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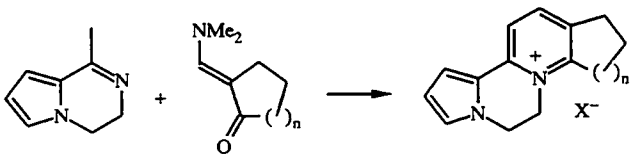
[3 + 3]-CYCLOCONDENSATION OF AMINOMETHYLENE-CYCLOALKANONES WITH CYCLIC AZOMETHINES — A NEW APPROACH TO CONDENSED NITROGEN HETEROCYCLES

O. V. Gulyakevich, A. L. Mikhal'chuk, V. P. Peresada, A. M. Likhosherstov, and A. A. Akhrem

A new method was developed for the synthesis of condensed azinium salts with a nitrogen atom in the ring fusion based on the [3 + 3]-cyclocondensation of aminomethylenecycloalkanones and cyclic azomethines.

The reactions of Schiff bases with carbonyl and β-dicarbonyl compounds or their enol derivatives are well known [1, 2] and have been used for the construction of the molecular skeletons of both carbocyclic [3] and heterocyclic compounds [4, 5]. Increasingly complicated compounds with given regio- and stereofunctional design, which may be considered specially prepared molecular fragments or "synthones" capable of fusion in the final synthetic steps, are used in such reactions [6, 7]. Despite the developments in this area of organic synthesis, which began more than a century ago with the work of Ganch in 1882 and Debner in 1886, its synthetic potential has not yet been exhausted as indicated by recent advances [8-10].

Our studies on the synthesis of benzo[*a*]quinolizine and related azine derivatives using the reactions of cyclic Schiff bases and β-dicarbonyl compounds and their enol derivatives have shown that cyclic azomethines react with β-aminoenones in the presence of acid to give azinium derivatives. Thus, for example, the reaction of 1-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (I) with 2-dimethylaminomethylenecycloalkanones (IIa and IIb) in acetic acid or ethanolic HCl upon heating gives cyclopenta[5,6]pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazinium (IIIa and IIIb) and pyrrolo[2,1′:3,4] pyrazino[1,2-*a*]quinolinium acetates and chlorides (IVa and IVb), respectively. Azinium derivatives III and IV are formed in yields up to 95%. The required anion may be introduced either during the reaction (methods A and B) or by exchange during isolation of the salt (method C).



I IIa, b IIIa,b; IVa, b

IIa, IIIa, b n = 1; IIb, IVa, b n = 2; IIIa, IVa X = OAc; IIIb, IVb X = Cl

This reaction, which, in essence, is the [3 + 3]-cyclocondensation of cyclic azomethines and aminoenones, opens fundamentally new approaches to the synthesis of condensed nitrogen heterocycles and provides a relative simple and useful synthesis of azinium derivatives employing readily available aminoenones [11] and cyclic azomethines [12]. On the other hand, these results considerably expand the scope for fusion reactions of azomethines with electrophilic olefins and permit us to plan the synthesis of many other azinium derivatives using this reaction.

The azinium salts obtained hold undoubted interest as intermediates for azine derivatives, which are presently difficult to obtain, and as model structures in the study of the interrelationship of structure and biological function of the immunomodulating and anxiolytic action of 5,8-diazasteroids [13] and other azinium derivatives, which are well represented in the arsenal of modern therapeutic and technical agents [14, 15].

Institute of Bioorganic Chemistry, Academy of Sciences of Belarus, 220141 Minsk. Institute of Pharmacology, Ministry of Health of the Russian Federation, 117607 Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 972-974, July, 1997. Original article submitted December 15, 1996.

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EXPERIMENTAL

The reaction course was monitored by thin-layer chromatography on standard Silufol UV-254 plates with 8:1.5:0.5 chloroform–methanol–water as the eluent. The plates were developed with UV light or iodine vapor with subsequent roasting at 250-350°C. The melting points were determined on a Boetius block. The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The electronic absorption spectra were taken on a Specord M-400 spectrophotometer for ethanol solutions. The mass spectra were taken on a Varian MAT-311 mass spectrometer. The ionizing radiation energy was 70 eV.

1H-2,3,5,6-Tetrahydrocyclopenta[5,6]pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazinium Acetate (IIIa). A. A mixture of 1.34 g (10 mmoles) azomethine I and 1.53 g (11 mmoles) aminoenone IIa was heated for 1 h at about 100°C in 5 ml glacial acetic acid. The reaction mixture was then evaporated to dryness. The residue was dissolved in 5 ml water and extracted with chloroform. The extracts were discarded, while the aqueous phase was saturated with sodium acetate and again extracted with chloroform. The combined extracts were dried over sodium sulfate, filtered, and evaporated. The residue was crystallized from chloroform–hexane to give 2.3 g (82.5%) acetate IIIa as pale yellow crystals, mp >200°C (dec.), $[M-AcO]^+$ 211. IR spectrum (ν, cm^{-1}): 3450-2400, 1725, 1625, 1587, 1556, 1500-1480, 1440, 1380-1360, 1321, 1291, 1241, 1219, 1198, 1171, 1157, 1094, 1078, 860, 828. UV spectrum [λ_{max}, nm (ε)]: 200 (8700), 210 (6950), 388 (15,800). Found: C, 70.93; H, 6.64; N, 10.25%. Calculated for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%.

1H-2,3,5,6-Tetrahydrocyclopenta[5,6]pyrido[1,2-*a*]pyrrolo[1,2-*c*]pyrazinium Chloride (IIIb). B. A mixture of azomethine and aminoenone analogous to that described in method A was heated at reflux for 1 h in 10 ml methanol saturated with HCl by the addition of 0.11 ml acetyl chloride. The reaction mixture was then evaporated. The residue was dissolved in water and extracted with chloroform. The extracts were discarded, while the aqueous phase was saturated with sodium chloride and again extracted with chloroform. Usual work-up of the combined extracts gave 2.0 g (81%) chloride IIIb as bright yellow crystals, mp >200°C (dec., ethanol–ether), $[M-Cl]^+$ 211. IR spectrum (ν, cm^{-1}): 3500-2600, 1630, 1590, 1558, 1505-1477, 1380-1360, 1289, 1198, 1160, 1095, 860, 829, 759. UV spectrum [λ_{max}, nm (ε)]: 201 (9400), 210 (8400), 291 (6900), 387 (16,300). Found: 68.08; H, 6.01; Cl, 14.41; N, 11.27%. Calculated for $C_{14}H_{15}ClN_2$: C, 68.15; H, 6.13; Cl, 14.37; N, 11.35%.

Chloride IIIb was also obtained by anion exchange. C. The aqueous phase of the reaction mixture obtained in method A after the first chloroform extraction was treated with 0.5 ml conc. hydrochloric acid and saturated with sodium chloride. Subsequent work-up according to the description for methods A and B gave 2.1 g (85%) chloride IIIb, which was identical to the sample obtained according to method B.

1,2,3,4,6,7-Hexahydropyrrolo[2′,1′:3,4]pyrazino[1,2-*a*]quinolinium Acetate (IVa). A mixture of 1.34 g (10 mmoles) azomethine I and 1.76 g (11.5 mmoles) aminoenone IIb was treated analogously to method A to give 2.3 g (81%) acetate IVa as pale yellow crystals, mp 225-230°C (dec., chloroform–hexane), $[M-AcO]^+$ 225. IR spectrum (ν, cm^{-1}): 3550-2800, 1728, 1630, 1585, 1500, 1420, 1380, 1300, 1275, 1230, 1178, 1080, 853. UV spectrum [λ_{max}, nm (ε)]: 200 (9900), 290 (6400), 387 (15,000). Found: C, 71.80; H, 7.10; N, 9.77%. Calculated for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85%.

1,2,3,4,6,7-Hexahydropyrrolo[2′,1′:3,4]pyrazino[1,2-*a*]quinolinium Chloride (IVb). The mixture of azomethine and aminoenone described in the previous experiment was treated according to method B to give 2.4 g (92%) chloride IVb as yellow-green crystals, mp 238-242°C (dec., methanol–ether), $[M-Cl]^+$ 225. IR spectrum (ν, cm^{-1}): 3550-3200, 1628, 1583, 1497, 1419, 1383, 1299, 1178, 1080, 774, 747. UV spectrum [λ_{max}, nm (ε)]: 202 (10,900), 286 (6400), 385 (15,470). Found: C, 68.93; H, 6.47; Cl, 13.66; N, 10.52%. Calculated for $C_{15}H_{17}ClN_2$: C, 69.09; H, 6.57; Cl, 13.60; N, 10.74%.

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