REACTION OF 2-METHYLPYRROLO[3,2-h]QUINOLINE WITH N-ACYL SALTS OF HETEROAROMATIC CATIONS IN SITU

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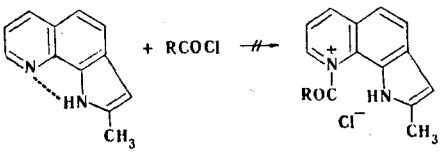
The reaction of pyrroloquinoline with N-acylpyridinium, N-acylquinolinium, N-acylisoquinolinium, and N-acylbenzimidazolium salts (formed as a result of the reaction with carboxylic acid chlorides), which leads to partially hydrogenated N-acyl derivatives of pyrroloquinoline, was investigated. The reaction of pyrroloquinoline with acridine hydrochloride, as a result of which its acridine derivative was obtained, was carried out.

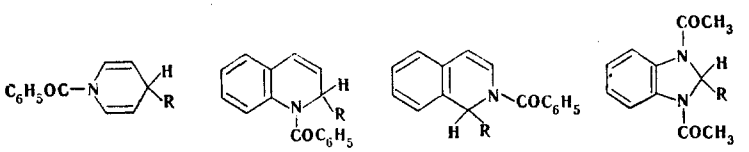
A necessary condition for the successful hetarylation of heteroaromatic cations by N-acyl salts is sufficiently high nucleophilicity of the compounds to be hetarylated, which include indole and other π-surplus heterocycles [1]. It seemed of interest to verify the possibility of extension of this reaction to pyrroloquinoline, the nucleophilicity of the pyrrole ring in which should be reduced because of annelation of the electrophilic quinoline ring. The possibility of the use of pyrroloquinoline as hetarylating agents as a result of the formation from them of the corresponding N-acyl heteroaromatic cations during the reaction also was not excluded. With this in mind, we investigated the behavior of one of the representatives of pyrroloquinolines — 2-methylpyrrolo[3,2-h]quinoline — in the hetarylation reaction. It was found that I does not react with acyl halides, evidently because of the formation of an intramolecular hydrogen bond and shielding of the nitrogen atom of the quinoline ring:



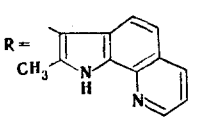
I II

The broad weak band in the IR spectrum of this compound at 3200-3300 cm^{-1}, which corresponds to an NH group and remains unchanged when the solution is diluted, constitutes evidence in favor of the presence of an intramolecular hydrogen bond.

By reaction of I with pyridine, quinoline, and isoquinoline in the presence of benzoyl chloride we were able to obtain III, IV, and V. Benzimidazole also reacts with this compound in the presence of acetic anhydride to give VI:



III IV V VI



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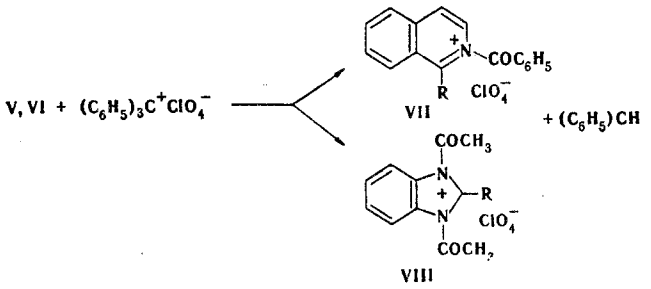
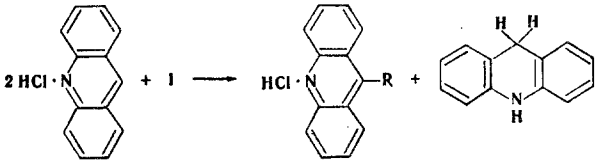
Compounds V and VI converted to stable N-acyl salts VII and VIII in quantitative yields on reaction with hydride-ion acceptors (for example, a solution of triphenylmethyl perchlorate in acetonitrile):



When salt VIII is treated with concentrated ammonium hydroxide, it is converted quantitatively to the colored anhydro base, which reacts with $HClO_4$ and is readily converted to the starting salt.

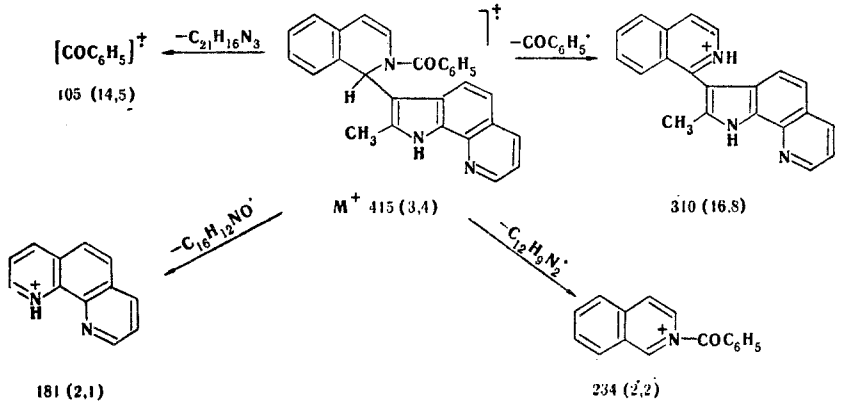
It was found to be more convenient to introduce an acridine residue in the pyrroloquinoline ring by means of protic acridinium salts, as in the acridinylation of dialkylanilines and indoles [2].



It has been established that reactions of this type proceed through hydride transfer from the intermediately formed dihydro derivative to the more electrophilic acridine hydrochloride to give acridan X and final hetarylation product IX.

Intense absorption bands of the C=O group of an acyl residue (1660-1680 cm^{-1}) and of the NH group of the pyrrole ring (3480-3490 and 3200-3300 cm^{-1}) are observed in the IR spectra of III, IV, V, and VI. A 100 cm^{-1} shift of the absorption maximum of the carbonyl group to the higher-frequency region as compared with the corresponding amides V and VI is observed in the spectra of salts VII and VIII; this constitutes evidence in favor of a bond between the carbonyl group and the nitrogen atom bearing a positive charge [3].

The fragmentation of the molecular ion (M^+) of V proceeds via the pathways characteristic for benzoylated dihetaryl compounds [4]. The peaks of ions that are formed due to cleavage of the amide bond in the starting molecule ($C_6H_5CO^+$ and $[M - C_6H_5CO]^+$) are the maximum peaks in the mass spectrum. Processes that are accompanied by destruction of the C–C bond between the heterorings take place to a considerably lesser extent:



EXPERIMENTAL

The IR spectra of chloroform (III-VI, IX) and acetonitrile (VII and VIII) solutions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of d_6-DMSO solutions of the compounds were obtained with an XL-100 spectrometer at room temperature with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT-311 spectrometer at an accelerating voltage of 3 kV, a cathode-emission current of 300 mA, an ionizing voltage of 70 eV, and an ion-source temperature of 115-130°C. Chromatography on Silufol was accomplished by elution with chloroform and development with iodine vapors and UV light. The picrates were crystallized from glacial acetic acid.

2-Methyl-3-(1-benzoyl-1,4-dihydro-4-pyridyl)pyrrolo[3,2-h]quinoline (III). A mixture of 0.9 g (0.01 mole) of pyridine, 0.9 g (0.005 mole) of 2-methyl-1H-pyrrolo[3,2-h]quinoline, obtained by the method in [5], and 0.7 g (0.005 mole) of benzoyl chloride in 20 ml of dry benzene was refluxed for 15 h, after which it was made alkaline, and the resulting precipitate was removed by filtration and recrystallized from ethanol to give 0.9 g (50%) of III with mp 162-163°C and R_f 0.60. IR spectrum: 1665, 3482, and 3240 cm^{-1}. Found: C 78.7; H 5.4; N 11.7%. $C_{24}H_{19}N_3O$. Calculated: C 78.9; H 5.2; N 11.5%. The picrate had mp 259-260°C. Found: N 14.4%. $C_{24}H_{19}N_3O \cdot C_6H_3N_3O_7$. Calculated: N 14.1%.

2-Methyl-3-(1-benzoyl-1,2-dihydro-2-quinolinyl)pyrrolo[3,2-h]quinoline (IV). This compound was similarly obtained in 25% yield and had mp 179-180°C (from n-butanol) and R_f 0.55. IR spectrum: 1665, 3480, and 3245 cm^{-1}. Found: C 80.9; H 5.4; N 10.4%. $C_{28}H_{21}N_3O$. Calculated: C 81.0; H 5.1; N 10.1%. The picrate had mp 190-191°C. Found: N 13.3%. $C_{28}H_{21}N_3O \cdot C_6H_3N_3O_7$. Calculated: N 13.0%.

2-Methyl-3-(2-benzoyl-1,2-dihydro-1-isoquinolyl)pyrrolo[3,2-h]quinoline (V). This compound was similarly obtained in 37% yield and had mp 178-179°C (from n-butanol) and R_f 0.50. IR spectrum: 1680, 3490, and 3225 cm^{-1}. PMR spectrum, δ: 12.2 (NH), 2.65 (CH_3), 8.96 (2-H), and 6.40-8.80 ppm (aromatic protons). Mass spectrum, m/e: 51 (6.1),* 77 (39.4); 102 (5.0); 105 (86.5); 106 (7.0); 128 (5.8); 181 (12.6); 182 (5.8); 234 (13.4); 281 (5.6); 308 (14.4); 309 (6.9); 310 (100.0); 311 (25.3); 415 (20.4); 416 (6.2). Found: C 81.3; H 5.1; N 10.4%. $C_{28}H_{21}N_3O$ Calculated: C 81.0; H 5.1; N 10.1%. The picrate had mp 235-236°C. Found: N 12.9%. $C_{28}H_{21}N_3O \cdot C_6H_3N_3O_7$. Calculated: N 13.0%.

2-Methyl-3-[2-(2-thenoyl)-1,2-dihydro-1-isoquinolyl]pyrrolo[3,2-h]quinoline. This compound was similarly obtained in 55% yield and had mp 129-130°C (from n-butanol) and R_f 0.55. IR spectrum: 1670, 3485, and 3300 cm^{-1}. Found: C 74.0; H 4.5; N 10.0; S 7.8%. $C_{26}H_{19}N_3OS$. Calculated: C 74.1; H 4.5; N 9.9; S 7.6%. The picrate had mp 167-168°C. Found: N 13.0%. $C_{26}H_{19}N_3OS \cdot C_6H_3N_3O_7$. Calculated: N 12.9%.

2-Methyl-3-(9-acridinyl)pyrrolo[3,2-h]quinoline (IX). A mixture of 1.8 g (0.01 mole) of 2-methylpyrrolo[3,2-h]quinoline, 4.2 g (0.02 mole) of acridine hydrochloride, and 10 ml of dry dimethylformamide (DMF) was heated at 100°C for 6 h, after which it was worked up to give 2 g (55%) of a product with mp 277-278°C (from n-butanol) and R_f 0.50. IR spectrum: 3495 and 3290 cm^{-1}. PMR spectrum, δ: 1.65 (CH_3), 10.40 (NH), and 6.43-8.74 ppm (aromatic protons). Mass spectrum, m/e: 172 (12.42); 173 (3.39); 178 (4.74); 179 (9.11); 179.5 (8.48); 180 (3.74); 181.3 (4.46); 344 (7.88); 345 (7.29); 355 (3.20); 356 (3.47); 357 (12.28); 358 (15.08); 358.7 (36.27); 359 (100); 361 (29.65); 362 (4.39). Found: C 83.3; H 4.3; N 11.7%. $C_{25}H_{17}N_3$. Calculated: C 83.6; H 4.3; N 11.7%. The picrate had mp 262-263°C. Found: N 14.5%. $C_{25}H_{17}N_3 \cdot C_6H_3N_3O_7$. Calculated: N 14.3%. Acridan [1.4 g (80%)], with mp 170-171°C (from methanol), was also isolated from the reaction mixture. No melting-point depression was observed for a mixture of this product with an authentic sample.

2-Methyl-3-(1,3-diacetyl-2-benzimidazolinyl)pyrrolo[3,2-h]quinoline (VI). This compound was obtained by reaction of 1.8 g (0.01 mole) of 2-methyl-1H-pyrrolo[3,2-h]quinoline and 1.2 g (0.01 mole) of benzimidazole in 10 ml of acetic anhydride at 120°C for 6 h. Workup gave 2.4 g (63%) of a product with mp 294-295°C (from n-butanol) and R_f 0.50. IR spectrum: 1672, 3492, and 3242 cm^{-1}. PMR spectrum, δ: 10.40 (NH), 2.60 ($COCH_3$), 1.85 (CH_3), and 10.80 ppm (2-H). Mass spectrum, m/e: 43 (31.30); 44 (6.69); 65 (6.94); 73 (3.83); 92 6.53); 93 (4.94); 118 (4.36); 119 (19.54); 126 (3.42); 127 (4.51); 153 (6.99); 154 (9.29); 161 (32.15); 168 (7.64); 179 (10.24); 180 (3.64); 181 (48.88); 182 (100); 183 (32.43); 193 (5.24); 194 (4.18);

*The numbers in parentheses denote the intensities in percent of the total ion current.

196 (5.77); 203 (53.76); 204 (8.69); 206 (13.88); 207 (4.98); 208 (7.09); 209 (23.47); 210 (7.51); 224 (13.45); 235 (4.04); 257 (3.55); 283 (10.89); 284 (14.48); 285 (14.41); 285 (4.91); 286 (3.61); 298 (14.10); 299 (12.28); 300 (73.72); 301 (17.65); 310 (15.14); 311 (4.10); 324 (4.44); 325 (3.13); 326 (9.19); 328 (15.04); 329 (4.63); 342 (9.46); 343 (4.57); 385 (43.39; 386 (11.98). Found: C 80.1; H 5.5; N 14.9%. $C_{23}H_{20}N_4O_3$. Calculated: C 79.9; H 5.2; N 14.6%. The picrate had mp 280-281°C. Found N 16.3%. $C_{23}H_{20}N_4O_2 \cdot C_6H_3N_3O_7$. Calculated: N 16.0%.

2-Methyl-3-(2-benzoyl-1-isoquinolium)pyrrolo[3,2-h]quinoline Perchlorate (VII). A solution of 0.6 g (1.75 mmole) of triphenylmethyl perchlorate in 10 ml of dry acetonitrile was added to a solution of 0.7 g (1.75 mmole) of 2-methyl-3-(2-benzoyl-1,2-dihydro-1-isoquinolyl) pyrrolo[3,2-h]quinoline in 10 ml of dry acetonitrile, and the mixture was maintanined at room temperature for 5 min. It was then poured into 150 ml of dry ether, and the resulting precipitate was removed by filtration and purified by reprecipitation from acetonitrile by the addition of ether. Workup gave 0.7 g (67%) of a product with mp 201-202°C. IR spectrum: 1760 cm^{-1}. Found: C 65.5; H 4.3; Cl 6.5; N 8.0%. $C_{28}H_{20}ClN_3O_5$. Calculated: C 65.4; H 4.0; Cl 6.9; N 8.1%. The reaction mixture also yielded 0.27 g (90%) of triphenylmethane with mp 92-93°C (from methanol). No melting-point depression was observed for a mixture of this product with an authentic sample.

2-Methyl-3-(1,3-diacetyl-2-benzimidazolium)pyrrolo[3,2-h]quinoline Perchlorate (VIII). This compound was similarly obtained in 84% yield and had mp 225-226°C (acetonitrile—ether). IR spectrum: 1756 cm^{-1}. Found: C 57.0; H 4.7; Cl 7.6; N 11.7%. $C_{23}H_{19}N_4O_6Cl$. Calculated: C 57.2; H 4.0; Cl 7.3; N 11.6%.

2-Methyl-3-(1,3-diacetyl-2-benzimidazolinylidene)pyrrolo[3,2-h]quinoline. A mixture of 0.25 g (5 mmole) of 2-methyl-3-(1,3-diacetyl-2-benzimidazolium)pyrrolo[3,2-h]quinoline perchlorate and 5 ml of concentrated NH_4OH was maintained at 25°C for 5 min, after which the precipitate was removed by filtration and recrystallized from methanol to give 0.1 g (50%) of a product with mp 266-267°C and R_f 0.70. IR spectrum: 1665 cm^{-1}. Found: C 71.7; H 5.3; N 14.3%. $C_{23}H_{19}N_4O_2$. Calculated: C 72.0; H 5.0; N 14.6%.

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