REACTION OF INDOLE WITH N-ACYLIMMONIUM SALTS IN SITU*

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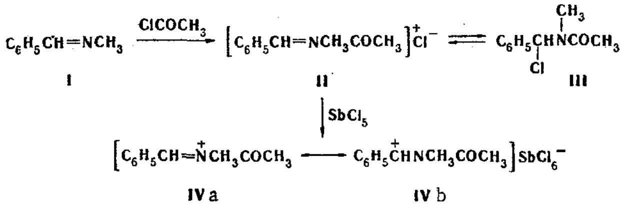
The possibility of direct amidomethylation of indole and some other organic compounds with N-acylimmonium salts formed by reaction of azomethines with acylating agents was observed.

In principle, the alkylation of indole with N-alkylimmonium salts at the moment of their formation is well known and widely used in organic synthesis: Mannich bases and 3-formylindoles are usually obtained by this method, and N-alkylimmonium salts of the $\rangle C{=}\overset{+}{N}R_2$ type and their analogs are used in situ as the alkylating agents. The preparation of 3-(2-piperidyl)indoles by the action of N-alkyl salts of 1,2,3,4-tetrahydropyridines [2] is also based on this principle. It seemed tempting to us to realize direct amidomethylation of indoles using N-acylimmonium salts as the alkylating agents. Salts of this sort are readily formed by the action of acyl halides on azomethines in anhydrous aprotic solvents under conditions that exclude contact with moisture. However, no one has yet isolated them preparatively [3].

It was found that N-acylimmonium salts are stable in the case of weak nucleophilic anions such as $SbCl_6^-$. When other nucleophiles are absent, other anions rapidly react with the immonium cations to give a σ bond between them, similar to what is observed in the case of pyridinium salts, but in this case the reaction is considerably more vigorous. Thus the halide anions in pyridinium salts participate only in a weak donor–acceptor interaction with the cations [4], and the iodide ion forms a colored charge-transfer complex [5], but not one case involving the formation of a σ bond with the α- and γ-carbon atoms of the pyridine ring has been observed. However in N-acylimmonium salts addition of chloride anions apparently proceeds extremely rapidly to give ether-soluble III.



Salt IV with anion $SbCl_6^-$ proved to be a quite stable white crystalline compound that is insoluble in ether and other nonpolar solvents. The band of stretching vibrations of the carbonyl group of this compound is found at ~ 1700 cm^{-1}, i.e., it is shifted by 40-50 cm^{-1} as compared with compounds of the III type. The ν_{CO} band is usually recorded at 1750-1800 cm^{-1} in the spectra of N-acyl salts of tertiary amines and pyridines [6]. This sort of difference in the position of the ν_{CO} band in the spectra of N-acylimmonium salt IV as compared with N-acylammonium salts evidently should be explained by the larger contribution of resonance structure IVb to the ground state of the salt. This assumption is confirmed by an investigation of the PMR spectrum of salt IV. Thus the signal of the methyl group in the spectrum of azomethine I is found as a narrow doublet at 3.35 ppm, whereas this signal in the spectrum of salt IV is shifted somewhat to weaker field (3.64 ppm). Thus the shift of the signal due to adjacency of ths positively charged nitrogen atom in the salts was 0.29 ppm. However, the signal of the proton of the $\overset{+}{C}$H group of salt IV is shifted considerably more markedly to the weak-field region (8.97 ppm) as compared with I, in the spectrum of which this signal is found in the aromatic proton region with a multiplet centered at 7.48 ppm (i.e., the shift of the signal is ~1.50 ppm). These results are in good agreement with the data in [7] for protonated azomethines.

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*See [1] for a preliminary communication.

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TABLE 1. β-Amidomethyl Derivatives of Indole $RC_6H_5CHR'COR''$

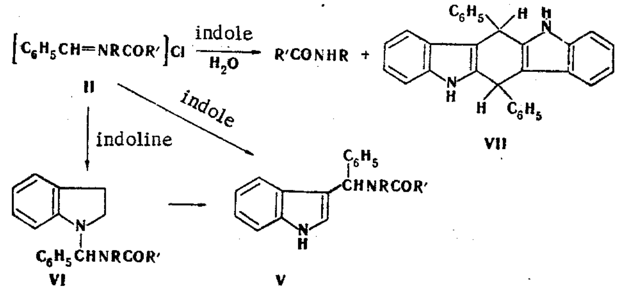
Compound	R	R′	R″	mp, °C*	Empirical formula	Found, %			Calc., %			IR spectrum, cm⁻¹		Yield, %
						C	H	N	C	H	N	CO	NH	
Va	3-Indolyl	CH_3	C_6H_5	99—100	$C_{23}H_{20}N_2O$	80,7	6,4	8,5	81,2	5,9	8,2	1630	3480	65
Vb	3-Indolyl	C_6H_5	C_6H_5	196—198	$C_{28}H_{22}N_2O$	83,5	5,4	7,2	83,6	5,5	7,0	1650	3480	60
Vc	2-Methyl-3-indolyl	C_6H_5	C_6H_5	225—227	$C_{29}H_{24}N_2O$	83,9	6,2	7,0	83,6	5,8	6,7	1631	3480	70
Vd	1-Methyl-3-indolyl	C_6H_5	C_6H_5	120—122	$C_{29}H_{24}N_2O$	83,2	6,1	6,8	83,6	5,8	6.7	1633	—	30
Ve	3-Indolyl	C_6H_5	CH_3	150—152	$C_{23}H_{20}N_2O$	80,7	6,2	8,2	81,2	5,9	8,2	1650	3475	69
VI	2,3-Dihydro-1-indolyl	CH_3	C_6H_5	83—84	$C_{23}H_{22}N_2O$	80,5	6,5	8,4	80,7	6.5	8.2	1630	—	80
X	2-Pyrrolyl	CH_3	C_6H_5	133—135	$C_{19}H_{18}N_2O$	78,2	6,0	10.0	78,6	6,2	9.7	1632	3460	64

*Compound Va was recrystallized from benzene–petroleum ether (1 : 1), Vb and Vc were recrystallized from benzene, Vd, VI, and X were recrystallized from diethyl ether, and Ve was recrystallized from methanol.

N-Methylacetamide and benzaldehyde are formed by the action of water on salt IV; this is similar to what is observed when moisture enters the reaction mixture in the reaction of azomethine I with acetyl chloride in air at room temperature.

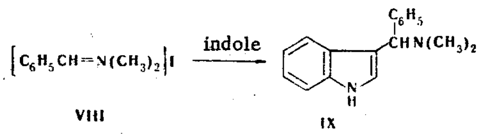
It was found to be more convenient to use salts of the II type rather than crystalline compounds of the IV type for the direct amidomethylation of indoles. Thus we obtained salts of the II type, which are reversibly converted to compounds of the III type, by reaction, in an atmosphere of thoroughly dried inert gas, of benzylideneaniline, benzylidenemethylamine, or other azomethines with acyl chlorides at reduced temperatures in absolute ether solutions. Cation IVa ⟷ IVb, which at the instant of its formation electrophilically attacks indole in the 3 position to give amidomethyl derivatives V (Table 1), is formed when a mixture of triethylamine, pyridine, or some other tertiary amine and indole is added to the reaction mixtures.

When we added indoline to the reaction medium in place of indole, we obtained the corresponding N-amidomethyl derivative of the VI type. However, when we carried out the reaction in air at room temperature under conditions that do not exclude contact with moisture, the salts undergo hydrolysis to give acetamide or benzamides and products (VII) of the reaction of the resulting aromatic aldehydes with indole.



The IR spectra of V contain ν_{CO} bands (1630-1650 cm⁻¹), ν_{NH} bands (3460 cm⁻¹), and bands of indole ring vibrations. The well-known Erlich test for indole is positive, and this also confirms the structure of the compounds obtained. The same compounds are also formed by the action of azomethines in mixtures with acyl chlorides on indolylmagnesium bromide or indolylsodium. Compound Va was also obtained by dehydrogenation of the product of amidomethylation of indoline VI with chloranil (probably because of thermal rearrangement of 1-substituted indole VIa to derivative V).

It was found that the alkylation of indole proceeds smoothly by means of N-alkylimmonium salts VIII, which are readily formed by quaternization of azomethines:



EXPERIMENTAL METHOD

The IR spectra of KBr pellets or $CHCl_3$ solutions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of acetonitrile solutions were recorded with a YaMR-5535 spectrometer (operating frequency 40 MHz) at 25° with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was carried out in a benzene–hexane–chloroform (6 : 1 : 30) system with development by iodine vapors and UV light.

N-Acetylbenzylidenemethylimmonium Hexachlorostibnate (IV). A solution of 3.93 g (0.05 mole) of acetyl chloride in 40 ml of methylene chloride was added dropwise at 0° in a dry nitrogen atmosphere to a solution of 5.95 g (0.05 mole) of benzylidenemethylamine in 40 ml of dry methylene chloride, after which the solution was cooled to −78°, and 9.95 g (0.05 mole) of $SbCl_5$ in 80 ml of methylene chloride was added. The color of the reaction changed from red to yellow. The mixture was stirred for 1 h after which it was rapidly filtered in a dry nitrogen atmosphere to give 14.0 g (56.3%) of a white crystalline substance with mp 188-190°. IR spectrum: 1680 cm^{-1} (C=O). PMR spectrum (in CH_3CN): 8.97 (1H, s, CH) 7.9 ±0.1 (5H, m, Ar), and 3.64 ppm (3H, d, $\overset{\oplus}{N}=CH_3$). Found: N 2.9%. $C_{10}H_{12}Cl_6OSb$. Calculated: N 2.8%.

Typical Method of Amidomethylation. A solution of 0.05 mole of acylchloride in 20 ml of dry ether was added dropwise with cooling to 0-5° in a dry nitrogen atmosphere to a solution of 0.05 mole of azomethine in 20 ml of absolute ether or DMF, after which the mixture was allowed to stand at room temperature for 2 h. It was then cooled again to 0° after which a solution of 0.05 mole of triethylamine (pyridine or quinoline) in 15 ml of ether and 0.05 mole of indole (indoline, pyrrole or other alkylable substances) in 15 ml of ether were added with stirring. The mixture was then allowed to stand at room temperature for 1 h, the precipitated triethylamine hydrochloride was separated, and the reaction mixture was decomposed with ammonium hydroxide. The ether layer was collected and dried, the ether was removed by distillation, and the residue was recrystallized from a suitable solvent. When DMF was used, the order of isolation of the reaction products was different: At the end of the reaction, the mixture was decomposed with ammonium hydroxide and extracted with several portions of ether. The ether extracts were washed with distilled water, dried, and evaporated.

We obtained the previously described [8] VII by addition of acyl halides to azomethines at room temperatures in air. Under similar conditions in the reaction of 3-indolideneaniline, benzoyl chloride, and indole we isolated a product of reaction of indole and 3-formylindole of the VII type with mp 245-247° (aqueous acetone). Found: C 83.0; H 5.3; N 11.5%; M 488.6 (mass spectroscopically). $C_{34}H_{24}N_4$. Calculated: C 83.4; H 5.0; N 11.6%; M 488.6.

3-(N,N-Dimethylaminobenzylidene)indole (IX). A mixture of 5.95 g (0.05 mole) of methyl iodide and benzylidenemethylamine was heated at 80° for 16 h, after which the resulting solid salt VIII was dissolved in 20 ml of absolute DMF. Triethylamine [4.95 g (0.05 mole)] and 5.85 g (0.05 mole) of indole were added to the solution, and the mixture was stirred at room temperature for 1 h. It was then decomposed with ammonium hydroxide and extracted three to four times with ether in small portions. The ether extracts were dried and evaporated, and the oily residue was vacuum fractionated with collection of the fractions with bp 164-166° (6 mm). A product with R_f 0.65 was obtained in 25% yield. Found: C 81.1; H 7.2; N 11.6%. $C_{17}H_{18}N_2$. Calculated: C 81.6; H 7.25; N 11.2%.

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