PYRANO[3,2-c]AZEPINE, A NEW HETEROCYCLIC SYSTEM. A NEW APPROACH TO PYRIDO[3,2-c]AZEPINES+

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Abstract - 3-Benzoylamino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrocoumarin (**1a**) was used as a synthon in the preparation of the first derivatives of the pyrano[3,2-c]azepine system **2** and in two approaches to pyrido[3,2-c]azepines **4**.

Recently we have described a simple one-pot synthesis of some 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarins,[1] which contain a didehydroamino acid unit[2] as a part of their structures. Now we report some further transformations of these compounds.

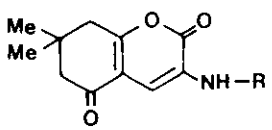
Ring expansion of cyclic ketones with hydrazoic acid (the Schmidt reaction) usually gives isomeric lactams, accompanied in some cases by an aromatized product, which could be considered as a product of the Semmler-Wolff aromatization.[3,4] The latter reaction is the reason why many substituted 5,6,7,8-tetrahydroquinolin-5-ones are not suitable precursors for the lactam synthesis.[4] In contrast to these results, the coumarin derivatives (**1a**[1] and **1b**) (the latter was prepared from **1a** and concentrated sulfuric acid in high yield) are very appropriate synthons for the synthesis of 6,7,8,9-tetrahydropyrano[3,2-c]azepine-2,5-diones (**2a** and **2b**), which were isolated as the only products in 91 and 71% yields when applying the Schmidt reaction with a large excess of hydrazoic acid to compounds (**1a** and **1b**), respectively. No traces of isomeric lactams and other products were noticed. The amino derivative (**2b**) was also formed on gentle heating of the compound (**2a**) in concentrated sulfuric acid (97% yield). The structures (**2a** and **2b**) were assigned by means of ^{1}H nmr spectra, which show a doublet for the 7-CH_2 group, a triplet for the neighboring NH group (J=5.9 Hz) and a singlet for the

+Dedicated to the memory of Professor Tetsuji Kametani.

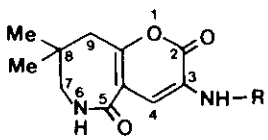
9-CH_2 group.

Another interesting conversion is the reaction of the condensed pyranone ring with nitrogen-containing nucleophiles.[5] The coumarin derivative (**1a**) was converted with ammonia, hydroxylamine and hydrazine in alcoholic solution into 2,5-dioxo-1,2,5,6,7,8-hexahydroquinolines (**3a-c**) in 58-83% yield, or into **3d** with the sodium salt of glycine in boiling N,N-dimethylformamide in 89% yield. Similarly, the pyrano[3,2-c]azepine derivative (**2a**) was transformed into 1,2,6,7,8,9-hexahydro-5H-pyrido[3,2-c]azepines (**4a-d**) in 27-55% yield. These reactions represent a new approach to the pyrido[3,2-c]azepines.[4,6] On the other hand, the carboxylic acid (**4d**) was formed in 80% yield when the Schmidt reaction was applied to the quinoline derivative (**3d**). The conversion of the quinoline system to the pyrido[3,2-c]azepine system was even more efficient when the carboxylic acid (**3d**) was first esterified in methanolic hydrogen chloride solution to the ester (**3e**) (83% yield), which was further converted into the final product (**4e**) by the Schmidt reaction in 84% yield.[7]

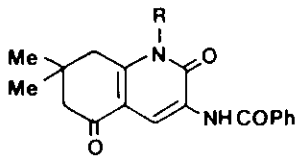
Similar transformations starting from 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarin and its 7-methyl derivative[1] are also under investigation.



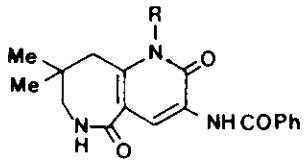
1 **a**: R = COPh
b: R = H



2 **a**: R = COPh
b: R = H



3 **a**: R = H
b: R = OH
c: R = NH_2
d: R = CH_2CO_2H
e: R = CH_2CO_2Me



4 **a**: R = H
b: R = OH
c: R = NH_2
d: R = CH_2CO_2H
e: R = CH_2CO_2Me

ACKNOWLEDGEMENT

This work was financially supported by the Research Council of Slovenia.

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7. General procedure for the Schmidt reaction. To a mixture of 5-oxo derivative (5 mmol) in chloroform (200 ml) and concentrated sulfuric acid (7.5 ml) at 0 °C excess of sodium azide (30 mmol) was added portionwise during 40-50 min; the reaction mixture was then stirred for 1.5 h at 0 °C and 2 h at room temperature. After the addition of ice and water (200 g) the products were isolated by different methods.

   All the new compounds gave satisfactory elemental analyses and spectroscopic data. Selected data for:

   1b: mp 195.5-196.5 °C (from AcOEt); ^{1}H nmr (90 MHz, solvent DMSO-d_6, standard Me_4Si) δ 6.60 (1H, s, 4-H), 5.44 (2H, s, NH_2), 2.67 (2H, s, CH_2), 2.34 (2H, s, CH_2), 1.04 (6H, s, two Me).

2a: mp 254-256 °C (DMF/MeOH); ir (KBr) 1735, 1700, 1680, 1540 cm^{-1}; ^1H nmr (DMSO-d_6) δ 9.18 (1H, s, NH), 8.23 (1H, s, 4-H), 7.98 (1H, t, J=5.9 Hz, 6H), 7.90 (2H, m, Ph), 7.52 (3H, m, Ph), 2.87 (2H, d, J=5.9 Hz, 7-CH_2), 2.54 (2H, s, 9-CH_2), 1.03 (6H, s, two Me); ms (m/z) 326 (M^+).

2b: mp 194-196 °C (AcOEt); ^1H nmr (DMSO-d_6) δ 8.13 (1H, t, J=5.9 Hz, 6-H), 6.46 (1H, s, 4-H), 5.35 (2H, s, NH_2), 2.73 (2H, d, J=5.9 Hz, 7-CH_2), 2.37 (2H, s, 9-CH_2), 0.95 (6H, s, two Me); ms (m/z) 222 (M^+).

3a: mp 264-266 °C (MeOH); ^1H nmr (DMSO-d_6) δ 9.26 (1H, s, NH), 8.60 (1H, s, 4-H), 7.94 (2H, m, Ph), 7.60 (3H, m, Ph), 2.73 (2H, s, CH_2), 2.39 (2H, s, CH_2), 1.05 (6H, s, two Me); ms (m/z) 310 (M^+).

3b: mp 220-223 °C (MeOH); ^1H nmr (DMSO-d_6) δ 9.41 (1H, s, NH or OH), 8.55 (1H, s, 4-H), 7.95 (2H, m, Ph), 7.60 (3H, m, Ph), 2.97 (2H, s, CH_2), 2.43 (2H, s, CH_2), 1.08 (6H, s, two Me); ms (m/z) 326 (M^+).

3c: mp 184-185 °C (EtOH); ^1H nmr (DMSO-d_6) δ 9.39 (1H, s, NH), 8.60 (1H, s, 4-H), 7.94 (2H, m, Ph), 7.60 (3H, m, Ph), 6.24 (2H, s, NH_2), 3.05 (2H, s, CH_2), 2.43 (2H, s, CH_2), 1.08 (6H, s, two Me); ms (m/z) 325 (M^+).

3d: mp 236-239 °C (MeOH); ir (KBr) 1755, 1690, 1640br cm^{-1}; ^1H nmr (DMSO-d_6) δ 9.36 (1H, s, NH), 8.70 (1H, s, 4-H), 7.95 (2H, m, Ph), 7.59 (3H, m, Ph), 4.95 (2H, s, $\underline{CH_2}CO_2H$), 2.84 (2H, s, CH_2), 2.44 (2H, s, CH_2), 1.06 (6H, s, two Me).

3e: mp 192-194 °C (MeOH).

4a: mp above 320 °C (DMF/MeOH); ^1H nmr (DMSO-d_6) δ 9.23 (1H, s, NH), 8.43 (1H, s, 4-H), 8.10 (1H, t, J=5.6 Hz, 6-H), 7.92 (3H, m, NH, Ph), 7.59 (3H, m, Ph), 2.71 (2H, d, J=5.6 Hz, 7-CH_2), 2.50 (2H, s, 9-CH_2), 0.96 (6H, s, two Me).

4b: mp 280-283 °C, dec (MeOH); ^1H nmr (DMSO-d_6) δ 9.35 (s, NH or OH), 8.32 (1H, s, 4-H), 8.24 (1H, t, J=5.7 Hz, 6-H), 7.92 (2H, m, Ph), 7.58 (3H, m, Ph), 2.79 (2H, s, 9-CH_2), 2.70 (2H, d, J=5.7 Hz, 7-CH_2), 0.99 (6H, s, two Me).

4c: mp 310-313 °C, dec (DMF/MeOH); ^1H nmr (DMSO-d_6, 70 °C) δ 9.16 (1H, s, NH), 8.38 (1H, s, 4-H), 8.03 (1H, t, J=5.6 Hz, 6-H), 7.90 (2H, m, Ph), 7.56 (3H, m, Ph), 5.88 (2H, s, NH_2), 2.93 (2H, s, 9-CH_2), 2.71 (2H, d, J=5.6 Hz, 7-CH_2), 1.00 (6H, s, two Me).

4d: mp 273-275 °C (MeOH); ir (KBr) 1750, 1690, 1630br cm^{-1}; ^1H nmr (DMSO-d_6, 93 °C) δ 9.14 (1H, s, NH), 8.44 (1H, s, 4-H), 8.00 (1H, t, J=5.9 Hz, 6-H), 7.90 (2H, m, Ph), 7.58 (3H, m, Ph), 4.91 (2H, s, $\underline{CH_2}CO_2H$), 2.73 (2H, d, J=5.9 Hz, 7-CH_2), 2.62 (2H, s, 9-CH_2), 1.01 (6H, s, two Me).

4e: mp 277-281 °C, dec (MeOH).

Received, 20th June, 1989