[1,5]-REARRANGEMENT OF 4a-HETEROACYL-4a,5,8,8a-TETRAHYDRO-1,4-NAPHTHOQUINONES

R.T. Pardasani[a*], P. Pardasani[a], M.M. Agrawal[a], R. Ghosh[a], G. Mathur[a], S. Yadav[a] and T. Mukherjee[b]
[a]Department of Chemistry, University of Rajasthan, Jaipur 302004 India
[b]Chemistry Division, Bhabha Atomic Research Centre, Mumbai 400085 India

ABSTRACT: 2-Heteroacyl-5,8-dihydro-1,4-dihydroxynaphthalene derivatives have been prepared by [1,5]-sigmatropic rearrangement of the adduct tetrahydro-1,4-naphthoquinones. The structures of the synthesised products have been established by spectral data as well as by semiempirical molecular orbital calculations.

INTRODUCTION

Heteroanthracyclinone analogues 4 exhibiting various biological properties contain 1,4 - dihydroxynaphthalenes as the basic carbon skeleton. During the last two decades, various chemical modifications have been made leading to the development of new analogues with improved chemotherapeutic activities[1]. In persuing our interest on quinone studies, we have previously reported the synthesis of some benzothioxanthentriones[2] which may serve as useful precursors for the total synthesis of heteroanthracyclinones. An alternative strategy to synthesize these compounds may be *via* [1,5]-rearrangement of the adducts 2 which in turn may be obtained by Diels-Alder reaction of heteroacyl-1,4-benzoquinones with 1,3-butadienes (Scheme 1).

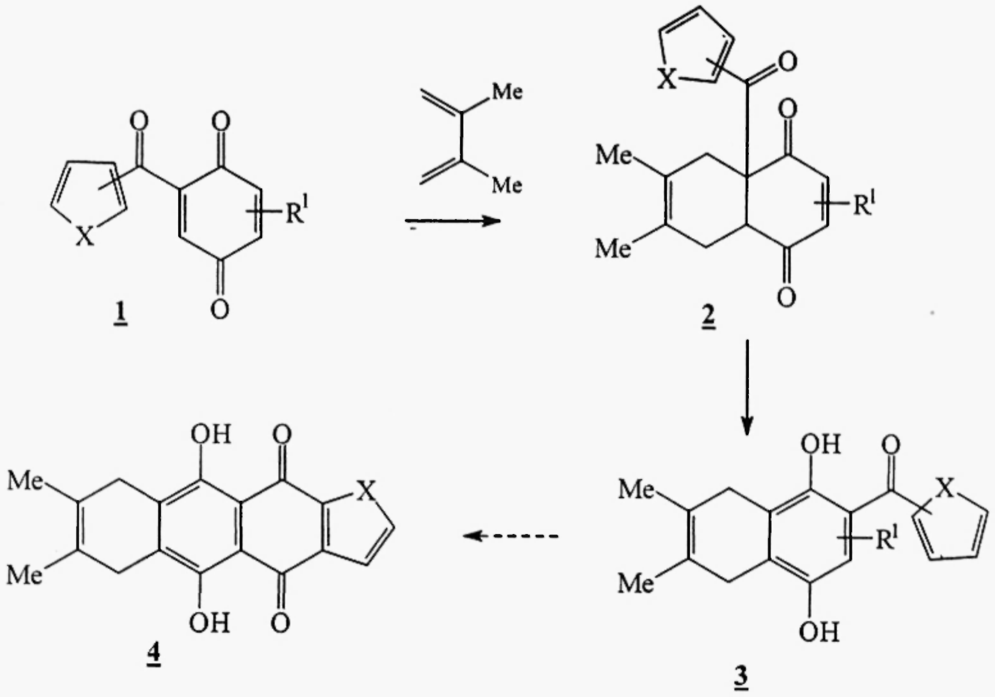
In persuit of this theme, we have recently reported the synthesis of quinones[3] 1 and a detailed synthetic and semiempirical study of the [4+2]-cycloaddition reaction has been communicated.[4] Herein we report the synthetic and semiempirical aspect of the [1,5]-sigmatropic rearrangement.

RESULTS AND DISCUSSION

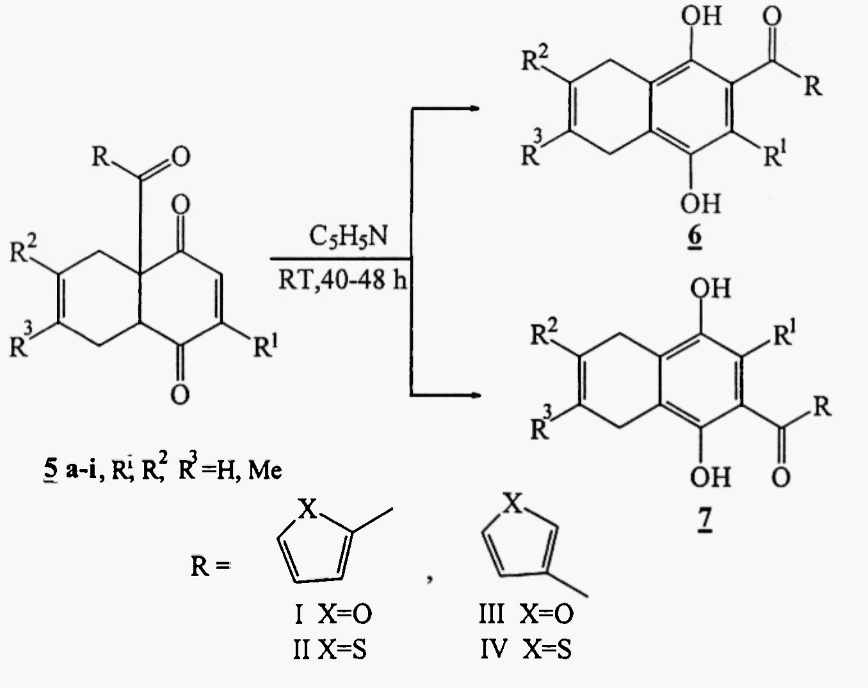
The [1,5]-sigmatropic rearrangement of the adducts 5 was smoothly carried out in dry pyridine at room temperature for 40-48 hours in 81-95% yield to afford regioisomeric mixture of substituted 1,4-dihydroxynaphthalene 6 and 7 as yellow to red solids and semi-solids (Scheme 2). Various substituents incorporated are listed in Table 1.

The rearrangement appears to take place *via* intermediate formation of the enol 8 followed by the [1,5]-heteroacyl migration to give another enol 9 as reported earlier by Bruce[6,7], Sammes[5] and co-workers in case of acyl adducts. Subsequent aromatisation then affords dihydroxynaphthalenes 6. Alternatively, enol 8 may initially undergo [1,2]-heteroacyl migration to afford enol 10 which on subsequent [1,5]-heteroacyl migration followed by aromatization would afford regioisomeric dihydroxynaphthalenes 7. (Scheme 3)

However, the rearrangement may be designed to occur regiospecifically if the position 2 in the adduct 5 is blocked with a suitable substituent, for example, a methyl group. Indeed when the adducts 5 (**j-m**) were allowed to rearrange in pyridine at room temperature for 48 hours, it regiospecifically produced the compounds 6 (**j-m**).



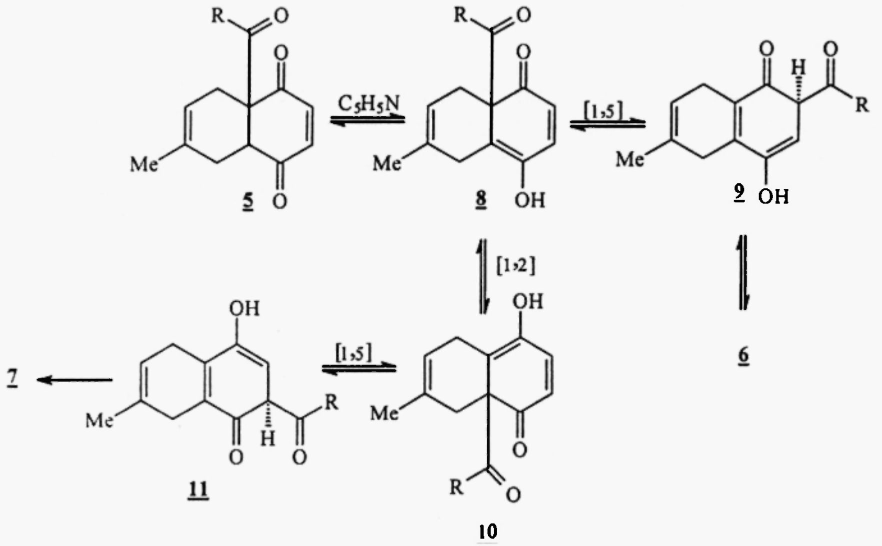
SCHEME 1



SCHEME 2

Table 1 : SUBSTITUTION PATTERN IN 1,4-DIHYDROXYNAPHTHALENES (6/7)

Compound	R	R^1	R^2	R^3	Compound	R	R^1	R^2	R^3
6a	I	H	H	CH_3	6h	II	CH_3	CH_3	CH_3
6b	I	H	CH_3	CH_3	6i	IV	H	H	CH_3
6c	I	CH_3	CH_3	H	6j	I	CH_3	H	CH_3
6d	I	CH_3	CH_3	CH_3	6k	II	CH_3	H	CH_3
6e	III	H	H	CH_3	6l	III	CH_3	H	CH_3
6f	II	H	H	CH_3	6m	IV	CH_3	H	CH_3
6g	II	H	CH_3	CH_3					



SCHEME 3

The proposed mechanism has been supplemented on the basis of heat of formation calculated through semiempirical molecular orbital methods. Thus the ground state geometries of the final products and the intermediate enols were optimised using AMI methods and the heat of formation of various intermediates are compiled in Table 2.

From the above Table, it is evident that dihydroxynaphthalenes 6 and 7 have almost equal heat of formation and therefore there exists equal possibility of their formation. In other words, the regiospecificity will be lost and it was-indeed observed experimentally when the adducts **5 (a,b,e,f,g,i)** were allowed to rearrange at room temperature in pyridine for 48 hours.

The rearranged products were characterised by their infra-red and ^1H NMR spectral data (Table 4).The hydroxyl absorption band appeared in the region of 3400-3260 cm^{-1} as broad peaks and the carbonyl stretching band was found in the range of 1670-1640 cm^{-1} as sharp strong peak. ^1H NMR spectra of the rearranged product showed singlets due to C-3, 6 and 7 methyl protons at δ 1.60-2.1 ppm. A multiplet between δ 2.02-2.90 was due to 2×H-5 protons and another multiplet at δ 3.02-3.30 ppm was assignable to 2×H-8 protons. Hydroxyl protons appeared as broad singlets in the range of δ 4.45-5.48 and 11.75-12.04 ppm. A singlet in the region of δ 6.50-7.04 was associated with the H-3 proton. Thienoyl/furanoyl protons (H-3',4',5') displayed multiplets/double doublets with a coupling constants in the range of 1.5-4.0 Hz. The structures of all the products were further established by elemental analyses (Table3).

Table 2: HEAT OF FORMATION (H_f) FOR REARRANGED PRODUCTS, AM1 VALUES IN KCal / mol

Products	5	6	7	8	9	10	11
a	-57.51	-85.26	-85.64	-54.75	-64.06	-53.99	-64.45
f	-35.48	-73.54	-72.52	-31.45	-43.52	-32.49	-42.59
j	-65.38	-88.89	-	-61.77	-72.90	-61.64	-
k	-43.36	-67.26	-	-38.37	-50.09	-39.70	-

EXPERIMENTAL

Melting points were determined in open glass capillary and are uncorrected. The IR spectra were recorded on Nicolet Magna IR™ spectrometer model 550 in KBr pellets. ^{1}H NMR spectra were recorded on Jeol FX 90Q model at 89.55 MHz with TMS as internal standard, chemical shift are given in δ ppm. Pyridine and methanol were purified by standard procedure[8,9]. Elemental analysis were performed by Perkin Elmer series 11 C,H,N,S,O analyser-2400. The semiempirical calculations were carried out on PCL-Pentium PS computer using MOPAC 93.

Synthesis of 1,4-dihydroxynaphthalene derivatives : The following procedure is representative. The adduct tetrahydronaphthoquinone derivative 5 (0.20g, 0.68mmol) was dissolved in dry pyridine (0.4ml) and left at room temperature for 48 hour. The solvent was removed under reduced pressure and the residue was exchanged with methanol (1×3ml) to obtain yellowish to reddish-brown solid/semi-solid.

ACKNOWLEDGEMENT

We thank BRNS, Department of Atomic Energy, Mumbai and CSIR, New Delhi for the financial support.

REFERENCES

1. J.W. Lown, Chem. Soc. Rev. 22, 165,(1993).
2. R.T. Pardasani, P. Singh, A. Prashant and B. Choudhary, P, S , Si and related compounds 86, 21,(1994).
3. R.T. Pardasani, P. Pardasani, S. Muktawat, R. Ghosh and T. Mukherjee, Heterocycl. Commun. 4, 77, (1998).
4. R.T. Pardasani, P. Pardasani, S. Muktawat, R. Ghosh, G. Mathur, E.D. Jemmis and K.T. Giju, J. Chem. Res. (2000), Communicated.
5. C. Cooper, P.G. Sammes, J. Chem. Soc., Perkin Trans 1, 2407, (1984).
6. F.B.H. Ahmed, J.M. Bruce, J. Khalafy, K. Sabetian, J. Chem. Soc., Chem. Commun. 169, (1981).
7. F.B.H. Ahmed, J.M.Bruce, J. Khalafy, J. Pejanovic, K. Sabetian and I. Watt, J. Chem. Soc., Chem. Commun.,166, (1981).
8. D.D. Perrin, W.L.F. Armarego, D.R. Perrin, Purification of Laboratory Chemicals, II Edn., Pergamon, Oxford, 1998.
9. "Vogel's Text Book of Practical Organic Chemistry" IV Edn., ELBS / Longman, 1984.

Received on October 9, 2000

Table 3: PHYSICAL AND ANALYTICAL DATA OF 1,4-DIHYDROXYNAPHTHALENES

Compd	Physical state	M.pt. °C	Yield %	Molecular Formula	Elemental analyses Found (calculated)		
					C	H	S
6a	Yellowish solid	128	90	$C_{16}H_{14}O_4$	71.08 (71.11)	5.14 (5.18)	-
6b	Brownish semi-solid	-	90	$C_{17}H_{16}O_4$	-	-	-
6c	Reddish semi-solid	-	93	$C_{17}H_{16}O_4$	-	-	-
6d	Yellowish solid	132	88	$C_{18}H_{18}O_4$	72.45 (72.48)	6.00 (6.04)	-
6e	Brownish semi-solid	-	81	$C_{16}H_{14}O_4$	-	-	-
6f	Brown crystals	120	83	$C_{16}H_{14}O_3S$	67.09 (67.13)	4.85 (4.89)	11.13 (11.18)
6g	Brown red solid	130	89	$C_{17}H_{16}O_3S$	67.7 (68.0)	5.31 (5.33)	10.63 (10.66)
6h	Reddish brown semi-solid	-	91	$C_{18}H_{18}O_3S$	-	-	-
6i	Reddish brown solid	68	87	$C_{16}H_{14}O_3S$	67.10 (67.13)	4.85 (4.89)	11.16 (11.18)

Table 4: ^{1}H NMR SPECTRAL DATA OF 1,4-DIHYDROXYNAPHTHALENES $CDCl_3$ δ ppm

Compd	Methyl protons	H-5/7/8	H-3	Thienoyl/furanoyl Protons	-OH
6a	1.68s	2.24-2.94(m, 2xH-5 + 2xH-8), 6.60(sbr,H-7)	6.98s	7.38(d,J=1.5Hz,H-4') 7.52(d,J=4.0Hz,H-3') 8.02(d,J=1.5Hz,H-5')	5.48sbr 12.2s
6b	1.74sbr	2.02-3.20(m, 2xH-5 + 2xH-8)	6.92s	7.36(d,J=1.5Hz,H-4') 7.54(d,J=4.0Hz,H-3') 8.04(d,J=1.5Hz,H-5')	5.34sbr
6c	1.74sbr 2.05s	2.22-2.94(m, 2xH-5 + 2xH-8), 6.61(sbr, H-7)	-	7.45(m,H-4'),7.72(d,J=1.5Hz,H-3') 8.84(d,J=4.0Hz,H-5')	5.49sbr 11.8s
6d	1.68sbr 1.82s	2.32-3.02(m, 2xH-5 + 2xH-8)	-	7.38(d,J=1.5Hz,H-4') 7.52(d,J=1.5Hz,H-3') 7.66(d,J=1.5Hz,H-5')	5.48sbr 11.8s
6e	1.68sbr	2.04-2.49(m, 2xH-5 + 2xH-8), 6.62(sbr, H-7)	7.04s	7.34(d,J=4.0Hz,H-4') 7.52(d,J=1.5Hz,H-5') 8.02(s,H-2')	5.40sbr 12.0s
6f	1.94s	2.79-2.85(m, 2xH-5), 3.39 (m, 2xH-8), 5.81(q, H-7)	6.50s	7.3-732(m,H-4'),7.87(m, H-3') 8.09(dd,J_1=3.5Hz,J_2=1.5Hz,H-2')	4.50sbr 11.8s
6g	1.72s 1.80s	2.70-2.79(m, 2xH-5), 3.35 (m, 2xH-8)	6.52s	7.25-7.31(m,H-3'+4') 7.85(m, H-5')	4.50s 11.82s
6h	1.75s 1.82s 2.0s	2.70-2.77(m, 2xH-5), 3.30 (m, 2xH-8)	-	7.0-7.5(d, J=4.0Hz, H-4'),7.85(m, H-3') 8.3(dd J_1=3.5Hz,J_2= 1.7Hz,H-5')	5.0s 11.78s
6i	1.60s	2.90(m, 2xH-5),3.45(m, 2xH-8), 5.81(q, H-7)	6.50s	7.20(m,H-4') 7.36-7.70(m, H-5'+2')	4.52s 11.80s