3-HYDROXYPYRROLES. IV.[1]
RING-ENLARGEMENT OF 3-HYDROXYPYRROLE-2-CARBOXYLATES

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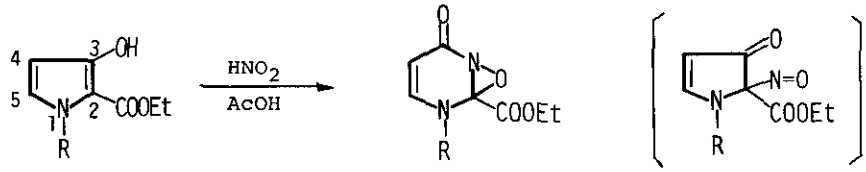
Abstract - 3-Hydroxypyrrole-2-carboxylates (1) yielded ring-expanded compounds, 4-pyrimidinone derivatives (2 and 10), on nitrosation and on the reaction with p-nitrobenzenediazonium chloride, respectively.

Ring-enlargement reactions are of interest in the mechanistic and synthetic aspects of heterocyclic chemistry. As for the pyrrole field, the conversion of pyrroles[2] or ring-fused pyrroles[3] into the pyrimidine or the ring-fused pyrimidine system is known. In this paper, we wish to report the transformation of the 3-hydroxypyrrole into the 4-pyrimidinone system.

In the course of our studies[4] on the reactivity of ethyl 3-hydroxypyrrole-2-carboxylates[5] (1) at C_2 and C_4 toward some electrophiles, we investigated the nitrosation of the 1-benzyl derivative (1; R=CH_2Ph), which resulted not in the formation of the 2- or 4-nitroso compound but in the ring-enlargement.

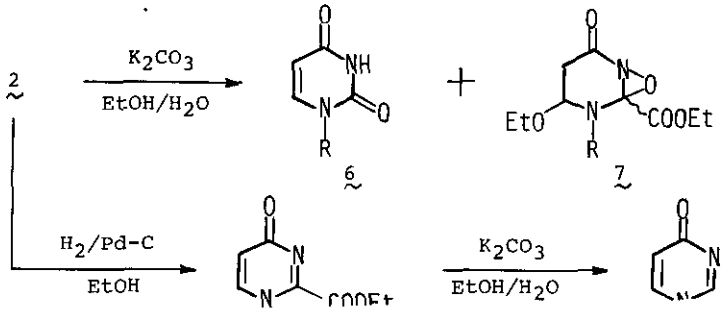


1 2 5

3 4

Compound 1 (R=CH_2Ph) yielded an unstable crystalline product (2) in 60% yield on treatment with sodium nitrite in acetic acid [2: mp 114-115°; IR($CHCl_3$) 1725, 1640, 1580 cm^{-1}; UV(EtOH) nm(ε) 250(7300), 307(2400); MS m/e 274(M^+, 0.6%), 91(100%);

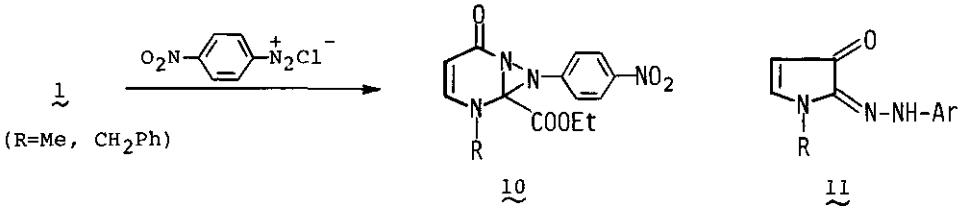
^{1}H-NMR($CDCl_3$) δ 1.33(3H, t, J=7.2Hz), 4.34(2H, q, J=7.2), 4.76(2H, s), 5.48(1H, d, J=9), 6.84(1H, d, J=9), 7.33(5H, s)]. The olefinic ring protons appear at δ 5.48 and 6.84 as doublets in the ^{1}H-NMR spectrum, and no hydroxyl absorption is detected in the IR spectrum, the feature indicating that the reaction occurred by an attack on C_2 in 1. The coupling constant (J=9Hz) is, however, fairly larger than that for pyrrolinones (3) (J=3∿4Hz)[4] and similar to that for a dihydropyridone (4) (J=8Hz),[6] and the UV absorption at 307 nm is not intense enough for the pyrrolinone system.[7] The facts suggest that the nitrosation product is, despite its satisfactory combustion data, not a nitrosopyrrolinone (5) but a six-membered compound.



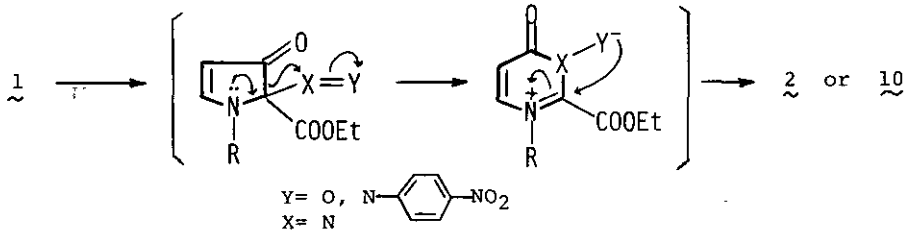
Compound 2 was hydrolyzed with potassium carbonate in aqueous ethanol to yield 1-benzyluracil (6)[8] (33% yield) and an ethanol-added product (7)[9] [7: 30% yield, a mixture of the diastereomers; IR($CHCl_3$) 1735, 1575 cm^{-1}; UV(EtOH) nm(ε) 295(2900); MS m/e 320(M^+, 7.3%), 91(100%); ^{1}H-NMR($CDCl_3$) δ 1.21(3H, t, J=7), 1.37(3H, t, J=7), 2.58 & 2.61(1H, d, J=5.5 for each), 4.05(2H, q, J=7), 4.34(2H, q, J=7), 4.58(2H, s), 5.87(1H, t, J=5.5), 7.26(5H, s)]. In addition, hydrogenation of 2 over palladium charcoal gave a 4-pyrimidinone-2-carboxylate (8) in 84% yield [8: mp 109.5-110°; IR($CHCl_3$) 1740, 1650, 1630 cm^{-1}; UV(EtOH) nm(ε) 247(13700); MS m/e 258(M^+, 13.4%), 91(100%); ^{1}H-NMR($CDCl_3$) δ 1.28(3H, t, J=7), 4.31(2H, q, J=7), 5.13(2H, s), 6.22(1H, d, J=8), 7.1∿7.5(5H, m), 7.42(1H, d, J=8)]. The 4-pyrimidinone carboxylated at C_2 is an uncommon type[10] of pyrimidine compounds, and the ester (8) was very easily hydrolyzed with potassium carbonate in aqueous ethanol at room temperature and decarboxylated on the usual work-up for isolation to yield 1-benzyl-4-pyrimidinone (9)[11] in quantitative yield. The newly produced C_2-proton in 9 appears at δ 8.23 (J=2.8Hz) as a doublet in the ^{1}H-NMR spectrum (in $CDCl_3$), being indicative of the exact location of the ester group in 8. On the basis of the derivation of six-membered compounds 6 and 8 from 2, it is evident that the nitrosation product from

1 (R=CH_2Ph) is the 4-pyrimidinone derivative (2).

Similar ring-expanded products (10) were obtained on the reaction between p-nitrobenzenediazonium chloride and 1 (R=Me, CH_2Ph) in the pH region 7 - 8 (acetate buffer) [10 (R=Me, 67% yield): mp 119-120°; IR($CHCl_3$) 1743, 1691, 1665, 1596 cm^{-1}; UV(EtOH) nm(ε) 333(10400), 255(10600), 232(12300); MS m/e 318(M^+, 36%), 277(100%); ^{1}H-NMR($CDCl_3$) δ 1.43(3H, t, J=7), 3.12(3H, s), 4.42(2H, q, J=7), 5.26(1H, d, J=9), 6.48(1H, d, J=9), 7.62(2H, d, J=9), 8.24(2H, d, J=9). 10 (R=CH_2Ph, 77% yield): mp 123.4-125.5°; IR($CHCl_3$) 1730, 1675, 1590 cm^{-1}; UV(EtOH) nm(ε) 330(11300), 255 (12500); MS m/e 394(M^+, 1.6%), 91(100%); ^{1}H-NMR($CDCl_3$) δ 1.34(3H, t, J=7), 4.33(2H, q, J=7), 4.60(2H, s), 5.27(1H, d, J=9), 6.56(1H, d, J=9), 7.32(5H, m), 7.64(2H, d, J=9), 8.22(2H, d, J=9)]. In contrast, the reaction in the pH region above 9 gave no pyrimidinones but the arylhydrazones (11) possibly via the pathway similar to that of the Japp-Klingemann reaction[12] [11 (R=Me, Ar=Ph): mp 109-112°; IR(Nujol) 1627, 1595, 1588 cm^{-1}; UV(EtOH) nm 258, 372, 467; MS m/e 201(M^+, 100%); ^{1}H-NMR ($CDCl_3$) δ 3.35(3H, s), 5.37(1H, d, J=4), 7.45(1H, d, J=4), 6.8∿7.3(5H, m)].



The reaction mechanism of the ring-enlargement may be speculated as depicted below: When a polar double bond moiety is introduced as the second C-2 substituent in the pyrrolinone system, the ring-expansion occurs via a 'push-pull' mechanism by participation of the ring-nitrogen lone pair.[13] Further exploration of these and related reactions is under investigation.



All new compounds described above gave satisfactory combustion data.

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5. T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, and K. Yamada, Chem. Pharm. Bull. (Tokyo), 1978, 26, 2224.
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7. The pyrrolinone system (3) displays an intensive UV absorption in the region of about 300 to 330 nm: see refs. 1 and 4. Compound 2 is so labile that it decomposes gradually on standing in several solvents. The maximum absorption at 307 nm may result from the decomposed products. By the way, the low intensity of the UV absorption and the less-deshielded NMR feature of the olefinic ring protons also exclude any conjugated N-oxide structure for 2.
8. A. Nováček, Coll. Czech. Chem. Commun., 1971, 36, 4066.
9. Compound 7 was also obtained in good yield on refluxing the ethanol solution of 2 for a few hours.
10. Only two, 4-hydroxy-2-pyrimidinecarboxylic acid and ethyl 1,4-dihydro-6-hydroxy-4-oxo-2-pyrimidinecarboxylate, have been reported: the former by W. Huber and H.A. Hölscher (Ber., 1938, 71B, 87), the latter by B. Narr, J. Roch, E. Mueller, and W. Haarmann (Chem. Abstr., 1975, 83, 43369h).
11. L. Bauer, G.E. Wright, B.A. Mikrut, and C.L. Bell, J. Heterocyclic Chem., 1965, 2, 447. The authors described the ^{1}H-NMR data for 9 measured in DMSO.
12. R.R. Phillips, Organic Reactions, ed. by R. Adams, 1959, Vol. 10, pp. 143 - 178.
13. A similar reaction mechanism has been presented: see T. Eicher, J.L. Weber and G. Chatila, Liebigs Ann. Chem., 1978, 1203.

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