7. R. I. Abraham, R. D. Lapper, K. M. Smith, and I. F. Unsworth, J. Chem. Soc., Perkin II, No. 9, 1004 (1974).
8. Yu. E. Sklyar, R. P. Evstigneeva, O. D. Saralidze, and N. A. Preobrazhenskii, Dokl. Akad. Nauk SSSR, 157, 367 (1964).
9. Yu. E. Sklyar, R. P. Evstigneeva, and N. A. Preobrazhenskii, Khim. Geterotsikl. Soedin., No. 2, 216 (1966).
10. I. Kozerski, Org. Magn. Reson., 9, 395 (1977).
11. R. I. Pugmire and D. M. Grant, J. Am. Chem. Soc., 90, 4232 (1968).
12. I. Dabrowski, K. Kamienska-Trela, and L. Kozerski, Org. Magn. Reson., 6, 43 (1974).
13. G. A. Olah and A. M. White, J. Am. Chem. Soc., 91, 5801 (1969).
14. L. M. Jackman and D. P. Kelley, J. Chem. Soc., B, No. 1, 102 (1970).
15. J. Chiang and E. B. Whipple, J. Am. Chem. Soc., 85, 2763 (1963).
16. O. A. Gansow and W. Schrittenhelm, J. Am. Chem. Soc., 93, 4294 (1971).

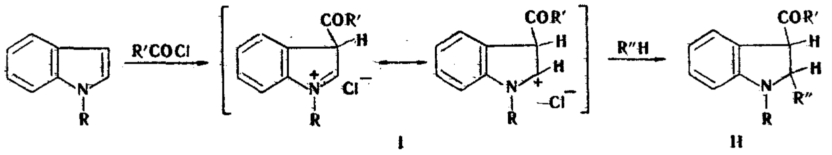
NEW NUCLEOPHILIC SUBSTITUTION REACTIONS IN THE INDOLE SERIES*

T. V. Stupnikova, L. A. Rybenko,
A. K. Sheinkman, and N. A. Klyuev

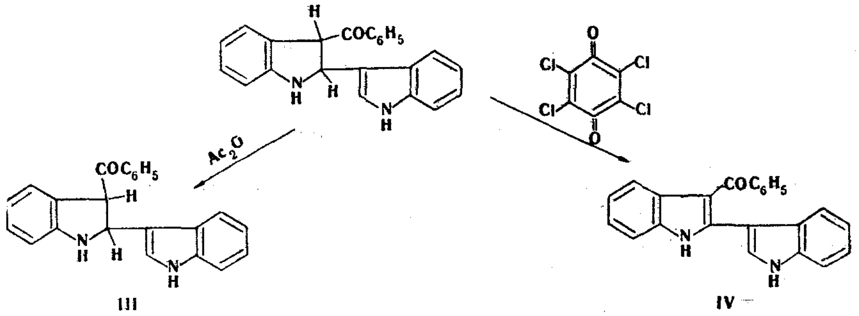
UDC 547.759.2

The direct incorporation of residues of π-surplus heterocycles, CH acids, and inorganic anions in the indole ring was accomplished by the reaction of indole with various nucleophilic organic compounds in the presence of acylating agents.

Indole is a π-surplus heterocycle [2] that readily undergoes various electropholic substitution reactions [3] but does not react with nucleophilic reagents. In the present paper we propose a method for the activation of indole in reactions with nucleophiles by converting it to the electrophilic 3-acylindoleninium cation by the action of acylating agents. It was found that indole reacts readily with various π-surplus heterocycles, CH acids, and other nucleophilic compounds in an inert solvent in the presence of acylating agents. In this case we assume the intermediate formation of 3-acylindoleninium cation I, which gives addition products II with various nucleophiles:



The synthesized indolines II (when R = H) are readily acylated by, for example, refluxing in acetic anhydride to give 1-acetyl-3-acyl derivatives (III) and are dehydrogenated to the corresponding indoles IV by the action of chloranil or nitrobenzene; some of the resulting indoles (when R = H) have been described in the literature:



---

*See [1] for the preliminary communication.

Donetsk State University, Donetsk 340055. Dnepropetrovsk Construction-Engineering Institute, Dnepropetrovsk 320092. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 493-496, April, 1979. Original article submitted April 24, 1978.

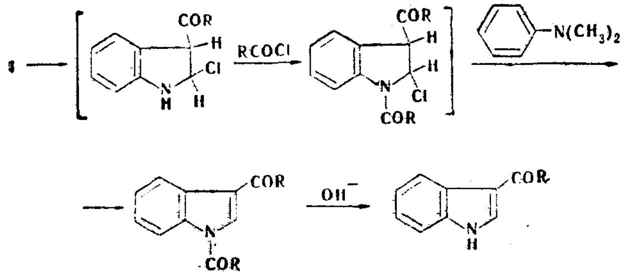
0009-3122/79/1504-0400$07.50

Bands of 3390, 3430, and 3490 cm^{-1} are observed in the IR spectra of II. One of these bands vanishes in dilute chloroform solution, and this makes it possible to form the judgment that it belongs to an NH group bonded by an intermolecular hydrogen bond. Two other bands at 3390 and 3490 cm^{-1} correspond to the stretching vibrations of indoline and indole NH groups. Absorption in this region is absent when R = CH_3 and R" = N-methyl-3-indolyl in II. A series of intense bands belonging to the carbonyl groups of the acyl and ester residues are observed in the IR spectra of II at 1670-1740 cm^{-1} when R" = $CH(COOC_2H_5)_2$, $CH(CN)COOC_2H_5$, $CH(COCH_3)COOC_2H_5$. The maximum at 3390 cm^{-1} vanishes in the IR spectrum of III, while a distinct maximum corresponding to an indole NH group is observed at 3495 cm^{-1}, and a $\nu_{C=O}$ band of an acyl residue appears at 1650 cm^{-1}. A broad band that evidently arises as a result of the superimposition of bands corresponding to two identical NH groups of indole rings at 3480-3495 cm^{-1} and a strong band at 1690 cm^{-1} (C=O) are observed in the IR spectrum of IV.

The fragmentation of the molecular ion in the mass spectra of II proceeds via a pathway similar to that observed for various bisheteroaromatic systems. Initially one observes elimination of an acyl residue (R'CO) from M^+, which is accompanied by the appearance of the spectrum of $(M-COR')^+$ and $(COR')^+$ fragments, whereas this process is accompanied by the appearance of $(M-CH_2=C=O)^+$ and ($CH_2=C=O$) fragments in the case of the acetyl derivatives. The next step is cleavage of the C-C bond between the two hetaryl rings, which is characterized by $(M-COR'-R'')^+$ and (R") fragment ions. In addition to this fragmentation pathway, one also observes parallel cleavage of the C-C bond between the two heterorings in the molecular ion itself, which leads to the appearance in the spectrum of (M-R") and $(R'')^+$ ion peaks. A multiplet of aromatic protons (6.8-8.1), a 2-H doublet (6.2-6.3), a 3-H doublet (3.87), and indole NH (10.5) and indoline NH (9.72 ppm) peaks are observed in the PMR spectra of II.

We were able to use the method discussed in this paper to introduce into the 2 position of indole not only various CH acids and π-surplus heterocycles but also some inorganic and organic anions: H^- (by the action of lithium aluminum hydride), NO_2^-, and $OC_2H_5^-$. It is not possible to introduce the hydroxide ion into the indole ring, since in this case the acid chlorides are hydrolyzed to the corresponding carboxylic acids, and 3-acylindoleninium cations are not formed. When we carried out the reaction in acetic anhydride, we obtained 1,3-diacetyl derivatives of II (except on those cases in which 1-methylindole was subjected to the reaction).

The reaction of indole with dialkylanilines in the presence of acylating agents does not lead to the formation of compounds of the II type but rather proceeds in a somewhat different manner. In these cases we isolated 1,3-diacylindoles V, which can be converted to the described 3-acylindoles VI by alkaline hydrolysis. The reaction evidently also proceeds through the formation of 3-acylindoleninium cation I, which in the step involving the reaction with basic N,N-dialkylanilines loses a molecule of HCl to give final compound V:



V VI

EXPERIMENTAL

The PMR spectra of solutions of the compounds in dimethyl sulfoxide (DMSO) were recorded with a Varian XI-100 spectrometer at 35°C with tetramethylsilane as the internal standard. The accuracy in the measurement of the chemical shifts was ±0.01. The mass spectra were obtained by the technique of direct introduction of the samples into the ion source with a Varian MAT-311 spectrometer (the accelerating voltage was 3 kV, the cathode emission current was 1 mA, and the ionizing voltage was 70 eV). The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. Chromatography was carried out in a loose layer of Al_2O_3 (activity II on the Brockmann scale) with a chloroform–benzene–hexane system (30:6:1). The chromatograms were developed with iodine vapors and in UV light.

TABLE 1. 2-Substituted 3-Acylindolines

No.	R	R′	R″	mp, °C	R_f	Found, %			Empirical formula	Calc., %			Yield, %
						C	H	N		C	H	N	
1	H	C_6H_5	3-Indolyl	219—220[b]	0,25	81,6	5,3	8,0	$C_{23}H_{18}N_2O$	81,6	5,3	8,3	60
2	H	C_2H_5	The same	188—189[b]	0,20	78,3	5,9	9,4	$C_{19}H_{18}N_2O$	78,6	6,2	9,7	52
3	H	$CHBrCH(CH_3)_2$[в]	„ „	208—210[b]	0,30	63,1	5,0	6,7	$C_{21}H_{21}N_2OBr$	63,4	5,3	7,0	50
4	H	2-Thienyl[d]	„ „	210—211[b]	0,20	73,0	4,3	8,0	$C_{21}H_{16}N_2OS$	73,3	4,6	8,1	44
5	H	2-Furyl	„ „	203—204[b]	0,20	76,5	4,6	8,2	$C_{21}H_{16}N_2O_2$	76,8	4,9	8,5	33
6	H	CH_3	2-Methyl-3-indolyl	254[b]	0,30	78,3	5,9	9,9	$C_{19}H_{18}N_2O$	78,6	6,2	9,6	20
7	H	C_6H_5	The same	236—238[b]	0,30	81,5	5,4	8,3	$C_{24}H_{20}N_2O$	81,8	5,7	8,0	20
8	H	2-Thienyl[e]	„ „	204—205[b]	0,40	73,5	4,8	7,5	$C_{22}H_{18}N_2OS$	73,8	5,0	7,8	42
9	H	2-Furyl	„ „	223—224[b]	0,20	76,9	5,0	8,0	$C_{22}H_{18}N_2O_2$	77,2	5,3	8,2	60
10	H	CH_3	„ „	180—181	0,20	74,4	5,9	5,5	$C_{15}H_{15}NO_2$	74,7	6,2	5,8	12
11	H	C_6H_5	2-Methyl-5-furyl	199—200	0,30	78,9	5,3	4,3	$C_{20}H_{17}NO_2$	79,2	5,6	4,6	12
12	H	C_2H_5	The same	194—195	0,20	75,0	6,3	5,2	$C_{16}H_{17}NO_2$	75,3	6,6	5,5	10
13	H	CH_3	2-Heptyl-5-furyl	110—111	0,50	77,2	8,0	4,0	$C_{21}H_{27}NO_2$	77,5	8,3	4,3	10
14	H	C_6H_5	The same	190—191	0,20	78,0	8,2	3,8	$C_{22}H_{29}NO_2$	77,9	8,5	4,1	12
15	H	C_6H_5	„ „	187—188	0,30	80,3	7,2	3,7	$C_{26}H_{29}NO_2$	80,6	7,5	3,9	11
16	H	2-Furyl	„ „	198—199	0,20	76,1	6,9	3,4	$C_{24}H_{27}NO_3$	76,4	7,2	3,7	14
17	H	2-Thienyl[f]	„ „	192—194	0,20	73,0	6,6	3,3	$C_{24}H_{27}NO_2S$	73,3	6,9	3,6	13
18	H	C_6H_5	1-Methyl-3-indolyl	155—156[g]	0,30	81,5	5,4	7,7	$C_{24}H_{20}N_2O$	81,8	5,7	8,0	50
19	CH_3	C_6H_5	The same	132—133[g]	0,70	81,8	5,7	7,3	$C_{25}H_{22}N_2O$	82,1	6,0	7,9	50
20	CH_3	C_6H_5	2-Methyl-3-indolyl	232—233[b]	0,30	82,3	6,0	7,7	$C_{25}H_{22}N_2O$	82,1	6,0	7,6	41
21	H	C_6H_5	H	118—120[g]	0,30	80,4	5,5	6,0	$C_{15}H_{13}NO$	80,7	5,8	6,3	4
22	H	C_6H_5	NO_2	170—171[g]	0,20	67,3	4,6	10,1	$C_{15}H_{12}N_2O_3$	67,1	4,4	10,4	8
23	H	C_6H_5	OC_2H_5	145—146[g]	0,15	76,6	5,3	5,0	$C_{17}H_{15}NO_2$	76,9	5,6	5,3	5
24	H	C_6H_5	$CH(CN)COOC_2H_5$	145—146	0,30	71,5	5,1	8,0	$C_{20}H_{18}N_2O_3$	71,8	5,4	8,3	50
25	H	C_6H_5	$CH(COCH_3)COOC_2H_5$	165—166[g]	0,30	71,5	5,6	3,6	$C_{21}H_{21}NO_4$	71,8	5,9	3,9	14
26	$COCH_3$	CH_3	$CH(CN)COOC_2H_5$	188—189[g]	0,30	64,6	5,4	8,6	$C_{17}H_{18}N_2O_4$	64,9	5,7	8,9	13

---

a) From methanol. b) From n-butanol. c) Found: Br 19.9%. Calculated: Br 20.2%. d) Found: S 9.0%. Calculated: S 9.3%. e) Found: S 8.7%. Calculated: S 9.0%. f) Found: S 7.9%. Calculated: S 8.2%. g) From benzene—hexane (1:1).

2-(3-Indolyl)-3-acetylindoline. A mixture of 2.4 g (0.02 mole) of indole and 0.7 g (0.01 mole) of acetyl chloride in 10 ml of dry benzene was shaken at room temperature for 30 min, and the resulting precipitate was removed by filtration, washed with methanol, and recrystallized from n-butanol to give 1.5 g (54%) of a product with mp 206-207°C and R_f 0.3. IR spectrum: 1680 (C=O); 3380; 3490 cm^{-1} (NH). Found: C 78.3; H 6.0; N 10.3%. $C_{18}H_{16}N_2O$. Calculated: C 78.2; H 5.8; N 10.1%.

Other heterocyclic derivatives of indole, the principal characteristics of which are presented in Table 1, where similarly obtained.

1-Acetyl-2-(3-indolyl)-3-benzoylindoline. A solution of 1.6 g (5 mmole) of 2-(3-indolyl)-3-benzoylindoline in 10 ml of acetic anhydride was refluxed for 6 h, after which the acetic anhydride was removed by vacuum distillation, and the residue was treated with a 10% solution of alkali. The resulting precipitate was recrystallized from benzene—hexane (1:1) to give 1.6 g (76%) of a product with mp 120-121°C and R_f 0.9. IR spectrum: 1650; 1670 (C=O); 3490 cm^{-1} (NH). Found: C 78.6; H 5.3; N 7.1%. $C_{25}H_{20}N_2O_2$. Calculated: C 78.9; H 5.5; N 7.4%.

2-(3-Indolyl)-3-benzoylindole. A) A mixture of 3.4 g (0.01 mole) of 2-(3-indolyl)-3-benzoylindoline and 2.4 g (0.01 mole) of chloranil in 100 ml of xylene was refluxed for 3 h, after which it was cooled and washed with a 20% solution of alkali, several times with water, and 10% hydrochloric acid. The precipitate was removed by filtration and purified by chromatography with a column filled with Al_2O_3 (elution with methanol) to give 2.9 g (81%) of a product with mp 178-179°C (from benzene) and R_f 0.2. IR spectrum: 1680 (C=O) and 3400 cm^{-1} (NH). Found: C 82.5; H 4.9; N 8.5%. $C_{23}H_{16}N_2O$. Calculated: C 82.3; H 4.7; N 8.3%.

B) A solution of 1.7 g (5 mmole) of 2-(3-indolyl)-3-benzoylindoline in 10 ml of nitrobenzene was maintained at 120°C for 6 h, after which the nitrobenzene was removed by vacuum distillation, and the residue was recrystallized from benzene to give 1.6 g (94%) of a product with mp 178-179°C and R_f 0.2. No melting point depression was observed for a mixture of this product with the compound obtained by method A.

1,3-Diacetyl-2-dicarbethoxymethylindoline. A mixture of 1.2 g (0.01 mole) of indole and 1.6 g (0.01 mole) of malonic ester in 10 ml of acetic anhydride was maintained at 120°C for 6 h, after which it was cooled, and 100 ml of water was added. The aqueous mixture was extracted with ether, the ether was removed by distillation, and the resulting precipitate was removed by filtration and recrystallized from n-butanol to give 1 g (25%) of a product with mp 174-175°C and R_f 0.3. IR spectrum: 1650; 1750 cm^{-1} (C=O). Found: C 63.1; H 6.3; N 3.8%. $C_{19}H_{23}NO_6$. Calculated: C 62.8; H 6.0; N 3.5%.

1,3-Dibenzoylindole. A mixture of 1.2 g (0.01 mole) of indole, 1.4 g (0.01 mole) of benzoyl chloride, 1.5 g (0.01 mole) of diethylaniline, and 10 ml of dry benzene was refluxed for 5 h, after which it was subjected to steam distillation, and the residue was recrystallized from methanol to give 1 g (62%) of a product with mp 170-171°C and R_f 0.5. IR spectrum: 1650, 1700 cm^{-1} (C=O). Found: C 81.5; H 4.3; N 4.1%. $C_{22}H_{15}NO_2$. Calculated: C 81.2; H 4.6; N 4.3%.

3-Benzoylindole. This compound, with mp 238-239°C (from methanol) (mp 238-239°C [4]), was obtained in 77% yield by alkaline hydrolysis of 1,3-dibenzoylindole.

1,3-Di(2-thenoyl)indole. This compound, with mp 178-179°C (from n-butanol) and R_f 0.3, was similarly obtained in 50% yield. IR spectrum: 1720 cm^{-1} (C=O). Found: C 63.6; H 3.0; N 3.9; S 18.6%. $C_{18}H_{11}NO_2S_2$. Calculation: C 63.9; H 3.2; N 4.1; S 18.9%.

LITERATURE CITED

1. A. K. Sheinkman, T. V. Stupnikova, and L. A. Rybenko, Khim. Geterotsikl. Soedin., No. 4, 561 (1977).
2. A. F. Pozharskii, Khim. Geterotsikl. Soedin., No. 6, 723 (1977).
3. R. J. Sundberg, The Chemistry of Indoles, Academic Press, New York (1970), p. 11.
4. G. I. Zhugietu, V. A. Budylin, and A. N. Kost, The Preparative Chemistry of Indole [in Russian], Shtiintsa, Kishinev (1975), p. 128.