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A NEW SYNTHESIS OF 3,3′-BI(2-METHYL-1,4-NAPHTHOQUINONE)

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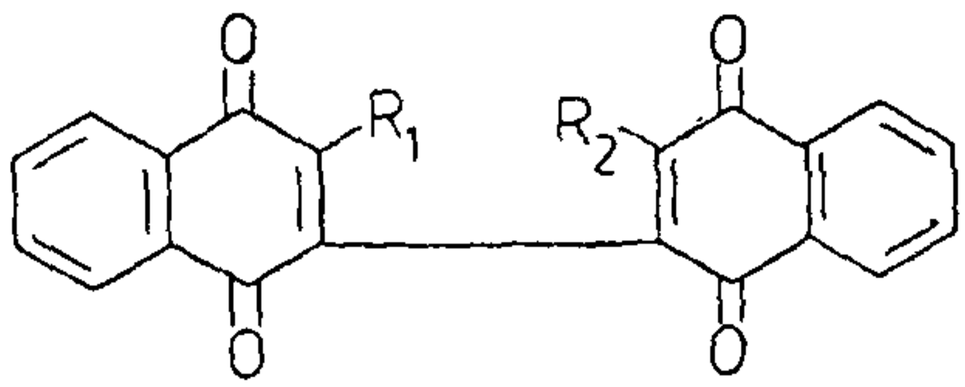
ABSTRACT

2,2′-Bi(1,4-naphthoquinone)(II), obtained by the dimerisation of 1,4-naphthoquinone, on treatment with lead tetraacetate in acetic acid, affords 2-methyl-3,3′-bi(1,4-naphthoquinone) (III), 3,3′-bi(2-methyl-1,4-naphthoquinone)(I) and 2-acetoxy-2′-methyl-3,3′-bi(1,4-naphthoquinone) (IV). Compound I thus prepared is found to be identical with its natural sample. Compound IV, on hydrolysis with methanolic and ethanolic sulphuric acid, gives 2-methoxy-2′-methyl-3,3′-bi(1,4-naphthoquinone)(V) and 2-ethoxy-2′-methyl-3,3′-bi(1,4-naphthoquinone)(VII), respectively. Treatment of compound IV with methanolic potassium hydroxide affords 2-hydroxy-2′-methyl-3,3′-bi(1,4-naphthoquinone) (VI).

FIESER and Chang[1], in an attempt to improve a procedure for the synthesis of 2-methyl-1,4-naphthoquinone, discovered the methylation ability of lead tetraacetate when they oxidised naphthoquinone derivatives. They also observed that longer alkyl chains could be introduced in the quinone nucleus by employing higher homologues of the lead(IV) salts which could also be generated *in situ*. Recently, this method was employed for the synthesis of some medicinally important compounds[2]. In continuation of our work[3] on the synthesis of 3,3′-bi(2-methyl-1,4-naphthoquinone)(I), a naturally occurring binaphthoquinone isolated[4] from *Asplenium laciniatum*, we wish to report a new synthesis of I by the C-methylation of 2,2′-bi (1,4-naphthoquinone)(II) using lead tetraacetate.

2,2′-Bi(1,4-naphthoquinone)(II) was prepared by the dimerisation of 1,4-naphthoquinone in a mixture of alcohol, quinoline and acetic acid[5]. Compound II was then taken in glacial acetic acid containing malonic acid and treated with lead tetraacetate on a steam bath, the addition of the reagent being made in lots. The reaction mixture was worked up and the crude product obtained was then subjected to column chromatography over silica gel when four compounds A, B, C and D were obtained.

Compound A, which answered Craven's test[6] indicating a quinonoid proton in it, could not be analysed due to the paucity of the material. Compound B, which also gave positive Craven's test, was characterised to be 2-methyl-3,3′-bi(1,4-naphthoquinone)(III) on the basis of spectral data. Compound C did not respond to Craven's test, indicating the absence of the quinonoid proton. Its spectral data revealed its structure to be 3,3′-bi(2-methyl-1,4-naphthoquinone)(I). It was found to agree completely with its natural sample[4] (co-TLC, m.m.p., co-IR, and NMR). Compound D was characterised to be 2-acetoxy-2′-methyl-3,3′-bi (1,4-naphthoquinone)(IV) on the basis of its spectral studies, coupled with the observation that it did not answer the Craven's test. The formation of IV is due to the acetoxylation as well as methylation of II. Acetoxylation in quinones using lead tetraacetate in acetic acid has not been observed so far, which, however, has been observed in other systems[7]. To further prove the presence of an acetoxyl group in compound D, its hydrolysis was studied. It was found that with 5% methanolic sulphuric acid, compound D yielded 2-methoxy-2′-methyl-3,3′-bi(1,4-naphthoquinone)(V), instead of the expected 2-hydroxy-2′-methyl-3,3′-bi(1,4-naphthoquinone)(VI). Similarly with 5% ethanolic sulphuric acid, compound D gave 2-ethoxy-2′-methyl-3,3′-bi(1,4-naphthoquinone)(VII). However, hydrolysis of D with 2% methanolic potassium hydroxide yielded 2-hydroxy-2′-methyl-3,3′-bi(1,4-naphthoquinone)(VI), which could be reacetylated to D (IV).



I, $R_1 = R_2 = CH_3$; II, $R_1 = R_2 = H$; III, $R_1 = CH_3$, $R_2 = H$; IV. $R_1 = OCOCH_3$, $R_2 = CH_3$; V, $R_1 = OCH_3$, $R_2 = CH_3$; VI, $R_1 = OH$, $R_2 = CH_3$; VII, $R_1 = OC_2H_5$, $R_2 = CH_3$

EXPERIMENTAL PROCEDURE

Recorded melting points are uncorrected. UV spectra (λ_{max} in nm and log ϵ in parentheses) were recorded in ethanol on a Beckman DU-2 spectrophotometer. IR spectra (ν_{max} in cm^{-1}) were recorded in KBr on a Perkin-Elmer model 137 spectrophotometer. NMR spectra (chemical shift in δ, ppm) were recorded in $CDCl_3$ on a Varian A-60 spectrometer, using TMS as internal standard.

Reaction of 2,2′-bi(1,4-naphthoquinone)(II) with lead tetraacetate

A mixture of 2,2′-bi(1,4-naphthoquinone) (II, 2·5 g), malonic acid (2·5 g) and glacial acetic acid (50 ml)

was heated on a steam bath and then lead tetraacetate (3 g) was added to it. A brownish solid soon began to separate from the upper part of the reaction mixture with gas evolution. After heating for about half an hour, the precipitate had lightened in colour and appeared as a curdy white solid which filled the entire solution. After heating for another half an hour, a second lot of lead tetraacetate (3 g) was added to it with further gas evolution. The addition of lead tetraacetate was repeated after every hour till no gas evolved. A total of 24 g of lead tetraacetate was added. The reaction mixture was cooled and glycerol (1 ml) was added in order to destroy the excess of the reagent. It was then poured into water (500 ml) and the precipitated yellow material was filtered. It was washed with water and dried. The crude reaction product thus obtained was then subjected to column chromatography over silical gel when compounds A, B, C and D were obtained.

Compound A

It was eluted with petroleum ether: benzene (50 : 50) and crystallised from ethanol as yellow needles (30 mg), m.p. 300–04° (decomp.). It gave a positive Craven's test IR: 1670.

Paucity of the material, however, precluded its identification.

Compound B: 2-methyl-3,3'-bi(1,4-naphthoquinone), III

It was eluted with petroleum ether: benzene (25: 75) and crystallised from methanol as bright yellow needles (130 mg), m.p. 206–08°. It answered Craven's test. (Found: C, 76·4: H, 4·1; $C_{21}H_{12}O_4$ requires: C, 76·8; H, 3·7%). IR: 1665; UV: 248, 263 and 332 (4·54, 4·41 and 3·68). NMR: 2·16 (s, 3H, $C\underline{H}_3$–C =C–), 6·98 (s, 1H, –C$\underline{H}$=C–, quinonoid proton and 7·65–8·28 (m, 8H, Ar$\underline{H}$).

On the basis of the above observations, the structure of the compound B was assigned as 2-methyl-3,3'-bi (1,4–naphthoquinone)(III).

Compound C : 3,3'-bi(2-methyl-1,4-naphthoquinone), I

It was eluted with benzene and crystallised from ethanol as yellow crystals (400 mg), m.p. 244–46° (decomp.) and did not give Craven's test. It was characterised as 3,3'-bi(2-methyl-1,4-naphthoquinone)(I) on the basis of the following observations.

(Found: C, 77·1; H, 4·5; $C_{22}H_{14}O_4$ requires: C, 77·2; H, 4·1%).

IR : 1668;

UV : 246, 252, 262 and 335 (4·56, 4·61, 4·50 and 3·76).

NMR : 2·10 (s, 6H, 2 × –C=C–$C_3\underline{H}_3$) and 7·60–8·26 (m, 8H, Ar$\underline{H}$).

Its structure was confirmed by its direct comparison with the natural sample of (I).

Compound D: 2-acetoxy-2'-methyl-3,3'-bi(1,4-naphthoquinone), IV.

It was eluted with benzene : ethyl acetate (99 : 1) and crystallised from chloroform-methanol as yellow needles (400 mg), m.p. 288–91° (dccomp.). It did not answer Craven's test. (Found: C, 71·6; H, 3·7; $C_{23}H_{14}O_6$ *requires*: C,71·5; H, 3·6%). *IR: 1750*, 1670; UV: 258, 286 and 330 (4·56, 3·72 and 3·58); NMR: 1·98 (s, 3H, $C\underline{H}_3$–C=C–), 2·13 (s, 3H, $C\underline{H}_3$COO–C=C–) and 7·66–8·32 (m, 8H, Ar$\underline{H}$).

On the basis of the above data, the structure of compound D was deduced as 2-acetoxy-2'-methyl-3, 3'-bi(1,4-naphthoquinone)(IV), which was confirmed by its acid and alkaline hydrolysis.

Hydrolysis of compound D with methanolic sulphuric acid : Formation of 2-methoxy-2'-methyl-3,3'-bi(1,4-naphthoquinone(V)

Finely powdered compound D (80 mg) was refluxed with methanolic sulphuric acid (5%, 15 ml) for nearly 1 h. It was then concentrated to half of its volume and poured into water (100 ml). The whole was extracted with chloroform, the latter washed with water and dried over anhyd. Na_2SO_4. The solvent was evaporated and the residue was passed through a small column of silica gel for purification. The fraction eluted with benzene gave 2-methoxy-2'-methyl-3, 3'-bi(1,4-naphthoquinone)(V) which was crystallised from ethanol as light orange needles (45 mg), m.p. 269–71°. (Found: C, 73·9; H, 3·8; $C_{22}H_{14}O_5$ requires: C, 73·7; H, 3·9%).

IR : 1672; UV: 256, 259, 292 and 332 (4·52, 4·54, 3·97 and 3·73).

NMR: 1·90 (s, 3H, $C\underline{H}_3$–C=C–), 3·21 (s, 3H, $C\underline{H}_3$O–C=C–) and 7·65–8·31 (m, 8H, Ar$\underline{H}$).

Mass: m/e 358 (M^+, 7%), 343 (51%), 329 (38%), 328 (100%), 327 (23%), 315 (19%), 301 (10%), 300 (7%), 299 (13%), 271 (8%), 215 (17%), 213(13%), 202 (7%), 105 (7%), 77 (6%) and 76 (6%).

Hydrolysis of compound D with ethanolic sulphuric acid: Formation of 2-ethoxy-2'-methyl-3,3'-bi(1,4-naphthoquinone) (VII)

Finely powdered compound D (80 mg) was refluxed with ethanolic sulphuric acid (5%, 15 ml) for 1 h. It was worked up as described above and was purified by column chromatography over silica gel when the fraction eluted with benzene yielded 2-ethoxy-2'-methyl-3,3'-bi(1,4-naphthoquinone) (VII) which crystallised from ethanol as orange needles (40 mg), m.p. 222–25°. (Found: C, 74·4; H, 4·4 : $C_{26}H_{16}O_5$ requires : C, 74·2; H, 4·3%).

IR: 1680, 1660; UV: 257, 261, 290 and 330 (4·53, 4·54, 4·00 and 3·75).

NMR: 1·17 (t, J = 7·0 Hz, 3H, CH_3–CH_2–O–C =C–), 1·91 (s, 3H, CH_3– C=C–), 3·31 (q, J = 7·0 Hz, 2H, CH_3–CH_2–O–C=C–) and 7·62–8·25 (m,8H,ArH).

Hydrolysis of compound D with methanolic potash : Formation of 2-hydroxy-2′-methyl-3,3′-bi(1,4-naphthoquinone) (VI)

Compound D (150 mg) was heated with methanolic potassium hydroxide (2%, 10 ml) on a water bath. The heating was discontinued after 20 min when whole of the compound dissolved and the solution acquired a pink colour. It was cooled, diluted with water and acidified with dil HCl. The acidified solution was then extracted with chloroform, the latter washed with water and dried (anhyd. Na_2SO_4). It was concentrated and the residue crystallised from ethanol as light orange needles (50 mg), m.p. 294–98° (decomp.) (Found : C, 73·5; H, 3·9; $C_{21}H_{12}O_5$ requires: C, 73·3; H, 3·5%).

IR: 3400, 1668; 1650; UV : 253, 258, 290 and 335 (4·54, 4·61, 3·86 and 3·62).

NMR: $CDCl_3$ + $(CD_3)_2$ CO; 1·89 (s, 3H, CH_3–C= C–) and 7·63–8·28 (m,8H,ArH).

On the basis of the above data, the structure of this compound was assigned to be 2-hydroxy-2′-methyl-3,3′-bi(1,4-naphthoquinone (VI), since it could be re-acetylated to 2-acetoxy 2′-methyl-3,3′-bi(1,4-naphthoquinone) (IV) in pyridine solution.

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STUDIES ON THE *IN VITRO* EFFECT OF DIFFERENT BENZODIAZEPINES ON CHOLINESTERASE ACTIVITY OF HUMAN FETAL BRAIN

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ABSTRACT

An investigation on the *in vitro* effects of different benzodiazepines on human fetal brain cholinesterase activity at different gestational ages were studied. The enzyme activity was found to be inhibited in the cerebrum and cerebellum in a characteristic manner. Results of the kinetic pattern indicated that the catalytic function of the enzyme is mainly affected.

INTRODUCTION

CONSIDERABLE volume of evidence have accumulated regarding the pharmacological effects of different benzodiazepines[1–3]. Recently, this group of drugs has been used in early pregnancy for their minimal sedation and relief of tension. It has also been reported that diazepam can cross the placental barrier[4] in early pregnancy and thereby accumulate in fetal blood[5] and fetal tissues, particularly in brain[6–8]. Piercy *et al.*[9], observed that diazepam arrests the 'fetal respiratory like activity' by affecting fetal central nervous system (CNS), when injected intravenously during pregnancy. Different drugs[10–11] and stress conditions[12,13] which retard the normal brain development have been found to inhibit the acetylcholinesterase (AChE, EC 3·1·1·7) activity. Besides this, cholinesterase (ChE) plays important role in neurogenesis, maturation of synaptic organisations and in normal brain development[14–18]. However, no reports are available on the effects of different benzodiazepines on cholinesterase activity of developing brain. In the present communication, an attempt has been made to study the *in vitro* effects of different benzodiazepines like diazepam (DZ), desmethyldiazepam (DDZ), nitrazepam (NZ) and chlordiazepoxide (CZ) on cholinesterase activity of human fetal brain.