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CHEMISTRY OF THE PSEUDOBASIC AMINO ALCOHOLS. PART 40. SYNTHESIS OF THREE NEW CONDENSED NITROGEN HETEROCYCLIC SYSTEMS

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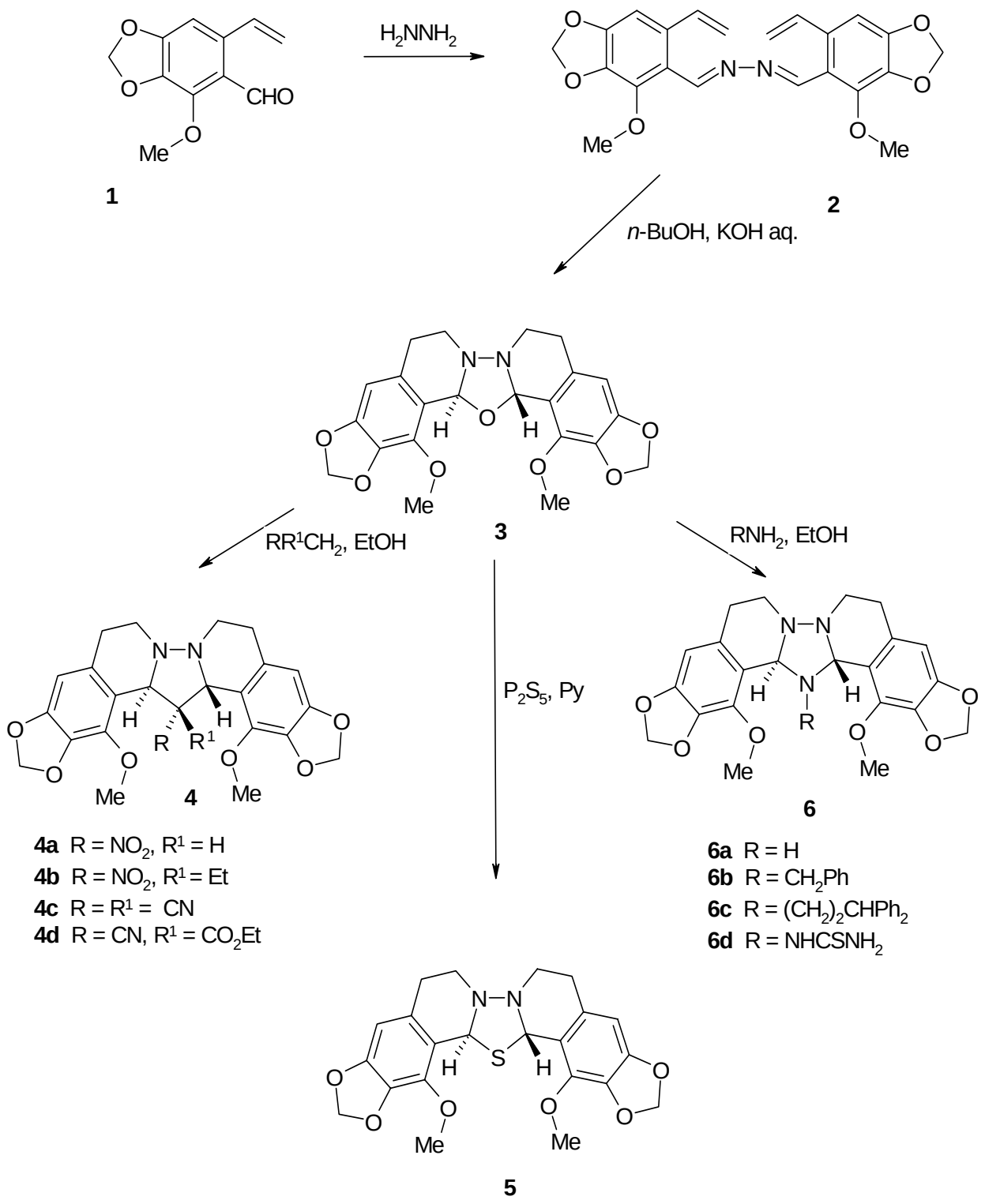
Abstract – Replacement of the central oxygen atom of the heptacyclic condensed diisoquinoline **3** by reaction with hydrazine, hydroxylamine or thiourea in a simple method gave three new heterocyclic ring systems involving 1,2,4,5-tetrazine (**7**), 1,2,4,5-oxatriazine (**8**) and 1,2,4,6-tetrazepine (**9**) central rings.

INTRODUCTION

More than half a century ago, we reported[1] a new isoquinoline ring-closure method by reacting cotarnone (**1**) (available by degradation of *Papaver* alkaloids) with amines. When azine **2** (formed from **1** and hydrazine) was heated with *n*-butanol and alkali, the condensed heterocycle **3** was obtained.[2] We recently described a simple new method for the transformation of intramolecular bis-pseudosalts[3] containing an N–N' bond, involving a double intramolecular nucleophilic substitution.[4] With this procedure, we substituted the O atom of the central oxadiazole ring of **3** with C, S and N atoms, leading to several members of the novel heterocyclic ring systems **4, 5** and **6** (Scheme 1). In the cases of compounds **4a-d, 5** and **6a-c**, the nucleophilic C, S and N atoms of the reagents permitted the transformation of only the central oxadiazole ring into another azole ring. In contrast, thiosemicarbazide, used for the preparation of **6d**, has more than one N atom bearing a mobile hydrogen and, in principle, formation of a ring comprising more than five atoms was therefore also conceivable. However, even with thiosemicarbazide, only the heptacycle **6d** containing a five-membered central triazole ring could be obtained.

This prompted us to investigate whether the tendency to form exclusively a five-membered central ring was also valid for other reagents containing more than one atom amenable to nucleophilic substitution.

In the present paper, we report on the reactions of **3** with hydrazine, hydroxylamine and thiourea.

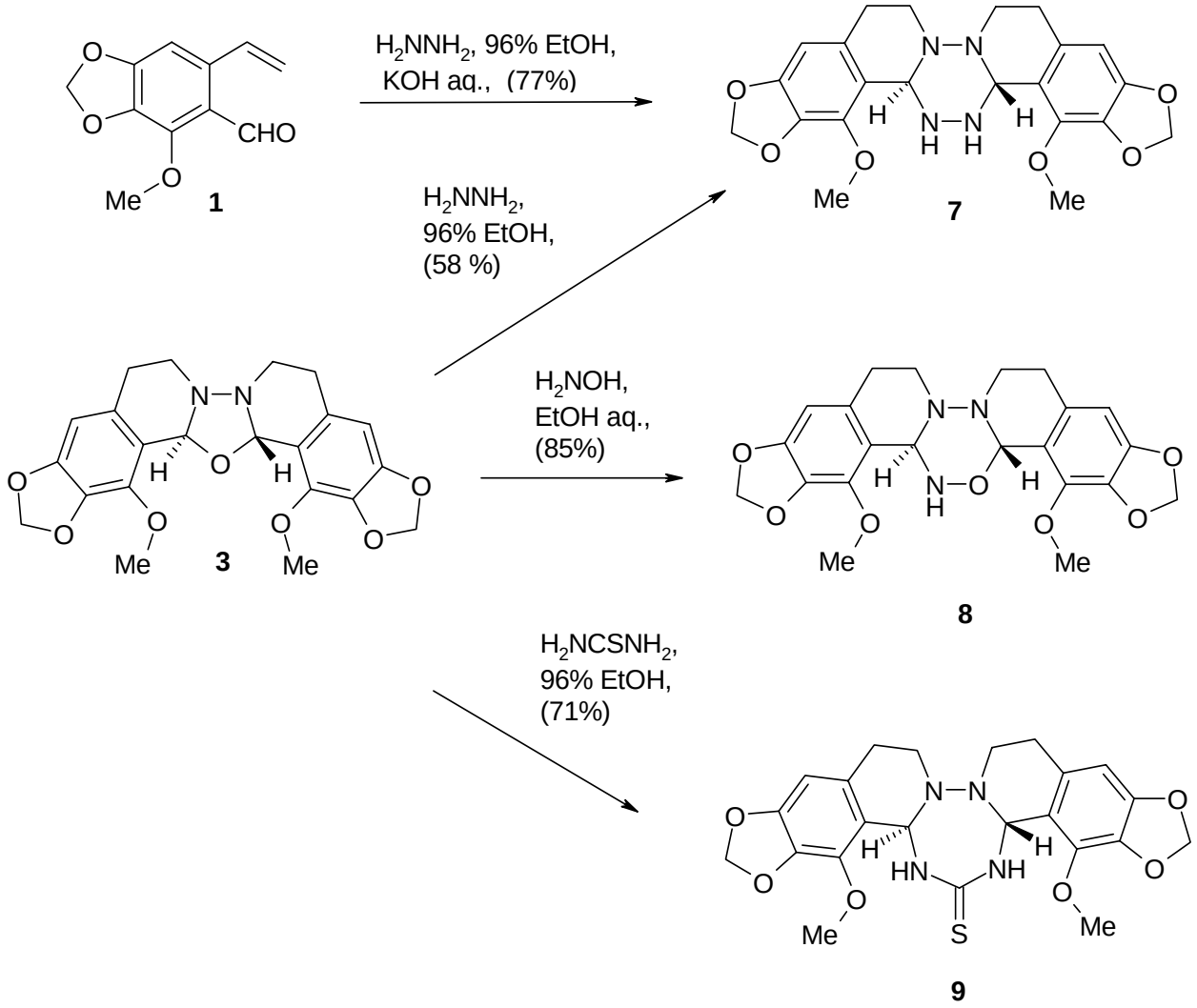


Scheme 1

RESULTS AND DISCUSSION

In view of our favorable experience with ammonia and amines (**3** → **6**) (Scheme 1),[4] **3** was reacted with hydrazine, hydroxylamine and thiourea in ethanol in a closed vessel at 90 °C. The results are shown in Scheme 2, from which it is apparent that, in contrast with what was found with thiosemicarbazide (**3** →

6d), in none of the cases did an oxadiazole → triazole transformation take place.



Scheme 2

The reaction of **3** with hydrazine gave rise to **7,** containing a 1,2,4,5-tetrazine central ring. The same product could be obtained in better yield directly from cotarnone (**1**) with an excess of hydrazine in ethanolic alkali, using our original isoquinoline ring-closure method[1] mentioned above.

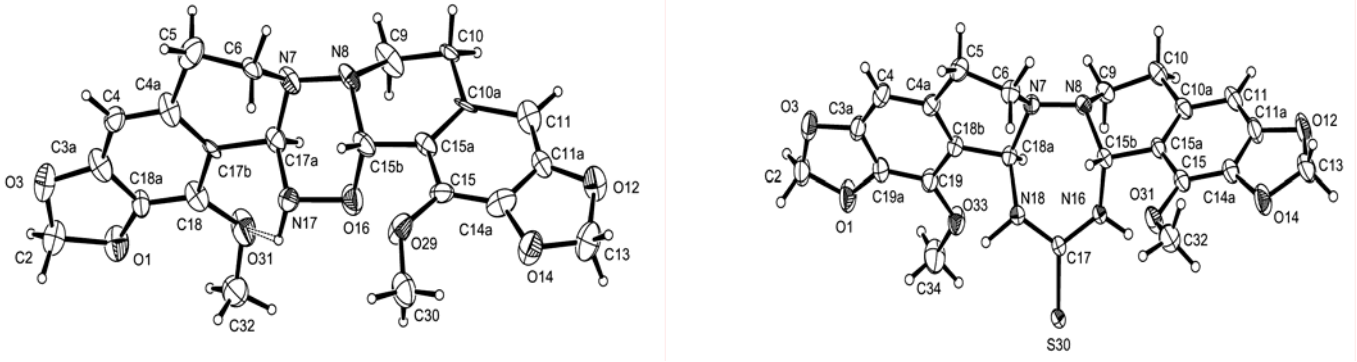
The outcome of the reaction with hydroxylamine was surprising inasmuch that, instead of the expected oxadiazole → triazole transformation, the product was heptacycle **8** containing a central 1,2,4,5-oxatriazine ring. The formation of **8** was unexpected, because the very extensive literature covering the reactions of hydroxylamine furnishes no example in which both O and N atoms establish covalent bonds with carbon atoms of the same type.

The reaction of **3** with thiourea did not lead (as with the transformation **3** → **6d**) to a product with a five-membered central ring either, but to the condensed heptacycle **9,** containing a central 1,2,4,6-tetrazepine ring.

It is to be noted that, under the equilibrium conditions applied, only the most stable diastereomers, i.e. those involving 15b-*H* and 17a-*H* in **7** and **8** and similarly 15b-*H* and 18a-*H* in **9** in the *trans* disposition, were formed.

The structures of the new compounds were supported by elemental analyses, IR, ^{1}H, ^{13}C NMR spectroscopy, and (for **8** and **9)** X-ray crystallography.

The molecular structures of **8** and **9,** with the numbering, are depicted in Figure 1. The central six-membered ring (N7, N8, C15b, O16, N17, C17a) of **8** has a chair conformation. The attached six-membered rings (N8, C9, C10, C10a, C15a, C15b and C4a, C5, C6, N7, C17a, C17b) have twisted conformations with N8 and N7 below and C9 and C6 above the ring. As a consequence, C6 and C9 are axial to the central six-membered ring. In **9,** the six-membered rings attached to the central one (N8, C9, C10, C10a, C15a, C15b and C4a, C5, C6, N7, C18a, C18b) have an envelope conformation, with N8 above and N7 below the ring.



8 **9**

Figure 1. Crystallographic structures of 8 and 9, shown for one of the enantiomers.

CONCLUSIONS

We have synthetized the first members (**7**, **8**, and **9**) of three new condensed ring systems:

bis[1,3]dioxolo[4,5-*g*:4,5-*g'*](1,2,4,5)tetrazino[3,2-*a*:6,1-*a*']diisoquinoline,

bis[1,3]dioxolo[4,5-*g*:4,5-*g*'](1,2,4,5)oxatriazino[3,4-*a*:6,5-*a*']diisoquinoline, and

bis[1,3]dioxolo[4,5-*g*:4,5-*g***'**](1,2,4,6)tetrazepino[3,2-*a*:7,1-*a*']diisoquinoline.

The results presented here allow the extension of the simple method published recently[4] for the transformation of intramolecular bis-pseudosalts to the straightforward synthesis of novel condensed heterocyclic ring systems with various ring sizes.

EXPERIMENTAL

GENERAL

IR spectra were recorded in KBr pellets with a Zeiss Specord M-80 instrument. ^{1}H (400 MHz) and ^{13}C

(100 MHz) NMR spectra were recorded on a Bruker DRX-400 instrument at room temperature, in $CDCl_3$ for **7** and **9**, and in DMSO-d_6 for **8.** Melting points were recorded in a Kofler hot-stage and are uncorrected.

X-RAY CRYSTALLOGRAPHY

The data were collected on an MSC-Rigaku AFC6S diffractometer, using monochromated Cu Kα radiation (λ=1.5418 Å).

All structures were solved by a 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 **8**. $C_{22}H_{23}N_3O_7$, M=441.43, monoclinic, space group *Cc*, *a*=27.32(4) Å, *b*=5.80(5) Å, *c*=13.01(2) Å, β=103.01(15)°, *U*=2009(17) Å^3, *F*(000)=928, *Z*=4, D_x=1.460 Mg m^{-3}, μ=0.924 mm^{-1}, 1976 reflections (3.32°≤ϑ≤75.18°), 1970 unique data, final $wR_2(F^2)$=0.2765 for all data (289 refined parameters), conventional $R1(F)$=0.0619 for 657 reflections with $I \geq 2\sigma$, GOF=1.009.

Crystal data for **9**. $C_{30}H_{32}N_4O_6S$ (the crystals contain one molecule of toluene), *M*=576.66, monoclinic, space group $P2_1/n$, *a*=17.162(8) Å, *b*=9.563(4) Å, *c*=17.432(4) Å, β=99.27(3)°, *U*=2823.5(19) Å^3, *F*(000)=1216, *Z*=4, D_x=1.357 Mg m^{-3}, μ=1.446 mm^{-1}, 5999 reflections (3.35°≤ϑ≤75.11°), 5804 unique data (R_{merge}=0.0255), final $wR_2(F^2)$=0.1407 for all data (391 refined parameters), conventional $R1(F)$=0.0463 for 3801 reflections with $I \geq 2\sigma$, GOF=1.016.

SYNTHESES

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

(15b*S,17a*S**)-15,18-Dimethoxy-5,6,9,10,15b,16,17,17a-octahydrobis[1,3]dioxolo[4,5-*g*:4,5-*g*']-[1,2,4,5]tetrazino[3,2-*a*:6,1-*a*']diisoquinoline (7)**

a) Following the reaction of **1**[1] (1.0 g, 5 mmol), hydrazine hydrate (1.0 g, 20 mmol), and KOH (56 mg, 0.1 mmol) in 96% EtOH (20 mL) and cooling, the product was filtered off and washed with EtOH (2 x 10 mL) **7** (0.85g, 77%) was obtained as colorless crystals, mp 233-235 °C. Recrystallization from DMF-toluene (1:1) did not change the mp. [Anal. Calcd for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.71. Found: C, 59.84; H, 5.29; N, 12.51.] $IR_{\nu max}$ 3229, 2886, 2822, 1628, 1483, 1390, 1273, 1255, 1224, 1077, 1025, 971, 835, 810, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (m, 2H, 5-H_e, 10-H_e), 3.00 (m, 2H, 5-H_{ax}, 10-H_{ax}), 3.05 (m, 2H, 6-H_e, 9-H_e), 4.03 (s, 6H, OCH_3), 4.05 (m, 2H, 6-H_{ax}, 9-H_{ax}), 5.72 (s, 2H, 15b-H, 17a-H), 5.89 (s, 4H, 2-H_2, 13-H_2), 6.34 (s, 2H, 4-H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ =

29.8 (C-5, C-10), 42.5 (C-6, C-9), 60.1 (OCH_3), 60.6 (C-15b, C-17a), 100.9 (C-2, C-13), 102.8 (C-4, C-11), 119.6 (C-15a, C-17b), 129.8 (C-4a, C-10a), 134.8 (C-14a, C-18a), 141.0 (C-15, C-18), 149.0 (C-3a, C-11a) ppm. b) Compound **3**[2] (0.21 g, 0.5 mmol) was reacted with hydrazine hydrate (0.1 g, 2 mmol), in 96% EtOH (30 mL). After evaporation and trituration of the residue with water (2 x 10 mL), the product solidified. Recrystallization from DMF-toluene (1:1, 70 mL) afforded **7** (0.63 g, 58%), mp 232-235 °C.

(15b*S,17a*S**)-15,18-Dimethoxy-5,6,10,15b,17a-hexahydro-9*H*-bis[1,3]dioxolo[4,5-*g*:4,5-*g*']-[1,2,4,5]-oxatriazino[3,4-*a*:6,5-*a*']diisoquinoline (8)**

Compound **3**[2] (0.32 g, 75 mmol), was reacted with hydroxylamine sulfate (3.28 g, 20 mmol) and sodium carbonate (2.23 g, 21 mmol) in a mixture of 96% EtOH (20 mL) and water (10 mL). The product was filtered off and washed with water (4 x 15 mL) to give **8** (0.28 g, 85%) as colorless crystals, mp 228-229 °C (unchanged on recrystallization from CCl_4). For the X-ray measurement, **8** (0.1 g) was crystallized from CCl_4 (35 mL). Anal. Calcd for $C_{22}H_{23}N_3O_7$: C, 59.86; H, 5.25; N, 9.52. Found: C, 59.77; H, 5.31, N, 9.36. IR_{vmax} 3254, 3060, 2885, 1626, 1480, 1383,1313, 1263, 1222, 1114, 1043, 954, 933, 901, 833, 776 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.63 (m, 2H, 5-H_e, 10-H_e), 2.75-2.92 (m, 4H, 5-H_{ax}, 6-H_e, 9-H_e, 10-H_{ax},), 3.73, 3.93 (each m, each 1 H, 6-H_a, 9-H_a), 3.90, 3.96 (each s each 3H, OCH_3), 5.61 (d $J_{17,17a}$ = 5.6 Hz, 1H, 17-H), 5.96 – 5.97 (m, 5H, 2-H_2, 13-H_2, 15b-H), 6.36 (d $J_{17,17a}$ = 5.6 Hz, 1H, 17a-H), 6.43, 6.44 (each s, each 1H, 4-H, 11-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 29.2, 29.4 (C-5, C-10), 42.8 (C-9), 43.5 (C-6), 59.8, 59.9 (OCH_3), 62.9 (C-17a), 78.3 (C-15b), 101.1, 101.2 (C-2, C-13), 102.4, 102.5 (C-4, C-11), 116.6 (C15a,), 117.9 (C-17b), 130.5, 130.6 (C-4a, C-10a), 133.9 (C-14a), 134.7 (C-18a), 140.9, 141.7 (C-15, C-18), 149.1, 149.5 (C-3a, C-11a) ppm.

(15b*S,18a*S**)-15,19-Dimethoxy-5,6,9,10,15b,16,18,18a-octahydro-17*H*-bis[1,3]dioxolo[4,5-*g*:4,5-*g*']-[1,2,4,6]tetrazepino[3,2-*a*:7,1-*a*']diisoquinoline-17-thione (9)**

Compound **3**[2] (0.21 g, 0.5 mmol) was reacted with thiourea (0.15 g, 2.0 mmol) in 96% EtOH (20 mL). After cooling, the product was filtered off and washed with EtOH (2 x 10 mL) to give **9** (0.17 g, 71%) as colorless crystals, mp 201-203 °C (unchanged on recrystallization from toluene and drying in a vacuum-desiccator over paraffin). Anal. Calcd for $C_{23}H_{24}N_4O_6S$: C, 57.01; H, 4.99, N, 11.56. Found: C, 56.97; H, 4.99; N, 11.59. For the X-ray studies, **9** (0.1 g) was crystallized from toluene (50 mL) and measured without drying. IR_{vmax} 3363, 2921, 1628, 1502, 1477, 1460, 1411, 1384, 1360, 1335, 1269, 1219, 1174, 1153, 1105, 1065,1042, 974, 933, 806. cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.67 (dd, $J_{5e,5ax} = J_{10e,5ax}$ = 16.3, $J_{5e,6ax} = J_{9ax,10e}$ = 4.2 Hz, 2H, 5-H_e, 10-H_e), 2.90 (dd, $J_{6e,6ax} = J_{9e,9ax}$ = 11.2, $J_{5ax,6e} = J_{9e,10ax}$ = 7.2 Hz, 2H, 6-H_e, 9-H_e), 3.73 (ddd, $J_{5e,5ax} = J_{10e,10ax}$ = 16.3, $J_{5ax,6ax} = J_{9ax,10ax}$ = 11.2, $J_{5ax,6e} = J_{9e,}$

J_{10ax} = 7.2 Hz, 2H, 5-H_{ax}, 10-H_{ax}), 3.73 (td, $J_{6e, 6ax} = J_{9e, 9ax} = J_{5ax, 6ax} = J_{9ax, 10ax}$ = 11.2, $J_{5e, 6ax} = J_{9ax, 10e}$ = 4.2 Hz, 2H, 6-H_{ax}, 9-H_{ax}), 4.14 (s, 6H, OCH_3), 5.88 (b, 4H, 15b-H, 16-H, 18-H, 18a-H), 5.90 (d, $J_{2a, 2b} = J_{13a, 13b}$ =1.3 Hz, 2H, 2-H_a, 13-H_a), 5.92 (d, $J_{2a, 2b} = J_{13a, 13b}$ =1.3 Hz, 2H, 2-H_b, 13-H_b) 6.30 (s, 2H, 4-H, 11-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.6 (C-5, C-10), 44.1 (C-6, C-9), 59.9 (OCH_3), 65.7 (C-15b, C-18a), 101.0 (C-2, C-13), 102.3 (C-4, C-11), 119.2 (C-15a, C-18b), 129.7 (C-4a, C-10a), 133.9 (C-14a, C-19a), 139.9 (C-15, C-19), 149.8 (C-3a, C-11a), 191.8 (C-17) ppm.

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