DIAZAPOLYCYCLIC COMPOUNDS XXVI[1]. DIAZAQUINONE ADDUCTS FROM ISOPRENOID COMPOUNDS

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Abstract — Diazaquinones such as phthalazine- and benzo(g)-phthalazine-1,4-dione react with isoprenoid compounds to give 4+2 diazapolycyclic adducts. Treatment with β-myrcene, allo-ocimene, neoalloocimene or ergocalciferol affords the expected cycloaddition products in good yields, whereas no reaction is found with β-ionone or retinol acetate. Some side-chain derivatives of these adducts have also been prepared.

Since the synthesis of the first adduct between pyridazine-3,6-dione and 1,3-butadiene was accomplished two decades ago, diazaquinones have been extensively used as dienophiles in Diels-Alder type cycloadditions[2]. The intervening years have witnessed the great utility of these compounds in preparing heterocyclic systems difficult to obtain by other procedures. Although the reaction has been extended to a wide range of diazaquinones, only a few alkyl and aryl derivatives of 1,3-butadiene and cyclic analogues are usually handled in order to provide the corresponding adducts. This is mainly because the highly unstable diazaquinone is formed "in situ" by oxidizing the cyclic hydrazide, and undesired side-reactions take place between the oxidant and more sophisticated dienes. However, some steroids have been shown to give 1,4-cycloaddition adducts with pyridazine-3,6-dione and phthalazine-1,4-dione[3].

This paper deals with the Diels-Alder cycloadditions of diazaquinones with isoprenoid type dienes. The reaction of dienic isoprenoids with dienophiles is well known[4-8], but their behaviour towards diazaquinones has apparently not been

investigated. It could be of synthetic potential for the preparation of diazaquinonic systems containing a long and easy to handle unsaturated side-chain in the terminal tetrahydropyridazine ring moiety, of current interest in chemotherapy of intercalating drugs.

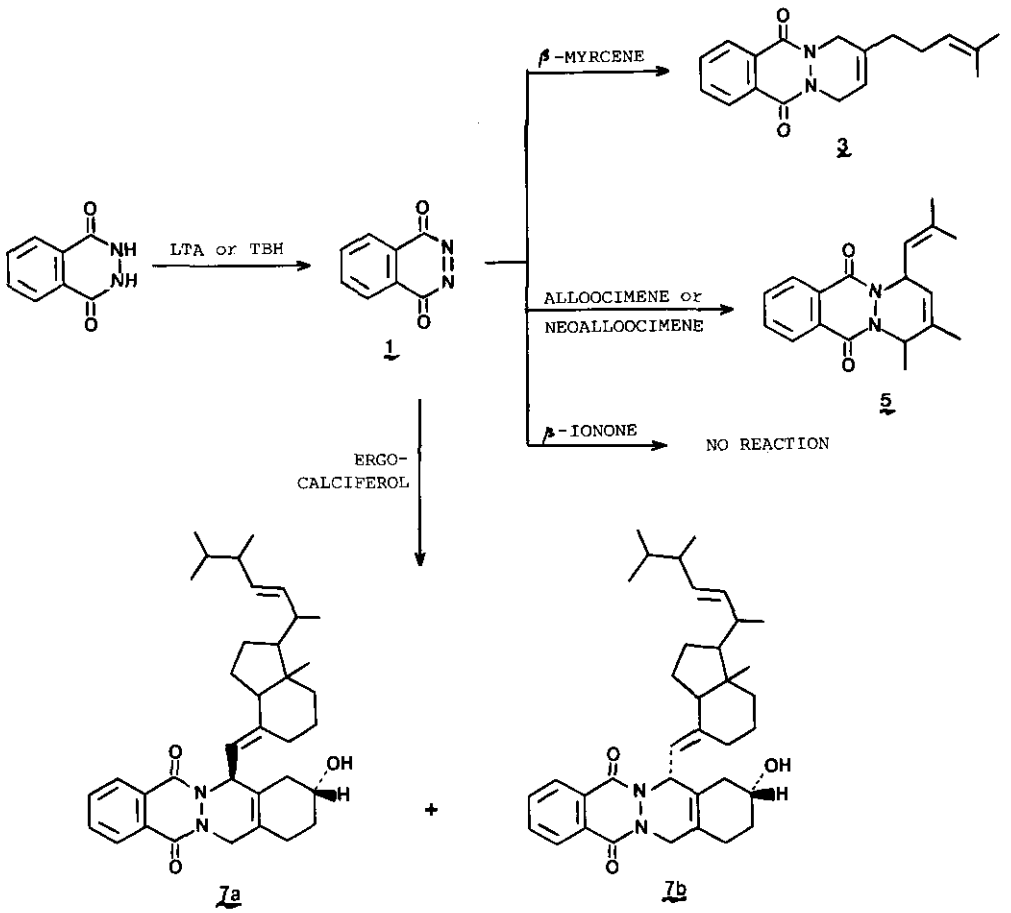
Either phthalazine-1,4-dione (1) or benzo(g)phthalazine-1,4-dione (2) were tried as dienophiles. According to previously reported procedures[2], both diazaquinones were formed "in situ" from the cyclic hydrazides, which were alternatively oxidized by lead tetraacetate (LTA) at room temperature or tert-butyl hypochlorite (TBH) at -70°C. Reactions performed and conditions are exposed in Table I, together with yields of the adducts obtained. See also Schemes I and II. The diene polymerization was low under the mild conditions employed, and no inhibitor was used.

Table I. 1,4-Cycloaddition reactions

Diazaquinone	Diene	Adduct[a]	Oxidant[b]	Time (hours)	Yield (%)	Mp[c] (°C)
1	β-Myrcene	3	TBH	3	76	113-5 (d)
2	β-Myrcene	4	LTA	12	69	163-4 (d)
1	Neoalloocimene	5	TBH	3	78	114-5 (d)
1	Alloocimene	5	TBH	3	7	"
2	Neoalloocimene	6	LTA	24	70	163-5 (d)
2	Alloocimene	6	LTA	24	14	"
1	β-Ionone	-	TBH/LTA	3/12	-	-
1	Ergocalciferol	7	LTA	12	47	170-5 (d)
1	Retinol acetate	-	TBH/LTA	3/12	-	-

a) Satisfactory elemental analyses were obtained. b) Solvents: CH_2Cl_2(LTA), acetone(TBH). c) From ethanol.

In spite of the fact that neoalloocimene and β-myrcene are less reactive than the respective methyl-substituted butadienes, both terpenes gave the expected adducts in very high yields. Treatment of β-myrcene with 1 and 2 respectively afforded 2-(4-methyl-3-pentenyl)-6,11-dioxo-1,4,6,11-tetrahydropyridazino(1,2-b)naphthalazine (3) and 2-(4-methyl-3-pentenyl)-6,11-dioxo-1,4,6,13-tetrahydrobenzo(g)-pyridazino(1,2-b)phthalazine (4). The most relevant spectral data for these and other compounds studied in this paper are summarized in table II. The cyclic structure of 3 and 4 is mainly supported in the ^{1}H-nmr spectra by the broad

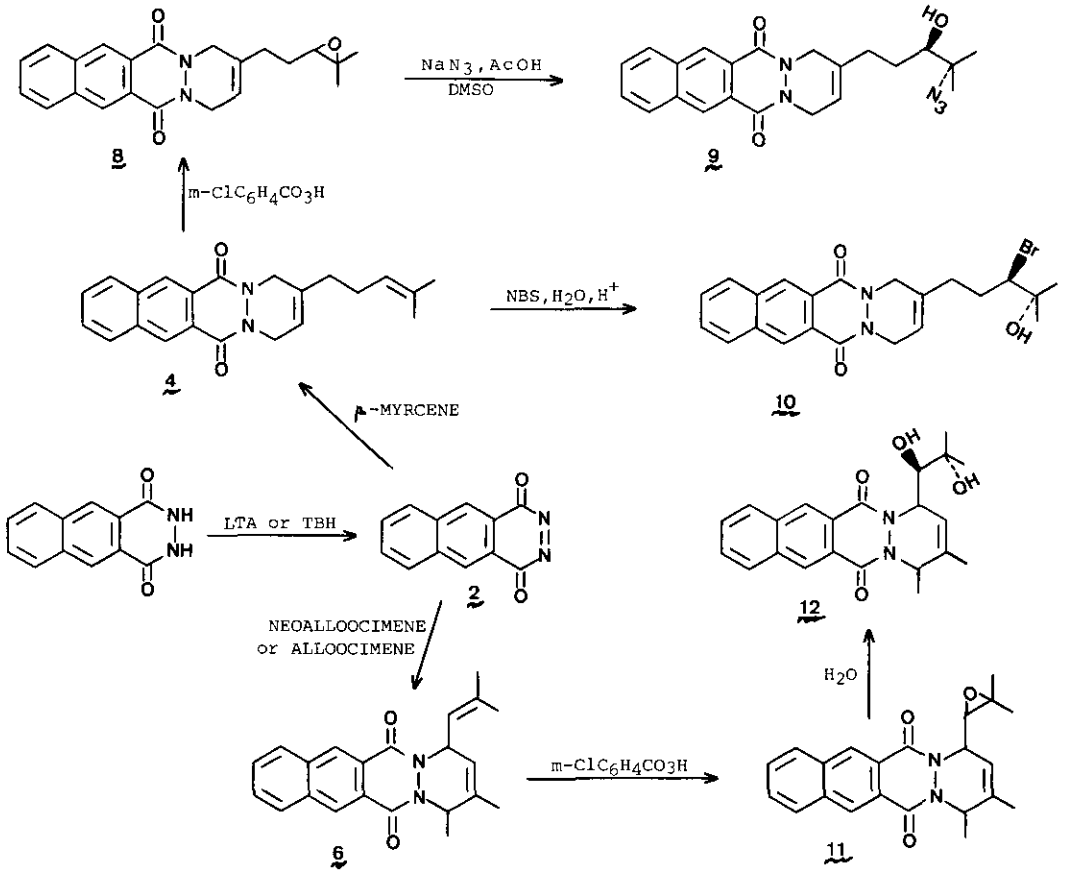


Scheme 1

singlets centred at 4.45 and 4.60 ppm corresponding to N-CH_2- signals. Although these methylene groups usually appear as a clearly differentiated AB system owing to the deshielding effect of the carbonyl over the almost coplanar equatorial proton, it is not so in the 2-substituted isoprene adducts, which exhibit a resembling tetrahydropyridazine ring spectrum, probably due to some kind of conformational equilibrium[9].

In a similar way, alloocimene (2,6-dimethyl-4-trans-6-trans-2,4,6-octatriene) and neoalloocimene (2,6-dimethyl-4-trans-6-cis-2,4,6-octatriene) reacted with 1 and 2 to give 4-isobutenyl-1,2-dimethyl-6,11-dioxo-1,4,6,11-tetrahydropyridazino(1,2-b)-phthalazine (5) and 4-isobutenyl-1,2-dimethyl-6,13-dioxo-1,4,6,13-tetrahydrobenzo-pyridazino(1,2-b)phthalazine (6). The tetrahydropyridazine ring moiety shows in both cases a ^{1}H NMR spectrum with two quadruplets referable to the methinic protons and clearly deshielded by the C=O groups, indicating a pseudoaxial

orientation of the substituents at C_1 and C_4, as it is usual in diazaquinone adducts[10]. Although the same adducts are obtained with both isomeric dienes, yields are substantially lower when alloocimene is employed, and considerable part of the diene is recovered. This fact is not in accordance with previous work concerning the reactivity of these two isomers, as it has been reported that neoalloocimene only reacts by isomerizing to alloocimene, owing to the steric hindrance of the s-cis form[4,6]. On the other hand, two isomeric adducts are usually formed in cycloadditions of both terpenes, predominating that one with the C_1 and C_4 substituents in a cis orientation. However, the same authors find higher yields and inverse isomers ratio in the cycloaddition of neoalloocimene with triazoline-3,5-diones[6]. In our results, only one adduct has been isolated in every case. We think that steric requirements of the rigid diazaquinone ring moiety favour the reaction of the trans-cis isomer, and also account for the exclusive formation of the adduct having the C_1 and C_4 substituents in



Scheme 2

the less hindered pseudoaxial position.

In spite of the lack of reactivity usually shown by the deactivated dienic system of β-ionone, this compound was treated with 2 by the LTA and TBA methods in order to check the high dienophilic character of the diazaquinone, but no reaction was observed in all essays performed.

We were also interested in testing the behaviour of vitamin D towards diazaquinones, because protection of the diene system in steroid type isoprenoids via cycloaddition with the appropriate dienophiles offers an attractive route to stereospecific structural modifications[3b,8]. Transformations on vitamin D_3 and derivatives by means of triazoline-3,5-dione adducts have shown to be of great interest. Therefore, the reaction of 1 with ergocalciferol was performed to give a 4:1 mixture of cycloadducts 7a and 7b in 47% overall yield. The ^1H NMR spectrum of 7a exhibit the methinic proton at C_1 as a highly deshielded doublet (5.88 ppm, 6.01 in 7b) with J=9.5 Hz (10.5 in 7b), and the C_4 methylene as an AB system (J= 17.4 Hz), as well as the aromatic protons indicative of the diazaquinone moiety. The bridged CH attached to the side-chain double bond has a coupling constant of 6.0 Hz. (not determined in 7b). The ^{13}C spectrum shows C=O signals at 158.6 and 166.6 ppm, CH_2-N at 66.30 and 66.14 ppm and CH-N at 48.28 and 48.09 ppm. The assignment of isomers 7a and 7b was made according to resembling results reported by Reisch and Zbiral in the cycloaddition of 4-phenyl-1,2,4-triazoline-3,5-dione to cholecalciferol[8b].

The reaction of retinol acetate with 1 and 2 was also intended, but the isoprenoid compound was recovered unchanged in all essays performed.

The good yields obtained in most of the aforementioned cycloadditions prompted us to try the functionalized introduction of substituents at the side-chain moiety of the diazaquinone adducts. Epoxidation could provide practical access to a variety of derivatives of presumable biological interest. Treatment of the myrcene adduct 4 with m-chloroperbenzoic acid in boiling chloroform during 4 h afforded as the only epoxidation product 2-(3,4-epoxi-4-methylpentyl)-6,13-dioxo-1,4,6,13-tetrahydrobenzo(g)pyridazino(1,2-b)phthalazine (8) in a 71% yield. Consequently, specific epoxidation at the more activated side-chain double bond was achieved. The site of epoxidation can be easily demonstrated by means of the ^1H NMR spectrum which has the same 5.82 ppm multiplet referable to the ring ethylenic proton than 4, whereas the 5.12 ppm signal of the hydrogen at the side-chain double bond moves upfield to 2.75 ppm. The two methyl groups show also upfield shifts of 0.4 ppm.

Table II. Relevant spectral data of cycloadducts and derivatives

Compd.	MS[a] m/z of M^+	IR[b] (cm^{-1}) KBr	^1H NMR ($CDCl_3$/TMS int), (ppm), J(Hz)[c] Tetrahydropyridazine ring	Side chain	Aromatic
3	296 (77%)	1640(CO), 1600, 1350, 780, 700.	4.45(bs,4,CH_2-N), 5.65(m,1, CH=C)	1.60(s,3,Me), 1.65(s, 3,Me), 4.95(m,1,CH=C)	7.50(m,2), 8.02 m,2), 8.77(s,2)
4	346 (89%)	3050, 1645(CO), 1625, 800, 755.	4.60(bs,4,CH_2-N), 5.75(m,1, CH=C)	1.62(s,3,Me), 1.70(s, 3,Me), 5.12(m,1,CH=C)	7.60(m,2), 8.02 (m,2), 8.77(s,2)
5	296 (100%)	1630(CO), 1610, 1340, 785, 695.	5.20(q,1,CH-N, J_{Me}=6.2), 5.55 (o,1,CH=C, J=6.3, J_{Me}=1.8), 5.85(q,1,CH-N, J=8.0, 6.3)	1.85(m,3,Me), 1.90(m, 3,Me), 5.04(m,1,CH=C, J=6.3, J_{Me}=1.7)[e]	7.45(m,2), 8.05 (m,2)
6	346 (100%)	3115, 1630(CO), 1615, 940, 765.	5.33(q,1,CH-N, J_{Me}=6.4), 5.68 (o,1,CH=C, J=6.2, J_{Me}=1.8), 6.03(q,1,CH-N, J=7.4, 6.2)	1.90(m,3,Me), 1.95(m, 3,Me), 5.16(m,1,CH=C, J=6.2, J_{Me}=1.8)[e]	7.67(m,2), 8.07 (m,2)
7[f]	556 (36%)	3600-200(OH), 1650(CO), 1620, 1370, 755.	4.17(d,1,CH_2-N, J=17.4), 4.77 (d,1,CH_2-N), 5.88(d,1,CH-N, J=9.5), 4.12(m,1,CH-O)	0.78,0.82,0.87(d,3,Me), 0.81(s,3,Me), 2.85(d,1, CH-C=, J=6.0), 4.75(d, 1,CH=C)	7.80(m,2), 8.25 (m,2)
8	362 (34%)	2870(C-O-C), 2850[d] (C-O-C), 1640 (CO), 940, 745.	4.60(bs,4,CH_2-N), 5.80(m,1, CH=C, $W_{\frac{1}{2}}$=8.0)	1.24(s,3,Me), 1.30(s, 3,Me), 2.38(t,2,CH_2-C=), 2.75(t,1,CH-O, J=6.0)	7.65(m,2), 8.08 (m,2), 8.50(s,2)
9	405 (24%)	3500-200(OH), 2100 (N_3), 1650(CO).	4.55(bs,4,CH_2-N), 5.68(m,1, CH=C)	1.23(s,3,Me), 1.30(s, 3,Me), 3.35(m,1,CH-O)	7.50(m,2), 7.87 (m,2), 8.60(s,2)
10	440-2 (1%)	3600-100(OH), 1640(CO), 755.	4.50(bs,4,CH_2-N), 5.82(m,1, CH=C)	1.25(s,3,Me), 1.33(s, 3,Me), 3.95(m,1,CH-Br)	7.75(m,2), 8.28 (m,2), 8.60(s,2)
12	380 (2%)	3500-200(OH) 1635(CO), 1605, 1190, 745.	5.20(q,1,CH-N, J_{Me}=6.7), 5.63(dd,1,CH-N), 5.80(d,1, CH=C, J=4.9)	1.36(s,3,Me), 1.49(s, 3,Me), 3.20(bm,2,OH), 4.10(d,1,CH-O, J=1.9)	7.65(m,2), 8.01 (m,2), 8.68(s,1) 8.70(s,1)

a) Hitachi Perkin-Elmer RMV-6M6, b) Pye Unicam SP3-200, c) Varian EM 390, d) In nujol, e) Allylic coupling, f) ^1H NMR data correspond to isomer 7a, for 7b: 0.89, 0.94, 1.01(d,3,Me), 0.82(s,3,Me), 6.01(d,1,CH-N, J=10.5).

Further opening of the oxirane ring at 8 with sodium azide/acetic acid (dimethylsulphoxide, 70°C, 8 h) gave 2-(4-azido-3-hydroxy-4-methylpentyl)-6,13-dioxo-1,4,6,13-tetrahydrobenzo(g)pyridazino(1,2-b)phthalazine (9) in 22% yield. The selective reactivity at the side-chain double bond was corroborated by treatment of adduct 4 with N-bromosuccinimide in aqueous suspension (24 h, 50°C), which afforded 2-(3-bromo-4-hydroxy-4-methylpentyl)-6,13-dioxo-1,4,6,13-tetrahydrobenzo(g)pyridazino(1,2-b)phthalazine (10) in 40% yield. As above, no reaction was observed at the ring double bond under described conditions, and orientation of the electrophilic addition was as expected. Structural assignment was also based on the NMR upfield shift of the side-chain ethylenic proton (5.12 to 3.90 ppm), whereas the CH=C tetrahydropyridazine ring signal remained unaffected. The bromine position was illustrated by the consistent deshielding effect taking place over H-C_3 with respect to 8 and the low values found for the two methyl groups.

Finally, reaction of the alloocimene adduct 6 with m-chloroperbenzoic acid (boiling $CHCl_3$, 24 h) exclusively yielded the side-chain epoxide 11, which was not isolated but directly opened in the presence of water to give 4-(1,2-dihydroxy-2-methylpropyl)-1,2-dimethyl-6,13-dioxo-1,4,6,13-tetrahydrobenzo(g)-pyridazino(1,2-b)phthalazine (12) in a 32% overall yield. The side-chain ethylenic proton of 6 moved upfield about 1.06 ppm and the two neighbouring methyl groups 0.45 ppm, while the ring moiety was scarcely affected except H-C_4, which was shielded on the range of 0.30 ppm.

On the basis of these results it seems that selective manipulation of the side-chain double bond can be performed in order to introduce the substituents of choice. Although yields obtained were not very high, it should be noted that the identified compounds were obtained together with a considerable amount of unreacted starting material, and no trace of other products was detected.

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