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STRUCTURE OF A DIMERIC PIPERIDONE–ALDEHYDE CONDENSATION PRODUCT[a]

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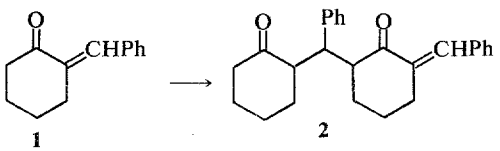
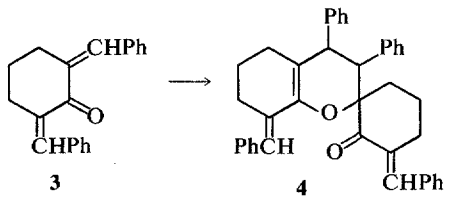
Abstract—The base-catalyzed condensation of benzaldehyde with 1-methyl-4-piperidone (**5**) gave two isomeric products which were dimers of 3-benzylidene-1-methyl-4-piperidone (**7**). Reactions of the dimers and their mass spectral data are examined on the basis of the X-ray structural analysis of the dibromo derivative of the dimer which was identified as 4-*p*-bromobenzylidene-9-*p*-bromophenyl-10a-hydroxy-2,7-dimethyl-2,7-diaza-10-oxa-1,2,3,4,5,6,7,8,8a,10a,-decahydroanthracene (**10b**).

Aldol condensations of aldehydes with cyclic ketones have been reported in several instances to yield products resulting from further reaction of the initially formed α,β-unsaturated ketones.[1-4] The pathways by which these reactions occur are not predictable. Tilichenko and Kharchenko[1] reported that 2-benzylidenecyclohexanone (**1**) on standing in aqueous base for several hours yielded quantitatively a self-condensation adduct of structure **2**,



1 **2**

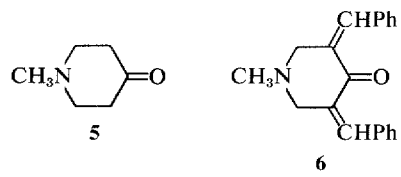


3 **4**

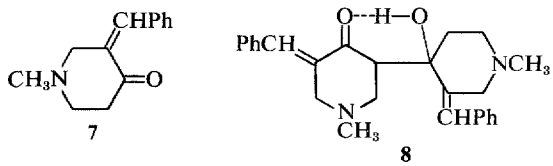
while House and Hortmann[2] described the dimerization of 2,6-dibenzylidenecyclohexanone (**3**) to produce **4**. Similar products have been isolated from reactions using furfural[3a,b] or other aldehydes with acyclic[3c] as well as other cyclic ketones.[4]

McElvain and Rorig[5] described the isolation of two products from the base-catalyzed condensation of 1-methyl-4-piperidone (**5**) with benzaldehyde. One product was identified as 3,5-dibenzylidene-1-methyl-4-piperidone (**6**). McElvain and Parker[6] showed later that the second product was not the expected 3-benzylidene-1-methyl-4-piperidone (**7**) but that it was a dimeric form of **7** for which they proposed the structure **8**. Such a product could arise by the aldol condensation of **7**.

These experiments suggest that the α,β-unsaturated ketones from the mixed aldol condensation can undergo a second aldol condensation to



5 **6**



7 **8**

[a]A portion of these results was presented before the Organic Division, 164th Meeting of the American Chemical Society, New York, August, 1972, Abstracts ORGN 114.

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yield products such as **8** or that they may give Michael addition products (e.g., **2**) or a type of Diels-Alder addition reaction with the carbonyl group as the dienophile to yield compounds such as **4**. In order to explore these reactions as possible routes for further synthetic studies, the reactions described by McElvain and his collaborators[5,6] were repeated. The condensation of **5** with benzaldehyde could be carried out to produce **6** as previously described,[5] or, with smaller quantities of aldehyde, the reaction gave two compounds of high molecular weight, one of which (**A**) was identical to that described by McElvain and Parker[6] while the second product (**B**) was obtained from the oil remaining after crystallization of **A**.

Spectral analysis of **A** and **B** was complicated by the insolubility of **A** in standard solvents for NMR spectral analysis and by the instability of solutions of **B**. The UV spectrum of **A** suggested the presence of the 1-phenylbutadiene chromophore (λ_{max} 290 nm (ϵ 26,000)), while that of **B** gave a similar band of reduced intensity (λ_{max} 287 nm (ϵ 15,500)). The IR spectrum of **A** in chloroform gave a sharp OH band at 3580 cm^{-1} and a broad band at 3200 cm^{-1}. A nujol mull gave a strong band at 1640 cm^{-1} which was weakened in chloroform solution and was at first assigned to a keto-enol equilibrium. This was supported by a positive ferric chloride test, but no enolic proton could be located in the NMR spectrum. In contrast, **B** gave no OH band but had a carbonyl stretch at 1720 cm^{-1}.

The NMR spectra of both **A** and **B** showed aromatic peaks as singlets at τ 2·75 and N-Me groups at τ 7·9. In the spectrum of **A**, a singlet at τ 2·95 may be assigned to a vinylic proton shifted downfield by the phenyl ring. A small band at τ 5·95 disappeared on treatment with deuterium oxide which confirmed the alcohol group.

Integration suggested a ratio of 5 phenyl:1 vinyl:3 methyl:1 OH, but the OH and vinyl protons were less than one proton in each case. A better fit gave 10:1:6:1 and 12 protons of the heterocyclic rings unassigned. The asymmetry of the structure gave rise to a more complicated spectrum than could be resolved, and the insolubility of **A** in other solvents precluded further study.

Derivatives of **A** included HCl and HBr salts, O-acetyl ester, a monoxime, and a picrate which analyzed by UV for one basic nitrogen per picrate anion. Similar derivatives were prepared for **B** excepting an oxime or picrate. The acetate derivatives (IR, 1755 cm^{-1}) were subjected to high pressure liquid chromatographic analysis and the product from **A** gave a single peak while that from **B** held at least five separable components. The instability of **B**-acetate and the isomerization of **B** to a mixture of **A** and **B** on heating, suggested that the acetates might be enolic and isomeric at the benzylidene methinyl group.

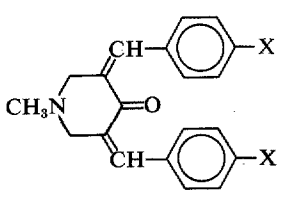
Catalytic hydrogenation of **A** gave mixtures of products which could not be separated satisfactorily even with TLC. It is probable that the reasonably flat molecule which was ultimately characterized by X-ray analysis was reduced from either side giving additional diastereomers. Similar problems arose from metal hydride reduction, and little information could be gleaned which was of value for structural elucidation.

The most valuable data were deduced from the mass spectral analysis, although attempts at formulating a structure for **A** were not successful. Loss of water gave a significant peak which confirmed the presence of an OH group. Significant peaks at M-31 and M-44 indicated the elimination of methylamine and carbon dioxide. The loss of CO_2 was especially significant and suggested that two oxygens were attached to a single carbon, but other data were not consistent with an acid derivative leaving a ketal or hemiketal as the only plausible functional groups at the oxygen center.

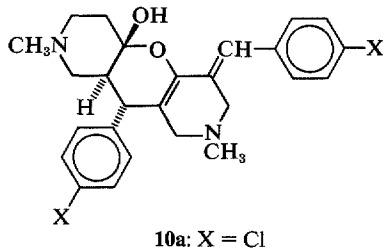
The mass spectral data do not identify the locations of the benzylidene groups. The structure proposed by McElvain and Parker[6] cannot accommodate the ketal unit nor a fragmentation that would produce a dibenzylidenepiperidone ion at *m/e* 289. The dimer **A** is cleaved symmetrically, and a significant monomeric peak suggests a facile cleavage.

The fragmentation of 3,5-dibenzylidene-1-methyl-4-piperidone (**6**) was examined under the same conditions and the major ions were the molecular ion at *m/e* 289, ions produced by elimination of CO and CH_2=NH at *m/e* 261 and 260, respectively, and the ion at *m/e* 246 from elimination of CH_3N=CH_2. Other key ions at *m/e* 184, 170, 131, 115, 103 and 91 are all present in significant amounts in the spectrum of **A**. The spectrum of the dimer is more complicated and shows additional significant peaks. A double positive charged ion at *m/e* 144–145 is abundant in the spectrum of the dibenzylidenepiperidone **6** but is present only in trace amounts in the mass spectrum of **A**.

The structure of **A** was finally resolved by X-ray crystallography. The instability of the hydrobromide salt of **A** precluded its use for this determination. The condensations of *p*-chloro- and *p*-bromobenzaldehyde with 1-methyl-4-piperidone (**5**) yielded the 3,5-diarylidene-1-methyl-4-piperidone derivatives (**9a**, **9b**) along with dimeric products (**10**) analogous to **A** discussed above. The products **9** were bright yellow in color while the dimers (**10**) were white. The IR spectra were similar to that of **A** and showed strong OH bands, no carbonyl bands, a diene band at 1650 cm^{-1}, and the *p*-disubstituted benzene bands. The UV spectra were very similar except that the broad peak at 283 nm is moved to longer wavelengths, about 295 nm for the chloro derivative **10a** and 300 nm for the bromo (**10b**) isomer. The mass spectral patterns were also strikingly similar with the same fragmentation pattern as



9a: X = Cl
9b: X = Br

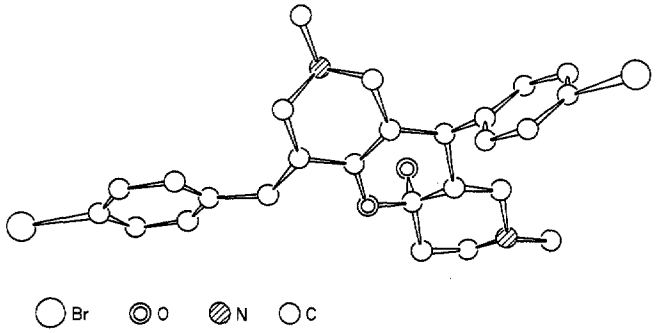


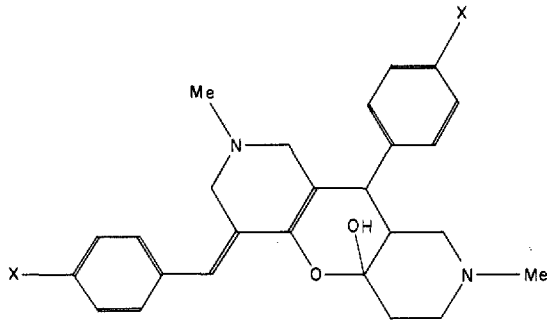
10a: X = Cl
10b: X = Br

shown by **A**. The molecular ions were clearly dimeric, and each gave low intensity monomeric ions.

X-ray diffraction measurements showed that the *p*-bromo derivative (**10b**) crystallizes in the orthorhombic space group P_{bca} with one dimer molecule plus one water molecule of crystallization per asymmetric unit ($Z = 8$). The lattice parameters are $a = 11{\cdot}530$, $b = 8{\cdot}399$, $c = 52{\cdot}930$ Å. The structure was solved by the heavy-atom method using 3075 observed independent reflexions which were measured on a Picker diffractometer. Refinement by block-diagonal least-squares calculations led to a final R value of 0·081.

The structure of **10b** is shown in Fig 1. The tricyclic system with the symmetrical substitution pattern of the hetero-atoms is unusual although one report of an aromatic derivative may be cited.[7] The chair-shaped piperidine ring is *trans*-fused to the dihydropyran ring which was the half-chair form. The tetrahydropyridine ring has the sofa form, with the nitrogen atom displaced about 0·7 Å from the mean plane through the other five atoms. The OH group is axial, while the two Me groups are equatorial. The phenyl group is quasi-equatorial and is *trans* with respect to the OH group. The tricyclic portion of the molecule (disregarding the sub-





Dimer A: X=H

Crystal structure: X=Br

Fig 1. (a) Crystal structure of the *p*-bromo derivative of dimer **A**. (b) Molecular formula corresponding to crystal structure where OH is *trans* to aromatic ring at C-9.

stituents) is relatively flat; the maximum deviation from the mean plane through the 14 atoms is 0·65 Å (by the N atom of the tetrahydropyridine ring). Full details of the X-ray analysis, including bond lengths and angles, will be published elsewhere.[8]

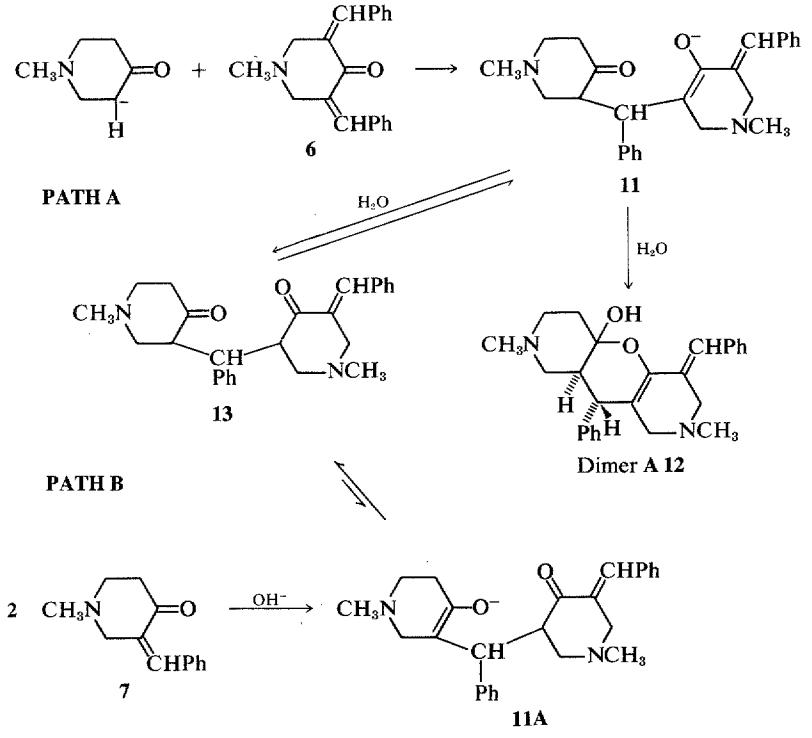
The hemiketal structure was unexpected but readily explains the lability of the functional group. The dimerization route may occur by a Michael addition of the piperidone anion of **5** to the dibenzylidene derivative **6** yielding the enolate anion **11** (Scheme, Path A). Addition of the oxyanion to the other CO group followed by protonation would yield **12**, while direct protonation of **11** would lead to the diketone **13**. The dimeric product **A** has the structure 4-benzylidene-9-phenyl-10a-hydroxy-2,7-dimethyl-2,7-diaza-10-oxa-1, 2, 3, 4, 5, 6, 7, 8, 8a, 10a-decahydroanthracene (**12**), and the structure of dimer **B** is probably 3-benzylidene-5-(α-1′-methyl-4′ - oxo - 3′ - piperidyl)benzyl - 1 - methyl - 4 - piperidone (**13**).

An alternative pathway for the formation of **12** cannot be excluded but seems less probable. It requires the condensation of two molecules of the monomer **7** (Path B) to yield **11a** which would produce the dimer **A** (**12**) via **13** and **11**.

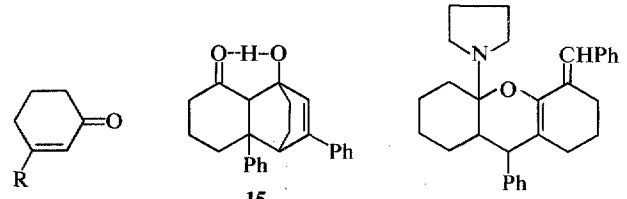
The formation of dimeric products by Michael addition reactions has been observed in basic condensations of 3-methylcyclohexenone (**14a**) and its substituted derivatives.[9-11] The reaction was initiated by anion formation of the 3-Me group. 3-Phenylcyclohexenone (**14b**), however, was found to produce a dimeric product[11] generated by the Michael addition of the C-4 anion of **14b** to the enone of a second molecule. Intramolecular cyclization by an aldol reaction would lead to **15**. Eight other possible structures can be suggested by combinations of these reactions, but the structure of **15** was reasonably established.[11] Examination of molecular models suggests that a hemiketal product from **14** analogous to dimer **A** would be more sterically crowded than **15**, probably due to the endocyclic enone system.

The formation of the dimeric compound **A** by Path A proposed in the Scheme has an interesting enamine counterpart reported recently. In the investigation of reactions of the enamines of cyclohexanone, Lewis *et al.*[12] isolated the aminoketal **16** from the enamine addition to 2,6-dibenzylidenecyclohexanone (**3**), but **16** was resistant to hydrolysis and failed to yield a hemiketal or diketone analogous to either **12** or **13**.

In view of the fact that 2-benzylidenecyclohexanone (**1**) can be isolated,[12-14] an alternative approach to the preparation of the heterocyclic analog, 3-benzylidene-1-methyl-4-piperidone (**7**) was considered. The condensation of the less basic compound 1-benzoyl-4-piperidone with benzaldehyde was reported by McElvain and



SCHEME



14a: R = CH_3
14b: R = C_6H_5

15 **16**

McMahon[15] to yield 1-benzoyl-3-benzylidene-4-piperidone. Hydrolysis of the amide and methylation should yield the desired product (**7**). Examination of the report,[15] however, revealed that the pattern in melting point which characterized the dimeric products reported previously[5,6] was also evident in this case. It is highly probable that the product melting at 240° from this condensation is in fact dimeric and is the N-benzoyl analog of **12**.

EXPERIMENTAL

M.ps were determined on a Hoover capillary m.p. apparatus and are corrected. IR spectra were obtained on Perkin-Elmer models 137, 337, and 700 spectrophotometers with the liquids as films and solids in KBr pellets unless otherwise stated. The NMR spectra were recorded on a Varian A-60 in deuterated chloroform. Chemical shifts are given in τ units relative to TMS. Microanalyses were determined on an F and M Model 180, C,H,N analyzer. UV spectral data were obtained with a Cary 15 spectrophotometer using ethanolic solutions.

4-Benzylidene-9-phenyl-10a-hydroxy-2, 7-dimethyl-2, 7-diaza-10-oxa-1, 2, 3, 4, 5, 6, 7, 8, 8a, 10a-decahydroanthracene (**12**). To a soln of freshly distilled **5** (11·3 g, 0·1 mol) in 60% EtOH (70 ml), benzaldehyde (10·6 g, 0·1 mol) and KOH (4·0 g) was added. The yellow to orange mixture was stirred magnetically for 2·5 hr. A seed crystal, obtained from an earlier reaction, was added to the soln and the mixture stirred at room temp for 8 hr and placed in a refrigerator overnight. The ppt was collected by suction filtration and washed with EtOH, reserving the mother liquor. The crude, pale yellow product, 4·3 g (21%) of **12**, melted at 211–216° dec.

The deep red mother liquor was heated to reflux temp and allowed to cool. The solid was collected by filtration, washed with EtOH, and dried, giving 2·5 g of **12** (12%), m.p. 215–218·5° dec. In a similar manner, three additional crops of product were obtained, 2·7 g (13%), m.p. 213–216° dec. Recrystallization from EtOH of all solid yielded nearly white crystals, 7·6 g, m.p. 222·5–224·5° dec (lit.[5] m.p. 224–225°).

A sample prepared for analysis by repeated recrystallization from EtOH melted at 223–225° dec; UV (*c* $3{\cdot}83\times10^{-5}$, EtOH) [nm(ϵ)] 283 ($2{\cdot}6\times10^4$); *m/e* 402 (M^+), 384, 371, 358, 302, 289, 260, 201, 184, 171, 131, 112, 70, 58. (Found: C, 77·88; H, 7·63; N, 6·92; M.W. 402 (*m/e*), 410, 402 (Rast). $C_{26}H_{28}N_2O_2$ requires: C, 77·58; H, 7·51; N, 6·96%, (M.W. 402)).

The *hydrobromide* was prepared in THF yielding a white solid which, after recrystallization from 95% EtOH, melted at 245–248·5° dec. The compound was not thermally stable, decomposing at room temp, and was not analyzed.

The *hydrochloride* was prepared in THF and recrystallized from EtOH-ether to yield a pale yellow solid, m.p. 239·0–241·0° dec (lit.[5] m.p. 243·5–244·5° dec).

The *picrate* was prepared in alcohol, and the solid was digested with boiling alcohol for 0·5 hr, yielding a yellow derivative, m.p. 170·5–172·5° dec. (Found: C, 53·16; H, 4·26. $(C_{19}H_{18}N_4O_8)_n$ requires: C, 53·02; H, 4·22%).

The molecular weight was determined *via* the UV absorption of the picrate anion, after the method of Cunningham *et al.*[16] (Found: 180, 170. Calc. for $C_{13}H_{11}NO$: 201). There is one basic nitrogen per picrate anion.

The *oxime* was prepared from the reaction of dimer A (**12**) with hydroxylamine HCl and excess NaOH in EtOH. The tan solid after recrystallization from EtOH-water melted at 130–134° and was probably a mixture of *syn* and *anti* isomers, IR (mull) 1590 cm^{-1} (C=N—OH). (Found: C, 72·14; H, 7·38; N, 13·14. $(C_{13}H_{16}N_2O)_2$ requires: C, 72·18; H, 7·47; N, 12·95%).

Attempts to prepare a semicarbazone or 2,4-dinitrophenylhydrazone derivative were unsuccessful.

The *O-acetyl derivative* was prepared by adding **12** (45·0 g, 0·224 mol) to a soln of Ac_2O (35 ml, 0·37 mol) in pyridine. The soln was heated under reflux for 2·5 hr, cooled, and poured into ice water with stirring. Dilute base was added to pH 8–10, and an orange oil precipitated. The aqueous layer was decanted, and cold water was added forming a semisolid which was crystallized from THF-ligroin. The product, 33·3 g (58%), melted at 178·5–180·5° after recrystallization from ligroin; UV (*c* $4{\cdot}72\times10^{-5}$, EtOH) [nm(ϵ)] 286·4 (31,000), 235 sh (8800), 227 sh (11,000). (Found: C, 75·31; H, 7·24. $C_{28}H_{32}N_2O_3$ requires: C, 75·65; H, 7·26%).

The acetate (1·2 g) was saponified with methanolic NaOH at room temp. The soln was poured into water and the ppt collected by filtration yielding 0·85 g (86%) of **12**, m.p. 216–219·5° dec. A mixture m.p. determination with an authentic sample melted at 217–223° dec. The IR and NMR spectra were identical.

3 - Benzylidene - 5 - (α - 1′ - methyl - 4′ - oxo - 3′ - piperidyl)benzyl - 1 - methyl - 4 piperidone (**13**). Addition of water to the mixture from which **12** had been isolated precipitated 8% of a bright yellow solid, m.p. 81–97·5°. Purification by acid-base extraction of a chloroform soln followed by extraction with EtOAc and ligroin yielded yellow crystals of the dimer **B** (**13**), m.p. 124–126·5°; UV (*c* $3{\cdot}03\times10^{-5}$) [nm(ϵ)]: 347 (732), 287 (15,500); IR (mull): no OH, 1720 (C=O), 765, 695 cm^{-1} (phenyl).

A soln of 10·9 g of **13** in 100 ml ether was heated under reflux for 12 hr and yielded 1·6 g of **12**, m.p. 221–223°, mixture m.p. 222–225°. A soln of 1 g of **12** in chloroform was irradiated with a Blak-Ray (UVL 22) for 2 hr and yielded a bright yellow solid, m.p. 120–220°, which was a mixture of the dimeric products.

The *hydrochloride* of **13**, m.p. 234–236° dec, was prepared in EtOH soln and recrystallized from EtOH-ether. After prolonged drying at 100° (0·1 Torr), it melted at 225–227·5° dec. (Found: C, 65·63; H, 6·88; N, 5·83. $(C_{13}H_{16}NOCl)_2$ requires: C, 65·67; H, 6·80; N, 5·89%).

Attempted reduction of **12** *and the acetate.* Catalytic hydrogenation of **12** in aqueous HCl over platinum oxide at 30 psig gave a mixture of reduction products which melted at 95–102°. Both OH and CO bands were found in the IR spectrum on repeated reduction, and no satisfactory separation was achieved by chromatographic means.

LAH reduction of **12** in THF at reflux temp gave a quantitative yield of product, m.p. 106–109°, whose m.p. varied after further attempts at purification.

The O-acetyl derivative was reduced over platinum oxide in acidified (pH 4) EtOH-water soln at 35 psig for 2·75 hr. The product (73%) melted at 84–93° and showed a CO absorption band at 1750 cm^{-1}. Column chromatography over alumina gave the ester, m.p. 93–95°, which was reduced with LAH. A quantitative yield of colorless product, m.p. 118–122°, was obtained, but analytical data failed to confirm the structure.

The products from all reductions appeared to be mixtures of isomers or to contain occluded hydrocarbon solvents. In several cases, the analytical data gave a high carbon content. Chromatographic methods failed to separate the apparent mixtures of isomers, and reduction methods were abandoned because of the multiplicity of possible reactions.

4-p-Chlorobenzylidene-9-p-chlorophenyl-10a-hydroxy 2,7-dimethyl-2,7-diaza-10-oxa-1, 2, 3, 4, 5, 6, 7, 8, 8a, 10a-decahydroanthracene (**10a**). To a clear soln of freshly distilled **5** (2·8 g, 0·025 mol) and 4-chlorobenzaldehyde (3·6 g, 0·025 mol) in EtOH (15 ml) was added, with stirring, KOH (0·8 g) in 2·5 ml water. Upon addition the soln turned dark yellow and a solid precipitated. EtOH (5 ml) was added, and the mixture was heated at 50–60° (bath temp) for 30 min and much of the solid redissolved. The warm soln was filtered yielding a yellow solid, **9a** (0·8 g; 16%), m.p. 171–179·5°. Recrystallization from EtOH gave an analytical sample, m.p. 177–179° (lit.[17] m.p. 174–176°); IR 1711 (C=O), 1651 and 1618 (diene), 823 and 808 (aryl). (Found: C, 67·25; H, 4·92; N, 3·84. $C_{20}H_{17}Cl_2NO$ requires: C, 67·05; H, 4·78; N, 3·90%).

The orange filtrate was concentrated, and aqueous EtOH (10 ml, 60%) was added. The hot soln was allowed to crystallize for one day. The white solid, 4·1 g, was collected by filtration, washed with 60% EtOH, and dried. Two recrystallizations from EtOAc gave the dimer **10a** as a white powder, m.p. 192–194° dec; UV (c $4{\cdot}67\times10^{-5}$, EtOH) [nm(ϵ)] 295 ($3{\cdot}2\times10^4$); *m/e* 470 (M^+), 439, 426 (M—CO_2), 384, 357, 329, 234, 218, 205, 178, 165, 151, 112, 70, 58. (Found: C, 66·54; H, 6·01; N, 5·67. $(C_{13}H_{14}ClNO)_2$ requires: C, 66·24; H, 5·99; N, 5·94%).

4-p-Bromobenzylidene-9-p-bromphenyl-10a-hydroxy-2,7-dimethyl-2,7-diaza-10-oxa-1, 2, 3, 4, 5, 6, 7, 8, 8a, 10a-decahydroanthracene (**10b**). To a clear soln of freshly distilled **5** (2·8 g, 0·025 mol) and 4-bromobenzaldehyde (4·2 g, 0·023 mol) in EtOH (15 ml) was added, with stirring, KOH (0·8 g) in 2·5 ml water. Solid precipitated, 5 ml EtOH was added and the mixture was heated at 50–60° (bath temp) for 25 min. The warm mixture was separated by filtration, and the yellow solid (0·3 g, 5%) was washed with EtOH and dried. Recrystallization from EtOH gave an analytical sample, m.p. 180–182°, **9b**. (Found: C, 53·75; H, 3·81; N, 3·00. $C_{20}H_{17}Br_2NO$ requires: C, 53·72; H, 3·83; N, 3·13%).

The orange filtrate was concentrated on a rotary evaporator to give a yellow semisolid to which was added 10 ml of 60% EtOH. The mixture was heated on a steam bath until soln was effected and set aside for 30 min yielding a white solid (**10b**), 4·6 g (70%), which was recrystallized from EtOAc and melted 196–198° dec; UV (c $1{\cdot}39\times10^{-5}$, EtOH) [nm(ϵ)] 296 ($3{\cdot}0\times10^4$); *m/e* 560 (M^+), 542, 529, 516 (M^+—CO_2), 472, 419, 368, 304, 280, 264, 250, 224, 195, 183, 170, 112, 70, 58. (Found: C, 55·40; H, 4·96; N, 4·77. $(C_{13}H_{14}BrNO)_2$ requires: C, 55·73; H, 5·03; N, 4·99%).

A portion of the powder was dissolved in a minimum of hot 95% EtOH, filtered, and set aside to evaporate slowly at room temp. Crystals which were expected to be suitable for X-ray studies were obtained. The white needles gave m.p. 193–197° dec. The water molecule could not be removed without destroying the crystal structure and was located in the X-ray crystal structure determination. (Found: C, 54·22; H, 5·38; N, 4·86. $C_{26}H_{28}Br_2N_2O_2\cdot H_2O$ requires: C, 53·99; H, 5·22; N, 4·83%).

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