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DIELS-ALDER ADDUCTS FROM N-UNSUBSTITUTED TAUTOMERIC 2(1H)-PYRIDONE–2-HYDROXYPYRIDINES; 5,6-BENZO-2-AZABARRELENONES AND 5,6-BENZO-2-AZABARRELENES

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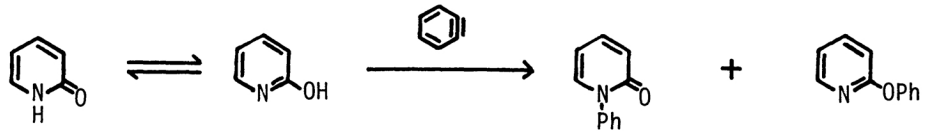
Diels-Alder reactions of several N-unsubstituted tautomeric 2(1H)-pyridone–2-hydroxypyridines with benzyne were examined and found to afford 5,6-benzo-2-azabarrelenones, which were converted to hitherto unknown 5,6-benzo-2-azabarrelenes.

It is now well established that 1 exists largely in the 2(1H)-pyridone tautomeric form 1A in solution,[1] whereas there is no significant difference in the fundamental stabilities of the tautomers, 1A and 1B in the gas phase.[2]

A study of the Diels-Alder reactivity of the these compounds with a highly reactive dienophile such as benzyne is of interest because reactions could provide insight into the structure-reactivity relationship of the tautomeric equilibrium. Furthermore, the resulting adducts probably could be converted to hitherto unknown 5,6-benzo-2-azabarrelene derivatives, which seem to be otherwise difficultly accessible and which contain many interesting physical and chemical features for study.

In contrast to the substantial amount of experimental work on the Diels-Alder reaction of N-substituted-2(1H)-pyridones with a variety of dienophile in recent years,[3] little attention has been focussed on similar reactions of N-unsubstituted-2(1H)-pyridones.[4] Earlier attempts at such reactions with benzyne were unsuccessful and resulted only in the formation of N-phenyl-2(1H)-pyridone (2) and 2-phenoxypyridine (3) in rather poor yield.[5] Interest in reactions of this type seems to have declined thereafter.



1A 1B 2 3

We have studied the Diels-Alder reaction of one series of 4-phenyl substituted-2(1H)-pyridones of (4a-e) with benzyne, and found that these compounds in fact underwent the Diels-Alder reaction with ease to give 5,6-benzo-2-azabicyclo[2.2.2]octadien-3-one derivatives (5,6-benzo-2-azabarrelenones), (5a-e). Success in this reaction is not only of interest in its own way, but also it opens a convenient route to 5,6-benzo-2-azabarrelenes.

The Diels-Alder reactions of 4 with benzyne were carried out according to the procedure reported by Bauer and co-workers.[3a] Work-up and chromatographic separation (alumina, benzene eluent) led to isolation of two products which were identified as 5a-e, and 2-phenoxypyridines (6a-e). Suprisingly, N-phenyl-2(1H)-pyridones were not isolated experimentally. The

structures of the adducts 5 follow from their spectral properties.[6,7] Further proof for the structures of 5 were provided by their facile conversion to N-methyl derivatives 7a-e on treatment with methyl iodide. These products were also obtained from the reaction of 1-methyl-2(1H)-pyridones (8a-e), derived from the methylation of 4a-e, with benzyne. These reaction sequences are shown below, and the results, including those of methylation of 4a-e, are summarized in Table I.

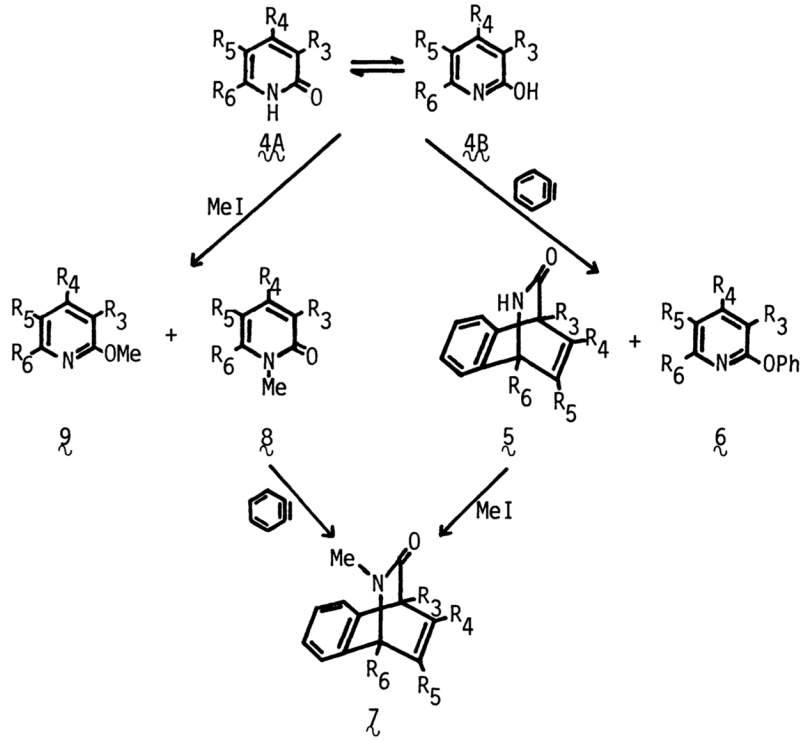


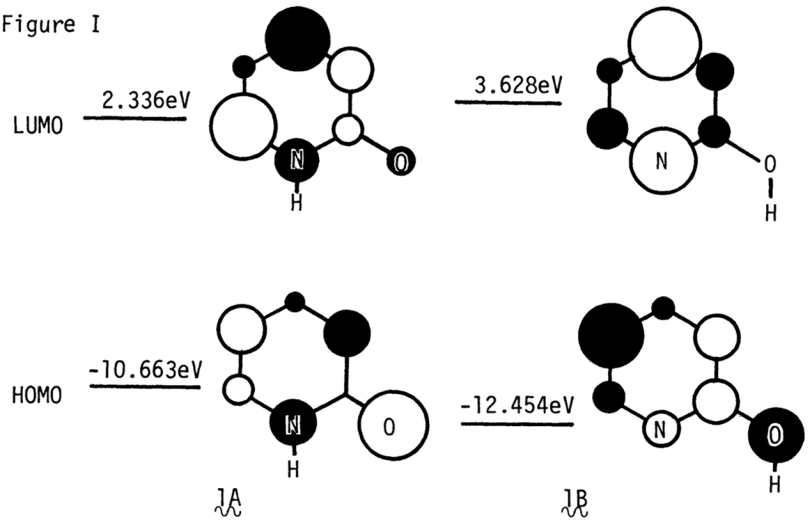
Table I. Product Distributions from Reaction of N-unsubstituted-2(1H)-Pyridones with Benzyne and Methyl Iodide[a]

2(1H)-Pyridones[b]	Substituents	Product Yield[c] %		Product Ratios[d] %	
		5	6	N-Me	O-Me
1	$R_3=R_4=R_5=R_6=H$	0	5.0[f]	95	5[g]
4a	$R_3=R_5=H$, $R_4=Ph$, $R_6=Me$	10.6	14.6	90	10
4b	$R_3=R_6=Me$, $R_4=Ph$, $R_5=H$	12.9	8.5	91	9
4c	$R_3=R_5=R_6=Me$, $R_4=Ph$	38.0	29.0	75	25
4d	$R_3=Me$, $R_4=Ph$, $R_5\sim R_6=-(CH_2)_4-$	28.6	33.6	87	13
4e	$R_3=Me$, $R_4=Ph$, $R_5\sim R_6=-(CH_2)_3-$	35.0	16.9	89	11

a. Methylations were carried out in DMF/K_2CO_3 at room temperature with stirring for 24 hrs. b. C. R. Hauser and C. J. Eby, J. Am. Chem. Soc., 79, 728 (1957) c. Isolated yield, not always optimized. d. Determined by ^1H NMR spectra. e. The rest of product was the starting 2(1H)-pyridone; total recovery was about 75-85% in each run. f. Reproduced from ref. 4. g. G. C. Hoptins, J. P. Jonak, H. J. Minnemeyer, and H. Tieckelmann, J. Org. Chem., 32, 4040 (1967)

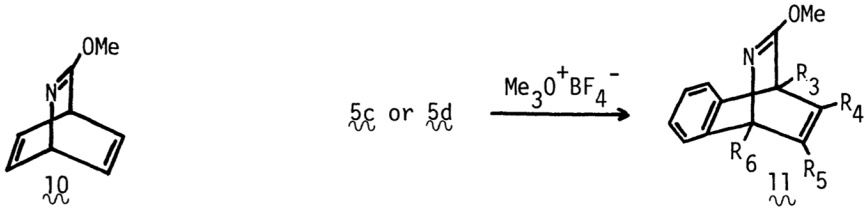
Introduction of a phenyl substituent to 2-pyridones (1) would raise the energies of HOMO and lower those of LUMO so that the Diels-Alder reactivity should be enhanced, assuming that the reaction proceeds along the line derived from a frontier molecular orbital theory. This effect, however, can not explain the noticeable difference in reactivity between 4a-b and 4c-e. The common difference of a structural feature of 4c-e from that of 4a-b is in presence of the substituent at C_5. In view of distribution of HOMO coefficients of 2(1H)-pyridone (1A) and 2-hydroxypyridine (1B) as shown in Figure I, the magnitude of a substituent effect at C_3 and C_5 should be the greatest. Thus, introduction of methyl substituent at C_3 and C_5 would efficiently raise HOMO energy on both forms, (1A) and (1B).[8] Thus, the reactivities with benzyne should be further enhanced with 4c-e in accord with the experimental results.

Figure I



Although 2-azabarrelene has considerable interest from a theoretical and a photochemical point of view, and ab initio (STO-3G) calculations[9] predict some stability for 2-azabarrelene as a result of a positive balance between the stabilizing through bond interactions and the destabilizing through space ones, it was not until last year (1980) that 2-azabarrelene (10) was synthesized[10] in rather poor overall yield from 2(1H)-pyridone derivative (less than 2% yield). 5,6-Benzo-2-azabarrelenes are still unknown.

The conversion of 5 into 5,6-benzo-2-azabarrelene (11) has been briefly explored. 5c and 5d were treated with trimethyloxonium tetrafluoroborate in the ordinary way to afford novel 5,6-benzo-2-azabarrelene (11), exclusively, as colorless crystalline products in good yield (70-80%), despite generating an antibicycloaromatic system.[11] The structure of 11 rests on the spectral properties.[12] It should be noted that 11 is quite stable at room temperature, and the mass spectrum shows an intense molecular ion peak, unlike 2-azabarrelenone (5), (7) and (10),[10] in which retro Diels-Alder fragmentation easily occurs to exhibit a base peak corresponding to the mass of the naphthalene derivatives.



We hope our results will spark new interest in this area of chemistry, and we are continuing to explore the scope and limitation of these reactions as well as the excited state chemistry of (11).

References

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4. One such reaction with maleimide has been reported to undergo the Diels-Alder reaction; Japn. Pat. s 50-14698 (1975), L. V. Vetaneli, N. P. Shusherina, A. U. Stepanyants, and E. A. Tarkhanova, Zh. Org. Khim., 13, 1926 (1977).
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6. All new compounds reported herein gave a satisfactory elemental analysis.
7. Selected spectral data are as follows: 4c mp 206-208°; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3H), 1.59 (s, 3H), 1.91 (s, 3H), 7.00-7.55 (m, 9H), 7.66 (s, 1H); IR (KBr): 1675 cm^{-1}; MS (70 eV): m/e=289 (4%, M^+), 246 (100%, M^+-HNCO). 4d mp 228-230° (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3H), 1.40-2.98 (m, 6H), 6.50-7.55 (m, 10H); IR (KBr): 1670 cm^{-1}; MS (70 eV): m/e=315 (2%, M^+), 272 (100%, M^+-HNCO).
8. This was confirmed by MO calculations supported by CNDO/2 method. We have carried out a number of calculations on various 2(1H)-pyridones and 2-hydroxypyridines. A detailed account of the calculations and the nature of the structure-reactivity relationship associated with the tautomeric properties on those compounds will be provided elsewhere.
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11. M. J. Goldstein and R. Hoffmann, J. Am. Chem. Soc., 93, 6193 (1971).
12. Spectral data are as follows: 11c mp 160-161° (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 3H), 1.61 (s, 3H), 2.12 (s, 3H), 3.96 (s, 3H), 6.50-7.51 (m, 9H); IR (KBr): 1630 cm^{-1}; MS (70 eV): m/e=303 (89%, M^+), 288 (100%, M^+-CH_3), 246 (37%, M^+-CH_3OCN). 11d mp 142-143° (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3H), 1.45-2.95 (m, 8H), 3.68 (s, 3H), 6.45-7.55 (m, 9H); IR (KBr) 1630 cm^{-1}; MS (70 eV): m/e=329 (100%, M^+), 314 (52%, M^+-CH_3), 282 (31%, M^+-CH_3OCN).

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