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Synthesis of novel tetra- and pentacyclic aza-cage systems

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Abstract—A novel route to substituted pentacyclic lactams and tetracyclic amides from bis(bromomethyl) and bis(chloromethyl) substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-diones is reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Reports on the synthesis of polycyclic cage compounds containing amine groups are limited although their potential as biologically active agents was recognised with the evaluation of 1-amino adamantane, commonly known as amantadine by Davis et al. as early as 1964.[1] Schwab et al.[2] have reported that amantadine can be beneficial to patients with Parkinson's disease and that the hydrophobicity of the hydrocarbon cage enables it to cross the blood brain barrier to enter the central nervous system. Boeyens et al. have synthesised pentacycloundecane amino acid derivatives which showed activity as calcium agonists.[3] In this context, we were interested in developing methods for the synthesis of polycyclic cage amines through the reaction of primary amines with bis halomethyl substituted pentacyclic systems. Reported literature in this area include: (i) the synthesis of aza-cage compounds through transannular cyclisations in pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione (PCUD) with amines by Sasaki et al.[4] (ii) reductive amination of PCUD giving rise to amine substituted cage compounds by Marchand et al.[5] and (iii) the nucleophilic addition of primary and secondary amines to PCUD leading to transannularly cyclised products by Bott et al.[6]

2. Results and discussion

The study was initiated by the treatment of 1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **1** and 1,9-bis(chloromethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undeca-8,11-dione **2** with an excess of methyl- or ethylamine. While we hoped for direct alkylation of the amine, we were also curious to see whether the amines would react with the carbonyl group leading to ring opening with loss of bromine as observed by us earlier[7] or produce transannularly cyclised products. The reactions took a fascinating route and provided several unexpected novel products (Scheme 1).

The synthesis of **1** has been reported by us earlier.[7] The synthesis of **2** was achieved[8] through a similar procedure starting from commercially available hydroquinone dimethyl ether **6** (Scheme 2). Bischloromethylation of **6** using paraformaldehyde and hydrochloric acid under sonication conditions readily yielded **7** which was oxidised to the quinone **8** using nitric acid. Diels–Alder addition of **8** to cyclopentadiene gave the required tricyclic diketone **9** which underwent [π2s+π2s] photocycloaddition smoothly leading to **2**.

The reaction of **1** with an excess of methylamine resulted in a mixture of products from which two products **3a** and **5a** could be separated by careful chromatography (Scheme 1). Compound **3a** was obtained as colourless crystals from dichloromethane–petroleum ether in 37% yield. The IR spectrum showed a strong broad peak at 3137 cm^{-1} (OH group) and at 1654 cm^{-1} (amide C=O). The ^{1}H NMR spectrum contained the following characteristic signals at: (i) δ 4.87 and 4.79 (exocyclic methylene group), (ii) a singlet at δ 3.58 (–CH$_2$Br) and (iii) a sharp singlet at δ 2.63 (methyl on the lactam nitrogen). Salient features in the ^{13}C NMR spectrum include the signals at: (i) δ 171.2 due to the lactam carbonyl, (ii) δ 143.6 and 108.9 due to the exocyclic double bond, (iii) δ 101.9 due to the quaternary carbon bearing the hydroxyl group and (iv) δ 63.1 due to the other quaternary carbon at C-6. The HRMS value of 310.0437 for [M$^+$+1] indicated the addition of 1 equiv. of the amine and loss of one bromine atom. All the above data put together suggested a structure as depicted for **3a**. This structure was further confirmed by single crystal X-ray diffraction studies (Fig. 1).

The second product **5a** was obtained in 25% yield and readily crystallised from dichloromethane–petroleum

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Keywords: amides; aza compounds; lactams; polycyclic compounds; polycyclic heterocyclic compounds.

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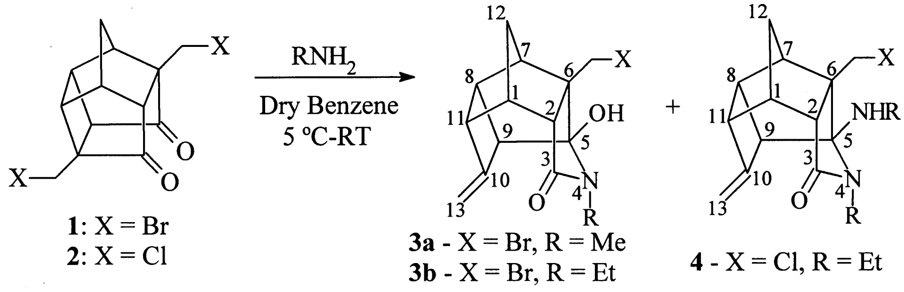
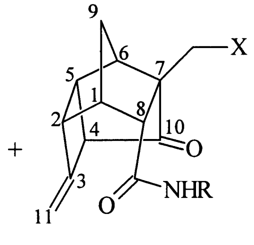


1: X = Br
2: X = Cl

3a - X = Br, R = Me
3b - X = Br, R = Et
3c - X = Cl, R = Me
3d - X = Cl, R = Et

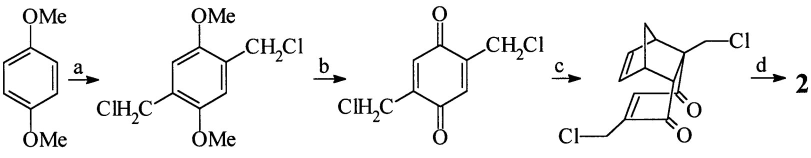
4 - X = Cl, R = Et

Reaction \ Yield of	3	4	5
1 + $MeNH_2$	37%	-	25%
1 + $EtNH_2$	23%	-	20%
2 + $MeNH_2$	36%	-	33%
2 + $EtNH_2$	30%	12%	14%



5a - X = Br, R = Me
5b - X = Br, R = Et
5c - X = Cl, R = Me
5d - X = Cl, R = Et

Scheme 1.



6 **7** **8** **9**

Scheme 2. *Reagents and conditions*: (a) paraformaldehyde (3 equiv.), conc. HCl, glacial acetic acid, sonication, 1 h, 68%; (b) conc. nitric acid, glacial acetic acid, 0°C-rt, 1 h, 26%; (c) cyclopentadiene (2 equiv.), dry benzene, 0°C-rt, 20 h, 87%; (d) *hν* (sunlight), dry ethyl acetate, argon atmosphere, 2 h 83%.

ether. A comparison of its spectra with that of **3a** showed some similarities and a few dissimilarities. For example, the IR spectrum contained two different carbonyl peaks at 1651 (amide C═O) and 1738 cm^{-1} (ring C═O). The ^{1}H NMR spectrum indicated the presence of the following characteristic signals: (i) two signals at δ 5.03 and 4.86 (exocyclic methylene group), (ii) a broad singlet at δ 5.26 indicated a deshielded proton on nitrogen, (iii) two doublets at δ 3.74 and 3.40 with a coupling constant of 10.4 Hz ($-CH_2Br$) and (iv) a doublet at δ 2.53 with a coupling constant of 4.6 Hz [$-C(O)NHCH_3$]. The last confirmed the secondary nature of the amide group. The ^{13}C NMR spectrum confirmed the presence of a carbonyl group, an amide group and an exocyclic double bond by signals at δ 214.5, 170.7, 146.6 and 111.6 respectively. The quaternary carbon at C-7 appeared at δ 56.8 and all other signals showed up upfield between δ 58.8 and 26.1 as expected. The HRMS value of 310.0386 which was the same as the first compound lent additional support to the compound being identified as **5a**.

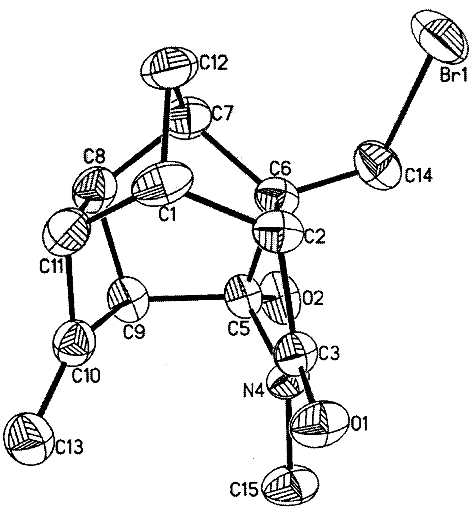
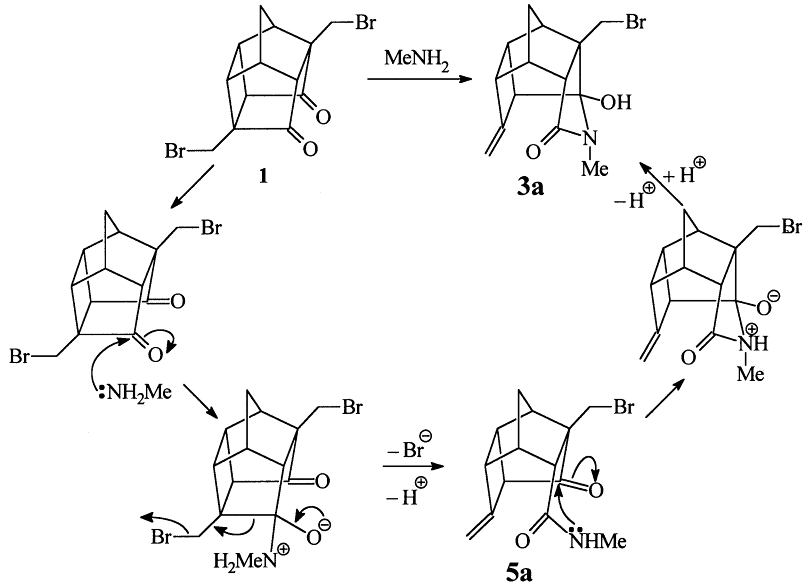
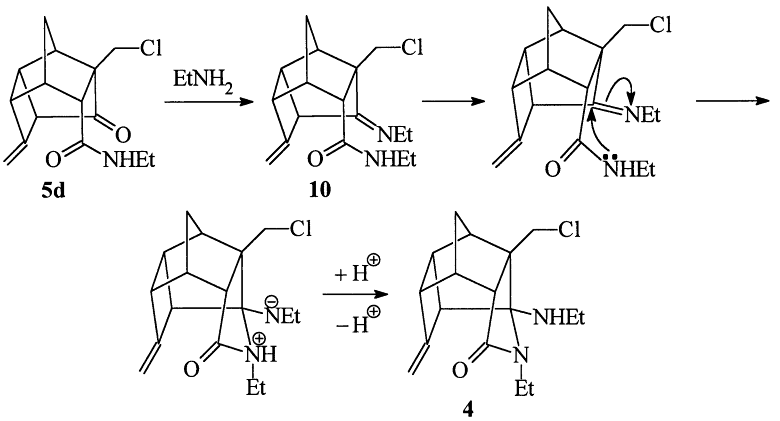


Figure 1. X-Ray crystal structure of **3a**.

The mechanism proposed for the formation of these totally unexpected compounds **3a** and **5a** envisages the initial addition of 1 equiv. of the amine to the carbonyl carbon. This leads to the rupture of a five-membered ring followed by formation of an exocyclic double bond and loss of the halogen as shown in Scheme 3 below. The loss of the halogen is probably facilitated by the excess amine present in the reaction mixture. Thus the product **5a** is formed. The amide nitrogen is then able to add to the second carbonyl carbon that is in the proximity due to the ring architecture. Formation of the lactam ring is then followed by proton



Scheme 3.



Scheme 4.

transfer leading to the generation of a hydroxyl group giving the compound **3a**.

The analogous products were obtained upon the reaction of **1** with ethylamine and **2** with methylamine and ethylamine. The reaction of **2** with ethylamine, however, yielded one more product which was separated by column chromatography and identified in the following manner as **4**. Its IR spectrum showed a peak at 3307 cm^{-1} (N–H group) and a peak at 1689 cm^{-1} (C=O group). The proton NMR spectrum gave an integration for 23 protons indicating that 2 equiv. of the amine had added to the starting material. Of these, the characteristic signals were assigned as follows: (i) the multiplet at δ 4.86–4.85 (two olefinic protons), (ii) the doublets which showed up at δ 3.72 and 3.59 ($-CH_2Cl$), (iii) the broad singlet at δ 3.14 (N–H), and (iv) overlapping multiplets between δ 1.20–1.09 (the two methyl groups of the ethylamine substituents). The ^{13}C NMR spectrum confirmed the addition of 2 equiv. of the amine to the starting material by showing 17 signals. Of these, the signal at δ 172.8 could be attributed to a lactam carbonyl, the signals at δ 144.8 and 109.9 to an exocyclic double bond and the one at δ 93.3 to a quaternary carbon with amine attached. This product **4** might have been produced in two steps (Scheme 4) viz.: (i) by the addition of ethylamine to **5d** leading to an imine **10** and (ii) with the lone pair on the amide nitrogen adding across to the electron deficient imine carbon. Proton rearrangement then gives the product **4**. The proposed structure received further confirmation from the HRMS value of 306.1497.

Thus, in conclusion a new ring opening pathway of the pentacyclic undecanedione system has been delineated and several new aza polycyclic compounds have been synthesised.

3. Experimental

All experiments were carried out in oven dried glass-ware. Analytical thin layer chromatography was performed on silica gel GF$_{254}$ TLC plates. Purification by gravity column chromatography was carried out using silica gel (100–200 mesh). Mixtures of ethyl acetate and hexane and pure ethyl acetate were used as eluent as required. Melting points were recorded on Aldrich Meltemp-II and are reported without corrections. IR spectra were run on a Nicolet (impact 400D FT-IR) spectrophotometer or Bomem MB-Series FT-IR spectrophotometer. NMR spectra were obtained using chloroform-d as solvent on Bruker DPX 300 MHz NMR spectrometer. Chemical shifts are given in δ scale with TMS as internal reference. Yields refer to quantities obtained after chromatography.

3.1. Procedure for the Diels–Alder reaction of 8

The quinone **8** (0.64 g, 3.2 mmol) was dissolved in dry benzene and the solution was cooled in an ice-water bath. Cyclopentadiene (0.60 mL, 7.3 mmol) was added slowly to this solution drop by drop. The reaction mixture was left stirring at room temperature for 20 h. It was worked up by removing benzene under reduced pressure and then purified on a silica-gel column. The compound was recrystallised from dichloromethane–petroleum ether and gave light yellow coloured crystals (0.74 g, 87% yield) of the Diels–Alder adduct 2,5-bis(chloromethyl)tricyclo[6.2.1.0^{2,7}]-undec-4,9-diene-3,6-dione, **9**.

3.1.1. Spectral data of 9. Mp (°C): 118–120. FT-IR (KBr, ν_{max}/cm^{-1}): 3020, 2982, 1670, 1625, 1432, 1073, 708. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.82 (s, 1H), 6.12 (s, 2H), 4.38–4.19 (m, 3H), 3.50–3.42 (m, 2H), 3.25–3.23 (m, 1H), 3.12 (s, 1H), 1.64 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 199.3, 196.8, 148.6, 140.1, 136.9, 136.4, 60.1, 55.0, 53.1, 51.8, 49.8, 47.2, 39.6.

3.2. Procedure for photolysis of 9

The Diels–Alder adduct **9** (0.74 g, 2.7 mmol) was dissolved in 80 mL of dry ethyl acetate, degassed with argon gas and exposed to bright sunlight for 2 h. TLC at the end of this period showed complete consumption of the UV active starting material along with the formation a non-UV active product. The reaction was worked up by removing the solvent and the residue was purified by column chromatography on silica gel. The pure product was crystallised from a mixture of dichloromethane and petroleum ether to give off-white crystals of **2** (0.61 g, 83% yield).

3.2.1. Spectral data of 2. Mp (°C): 88–90. FT-IR (KBr, ν_{max}/cm^{-1}): 2970, 1757, 1738, 1430, 1284, 1146, 1100, 732. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.77–3.51 (m, 4H), 3.23–3.17 (m, 2H), 3.03–2.99 (m, 2H), 2.82–2.79 (m, 1H), 2.62 (d, J=3.4 Hz, 1H), 2.27 (d, J=11.7 Hz, 1H), 1.95 (d, J=11.7 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 208.9, 208.1, 62.8, 58.9, 52.6, 46.9, 46.2, 43.7, 41.9, 41.7, 41.5, 39.3, 34.9. C/H Analysis: calculated for $C_{13}H_{12}O_2Cl_2$ C: 57.58, H: 4.46; found C: 57.74, H: 4.45.

3.3. General procedure for the reaction of the pentacyclic compounds with methylamine or ethylamine

The compound **1** or **2** (~100 mg) was taken in 10 mL of dry benzene and the solution was cooled in an ice-water bath (5–10°C). Methylamine gas or ethylamine gas (produced by heating an aqueous solution of the amine in a water bath) was passed through this solution for 0.5 h and then the reaction mixture was allowed to come to room temperature and stirred for 0.5 h more. After this, the reaction was worked up by removing the solvent under reduced pressure on the rotavapor. The crude product mixture was loaded on a silica gel column and then successively eluted with 50, 80 and 90% ethyl acetate in petroleum ether followed by elution with pure ethyl acetate. The pure fractions were pooled together and crystallised from dichloromethane–petroleum ether mixture.

3.3.1. Spectral data for 4-azamethyl-6-bromomethyl-5-hydroxypentacyclo[5.4.1.0^{2,6}.0^{5,9}.0^{8,11}]dodec-10(13)-ene-3-one, 3a. Colourless crystalline solid, mp (°C): 200–202. FT-IR (KBr, ν_{max}/cm^{-1}): 3137, 2962, 2948, 1654, 1431, 1378, 1283, 1263, 1243, 1155, 1088, 1027, 899, 791. ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.87 (s, 1H), 4.79 (s, 1H), 3.79 (brs, 1H), 3.58 (s, 2H), 3.35 (brs, 1H), 3.07 (brs, 1H), 3.00–2.96 (m, 1H), 2.82–2.77 (m, 2H), 2.63 (s, 3H), 2.56 (d, J=4.9 Hz, 1H), 2.02 (d, J=10.4 Hz, 1H), 1.58 (d, J=10.5 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 171.2, 143.6, 108.9, 101.9, 63.1, 60.2, 55.9, 51.1, 49.5, 45.1, 44.4, 42.8, 34.7, 24.6. HRMS (M^{+}+1): 310.0437, $C_{14}H_{16}NO_2Br$ requires 309.0364. *Crystal data for* **3a**: CCDC No. 163822. $C_{14}H_{16}BrNO_2$, colourless crystalline solid, 0.30×0.24×0.20 mm^3, orthorhombic, space group: $P2_12_12_1$. Unit cell dimensions: a=6.4973(1) Å, α=90°; b=12.8707(2) Å, β=90°; c=15.6425(3) Å, γ=90°. R indices (all data): $R1$=0.0420, $wR2$=0.0857. Volume=1308.10(4) Å^3, Z=4. Density (calculated)=1.575 mg m^{-3}. F(000)=632. Absorption coefficient=3.136 mm^{-1}.

3.3.2. Spectral data for 7-bromomethyl-8-(*N*-methylcarbomoyl)tetracyclo[4.2.1.1^{4,7}.0^{2,5}]dec-3(11)-ene-10-one, 5a. Mp (°C): 129–131. FT-IR (KBr, ν_{max}/cm^{-1}): 2965, 2865, 1738, 1651, 1538, 1370, 1240, 1109, 885. ^{1}H NMR (300 MHz, CDCl$_3$+CCl$_4$): δ 5.26 (brs, 1H), 5.03 (s, 1H), 4.86 (s, 1H), 3.74 (d, J=10.4 Hz, 1H), 3.40 (d, J=10.4 Hz, 1H), 3.15–3.11 (m, 3H), 2.93–2.89 (m, 3H), 2.53 (d, J=4.6 Hz, 3H), 1.63 (d, J=10.4 Hz, 1H), 1.52 (d, J=10.4 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$+CCl$_4$): δ 214.5, 170.7, 146.6, 111.6, 58.8, 56.8, 46.2, 45.8, 44.5, 41.9, 39.6, 38.3, 33.8, 26.1. HRMS (M^{+}+1): 310.0386, $C_{14}H_{16}BrNO_2$ requires 309.0364.

3.3.3. Spectral data for 3b. Mp (°C): 231–233. FT-IR (KBr, ν_{max}/cm^{-1}): 3349, 3074, 2980, 2874, 1651, 1539, 1414, 1345, 1270, 1133, 1095, 877. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.94 (brs, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 3.75 (d, J=11.1 Hz, 1H), 3.69 (d, J=11.1 Hz, 1H), 3.39–3.32 (m, 3H), 3.09 (s, 1H), 3.04–2.97 (m, 3H), 2.79 (d, J=5.3 Hz, 1H), 2.15 (d, J=10.7 Hz, 1H), 1.55 (d, J=10.6 Hz, 1H), 1.25–1.12 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 176.6, 139.6, 113.8, 104.8, 55.7, 54.7 (2C), 50.2, 50.0, 47.3, 42.2, 40.6, 38.1, 36.3, 16.3. HRMS (M^{+}): 323.0519, $C_{15}H_{18}NO_2Br$ requires 323.0521.

3.3.4. Spectral data for 5b. Mp (°C): 159–161. FT-IR (KBr, ν_{max}/cm^{-1}): 3093, 2980, 2868, 1732, 1695, 1414, 1276, 1251, 1139, 883. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.23 (brs, 1H), 4.91 (s, 1H), 4.83 (s, 1H), 3.73 (d, J=10.7 Hz, 1H), 3.56 (d, J=10.7 Hz, 1H), 3.31 (brs, 1H), 3.21 (brs, 1H), 3.15–3.08 (m, 3H), 2.93–2.88 (m, 2H), 2.76 (d, J=4.9 Hz, 1H), 2.01 (d, J=10.4 Hz, 1H), 1.46 (d, J=10.3 Hz, 1H), 1.08 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3, 168.4, 138.9, 111.8, 55.0, 54.4, 49.3, 48.7, 41.5, 39.6, 37.3, 35.2, 34.4, 34.1, 14.3. HRMS (M^+): 323.0515, $C_{15}H_{18}NO_2Br$ requires 323.0521.

3.3.5. Spectral data for 3c. Mp (°C): 225–227. FT-IR (KBr, ν_{max}/cm^{-1}): 3090, 2968, 1651, 1439, 1376, 1251, 1133, 1020. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.86 (s, 1H), 3.98 (brs, 1H), 3.77 (brs, 2H), 3.39 (brs, 1H), 3.15 (brs, 1H), 3.09–3.03 (m, 1H), 2.90–2.85 (m, 2H), 2.70 (s, 3H), 2.64 (d, J=4.7 Hz, 1H), 2.03 (d, J=10.8 Hz, 1H), 1.67 (d, J=10.5 Hz, 1H). ^{13}C NMR (75 MHz, Acetone-d$_6$): δ 170.3, 144.9, 108.0, 72.5, 63.1, 60.7, 54.9, 51.6, 48.8, 46.6, 45.2, 44.8, 42.8, 24.3. HRMS (M^++1): 266.0958, $C_{14}H_{16}NO_2Cl$ requires 265.0869.

3.3.6. Spectral data for 5c. Mp (°C): 130–132. FT-IR (KBr, ν_{max}/cm^{-1}): 2962, 2868, 1732, 1670, 1539, 1432, 1382, 1258, 1089, 1014, 889, 789, 727. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.23 (brs, 1H), 5.03 (s, 1H), 4.80 (s, 1H), 3.80 (d, J=11.2 Hz, 1H), 3.58 (d, J=11.2 Hz, 1H), 3.10–2.97 (m, 2H), 2.95–2.93 (m, 1H), 2.91–2.83 (m, 3H), 2.53 (d, J=4.3 Hz, 3H), 1.95 (d, J=10.4 Hz, 1H), 1.54 (d, J=10.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6, 170.1, 146.6, 111.4, 58.8, 55.8, 50.4, 46.2, 44.3, 43.1, 39.7, 38.7, 36.1, 26.4. HRMS (M^+): 265.0932, $C_{14}H_{16}ClNO_2$ requires 265.0869.

3.3.7. Spectral data for 4-azaethyl-6-chloromethyl-5-(*N*-ethylamino)pentacyclo[5.4.1.0^{2,6}.0^{5,9}.0^{8,11}]dodec-10-(13)-ene-3-one, 4. Mp (°C): 158–160. FT-IR (KBr, ν_{max}/cm^{-1}): 3307, 2971, 2927, 2871, 1689, 1402, 1346, 1290, 1259, 1141, 879, 792. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86–4.85 (m, 2H), 3.72 (d, J=11.5 Hz, 1H), 3.59 (d, J=11.5 Hz, 1H), 3.54–3.47 (m, 2H), 3.14 (brs, 1H), 3.01–2.94 (m, 1H), 2.87–2.76 (m, 4H), 2.69–2.65 (m, 2H), 2.48–2.46 (m, 1H), 1.99 (d, J=10.2 Hz, 1H), 1.63 (d, J=10.3 Hz, 1H), 1.20–1.09 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 144.8, 109.9, 93.3, 62.5, 57.2, 55.9, 51.3, 50.7, 47.0, 45.5, 44.3, 42.1, 37.7, 35.9, 15.9, 15.4. HRMS (M^+): 306.1497, $C_{17}H_{23}N_2OCl$ requires 306.1498.

3.3.8. Spectral data for 3d. Mp (°C): 243–245. FT-IR (KBr, ν_{max}/cm^{-1}): 3089, 2977, 2927, 1651, 1452, 1415, 1278, 1128, 1097, 879. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.87 (s, 2H), 3.84 (d, J=11.8 Hz, 1H), 3.73 (d, J=11.8 Hz, 1H), 3.63–3.56 (m, 1H), 3.43–3.36 (m, 1H), 3.14 (brs, 1H), 3.09–3.05 (m, 1H), 2.88–2.71 (m, 3H), 2.61 (d, J=5.3 Hz, 1H), 1.98 (d, J=10.5 Hz, 1H), 1.73 (s, 1H), 1.67 (d, J=10.5 Hz, 1H), 1.19–1.11 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 143.9, 110.0, 103.9, 63.3, 60.7, 55.7, 51.5, 49.2, 46.1, 45.4, 44.9, 42.8, 35.3, 15.2. HRMS (M^+): 279.1021, $C_{15}H_{18}ClNO_2$ requires 279.1026.

3.3.9. Spectral data for 5d. Mp (°C): 98–100. FT-IR (KBr, ν_{max}/cm^{-1}): 2971, 2871, 1738, 1645, 1533, 1458, 1278, 1147, 892. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.21 (brs, 1H), 5.06 (s, 1H), 4.86 (s, 1H), 3.82 (d, J=11.4 Hz, 1H), 3.57 (d, J=11.4 Hz, 1H), 3.21–3.18 (m, 1H), 3.10 (s, 2H), 3.08–2.95 (m, 4H), 2.86 (brs, 1H), 1.62 (d, J=10.4 Hz, 1H), 1.52 (d, J=10.4 Hz, 1H), 0.97 (t, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.3, 169.9, 146.4, 112.0, 58.9, 57.0, 46.2, 45.5, 44.1, 43.2, 41.9, 39.8, 38.9, 34.3, 14.1. HRMS (M^+): 279.1024, $C_{15}H_{18}ClNO_2$ requires 279.1026.

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