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LETTERS TO THE EDITOR

Synthesis of Fused Indolizine Derivatives (Pyrrolo[1,2-*a*]quinolines) by Annulation of 2-Methyl-1-pyrrolidine with 2-Acylcyclohexane-1,3-diones

O. V. Gulyakevich, P. V. Kurman, and A. L. Mikhal'chuk

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, Belarus

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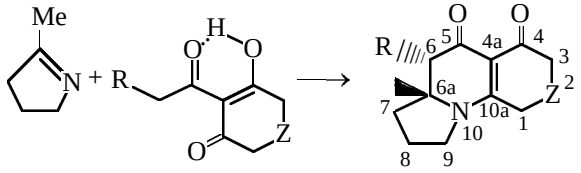
Annulation of cyclic Schiff bases (3,4-dihydroisoquinolines, 4,9-dihydro-3*H*-β-carbolines, etc) with β-di- and β,β'-tricarbonyl compounds (β-diketones, β-keto esters, 2-acylcyclane-1,3-diones, and 3-acyl derivatives of tetramic, tetronic, and thiotetronic acids, etc.) has assumed increasing importance in the design of molecular skeletons of fused nitrogenous heterocycles with an angular nitrogen atom [1–4]. At present the best explored of such reactions are [2 + 4] cyclocondensations of cyclic azomethines (3,4-dihydroisoquinolines, 3,4-dihydropyrrolo[1,2-*a*]pyrazines, 4,9-dihydro-3*H*-β-carbolines) with 2-acylcyclane-1,3-diones and their heterocyclic analogs (acyltetronic, -tetramic, -thiotetronic, and -barbituric acids) and annulation of 3,4-dihydroisoquinolines and 4,9-dihydro-3*H*-β-carbolines with β-keto esters [1, 2]. At the same time, annulation of monocyclic and acyclic azomethines (annulation of the C=N bond) has scarcely been studied, as evidenced by the fact that there have been only two mutually contradictory communications concerning benzalaniline reaction with 2-acylcyclane-1,3-diones [1, 5], as well as by the lack of information on annulation of monocyclic azomethines with β-di- and β,β'-tricarbonyl compounds. This situation is probably explained by the hydrolytic instability of acyclic and monocyclic azomethines and the known tendency of the latter for self-condensation [6, 7].

Proceeding with the research into the synthesis of fused heterocyclic compounds by annulation of Schiff bases with carbonyl compounds and their enol derivatives, we considered it urgent to extend these reactions to mono- and acyclic azomethines, aiming at developing one-stage syntheses of derivatives of quinolizine, indolizine, pyridine, and other theoretically and practically important azines.

In view of the valuable biological properties [8] and limited availability of compounds with an indolizine fragment [9], of particular concern was to extend the above annulation reactions to monocyclic azomethines, specifically the commercially available 2-methyl-1-pyrroline. On the other hand, reactions of monocyclic azomethines, in particular pyrrolines, with β-di- and β,β'-tricarbonyl compounds are important to study for elucidating the mechanism of and the role of stereochemical factors in such annulation reactions and the scope of their application.

The condensations of 2-methyl-1-pyrroline (**I**) with 2-acylcyclohexane-1,3-diones **IIa** and **IIb** were performed by analogy with the previously studied annulation of 3,4-dihydroisoquinolines with acetylcyclohexane-1,3-diones [1–3], by refluxing equimolar reagent mixtures in ethanol. It was found that the reactions give rise to angularly methylated fused derivatives of indolizine or pyrrolo[1,2-*a*]quinolines **IIIa** and **IIIb**; the yields of the latter compounds attain 65% (per individual reaction product).



I **IIa, IIb** **IIIa, IIIb**

II, III, R = H (**a**), Me (**b**); Z = CH_2 (**a**), CMe_2 (**b**).

The structure and composition assigned to pyrrolo[1,2-*a*]quinolines and their purity were confirmed by elemental analysis, GC–MS, IR and UV spectroscopy, as well as by comparison of their characteristics with those of structurally related 8-azasteroids [1–3].

Thus, the extension of annulation of 3,4-di-

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hydroisoquinolines with β-di- and β,β'-tricarbonyl compounds or their enol derivatives to 2-methyl-1-pyrroline (**I**) opens up quite an effective one-stage synthetic approach to new fused indolizine derivatives, specifically pyrrolo[1,2-*a*]quinolines **IIIa** and **IIIb**.

6a-Methyl-1,2,3,4,5,6,6a,7,8,9-decahydropyrrolo-[1,2-*a*]quinoline-4,5-dione (IIIa). A mixture of 0.42 g of pyrroline **I** and 0.77 g of 2-acetylcyclohexane-1,3-dione (**IIa**) was refluxed in 5 ml of absolute ethanol, following the reaction progress by TLC. After 7 h, the solvent was evaporated, and the crystalline residue was repeatedly washed with diethyl ether and dissolved in ethanol. The resulting solution was diluted with diethyl ether and left to stand at 5°C for 12 h. The crystals that formed were recrystallized from ethanol–diethyl ether (2 : 5) to obtain 0.77 g (63%) of pyrroloquinoline IIIa as colorless crystals, mp 165–167°C. IR spectrum, ν, cm^{-1}: 3000–2830, 1675, 1568–1538, 1451, 1419, 1397, 1344. UV spectrum, λ_{max}, nm (ε): 266.2 (17 630), 305 (17 335); λ_{min}, nm (ε): 221.6 (670), 281.9 (10 065). Found, %: C 71.21, 71.16; H 7.81, 7.77; N 6.39, 6.23. M^+ 219. Calculated, %: C 71.14; H 7.73; N 6.31. *M* 219.28.

2,2,6,6a-Tetramethyl-1,2,3,4,5,6,6a,7,8,9-decahydropyrrolo[1,2-*a*]quinoline-4,5-dione (IIIb). A mixture of 0.42 g of pyrroline **I** and 0.98 g of β,β'-triketone **IIa** was refluxed in 5 ml of absolute ethanol, following the reaction progress by TLC. After 6 h, the reaction mixture was reduced by half, diluted with diethyl ether until slightly turbid, and left to stand at 5°C for 12 h. The crystals that formed were filtered off, washed with diethyl ether, and recrystallized from ethanol–diethyl ether (1 : 3) to obtain 0.88 g (67%) of pyrroloquinoline **IIIb** as pale rose crystals, mp 188–191°C. IR spectrum, ν, cm^{-1}: 3000–2830, 1680, 1610, 1565 sh, 1546, 1450, 1430 sh, 1420, 1370, 1348, 1287. UV spectrum, λ_{max}, nm (ε): 266.9 (14075), 305.4 (15425); λ_{min}, nm (ε): 219.3 (550), 281.9 (8160). Found, %: C 73.53, 73.49; H 8.87, 8.84; N 5.36, 5.21. M^+ 261. Calculated, %: C 73.44; H 8.91; N 5.25. *M* 261.36.

The IR spectra were obtained on a UR-20 instrument. The UV spectra were taken on a Specord M-400 spectrophotometer in ethanol. The mass spectra were measured on an HP-5890/5972 GC–MS system [HP-5MS quartz capillary column, 30 m × 0.25 mm × 0.25 μm, carrier gas helium (0.7–1 ml/min), injector temperature 250°C, temperature program 40–300°C (6 deg/min), ionizing energy 70 eV].

The reaction progress was followed and the purity of compounds **IIIa** and **IIIb** was checked by TLC on Silufol UV-254 plates, eluent chloroform–methanol, 9 : 1; development in UV light or in iodine vapor, followed by calcination at 250–300°C. The melting points were measured on a Boetius hot stage.

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