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SYNTHESIS OF THE NATURALLY OCCURRING NAPHTHO- |2,3-b| Pyran-5,10-QUINONES α -CARYOPTERONE, DIHYDRO-a-CARYOPTERONE AND THEIR ISOMERS 6-HYDROXY-DEHYDRO-a-LAPACHONE AND 6-HYDROXY- α -LAPACHONE

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Abstract - Isomeric 6- and 9-hydroxy-naphtho-2,3-b/pyran-5,10-quinones were synthesised by alkylation-cyclisation of 2- and 3-hydroxyjuglone in a single step and can be distinguished by UV-visible spectra in the presence of additives and HNMR.

From the trunkwood of Lundia densiflora (Pyr) DC, an Amazonian Brazil an species of the Bignoniaceae family, we have isolated a laphthoquinone (m p 118-119⁰C)¹ whose spectral data suggested its identity with dihydro- α -caryopterone (=9-hydroxy- α -lapachone)(1) that occurs in Catalpa ovata, a Bignoniaceous Japanese plant² A dehydroanalogue, α -caryopterone $(=9-hydroxy-dehydro-\alpha-lapachone)(2)$ was obtained from Caryopteris clandonensis (Verbenaceae)³. We describe here the synthesis of these two naturally occuring naphthoquinones as well as of their isomers, the 6-hydroxyanalogues (3) and (4)



The isomeric 2- and 3-hydroxyjuglone (5 and 6) were prepared from 1,5-dihydroxynaphthalene which was oxidized to juglone (7) with a cupric complex of oxygen and acetonitrile as described by Capdevielle and Maumy 4 . Amination of juglone with an aqueous dimethylamine solution (33% w/v) at room temperature afforded a crude mixture from which the 2- and 3-N,N-dimethylaminojuglone were separated by silica column chromatography eluted with mixtures of hexane-dichloromethane of increasing polarities (8 30%, m p $146-147^{\circ}$ C, 9 20%, m p $154-156^{\circ}$ C) The only dimethylaminojuglone which Thomson obtained by direct addition of dimethylamine to juglone was 2-N,N-dimethylaminojuglone

 $(\underline{8})$, with a low yield $(34\%)^5$. The regionsomer 3-N,N-dimethylaminojuglone $(\underline{9})$ was prepared by the reaction of 3-chlorojuglone with aqueous dimethylamine⁵ Hydrolysis of the isomeric dimethylaminojuglones ($\underline{8}$) and ($\underline{9}$) with conc. HCl under reflux afforded in good yields (90%) the corresponding 2- and 3-hydroxyjuglone ($\underline{5}$ m p. 218-220° C, $\underline{6}$: m p. 218-222° C) which were previously obtained and characterized by Thomson⁶ He also prepared the 2-hydroxyisomer ($\underline{8}$) by hydrolysis of 2-dimethylaminojuglone ($\underline{8}$) and 3-hydroxyjuglone ($\underline{6}$) by four different ways by oxidation of α -hydroxyjuglone, by hydrolysis of 3-anilinojuglone, by Thiele acetylation of juglone, followed by hydrolysis and c idation of 1,3,4,5-tetraacetoxynaphatalene and by the reaction of 3-chlorojiglone with sodium hydroxyde⁶

The isomeric 2- and 3-hydroxyjuglone (5) and (6) were converted to the corresponding 6- and 9-hydroxyxyloidone (6- and 9-hydroxy-dehydro- α lapachone) (4 nd 2) by a single step alkylation cyclisation in a triethylamine catalysed reaction with 3-methyl-2-butenal, in benzene under reflux, described by Pinto et al for the synthesis of xyloidones from 2-hydroxy-1,4naphtoquinone and α , β -unsaturated aldehydes⁷ The crude reaction mixture, in each case, was submitted to chromatographic separation on silica-gel columns eluted with mixtures of hexane-ethyl acetate giving the xyloidones(4 \cdot 18% , 2° 12%). Of the two prepared quinones, one (2 m p 160-165° C dec.) corresponds to the naturally occurring α -caryopterone(m.p. 170-172°C de()^{3,8} and the other (4: m p. 156-158⁰ C) is a novel compound. The formation of the xyloidones (2) and (4) by this procedure can be rationalised in terms of the intermediates (10) and (11) that would arise by dehydration of the alcohols which are produced by alkylation. These intermediates are analogous to (12) which is thought to be implicated in the oxidative cyclisation of the methoxyderiva ives of lapachoi (13) and isolapachol (14) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)⁸







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. = H

Catalytic hydrogenation of $(\underline{2})$ and $(\underline{4})$ in THF, in the presence of palladium on charcoal, afforded the dihydroderivatives $(\underline{1})$ (m p $122-124^{\circ}$ C, lit.³ m p $120-122^{\circ}$ C) and $(\underline{3})$ (m p. $178-180^{\circ}$ C) The 9-hydroxy isomer $(\underline{1})$ was shown to be identical with the natural compound isolated from Lundia densifiora¹ which corresponds then to dihydro- α -caryopterone³

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The members of each of the constitutional isomeric pairs (2 and 4), (1 and 3) can be distinguished by the chemical shifts of the hydroxylic protons in the ¹HNMR spectra These are of higher δ values for the 6-hydroxy isomers $|3 \quad \delta_{OH}(\text{CDCl}_3)12 \quad 35, \quad 4. \quad \delta_{OH}(\text{CDCl}_3)12 \quad 23|$ than for the 9-hydroxy $|1 \quad \delta_{OH}(\text{CDCl}_3)11 \quad 82, \quad 2 \quad \delta_{OH}(\text{CDCl}_3)11 \quad 98|$ due to stronger hydrogen bonds associated with the resonance effect in the 6-isomers (3 and 4) and in agreement with the observed stronger deshielding of the C-5 hydroxyl proton in 2-hydroxy- than in 3-hydroxyjuglone (5 $\delta 12 \quad 28, \quad 6. \quad \delta 11 \quad 04)^9$.

The resonance effect involving the heterocyclic oxygen and the carbonyl group at C-5 is also the explanation for the distinct behaviour of the 9-hydroxy isomers (1) and (2) in relation to the 6-isomers (3) and (4) in the ultraviolet-visible in the presence of additives. The spectra of the four compounds show the expected bathochromic shifts upon addition of aluminium trichloride but these effects are reversed by hydrochloric acid in the former group (1 and 2) but not in the second one (3 and 4). This observation can be very useful for the location of hydroxyl groups in natural naphthoquinones oxygenated at the quinone molety, particularly for the prenylnaphthoquinones which are typical constituents of plants of the Bignoniaceae family 10

Synthesis of the naturally occuring 9-hydroxy-naphtho-|2,3-b|pyran-5,10-quinones (<u>1</u>) and (<u>2</u>) via oxidative cyclisation with DDQ of the substituted α - and β -prenylnaphthoquinoes (<u>14</u>), (<u>15</u>) and (<u>13</u>) was reported⁸,11,12

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