Diazapolycyclic Compounds. XVI.
Nmr Stereochemical Studies on the Acid-Catalyzed Oxirane Ring-Opening Reactions of Unsubstituted, 2-Methyl- and 2,3-Dimethyl- Substituted 2,3-Epoxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-diones

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Addition reactions in acidic media have been performed on the oxirane ring of unsubstituted, 2-methyl- and 2,3-dimethyl- substituted 2,3-epoxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-diones. These reactions proceed in a stereospecific way; the Furst-Plattner rule of 1,2-*trans*-diaxial ring-opening is obeyed as can be deduced from the nmr stereochemical study on the terminal piperidazine-ring moiety of the addition products. Acylation shift effects and 1,3-*syn*-diaxial interactions have been utilized to assist stereochemical assignments. The geometry of the ring corresponds in most cases to a chair slightly distorted by the sp^2-sp^3 character of the nitrogens. Some of the less highly substituted among the cleavage products show certain peculiarities in their spectra, and are presumed to be in conformational equilibrium.

In previous work (1,2) we have described the synthesis of 8a,10a- and 4a,12a-diazatetracyclic systems by the Diels-Alder reaction of either phthalazine or benzo[g]phthalazine-1,4-diones with dienes derived from dimethylene-cyclohexane or 1,3-butadiene. In order to introduce at the terminal piperidazine-ring moiety of these compounds, different substituents capable of modifying their biological properties, the double bonds formed in the cycloadditions were epoxidized. The stereochemistry of the epoxides thus obtained has been studied by means of X-ray diffraction and nmr techniques (3). The present paper deals with some considerations concerning the stereochemistry observed for the products obtained by cleavage reactions in acidic media of epoxides **1, 2** and **3**, an especially interesting problem for us, since the structure-biological activity relationship in these compounds is now being analyzed.

By treatment of the epoxides **1-3** with dimethyl sulphoxide containing the boron trifluoride-etherate complex as an acid catalyst, followed by hydrolysis of the intermediate sulphoxonium salts (4,5), the 1,2-glycols **4a, 5a** and **6a** were formed in 50-60% yields. On the other hand, the reaction of **1** and **2** with hydrogen bromide in methanol solution afforded the bromohydrins **4b** and **6b** in 70% yields. In both cases, higher temperatures and longer reaction times are required with respect to what is usual in epoxides, because the reactivity of the three-membered ring is diminished in these compounds by the electron-

withdrawing effect of the carbonyl groups (6).

In order to assign the orientation of the substituents in the piperidazine ring, it should be noted that the stereochemical course in ring opening of epoxides in acidic media is strongly influenced by several factors, such as the structure of the starting epoxide, the solvent employed or the type of reactant. Then, various results can be obtained, ranging from a complete retention to a complete inversion of configuration (7), although in epoxides fused to six-membered rings inversion usually predominates (8,9).

In search of more nmr data to facilitate the stereochemical assignments, other 2,3-disubstituted diazatetracyclic derivatives have been prepared. Direct bromination of the double bond in the cycloaddition adducts of benzo[g]phthalazine-1,4-dione with 2,3-dimethyl-, 2-methyl- and unsubstituted 1,3-butadiene led to the corresponding *trans*-dibromides **4c, 5c** and **6c**. Moreover, the acetylated derivatives **4d, 4e, 5e** and **6d** were synthesized, as it was interesting to know the variations introduced in the chemical shifts of neighbouring protons to the hydroxy groups by a reaction in which the configuration is retained.

The adjoining tables list some of the chemical shifts and coupling constants obtained. Double resonance experiments have often been necessary for the assignment of the different signals to the corresponding protons. Spectra were recorded in different solvents when solubilities made it possible, and solvent shift effects have been measured
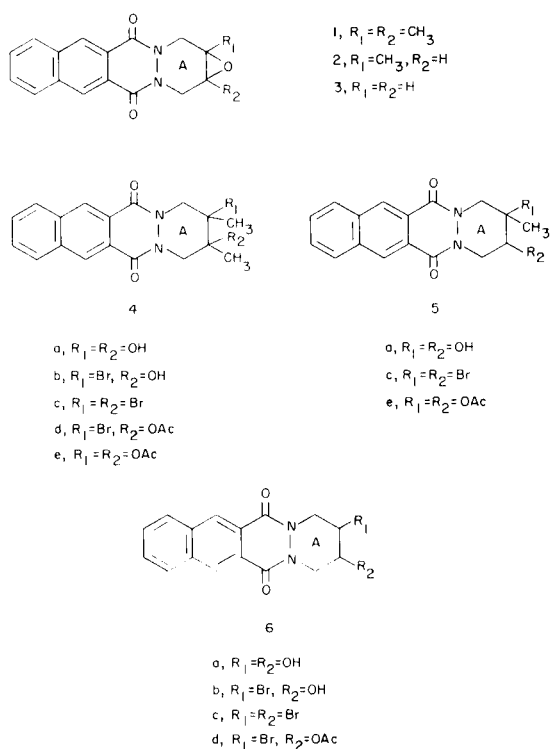
and discussed. From the solvent shifts and coupling constant values, conformational arrangements close to a chair form can be derived for the terminal piperidazine-ring moiety in solvents employed. These arrangements are consistent with the available X-ray diffraction data (10). For a proper analysis of the results obtained from the nmr spectra of all these compounds, a classification into three groups has been made, according to the number of substituents attached to the terminal piperidazine ring. This ring will be referred to as "ring A" in all the following discussions.

a) 2,2,3,3-Tetrasubstituted Derivatives (4).

Only one stereoisomer of compounds 4a-e was obtained in the reactions performed. The four methylene protons appear as an AB system when $R_1 = R_2$; two different AB systems are observed when $R_1 \neq R_2$. The geminal coupling constants are influenced by the nature of the vicinal substituents (Table 1) and, as could be expected, J gem diminishes with the electronegativity of the substituent (11). This fact was useful in the assignment of the signals in those spectra in which R_1 differs from R_2.

The effect of solvent change upon the chemical shifts of the methylene protons is exemplified in Table 2 for compound 4d. When deuterated chloroform is replaced by trifluoroacetic acid, the four protons of ring A are deshielded, but the two axial hydrogens are deshielded to a greater extent than the equatorial ones, and the chemical shift difference between axial and equatorial
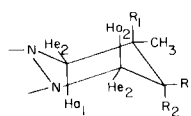
protons decreases. This can be explained by assuming that in the strong acid medium protonation of the amido groups occurs (12), and the anisotropic effect on the coplanar equatorial hydrogens is diminished. Replacement of deuterated chloroform by deuterated dimethyl sulphoxide has a shielding effect upon the equatorial protons (0.2-0.3 ppm), whereas the axial ones are almost unaffected by the solvent change, this fact being explained by the more ready access of the less hindered equatorial hydrogens to solvent molecules.

Evidence for the stereochemistry of the hydroxy groups has been obtained from the acetylation shift effect (13-15). As can be seen in Table 1, acetylation of the glycol 4a causes a downfield shift of 0.95 ppm in the adjacent equatorial hydrogens, while the axial ones show the same chemical shift in both the glycol and the acetylated derivative. Identical results are obtained in the acetylation of the bromohydrin 4b, with shifts of 1.0 ppm and 0.15 ppm for the axial and equatorial protons, respectively. From these data, an axial orientation is established for the hydroxy groups in 4a and 4b.

On the other hand, by studying the spectra corresponding to the three brominated derivatives 4b, 4c and 4d, 1,3-syn-diaxial interactions between the bromine atoms and protons of ring A are observed. Comparison between the chemical shifts of the methylene protons adjacent to -OH in the glycol 4a and the bromohydrin 4b indicates that the equatorial hydrogen H_{e_2} has identical values in both compounds, but the axial one, H_{a_2}, is deshielded by 0.15 ppm when the -OH in 1,3-diaxial arrangement is replaced by a bromine atom. This downfield shift cannot be explained on the basis of the inductive effect of the bromine, because in that case the two methylene protons would be equally affected; however, a 1,3-syn-diaxial interaction can be assumed, due to the bulky and polar nature of the new substituent. Further evidence is obtained by comparing the spectra of 4c and 4d: whereas the chemical shift of the equatorial hydrogen H_{e_1} adjacent to bromine is the same in both compounds, a downfield shift of 0.22 ppm is shown by the corresponding axial proton H_{a_1} when a new bromine atom providing a 1,3-diaxial H_{a_1}/ bromine interaction is attached to ring A. Similar nmr data are found for these interactions in diverse cyclohexane derivatives (16, 17). By analyzing the chemical shifts measured in all these compounds, it can be assumed that the bromine atom is the only one among the substituents involved in which this effect is significant.

From the arguments presented above, it can be concluded that these addition reactions to the oxirane ring can take place in a stereospecific way, and that the Furst-Plattner rule of trans-diaxial ring cleavage is obeyed. The properties of dimethyl sulphoxide as a solvent favoring the trans-diaxial opening (4) are also confirmed in this case.

Table 1

Nmr Data of Ring A in Compounds 4 and 5 (a)

Compound No.	R₁	R₂	R₃	δH_{e_1}	δH_{a_1}	δH_{e_2}	δH_{a_2}	δH_m	$J_{H_{e_1}H_{a_1}}$	$J_{H_{e_2}H_{a_2}}$	$J_{H_{e_2}H_m}$	$J_{H_{a_2}H_m}$
4a	OH	OH	CH₃	4.65	3.70	4.65	3.70	—	13.3	13.3	—	—
4b	Br	OH	CH₃	4.85	3.95	4.65	3.85	—	14.5	13.3	—	—
4c	Br	Br	CH₃	4.90	4.08	4.90	4.08	—	14.5	14.5	—	—
4d	Br	OAc	CH₃	4.90	3.90	5.60	4.00	—	14.5	14.8	—	—
4e	OAc	OAc	CH₃	5.60	3.70	5.60	3.70	—	14.8	14.8	—	—
5a	OH	OH	Hₘ	4.35	3.70	4.20	3.80	3.70	13.2	13.2	4.0	2.7
5c (b)	Br	Br	Hₘ	5.32	4.78	5.22	4.22	4.80	14.5	14.5	4.0	2.8
5e	OAc	OAc	Hₘ	5.30	3.80	4.95	3.85	5.55	14.0	14.0	3.5	3.0

(a) Spectra were measured in dimethyl sulphoxide at room temperature. Shifts are given in ppm. Coupling constants are given in Hz. (b) Compound 5c was recorded in trifluoroacetic acid (only coupling constant data are comparable).

Table 2

Effect of the Solvent Changes upon the Chemical Shifts of the Methylene Protons in 4d (ppm)

Proton	δ (Deuteriochloroform-DMSO)	δ (Trifluoroacetic Acid-Deuteriochloroform)
Hₑ₁	+ 0.22	+ 0.28
Hₐ₁	+ 0.07	+ 0.37
Hₑ₂	+ 0.30	+ 0.32
Hₐ₂	+ 0.05	+ 0.43

Finally, it is interesting to note that the deshielding effects observed in the hydrogens of ring A when the hydroxy groups are substituted by acetoxy or bromine can be rationalized in the following way: (a) a deshielding influence due to an acetoxy group (+ 1 ppm on the vicinal equatorial proton, negligible on the axial proton); (b) an inductive effect due to a bromine atom (+ 0.2-0.3 ppm on the adjacent methylene group, negligible on the other methylene group); (c) a spacial interaction due to an axial bromine (+ 0.2 ppm on the proton in a 1,3-diaxial arrangement).

Nevertheless, these parameters only correspond to a first approach and cannot be assigned exclusively to inductive or steric effects of the substituents, as the contribution of other geometrical and electronic factors (for example, presence of nitrogen atoms on the ring and lone-pairs associated with them) should also be considered. Moreover, these relations are valid when the spectra are measured either in chloroform or dimethyl sulphoxide solutions, but cannot be utilized in spectra recorded in tri-fluoroacetic acid, probably due to the protonating nature of this last solvent.

The chair conformation assumed for these compounds on the basis of the nmr data has been confirmed by X-ray crystallography (10). The torsional angles obtained for the

Table 3

Selected Torsional Angles (°) in the Ring A of 4a (a)

Atoms	Angles
C₁-C₂-C₃-C₄	54.5
C₂-C₃-C₄-N	-55.3
C₃-C₄-N-N	53.8
C₄-N-N-C₁	-50.8
N-N-C₁-C₂	52.3
N-C₁-C₂-C₃	-54.2

(a) Values obtained from X-ray diffraction data on this compound.

ring A corresponding to 4a (Table 3) are evidence of a chair form, although slightly distorted by the intermediate sp²-sp³ character of the amidic nitrogens (with bond angles of 113°). The two hydroxy substituents are found to be in a trans-diaxial orientation and the equatorial protons of the vicinal methylene groups fall fully into the deshielding plane of the nearby C = O, in accordance with the significant difference found between their chemical shifts and those of the corresponding axial ones.

b) 2,2,3-Trisubstituted Derivatives (5).

The spectra corresponding to these compounds exhibit an AB system formed by the protons adjacent to the

Table 4

Chemical Shifts of the Ring A Protons in Derivatives 6a-d (ppm)

Compound No.	R_1	R_2	$\delta\ CH_2$	$\delta\ CH$
6a	OH	OH	4.20	3.80
6b	Br	OH	4.55 (H_{e_1})	4.38 (H_{m_1})
			4.35 (H_{a_1})	4.05 (H_{m_2})
			4.42 (H_{e_2})	
			4.05 (H_{a_2})	
6c	Br	Br	4.67	4.67
6d	Br	OAc	4.50	4.50 (H_{m_1})
				5.40 (H_{m_2})

methyl group (H_{e_1} and H_{a_1}) and an ABX system due to the methinic H_m and the nearby methylenic H_{e_2} and H_{a_2}. An axial acetylation shift is again observed when comparing the chemical shifts (Table 1) of the four methylene protons, since only the equatorial hydrogens H_{e_1} and H_{e_2} suffer a pronounced downfield shift (0.95 and 0.75 ppm, respectively) when the hydroxy groups are acetylated.

Additional proof regarding the *trans*-diaxial character of 5a and 5b can be derived from the presence of the methine proton H_m. The small value found for the coupling constant between H_m and the axial H_{a_2} (2.7 and 3.0 Hz for, respectively 5a and 5e) indicates an equatorial orientation for H_m. The very large downfield shift (+ 1.85 ppm) experienced by H_m in the acetylation of 5a can only be explained by supposing that this proton is deshielded both by the geminal and vicinal acetoxy groups. Consequently, H_m and the vicinal acetoxy bear an equatorial-axial relationship.

The fact that the axial-equatorial coupling $J_{H_{a_2}H_m}$ is smaller than the equatorial-equatorial one $J_{H_{e_2}H_m}$ in all these compounds, contrary to what would be expected from the Karplus relationship, can be easily explained on the basis of the *trans*-coplanarity shown by H_{a_2} and the corresponding electronegative oxygen atom. It is well known that the aminorating influence of an electronegative substituent X upon J *vic* is greatest when X is transcoplanar to one of the coupling protons (18). Similar variations in the J *vic* values have been found in a previous work (2) for analogous diazatetracyclic derivatives.

Long-range W couplings $H_{e_1}/C_1/C_2/C_3/H_m$ (J = 0.6-0.8 Hz)are observed in the three compounds. The coupling constant values of ring A protons in 5a and 5e show clear analogies with those of the *trans*-dibromo derivative 5c. Both of these facts are also consistent with the assignments established above.

Comparison of the chemical shift data obtained for the methylene groups of these compounds with the corresponding ones for the derivatives 4 shows that $\delta\ H_e$ -$\delta\ H_a$ values are significantly smaller in the trisubstituted rings

($\delta\ H_a$ increases while $\delta\ H_e$ diminishes), the differences being more pronounced in the methylene adjacent to the methinic proton H_m. These results are consistent with a modification in the configuration of ring A when the methyl group is substituted by hydrogen. Steric interactions are reduced, and H_m moves closer to the vicinal OH, causing the $O-C_3-C_4-O$ torsional angle to decrease. This change brings the axial methylenic protons nearer to the deshielding plane of the C = O amidic group, while the corresponding equatorial ones move slightly away. As could be expected, this effect is more appreciated in the methylene adjacent to the carbon atom in which the substitution takes place. All this can be summarized by assuming that when the steric requirements of the substituents are less strict, the distorting effect of the amide groups predominates, and the planarity of the ring increases as it moves away from the chair form. Similar configurational modifications have been observed when introducing different substituents in other positions of the ring A, and will be discussed elsewhere.

c) 2,3-Disubstituted Derivatives (6).

Unexpectedly, significant differences are found when comparing the nmr spectra of the derivatives 6a-d, and those of the previously studied compounds. In the latter, axial and equatorial methylene protons are easily differentiated by their chemical shifts, mainly due to the anisotropic effect of the amidic C = O groups upon the nearby equatorial protons (19). However, both methylenic hydrogens form a unique narrow signal in compounds 6a-d, with the only exception of the bromohydrin 6b, which exhibits similar characteristics to those found in the methyl-substituted compounds.

The chemical shifts of the ring A protons for these compounds are summarized in Table 4. Table 5 lists both the width at half-height (W1/2) of the methylene signals for 6a, 6c and 6d, and the chemical shift difference ($\Delta\delta$) between axial and equatorial methylene protons in the corresponding tetrasubstituted compounds. From all these data, which cannot be justified by molecular symmetry, it can be assumed that some kind of conformational equilibrium occurs. The rigid character of the residual

portion of the molecule attached to ring A suggests that this equilibrium should take place through nitrogen inversion, a process which is frequently found in substituted piperidazines (20,21). The different behaviour shown by these derivatives with respect to the tri- and tetra-substituted compounds may be explained by considering that the steric and energetic requirements for the equilibrium must be diminished in the less highly substituted derivatives 6.

As mentioned above, an exception is that of the bromohydrin 6b, which exhibits not only a clear difference between axial and equatorial protons (with J gem of 11.0 and 9.5 Hz for protons adjacent, respectively to bromine and the hydroxy group), but also a 1,2-*trans*-diaxial arrangement of the bromine and hydroxy groups, as can be derived from the small values found for the vicinal coupling constants between the methylene and methine protons (J *vic* < 3 Hz in all cases).

Unfortunately, studies of the low-temperature nmr spectra for a more detailed analysis of the conformational changes could not be performed, owing to the insolubility of these compounds in the usual solvents at temperature below 0°.

Table 5

Parameters of the Methylene Group in Compounds 4 and 6

Compound No.	Δ δCH₂	Compound No.	W½ CH₂
4a	0.95 ppm	6a	8 Hz
4c	0.82 ppm	6c	4 Hz
4d	1.00 ppm	6d	9 Hz
	1.60 ppm		

EXPERIMENTAL

Melting points are uncorrected, and were determined in capillary tubes. Ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Nmr spectra were obtained with Perkin-Elmer R-12 and Varian XL-100 spectrophotometers, using TMS as internal standard. Chemical shifts are given in ppm (δ scale). Thin layer chromatography plates were prepared with silica gel Merck G.

2,3-Dihydroxy-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (5a).

To a solution of the epoxide 2 (0.5 g. or 0.0016 mole) in 30 ml. of freshly distilled dimethyl sulphoxide, 2 ml. of the boron trifluoride-etherate complex were added. The mixture was stirred at 70-80° for eight hours, and for 24 hours more at room temperature. The dark-red solution obtained was poured over 200 ml. of ice-water and then left in the refrigerator overnight. The precipitate thus formed was filtered and chromatographed (preparative tlc) using an ethyl acetate/benzene/chloroform mixture (85/10/5) as eluent to give a white solid which recrystallised from water affording 0.28 g. (53% yield) of pure 5a, m.p. 206-207°; ir (potassium bromide): ν max 3500-3100 (associated OH), 2940, 1645 (C = O), 1620, 1465, 1395, 1280, 1095 (tertiary OH), 1035 (secondary OH), 910, 765 cm⁻¹.

Anal. Calcd. for C₁₇H₁₆N₂O₄: C, 65.38; H, 5.12; N, 8.97. Found: C, 65.60; H, 4.99; N, 8.89.

2,3-Dihydroxy-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (4a).

This compound was prepared as described above for 5a from 0.65 g. (0.0020 mole) of the epoxide 1 in 25 ml. of dimethyl sulphoxide, to give a solid which recrystallised from water in white needles affording 0.36 g. (52% yield) of 4a, m.p. 306-307°; ir (potassium bromide): ν max 3600-3200 (OH), 2950, 1645 (C = O), 1620, 1465, 1395, 1060 (tertiary OH), 915, 765, 730 cm⁻¹.

Anal. Calcd. for C₁₈H₁₈N₂O₄: C, 66.25; H, 5.52; N, 8.57. Found: C, 66.52; H, 5.40; N, 8.82.

2,3-Dihydroxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (6a).

This compound was prepared as described above for 5a from 0.60 g. (0.0018 mole) of the epoxide 3 in 30 ml. of dimethyl sulphoxide. Thin-layer preparative chromatography of the reaction mixture in benzene/ethanol (50/1) as eluent gave a solid which recrystallised from water affording 0.3 g. (60% yield) of 6a, m.p. 235-236°; ir (potassium bromide): ν max 3600-3100 (associated OH), 2930, 1645 (C = O), 1620, 1465, 1370, 1210, 1080 (secondary OH), 915, 765, 725 cm⁻¹.

Anal. Calcd. for C₁₆H₁₄N₂O₄: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.39; H, 4,63; N, 9.46.

2-Bromo-3-hydroxy-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (4b).

To a solution of 60% aqueous hydrobromic acid (3 ml.) in 10 ml. of ethanol, 0.5 g. (0.0016 mole) of the epoxide 1 were added. The suspension was stirred at 50° for 48 hours. After cooling at room temperature, the precipitate was filtered and washed repeatedly with water to free it from acid. Recrystallisation from water furnished 0.38 g. (60% yield) of the title compound, m.p. 218°; ir (potassium bromide): ν max 3650-3100 (associated OH), 3030, 2930, 1645 (C = O), 1625, 1460, 1360, 1215, 1135, 1065 (tertiary OH), 930, 765 730 cm⁻¹.

Anal. Calcd. for C₁₈H₁₇BrN₂O₃: C, 55.53; H, 4.37; Br, 20.56; N, 7.19. Found: C, 55.66; H, 4.51; Br, 20.40; N, 7.30.

2-Bromo-3-hydroxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (6b).

This compound was prepared as described above for 4b from 0.4 g. (0.0012 mole) of the epoxide 3 in 10 ml. of ethanol containing 2.5 ml. of 60% aqueous hydrobromic acid. Thin-layer preparative chromatography of the reaction mixture in benzene/ethanol (10/1) as eluent gave a solid which crystallised from water affording 0.35 g. (70% yield) of 6b, m.p. 227°; ir (potassium bromide): ν max 3400 (OH), 2915, 1660 (C = O), 1625, 1465, 1350, 1310, 1205, 1040 (secondary OH), 920, 765, 695 cm⁻¹.

Anal. Calcd. for C₁₆H₁₃BrN₂O₃: C, 53.18; H, 3.60; Br, 22.16; N, 7.75. Found: C, 53.47; H, 3.82; Br, 21.86; N, 7.73.

2,3-Dibromo-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (4c).

To a stirred solution of 2,3-dimethyl-4a,12a-diaza-1,4,4a,5,12,12a-hexahydronaphthacene-5,12-dione (2) in freshly distilled dimethyl sulphoxide (0.7 g. or 0.0024 mole in 30 ml.), 0.4 g. of bromine (0.0024 mole) in 10 ml. of dimethyl sulphoxide were added dropwise. The mixture was heated at 40° for three hours and allowed to cool at room temperature once the solution was completely decolorised. The resulting oil was poured over 100 ml. of ice-water and stirred vigorously for 20 minutes. The pale yellow precipitate formed was filtered and washed repeatedly with water to free from acid. Recrystallisation from ethanol gave 0.9 g. (79% yield) of 4c, m.p. 176-177°; ir (potassium bromide): ν max 3050, 2900, 1665 (C = O), 1630, 1385, 1275, 1215, 760, 725, 715 cm⁻¹.

Anal. Calcd. for C₁₈H₁₆Br₂N₂O₂: C, 47.79; H, 3.54; Br, 35.40; N, 6.19. Found: C, 47.87; H, 3.71; Br, 35.68; N, 6.21.

2,3-Dibromo-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (5c).

This compound was prepared as described above for 4c from 0.5 g. (0.0018 mole) of 2-methyl-4a,12a-diaza-1,4,4a,5,12,12a-hexahydronaphth-

acene-5,12-dione (2) in 25 ml. of dimethyl sulphoxide. Recrystallisation from ethanol afforded 0.75 g. (93% yield) of **5c**, m.p. 189-190°; ir (potassium bromide): ν max 2990, 1670 (C = O), 1635, 1390, 1365, 1220, 940, 920, 770 cm⁻¹.

Anal. Calcd. for $C_{17}H_{14}Br_2N_2O_2$: C, 46.57; H, 3.20; Br, 36.53; N, 6.39. Found: C, 46.31; H, 3.14; Br, 36.82; N, 5.98.

2,3-Dibromo-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**6c**).

This compound was prepared as described above for **4c** from 0.7 g. (0.0028 mole) of 4a,12a-diaza-1,4,4a,5,12,12a-hexahydronaphthacene-5,12-dione (2) in 30 ml. of dimethyl sulphoxide. Recrystallisation from acetone afforded 0.95 g. (87% yield) of **6c**, m.p. 228°; ir (potassium bromide): ν max 3040, 1655 (C = O), 1625, 1465, 1345, 1285, 1145, 960, 915, 895, 765, 715, 665 cm⁻¹.

Anal. Calcd. for $C_{16}H_{12}Br_2N_2O_2$: C, 45.28; H, 2.83; Br, 37.83; N, 6.60. Found: C, 45.51; H, 2.94; Br, 38.13; N, 6.54.

2-Bromo-3-acetoxy-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**4d**).

To a solution of **4b** in freshly distilled isopropenyl acetate (0.3 g. or 0.0008 mole in 20 ml.), 0.05 g. of *p*-toluensulphonic acid were added. The reaction mixture was refluxed for three hours, cooled to room temperature and successively washed with 5% aqueous sodium bicarbonate and water. Then, the organic layer was dried over magnesium sulphate and the excess of isopropenyl acetate evaporated under reduced pressure. The oily residue was chromatographed by preparative tlc eluted with a mixture ether/petroleum ether/chloroform (2/7/1) to give 0.25 g. (76% yield) of pure **4d**, m.p. 198°; ir (potassium bromide): ν max 3015, 1750 (C = O ester), 1665 (C = O amide), 1630, 1455, 1385, 1265, 1235 (C-O acetate), 1110, 920, 755 cm⁻¹.

Anal. Calcd. for $C_{20}H_{19}BrN_2O_4$: C, 55.68; H, 4.41; Br, 18.56; N, 6.49. Found: C, 55.64; H, 4.66; Br, 18.86; N, 6.47.

2-Bromo-3-acetoxy-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**6d**).

This compound was prepared as described above for **4d** from 0.2 g. (0.0006 mole) of **6b** in 20 ml. of isopropenyl acetate. Thin-layer preparative chromatography of the residue in benzene/ethanol (10/1) as eluent furnished 0.2 g. of pure **6d**, m.p. 188° (90% yield); ir (potassium bromide): ν max 3040, 1750 (C = O ester), 1660 (C = O amide), 1630, 1460, 1270, 1225 (C-O acetate), 1085, 970, 915, 755 cm⁻¹.

Anal. Calcd. for $C_{18}H_{15}BrN_2O_4$: C, 53.60; H, 3.73; Br, 19.86; N, 6.96. Found: C, 53.87; H, 3.74; Br, 20.16; N, 7.18.

2,3-Diacetoxy-2,3-dimethyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**4e**).

This compound was prepared as described above for **4d** from 0.25 g. (0.0008 mole) of **4a** in 15 ml. of isopropenyl acetate. Recrystallisation of the residue from ethanol afforded 0.25 g. (85% yield) of **4e**, m.p. 244-245°; ir (potassium bromide): ν max 3060, 1745 (C = O acetate), 1655 (C = O amide), 1630, 1465, 1280, 1235 (C-O acetate), 915, 760 cm⁻¹.

Anal. Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.39; H, 5.36; N, 6.82. Found: C, 64.17; H, 5.49; N, 6.81.

2,3-Diacetoxy-2-methyl-4a,12a-diaza-1,2,3,4,4a,5,12,12a-octahydronaphthacene-5,12-dione (**5e**).

This compound was prepared as described above for **4d** from 0.4 g.

(0.0013 mole) of **5a** in 20 ml. of isopropenyl acetate. Recrystallisation of the residue from ethanol afforded 0.45 g. (88% yield) of the title compound, m.p. 213-214°; ir (potassium bromide): ν max 3030, 1755 (C = O acetate), 1665 (C = O amide), 1630, 1385, 1235 (C-O acetate), 1040, 755 cm⁻¹.

Anal. Calcd. for $C_{21}H_{20}N_2O_6$: C, 63.64; H, 5.00; N, 7.07. Found: C, 63.87; H, 4.79; N, 6.82.

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