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Synthesis of new condensed nitrogen heterocyclic systems

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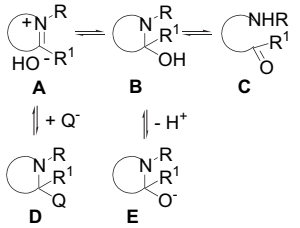
Dedicated to Professor C. Szántay on his 80th birthday

Abstract

A cotarnine alkaloid-based synthesis was developed for new heptacyclic condensed diisoquinolines via the double intramolecular pseudosalt bis[1,3]dioxolo[4,5-*g*;4′,5′-*g*′][1,3,4]oxadiazolo[2,3-*a*;5,4-*a*′]diisoquinoline **6**. Substitution of the central O atom in **6** by C, S, or N nucleophiles afforded the first representatives of the new ring systems bis[1,3]dioxolo[4,5-*g*:4,5-*g*′]pyrazolo[3,2-*a*:5,1-*a*′]diisoquinoline (**7a–d**), bis[1,3]dioxolo[4,5-*g*:4,5-*g*′][1,3,4]thiadiazolo[2,3-*a*:5,4-*a*′]diisoquinoline (**8**), and bis[1,3]dioxolo[4,5-*g*:4,5-*g*′][1,2,4]triazolo[3,2-*a*:5,1-*a*′]diisoquinoline (**9a–d**) under simple reaction conditions.

1. Introduction

It has been known for more than a century that in aqueous media certain heteroaromatic and hydroaromatic quaternary iminium hydroxides (Scheme 1, **A**) are in equilibrium with the isomeric aminocarbinols (**B**) (named pseudobases by Hantzsch[1]) and also with the open-chain carbonylamino tautomers of the latter (**C**).[2] Besides hydroxy groups, the iminium cations **A** undergo covalent bonding also with other nucleophlic anions; Hantzsch referred to the products as pseudosalts (Scheme 1, **D**, where Q denotes a substituted C, O, S, or N atom), a term accepted by Ingold.[3]



Scheme 1.

Upon the action of strong acids (e.g., hydrochloric acid), similarly to pseudobases **B**, pseudosalts **D** are transformed via covalent bond cleavage to the corresponding cations **A** (salts). With the aid of advanced spectroscopic methods, formation of the pseudobasic anion **E** (alkoxide) by deprotonation could be demonstrated in the complex equilibrium system.[2c,4]

Our interest in pseudobases started 50 years ago[5] with the study of cotarnine alkaloid, a pseudobase obtained from papaver alkaloids, and has continued up to the present.[6] Among others, a new isoquinoline synthesis was developed,[5] which was later adapted for the synthesis of *N*,*N*′-bisisoquinolines[7] (Scheme 2).

When azine **2**, formed[5] from cotarnone (**1**) and hydrazine, is boiled with alkali in aqueous *n*-butanol, an equilibrium mixture (**3**⇄**4**⇄**5**⇄**6**) of bis-pseudobases is formed, from which intramolecular ether **6** crystallizes out in excellent yield on cooling (Scheme 2).[7]

Following the Hantzsch notation, the symmetrical oxadiazolo-diisoquinoline **6** can be regarded as a double intramolecular pseudosalt. The structural rearrangement of pseudosalts

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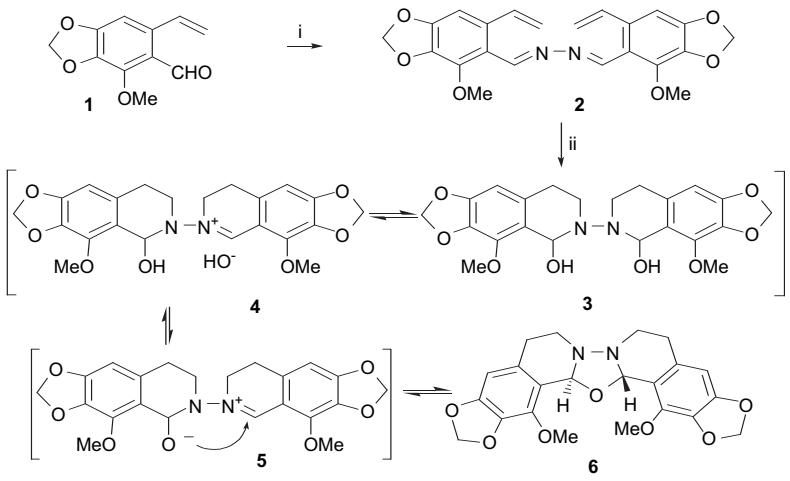


Scheme 2. Reagents and conditions: (i) H_2NNH_2, 20 °C; (ii) *n*-BuOH, KOH, H_2O, Δ, 4 h.

has long been known as demonstrated by our own earlier work[8] and more recent examples.[9] It therefore seemed probable that, on reaction with appropriate nucleophiles, the bis-pseudosalt **6** would form two new covalent bonds, giving rise by substitution of the central O atom to novel heterocyclic ring systems.

There are a number of examples in the literature for the preparation of bis-heterocycles containing an *N*–*N*′ bond,[10] and intramolecular ethers analogous to **6** are also known.[11] However, we are not aware of any examples of intended exchange reactions of intramolecular bis-pseudosalts analogous to **6** with the aim of the formation of two covalent bonds.

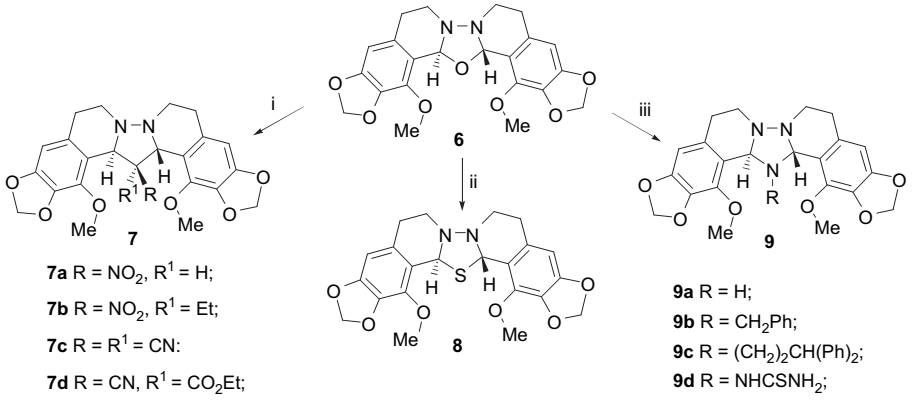
In this paper we report the replacement of the central O atom of the condensed heterocycle **6** by a C, S, or N atom, leading to three new heterocyclic systems.

2. Results and discussion

Our earlier experience[8] on the replacement 1-substituent of 1-alkoxy- and 1-arylamino-2-aryl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolines with N and O nucleophiles, respectively, led us to anticipate the desired transformations of **6** with C, S, or N nucleophiles would proceed without difficulty. In fact, heating **6** with an excess of a nucleophile in 96% ethanol (or in pyridine for **8**) in a closed vessel at 90 °C for 8 h was sufficient. Our results are summarized in Scheme 3.

O–C exchange, i.e., transformation of the central oxadiazole ring in **6** to a pyrazole ring (**6**→**7a**–**d**) was achieved simply by heating **6** with an excess of CH acidic compounds. O–S exchange was carried out by extending the method for carbonyl oxygens[12] by using phosphorus pentasulfide in pyridine. Ammonia and three primary amines were applied to transform the central oxadiazole ring of **6** to a triazole ring. It is reasonable to assume that the formation of the new ring systems in **7**, **8**, and **9** proceeds through the cation **4** as shown in Scheme 2. One covalent C–C, C–S, or C–N bond is first produced, and this is followed by the formation of the corresponding anion and ring closure analogous to the process **5**→**6**. In all cases only the thermodynamically most stable diastereomers, containing the 15b-H and 16a-H in trans positions, were formed under the equilibrium conditions.

The structures of the new compounds were supported by elemental analysis, IR, ^{1}H, ^{13}C and in case of **9d** by ^{15}N NMR spectroscopy, and, for **7a**, **7c**, **8**, **9a**, and **9c**, X-ray



7a R = NO_2, R^1 = H;
7b R = NO_2, R^1 = Et;
7c R = R^1 = CN:
7d R = CN, R^1 = CO_2Et;

9a R = H;
9b R = CH_2Ph;
9c R = $(CH_2)_2CH(Ph)_2$;
9d R = $NHCSNH_2$;

Scheme 3. Reagents and conditions: (i) 96% EtOH, 90 °C, 8 h, **7a** $MeNO_2$ (6 equiv), 98%, **7b** *n*-$PrNO_2$ (6 equiv), 68%, **7c** $CH_2(CN)_2$ (6 equiv); 80%, **7d** $CH_2CN(CO_2Et)$ (6 equiv), 69%; (ii) pyridine, 90 °C, 8 h, **8** P_2S_5 (4 equiv), 86%; (iii) 96% EtOH, 90 °C, 8 h, **9a** NH_3 (20 equiv), 85%, **9b** $PhCH_2NH_2$ (4 equiv), 68%, **9c** $Ph_2CH(CH_2)_2NH_2$ (4 equiv), 74%, **9d** $H_2NCSNHNH_2$ (4 equiv), 80%.

crystallography. The molecular structure of **7a** with the ring system numbering is depicted in Figure 1.

The conformations of the ring system in solid state are very similar in **7a**, **7c**, **8**, and **9a**, but different in **9c**, as illustrated by the endocyclic torsion angles in Figure 2.

The five-membered ring of **7a**, **7c**, **8**, and **9a** has a twisted conformation with N7 below and N8 above the ring. The two connected six-membered rings (N8, C9, C10, C10a, C15a, and C15b, and C4a, C5, C6, N7, C16a, and C16b) have an envelope conformation with C9 and C6 atoms, respectively, above the ring (see **7a** in Fig. 3a). As a consequence, C6 and C9 are axial to the five-membered ring. If R and R^1 substituents are identical in **7a** and **8**, the molecule may display crystallographic twofold symmetry. This is so in **8**. In contrast with the above structures, the bulky substituent on N16 in **9c** causes a significant change in the conformation of the central five-membered ring: it is an in envelope conformation with N16 above the ring, bringing the bulky substituent on N16 into an axial position (Fig. 3b).

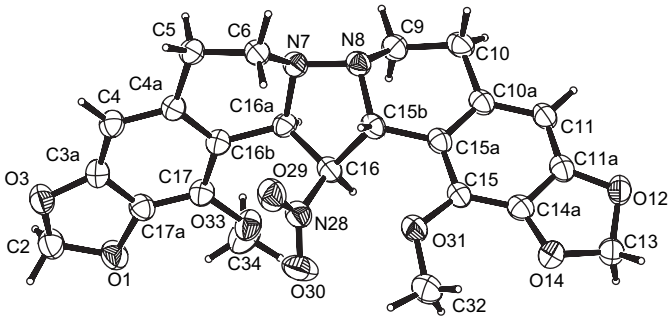


Figure 1. Molecular structure of **7a** with the ring system numbering.

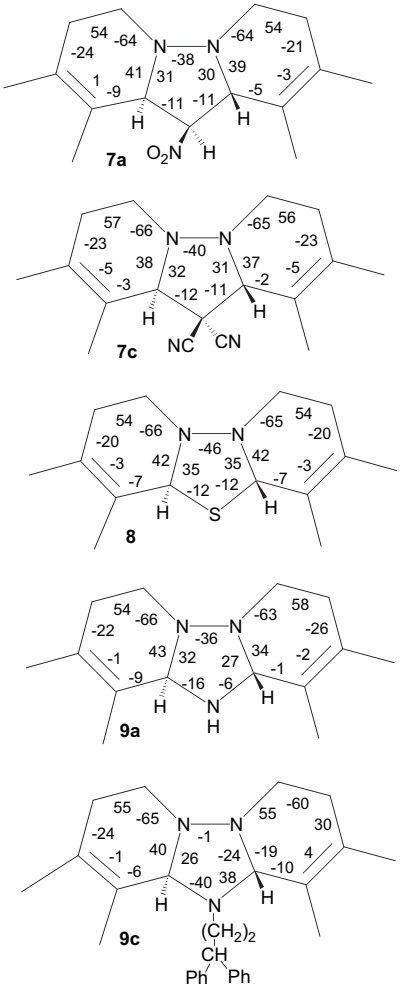


Figure 2. Endocyclic torsion angles for the central rings of **7a**, **7c**, **8**, **9a**, and **9c**.

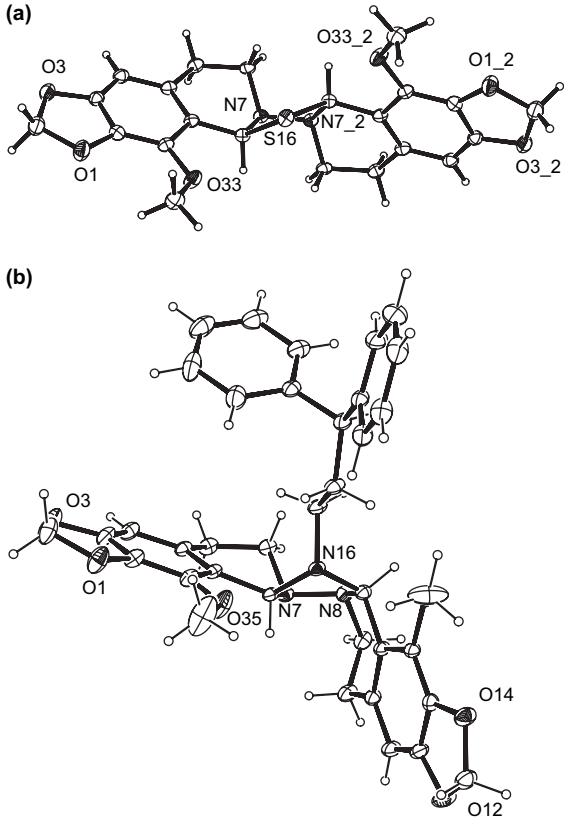


Figure 3. Comparison of the ring system conformations in **8** and **9c**.

3. Conclusions

The first members (**7a**–**d**, **8**, and **9a**–**d**) of three new ring systems, bis[1,3]dioxolo[4,5-*g*:4,5-*g*′]pyrazolo[3,2-*a*:5,1-*a*′]diisoquinoline, bis[1,3]dioxolo[4,5-*g*:4,5-*g*′][1,3,4]thiadiazolo[2,3-*a*:5,4-*a*′]diisoquinoline, and bis[1,3]dioxolo[4,5-*g*:4,5-*g*′][1,2,4]triazolo[3,2-*a*:5,1-*a*′]diisoquinoline, were synthesized by a simple novel method. The essence of the procedure is that the O atom of the central oxadiazole ring of bis[1,3]dioxolo[4,5-*g*:4,5-*g*′][1,3,4]oxadiazolo[2,3-*a*:5,4-*a*′]diisoquinoline (**6**), an intramolecular bis-pseudosalt, is replaced by a C, S, or N atom. This novel synthetic method can probably be extended to further heterocylic systems, starting from other bis-azaheterocyclics.

4. Experimental

4.1. General

IR spectra were recorded on a Zeiss Specord M-80 instrument in KBr pellets. ^{1}H (400 MHz), ^{13}C (100 MHz), and ^{15}N NMR (40.6 MHz) spectra were recorded on a Bruker DRX-400 instrument at room temperature in $CDCl_3$ unless noted otherwise. The J values are given in hertz. Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected.

4.2. X-ray crystallography

The data were collected on an MSC-Rigaku AFC6S diffractometer, using monochromated Cu Kα radiation (λ=1.5418 Å) except for **7a**, where the data were collected on an MSC-Rigaku RAxis instrument, using Mo Kα radiation (λ=0.7107 Å). All structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using, SHELXL software. All non-H atoms were refined with anisotropic displacement parameters. H atoms were placed in calculated positions and refined by using the 'riding model'. Crystallographic data for structures have been deposited as supplementary publications with the Cambridge Crystallographic Data Centre.

Crystal data for **7a**. $C_{23}H_{23}N_3O_8$ M=469.44, triclinic, space group P-1, a=9.306(2) Å, b=14.778(2) Å, c=8.548(2) Å, α=94.57(1)°, β=113.06(1)°, γ=101.96(1)°, U=1041.3(4) Å^3, F(000)=492, Z=2, D_x=1.497 Mg m^{-3}, μ=0.115 mm^{-1}, 4973 reflections (1.43°≤ϑ≤23.24°), 2833 unique data (R_{merge}=0.0467), final $wR_2(F^2)$=0.2388 for all data (313 refined parameters), conventional $R1(F)$=0.0646 for 2070 reflections with $I\geq 2\sigma$, GOF=0.985.

Crystal data for **7c**. $C_{25}H_{22}N_4O_6$, M=474.47, triclinic, space group P-1, a=8.908(3) Å, b=16.086(41) Å, c=8.316(2) Å, α=94.13(7)°, β=110.89(2)°, γ=75.60(6)°, U=1078.3(28) Å^3, F(000)=496, Z=2, D_x=1.461 Mg m^{-3}, μ=0.886 mm^{-1}, 4559 reflections (2.84°≤ϑ≤75.15°), 4281 unique data (R_{merge}=0.0497), final $wR_2(F^2)$=0.3154 for all data (331 refined parameters), conventional $R1(F)$=0.0080 for 2815 reflections with $I\geq 2\sigma$, GOF=1.182.

Crystal data for **8**. $C_{22}H_{22}N_2O_6S$, M=442.48, monoclinic, space group $C2/c$, a=25.691(4) Å, b=6.261(3) Å, c=12.785(2) Å, β=106.10(1)°, U=1976.0(9) Å^3, F(000)=928, Z=4, D_x=1.487 Mg m^{-3}, μ=1.849 mm^{-1}, 2005 reflections (3.38°≤ϑ≤75.13°), 1964 unique data (R_{merge}=0.0236), final $wR_2(F^2)$=0.2340 for all data (145 refined parameters), conventional $R1(F)$=0.053 for 1964 reflections with $I\geq 2\sigma$, GOF=0.819.

Crystal data for **9a**. $C_{22}H_{23}N_3O_6$, M=425.43, monoclinic, space group $P2_1/n$, a=10.040(4) Å, b=16.209(2) Å, c=12.030(2) Å, β=96.00(2)°, U=1947.1(9) Å^3, F(000)=896, Z=4, D_x=1.451 Mg m^{-3}, μ=0.891 mm^{-1}, 4116 reflections (4.59°≤ϑ≤75.16°), 3894 unique data (R_{merge}=0.1006), final $wR_2(F^2)$=0.2224 for all data (284 refined parameters), conventional $R1(F)$=0.0578 for 1133 reflections with $I\geq 2\sigma$, GOF=1.192.

Crystal data for **9c**. $C_{37}H_{37}N_3O_6$, M=619.70, triclinic, space group P-1, a=12.141(1) Å, b=13.451(3) Å, c=9.746(1) Å, α=92.77(1)°, β=104.71(1)°, γ=91.266(1)°, U=1536.7(4) Å^3, F(000)=656, Z=2, D_x=1.339 Mg m^{-3}, μ=0.741 mm^{-1}, 6400 reflections (3.29°≤ϑ≤75°), 6099 unique data (R_{merge}=0.1246), final $wR_2(F^2)$=0.2368 for all data (416 refined parameters), conventional $R1(F)$=0.0675 for 6099 reflections with $I\geq 2\sigma$, GOF=1.457.

4.3. Syntheses

All reactions were carried out in a screw cap Sovirel glass vessel with a wall thickness of 3 mm submerged in a water bath at 90 °C for 8 h.

4.3.1. (15bS*,16aS*)-15,17-Dimethoxy-16-nitro-5,6,9,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo-[4,5-g:4,5-g′]pyrazolo[3,2-a:5,1-a′]diisoquinoline (7a)

From the reaction of **6**[7] (0.21 g, 0.5 mmol) and nitromethane (0.18 g, 3 mmol) in 96% EtOH (30 mL), the product started to separate out during heating. After cooling, the product was filtered off, and washed with EtOH (2×10 mL) to give **7a** (0.23 g, 98%) as a colorless powder, mp 276–280 °C. Recrystallization from toluene did not change the mp [Found: C, 58.70; H, 4.77; N, 8.79. $C_{23}H_{23}N_3O_8$ requires C, 58.84; H, 4.94; N, 8.95.]. IR: ν_{max} 2956, 2892, 1625, 1541, 1482, 1391, 1369, 1222, 1112, 1050, 975, 756 cm^{-1}. ^{1}H NMR: δ=2.70 (m, 1H, 10-H$_e$), 2.76 (ddd, $J_{5ax,5e}$=16.3 Hz, $J_{5e,6ax}$=3.7 Hz, $J_{5e,6e}$=1.6 Hz, 1H, 5-H$_e$), 3.1–2.95 (m, 3H, 5-H$_{ax}$, 9-H$_e$, 10-H$_{ax}$), 3.13 (ddd, $J_{6ax,6e}$=10.2 Hz, $J_{5ax,6e}$=5.8 Hz, $J_{5e,6e}$=1.6 Hz, 1H, 6-H$_e$), 3.16 (m, 1H, 9-H$_{ax}$), 3.78 (ddd, $J_{5ax,6ax}$=12.2 Hz, $J_{6ax,6e}$=10.2 Hz, $J_{5e,6ax}$=3.7 Hz, 1H, 6-H$_{ax}$), 3.86 (s, 3H, 15-OCH$_3$), 4.03 (s, 3H, 17-OCH$_3$), 5.08 (d, $J_{16,16a}$=8.1 Hz, 1H, 16a-H), 5.31 (d, $J_{15b,16}$=6.8 Hz, 1H, 15b-H), 5.48 (dd, $J_{15b,16}$=6.8 Hz, $J_{16,16a}$=8.1 Hz, 1H, 16-H), 5.90, 5.89, 5.88, 5.85 (each d, J=1.5 Hz, each 1H, 2-H$_2$, 13-H$_2$), 6.30 (s, 1H, 4-H), 6.34 (s, 1H, 11-H) ppm. ^{13}C NMR δ=29.6, 30.0 (C-5, C-10), 46.3, 48.0 (C-6, C-9), 58.6, 59.2 (OCH$_3$), 60.6, 64.4 (C-15b, C-16a), 98.8 (C-16), 100.7, 100.9 (C-2, C-13), 101.5, 101.8 (C-4, C-11), 114.2, 118.1 (C-15a, C-16b), 129.0, 129.6 (C-4a, C-10a), 133.0, 133.5 (C-14a, C-17a), 140.0, 140.9 (C-15, C-17), 149.0, 149.2 (C-3a, C-11a) ppm.

4.3.2. (15bS*,16aS*)-16-Ethyl-15,17-dimethoxy-16-nitro-5,6,9,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo-[4,5-g:4,5-g′]pyrazolo[3,2-a:5,1-a′]diisoquinoline (7b)

The reaction of **6** (0.21 g, 0.5 mmol) and 1-nitropropane (0.27 g, 3 mmol) in 96% EtOH (30 mL) was performed as described above. The usual work-up and crystallization of the syrup obtained from toluene (100 mL) gave **7b**, 0.17 g (68%), as colorless crystals, mp 268–270 °C. Anal. Calcd for $C_{25}H_{27}N_3O_8$: C, 60.35; H, 5.47; N, 8.45. Found: C, 60.65; H, 5.75; N, 8.39. IR: ν_{max}, 2948, 2884, 1621, 1535, 1483, 1459, 1389, 1344, 1274, 1255, 1108, 1070, 971, 938, 790 cm^{-1}. ^{1}H NMR: δ=0.82 (t, J_{CH_2,CH_3}=7.5 Hz, 3H, CH$_3$), 2.11 (dq, ^2J=15.0 Hz, J_{CH_2,CH_3}=7.5 Hz, 1H, CH$_{2a}$), 2.74 (dq, ^2J=15.0 Hz, J_{CH_2,CH_3}=7.5 Hz, 1H, CH$_{2b}$), 2.82 (m, 1H, 5-H$_e$, 10-H$_e$), 2.98

(m, 1H, 10-H_a), 3.06–3.18 (m, 3H, 5-H_a, 6-H_e, 9-H_e), 3.25 (m, 1H, 9-H_a), 3.82 (s, 3H, 15-OCH_3), 3.97 (s, 3H, 17-OCH_3), 4.00 (ddd, $J_{5a,6a}$=12.0 Hz, $J_{6a,6e}$=10.4 Hz, $J_{5e,6a}$=4.6 Hz, 1H, 6-H_a), 5.01 (s, 1H, 16a-H), 5.76 (s, 1H, 15b-H), 5.85, 5.88, 5.89, 5.91 (each d, J=1.5 Hz, each 1H, 2-H_2, 13-H_2), 6.30 (s, 1H, 4-H), 6.34 (s, 1H, 11-H) ppm. ^{13}C NMR δ=10.1 (CH_3), 26.0 (CH_2), 29.4, 29.6 (C-5, C-10), 45.8, 46.0 (C-6, C-9), 58.5, 58.9 (OCH_3), 63.7, 66.3 (C-15b, C-16a), 100.7, 100.8 (C-2, C-13), 101.9, 102.3 (C-4, C-11), 107.2 (C-16), 115.1, 116.8 (C-15a, C-16b), 128.5, 130.3 (C-4a, C-10a), 133.4, 133.7 (C-14a, C-17a), 140.5, 141.1 (C-15, C-17), 148.9, 149.1 (C-3a, C-11a) ppm.

4.3.3. (15bR,16aR*)-15,17-Dimethoxy-5,6,9,10,16a16,-hexahydro-15bH-bis[1,3]dioxolo[4,5-g:4,5-g′]pyrazolo-[3,2-a:5,1-a′]diisoquinoline-16,16-dicarbonitrile (**7c**)*

When a mixture of **6** (0.21 g, 0.5 mmol) and malononitrile (0.20 g, 3 mmol) was heated in 96% EtOH (30 mL), precipitation of the product soon started. After completion of the reaction the product was filtered off, washed with 96% EtOH (2×20 mL), and recrystallized from DMF (25 mL) to give **7c** as glistening colorless crystals, 0.19 g (80%), mp>360 °C. Anal. Calcd for $C_{25}H_{22}N_4O_6$: C, 63.28; H, 4.67; N, 11.81. Found: C, 63.20; H, 4.76; N, 11.83. IR: ν_{max} 2943, 2868, 2248, 1626, 1481, 1462, 1429, 1391, 1224, 1107, 1055, 939, 838 cm^{-1}. ^{1}H NMR: δ=2.76 (m, 2H, 5-H_a, 10-H_a), 3.00–3.15 (m, 6H, 5-H_b, 10-H_b, 6-H_2, 9-H_2), 4.16 (s, 6H, OCH_3), 5.21 (s, 2H, 15b-H, 16a-H), 5.95 (d, ^2J=1.4 Hz, 2H, 2-H_a, 13-H_a), 5.96 (d, ^2J=1.4 Hz, 2H, 2-H_b, 13-H_b), 6.38 (s, 2H, 4-H, 11-H) ppm. ^{13}C NMR: δ=29.8 (C-5, C-10), 47.3 (C-6, C-9), 49.4 (C-16), 58.7 (OCH_3), 68.9 (C-5b, C-16a), 101.1 (C-2, C-13), 101.9 (C-4, C-11), 114.8, 115.8 (C-15a, C-16b, CN), 129.9 (C-4a, C-10a), 133.5 (C-14a, C-17a), 140.8 (C-15, C-17), 150.0 (C-3a, C-11a) ppm.

4.3.4. Ethyl (15bS,16aS*)-16-cyano-15,17-dimethoxy-5,6,9,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo-[4,5-g:4,5-g′]pyrazolo[3,2-a:5,1-a′]diisoquinoline-16-carbo-xylate (**7d**)*

Compound **6** (0.21 g, 0.5 mmol) was reacted with ethyl cyanoacetate (0.34 g, 3 mmol) in 96% EtOH (30 mL). Evaporation and recrystallization of the residue from toluene (70 mL) gave **7d**, 0.18 g (69%), as colorless crystals, mp 273–275 °C. Anal. Calcd for $C_{27}H_{27}N_3O_8$: C, 62.18, H; 5.21; N, 8.06. Found: C, 62.24; H, 5.13; N, 8.28. IR: ν_{max} 2957, 2850, 2244, 1731, 1624, 1487, 1392, 1226, 1114, 1049, 946, 795 cm^{-1}. ^{1}H NMR: δ=1.35 (t, J=7.2 Hz, 3H, CH_3), 2.72 (m, 1H, 10-H_e), 2.78 (m, 1H, 5-H_e), 2.95–3.15 (m, 4H, 5-H_{ax}, 6-H_e, 9-H_e, 10-H_{ax}), 3.30 (m, 1H, 6-H_{ax}), 3.68 (m, 1H, 9-H_{ax}), 3.89 (s, 3H, 17-OCH_3), 3.90–4.08 (m, 2H, OCH_2), 4.11 (s, 3H, OCH_3), 5.30 (s, 1H, 16a-H), 5.35 (s, 1H, 15b-H), 5.86 (d, J=1.5 Hz, 1H, 13-H_a), 5.87 (d, J=1.5 Hz, 1H, 13-H_b), 5.89 (d, J=1.5 Hz, 1H, 2-H_a), 5.90 (d, J=1.5 Hz, 1H, 2-H_b), 6.29 (s, 1H, 11-H), 6.38 (s, 1H, 4-H) ppm. ^{13}C NMR: δ=13.8 (CH_3), 29.4 (C-10), 30.2 (C-5), 46.2 (C-9), 47.0 (C-6), 58.5 (15-OCH_3), 59.0 (17-OCH_3), 62.1 (OCH_2), 62.9 (C-16), 67.7 (C-16a), 68.3 (C-15b), 100.7, 100.9 (C-2, C-13), 102.3 (C-11), 104.6 (C-4), 115.0 (C-15a), 116.7 (C-16b), 119.4 (CN), 129.5 (C-4a), 129.8 (C-10a), 132.7 (C-14a), 133.5 (C-17a), 140.5, 140.6 (C-15, C-17), 149.2 (C-11a), 149.3 (C-3a), 167.8 (COO) ppm.

4.3.5. (15bR,16aR*)-15,17-Dimethoxy-5,6,9,10-tetra-hydro-15bH,16aH-bis[1,3]dioxolo[4,5-g:4,5-g′][1,3,4]-thiadiazolo[2,3-a:5,4-a′]diisoquinoline (**8**)*

Compound **6** (0.42 g, 1.0 mmol) was reacted in the usual way with phosphorus pentasulfide (0.89 g, 4 mmol) in pyridine (10 mL). After evaporation of the solvent, the residue was triturated with water (20 mL), which had been adjusted to pH 8 by the addition of 2 N NaOH. The precipitate was filtered off, washed with water (2×20 mL), EtOH (2×25 mL), and with Et_2O (2×5 mL), to give 0.38 g (86%) of pure **8**, mp 274–276 °C. Recrystallization from chloroform–toluene (1:1) did not change the mp. Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.72; H, 5.01; N, 6.33; S, 7.25. Found: C, 59.84; H, 4.78; N, 6.10; S, 7.17. $C_{22}H_{22}N_2O_6S$ IR: ν_{max} 2900, 2846, 1624, 1481, 1456, 1400, 1389, 1271, 1228, 1112, 1050, 967, 933, 799 cm^{-1}. ^{1}H NMR: δ=2.72 (m, 2H, 5-H_a, 10-H_a), 2.95 (m, 2H, 5-H_b, 10-H_b), 3.08–3.23 (m, 4H, 6-H_2, 9-H_2), 4.03 (s, 6H, OCH_3), 5.89 (d, ^2J=1.4 Hz, 2H, 2-H_a, 13-H_a), 5.90 (d, ^2J=1.4 Hz, 2H, 2-H_b, 13-H_b), 5.97 (s, 2H, 15b-H, 16a-H), 6.34 (s, 2H, 4-H, 11-H) ppm. ^{13}C NMR: δ=30.1 (C-5, C-10), 46.6 (C-6, C-9), 59.4 (OCH_3), 67.2 (C-15b, C-16a), 100.8 (C-2, C-13), 102.1 (C-4, C-11), 119.7 (C-15a, C-16b), 127.9 (C-4a, C-10a), 134.1 (C-14a, C-17a), 140.7 (C-15, C-17), 148.8 (C-3a, C-11a) ppm.

4.3.6. (15bS,16aS*)-15,17-Dimethoxy-5,6,9,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo[4,5-g:4,5-g′]-[1,2,4]triazolo[3,2-a:5,1-a′]diisoquinoline (**9a**)*

Compound **6** (0.21 g, 0.5 mmol) was reacted with NH_3 (0.17 g, 10 mmol) in 96% EtOH (30 mL). The usual work-up and recrystallization from toluene (50 mL) gave **9a**, 0.18 g (85%), as colorless crystals, mp 220–223 °C. Anal. Calcd for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 62.16; H, 5.42; N, 10.0. IR: ν_{max} 3387, 3342, 2885, 1621, 1479, 1432, 1387, 1355, 1257, 1224, 1065, 983, 799 cm^{-1}. ^{1}H NMR: δ=2.72 (m, 2H, 5-H_a, 10-H_a), 2.94 (m, 2H, 5-H_b, 10-H_b), 3.13 (m, 4H, 6-H_2, 9-H_2), 4.00 (s, 6H, OCH_3), 5.32 (s, 2H, 15b-H, 16a-H), 5.89 (s, 4H, 2-H_2, 13-H_2), 6.34 (s, 2H, 4-H, 11-H) ppm. ^{13}C NMR: δ=29.5 (C-5, C-10), 47.1 (C-6, C-9), 59.5 (OCH_3), 68.1 (C-15b, C-16a), 100.8 (C-2, C-13), 102.0 (C-4, C-11), 120.6 (C-15a, C-16b), 129.4 (C-4a, C-10a), 134.5 (C-14a, C-17a), 141.9 (C-15, C-17), 148.7 (C-3a, C-11a) ppm.

4.3.7. (15bS,16aS*)-16-Benzyl-15,17-dimethoxy-5,6,9,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo-[4,5-g:4,5-g′][1,2,4]triazolo[3,2-a:5,1-a′]diisoquinoline (**9b**)*

Compound **6** (0.21 g, 0.5 mmol) was reacted with benzylamine (0.34 g, 4 mmol) in 96% EtOH (30 mL). After evaporation, trituration of the residue with water (3×20 mL) caused the product to solidify. Recrystallization from *n*-hexane (60 mL) afforded **9b**, 0.17 g (68%), as a colorless crystalline powder, mp 145–147 °C. Anal. Calcd for $C_{29}H_{29}N_3O_6$: C,

67.56; H, 5.67; N, 8.15. Found: C, 67.65; H, 5.73; N, 8.10. IR: ν_{max} 2913, 1618, 1481, 1385, 1360, 1318, 1224, 1054, 965, 936, 821, 734 cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.60 (ddd, $J_{5a,5b}$=$J_{10a,110b}$=15.7 Hz, $J_{5a,6b}$=$J_{9b,10a}$=7.8 Hz, $J_{5a,6a}$=$J_{9a,10a}$=4.3 Hz, 2H, 5-H_a, 10-H_a), 2.88 (ddd, $J_{5a,5b}$=$J_{10a,10b}$=15.7 Hz, $J_{5b,6a}$=$J_{9a,10b}$=6.4 Hz, $J_{5b,6b}$=$J_{9b,10b}$=4.0 Hz, 2H, 5-H_b, 10-H_b), 2.98 (ddd, $J_{6a,6b}$=$J_{9a,9b}$=11.7 Hz, $J_{5b,6a}$=$J_{9a,10b}$=6.4 Hz, $J_{5a,6a}$=$J_{9a,10a}$=4.3 Hz, 2H, 6-H_a, 9-H_a), 3.18 (ddd, $J_{6a,6b}$=$J_{9a,9b}$=11.7 Hz, $J_{5a,6b}$=$J_{9b,10a}$=7.8 Hz, $J_{5b,6b}$=$J_{9b,10b}$=4.0 Hz, 2H, 6-H_b, 9-H_b), 3.43 (s, 6H, OCH_3), 3.74 (d, ^2J=15.0 Hz, 1H, CH_{2a}), 3.84 (d, ^2J=15.0 Hz, 1H, CH_{2b}), 5.15 (s, 2H, 15b-H, 16a-H), 5.88 (s, 4H, 2-H_2, 13-H_2), 6.43 (s, 2H, 4-H, 11-H), 7.07–7.18 (m, 5H, Ph) ppm. ^{13}C NMR (DMSO-d_6): δ=28.2 (C-5, C-10), 49.0 (C-6, C-9), 56.2 (CH_2), 58.6 (OCH_3), 75.0 (C-15b, C-16a), 100.7 (C-2, C-13), 101.9 (C-4, C-11), 118.6 (C-15a, C-16b), 125.9 (C-4′), 127.4, 127.9 (C-2′, C-3′, C-5′, C-6′), 131.7 (C-4a, C-10a), 133.9 (C-14a, C-17a), 141.4 (C-15, C-17), 142.3 (C-1′), 148.4 (C-3a, C-11a) ppm.

4.3.8. (15bS,16aS*)-16-(3,3-Diphenylpropyl)-15,17-dimethoxy-5,6,9,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo[4,5-g:4,5-g′][1,2,4]triazolo[3,2-a:5,1-a′]diisoquinoline (**9c**)*

Compound **6** (0.21 g, 0.5 mmol) was reacted with 3,3-diphenylpropylamine (0.42 g, 2 mmol) in 96% EtOH (30 mL). The usual work-up and recrystallization from *n*-hexane–toluene (1:1) (70 mL) gave **9c**, 0.23 g (74%), as colorless crystals, mp 195–197 °C. Anal. Calcd for $C_{37}H_{37}N_3O_6$: C, 71.73; H, 6.02; N, 6.78. Found C, 71.55; H, 5.97; N, 6.61. IR: ν_{max} 2928, 2870, 1618, 1478, 1371, 1324, 1223, 1103, 1049, 955, 931, 752, 704 cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.05–2.35 (m, 2H, CH_2), 2.48 (m, 2H, 5-H_a, 10-H_a), 2.55–2.80 (m, 2H, NCH_2), 2.88 (m, 2H, 5-H_b, 10-H_b), 2.99 (m, 2H, 6-H_a, 9-H_a), 3.30 (m, 2H, 6-H_b, 9-H_b), 3.76 (t, J_{CH,CH_2}=6.5 Hz, 1H, CH), 3.80 (s, 6H, OCH_3), 4.96 (s, 2H, 15b-H, 16a-H), 5.96 (s, 4H, 2-H_2, 13-H_2), 6.51 (s, 2H, 4-H, 11-H), 7.07–7.27 (m, 10H, Ph) ppm. ^{13}C NMR (DMSO-d_6): δ=27.2 (C-5, C-10), 36.5 (CH_2), 48.6 (CH), 48.8 (C-6, C-9), 50.8 (NCH_2), 59.2 (OCH_3), 74.5 (C-15b, C-16a), 100.9 (C-2, C-13), 102.3 (C-4, C-11), 119.3 (C-15a, C-16b), 125.9 (C-4′, C-4″), 127.4, 128.4, 128.5 (C-2′, C-3′, C-5′, C-6′, C-2″, C-3″, C-5″, C-6″), 131.8 (C-4a, C-10a), 134.8 (C-14a, C-17a), 141.4 (C-15, C-17), 145.2, 145.7 (C-1′, C-1″), 148.2 (C-3a, C-11a) ppm.

4.3.9. 1-[(15bS,16aS*)-15,17-dimethoxy-5,6,10,16,16a-hexahydro-15bH-bis[1,3]dioxolo[4,5-g:4,5-g′][1,2,4]-triazolo[3,2-a:5,1-a′]diisoquinolin-16-yl]thiourea (**9d**)*

Compound **6** (0.21 g, 0.5 mmol) was reacted with thiosemicarbazide (0.18 g, 2 mmol) in 96% EtOH (30 mL). The usual work-up and crystallization from EtOH (60 mL) gave **9d**, 0.2 g (80%), as colorless crystals, mp (dec) 177–180 °C. Anal. Calcd for $C_{23}H_{25}N_5O_6S$: C, 55.31; H, 5.04; N, 14.02. Found: C, 55.40; H, 5.21; N, 13.87. IR: ν_{max} 3129, 3359, 3313, 2932, 1615, 1585, 1503, 1482, 1429, 1393, 1224, 1111, 1068, 1050, 948 cm^{-1}. ^1H NMR (DMSO-d_6): δ=2.60–2.85 (m, 4H, 5-H_2, 10-H_2), 2.94 (m, 2H, 6-H_e, 9-H_e), 3.16 (m, 1H, 9-H_{ax}), 3.31 (m, 1H, 6-H_{ax}), 3.89 (s, 3H, 17-OCH_3), 3.94 (s, 3H, 15-OCH_3), 5.16 (s 1H, 16a-H), 5.31 (s, 1H, 15b-H), 5.90–5.96 (m, 4H, 2-H_2, 13-H_2), 6.44 (s, 1H, 11-H), 6.45 (s, 1H, 4-H), 6.84, 7.59 (each d, ^2J=4.0 Hz, each 1H, NH_2), 8.29 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ=28.8 (C-10), 29.1 (C-5), 45.8 (C-6), 48.5 (C-9), 59.0 (17-OCH_3), 59.9 (15-OCH_3), 72.7 (C-16a), 75.4 (C-15b), 100.8, 100.9 (C-2, C-13), 101.4 (C-4), 101.9 (C-11), 113.6 (C-16b), 118.2 (C-15a), 130.8 (C-4a), 130.9 (C-10a), 132.8 (C-17a), 133.9 (C-14a), 141.4 (C-17), 142.5 (C-15), 148.6 (C-11a), 149.3 (C-3a), 181.9 (C=S) ppm. ^{15}N NMR (DMSO-d_6): δ=103.3 (NH_2), 106.9, 118.2 (N-7, N-8), 125.1 (N-16), 146.9 (NH) ppm.

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