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POLYCYCLIC HYDROXYQUINONES. XXIV[1]. DIELS-ALDER REACTIONS OF 5-AMINO-8-HYDROXY-1,4-NAPHTHOQUINONE. NOVEL TRANSCYCLOADDITION REACTIONS WITH DERIVATIVES OF 1,4-DIHYDRO-1,4-METHANOANTHRACENE-9,10-DIONE.

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Abstract - Diels-Alder reactions of 5-amino-8-hydroxy-1,4-naphthoquinone (1a) and derivatives (1b-e) with cyclopentadiene and 2,3-dimethylbuta-1,3-diene afford the corresponding adducts 2a-e and 4a-e in good yields. Adducts 2a and 4a, by oxidation under alkaline conditions in the presence of air, are converted into quinones 3a and 5a, respectively. Quinone 3a undergoes a novel transcycloaddition reaction with 2,3-dimethylbuta-1,3-diene, which involves cycloaddition to give the angular adducts 7n and 7x, followed by cycloreversion to afford 5a and cyclopentadiene. Quinone 3a similarly undergoes a transcycloaddition with diazomethane to yield a single benz[f]indazol 9. The reverse regiochemistry is observed starting from the O,N-diacyl derivative 3e. Similar transcycloadditions with 5,8-dimethoxy-1,4-dihydro-1,4-methanoanthracene-9,10-dione are reported.

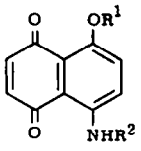
In previous papers[2,3] we have reported that the tetracyclic system of anthracyclinones, the aglycones of the therapeutically useful anthracyclines, may be elaborated *via* two successive Diels-Alder reactions starting from naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) as a BC synthon. This strategy has been applied by us[4] and Kelly[5,6] to regiospecific synthesis of anthracyclinones.

Recently, we described[7] the preparation of 5-amino-8-hydroxy-1,4-naphthoquinone (1a), closely related to naphthazarin, and several N- and/or O-substituted derivatives thereof (1b-e). In principle, the aminohydroxyquinone 1a and its derivatives could be versatile synthons for the construction of the tetracyclic system of anthracyclinones. In this case, the presence of the NHR substituent not only would facilitate regioselective cycloadditions, but also could serve as a precursor of other groups or, *via* deamination, for the synthesis of deoxyanthracyclinones.

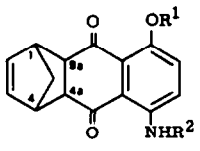
This paper describes the Diels-Alder reactions of aminohydroxynaphthoquinones of type 1 with two simple dienes: 2,3-dimethylbuta-1,3-diene, and cyclopentadiene. Moreover, in an attempt to elaborate the linear tetracyclic system of anthracyclinones from the cyclopentadiene adducts, we have found a novel and interesting type of "transcycloaddition" reaction.

Diels-Alder reaction of 5-amino-8-hydroxy-1,4-naphthoquinone (1a) with cyclopentadiene occurred at room temperature, in benzene as solvent, to give the adduct 2a, in 85% yield, as an approximately 8:1 mixture of the *endo* and *exo* isomers ($2a_n$ and $2a_x$, respectively). The diastereomers were readily separable by chromatography and their assignment could be made on the basis of their ^{1}H-NMR spectra. Thus, the major *endo*-isomer ($2a_n$) showed the H-4a and H-9a *exo*-protons at δ 3.35, whereas in the minor *exo*-isomer ($2a_x$) the *endo*-protons appeared,

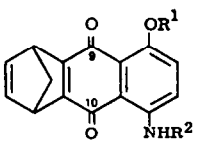
as expected, at higher field (δ 2.94). The ratio of endo/exo adducts could also be determined by direct integration of the ^{1}H-NMR spectrum of the reaction mixture itself. The other derivatives (1b-e) reacted with cyclopentadiene, under similar conditions, to yield only the respective endo-adducts 2b-e in good yields.



1a-e

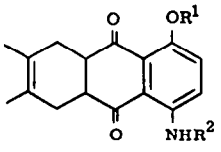


2a-e

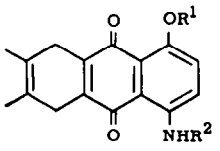


3a-e

	a	b	c	d	e
R^1	H	H	H	H	Ac
R^2	H	Me	Ac	Bz	Ac



4a-e



5a-e

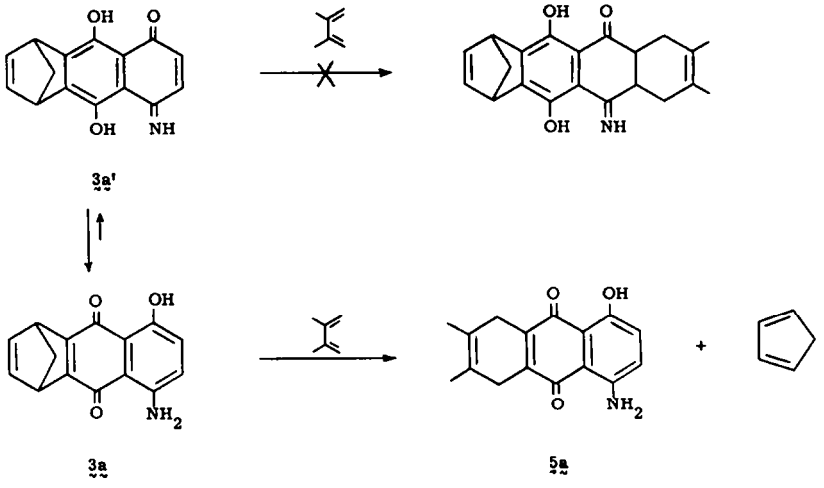
Treatment of the adduct 2a, as the entire endo-exo mixture, with diluted base in the presence of air, followed by acidification, afforded the 5-amino-8-hydroxy-1,4-dihydro-1,4-methanoanthracene-9,10-dione (3a) in 75% yield. Its ^{1}H-NMR spectrum was consistent with the proposed structure and, as expected, showed the disappearance of the H-4a and H-9a signals and a low field shift of the remainder signals. A similar mild alkaline air oxidation of adduct 2b led to the corresponding derivative 3b. In the case of 3c, however, even by using very dilute alkaline solutions, a considerable proportion of the deacylated derivative 3a was also obtained. Therefore, compounds 3c-e were preferably obtained from 3a by conventional acylation methods.

The cycloaddition reactions of quinones 1a-e with 2,3-dimethylbuta-1,3-diene were conducted in toluene under reflux, over a period of two hours, to yield the corresponding adducts 4a-e in good yields. Their analytical data and ^{1}H-NMR spectra were consistent with the expected structures. Mild alkaline air oxidation of the adducts 4a-b gave, after acidification, the quinones 5a,b the structures of which were established by ^{1}H-NMR. The reaction conditions used are expected to proceed with concomitant hydrolysis of the N- and/or O-acyl groups; therefore, compounds 5c-e were preferably obtained by acylation of 5a, using conventional methods.

As in naphthazarin itself, quinone 3a could exist in equilibrium with 3a', the latter form presumably being the less stable tautomer[8]. A similar tautomerism would be expected in quinone 5a. The existence of tautomers of the type 3a', even in small amounts, would enable a second cycloaddition reaction to give the desired linear tetracyclic system. We have found, however, that the quinone 5a does not react with 2,3-dimethylbuta-1,3-diene, by refluxing in toluene under the conventional conditions of the Diels-Alder reaction.

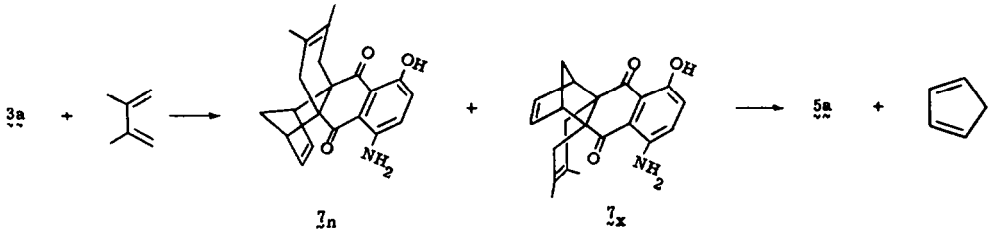
Thus, the reaction was attempted with the cyclopentadiene derivative 3a, in which the presence of the bicyclic system attached to the quinone ring could reduce the stability of 3a, favouring the tautomer 3a', in accord with our previous experience[9]. The reaction with 2,3-dimethylbuta-1,3-diene was carried out in toluene at 110° C and, after 48 hours, a compound was obtained in 80 % yield, the physical and spectral data of which were identical with those of compound 5a. A plausible rationalization for this result would be to postulate that the cyclo-

addition is tautomer specific[10] and occurs exclusively at the internal quinone double bond of the



major tautomer 3a, rather than at the external quinonimine double bond of 3a', to give angular adducts of type 7. These could readily undergo a retro-Diels-Alder reaction to afford 5a with extrusion of cyclopentadiene.

In order to corroborate the intermediacy of the angular adducts, the reaction of 3a with cyclopentadiene was carried out in benzene at room temperature over a period of one month. After chromatography, a product was isolated, the spectral data of which were consistent with those expected for a diastereomeric mixture of the internal cycloadducts 7_n and 7_x (which possess an endo or exo arrangement of the quinone moiety, respectively) in the ratio of approximately 3:1. In fact, the mass spectrum showed a molecular ion at m/z 335 in accord with the proposed structures. Moreover, the presence of two diastereomers was apparent because two signals of vinylic protons at δ 6.05 and δ 6.42 and two methyl resonances at δ1.60 and 1.77 were observed in the ^{1}H-NMR spectrum. The relative isomer distribution was determined by integration of the vinylic region in the ^{1}H-NMR spectrum of the crude reaction mixture, and the stereochemical assignments were achieved by spectral comparison with the endo and exo adducts $2a_n$ and $2a_x$ described above.

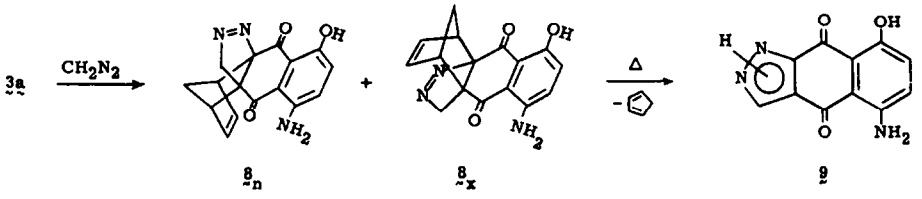


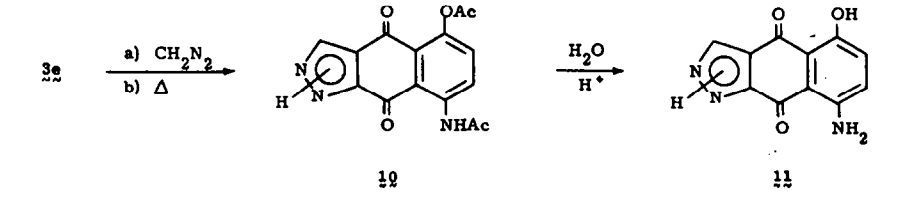
Overall, the sequence 3a $\longrightarrow$ $7_n + 7_x$ $\longrightarrow$ 5a may be considered as a "transcycloaddition" reaction, via cycloaddition (to give the intermediate angular adducts 7_n+7_x) followed by cycloreversion (to afford 5a), in which the cyclopentadiene moiety of 3a has been replaced by the new diene.

In a similar manner, the quinones 3b-e undergo the transcycloaddition with 2,3-dimethyl-

buta-1,3-diene to afford the respective derivatives 5b-e in good yields.

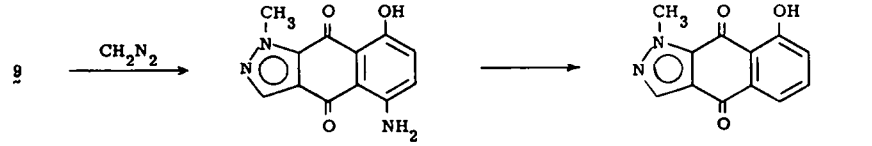
In order to broaden the scope of the transcycloaddition reaction, we have also studied the behaviour of quinone 3a towards diazomethane as a 1,3-dipole. In fact, treatment of 3a with an equimolar amount of diazomethane at -18°C led to a mixture of the diastereomeric pyrazolines 8n and 8x, as deduced from the ^{1}H-NMR spectrum of the crude reaction mixture. Thermal decomposition of the crude mixture 8n+8x afforded a single benz[f]indazol 9, thus indicating the regiospecificity of the dipolar 1,3-cycloaddition.

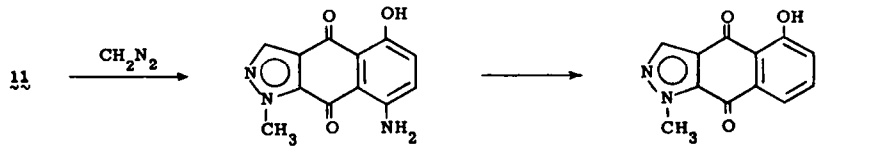




The regiochemistry of adducts 8n and 8x was ascertained by the chemical correlations discussed below. The direction of the cycloaddition with 3a would be explained in terms of the activation of the C-9 carbonyl by the strong intramolecular hydrogen bonding with the peri-hydroxy group. This effect of the chelated OH substituent has been reported for juglone and confirmed by molecular orbital calculations[11,12]. Presumably this effect would be reinforced by the presence of the NH_2 group in C-5 because of deactivation of the C-10 carbonyl by resonance donation.

Similarly, the N,O-diacyl derivative 3e reacted in a regiospecific manner with diazomethane to give the benz[f]indazol 10, which after hydrolysis afforded 11, the physical and spectral data of which were different from those of 9. This fact suggests that the regiochemical

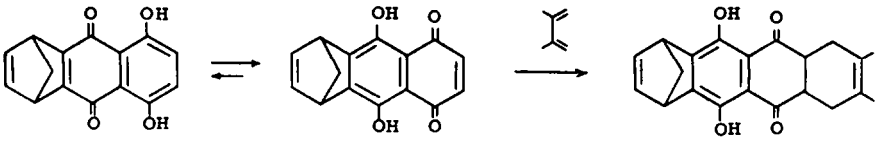




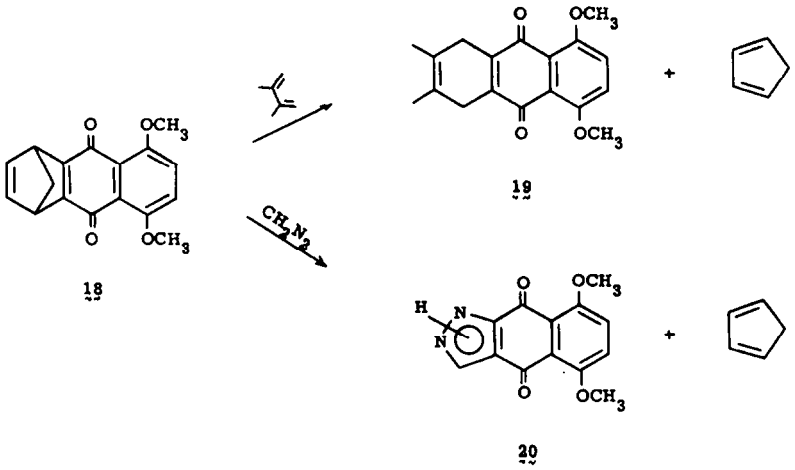
reversal observed might result from the acylation of the OH group in 3a, the direction of the cycloaddition being now controlled by the hydrogen bonding of the C-10 carbonyl with the peri-NHAc group.

Since it was impossible to assign an unambigous regiochemistry to either of the benz[f]-indazoles 9 and 11 by spectral means, it was essential to resort to chemical correlations. Thus we have effected the following sequence of reactions. Methylation of 9 and 11 with diazomethane proceeded regiospecifically in each case to give 12 and 13 respectively. Deamination of the latter compounds, via diazotization and treatment with hypophosphorous acid, afforded 14 and 15, respectively, the physical and spectral data of which were identical with those reported in the literature[12] for these compounds.

In view of the above results, we explored further the transcycloaddition reaction with naphthazarin derivatives of the type 16, in which the tautomer specificity observed in quinone 3a could be reversed. The quinone 16 exists in a tautomeric equilibrium, in which 16' appears to be the predominant tautomer[9]. This fact was confirmed by the observation that the ^{1}H-NMR spectrum of the compound in $CDCl_3$ showed a singlet at δ 7.05 assignable to a quinonoid proton, rather than to an aromatic one. The Diels-Alder reaction between 2,3-dimethylbuta-1,3-diene and 16 was conducted in boiling toluene for 4 hours to afford the linearly annelated adduct 17. This result confirms that the cycloaddition is tautomer specific and proceeds exclusively at the external double bond of the tautomer 16'.



16 16' 17



18 19 20

In contrast, 5,8-dimethoxy-1,4-dihydro-1,4-methanoanthracene-9,10-dione (18), which may be considered as a fixed derivative of the tautomer 16, reacted with 2,3-dimethylbuta-1,3-diene to give the quinone 19 via a transcycloaddition reaction similar to those described above. Compound 18 also gave a transcycloaddition reaction with diazomethane to afford the benz[f]-indazol 20, identical with the compound obtained from a direct 1,3-dipolar cycloaddition of diazomethane to naphthazarin dimethyl ether in equimolar amounts.

The novel transcycloaddition reaction with naphthoquinone derivatives of the types 3 and 18 is evidently of interest in organic synthesis. Thus, this approach offers the possibility of effecting cycloaddition reactions followed by a regeneration of the quinone unit by cycloreversion, under mild conditions. Therefore, this methodology represents a convenient alternative to the use of halo or sulfinyl quinones[13], which undergo a facile elimination of HX or PhSOH to regenerate the quinone system during the Diels-Alder reaction.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer model 257 grating spectrometer as nujol mulls, $\bar{\nu}$ values in cm^{-1}. ^{1}H-NMR spectra on a Varian EM-390 spectrometer, in $CDCl_3$ solutions (unless otherwise stated); signals are reported in δ units with TMS = 0 ppm as internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6MG spectrometer. Silica gel Merck F_{254} (2 mm layers) and DC-Alufolien 60 F_{254} were normally used for preparative and analytical t.l.c., respectively.

Diels-Alder reaction of quinones 1a-e with cyclopentadiene. General procedure.

A solution of freshly distilled cyclopentadiene (5 mmol) and the quinone 1 (3 mmol) in benzene (80 ml) was stirred at room temperature for 36 h. The solvent was removed and the residue was purified by crystallization.

2a: Yield 85%. The endo and exo isomers were separated by preparative t.l.c. (chloroform); endo isomer ($2a_n$): m.p. 136° C (benzene-light petroleum) (75%). IR: 3340, 3328, 1609. ^{1}H-NMR: 1.57 (m, 2H, CH_2); 3.35 (m, 2H, C-4a, C-9a); 3.65 (m, 2H, C-1, C-4); 6.01 (m, 2H, C-2, C-3); 6.96, 7.11 (2H, AB q, C-6, C-7, J = 8.6 Hz); 6.11 (br s, 2H, NH_2); 12.80 (s, 1H, OH). MS: 255 (M^+) (66), 189 (100), 161, 133. (Calcd. for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13; N, 5.48. Found: C, 70.67; H, 5.27; N, 5.42); exo isomer ($2a_x$): m.p. 165° C (benzene-light petroleum) (9%). IR: 3390, 3290, 1610. ^{1}H-NMR: 1.31 (m, 2H, CH_2); 2.94 (m, 2H, C-4a, C-9a); 3.39 (m, 2H, C-1, C-4); 6.38 (m, 2H, C-2, C-3); 7.03, 7.19 (2H, AB q, C-6, C-7, J = 8.6 Hz); 6.50 (br s, 2H, NH_2); 12.91 (s, 1H, OH). MS: 255 (M^+) (66), 189 (100), 161, 133. (Calcd. for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13; N, 5.48. Found: C, 70.77; H, 5.28; N, 5.42).

2b: m.p. 138-139° C (benzene-light petroleum) (80%). IR: 3300, 1610. ^{1}H-NMR: 1.51 (m, 2H, CH_2); 2.95 (d, 3H, CH_3, J = 4.5 Hz); 3.38 (m, 2H, C-4a, C-9a); 3.65 (m, 2H, C-1, C-4); 6.05 (m, 2H, C-2, C-3); 7.04, 7.15 (2H, AB q, C-6, C-7, J = 9.0 Hz); 9.5 (br s, 1H, NH); 12.92 (s, 1H, OH). MS: 269 (M^+) (34), 203 (100), 186 (7). (Calcd. for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.07; H, 5.56; N, 5.29).

2c: m.p. 153° C (benzene-hexane) (90%). IR: 1690, 1630. ^{1}H-NMR: 1.55 (m, 2H, CH_2); 2.22 (s, 3H, $NCOCH_3$); 3.40 (m, 2H, C-4a, C-9a); 3.65 (m, 2H, C-1, C-4); 6.01 (m, 2H, C-2, C-3); 7.21 (d, 1H, A of AB, C-7, J = 9.0 Hz); 8.93 (d, 1H, B of AB, C-6); 11.86 (br s, 1H, NH); 12.90 (s, 1H, OH). MS: 297 (M^+), 231, 189 (100), 161, 133. (Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.60; H, 4.99; N, 4.64).

2d: m.p. 157-158° C (benzene-hexane) (95%). IR: 3190, 1675, 1630. ^{1}H-NMR: 1.62 (m, 2H, CH_2); 3.54 (m, 2H, C-4a, C-9a); 3.77 (m, 2H, C-1, C-4); 6.18 (m, 2H, C-2, C-3); 7.5--7.9 (m, 3H, arom.); 7.62 (d, 1H, A of AB, C-7, J = 10.0 Hz); 8.0 - 8.4 (m, 2H, arom.); 9.38 (d, 1H, B of AB, C-6); 13.26 (br s, 1H, NH); 13.31 (s, 1H, OH). MS: 359 (M^+) (2), 293 (28), 105 (100). (Calcd. for $C_{22}H_{17}NO_4$: C, 73.52; H, 4.76; N, 3.89). Found: C, 73.81; H, 5.06; N, 4.17).

2e: m.p. 157-159° C (benzene-hexane) (75%). IR: 1770, 1710, 1700, 1660. ^{1}H-NMR: 1.50 (m, 2H, CH_2); 2.22 (s, 3H, $NCOCH_3$); 2.29 (s, 3H, $OCOCH_3$); 3.35 - 3.65 (m, 4H, C-4a, C-9a, C-1, C-4); 6.05 (m, 2H, C-2, C-3); 7.27 (d, 1H, A of AB, C-7, J = 9.0 Hz); 8.93 (d, 1H, B of AB, C-6); 11.62 (br s, 1H, NH). MS: 297 (M^+-42) (3), 231 (21), 189 (73), 43 (100). (Calcd. for $C_{19}H_{17}NO_5$: C, 67.26; H, 5.01; N, 4.13. Found: C, 67.53; H, 5.30; N, 3.89).

Diels-Alder reaction of quinones 1a-e with 2,3-dimethylbuta-1,3-diene. General procedure.

A solution of 2,3-dimethylbuta-1,3-diene (6 mmol) and the quinone 1 (3 mmol) in toluene (60 ml) was heated under reflux for 2 h. The solvent was removed and the residue was purified by crystallization.

4a: m.p. 170-173° C (hexane) (75%). IR: 3450, 3340, 1640, 1610. ^{1}H-NMR: 1.68 (br s, 6H, CH_3); 1.9 - 2.85 (m, 4H, C-1, C-4); 3.05 - 3.45 (m, 2H, C-4a, C-9a); 5.95 (br s, 2H, NH_2); 7.04, 7.18 (2H, AB q, C-6, C-7, J = 9.3 Hz); 12.35 (s, 1H, OH). MS: 271 (M^+) (100),

256 (62), 238 (25). (Calcd. for $C_{16}H_{17}NO_3$: C, 70.82; H, 6.31; N, 5.16. Found: C, 70.88; H, 6.28; N, 5.46).

4b: m.p. 130-133°C (benzene-light petroleum) (80%). IR: 3330, 1640, 1600. ^{1}H-NMR: 1.67 (br s, 6H, CH_3); 1.9 - 2.8 (m, 4H, C-1, C-4); 2.96 (d, 3H, NCH_3, J = 4.5 Hz); 3.0 - 3.35 (m, 2H, C-4a, C-9a); 7.10, 7.23 (2H, AB q, C-6, C-7, J = 9.0 Hz); 9.05 (br s, 1H, NH); 12.17 (s, 1H, OH). MS: 285 (M^+) (100), 252 (37), 203 (26). (Calcd. for $C_{17}H_{19}NO_3$: C, 71.60; H, 6.66; N, 4.90. Found: C, 71.40; H, 6.46; N, 4.55).

4c: m.p. 173-177°C (benzene-hexane) (80%). IR: 3305, 3290, 1700, 1655. ^{1}H-NMR: 1.66 (br s, 6H, CH_3); 2.20 (s, 3H, $NCOCH_3$); 1.95 - 2.75 (m, 4H, C-1, C-4); 3.1 - 3.55 (m, 2H, C-4a, C-9a); 7.19 (d, 1H, A of AB, C-7, J = 9.0 Hz); 8.98 (d, 1H, B of AB, C-6); 11.57 (br s, 1H, NH); 12.37 (s, 1H, OH). MS: 313 (M^+) (100), 271 (52). (Calcd. for $C_{18}H_{19}NO_4$: C, 69.03; H, 6.06; N, 4.47. Found: C, 69.34; H, 6.27; N, 4.45).

4d: m.p. 180-183°C (benzene-hexane) (80%). IR: 1680, 1610. ^{1}H-NMR: 1.66 (br s, 6H, CH_3); 1.95 - 2.65 (m, 4H, C-1, C-4); 3.15 - 3.55 (m, 2H, C-4a, C-9a); 7.3 - 7.7 (m, 3H, arom.); 7.33 (d, 1H, A de AB, C-7, J = 9.3 Hz); 7.85 - 8.15 (m, 2H, arom.); 9.20 (d, 1H, B of AB, C-6); 12.30 (s, 1H, OH); 12.40 (br s, 1H, NH). MS: 375 (M^+) (79), 270 (38); 105 (100). (Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.63; N, 3.73. Found: C, 73.63; H, 5.41; N, 3.43).

4e: m.p. 179-182°C (benzene-hexane) (75%). IR: 1770, 1700, 1660. ^{1}H-NMR: 1.64 (br s, 6H, CH_3); 2.24 (s, 3H, $NCOCH_3$); 3.32 (s, 3H, $OCOCH_3$); 1.9 - 2.65 (m, 4H, C-1, C-4); 3.1 - 3.45 (m, 2H, C-4a, C-9a); 7.33 (d, 1H, A of AB, C-7, J - 9.0 Hz); 9.04 (d, 1H, B of AB, C-6); 11.93 (br s, 1H, NH). MS: 313 (M^+ -42) (5), 271 (20), 43 (100). (Calcd. for $C_{20}H_{21}NO_5$: C, 67.60; H, 5.92; N, 3.94. Found: C, 67.31; H, 5.88; N, 3.76).

Alkaline air oxidation of adducts 2a,b and 4a,b. General procedure

A mixture of the adduct 2 or 4 (1 mmol) and 5% aqueous sodium hydroxide (15 ml) was stirred at room temperature until no starting material remained (disappearance of the adduct was monitored by t.l.c.). The reaction mixture was acidified with 10% hydrochloric acid. The precipitate was collected, washed with water and purified by crystallization.

3a: m.p. 196-199°C (light petroleum) (75%). IR: 3345, 3260, 3170, 1585. ^{1}H-NMR: 2.25 (m, 2H, CH_2); 4.13 (m, 2H, C-1, C-4); 6.71 (m, 2H, C-2, C-3); 6.69, 6.85 (2H, AB q, C-6, C-7, J = 9.0 Hz); 6.80 (br s, 2H, NH_2); 13.22 (s, 1H, OH). MS: 253 (M^+) (100), 227, 196. (Calcd. for $C_{15}H_{11}NO_3$: C, 71.13; H, 4.37; N, 5.83. Found: C, 71.25; H, 4.67; N, 5.96).

3b: m.p. 305°C (d) (benzene-hexane) (75%). IR: 1590. ^{1}H-NMR: 2.36 (m, 2H, CH_2); 3.10 (s, 3H, NCH_3); 4.30 (m, 2H, C-1, C-4); 6.93 (m, 2H, C-2, C-3); 7.12 (s, 2H, C-6, C-7); 10.63 (br s, 1H, NH); 14.13 (s, 1H, OH). MS: 267 (M^+) (100). (Calcd. for $C_{16}H_{13}NO_3$: C, 71.89; H, 4.90; N, 5.24. Found: C, 71.88; H, 5.12; N, 5.17).

5a: m.p. 237-240°C (benzene-hexane) (80%). IR: 3440, 3280, 1580. ^{1}H-NMR: 1.72 (br s, 6H, CH_3); 3.13 (m, 4H, C-1, C-4); 6.83 (br s, 2H, NH_2); 6.90, 7.04 (2H, AB q, C-6, C-7, J = 9.0 Hz); 13.31 (s, 1H, OH). MS: 269 (M^+) (54), 254 (100). (Calcd. for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.60; H, 5.50; N, 5.42).

5b: m.p. 212-215°C (benzene-hexane) (75%). IR: 1590. ^{1}H-NMR: 1.77 (br s, 6H, CH_3); 3.02 (d, 3H, NCH_3, J = 4.5 Hz); 3.1 (m, 4H, C-1, C-4); 7.12 (s, 2H, C-6, C-7); 10.02 (br s, 1H, NH); 13.63 (s, 1H, OH). MS: 283 (M^+) (77), 268 (100), 253 (49). (Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.04; N, 4.94. Found: C, 72.22; H, 6.34; N, 4.72).

N-Acetyl derivatives 3c, 5c. General procedure

A mixture of 3a or 5a (3 mmol), sodium acetate (800 mg) and acetic anhydride (50 ml) was allowed to stand at room temperature for 48 h. The resulting solution was poured into ice/water to give a precipitate, which was collected, washed with water and purified by crystallization.

3c: m.p. 225-230°C (d) (cyclohexane) (70%). IR: 3320, 1705, 1650, 1600. ^{1}H-NMR: 2.25 (s, 3H, $NCOCH_3$); 2.35 (m, 2H, CH_2); 4.25 (m, 2H, C-1, C-4); 6.91 (m, 2H, C-2, C-3); 7.24 (d, 1H, A of AB, C-7, J = 9.0 Hz); 8.93 (d, 1H, B of AB, C-6); 12.12 (br s, 1H, NH); 12.89 (s, 1H, OH). MS: 295 (M^+) (5), 253 (100), 227. (Calcd. for $C_{17}H_{13}NO_4$: C, 69.17; H, 4.40; N, 4.74. Found: C, 68.93; H, 4.18; N, 4.55).

5c: m.p. 210-215°C (d) (benzene-hexane) (70%). IR: 1700, 1610, 1590. ^{1}H-NMR: 1.77 (br s, 6H, CH_3); 2.27 (s, 3H, $NCOCH_3$); 3.10 (m, 4H, C-1, C-4); 7.20 (d, 1H, A of AB, C-7, J = 9.0 Hz); 8.97 (d, 1H, B of AB, C-6); 12.00 (br s, 1H, NH); 12.80 (s, 1H, OH). MS: 311 (M^+) (42), 267 (100), 254 (89). (Calcd. for $C_{18}H_{17}NO_4$: C, 69.47; H, 5.46; N, 4.49. Found: C, 69.55; H, 5.71; N, 4.17).

N-Benzoyl derivatives 3d, 5d. General procedure

A mixture of 3a or 5a (3 mmol) and benzoyl chloride (6 ml) in dioxane (200 ml) was heated under reflux until the starting material was consumed (disappearance of 3a or 5a was

monitored by t.l.c.). Then the reaction mixture was warmed with water (200 ml) for 10 min. The precipitate obtained was collected, washed with water and purified by crystallization.

3d: m.p. 117-120° C (cyclohexane) (80%). IR: 1680, 1620, 1610, 1590. ^{1}H-NMR: 2.39 (m, 2H, CH_2); 4.26 (m, 2H, C-1, C-4); 6.95 (m, 2H, C-2, C-3); 7.4-7.8 (m, 3H, arom.); 7.47 (d, 1H, A of AB, C-7, J = 9.0 Hz); 8.0-8.3 (m, 2H, arom.); 9.22 (d, 1H, B of AB, C-6); 13.04 (s, 1H, OH); 13.17 (br s, 1H, NH). MS: 357 (M^+) (1), 105 (100), 77 (58). (Calcd. for $C_{22}H_{15}NO_4$: C, 73.97; H, 4.19; N, 3.91. Found: C, 73.67; H, 4.29; N, 3.81).

5d: m.p. 291-295° C (benzene-hexane)(75%). IR: 1690, 1620, 1610, 1590. ^{1}H-NMR: 1.74 (br s, 6H, CH_3); 3.13 (m, 4H, C-1, C-4); 7.29 (d, 1H, A of AB, C-7, J = 10.0 Hz); 7.4-7.8 (m, 3H, arom.); 7.9-8.25 (m, 2H, arom.); 9.18 (d, 1H, B of AB, C-6); 12.92 (s, 1H, OH); 13.09 (br s, 1H, NH). MS: 373 (M^+) (3), 105 (100). (Calcd. for $C_{23}H_{19}NO_4$: C, 74.02; H, 5.09; N, 3.75. Found: C, 74.30; H, 4.91; N, 3.48).

N,O-Diacetyl derivatives 3e, 5e. General procedure

A mixture of 3a or 5a (3 mmol), sodium acetate (1.6 g) and acetic anhydride (100 ml) was heated under reflux for 1 h. The resulting solution was poured into ice/water to give a precipitate which was collected, washed with water and purified by crystallization.

3e: m.p. 201-206° C (benzene-hexane) (70%). IR: 1770, 1700, 1660, 1640, 1610. ^{1}H-NMR: 2.25 (m, 2H, CH_2); 2.29 (s, 3H, $NCOCH_3$); 2.42 (s, 3H, $OCOCH_3$); 4.18 (m, 2H, C-1, C-4); 6.87 (m, 2H, C-2, C-3); 7.27 (d, 1H, A of AB, C-7, J = 9.0 Hz); 9.06 (d, 1H, B of AB, C-6); 12.19 (br s, 1H, NH). MS: 337 (M^+) (5), 295 (63), 253 (100), 227 (18). (Calcd. for $C_{19}H_{15}NO_5$: C, 65.58; H, 4.45; N, 4.15. Found: C, 65.88; H, 4.71; N, 3.99).

5e: m.p. 192-195° C (benzene-hexane) (70%). IR: 1770, 1700, 1665, 1630. ^{1}H-NMR: 1.73 (br s, 6H, CH_3); 2.26 (s, 3H, $NCOCH_3$); 2.39 (s, 3H, $OCOCH_3$); 3.06 (m, 4H, C-1, C-4); 7.26 (d, 1H, A of AB, C-7, J = 9.0 Hz); 9.06 (d, 1H, B of AB, C-6); 12.21 (br s, 1H, NH). MS: 353 (M^+) (2), 311 (27), 309 (44), 267 (100), 254 (36). (Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.38; N, 3.96. Found: C, 67.90; H, 5.15; N, 3.74).

Transcycloaddition of 3a-e with 2,3-dimethylbuta-1,3-diene. General procedure

A solution of 2,3-dimethylbuta-1,3-diene (6 mmol) and the quinone 3 (2 mmol) in toluene (80 ml) was heated under reflux for 48 h. The solvent was removed and the residue was purified by crystallization to afford 5. Yield 75-80%.

Diels-Alder reaction of 3a with 2,3-dimethylbuta-1,3-diene

A solution of 2,3-dimethylbuta-1,3-diene (3 mmol) and the quinone 3a (1 mmol) in benzene (50 ml) was allowed to stand at room temperature for one month. The solvent was removed and the solid residue was separated by preparative t.l.c. (benzene-ethyl acetate 4:1) to give the mixture 7n + 7x (50%). IR: 3330, 1700, 1620, 1600. ^{1}H-NMR: 1.44 (m, 2H, CH_2, 7x); 1.50 (m, 2H, CH_2, 7n); 1.60 (br s, 6H, CH_3, 7n); 1.77 (br s, 6H, CH_3, 7x); 1.8 - 2.95 (m, 4H, CH_2-C=C); 2.70 (m, 2H, CH, 7x); 3.17 (m, 2H, CH, 7n); 6.05 (m, 2H, olef., 7n); 6.42, m, 2H, olef., 7x); 6.48 (br s, 2H, NH_2); 6.89, 7.02 (2H, AB q, arom., J = 9.0 Hz); 6.99, 7.12 (2H, AB q, arom., J = 9.0 Hz); 12.87 (s, 1H, OH, 7n); 13.01 (s, 1H, OH, 7x). MS: 331 (M^+), 269. Minor amounts of 5a (30%) m.p. 237-240° C and recovered 3a (10%) m.p. 196-199° C were also isolated.

Transcycloaddition of 3a with diazomethane

To a solution of the quinone 3a (1 mmol) in diethyl ether (90 ml) cooled to -18° C was added an ethereal solution of diazomethane (3 ml) (0.6 mmol/ml) and the mixture was kept at -18° C for 96 h. The solvent was removed and the solid was a crude mixture 8n + 8x. IR: 3440, 3320, 1620, 1590. ^{1}H-NMR: 1.24 (m, 2H, CH_2, 8x); 1.50 (m, 2H, CH_2, 8n), 3.34 (m, 2H, CH, 8x); 4.08 (m, 2H, CH, 8n); 4.41 (m, 2H, NCH_2, 8n); 4.74 (m, 2H, NCH_2, 8x); 6.15 (m, 2H, olef., 8n); 6.32 (m, 2H, olef., 8x); 6.62 (br s, 2H, NH_2); 6.95-7.2 (m, 2H, arom.); 12.97 (s, 1H, OH, 8n); 13.11 (s, 1H, OH, 8x). The crude mixture was heated under reflux in toluene for 48 h. The 5-amino-8-hydroxybenz[f]indazole-4,9-dione (9), was collected and recrystallized from toluene, m.p. 350° C (75%). IR: 3410, 3290, 3140, 3090, 1610. ^{1}H-NMR (D_6-DMSO): 7.19, 7.32 (2H, AB q, C-6, C-7, J = 9.0 Hz); 7.13 (br s, 2H, NH_2); 8.43 (s, 1H, C-3); 13.51 (s, 1H, OH); 14.55 (br s, 1H, NH). MS: 229 (M^+). (Calcd. for $C_{11}H_7N_3O_3$: C, 57.67; H, 3.05; N, 18.33. Found: C, 57.63; H, 3.27; N, 18.15).

Transcycloaddition of 3e with diazomethane

To a solution of the quinone 3e (1 mmol) in diethyl ether (90 ml) cooled to -18° C was added an ethereal solution of diazomethane (3 ml) (0.6 mmol/ml) and the mixture was kept at -18° C for 72 h. The solvent was removed and the residue was heated under reflux in toluene for 48 h. The 5-acetoxy-8-acetylaminobenz[f]indazole-4,9-dione (10) was collected and recrystallized from benzene-hexane, m.p. 247-252° C (75%). IR: 3120, 3100, 3045, 1760, 1700, 1680, 1660.

^{1}H-NMR (D_6-DMSO): 2.23 (s, 3H, $NCOCH_3$); 2.33 (s, 3H, $OCOCH_3$); 7.18 (s, 1H, NH); 7.51 (d, 1H, A of AB, C-6, J = 9.0 Hz); 8.43 (s, 1H, C-3); 8.87 (d, 1H, B of AB, C-7, J = 9.0 Hz); 12.08 (br s, 1H, NH). MS: 313 (M^+) (10); 271 (31), 229 (100). (Calcd. for $C_{15}H_{11}O_5N_3$: C, 57.50; H, 3.51; N, 13.42. Found: C, 57.30; H, 3.42; N, 13.30).

8-Amino-5-hydroxybenz[f]indazole-4,9-dione (11)

Hydrolysis of 10 (0.3 mmol) by refluxing 5 min with 6N HCl (15 ml) afforded 11, m.p. 340° C (toluene) (70%). IR: 3400, 3290, 3140, 1625, 1600. ^{1}H-NMR (D_6-DMSO): 7.18, 7.27 (2H, AB q, C-6, C-7, J = 9.0 Hz); 8.39 (s, 1H, C-3); 13.81 (s, 1H, OH). MS: 229 (M^+). (Calcd. for $C_{11}H_7N_3O_3$: C, 57.67; H, 3.05; N, 18.33. Found: C, 57.47; H, 3.15; N, 18.20).

5-Amino-8-hydroxy-1-methylbenz[f]indazole-4,9-dione (12)

To a solution of 9 (1 mmol) in diethyl ether (90 ml) cooled to -18° C was added an ethereal solution of diazomethane (6 ml) and the mixture was kept at -18° C for 1 week. The solvent was removed and the residue crystallized from benzene-hexane, m.p. 268-269° C (80%). IR: 3370, 3300, 3280, 1610. ^{1}H-NMR (D_6-DMSO): 4.24 (s, 3H, NCH_3); 7.19, 7.32 (2H, AB q, C-6, C-7, J = 9.0 Hz); 8.05 (s, 1H, C-3); 8.12 (br s, 2H, NH_2); 13.28 (s, 1H, OH). MS: 243 (M^+)(3), 229, (100). (Calcd. for $C_{12}H_9N_3O_3$: C, 59.25; H, 3.70; N, 17.28. Found: C, 59.15; H, 3.50; N, 17.18).

8-Amino-5-hydroxy-1-methylbenz[f]indazole-4,9-dione (13)

According to the above procedure 11 was converted into 13, m.p. 260-265° C (benzene-hexane) (80%). IR: 3420, 3300, 3130, 1620. ^{1}H-NMR (D_6-DMSO): 4.19 (s, 3H, NCH_3); 7.14, 7.23 (2H, AB q, C-6, C-7, J = 9.0 Hz); 8.05 (s, 1H, C-3); 8.32 (br s, 2H, NH_2); 13.78 (br s, 1H, OH). MS: 243 (M^+) (100); 229 (90). (Calcd. for $C_{12}H_9N_3O_3$: C, 59.25; H, 3.70; N, 17.28. Found: C, 59.20; H, 3.60; N, 17.20).

8-Hydroxy-1-methylbenz[f]indazole-4,9-dione (14)

Sodium nitrite (200 mg, 2.89 mmol) was added to a magnetically stirred solution of 12 (258 mg, 1.06 mmol) in sodium hydroxide (350 mg in 50 ml of water) and the mixture was then added over a solution of hypophosphorous acid (20 ml) in ice (50 g). After 15 min, if a positive test for free nitrous acid appeared, the mixture was warmed at 70° C for 2 h and allowed to stand at room temperature for 10 h. The precipitate was collected, washed with water and crystallized from chloroform-methanol, m.p. 205-208° C (lit.[12] 206° C). The spectral data were also identical with those reported in the literature.[12]

5-Hydroxy-1-methylbenz[f]indazole-4,9-dione (15)

According to the above procedure, the indazoledione 13 was converted into 15 in 50% yield. Recrystallized from chloroform-metanol, m.p. 197° C (lit.[12] 197° C). The spectral data were also identical with those reported in the literature.[12]

5,8-Dihydroxy-1,4-dihydro-1,4-methanoanthracene-9,10-dione (16)

Reaction of naphthazarin with cyclopentadiene following the general procedure afforded the adduct in 80% yield, m.p. 138-141° C (lit.[14] 138-143° C). Alkaline air oxidation of the adduct following the general procedure afforded 16 (70%). m.p. 189-190° C (ethanol) (lit.[15] 190-191° C). IR: 1610. ^{1}H-NMR: 2.37 (m, 2H, CH_2); 4.37 (m, 2H, C-1, C-4); 6.98 (m, 2H, C-2, C-3); 7.05 (s, 2H, C-6, C-7); 12.73 (s, 2H, OH).

5,12-Dihydroxy-8,9-dimethyl-1,4,6a,7,10,10a-hexahydro-1,4-methano-6,11-naphthacenedione (17)

A solution of 2,3-dimethylbuta-1,3-diene (2 mmol) and the quinone 16 (1 mmol) in toluene (30 ml) was heated under reflux for 4 h. The solvent was removed and the residue was purified by crystallization from benzene-hexane, m.p. 187-190° C. IR: 1630. ^{1}H-NMR: 1.65 (br s, 6H, CH_3); 2.0-2.5 (m, 6H, CH_2); 3.22 (m, 2H, C-6a, C-10a); 4.32 (m, 2H, C-1, C-4); 6.86 (m, 2H, C-2, C-3); 11.93 (s, 2H, OH). MS: 336 (M^+) (33); 303 (27). (Calcd. for $C_{21}H_{20}O_4$: C, 75.02; H, 5.94. Found: C, 74.89; H, 6.16).

5,8-Dimethoxy-1,4-dihydro-1,4-methanoanthracene-9,10-dione (18)

Diels-Alder reaction of 5,8-dimethoxy-1,4-naphthoquinone with cyclopentadiene following the general procedure afforded the 5,8-dimethoxy-1,4,4a,9a-tetrahydro-1,4-methanoanthracene-9,10-dione, m.p. 153-154° C (benzene-hexane) (70%). IR: 1695. ^{1}H-NMR: 1.51 (m, 2H, CH_2); 3.43 (m, 2H, C-4a, C-9a); 3.50 (m, 2H, C-1, C-4); 3.85 (s, 6H, OCH_3); 6.08 (m, 2H, C-2, C-3); 7.10 (s, 2H, C-6, C-7). MS: 284 (M^+) (35), 218 (19), 66 (80), 43 (100). (Calcd. for $C_{17}H_{16}O_4$: C, 71.85; H, 5.63. Found: C, 71.71; H, 5.65). Alkaline air oxidation of the adduct following the general procedure afforded 18, m.p. 112-113° C (benzene-hexane) (70%). IR: 1650. ^{1}H-NMR: 2.24 (m, 2H, CH_2); 3.95 (s, 6H, OCH_3); 4.17 (m, 2H, C-1, C-4); 6.86 (m, 2H, C-2, C-3); 7.29 (s, 2H, C-6, C-7). MS: 282 (M^+) (80), 239 (40), 43 (100). (Calcd. for $C_{17}H_{14}O_4$:

C, 72.36; H, 4.96. Found: C, 72.06; H, 5.26).

Transcycloaddition of 18 with 2,3-dimethylbuta-1,3-diene

A solution of 2,3-dimethylbuta-1,3-diene (2 mmol) and the quinone 18 (1 mmol) in toluene (40 ml) was heated under reflux for 4 h. The solvent was removed and the residue was purified by crystallization from benzene-hexane to give the 2,3-dimethyl-5,8-dimethoxy-1,4-dihydroanthracene-9,10-dione (19), m.p. 241-243°C (70%). IR: 1650. ^{1}H-NMR: 1.73 (br s, 6H, CH_3), 3.09 (m, 4H, C-1, C-4); 3.92 (s, 6H, OCH_3); 7.32 (s, 2H, C-6, C-7). MS: 298 (M^+), 267 (10), 43 (100). (Calcd. for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04. Found: C, 72.27; H, 5.95).

Transcycloaddition of 18 with diazomethane

To a solution of the quinone 18 (1 mmol) in diethyl ether (80 ml) cooled to -18°C was added an ethereal solution of diazomethane (3 ml) (0.6 mmol/ml) and the mixture was kept at -18°C for 7 h. The solvent was removed and the residue was heated under reflux in toluene for 24 h. The precipitate, the 5,8-dimethoxybenz[f]indazole-4,9-dione (20), was collected and recrystallized from benzene-hexane, m.p. 238-240°C (75%). IR: 1660, 1590. ^{1}H-NMR: 3.82 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 7.51 (s, 2H, C-6, C-7); 8.13 (s, 1H, C-3). MS: 258 (M^+), (100), 241 (10), 229 (48). (Calcd. for $C_{13}H_{10}O_4N_2$: C, 60.46; H, 3.87; N, 10.85. Found: C, 60.26; H, 3.97; N, 10.75).

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REFERENCES AND NOTES

1. Part XXIII: F. Fariña, M.T. Molina and M.C. Paredes, Synth. Commun., in press.
2. F. Fariña and J.C. Vega, Tetrahedron Lett., 1655 (1972).
3. F. Fariña and P. Prados, Tetrahedron Lett., 477 (1979).
4. A. Echavarren, F. Fariña and P. Prados, Tetrahedron, 40, 4561 (1984).
5. T.R. Kelly, J. Vaya and L. Ananthasubramanian, J. Am. Chem. Soc., 102, 5983 (1980).
6. T.R. Kelly, L. Ananthasubramanian, K. Borah, J.W. Gillard, R.N. Goerner, Jr., P.F. King, J.M. Lyding, W-G. Tsang and J. Vaya, Tetrahedron, 40, 4569 (1984).
7. F. Fariña, R. Martínez-Utrilla, M.C. Paredes and V. Stefani, Synthesis, 781 (1985).
8. The presence of 5,9- or 8,10-quinonoid tautomers is not excluded, but they appear to be energetically less favourable.
9. See: S. Alvarado, F. Fariña and J.L. Martín, Tetrahedron Lett., 3370 (1970) for a closely related example.
10. P. Cano, A. Echavarren, F. Fariña and P. Prados, J. Org. Chem., 48, 5373 (1983).
11. M.D. Rozeboom, I-M. Tegmo-Larsson and K.N. Houk, J. Org. Chem., 46, 2338 (1981).
12. H. Laatsch, Liebigs Ann. Chem., 251 (1985).
13. G.A. Kraus and S.H. Woo, J. Org. Chem., 51, 114 (1986).
14. R.E. Winkler, Helv. Chim. Acta, 51, 592 (1968).
15. V.K. Tandon, S. Rajeshwar, J.M. Wharnna and N. Anand, Indian J. Chem., 15B, 839 (1972).