Transannular cyclization reactions of cyclooctane-1,5-dione and 5-ethoxycarbonylmethylenecyclooctanone upon treatment with diamines. An efficient one-pot synthesis of substituted 2,6-diazatricyclo[5.3.3.$0^{1,6}$]- and 2,5-diazatricyclo[4.3.3.$0^{1,5}$]-alkanes and a study of their acetylation products

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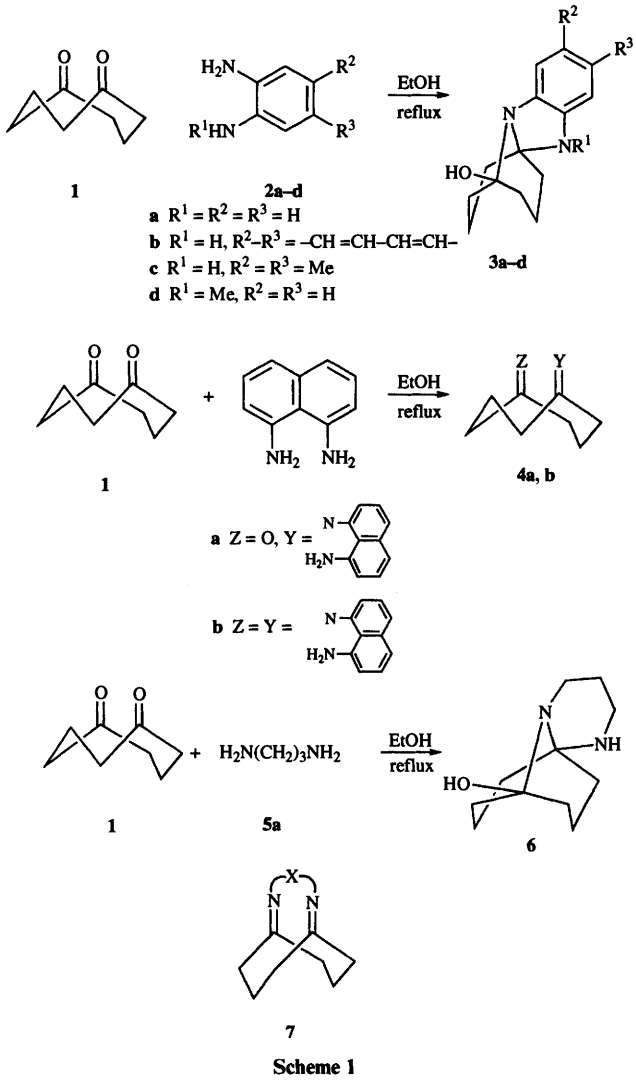
Cyclooctane-1,5-dione 1 undergoes transannular cyclization upon treatment with 1,2-diaminoarenes 2a–d or 1,3-diaminopropane 5a to afford the 2,5-diazatricyclo[4.3.3.$0^{1,5}$]dodecan-6-ols 3a–d or 2,6-diazatricyclo[5.3.3.$0^{1,6}$]tridecan-7-ol 6 respectively, in moderate to good yields. The ethoxycarbonylmethyldiazatricyclo analogues 22a,b result from a similar reaction of 5-ethoxycarbonylmethylenecyclooctanone 19 with diaminoalkanes 5a,b. Acetylation of tricyclo compound 3d leads, among others, to the unexpected product 2-diacetylmethylidene-1-(5-oxocyclooct-1-en-1-yl)-3-methyl-2,3-dihydrobenzimidazole 12.

The existence of through-space transannular interactions, due to the close proximity of the carbonyl or methylene groups of 1,5-disubstituted oxo- or methylene-cyclooctanes has been demonstrated by ^{13}C NMR spectroscopy[1,2] and an *ab initio* MO study.[2] It has also been established for the bicyclo[3.3.1]-nonanes[3] obtained as products from the reactions of these compounds with electrophiles, as well as for the [3.3.2]propellanes[4] formed through photocyclization reactions.

Continuing our interest in the transannular cyclizations of hydrazono and oximino derivatives of cyclooctane-1,5-dione[5] and 5-ethoxycarbonylmethylenecyclooctanone,[6] we have undertaken an investigation of the reactions of **1** and **19** with 1,2-diaminoarenes and 1,2- or 1,3-diaminoalkanes, intending the synthesis of heterotricyclic products. Transannular cycloketalization is known to occur for some rigid bicyclo[3.3.1]nonanediones[7a,b] as well as for some 'cage' pentacyclodiketones[8a–g] and their imino derivatives upon treatment with nucleophiles, under basic conditions. The ketal hydroxy group is displaced[7a] by the nucleophile under further treatment. This being the case, we anticipated that the reaction of one amino group of the diamines **2** or **5** with a carbonyl group of the mesocyclic system **1** would initially result in the formation of analogous transannular cycloketalization products of type **14**, or eventually in the formation of mono-imino derivatives of type **4**, in cases where no transannular reaction occurred. Sequential intramolecular nucleophilic action of the remaining free amino group of the diamine moiety on the ketal carbon atom of **14** or to the imino carbon of **4** induced by an electrophile would cause the formation of tricyclic products through a transannular reaction. The bicyclo[3.3.*n*]diimino derivatives of type **7** were also considered possible products, particularly from the reactions of **1**. Compounds **7** would be regarded as the diaza analogues of mesocyclic bridged dienes[9] and like them, would be expected to be transformed to tricyclic compounds by treatment with electrophilic or nucleophilic reagents. We report herein the successful implementation of this approach.



Scheme 1

Results and discussion

Boiling of equimolar amounts of cyclooctane-1,5-dione **1** and 1,2-diaminoarene **2a–d** in ethanol solution resulted in the formation of the 2,5-diazatricyclo[4.3.3.$0^{1,5}$]dodecan-6-ols **3a–d** (Scheme 1). Under similar conditions, 2,6-diazatricyclo[5.3.3.$0^{1,6}$]tridecan-7-ol **6** was formed from the reaction of **1** with an equimolar amount of 1,3-diaminopropane **5a**. The spectral and analytical data of products **3** and **6** are in

good agreement with the proposed structures. The molecular ion peak in the mass spectra intimates the abstraction of one molecule of water from the 1 : 1 product. In the IR spectra, none of the products exhibit absorption in the carbonyl region, but all show characteristic absorptions in the region 3180–3450 cm^{-1}. The existence of –NH– or –OH groups is confirmed by two broad proton peaks at δ 2.90–4.13 in the ^1H NMR spectra that disappear upon addition of deuterium oxide. The absence of peaks corresponding to imino or carbonyl carbon atoms and the simultaneous presence of two peaks corresponding to quaternary carbons, in the region δ 83.3–86.1 for **3** and at δ 70.6 and 85.1 for **6**, in the ^{13}C NMR spectra, indicate a structure consistent with the proposed one. The observed chemical shifts agree with those mentioned in the literature for analogous systems.[8c,e,f] When the ^1H and ^{13}C NMR spectra of **3** and **6** were recorded on a 300 MHz spectrometer, dynamic effects probably due to the inversion of the two imidazoline-ring nitrogen atoms were observed. Thus, at 30 °C, some peaks attributed to groups vicinal to the nitrogen atoms are broadened and in some cases the signals are absent. At higher temperatures (50 °C) these broadened peaks become narrower. For example, in the ^{13}C NMR spectrum of **3d** recorded at 30 °C (75.5 MHz), two of the five signals (δ 138.5 and 106.0) in the aromatic region, the signal at δ 85.9 for the two quaternary aliphatic carbons as well as two signals (δ 34.6 and 28.4) that can be distinguished for three of the four aliphatic carbons appear as broad peaks. In the spectrum recorded at 50 °C, these signals appear as sharp peaks. The possibility that this dynamic NMR behaviour could result from a hemiaminal–amino ketone tautomerism (**3** $\rightleftharpoons$ **15**) observed in similar aminoketal systems, such as some 1-hydroxytropanes[10a] or 1-hydroxy-homotropanes,[10b] is excluded for the range of temperatures examined. Also, the carbonyl group was not detected in the ^{13}C NMR spectrum of **3d**, and the IR spectrum of this compound, taken in chloroform solution, exhibited only the O–H absorption (3520 cm^{-1}) and not even a trace of C=O absorption as would be expected if the above mentioned equilibrium existed.

The structure of compounds **3** was confirmed unambiguously by a crystallographic X-ray analysis[11] carried out on **3d**. The perspective view of the molecule is given in Fig. 1, while selected bond lengths and bond angles indicative of N1 and N2 hybridization are quoted in Table 1.

The presence of the NH group was further established by the acetylation of **3a** upon treatment with acetic anhydride (in the presence of pyridine) in refluxing benzene [eqn. (1)]. The

$$\mathbf{3a} + (MeCO)_2O \xrightarrow[\text{reflux}]{\text{pyridine, } C_6H_6} \mathbf{3e}\ (R^1 = MeCO,\ R^2 = R^3 = H) \quad (1)$$

mono-acetyl derivative **3e** obtained exhibits a carbonyl absorption at 1655 cm^{-1} as well as a hydroxy absorption at 3410 cm^{-1}. The direct derivatization of the hydroxy group of 9-oxabicyclo[3.3.1]nonan-1-ol, a compound that resembles **3a**, is difficult to achieve[12] and gives instead 5-oxocyclooctyl derivatives or cyclooct-4-enone. Indeed, our efforts to acetylate the tertiary hydroxy group, attempted by refluxing **3d** in dry toluene with an excess of acetic anhydride, gave the unexpected 2-diacetylmethylidenebenzimidazole derivative **12** along with cyclooctane-1,5-dione **1**, *N*,*N*′-diacetyl-*N*-methyl-*o*-phenylenediamine and 1,2-dimethylbenzimidazole. Product **12** exhibits two carbonyl absorptions at 1665 and 1690 cm^{-1} in the IR spectrum and gives a molecular ion peak in the mass spectrum. The characteristic features in the ^1H NMR spectrum, which are indicative of the proposed structure **12**, are the one proton triplet at δ 6.33, attributed to the cyclooctenone ring olefinic proton, the deshielded one-methyl singlet at δ 3.77, as well as the deshielding of the aromatic protons which resonate at δ 7.43–7.60. The acetyl protons appear to be equivalent, giving a singlet at δ 2.18 (80 MHz). This singlet broadens and is almost covered by the methylenic protons multiplet at δ 1.52–3.10 when the spectrum is recorded on a 300 MHz spectrometer. The broadening is attributed to restricted rotation about the exocyclic C=C bond as well as about the bonds that connect this double bond with the two acetyl substituents and is supposed to originate from a sufficient degree of conjugation between the imidazole nitrogen atoms and the diacetylmethylidene conjugated system. Such situations are known to exist in enamines, especially those bearing electron withdrawing substituents at the position β to the amino group.[13] These dynamic effects are also recognizable in the ^{13}C NMR spectrum (75.5 MHz) of **12**, where the signals of an aliphatic carbon (probably the CH_3CO) at δ 29.2 and of another (probably the C-2 of the imidazole ring) at δ 136.1 appear as broad peaks, whereas peaks for the acetyl carbonyl carbon as well as the bis-acetyl substituted carbon atom are not detected in the spectrum. In the carbonyl region, only one signal (δ 213.5) appears. The deshielding of the olefinic proton of the cyclooctenone ring indicates the lack of conjugation between the C=C bond and the nitrogen lone pair which may be due to steric hindrance, as evidenced by the failure of this enamine group to be hydrolysed. Instead, treatment of **12** with methanolic hydrochloric acid under reflux resulted in the formation of monoacetyl-methylidenebenzimidazole **11** [eqn. (2)]. The less crowded, in relation to **12**, hydrolysis product **11** exhibits a ^{13}C NMR

$$\mathbf{12} + HCl \xrightarrow[\text{reflux}]{MeOH} \mathbf{11} \quad (2)$$

spectrum (75.5 MHz) which resembles that of **12**. The obvious differences are the appearance of a broad singlet at δ 4.68, attributed to the =CHCO–proton as well as a clear one-methyl singlet at δ 2.11, attributed to the acetyl protons. In the ^{13}C NMR spectrum (75.5 MHz) which also resembles that of **12**, the signals at δ 29.7 and 136.7 are sharp peaks, whereas two more signals at δ 75.1 and 187.0 appear which are attributed to the $=CHCOCH_3$ and the acetyl carbonyl carbon respectively. The chemical shifts are in good agreement with those known for other enolate systems.[14] From the deshielded (δ 5.95) olefinic cyclooctenone ring proton of **11**, the absence of conjugation

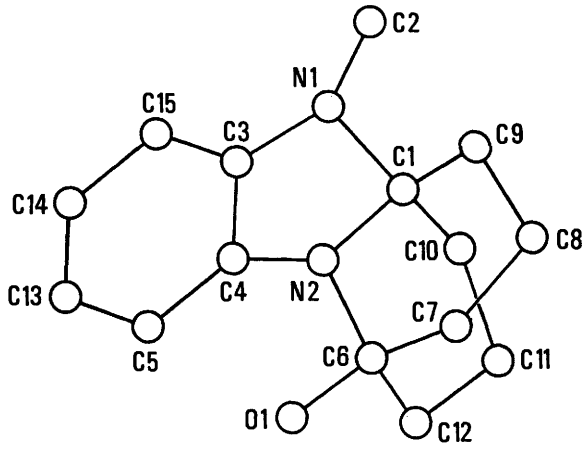
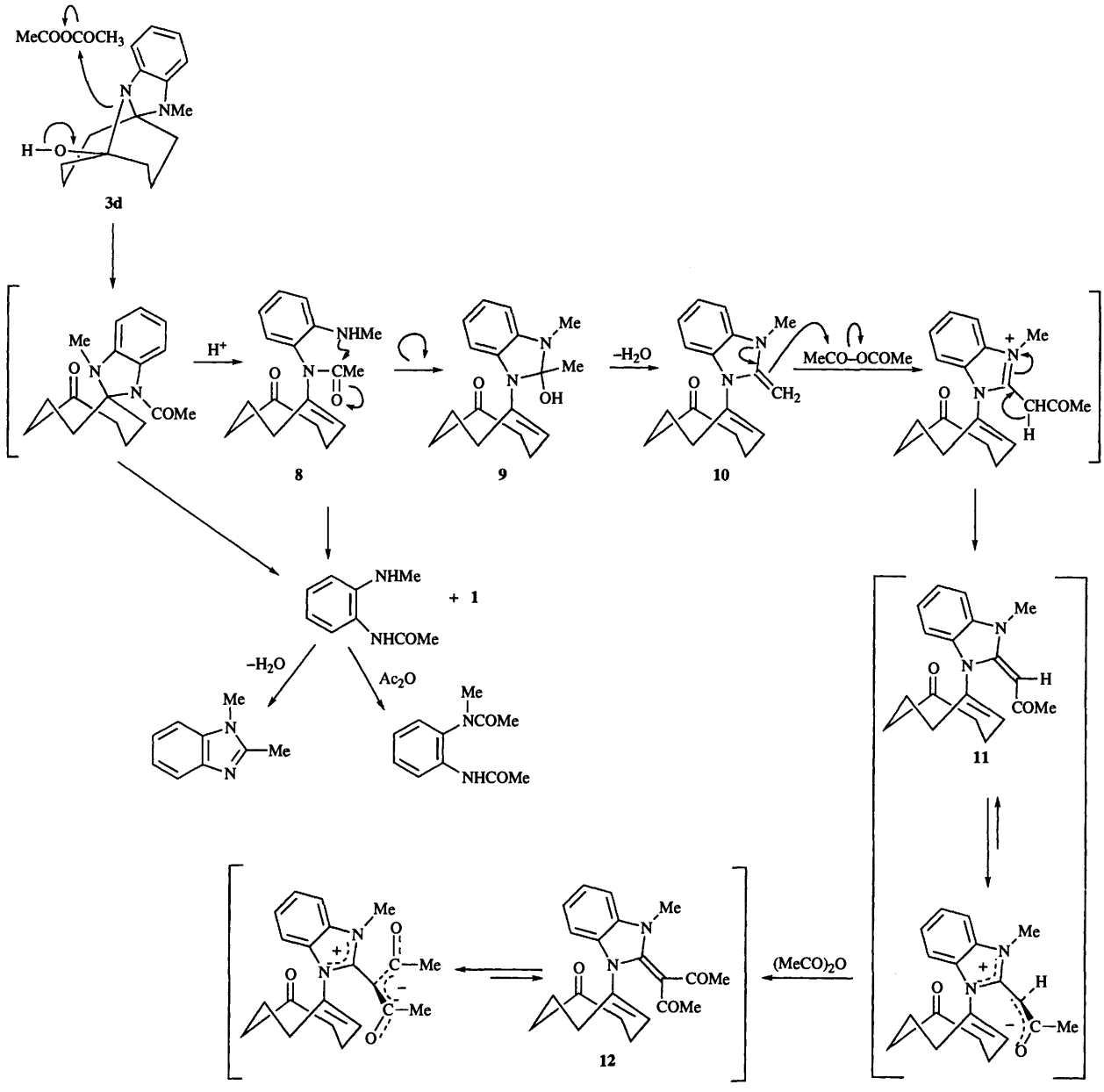


Fig. 1 X-Ray crystallographic perspective drawing of **3d**

Table 1 Bond lengths (Å) and bond angles (°) for **3d**

N1–C1	1.486(5)	C1–N1–C3	104.9(3)
N1–C2	1.455(5)	C1–N1–C2	119.4(3)
N1–C3	1.402(5)	C2–N1–C3	118.6(3)
N2–C1	1.469(5)	C1–N2–C6	112.4(3)
N2–C4	1.414(5)	C1–N2–C4	105.8(3)
N2–C6	1.467(5)	C4–N2–C6	123.2(3)



Scheme 2

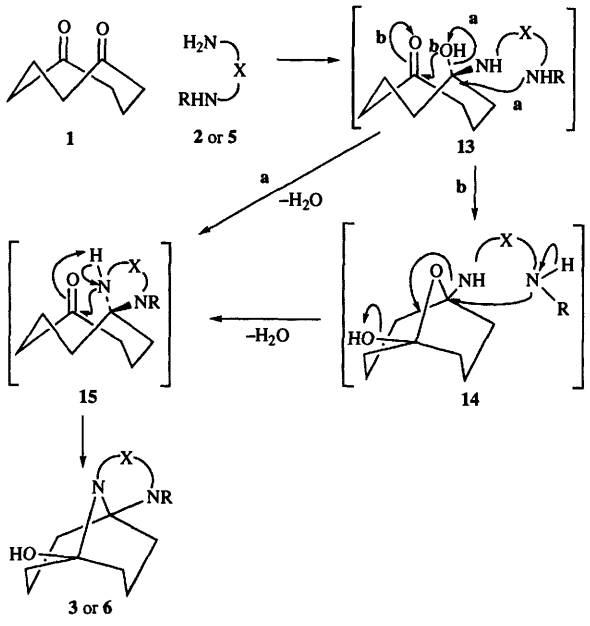
between the C=C bond and the nitrogen lone pair is deduced again, leading to the reasonable assumption that compound **11** is in the *Z*-form. *N*,*N*′-Diacetyl-*N*-methyl-*o*-phenylenediamine and 1,2-dimethylbenzimidazole are probably derived from the intermediate **8** through acidic hydrolysis of the enamine moiety and subsequent acetylation or cyclization respectively.

The structure of compound **12** has been confirmed by X-ray crystallographic analysis[15] from which its co-crystallization with one molecule of water comes to light. The C–N bond lengths of the imidazole ring (1.35–1.38 Å) as well as the exomethylenic bond length (1.43 Å) confirm the above mentioned conjugation. The C=C(COMe)$_2$ group seems almost coplanar and is inclined at an angle of about 70° relative to the plane of the benzimidazole ring.

The formation of compound **12** proceeds (Scheme 2) probably through the cyclooctenone derivative **8**, which is further cyclized to **9** and dehydrated to the 2-methylenebenzimidazole derivative **10**, following a procedure known for the preparation of benzimidazoles.[16] Double successive acetylation of the enamine **10** furnishes compound **12**.

Scheme 3 shows a reasonable mechanistic interpretation of the formation of **3** or **6**. As the non-bonding distance between the carbonyl groups in **1** has a magnitude[2] of 2.9 Å, the initial nucleophilic attack of the diamine **2** or **5** on **1** is supposed to take place probably on the *exo*-face of the carbonyl group. The following cycloketalization of the intermediate **13** to form **14** relies on the close proximity of the oxygen to the transannular carbon atom and resembles[7] an analogous process in other mesocyclic systems. Abstraction of water, accompanied by transannular cycloketalization, results in **3** or **6**. Alternatively, the direct formation of the intermediate **15** is considered equally possible.

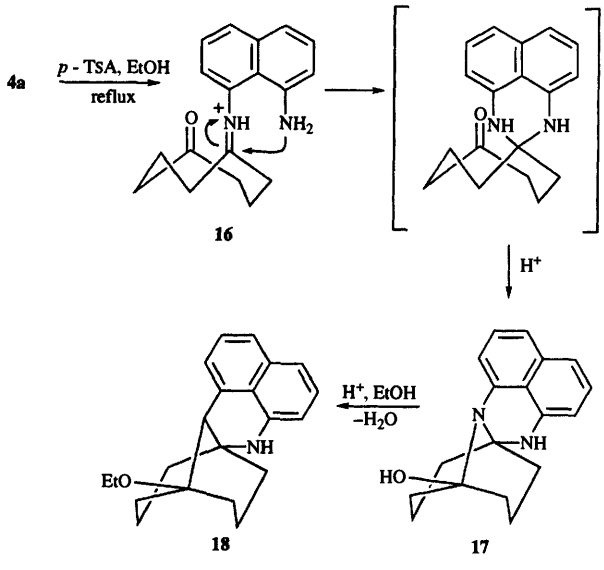
In contrast with the reactions of the diamines **2a–d** with **1**, the reaction of 1,8-diaminonaphthalene with **1** under similar conditions resulted in the imino derivatives **4a** and **4b**, while no tricyclic product was formed. This preference for the imino products may be due to more pronounced steric effects developed in the tetrahedral intermediate **13** (X = naphthalene-1,8-diyl) in relation to that derived from the reactions of the amines **2a–d**. The presence of the primary imino, carbonyl and amino groups in **4a** is apparent from the absorptions at 1650, 1685 and 3290 and 3310 cm^{-1}, respectively, in the IR spectrum. Nevertheless, the carbonyl and imino carbons are not detected in the ^{13}C NMR (75.5 MHz)



Scheme 3

spectrum, while some signals are again broad. Broad peaks are also observed in the ^{1}H NMR (300 MHz) spectrum of **4a** and are explained on the basis of dynamic effects, possibly due to the restricted rotation about the single N–C bond joining the imine nitrogen atom with the bulky 8-amino-1-naphthyl substituent, as is suggested by a molecular model of **4a**. Such hindered rotation is well established for 1,8-disubstituted naphthalenes[17] and the barriers are high enough to have been measured by dynamic NMR spectroscopy. Of course, the possibility that these dynamic effects result from a *syn–anti* isomerization of the imine moiety could not be eliminated as isomerizations of this type have by now been recognized from the temperature dependent NMR spectra of other imine systems.[18]

The imine **4a** remained unchanged after heating in ethanol solution or at 170 °C. It was converted to the tricyclic compound **18** under reflux in ethanol in the presence of an acid catalyst (toluene-*p*-sulfonic acid). Compound **18** is supposed to originate (Scheme 4) from the intermediate **17** by nucleophilic



Scheme 4

displacement of the protonated hydroxy group[19] from ethanol. The formation of **17** is attributed to nucleophilic attack of the primary amine group at the electrophilic carbon atom of the protonated imine **16**, followed by aza-cycloketalization.

With the aim of synthesizing derivatives of **3** and **6** bearing substituents other than the hydroxy group, we attempted the reaction of 5-ethoxycarbonylmethylenecyclooctanone **19** with diamines **2** and **5**. Diaminoarene **2a** failed to react with **19** in refluxing ethanol as well as under more vigorous conditions, *i.e.* heating of neat reactants at 120 °C. By heating the reactants at 170 °C, a complex reaction mixture was obtained, from which the desired tricyclic product could not be isolated. In contrast to the *o*-diaminoarenes **2**, the stronger nucleophiles **5a,b** reacted with **19** (by heating of the neat reactants at 120 °C) to form the tricyclic compounds **22a,b** (it is interesting to note that the reaction of **19** with **5a** failed under reflux in ethanol). The absence of vinylic protons is obvious in the ^{1}H NMR spectrum of **22a**, whereas the existence of the $-CH_2CO-$ group is indicated by a peak at δ 2.37. Peaks at δ 58.1 and 67.7 attributed to the quaternary carbon atoms C-7 and C-1 respectively, a peak at δ 171.7 due to the ester carbonyl group, and the absence of peaks corresponding to olefinic carbon atoms in the ^{13}C NMR spectrum of **22a** confirm the proposed structure. Additional structure corroboration is offered by the molecular ion peak in the mass spectrum.

A mechanistic scheme (Scheme 5) resembling that given for the formation of **3** or **6** is proposed for the formation of compounds **22**. The hemiaminal **20**, generated by the nucleophilic attack of the diamine **5** on **19**, is supposed to add through a transannular Michael-type reaction to the olefinic carbon atom of the α,β-unsaturated ester group, thus giving rise to a bicyclic[3.3.1]azaketal intermediate **21**. Subsequent nucleophilic attack of the remaining amino group of **21** at the ketal carbon atom, accompanied by simultaneous abstraction of water, results in the formation of **22**.

The compounds **3**, **6** and **22** have structural features of significant interest, such as the aminal function in **3** and **6** or their common 9-azabicyclo[3.3.1]nonane skeleton, which could be correlated with that of the 8-azabicyclo[3.2.1]octane framework of cocaine and the 9-azabicyclo[4.2.1]nonane ring system of anatoxin-α.[20] Furthermore, a carbocyclic homologue of their diazatricyclic skeleton constitutes the basic framework of quadrone,[21] a natural sesquiterpenoid with antitumour activity. To the best of our knowledge, only a few examples of similar hetero-tricyclic compounds are known in the literature.[22]

In conclusion, a convenient, one-pot route for the construction of functionalized hetero-tricycloalkanes from cyclooctane-1,5-dione or 5-ethoxycarbonylmethylenecyclooctanone and diamines is reported. The reactions could be applicable to the synthesis of a variety of hetero-tricycloalkanes, since the size of the rings and the substitution pattern, as well as the number and the position of the heteroatoms, could be varied, depending on the starting materials used.

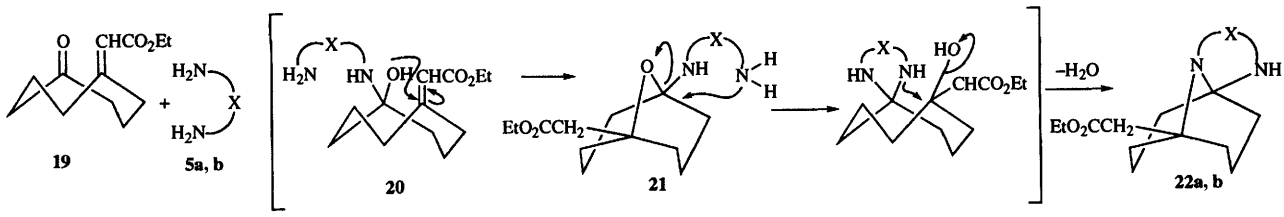
Experimental

Melting points: uncorrected, Kofler hot-stage apparatus. IR: Perkin-Elmer 297, Nujol mulls. ^{1}H NMR: in $CDCl_3$, Bruker AW-80 (80 MHz), or Bruker 300 AM (300 MHz), tetramethylsilane (Me_4Si) as internal standard, *J* values in Hz. ^{13}C NMR: in $CDCl_3$, Varian CFT 20 (20 MHz) or Bruker 300 AM (75.5 MHz), tetramethylsilane as internal standard. MS: Hitachi-Perkin-Elmer RMU-6L or VG-250 spectrometer, 70 eV. Analyses: Perkin-Elmer Model 240, CHN analyser. Light petroleum refers to the fraction of bp 40–60 °C.

The syntheses of cyclooctane-1,5-dione and 5-ethoxycarbonylmethylenecyclooctanone were carried out according to literature[4,6,23] procedures.

Reactions of cyclooctane-1,5-dione 1 with diaminoarenes 2a–d or 1,3-diaminopropane 5a. Preparation of compounds 3a–d and 6

General method. To a solution of cyclooctane-1,5-dione **1** (140 mg, 1 mmol) in ethanol (5 cm^3) was added an equimolar



a X = $-(CH_2)_3-$

b X = 

Scheme 5

amount of the appropriate diaminoarene **2a–d** or 1,3-diaminopropane **5a**. The solution was refluxed for 2–5 h, the solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel, using light petroleum–ethyl acetate (1:1) as the eluent to afford tricycloalkanes **3a–d** or **6**. The compounds **3a–c** and **6** were unstable and decomposed on prolonged storage at room temperature, especially in solution.

1,2,3,4,4a,5-Hexahydro-1,4a-propanopyrido[1,2-*a*]benzimidazol-1-ol 3a. The reaction of **1** with *o*-phenylenediamine **2a** (108 mg) gave compound **3a** (170 mg, 74%), mp 148–151 °C (from diethyl ether–light petroleum) (Found: C, 73.08; H, 7.73; N, 12.14. Calc. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16%); ν_{max}/cm^{-1} 3280 (OH), 3205 (NH); δ_H(300 MHz) 1.42–2.45 (12 H, m), 3.55 (2 H, br s), 6.48–6.79 and 6.93–7.35 (4 H, two m); δ_C(20 MHz) 21.0, 32.5, 35.1, 83.7, 85.8, 110.9, 111.8, 118.8, 121.5, 139.1, 140.0; *m/z* 230 (M^+, 32%), 215 (4), 201 (2), 187 (26), 159 (15), 145 (60), 132 (100).

1,2,3,4,4a,5-Hexahydro-1,4a-propanonaphth[2′,3′:4,5]imidazo[1,2-*a*]pyridin-1-ol 3b. The reaction of **1** with 2,3-diaminonaphthalene **2b** (158 mg) gave compound **3b** (200 mg, 71%), mp 161–164 °C (from ethyl acetate–light petroleum) (Found: C, 77.27; H, 7.31; N, 9.92. Calc. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99%); ν_{max}/cm^{-1} 3475 (OH), 3340 (NH); δ_H(300 MHz) 1.67–2.30 (12 H, m), 4.13 (2 H, br s), 6.80 (1 H, s), 7.00–7.68 (5 H, m); δ_C(75.5) 21.0, 33.4, 35.0, 83.3, 86.1, 104.9, 105.0, 122.6, 123.0, 125.7, 126.2, 129.6, 131.2, 139.4, 140.6; *m/z* 280 (M^+, 46%), 256 (3), 261 (3), 273 (43), 209 (12), 195 (55), 182 (100).

7,8-Dimethyl-1,2,3,4,4a,5-hexahydro-1,4a-propanopyrido[1,2-*a*]benzimidazol-1-ol 3c. The reaction of **1** with 4,5-dimethyl-*o*-phenylenediamine **2c** (136 mg) gave compound **3c** (150 mg, 58%), mp 149–152 °C (from diethyl ether–light petroleum) (Found: C, 74.41; H, 8.53; N, 10.62. Calc. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84%); ν_{max}/cm^{-1} 3420 (OH), 3280 (NH); δ_H(300 MHz) 1.52–2.52 (18 H, m), 3.15 (2 H, br s), 6.46 (1 H, s), 6.93 (1 H, s); *m/z* 258 (M^+, 50%), 243 (3), 229 (3), 215 (28), 187 (11), 173 (75), 160 (100).

5-Methyl-1,2,3,4,4a,5-hexahydro-1,4a-propanopyrido[1,2-*a*]benzimidazol-1-ol 3d. The reaction of **1** with *N*-methyl-*o*-phenylenediamine **2d** (122 mg) gave compound **3d** (180 mg, 74%), mp 122–125 °C (from diethyl ether–light petroleum) (Found: C, 73.45; H, 8.09; N, 11.49. Calc. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3520 (OH, 'free'), 3500–3150 (OH, hydrogen bonded), no absorption for C=O; δ_H(300 MHz, 30 °C) 1.35–2.65 (15 H, m), 2.95 (1 H, br s), 5.90–7.60 (4 H, two m); δ_H(300 MHz, 50 °C) 1.42–2.62 (16 H, m), 6.12–6.58 (4 H, br s); δ_C(75.5 MHz, 30 °C) 20.5, 28.4 (broad), 34.6 (broad), 85.9 (broad), 106.0 (broad), 109.8, 118.8, 138.5 (broad), 142.1; δ_C(75.5 MHz, 50 °C) 20.6, 28.5, 35.0, 85.4, 87.4, 105.7, 109.6, 118.7, 138.3, 142.1; *m/z* 244 (M^+, 25%), 229 (2), 215 (2), 201 (24), 173 (13), 159 (55), 146 (100), 131 (16), *m** 117.54 (146→131).

2,6-Diazatricyclo[5.3.3.0^{1,6}]tridecan-7-ol 6. The reaction of **1** with 1,3-diaminopropane **5a** (74 mg) gave compound **6** (100 mg, 51%), mp 120–123 °C (from ethanol–diethyl ether) (Found: C, 67.34; H, 10.31; N, 14.38. Calc. for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.27; N, 14.27%); ν_{max}/cm^{-1} 3300 (OH), 3180 (NH); δ_H(300 MHz, 30 °C) 1.38–2.55 (14 H, m), 2.55–3.80 (6 H, m); δ_C(75.5 MHz, 30 °C) 20.0, 27.6, 30.0 (broad), 37.4 (broad), 39.3 (broad), 70.6, 85.1; *m/z* 196 (M^+, 50%), 181 (39), 167 (47), 153 (99), 125 (41), 111 (98), 98 (100), *m** 102.12 (153→125).

Reactions of 5-ethoxycarbonylmethylenecyclooctanone 19 with diaminoalkanes 5a,b. Preparation of compounds 22

General method. A mixture of equimolar amounts of 5-ethoxycarbonylmethylenecyclooctanone **19** (210 mg, 1 mmol) and diaminoalkane **5a** or **5b** (1 mmol) was heated at 120 °C for 2 h. The reaction mixture was dissolved in dichloromethane and washed with brine to remove the unreacted diamine. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue, composed of crude compound **22a** or **22b**, was purified by column chromatography on silica gel with ethyl acetate–methanol–triethylamine (8:1:1) as the eluent.

7-Ethoxycarbonylmethyl-2,6-diazatricyclo[5.3.3.0^{1,6}]tridecane 22a. The reaction of **19** with **5a** (74 mg) yielded compound **22a** (148 mg, 56%) as an oil (Found: C, 67.90; H, 9.79; N, 10.47. Calc for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.51%); ν_{max}/cm^{-1} 3270 (NH), 1720 (C=O); δ_H(80 MHz) 1.22 (3 H, t, *J* 8), 1.32–2.68 (17 H, m), 2.68–3.21 (4 H, two overlapped t), 4.10 (2 H, q, *J* 8); δ_C(75.5 MHz, 30 °C) 14.3, 20.9, 28.2, 31.0 (broad), 31.7 (broad), 39.09, 39.13, 47.1, 58.1, 60.2, 67.7, 171.7; *m/z* 266 (M^+, 34%), 237 (19), 224 (24), 193 (26), 179 (30), 165 (13), 151 (100), 98 (34), 41 (31).

10-Ethoxycarbonylmethyl-2,9-diazatetracyclo[8.3.3.0^{1,9}.0^{3,8}]hexadecane 22b. The reaction of **19** with **5b** (114 mg) yielded compound **22b** (235 mg, 55%) as an oil (Found: C, 70.29; H, 9.80; N, 9.30. Calc. for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14%); ν_{max}/cm^{-1} 3280 (NH), 1722 (C=O); δ_H(300 MHz) 1.26 (3 H, t, *J* 7), 1.44–3.42 (25 H, m), 4.11 (2 H, q, *J* 7); *m/z* 306 (M^+, 71%), 277 (90), 264 (68), 249 (13), 233 (87), 219 (100), 205 (30), 191 (97), 163 (19), 149 (40), 138 (77), 123 (19), 108 (26), 96 (33), 81 (50), 67 (44), 54 (43), 41 (81).

Reaction of cyclooctane-1,5-dione 1 with 1,8-diaminonaphthalene. Preparation of 5-(8-aminonaphthyl)iminocyclooctanone 4a and 1,5-bis(8-aminonaphthyl)iminocyclooctane 4b

An ethanol solution of **1** (140 mg, 1 mmol) and 1,8-diaminonaphthalene (174 mg, 1.1 mmol) was refluxed for 10 h, until the dione was almost consumed as monitored by TLC. After cooling the reaction mixture, the product **4a** was separated as a solid and collected by filtration (100 mg, 24%). The filtrate was condensed to dryness and the residue subjected to column chromatography on silica gel with ethyl acetate–light petroleum (1:2) as the eluent to afford: (i) compound **4a** (138 mg, 49%), mp 185–186 °C (from dichloromethane–light petroleum) (Found: C, 76.89; H, 6.98; N, 9.81. Calc. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99%); ν_{max}/cm^{-1} 3310 and 3290 (NH_2), 1685 (C=O), 1650 (C=N); δ_H(300 MHz, 30 °C) 1.42–2.22 (8 H, m), 2.22–2.68 (4 H, m), 4.15 (2 H, br s), 6.32–

6.72 (2 H, m), 7.10–7.33 (4 H, m); δ_C(75.5 MHz, 30 °C) 19.9, 36.5 (broad), 42.8 (broad), 106.5 (broad), 117.7, 126.9, 134.6, 139.1 (broad), no peaks for C=O and C=N carbon atoms; *m/z* 280 (M^+, 99%), 252 (78), 209 (40), 195 (92), 182 (91), 168 (18), 154 (13), 140 (25), 127 (18), 115 (35), 91 (8), 43 (9); (ii) compound **4b** (39 mg, 9%, total yield 33%), mp 205–207 °C (from chloroform–ethanol) (Found: C, 79.83; H, 6.62; N, 13.54. Calc. for $C_{28}H_{28}N_4$: C, 79.97; H, 6.10; N, 13.32%); ν_{max}/cm^{-1} 3340 and 3300 (NH_2), 1615 (C=N); δ_H(80 MHz) 1.46–2.26 (12 H, m), 3.70 (4 H, br s), 6.31–6.88 (4 H, m), 6.88–7.51 (8 H, m).

Cyclization of imine 4a with toluene-*p*-sulfonic acid. Preparation of compound 18

To a solution of the imine **4a** (55 mg, 0.196 mmol) in ethanol (2 cm^3) was added a catalytic amount of toluene-*p*-sulfonic acid. After reflux for 2 h, the solvent was evaporated and the residue was chromatographed on silica gel, using light petroleum–ethyl acetate (3:1) as the eluent, to afford compound **18** (36 mg, 58%) as an oil (Found: C, 78.13; H, 7.73; N, 8.83. Calc. for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08%); ν_{max}/cm^{-1} 3360 (NH), 1070 (C–O ether); δ_H(300 MHz) 1.22 (3 H, t, *J* 7), 1.57–1.84 (6 H, m), 2.01–2.33 (5 H, m), 2.47–2.64 (2 H, m), 3.71 (2 H, q, *J* 7), 6.43 (1 H, d, *J* 7), 7.08–7.33 (4 H, m), 8.02 (1 H, d, *J* 8); δ_C(75.5 MHz) 15.4, 20.2, 31.6, 34.8, 55.7, 70.4, 91.6, 105.5, 112.1, 114.9, 117.3, 118.4, 126.1, 127.0, 134.6, 137.9, 141.2; *m/z* 308 (M^+, 66%), 208 (86), 261 (75), 252 (55), 235 (91), 207 (100), 195 (49), 183 (50), 168 (76), 153 (53), 140 (92), 126 (32), 115 (86), 55 (76).

Acetylation of compound 3a. Preparation of 1,2,3,4,4a,5-hexahydro-1,4a-propanopyrido[1,2-*a*]benzimidazol-1-yl acetate 3e

To a solution of **3a** (125 mg, 0.54 mmol) in acetic anhydride (1 cm^3) was added pyridine (1 cm^3), and the mixture was kept at room temperature for 5 d. Water (5 cm^3) was added and the reaction mixture was extracted with dichloromethane. The organic layer was succesively washed with dilute hydrochloric acid and water and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on a silica gel column with light petroleum–ethyl acetate (2:1) as the eluent yielding the acetyl derivative **3e** (91 mg, 52%), mp 134–137 °C (from dichloromethane–diethyl ether) (Found: C, 70.50; H, 7.35; N, 10.10. Calc. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29%); ν_{max}/cm^{-1} 3410 (OH), 1655 (C=O); δ_H(300 MHz) 1.70–2.06 (8 H, m), 2.06–2.28 (2 H, m), 2.36 (3 H, s), 2.55–2.85 (3 H, m), 6.66 (1 H, t, *J* 8), 6.74–7.00 (2 H, m), 7.37 (1 H, d, *J* 8); δ_C(75.5 MHz) 20.8, 25.75, 30.1 (broad), 35.6, 86.3, 88.0 (broad), 111.3, 114.0 (broad), 118.2, 124.3, 124.4, 167.9; *m/z* 272 (M^+, 35%), 229 (31), 215 (4), 201 (13), 187 (50), 174 (47), 159 (27), 145 (80), 132 (100), 43 (28). The acetyl derivative **3e** was also formed by refluxing equimolar amounts of **3a** and acetic anhydride in benzene for 3 h.

Acetylation of compound 3d

A solution of compound **3d** (180 mg, 0.74 mmol) and acetic anhydride (210 mg, 2.06 mmol) in dry toluene (3 cm^3) was refluxed for 5.5 h. Water (2 cm^3) was added and the mixture was refluxed for 10 min. After cooling, it was extracted with dichloromethane and the organic layer was dried over sodium sulfate and concentrated *in vacuo*. On trituration with diethyl ether, 2-*diacetylmethylidene*-1-(5-*oxocyclooctenyl*)-3-*methyl*-2,3-*dihydrobenzimidazole* **12** (65 mg, 25%) was precipitated. The filtrate was concentrated and the residue was subjected to column chromatography on silica gel, using ethyl acetate with increasing amounts of methanol (0–20%) as the eluent, to afford, in order of elution: (i) cyclooctane-1,5-dione **1** (37 mg, 36%), (ii) *N,N'*-diacetyl-*N*-methyl-*o*-phenylenediamine (11 mg, 7%), mp 169–171 °C (from ethanol) (lit.,[24] 172 °C), (iii) 1,2-dimethyl-1*H*-benzimidazole (30 mg, 28%), mp 106–109 °C (from hexane) (lit.,[25] 111–112 °C), (iv) compound **12** (52 mg, 20%, total yield 45%), mp 238–240 °C (from ethanol–diethyl ether) (Found: C, 68.27; H, 6.98; N, 7.38. Calc. for $C_{21}H_{24}N_2O_3 \cdot H_2O$: C, 68.09; H, 7.07; N, 7.56%); ν_{max}/cm^{-1} 3460, 3380 and 3280 (H_2O), 1690 (C=O), 1665 (C=O, acetyl); δ_H(300 MHz) 1.52–3.10 (16 H, m), 3.77 (3 H, s), 6.08 (1 H, t, *J* 9), 7.41–7.49 (1 H, m), 7.49–7.58 (3 H, m); δ_H(75.5 MHz) 22.4, 23.8, 29.2 (broad), 31.3, 31.4, 40.6, 46.9, 111.6, 113.0, 125.5, 126.1, 131.8, 132.0, 132.4, 136.1 (broad), 158.0, 213.5; *m/z* 352 (M^+, 18%), 310 (21), 309 (89), 295 (10), 281 (48), 267 (62), 253 (59), 239 (35), 225 (100), 209 (74), 173 (98), 157 (28), 146 (34), 77 (67), 43 (51).

Hydrolysis of compound 12. Preparation of (*Z*)-2-acetylmethylidene-1-(5-oxocyclooctenyl)-3-methyl-2,3-dihydrobenzimidazole 11

A solution of compound **12** (35 mg, 0.1 mmol) in methanol (2 cm^3) containing concentrated hydrochloric acid (0.8 cm^3) was refluxed for 2 h. The methanol was evaporated *in vacuo* and the residue was neutralized with a solution of sodium carbonate (40%) and extracted with dichloromethane. The organic layer was dried over sodium sulfate and after evaporation of the solvent the residue was subjected to column chromatography on silica gel, using a mixture of ethyl acetate–methanol (7:3) as the eluent, to afford **11** (19 mg, 61%) as an oil (Found: C, 73.29; H, 7.23; N, 9.18. Calc. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03%); ν_{max}/cm^{-1} 1690 (C=O); δ_H(300 MHz) 1.50–1.93 (2 H, m), 2.11 (3 H, s), 2.28–3.14 (8 H, m), 3.78 (3 H, s), 4.68 (1 H, m), 5.95 (1 H, t, *J* 9), 7.01 (1 H, d, *J* 6), 7.08–7.27 (3 H, m); δ_H(75.5 MHz) 22.5, 23.6, 29.7, 30.4, 34.3, 40.8, 47.2, 75.1, 108.9, 109.6, 122.6, 123.2, 131.9, 132.7, 133.9, 136.7, 152.6, 187.0, 213.5; *m/z* 310 (M^+, 9%), 269 (58), 268 (59), 267 (10), 253 (13), 239 (23), 225 (34), 211 (34), 198 (25), 183 (89), 146 (98), 132 (64), 77 (54), 43 (100).

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