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REGIOSELECTIVE REACTIONS OF ENAMINONES WITH ENONES—II†

INTRAMOLECULAR REARRANGEMENTS INVOLVING CARBON TO OXYGEN ACYL MIGRATIONS

LECH KOZERSKI,* E. CZERWINSKA and T. POBIEDZINSKA
Institute of Organic Chemistry, Polish Academy of Sciences, 00-961 Warszawa, Kasprzaka 44, Poland

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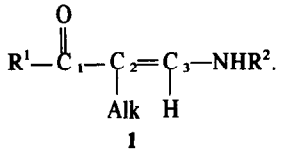
Abstract—Intramolecular dynamic behaviour helps in predicting the regioselectivity of reactions in ambident molecules. Thus the enaminones (1) react on the C-2 carbon atom with benzoquinone. Reaction proceeds with an intramolecular acyl shift following formation of the initial reaction complex upon reaction at position C-2 of the enaminone and the quinone. Under certain conditions the reaction is regiospecific and proceeds stereospecifically.

Our recent investigations on the title subject are directed toward revealing the relationship between the intramolecular dynamic behaviour of the molecule and the reactivity of its donor and/or acceptor centres in ambident systems. Thus, predictions can be made regarding the first reaction step which may occur on O, C-2 or N atoms in systems of the type 1



1

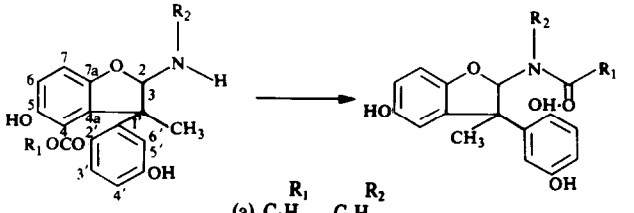
Recently it was shown that secondary enaminones, alkyl substituted on the C-2 atom, yield with *p*-benzoquinone derivatives of the 2H-1,5-benzodioxepin ring.[1] These compounds were formally identified as adducts of the quinone across positions 1,4 of the α,β-unsaturated ketone moiety of the enaminones in accord with the prediction that these enaminones should react on the oxygen atom.

Since reaction at position C-2 was also expected, evidence was sought but not found, for the formation of the derived indole or benzofuran ring systems which would be produced by such an attack.[2]

It was found that the structure of the products formed in this reaction depend dramatically on the bulkiness of the R_1-group in 1, the temperature of the reaction medium and the solvent polarity. The higher the temperature and smaller the R_1-substituent the higher the yields of the 2H-1,5-benzodioxepins formed. This is in agreement with the view that the molecules 1 with small R_1-groups are planar, which gives rise to high electron density on the oxygen atom. On the other hand, a slow reaction between the hard donor oxygen in 1 and the soft acceptor C–H atom of the quinone is promoted at elevated temperatures.

As expected, at low temperatures the kinetic product should be formed; the one between soft centres of both reactants, i.e. C-2 atom of 1 and a C–H atom of the quinone. In fact, when the reaction is carried out at −20°, in carbon tetrachloride, the compounds of formula 2 (for spectral characteristics see Table 1) are formed exclusively.

These compounds are recognized as products of reaction on the C-2 carbon atom of enamine 1; the proposed reaction scheme which plausibly explains the results, is



2‡(a–c) **3(a–c)**

	R_1	R_2
(a)	C_2H_5	C_2H_5
(b)	C_2H_5	CH_3
(c)	i-C_3H_7	CH_3

Scheme 1.

†For the first part of the series see Ref. 1.

‡The rationale for the *trans* stereochemistry in 2 is based on the phenomenon of the steric compression shift in the ^{13}C spectra of 2 and 3 observed at two stereochemical sites. There is steric interaction between the eclipsed C-3 methyl group and the nitrogen atom in 2 and between C-1′ and the nitrogen atom in 3, respectively. Since this steric interaction leads to lower frequencies shifts for the lines of the involved nuclei, it is expected that the C-3 methyl group should have smaller δ value in 2 with respect to 3 whereas C-1′ atom should have higher chemical shift in 2 as compared with 3. This is in fact observed in the ^{13}C spectra for both sites: C-3–CH_3; **2a**—20.93 ppm, **3a**—30.06 ppm, C-1′; **2a**—138.26 ppm, **3a**—128.11 ppm.

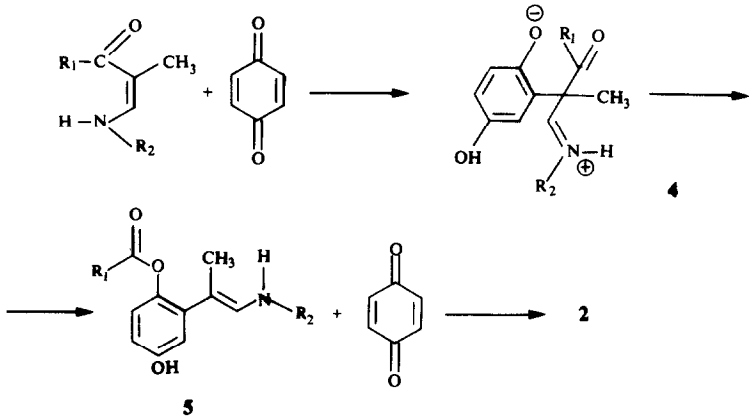
Table 1. Spectral characteristics of compounds of the structure 2 prepared from enaminones 1

Formula	MS (70eV) e/m, %	IR oil film ν (cm^{-1})	^1H NMR $(CD_3)_2CO$, TMS δ ppm	^{13}C NMR * 0.2 mol solution in $C_4D_8O_2$, TMS δ ppm
$C_{20}H_{23}NO_5$	357 (M,40%)	3450,3200	0.95 (t,3H,$\underline{CH_3}CH_2N$)	8.67 (q,$\underline{CH_3}CH_2CO$), 15.81 (q,$\underline{CH_3}CH_2N$),
2a	300 (0.5)	2980,	1.05 (t,3H,$\underline{CH_3}CH_2CO$)	20.93 (q,C-3-CH_3), 27.16 (t,CH_2CO),
	284 (86)	1730,1590	1.5 (s,3H,C-3-CH_3)	41.9 (t,CH_2N), 51.21 (s,C-3), 103.96
	256 (100)		2.15 (m,2H,CH_2CO)	(d,C-2), 109.95, 112.07, 114.62,
	227 (34)		2.8 (m,2H,CH_2N)	115.78, 116.34 (d,aromatic CH *),
	213 (25)		5.5 (s,1H,O-CH-N)	125.85 (d,C-3'), 136.71, 138.26,
	135 (29)		6.7-7.0 (m,6H arom.)	142.19 (s,C-1', C-2', C-4a) *, 150.76,
	110 (24)		8.0 (s,1H,OH)	151.42, 154.78 (s,C-5, C-5', C-7a) *,
			8.7 (s,1H,OH)	172.61 (s,$CH_3CH_2\underline{CO}$)
$C_{19}H_{21}NO_5$		3455,3200	1.1 (t,3H,CH_3CH_2CO)	
2b		2980	1.5 (s,3H,C-3-CH_3)	

	1730,1590	2.5 (s,3H,N-CH_3) 2.9 (m,2H,CH_2CO) 5.45 (s,1H,O-CH-N) 6.45-6.95 (m,6H arom.)	
$C_{20}H_{23}NO_5$ 2c	3450,3200 3000 1735, 1615	1.05, 1.15 (d,d,6H, ($\underline{CH_3}$)$_2$CH) 1.5 (s,3H,C-3-CH_3) 2.45 (s,3H,N-CH_3) 2.65 (m,1H, (CH_3)$_2\underline{CH}$) 5.4 (s,1H,O-CH-N) 6.45-6.95 (m,6H arom.)	18.48, 19.01 (q,q,($\underline{CH_3}$)$_2$CH), 20.93 (q,C-3-CH_3), 26.68 (q,N-CH_3), 34.18 (d,(CH_3)$_2\underline{CH}$), 51.38 (s,C-3), 103.41 (d,C-2), 109.92, 111.0, 113.76, 115.53, 116.13 (d,aromatic CH) *, 125.62 (d, C-3'), 136.40, 138.42, 142.44 (s,C-1', C-2', C-4a) *, 150.31, 151.41, 154.77 (s,C-5, C-5', C-7a) *, 174.9 (s,$CH\underline{CO}$)

* Multiplicities of the signals come from SFORD spectrum; specific assignments will be discussed in a forthcoming paper.

shown below:



Scheme 2.

The C-2 adduct, in the form of the zwitterion **4**, apparently undergoes an intramolecular rearrangement creating the ester and enamine function during a concerted[1,4] sigmatropic shift of the carbonyl group. The stereospecific formation of only one diastereomer of **2**, the one in which the amino group is in the *trans*-position to the phenyl group,† is a consequence of the requirements which should be fulfilled in the transition state. Since the transition state imposes planarity between the phenyl and carbonyl groups, the nitrogen substituent in the *trans*-position to the phenyl ring provides minimum steric interaction. The resulting intermediate enamine **5** is also less hindered in the *E*-configuration.[3] Since the barrier to double bond isomerization in enamines is high,[3] under the reaction conditions this configuration is preserved during the final reaction step, which involves a known 1,3-addition of excess quinone to the double bond of the enamine **5**.[2]

Support for the above considerations is brought about by experimental isolation of enamine **5** in the form of a diacetylated derivative.

The presented configuration of **2** was maintained only under reaction conditions allowing the spontaneous crystallisation of the ester, which, in a crystalline form, could be stored for a long time without changing its configuration. In solution, even at room temperature, the ester function of **2** undergoes a slow rearrangement to yield the corresponding amide **3** with the opposite configuration about the C-2–C-3 bond. This is not unexpected however, as the O–CH–NH moiety present in **2** can provide the facile change of configuration at the C-2 atom.[4] For this reason, the evidence for the proposed stereochemistry for **2** was acquired by means of trapping of the active ester in the form of a peracetylated derivative, which was characterised by physical methods (see Experimental).

The above reaction is a novel example of an S_Ei reaction which proceeds intramolecularly in a concerted fashion involving a [1,4]-sigmatropic shift[5] yielding, stereospecifically, only one diastereomer.

Further studies to uncover the general applicability of the reaction and to solve the mechanistic ambiguities are in progress.

EXPERIMENTAL

In a typical procedure 1 g of enaminone i-C_3H_7–CO–$C(CH_3)$=CH–$NHCH_3$ (7.2 mmol) was dissolved in 20 ml of carbon tetrachloride and cooled to −20°. A solution of 1.55 g (14.4 mmol) of *p*-benzoquinone in 20 ml of carbon tetrachloride with 5 ml of benzene was added over 0.5 h with stirring under anhydrous conditions. The resulting mixture was stored in the dark at −10° and a dark brown solid precipitated on the walls overnight. The solid was filtered off to give, on average, 2.0 g of crude ester contaminated with hydroquinone (*ca.* 30% of weight). The integration of NMR signals of the solid indicated a 65% yield. Careful evaporation of the filtrate below room temperature also yielded crude ester contaminated with smaller amounts of hydroquinone. The ester was easily recognized in the NMR spectrum by the characteristic sharp signals in acetone-d_6 solution at δ: 1.5 ppm (C-3 CH_3), 2.5 ppm (N–CH_3) and 5.3 ppm (N–C<u>H</u>–O). Attempts to isolate the pure ester by means of column chromatography were not successful due to the thermal instability of the active ester which rearranged to the amide **3** with a 50% loss of starting material. Nevertheless it was possible to obtain spectral characteristics of these compounds as exemplified in Table 1.

The configuration of the parent ester was maintained during acetylation in cold pyridine while three acetyl groups were introduced. Depending on the reaction conditions various amounts of di- and tri-acetylated derivatives of the amide **3** were also formed along with the tri-acetylated derivative of **2**.

In the usual acetylation procedure, the crude ester obtained as described above (2.0 g) was added to a cooled (−15°) mixture of 10 ml of pyridine and a threefold excess of acetic anhydride for each OH or NH group. The mixture was stirred for 0.5 h, left in refrigerator for 48 hr and, after the usual work up, the resulting brown oil was chromatographed on a silica gel column. The ester of the hydroquinone was eluted with a mixture of chloroform and carbon tetrachloride (1:1) and the product (1.5 g) collected using pure chloroform. The overall yield of both reactions was 40%. Analytical samples were obtained after crystallisation of the acetylated product from carbon tetrachloride. The analytical and spectral data confirm the structure of the triacetylated derivative of **2c**. For $C_{26}H_{29}NO_8$, calc: C, 64.59; H, 6.0; N, 2.89%; found: C, 64.2; H, 5.89; N, 2.9%. MS (70 eV) *m/e* (% of parent ion): 483 (M, 7%), 441 (5), 413 (3), 399 (2), 354 (8), 312 (6), 298 (15), 256 (18), 227 (12), 213 (3), 135 (4), 110 (12). IR (KBr) ν (cm^{-1}): 2980, 2920, 1760, 1660, 1480. ^1H NMR (CD_3NO_2, TMS, 100°C) δ ppm: 1.15, 1.27 (d, d, 3 H, 3 H, $(\underline{CH_3})_2CH$), 1.75 (s, 3 H, C-3 $\underline{CH_3}$), 2.05 (s, 3 H, N–CO$\underline{CH_3}$), 2.22 (s, 3 H, C-5'CO$\underline{CH_3}$), 2.30 (s, 3 H, C-5'CO$\underline{CH_3}$), 2.52 (m, 1 H, $\underline{CH}(CH_3)_2$), 2.98 (s, 3 H, N–$\underline{CH_3}$), 6.7–7.2 (m, 6 H arom., C-2 <u>H</u>).

^{13}C chemical shifts for **3a** are as follows: **3a**, ^{13}C NMR, 0.5 mole solution in CD_3OD, TMS, δ ppm: 9.97 (q, $\underline{CH_3}CH_2CO$), 14.05 (q, $\underline{CH_3}CH_2N$), 27.94 (t, $\underline{CH_2}CO$), 30.06 (q, C-3–$\underline{CH_3}$), 39.19 (t, CH_2N), 54.72 (s, C-3), 100.71 (d, C-2), 110.22, 113.90, 115.60, 115.74, 116.78, 117.47 (d, aromatic CH), 128.11 (s, C-1'), 134.84 (s, C-4a), 149.61, 150.19, 151.88, 152.21 (s, C-5, C-7a, C-2', C-5'), 176.30 (s, $CH_2\underline{CO}$).

The assignment of C-4a and C-1' signals in **3** are based on the comparison of the chemical shifts in di- and tri-acetylated deriva-

†See footnote (‡), p. 617.

tives of both diastereomers. The crystal structure has confirmed the stereochemistry inferred from ^{13}C NMR for **3**.

An intermediate enamine of the type **5** is formed when the reaction is carried out using a 1:1 molar ratio of enaminone and quinone. It can be isolated in the form of diacetylated derivative after subjecting the evaporated reaction mixture to the acetylation as described above. The separation of the diacetylated derivative of **5** and triacetylated derivative of **2** was accomplished by means of tlc on silica (Merck GF_{254}) using a mixture of carbon tetrachloride and diethyl ether (1:1). The analytical and spectral data for the *O,N*-di-acetylated enamine of type **5** ($R_1 = C_2H_5$, $R_2 = CH_3$) are given below. For $C_{17}H_{21}NO_5$ calc: C, 63.95; H, 6.58; N, 4.39%; found: C, 63.55; H, 6.38; N, 4.41%. MS (70 eV) *m/e* (% of parent ion): 319 (M, 18%), 277 (13), 263 (100), 221 (36), 179 (78), 148 (81), 190 (13). IR (oil film) ν (cm^{-1}): 2950, 3050, 1770, 1670, 1650. ^1H NMR ($CDCl_3$, TMS, 30°) δ ppm: 1.2 (t, 3 H, $OCOCH_2\underline{CH_3}$), 2.05 (s, 3 H, $C{=}C{-}\underline{CH_3}$), 2.27, 2.30 (s, s, 3 H, 3 H, $OCO\underline{CH_3}$, $NCO\underline{CH_3}$), 2.4 (m, 2 H, $OCO\underline{CH_2}CH_3$), 2.7 (s, 3 H, $N{-}CH_3$), 6.5, 6.9 (s, s, 1 H, $C\underline{H}{=}C$), 7.0–7.2 (m, 3 H arom.).

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