REACTIONS OF CYCLOAMMONIUM CATIONS

XIII.* REACTION OF INDOLE WITH SALTS OF SIX-MEMBERED NITROGEN HETEROCYCLES

A. K. Sheinkman, A. N. Kost,
S. G. Potashnikova, A. O. Ginzburg,
and S. N. Baranov

UDC 547.751

Only an indole trimer can be isolated from the reaction of indole with pyridine, quinoline, and isoquinoline in aqueous solutions of mineral acids. In anhydrous media the hydrochlorides of these heterocycles electrophilically attack the 3 position of the indole ring to form low yields of 3-hetarylindoles. Indole reacts with acridine, even in aqueous media, under the influence of protonating agents and is converted to 9-(3-indolyl)acridine and acridine in good yields. The acridinylation of indole and 1- and 2-alkyl- or phenylindoles in the presence of acylating agents proceeds similarly.

We previously reported the reaction of acylpyridinium [2], acylquinolinium [3], acylisoquinolinium [4], and acylacridinium salts [5] with nucleophilic aromatic compounds to give the corresponding diaryls or their dihydro derivatives. The facile acridinylation of aromatic amines has also been observed in [6, 7]. In the case of indole, the action of benzoylpyridinium salts leads to 3-(1-benzoyl-1,4-dihydro-4-pyridyl)-indole [8]. The benzoyl derivative of 2-(3-indolyl)-1,2-dihydroquinoline is similarly obtained by the reaction of indole, quinoline, and benzoyl chloride [9]. It might have been supposed that this sort of condensation would proceed also during direct protonation. In addition, it is known that indole and its homologs are converted to dimers or trimers under the influence of acids [10, 11].

We have investigated the reaction of indole with nitrogen heterocycles in the presence of mineral acids. It was found that pyridine, quinoline, and isoquinoline do not prevent the polymerization of indole. Only the starting substances and an indole trimer, viz., o-[2,2-di(3-indolyl)ethyl]aniline (I), could be isolated by the action of sulfuric acid (at room temperature for 10-48 h) from the reaction mass in all cases. The action of aqueous hydrochlorides of the same heterocyclic bases on indole produces a similar effect. Analogous reactions do not take place at all with 2-methylindole. We have obtained various derivatives of the indole trimer (the Schiff base and acyl derivatives) which confirm its structure.

In anhydrous aprotic solvents (benzene and dimethylformamide) the same salts react slowly with indole to form the corresponding 3-hetarylindoles in yields on the order of 2-3%, even after refluxing for 30 h. The bulk of the starting substances are recovered unchanged, and traces of trimer I are detected. The reaction proceeds somewhat better with sulfates and perchlorates but, even here, the yields do not exceed 5-6%. For example, indole and quinoline sulfate in dimethylformamide yielded 5% of 2-(3-indolyl)-quinoline (II) and a small amount of trimer I.

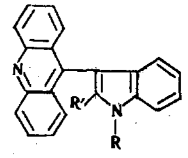
Thus, protonation of both indole and quinoline apparently occurs, but the cations formed in the process do not have the proper stability. The situation is different in the case of acridine. Protonation of acridine leads to the formation of cation III, which is stabilized due to charge delocalization with the participation of two benzene rings. Even in aqueous media in the reactions of cation III with indole up to 25% of 9-(3-indolyl)acridine (IV) is obtained along with trimer I. In anhydrous dimethylformamide, however,

---

*See [1] for communication XII.

Donets State University. M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 648-652, May, 1971. Original article submitted June 12, 1970.

TABLE 1. 9-(Indolyl)acridines (IV and V)



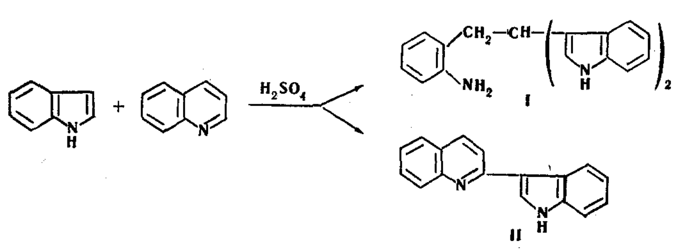
IVa–e

Comp.	R	R′	mp	Empirical formula	Found, %			Calc., %			Yield, %	
					C	H	N	C	H	N	meth. A	meth. B
IVa	H	H	297—298	$C_{21}H_{14}N_2$*	86,0	4,7	9,4	85,7	4,8	9,5	85	65
IVb	H	CH_3	313—314	$C_{22}H_{16}N_2$†	85,2	5,2	9,0	85,7	5,2	9,1	84	68
IVc	CH_3	H	292—293	$C_{22}H_{16}N_2$	85,9	5,2	9,1	85,7	5,2	9,1	99	64
IVd	C_6H_5	H	205—206	$C_{27}H_{18}N_2$	87,7	5,1	8,0	87,5	4,9	7,6	—	48
V			331—333	$C_{22}H_{16}N_2$	86,1	5,3	8,9	85,7	5,2	9,1	—	42

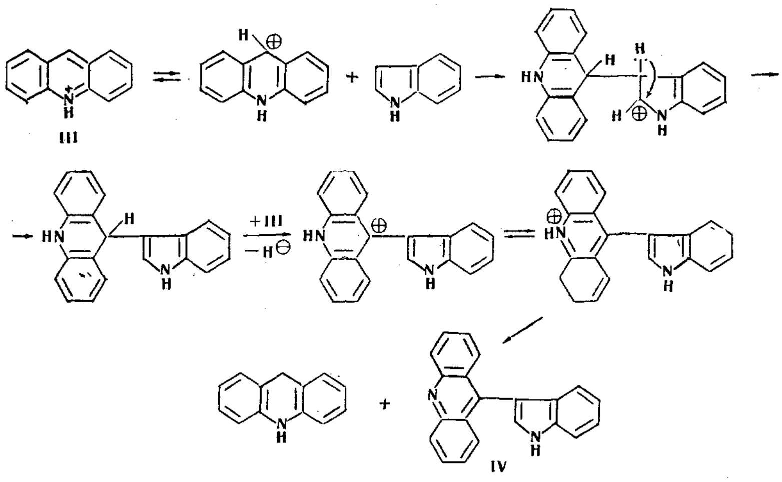
---

*The picrate melted at 313-31 (sic) deg (from ethanol). Found %: N 13.6. $C_{21}H_{14}N_2 \cdot C_6H_3N_3O_7$. Calculated %: N 13.4.

†The picrate melted at 269-270° (from ethanol). Found %: N 12.8. $C_{22}H_{16}N_2 \cdot C_6H_3N_3O_7$. Calculated %: N 13.0.

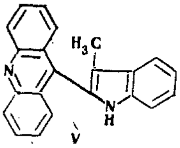


the indole polymers are not formed at all, and the major product is IV and acridan, which is apparently obtained due to disproportionation (with hydride transfer) of the intermediate dihydro compound under the influence of cation III.



Acridinylation of indole under the influence of acridine and benzoyl chloride proceeds just as readily and 9-benzoylacridan is formed as a side product. The reaction proceeds with good yields for a number of alkyl- or phenylindoles (Table 1). Since the 3-position in indole is always preferably involved in electrophilic substitution reactions, and since it was shown in [2,3,5-8] that direct hetarylation proceeds with the participation of the 4-position of the pyridine ring, the 2-position of the quinoline ring, or the 9-position of the acridine ring, we will assign structure IV to the compounds obtained, except for the compound obtained from 3-methylindole, which has structure V.

We will exclude the possibility of the participation of the NH group of the indole ring on the basis of the IR spectra (the presence of a band from the N−H bond at 3480-3500 cm^{-1}).



V

The data in Table 1 indicate that a CH_3 group in the 2- or 3-position has virtually no effect on the possibility of the introduction of a bulky acridinyl substituent into the neighboring (2- or 3-) position. This makes it possible to suppose that the reaction proceeds through a step involving one-electron transfer with the initial formation of a pseudo sandwich structure of the charge-transfer-complex type. The formation of such complexes in the case of pyridinium salts and indole has been recorded in a number of studies [12]. Thus the described reaction is a convenient route to the synthesis of indoloacridines. We note that, according to the results in [9], acylacridinium salts do not enter into this sort of reaction.

EXPERIMENTAL

Coal-tar indole, pyridine, quinoline, isoquinoline, and acridine were used in this research. Their purity, according to gas-liquid chromatography (UKh-1 chromatograph with 0.4% of an ethylene oxide−tetrahydrofuran copolymer on sodium chloride as the stationary phase) was no less than 97%.

Chromatography in a loose, thin layer of activity II aluminum oxide was carried out with elution by a methanol−hexane−benzene−chloroform system (1 : 1 : 6 : 30).

The IR spectra of chloroform solutions or KBr pellets were obtained with a UR-10 spectrophotometer.

Reaction of Indole with Quinoline and 20% H_2SO_4. A total of 27.5 ml of 20% sulfuric acid was added to a solution of 11.7 g (0.1 mole) of indole in 12.9 g (0.1 mole) of quinoline, after which the reaction mixture was shaken at room temperature for 24 h. The precipitated crystals were separated, washed with ammonium hydroxide, and recrystallized twice from ethanol to give 11.32 g (97%) of o-[2,2-di(3-indolyl)ethyl]aniline (I) with mp 170-171° [11] and R_f 0.54.

The reaction of indole with other nitrogen heterocycles in the presence of various amounts of 20% sulfuric acid was carried out similarly. In all cases I was obtained in yields of 30-80%.

1-(p-Dimethylaminobenzylideneimino-2-[2,2-di(3-indolyl)ethyl]benzene. A solution of 8.82 g (0.025 mole) of I and 4.48 g (0.03 mole) of p-dimethylaminobenzaldehyde in 35 ml of ethanol was refluxed for 7 h. The mixture was cooled, and the precipitate was separated and recrystallized from chloroform to give 6.2 g (50%) of a product with mp 212-215° and R_f 0.3. Found %: C 82.1; H 6.0; N 12.0. $C_{33}H_{30}N_4$. Calculated %: C 82.2; H 6.2; N 11.6.

1-(p-Isopropylbenzylideneimino-2-[2,2-di-(3-indolyl)ethyl]benzene. This was similarly obtained by refluxing 17.75 g (0.05 mole) of I and 8.76 g (0.06 mole) of cuminaldehyde in 70 ml of ethanol for 7 h to give 12 g (50%) of a product with mp 194-195° (acetone−water) and R_f 0.77. Found %: N 8.8. $C_{34}H_{31}N_3$. Calculated %: N 8.7.

1-(p-Nitrobenzylideneimino)-2-[2,2-di(3-indolyl)ethyl]benzene. This was obtained as described above in 50% yield by reaction of I with p-nitrobenzaldehyde and had mp 195-196° and R_f 0.73. Found %: C 76.2; H 5.4; N 11.5. $C_{31}H_{24}N_4O_2$. Calculated %: C 76.9; H 5.0; N 11.6.

Bands at 1590-1610 cm^{-1} (C=N) and 3480 cm^{-1} (N−H) are observed in the IR spectra of these compounds.

1-(p-Chlorobenzamido)-2-[2,2-di(3-indolyl)ethyl]benzene. A solution of 3.53 g (0.01 mole) of I, 0.78 g (0.01 mole) of pyridine, and 1.75 g (0.01 mole) of p-chlorobenzoyl chloride in 50 ml of absolute benzene was shaken for 1 h at room temperature. The resulting precipitate was treated with ammonium hydroxide and water, dried, and recrystallized from benzene to give 2.6 g (55%) of a product with mp 174-176° and R_f 0.62. Found %: C 76.0; H 5.2; Cl 7.0; N 8.4. $C_{31}H_{24}ClN_3O$. Calculated %: C 76.0; H 4.9; Cl 7.3; N 8.5.

1-(p-Bromobenzamido)-2-[2,2-di(3-indolyl)ethyl]benzene. This was similarly obtained in 60% yield and had mp 220-222° (from benzene) and R_f 0.58. Found %: N 8.0. $C_{31}H_{21}BrN_3O$. Calculated %: N 7.9.

1-Acetamido-2-[2,2-di(3-indolyl)ethyl]benzene. This was obtained by the reduction of 5.3 g (0.05 mole) of I with 4.25 g (0.1 mole) of acetic anhydride in 50 ml of absolute benzene to give 4 g (64%) of a product with mp 200-203° (from glacial acetic acid) (mp 202° [13]) and R_f 0.3.

Reaction of Indole with Quinoline Sulfate. A mixture of 22.7 g of quinoline sulfate and 11.7 g of indole in 30 ml of anhydrous dimethylformamide (DMF) was refluxed for 30 h, after which the DMF was removed in vacuo, the residue was made alkaline with ammonium hydroxide, and the resulting precipitate was separated, dried, and recrystallized from amyl alcohol to give 1.5 g (5%) of 2-(3-indolyl)quinoline (II) with mp 193-195° and R_f 0.78. IR spectrum: 3430 cm^{-1} (N−H). A sample of this product did not depress the melting point of samples obtained by an independent route [14, 15].

The filtrate was extracted repeatedly with benzene, the extracts were dried, the benzene was removed, and the residue was placed in a column filled with aluminum oxide and eluted with benzene−hexane−chloroform (6 : 1 : 30) to give 6 g of quinoline with R_f 0.7 (picrate mp 200-203°), 5 g of indole, and traces of I with R_f 0.54 (picrate mp 192-195° [11]).

The reaction of quinoline hydrochloride and perchlorate in benzene or DMF proceeds similarly. Only I was obtained in 25% yield in all cases in aqueous solution.

Only traces of triindole were obtained in the reaction of pyridine hydrochloride and sulfate under similar conditions, and the presence of 2-(3-indolyl)pyridine and 4-(3-indolyl)pyridine was detected chromatographically (the reference spots for the chromatograms were synthesized by the method in [15]). Almost quantitative amounts of unchanged indole and pyridine were isolated.

As described above, traces of I and 1-(3-indolyl)isoquinoline [14] with R_f 0.55 were obtained by the reaction of isoquinoline hydrochloride with indole.

9-(3-Indolyl)acridines (IV). A. A mixture of 5.36 g (0.025 mole) of acridine hydrochloride and 2.9 g (0.025 mole) of indole in 50 ml of anhydrous DMF was held at 70° for 2-3 h. The mixture was cooled, and the resulting precipitate was treated with ammonium hydroxide, washed repeatedly with water, dried, and recrystallized from amyl alcohol to give 3.1 g (85%) of IVa with mp 297-298° and R_f 0.76 (see Table 1). IR spectrum, cm^{-1}: 3430 (N−H) (KBr pellets), 3479 (NH) (CCl_4 solution).

The DMF mother liquor after separation of the precipitate was vacuum evaporated to dryness, and the residue was washed with ammonium hydroxide and water, dried, and recrystallized from ethanol to give 1.8 g (80%) of acridan with mp 171-172°. In aqueous media under similar conditions for 10 h, 20-25% of IVa, 18% I, and 20% acridan were obtained after 10 h [9].

B. A solution of 8.9 g (0.05 mole) of acridine, 3.5 g (0.025 mole) of freshly distilled benzoyl chloride, and 2.9 g (0.025 mole) of indole in 30 ml of anhydrous DMF was held at 70° for 3 h. The precipitate was filtered, treated with ammonium hydroxide, washed with water, dried, and recrystallized from amyl alcohol to give 4.7 g (65%) of 9-(3-indolyl)acridine with mp 296-297° and R_f 0.76; the picrate had mp 311-313°. A sample of this product did not depress the melting point of the samples described above. The hydrochloride had mp 323-325° (ether−ethanol). Found %: C 75.9; H 4.9; Cl 10.2. $C_{21}H_{14}N_2 \cdot HCl$. Calculated %: C 76.2; H 4.6; Cl 10.6. The DMF filtrate was vacuum evaporated, and the residue was treated with ammonium hydroxide, washed with water, dried, and recrystallized from ether and then from ethanol to give 2.9 g (48%) of colorless crystals of 10-benzoylacridan with mp 179-181° [16].

LITERATURE CITED

1. A. K. Sheinkman, G. V. Samoilenko, and S. N. Baranov, Dokl. Akad. Nauk SSSR, 196, 1377 (1971).
2. A. K. Sheinkman, N. F. Kazarinova, and E. P. Babin, Zh. Vses. Khim. Obshchestva, 7, 112 (1962).
3. A. K. Sheinkman, A. N. Kost, A. N. Prilepskaya, and Zh. V. Shiyan, Zh. Organ. Khim., 4, 1286 (1968).
4. A. K. Sheinkman, A. K. Tokarev, and S. N. Baranov, Khim. Geterotsikl. Soedin., 82 (1971).
5. A. K. Sheinkman, S. G. Potashnikova, and S. N. Baranov, Zh. Organ. Khim., 6, 614 (1970).
6. O. N. Chupakhin, V. A. Trofimov, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., 954 (1969).
7. V. A. Trofimov, Master's Dissertation [in Russian], Sverdlovsk (1969).
8. H. Dobeneck, H. Duebel, and F. Heichele, Angew. Chem., 71, 310 (1959).

9. H. Dobeneck and W. Goltzasche, Ber., 95, 1484 (1962).
10. G. Smith, Adv. Heterocycl. Chem., 2, 287 (1963).
11. W. Noland and W. Kuryla, J. Org. Chem., 25, 486 (1960).
12. É. M. Kosover, in: New Problems in Physical Organic Chemistry [in Russian], Mir (1969), p. 81.
13. K. Keller, Ber., 46, 726 (1913).
14. M. Colonna, R. Bruni, and A. Guerra, Gazz. Chim. Ital., 96, 1410 (1966).
15. A. K. Sheinkman, V. A. Ivanov, and S. N. Baranov, Dokl. Akad. Nauk UkrSSR, 619 (1970).
16. K. Bauer, Ber., 83, 10 (1950).