Studies on Quinones. VIII (1). The Application of Michael Adducts from 2-Hydroxy-1,4-naphthoquinones for the Preparation of Dihydronaphthopyrandiones (2)

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Dihydronaphthopyran-5,10-diones **7, 13, 16** and their corresponding dihydronaphthopyran-5,6-diones **8, 14, 17** have been obtained starting from Michael adducts of 2-hydroxy- and 2-hydroxy-7-methoxy-1,4-naphthoquinone (**1, 9**). An efficient synthesis of hydroxyhydrolapachol (**4**) employing 2-hydroxy-3-(3-oxobutyl)-1,4-naphthoquinone (**5**) is described.

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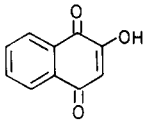
Introduction.

The dihydronaphthopyrandione system is a structural moiety present in a variety of naturally ocurring quinones *e.g.*, α- and β-lapachone (**2, 3**). Most of the reported methods for the synthesis of dihydronaphthopyrandiones involve initial C-3 alkylation of 2-hydroxy-1,4-naphthoquinone (**1**) with aldehydes (3,4) and with acyl peroxides (5,6).

It is known that the reaction of hydroxyquinone **1** with α,β-unsaturated ketones afforded the corresponding Michael adduct (7,8). This conjugated addition assembled, from our point of view, the structural components of potential α- and β-lapachone analogues. It is interesting to notice that the proper α- and β-lapachone (**2, 3**) have long been known by their antimicrobial (9) and antitumor activity (10,11).



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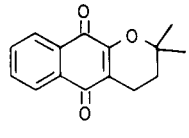

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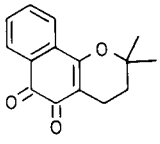

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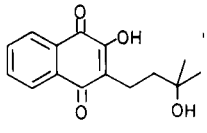

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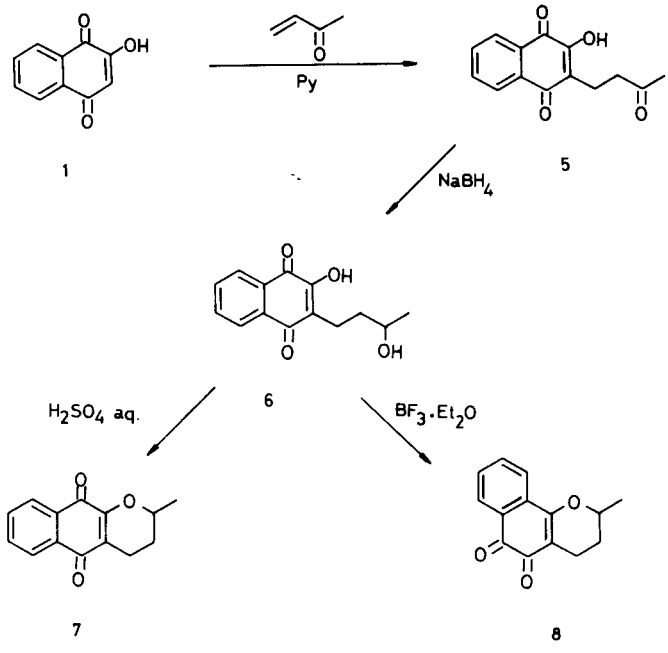
In this paper we report a new synthetic route to dihydronaphthopyrandiones related with α- and β-lapachone *via* Michael adducts. Furthermore we describe a convenient method for the synthesis of hydroxyhydrolapachol (**4**) which is a well known precursor of the lapachones **2** and **3** (12).

Results and Discussion.

The purpose of our work was to convert Michael adducts to dihydronapthopyrandiones by a sequence involving reduction and cyclization steps. The readily available Michael adduct **5** obtained by reaction of **1** with methyl vinyl ketone (8), was chosen as a model substrate for the desired sequence. Treatment of **5** with excess sodium borohydride in ethanol solution followed by air oxidation, afforded a yellow product identified as the hydroxyquinone **6**, in 91% yield.

Cyclization of the quinone **6**, in aqueous sulphuric acid, gave the α-lapachone analog **7** in 88% yield. Treatment of quinone **6** in benzene solution, containing boron trifluoride etherate produced the corresponding *o*-quinone **8**, in nearly quantitative yield (Scheme I). The structure of these heterocyclic quinones were established on the basis of their melting points (14) and spectral properties (15).

Scheme I



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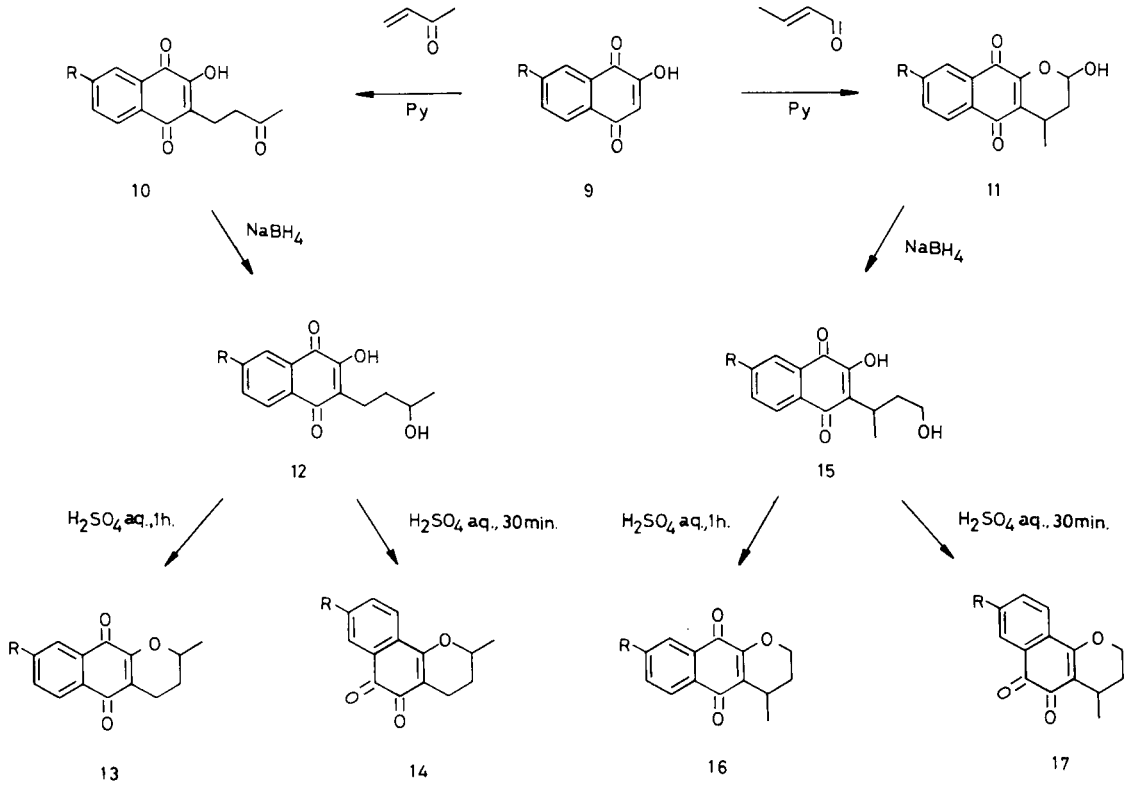
When the viability of the reduction-cyclization sequence to the synthesis of dihydronaphthopyrandiones



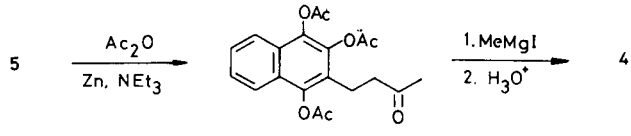
Scheme II (R=OMe)

was established, the extension of this model study was investigated. With this purpose the obtention of Michael adducts from 2-hydroxy-7-methoxy-1,4-naphthoquinone (**9**) and α,β-unsaturated carbonylic compounds was studied.

Hydroxyquinone **9** was prepared from 7-methoxy-1-tetralone according to the procedure of Baillie and Thomson (16). Reaction of **9** with methyl vinyl ketone in pyridine solution gave the respective Michael adduct **10** in 48% yield. Attempts to achieve conjugate addition of **9** to α,β-unsaturated aldehydes were not fully successful. In fact, treatment of **9** with acrolein, under a variety of conditions, invariably led to polymeric material. However, the reaction of the hydroxyquinone **9** with crotonaldehyde in pyridine solution afforded the expected Michael adduct (48%) in the hemiacetal form **11**.

Reduction of 2-hydroxy-3-(3-oxobutyl)-7-methoxy-1,4-naphthoquinone (**10**) under similar conditions as described for the transformation **5** → **6**, afforded the alcohol **12** in 80% yield. Subsequent treatment of the latter, under acid conditions, gave their corresponding dihydronaphthopyrandiones **13** and **14** in 60% and 90% yields, respectively. Applying the same sequence the dihydronaphthopyrandiones **16** and **17** were obtained from the Michael adduct **11** through the alcohol **15** (17). All these reactions are summarized in Scheme II.

Finally the synthesis of hydroxyhydrolapachol (**4**) from 2-hydroxy-3-(3-oxobutyl)-1,4-naphthoquinone (**5**) was attempted employing a similar sequence to that reported by Petit and Hougthon (6). The quinone **5** was reductively acetylated with zinc dust in acetic anhydride containing triethylamine to yield the triacetate **18** in 82% yield. Treatment of **18** with excess methylmagnesium iodide gave the expected hydroxyhydrolapachol (**4**) in 80% yield.



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In summary, we have developed a simple approach to dihydronaphthopyrandiones from 2-hydroxy-1,4-napthoquinones *via* Michael adducts. The synthesis of heterocyclic dihydropyrandiones based on these results are in progress.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler hot stage microscope. Unless otherwise stated, ir spectra were recorded in nujol mulls on a Perkin-Elmer 567 spectrometer. The uv-visible spectra

were taken in ethanol solution and recorded on a Pye-Unicam SP-1800 spectrometer. The ^{1}H-nmr spectra were measured in deuteriochloroform solution on a Varian XL-100 spectrometer using TMS as internal standard. Elemetal analyses were obtained courtesy of Instituto de Química Orgánica General (CSIC), Madrid, Spain.

2-Hydroxy-3-(3-hydroxybutyl)-1,4-napthoquinone (**6**).

To a solution of 2-hydroxy-3-(3-oxobutyl)-1,4-naphthoquinone (**5**) (500 mg, 2.05 mmoles) in 50 ml of ethanol was added sodium borohydride (500 mg, 15.63 mmoles). The mixture was heated under reflux for 1 hour. After cooling to room temperature the solution was poured into water (100 ml), acidified with diluted sulphuric acid (10%) and extracted with chloroform (2 × 50 ml). The combined extracts were concentrated under reduced pressure to give 460 mg of the yellow quinone **6** (1.87 mmoles), 91%). Recrystallization from hexane gave pure **6**, mp 92-93°; ir: 3350, 1660, 1635 cm^{-1}; uv: λ (log ε) 210 (4.22), 252 (4.40), 278 (4.30), 328 (3.48) nm; ^{1}H-nmr: δ 8.20-8.00 (m, 2H), 7.60-7.87 (m, 3H, 1H-exchangable with deuterium oxide), 3.74 (sext., J = 6 Hz, 1H), 2.75 (t, J = 7 Hz, 2H), 2.66-2.20 (br, 1H, exchangable with deuterium oxide), 1.72 (quart., J = 7 Hz, 2H), 1.24 (d, J = 6 Hz, 3H) ppm.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.31; H, 5.84.

3,4-Dihydro-2-methyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (**7**).

A solution of the hydroxyquinone **6** (80 mg, 0.325 mmole) in aqueous sulphuric acid (20%, 50 ml) was heated under reflux for 5 hours. By cooling the reaction mixture, 65 mg (0.285 mmole, 88%) of the dihydronaphthopyrandione **7** separated as yellow crystals, mp 121-122° (lit (14) mp 122.5°).

3,4-Dihydro-2-methyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione (**8**).

A solution of **6** (50 mg, 0.20 mmole) in dry benzene (15 ml) containing five drops of boron trifluoride-etherate was heated under reflux for 30 minutes. After this time the reaction mixture was evaporated to dryness. Crystallization of the residue from ethanol-cyclohexane gave 45 mg (0.19 mmole, 98%) of **8** as brick red needles, mp 163-164° [lit (14) mp 164°].

2-Hydroxy-3-(3-oxobutyl)-7-methoxy-1,4-napthoquinone (**10**).

2-Hydroxy-7-methoxy-1,4-naphthoquinone (**9**) (1 g, 4.90 mmoles) was dissolved in dry pyridine (50 ml). After the addition of methyl vinyl ketone (2 ml) the mixture was heated under reflux for 6 hours. The reaction mixture was cooled, acidified with hydrochloric acid and extracted with ether (3 × 50 ml). The combined organic solution was washed with water, dried over magnesium sulphate and concentrated. The remaining yellow solid was washed with ether to yield 0.65 g (2.37 mmoles, 48%) of **10**. Recrystallization from hexane-acetone gave analytically pure material; mp 154-155°; ir (potassium bromide): 3360, 1715, 1670, 1645 cm^{-1}; ^{1}H-nmr: δ 7.98 (d, J = 9 Hz, 1H), 7.55 (br. s, 1H, exchangable with deuterium oxide), 7.45 (d, J = 2 Hz, 1H), 7.15 (dd, J = 9, 2 Hz, 1H), 3.92 (s, 3H), 2.96-2.52 (m, 4H), 2.19 (s, 3H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.61; H, 5.15.

8-Methoxy-2-hydroxy-2*H*-4-methyl-3,4-dihydronaphtho[2,3-*b*]pyran-5-10-dione (**11**).

Quinone **9** (150 mg, 0.735 mmole) was dissolved in dry benzene containing triethylamine (1 ml) and crotonaldehyde (1 ml). The reaction mixture was heated under reflux for 3 hours. The resulting solution was evaporated to dryness and the residue chromatographed on silica gel using chloroform as eluent. This gave 90 mg (0.328 mmole, 44%) of pure **11** as a yellow solid; mp 161-163°; ir: 3350, 1667, 1612 cm^{-1}; ^{1}H-nmr: δ 8.00 (d, J = 9 Hz, 1H), 7.45 (d, J = 2 Hz, 1H), 7.20 (dd, J = 9, 2 Hz, 1H), 5.90 (br. s, 1H), 5.71 (t, J = 4 Hz, 1H), 3.96 (s, 3H), 3.18 (m, 1H), 2.04 (m, 2H), 1.34 (d, J = 6 Hz, 3H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.39; H, 5.33.

2-Hydroxy-3-(3-hydroxybutyl)-7-methoxy-1,4-naphthoquinone (**12**).

A mixture of the adduct **10** (200 mg, 0.73 mmole), ethanol (30 ml) sodium borohydride (200 mg, 6.25 mmoles) was heated at reflux for 1 hour. Work-up as described for the preparation of **6**, 163 mg. (0.59 mmole, 80%) of **12** was obtained. Recrystallization from hexane-tetrahydrofuran gave an analytically sample as yellow solid, mp 205°; ir : 3370, 1650 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.83 (d, J = 9 Hz, 1H), 7.32 (d, J = 2 Hz 1H), 7.21 (dd, J = 9, 2 Hz, 1H), 3.88 (s, 3H), 3.33 (br. s, 1H, exchangable with deuterium oxide), 3.56 (quint., J = 6 Hz, 1H), 2.50 (m, 2H), 1.26 (quart., J = 6 Hz, 1H), 2.50 (m, 2H), quart., J = 6 Hz, 2H), 1.09 (d, J = 6 Hz, 3H) ppm.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.88; H, 5.69.

8-Methoxy-2-methyl-2*H*-3,4-dihydronaphtho[2,3-*b*]pyran-5,10-dione (**13**).

A solution of the hydroxyquinone **12** (50 mg, 0.18 mmole) in aqueous sulphuric acid (20%, 50 ml) was heated under reflux for 1 hour. The resulting orange solution was cooled, diluted with water (50 ml) and extracted with ether (100 ml). The organic phase was washed with saturated aqueous bicarbonate, water and dried over magnesium sulphate. Concentration afforded a yellow solid which was recrystallized from hexane-acetone to give 28 mg of **13** (0.11 mmole), 60%), mp 163-164°; ir: 1680-1645 cm^{-1}; uv: λ (log ε) 262 (4.47), 294 (4.07), 337 (3.62) nm; ^{1}H-nmr: δ 7.91 (d, J = 9 Hz, 1H), 7.44 (d, J = 2 Hz, 1H), 7.08 (dd, J = 9, 2 Hz, 1H), 4.46 (m, 1H), 3.92 (s, 3H), 2.70-1.60 (m, 4H), 1.50 (d, J = 6 Hz, 3H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.58; H, 5.34.

8-Methoxy-2-methyl-2*H*-3,4-dihydronaphtho[3,4-*b*]pyran-5,6-dione (**14**).

A mixture of hydroxyquinone **12** (50 mg, 0.18 mmole), in hydrobromic acid (32%, 5 ml) was allowed to stand at room temperature for 30 minutes. The resulting deep red solution was diluted with water (50 ml) and worked up as mentioned in the synthesis of **13**. Recrystallization of the crude product from hexane-acetone gave 42 mg (0.162 mmole, 90%) of pure **14** as brick red needles, mp 171-172°; ir: 1700, 1640 cm^{-1}; uv: λ (log ε) 266 sh (4.44), 272 (4.47), 302 (3.74), 468 (3.21) nm; ^{1}H-nmr: δ 7.63 (d, J = 9 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.04 (dd, J = 9, 2 Hz, 1H), 4.51-4.13 (m, 1H), 3.80 (s, 3H), 2.87-1.91 (m, 4H), 1.54 (d, J = 6 Hz, 3H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_4$: , 69.75; H, 5.46. Found: C, 69.53; H, 5.32.

2-Hydroxy-3-(1-methyl-3-hydroxypropyl)-7-methoxy-1,4-naphthoquinone (**15**).

The same procedure described above for the synthesis of **12** was used to convert 50 mg (0.181 mmole) of the adduct **11** into 40 mg (0.144 mole, 79%) of quinone **15**. Crystallization of **15** from acetone-light petroleum ether (40-70°) gave yellow crystals, mp 98-99°. This compound led to **17** on standing and therefore an analytical sample can not be obtained; ir: 3400, 1660, 1620 cm^{-1}; ^{1}H-nmr: δ 8.05 (d, J = 9 Hz, 1H), 7.50 (d, J = 2 Hz, 1H), 7.22 (dd, J = 9, 2 Hz, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.74-3.16 (m, 3H), 2.26-2.50 (m, 3H), 1.34 (d, J = 6 Hz, 3H) ppm.

8-Methoxy-4-methyl-4*H*-3,4-dihydronaphtho[2,3-*b*]pyran-5,10-dione (**16**).

Quinone **15** (50 mg, 0.181 mmole) was cyclized by warming it in aqueous sulphuric acid (20%, 50 ml) under reflux for 1 hour. After the usual work-up the compound **16** was obtained as a yellow solid. Recrystallization from cyclohexane afforded 34 mg (0.132 mmole, 73%) of pure **16** as yellow platelets, mp 140-141°; ir: 1667, 1626 cm^{-1}; uv: λ (log ε) 261 (4.44), 293 (4.06), 337 (3.62) nm; ^{1}H-nmr: β (J = 9 Hz, 1H), 7.55 (d, J = 2 Hz, 1H), 7.15 (dd, J = 9, 2 Hz, 1H), 4.65-4.05 (m, 2H), 3.96 (s, 3H), 3.30-2.90 (m, 1H), 2.37-1.50 (m, 2H), 1.29 (d, J = 6 Hz, 3H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.71; H, 5.44.

8-Methoxy-4-methyl-4*H*-3,4-dihydronaphtho[3,4-*b*]pyran-5,6-dione (**17**).

The previous procedure described for the synthesis of **14** was employed to convert 50 mg (0.181 mmole) of **15** into the quinone **17**. Crystallization from cyclohexane afforded 35 mg (0.136 mmole, 75%) of pure **17** as red needles: mp 127-128°; ir: 1680, 1640 cm^{-1}; uv: λ (log ε) 264 sh (4.43); 270 (4.46), 300 (3.71), 464 (3.11) nm; ^{1}H-nmr: δ 7.70 (d, J = 9 Hz, 1H), 7.55 (d, J = 2 Hz, 1H), 7.14 (dd, J = 9, 2 Hz, 1H), 4.68-4.11 (m, 2H), 3.94 (s, 3H), 3.26-2.84 (m, 1H), 2.36-1.60 (m, 2H), 1.29 (d, J = 6 Hz,

3H) ppm.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.80; H, 5.61.

1,2,4-Tris(acetyloxy)-3-(3-oxobutyl)naphthalene (**18**).

A mixture containing the adduct **6** (500 mg, 2.05 mmoles), zinc dust (500 mg), five drops of triethylamine and acetic anhydride (15 ml) was heated under reflux. After 15 minutes, the solution was filtered and the precipitate washed with methanol. Removal of the solvent under reduced pressure and crystallization of the residue from methanol gave 630 mg, (1.69 mmoles, 82%) of triacetate **18**, mp 108-109°; ir: 1768, 1750, 1707 cm^{-1}; ^{1}H-nmr: δ 7.90-7.60 (m, 2H), 7.70-7.34 (m, 2H), 3.00-2.53 (m, 4H), 2.48 (s, 3H), 2.44 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H) ppm.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.57; H, 5.36.

Hydroxyhydrolapachol (**4**).

A solution of triacetate **18** (2.1 g, 564 mmoles) in dry benzene (50 ml) was added dropwise during 40 minutes to a stirred solution of methylmagnesium iodide [from methyl iodide (12 g) and magnesium (2.5 g) in dry ether (50 ml)]; stirring was continued for additional 8 hours at room temperature. The mixture was ice-cooled, *N*-hydrochloric acid (15 ml) was added and the aqueous layer was extracted with ether (2 × 50 ml). The combined organic extracts were dried over sodium sulphate and the solvent was removed under reduced pressure. Crystallization of the residue from cyclohexane gave 1.2 g (4.61 mmoles, 81%) of pure hydroxyhydrolapachol (**4**), mp 124° [lit (6), mp 125-125.5°]; ir: 3525, 3350, 1675, 1635 cm^{-1}; ^{1}H-nmr: δ 8.16-7.98 (m, 2H), 7.78-7.58 (m, 2H), 2.71 (t, J = 8 Hz, 2H), 2.25 (br, 1H, exchangeable with deuterium oxide), 1.71 (t, J = 8 Hz, 2H), 1.32 (s, 6H) ppm.

Acknowledgement.

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