcohol). Found %: C 72.9; H 5.5. $C_{18}H_{17}NO_3$. Calculated %: C 73.2; H 5.8.

3-(p-Methoxyphenacyl)indole. This was similarly obtained in 88% yield as a light-brown substance with mp 260° (from ethanol). Found %: C 76.4; H 5.5. $C_{17}H_{15}NO_2$. Calculated %: C 77.0; H 5.7.

2-Methyl-4-(p-anisyl)indolo[2,3-c]pyrylium Perchlorate. A cooled mixture of 1.3 ml of acetic anhydride and 0.3 ml of 70% perchloric acid was added dropwise to a solution of 0.6 g (2 mmole) of 3-(p-methoxyphenacyl)indole in 5 ml of glacial acetic acid, and the mixture was allowed to stand, during which 0.6 g (75%) of red-brown crystals of the pyrylium salt with mp 195° (from glacial acetic acid) precipitated. IR spectrum (ν_{max}, cm^{-1}): 1646 medium, 1618 weak, 1595 medium, 1546 strong, 1252 strong, 1180 strong, 1090 strong. Found %: C 58.6; H 4.3; Cl 8.9. $C_{19}H_{16}ClNO_6$. Calculated %: C 58.5; H 4.1; Cl 9.1.

2-Phenyl-4-(p-anisyl)indolo[2,3-c]pyrylium Perchlorate. A mixture of 1.3 g (5.0 mmole) of ketone, 1.5 g of benzoic acid, and 15 g of PPA was heated at 90° for 30-40 min, and the mixture was then poured into ice water. The resulting precipitate was ground thoroughly, filtered, washed with water, and dried. The red-brown pyrylium phosphate obtained was dissolved in 7 ml of glacial acetic acid, and 0.7-0.9 ml of 70% perchloric acid was added dropwise to it. The compound was precipitated with ether to give 1.03 g (47%) of a brown crystalline product with mp 203° (from glacial acetic acid). IR spectrum (ν_{max}, cm^{-1}): 1625 medium, 1609 weak, 1572 weak, 1260 strong, 1180 strong, 1095 strong. Found %: C 63.4; H 4.2; Cl 7.6. $C_{24}H_{18}ClNO_6$. Calculated %: C 63.8; H 4.0; Cl 7.9.

The other indolo[2,3-c]pyrylium salts were similarly obtained (Table 3).

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