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Reaction of acetylenic esters with 1,8-diaminonaphthalene, 1,8-dihydroxynaphthalene and 8-hydroxy-1,2,3,4-tetrahydroquinoline*

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Abstract. Addition of 1,8-diaminonaphthalene 1 to dimethylacetylene dicarboxylate (DMAD) leads to the perimidine 4*a* and the naphthodiazepine 3*a*. A similar reaction with the diethyl ester (DEAD) gave rise to 3*b* and 4*b*. The latter product has been incorrectly formulated as naphthodiazepine 2*b* in the literature. 1,8-Dihydroxynaphthalene 8 and DMAD gives rise to the naphthodioxane 9, which is hydrolysed to the diacid 11. 8-Hydroxy-1,2,3,4-tetrahydroquinoline (14) and acetylenic esters form pyridobenzoxazines 15, which exist as equilibrium mixture of 15 and 16 in solution. The ethyl ester is hydrogenated to the dihydroderivative 18*b*. ^1H and more particularly ^{13}C NMR spectra are used to assign structures to various products.

Keywords. Acetylenic esters; perimidine naphthodiazepine; naphthodioxane; pyridobenzoxazine.

1. Introduction

The reaction of acetylenic dicarboxylic acid esters with bifunctional nucleophiles leading to heterocyclic systems has been investigated rather extensively over the last decade (George *et al* 1976; Fuks and Viehe 1969). Two main types of reactions have been recognised (chart 1), the first resulting from a stoichiometric 1 : 1 addition leading to type A compounds and the second, cyclisation with concomitant elimination of a molecule of alkanol resulting in compounds of type B.

To a certain extent, the formation of (iii) or (iv) under type B can be predicted on the basis of the directospecificity of the nucleophilic groups XH and YH; the formation of one or both of the structures under A however is not readily rationalised. In addition, structural type B can exhibit geometrical isomerism around the exocyclic carboalkoxymethylidene grouping and thus four products are theoretically possible from the addition reaction. The availability of a proton on X or Y in type B compounds when these represent NH, leads to yet another

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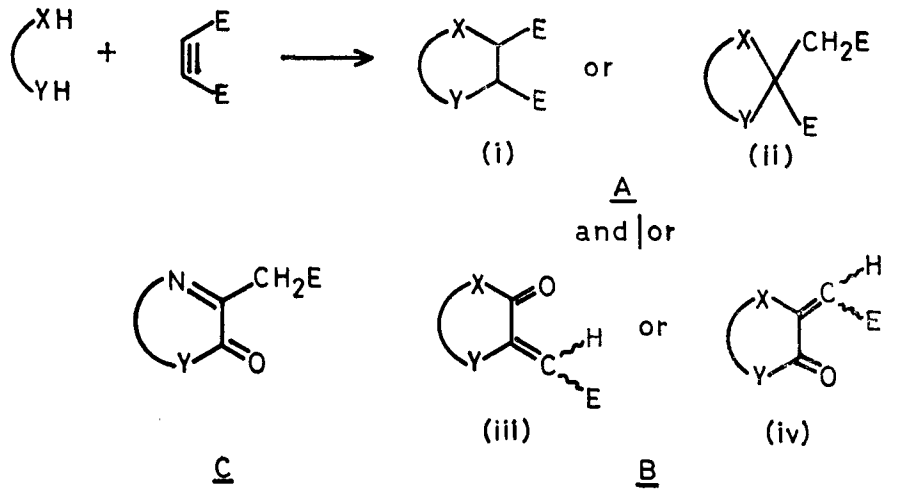

Chart 1.

possibility (C). The imine-enamine tautomerism of (C) and (B) becomes apparent from a study of proton resonance spectra in solutions and their equilibrium concentrations depend upon the solvent (Nair 1969).

Structural elucidations of the various products have relied heavily on analytical and spectroscopic data. Verifications by purely chemical methods have posed problems due to possibilities of interconversions under the reaction conditions utilised. We have been investigating the additions of a variety of dinucleophiles to acetylene dicarboxylic esters (Kalbag *et al* 1967; Nair 1969; Nagarajan *et al* 1971) and recently demonstrated the use of ^{13}C NMR spectroscopy for the solution of structural problems encountered in this chemistry (Vögeli *et al* 1978; Nagarajan *et al* 1979). We wish to report in this communication, our studies on the reactions of 1,8-diamino-naphthalene 1,1,8-dihydroxynaphthalene 8 and 8-hydroxy-1,2,3,4-tetrahydroquinoline 14 with dimethyl (DMAD) and diethyl (DEAD) acetylene dicarboxylate, providing examples for some of the pathways outlined in chart 1.

2. Reaction of 1,8-diaminonaphthalene (1) with DMAD and DEAD

It has been reported (Iwanami 1962) that reaction of 1 with DEAD leads to naphtho [1,8-ef] [1,4] diazepine derivatives 2*b* and 3*b* respectively.

The structures of the products were determined by elemental analysis, infrared spectra and analogy with similar reactions. In the case of the major product, assignment of structure 2*b* was claimed to be further substantiated by its identity with a synthetic specimen obtained from 1 and diethyl 1,2-dibromosuccinate. This evidence appeared ambiguous to us, especially since the alternative structure 4*b* also could arise out of these reactions. In the event, it turned out to be so indeed.

We have studied the reaction of 1 with DMAD and DEAD and determined ^1H and ^{13}C NMR spectra of the products. The data are presented in tables 1 and 2. The proton spectrum of the major product from 1 and DMAD showed

Table 1. ^{1}H NMR spectral data of naphthodiazepines 3, perimidines 4 and naphthodioxoles 9 and 11

Compound No.	Aromatic region δ (multiplicity)	OCH_3 δ	Others δ (multiplicity)
3*a*	C(5) H 6·87 (q) C(6)–C(10) H 7·05–7·54 (m)	3·73 (s)	=CH – 5·91 (s) NH 10·7 (bs) 11·0 (bs) (disappears with D_2O)
4*a*	C(4), C(9) H 6·58 (q) C(5)–C(8) H 7·13–7·35 (m)	3·66 (s) 3·73 (s)	CH_2 – 3·06 (s) 2NH–4·55 (bs) (disappears with D_2O)
3*b*	C(5) H–6·86 (q) C(6)–C(10); 7·15–7·6 (m)	..	=CH – 5·95 (s) $-OCH_2CH_3$ 4·23 (q) $-OCH_2CH_3$ 1·32 (t) –NH –10·7 –11·08
4*b*	C(4), C(9) H 6·45 (q) C(5) – C(8) H 7·05–7·2 (m)	.. ..	$-OCH_2-CH_3$ 3·8 – 4·3 (2q) $-OCH_2CH_3$ 0·86–1·33 (2t) $-CH_2$ 2·91 (s) NH 5·2 (bs)
9	C(4), C(9) H 6·96 (q) C(5) – C(8) H 7·10–7·60 (m)	3·58 (s) 3·72 (s)	CH_2 – 3·37 (s)
11	C(4), C(9) H 7 (q) C(5) – C(8) H 7·15–7·65 (m)	..	CH_2 – 3·33 (s) CO_2H – 10·7 (bs)

Table 2. ^{13}C NMR spectral shifts of naphthodiazepine 3, perimidine 4 and naphthodioxane 9.

Compound No.	CO (N)	CO (OR)	Aromatic region	C(*x*)	C(OCH_3)	Others
3*a*	158·0 (m)	166·8 (q)	C(5), C(8), 124·9 (d) (others not analysed)	92·5 (m)	52·7 (q)	..
4*a*		172·6 (q) 170·1 (q)	C(5), C(8), 127·1 (d) C(6), C(7), 118·2 (m) C(4), C(9), 106·4 (m)	43·6 (t)	51·9 (q) 52·9 (q)	C(2) 69·4 (t)
9		167·5 (q) 166·9 (q)	C(5), C(8), 127·4 (d) C(4), C(9), 109 (m) C(6), C(7), 121·1 (m)	42·7 (t)	52·0 (q) 53·0 (q)	C(2) – 98·1 (t)

a singlet for 2 protons at δ 3·06 and two singlets, each for one methoxyl group at δ 3·66 and 3·73, in addition to the signals in the aromatic region. The chemical shift of 3·06 was of the order found for a similar CH_2 group in the analogous compound 5*a* from our earlier work (Nagarajan *et al* 1971). This fact plus the appearance of two *separate* OCH_3 signals were incompatible with structure 2*a*.

Likewise the reaction of 1 with DEAD gave, as reported by Iwanami, a major product, m.p. 80–81°, showing a two proton singlet at δ 2·91 and two dissimilar ethyl groups. 2*a* (and 2*b*) would be expected to have a two proton singlet at about δ 4 in addition to showing one signal for the methoxyl (and one set for ethoxyl) group. 4*a* and 4*b* appeared to be better possibilities. Additional convincing evidence for structure 4*a* for the major product was obtaned from its ^{13}C spectrum. The presence of a triplet at δ 43·6 [C (*x*)] with an one bond J_{CH}

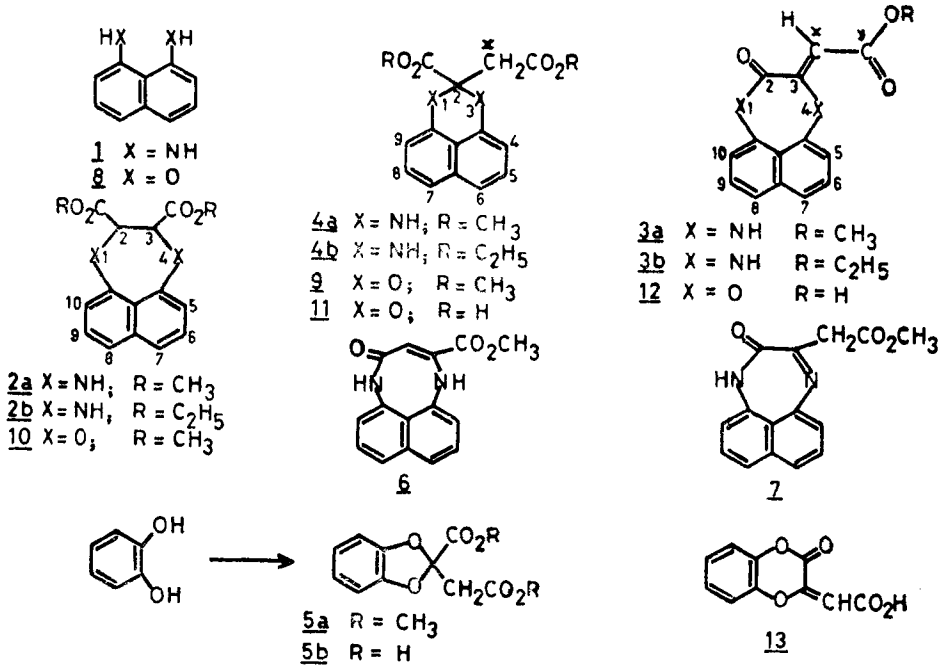

Chart 2.

of 137 Hz clearly spoke for the correctness of structure 4*a*. 2*a* would be expected to show a doublet for C(2) and C(3) at about δ 65. Further supportive features of the ^{13}C NMR spectrum of 4*a* were the presence of two separate signals for the methoxyl carbon atoms at δ 51·9 and 52·9 and also the appearance of C(2) at δ 69·4 as a triplet with a small *J* value of 6 Hz, due to a 2 bond interaction with the CH_2 protons. The structure of 2*b* accordingly stands corrected to 4*b*.

The structures of 3*a* and 3*b* followed from elemental analysis and the presence in the IR spectra of a highly chelated C=O band at 1640 cm^{-1}. The other possible, but unlikely structure that would fit the analytical values, *viz.*, 6 can be ruled out on the basis of the IR evidence. In the ^{13}C NMR spectrum of 3*a* the exocyclic methylene carbon atom, C(*x*) appeared as a doublet at δ 92·5 with a large one

bond J_{CH} of 172 Hz, and showing further fine structure, presumably due to coupling with NH. The signal due to C(y) was a quartet at δ 166·8; C (2) was a multiplet at δ 158·0 which could not be resolved because of unfavourable signal-to-noise ratio at the rather low concentrations at which the spectrum had to be run. It appeared however that the geometry (*Z* configuration) represented in 3*a* was more likely, since the *E* configuration would require a 3 J_{CH} of the order of 11 Hz, which was inconsistent with the line width of the multiplet. 3*a* moreover has a favourable arrangement for hydrogen bonding.

The ^{1}H NMR spectrum of 3*a* in DMSO-d_6 showed the olefinic proton as a singlet at δ 5·91. There was little evidence for the presence of species 7 in this as well as in the ^{13}C spectrum. A detailed solvent study was not undertaken. The ^{1}H NMR of spectrum of 3*b* in DMSO-d_6 likewise showed only one species to be present.

3. Reaction of 1,8-dihydroxynaphthalene (8) with DMAD

We have shown earlier (Nagarajan *et al* 1971) that catechol adds to DMAD to give 5*a*. Addition of 8 to DMAD in methanol gave a 1 : 1 adduct in 50% yield. The ^{1}H and ^{13}C NMR spectral data of the adduct are presented in tables 1 and 2 respectively. The former showed the characteristic CH_2 singlet at δ 3·37, besides two methoxyl singlets at δ 3·58 and 3·72, indicating structure 9 for the product.

The ^{13}C spectrum showed C (x) as a triplet at δ 42·7 with a one bond J_{CH} of 133 Hz and C (2) at δ 98·1 as a triplet, due to coupling with proton on C (x) (J = 5·9 Hz). The presence of two different OCH_3 groups was indicated by two quartets, one at δ 52·0 and another at δ 53·0, both with J_{CH} = 148 Hz, as well as the two carbonyl carbon atoms at δ 167·5 and 166·9 as overlapping quartets with small coupling constants. These data firmly rule out 10 to favour 9.

We had observed earlier during the alkaline hydrolysis of 5*a* that in addition to the expected diacid 5*b*, the rearranged lactone acid 13 was also obtained. However, similar hydrolysis of 9 led uniquely to the expected diacid 11, exhibiting a characteristic two proton singlet at δ 3·33 in the ^{1}H NMR spectrum (table 1). There was no evidence for the presence of the rearranged product 12. Evidently the formation of a dioxepine from a dioxane is sterically less favoured than that of the dioxane 13 from the dioxole 5.

4. Reaction of 8-hydroxy-1,2,3,4-tetrahydroquinoline (14) with DMAD and DEAD

We have reported (Nagarajan 1973) that the reaction of 14 with DMAD and DEAD gave rise to products whose ^{1}H and ^{13}C NMR spectra in solution showed them to be a mixture of 15 and 16 in a solvent dependent equilibrium. The ^{13}C NMR spectra have been discussed in detail (Vögeli *et al* 1978). In the spectrum of the DEAD product, the ring C=O resonances of 15*b* and 16*b* were clear doublets, the coupling constants with the vinyl proton being 5·6 and 11·3 Hz respectively. These data were used to assign the structures uniquely to the product, ruling out several other possibilities. We present in this paper experimental details for the products and a discussion of other spectral features, especially the ^{1}H NMR data.

The IR spectrum of the DEAD product with C=O bands at 1680 and 1740 cm^{-1} was not decisive in excluding the lactam structure 17; but catalytic hydrogenation gave rise to a single dihydro derivative 18 which showed the C=O bands in the IR spectrum at 1740 (ester) and 1780 cm^{-1} (phenolic lactone). The dihydroderivative of 17 would be 19 and exhibit the lactam C=O band at about 1680 cm^{-1} besides one due to the ester. The ^1H NMR spectrum of 18 was also consistent with this structure.

A fresh solution of the DEAD product in $CDCl_3$ exhibited a proton spectrum attributable almost entirely to 15*b*, one of the diagnostic signals for example being due to =CH– at δ 6·12; 16*b* was present only in traces, as evidenced by the intensity of the =CH signals at δ 5·28. In the course of 6 days, the NMR spectrum showed the attainment of equilibrium of 15*b* and 16*b* in the ratio of 5 : 1. This indicated that the DEAD product in the solid state was probably almost completely

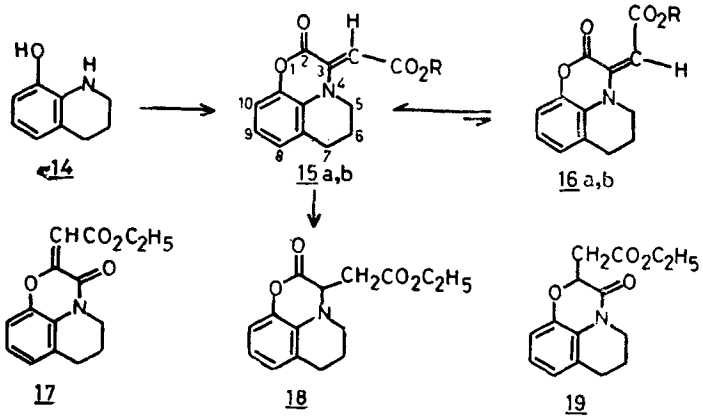

Chart 3.

15*b* at room temperature. Further its TLC behaviour also spoke for its homogeneity. But it melted over a range of temperature. This may indicate that it was isomerising to 16*b* even in the solid state, assuming absence of polymorphism. In DMSO-d_6, the diagnostic signals due to =CH for 15*b* and 16*b* were respectively at δ 5·98 and 5·60. At 0 hr, the proton spectrum indicated practically 100% of 15*b*, but after 2 days, the formation of about 4% of 16*b* was evident.

The addition product of 14 and DMAD consisted predominantly of 15*a*; a fresh $CDCl_3$ solution showed a composition of 95% of 15*a* (δ =CH 6·22) and 5% of 16*a* (δ =CH at 5·33) changing in 6 days to 85% and 15% respectively. In an equilibrated solution in DMSO-d_6 the composition was about 78 and 22% respectively (δ =CH 6·00 and 5·60 for 15*a* and 16*a*).

The formation of 15 and 16 from 14 is an expression of the greater nucleophilicity of the amino group in 14 compared to the phenol and corresponds to our earlier observations on 2-aminophenol (Kalbag *et al* 1967), which led to 20. While 20 is frozen in the *Z* configuration (Vögeli *et al* 1978) due to hydrogen bonding, the absence of this possiblity for the products from 14 lowers the energy barrier between 15 and 16 sufficiently to allow a small proportion of the latter to be formed in equilibrium.

5. Experimental

All melting points are uncorrected. NMR spectra were run in $CDCl_3$ and/or DMSO-d_6 solutions, using TMS as internal reference. Chemical shifts are quoted in ppm downfield from TMS. ^1H spectra were run at 60 or 90 MHz, and ^{13}C spectra at 22·63 MHz. The latter were taken on a WH 90 machine first under broad band decoupling to obtain chemical shifts and later in the gated decoupling mode to gather coupling information. The symols s, d, t, q, qi and bs mean respectively singlet, doublet, triplet, quartet, quintet and broad singlet. IR spectra were recorded for Nujol mulls on a Perkin Elmer Infracord spectrophotometer.

5.1. *Reaction of* 1,8-*diamino naphthalene* (1) *with DMAD*

To a solution of 1 (5 *g*) in methanol (50 ml) was added with stirring DMAD (4·5 *g*) in methanol (10 ml). The stirring was continued at ambient temperature for 24 hr; the separated solid was filtered and crystallised from a mixture of DMF and methanol to yield 3*a* (0·7 g), m.p. 252°; (Found: C, 66·89; H, 4·69; N, 10·37. $C_{15}H_{12}N_2O_3$ requires C, 67·15; H, 4·51; N, 10·44%); $\gamma_{c=o}$ 1640, 1670 cm^{-1}.

The filtrate on concentration to one half the original volume and cooling yielded a solid which after crystallisation from a mixture of methanol and water gave 4*a* (4 *g*), m.p. 137–140°; (Found : C, 64·12; H, 5·71; N, 9·53. $C_{16}H_{16}N_2O_4$ requires : C, 63·99; H, 5·37; N, 9·33%); $\gamma_{c=o}$ 1720, 1740 cm^{-1}.

5.2. *Reaction of* 1 *with DEAD*

To a solution of 1 (10 *g*) ethanol (100 ml) was added dropwise with stirring DEAD (10·8 g). The mixture was stirred at ambient temperature for 24 hr; the separated solid was filtered off and crystallised from DMF–ethanol to yield 3*b* (0·2 g) as maroon crystals; m.p. 238–240° (lit. m.p. 233–236°); (Found : C, 68·05; H, 5·21; N, 10·15, $C_{16}H_{14}N_2O_3$ requires C, 68·07; H, 5·00; N, 9·92%); $\gamma_{c=o}$ 1640, 1680 cm^{-1}.

The mother liquor on concentration and cooling yielded a brown solid which on crystallisation from a mixture of ethanol and water gave 4*b* (8 g) as brown crystals, m.p. 80° (lit. m.p. 80–81°); (Found C, 66·07; H, 6·30; N, 8·57. $C_{18}H_{20}N_2O_4$ requires C, 65·84; H, 6·14; N, 8·53%); $\gamma_{c=o}$ 1720 cm^{-1}.

5.3. *Reaction of* 1,8-*dihydroxynaphthalene* 8 *with DMAD*

To a solution of 0·1 g of sodium in methanol (100 ml) was added 8 (11·2 g) and DMAD (9·95 g). The mixture was heated under reflux overnight; the solution was concentrated *in vacuo* and the separated solid filtered off to yield 9 (11 g), which on crystallisation from methanol melted at 116–118°; (Found : C, 63·85; H, 5·00, $C_{16}H_{14}O_6$ requires C, 63·57; H, 4·67%); $\gamma_{c=o}$ 1740, 1760 cm^{-1}.

5.4. *Hydrolysis of naphthodioxane diester* 9

Treatment of 9 (6 g) in methanol (60 ml) with aqueous sodium hydroxide (2 g in 10 ml water) at room temperature overnight and acidification yielded 11 (4·4 g)

(from chloroform-ether), m.p. 223–224°; (Found : C, 61·02; H, 3·90. $C_{14}H_{10}O_6$ requires C, 61·32; H, 3·68%): $\gamma_{c=o}$ 1730 cm^{-1}.

5.5. *Reaction of* 8-*hydroxy*-1,2,3,4-*tetrahydroquinoline* 14 *with DEAD*

A solution of 14 (7·5 g) in ethanol (40 ml) was treated with DEAD (8·5 g) when an exothermic reaction ensued. A crystalline product separated soon which was filtered off after a few hours to yield 8·5 g of solid. Crystallisation from benzene-hexane afforded 15*b*; m.p. 115–120°;. (Found : C, 65·52; H, 5·71; N, 5·39. $C_{15}H_{15}NO_4$ requires C, 65·92; H, 5·53; N, 5·13%) $\gamma_{c=o}$ 1680, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 1·28 (CH_3, t); 2·03 (C–6 H_2; qi); 2·83 (C–7 H_2, t); 3·75 (C–5 H_2, t); 4·15 (O CH_2; q); 6·12 (=CH, s); 6·88 (C–8, C–9, C–10 H, s).

An equilibrated solution showed additionally signals due to 16*b* at 3·40 (C–5 H_2, t); 4·25 (OCH_2; q); 5·28 (=CH, s); 6·78 (C–8, C–9, C–10 H, s).

5.6. *Catalytic hydrogenation of* 15*b*

The foregoing compound (2·73 g) in ethyl acetate (40 ml) was shaken with hydrogen at 1 atmospheric pressure and at room temperature in the presence of 10% Pd–C (0·5 g) until 1 mole of hydrogen was absorbed. The mixture was filtered and the filtrate evaporated to give 18 as a homogeneous oil; $\gamma_{c=o}$ 1740, 1780 cm^{-1}; ^1H NMR (CCl_4); δ 1·15 (CH_3, t); 1·95 (C–6 H_2; qi); 2·67 (C–7 H_2 + CH_2 CO_2R, t); 3·10 (C–5 H_2, m); 4·0 (OCH_2, q); 4·20 (C–3 H, t); 6·50–6·85 (C–8, C–9, C–10, H, m).

5.7. *Reaction of* 14 *with DMAD*

Treatment of 14 (7·5 g) in methanol (40 ml) with DMAD (7·1 g) as before afforded 15*a* (6·8 g) (from benzene-hexane), m.p. 151–9°;. (Found : C, 64·96; H, 5·40; N, 5·24. $C_{14}H_{13}NO_4$ requires C, 64·86; H, 5·05; N, 5·40%). $\gamma_{c=o}$ 1680, 1735 cm^{-1}. ^1H NMR ($CDCl_3$); δ 2·08 (C–6 H_2; qi); 2·90 (C–7 H_2; t); 3·75 (C–5 H_2; t); 3·75 (OCH_3, s) 6·22 (=CH, s); 6·95 (C–8, C–9, C–10 H, s). Additional signals due to 16*a* appeared at δ 3·83 (OCH_3, s); 5·33 (=CH, s) and 6·88 (C–8, C–9, C–10 H, s).

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