

## 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-tetrahydro-coumarin (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.

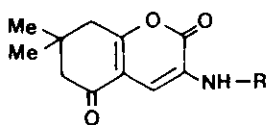
Recently we have described a simple one-pot synthesis of some 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarins,<sup>1</sup> which contain a dihydroamino acid unit<sup>2</sup> as a part of their structures. Now we report some further transformations of these compounds.

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.<sup>3-4</sup> The latter reaction is the reason why many substituted 5,6,7,8-tetrahydroquinolin-5-ones are not suitable precursors for the lactam synthesis.<sup>4</sup> In contrast to these results, the coumarin derivatives (1a<sup>1</sup> 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 <sup>1</sup>H nmr spectra, which show a doublet for the 7-CH<sub>2</sub> 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.

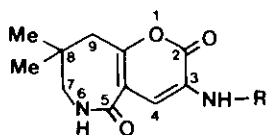
9-CH<sub>2</sub> group.

Another interesting conversion is the reaction of the condensed pyranone ring with nitrogen-containing nucleophiles.<sup>6</sup> 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-clazepine derivative (2a) was transformed into 1,2,6,7,8,9-hexahydro-5H-pyrido[3,2-clazepines (4a-d) in 27-55% yield. These reactions represent a new approach to the pyrido[3,2-clazepines.<sup>4,6</sup> 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-clazepine 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.<sup>7</sup> Similar transformations starting from 3-benzoylamino-5-oxo-5,6,7,8-tetrahydrocoumarin and its 7-methyl derivative<sup>1</sup> are also under investigation.



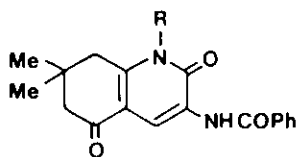
1 a: R = COPh

b: R = H



2 a: R = COPh

b: R = H



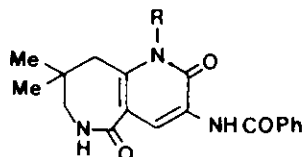
3 a: R = H

b: R = OH

c: R = NH<sub>2</sub>

d: R = CH<sub>2</sub>CO<sub>2</sub>H

e: R = CH<sub>2</sub>CO<sub>2</sub>Me



4 a: R = H

b: R = OH

c: R = NH<sub>2</sub>

d: R = CH<sub>2</sub>CO<sub>2</sub>H

e: R = CH<sub>2</sub>CO<sub>2</sub>Me

#### ACKNOWLEDGEMENT

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## REFERENCES AND NOTES

1. M. Kočevár, S. Polanc, M. Tišler, and B. Verčec, Synth. Commun., in press.
2. U. Schmidt, A. Lieberknecht, and J. Wild, Synthesis, 1988, 159.
3. D. V. Banthorp, "The Chemistry of the Azido Group: Rearrangements Involving Azido Groups," ed. by S. Patai, Interscience Publishers, London, 1971, pp. 397-440; A. J. Nunn and F. J. Rowell, J. Chem. Soc., Perkin Trans. 1, 1973, 2697; M. Kočevár, B. Stanovnik, and M. Tišler, Monatsh. Chem., 1988, 119, 597.
4. H. Klar, Arch. Pharm. (Weinheim, Ger.), 1976, 309, 550.
5. G. P. Ellis, "Comprehensive Heterocyclic Chemistry: Pyrans and Fused Pyrans: (ii) Reactivity," Vol. 3, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, pp. 647-736.
6. Y. Tamura, Y. Kita, and J. Uraoka, Chem. Pharm. Bull., 1972, 20, 876; A. N. Kost, L. N. Zukauskaitė, and A. Stankevicius, Tezisy Dokl. -Simp. Khim. Tekhnol. Geterosikl. Soedin. Coriuch. Iskop., 2nd 1973, 4 (Russ) (Chem. Abstr., 1976, 85, 177226j); L. N. Zukauskaitė, A. Stankevicius, and A. N. Kost, Khim. Geterosikl. Soedin., 1978, 63; F. Hollywood, Z. U. Khan, E. F. V. Scriven, R. K. Smalley, H. Suschitzky, D. R. Thomas, and R. Hull, J. Chem. Soc., Perkin Trans. 1, 1982, 431; Z. U. Khan, D. I. Patel, R. K. Smalley, E. F. V. Scriven, and H. Suschitzky, J. Chem. Soc., Perkin Trans. 1, 1983, 2495; D. I. Patel, E. F. V. Scriven, R. K. Smalley, and H. Suschitzky, J. Chem. Soc., Perkin Trans. 1, 1985, 1911; W. Danikiewicz and M. Makosza, J. Chem. Soc., Chem. Commun., 1985, 1792; D. I. Patel, R. K. Smalley, and D. I. C. Scopes, J. Chem. Res. (S), 1986, 204; J. Schofield, R. K. Smalley, D. I. C. Scopes, and D. I. Patel, J. Chem. Res. (S), 1987, 164.
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); <sup>1</sup>H nmr (90 MHz, solvent DMSO-d<sub>6</sub>, standard Me<sub>4</sub>Si) δ 6.60 (1H, s, 4-H), 5.44 (2H, s, NH<sub>2</sub>), 2.67 (2H, s, CH<sub>2</sub>), 2.34 (2H, s, CH<sub>2</sub>), 1.04 (6H, s, two Me).

**2a:** mp 254-256 °C (DMF/MeOH); ir (KBr) 1735, 1700, 1680, 1540  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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- $\text{CH}_2$ ), 2.54 (2H, s, 9- $\text{CH}_2$ ), 1.03 (6H, s, two Me); ms (m/z) 326 ( $\text{M}^+$ ).

**2b:** mp 194-196 °C (AcOEt);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  8.13 (1H, t,  $J=5.9$  Hz, 6-H), 6.46 (1H, s, 4-H), 5.35 (2H, s,  $\text{NH}_2$ ), 2.73 (2H, d,  $J=5.9$  Hz, 7- $\text{CH}_2$ ), 2.37 (2H, s, 9- $\text{CH}_2$ ), 0.95 (6H, s, two Me); ms (m/z) 222 ( $\text{M}^+$ ).

**3a:** mp 264-266 °C (MeOH);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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,  $\text{CH}_2$ ), 2.39 (2H, s,  $\text{CH}_2$ ), 1.05 (6H, s, two Me); ms (m/z) 310 ( $\text{M}^+$ ).

**3b:** mp 220-223 °C (MeOH);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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,  $\text{CH}_2$ ), 2.43 (2H, s,  $\text{CH}_2$ ), 1.08 (6H, s, two Me); ms (m/z) 326 ( $\text{M}^+$ ).

**3c:** mp 184-185 °C (EtOH);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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,  $\text{NH}_2$ ), 3.05 (2H, s,  $\text{CH}_2$ ), 2.43 (2H, s,  $\text{CH}_2$ ), 1.08 (6H, s, two Me); ms (m/z) 325 ( $\text{M}^+$ ).

**3d:** mp 236-239 °C (MeOH); ir (KBr) 1755, 1690, 1640  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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,  $\text{CH}_2\text{CO}_2\text{H}$ ), 2.84 (2H, s,  $\text{CH}_2$ ), 2.44 (2H, s,  $\text{CH}_2$ ), 1.06 (6H, s, two Me).

**3e:** mp 192-194 °C (MeOH).

**4a:** mp above 320 °C (DMF/MeOH);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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- $\text{CH}_2$ ), 2.50 (2H, s, 9- $\text{CH}_2$ ), 0.96 (6H, s, two Me).

**4b:** mp 280-283 °C, dec (MeOH);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$  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- $\text{CH}_2$ ), 2.70 (2H, d,  $J=5.7$  Hz, 7- $\text{CH}_2$ ), 0.99 (6H, s, two Me).

**4c:** mp 310-313 °C, dec (DMF/MeOH);  $^1\text{H}$  nmr (DMSO- $d_6$ , 70 °C)  $\delta$  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,  $\text{NH}_2$ ), 2.93 (2H, s, 9- $\text{CH}_2$ ), 2.71 (2H, d,  $J=5.6$  Hz, 7- $\text{CH}_2$ ), 1.00 (6H, s, two Me).

**4d:** mp 273-275 °C (MeOH); ir (KBr) 1750, 1690, 1630  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ , 93 °C)  $\delta$  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,  $\text{CH}_2\text{CO}_2\text{H}$ ), 2.73 (2H, d,  $J=5.9$  Hz, 7- $\text{CH}_2$ ), 2.62 (2H, s, 9- $\text{CH}_2$ ), 1.01 (6H, s, two Me).

**4e:** mp 277-281 °C, dec (MeOH).

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