CHEMICAL MODIFICATION OF PLANT ALKALOIDS. 5. SPIROCYCLIC SYSTEMS BASED ON COTARNINE AND BARBITURIC ACIDS

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Cotarnine was reacted with barbituric acid and its N*-alkylbartituric and 1,3-dimethyl-2-thio analogs under forcing conditions to produce spirocyclic systems. Adducts, further transformations of which included skeletal rearrangements (a type of T-reaction) and subsequent deamination, were formed in the first step. The reaction of* N*-methylcotarnine and 1,3-dimethylbarbituric acid was analogous. The properties of the spirocyclic products were studied. They were further modified at the CH-acid and aromatic moieties.*

Key words: reaction of cotarnine with barbituric acid, spirocyclic products.

Cotarnine (**1**) is a biogenesis product of plants from the families Papaveraceae and Ranunculaceae. For example, it is one of the main alkaloids from *P. pseudoorientale* [1]. Cotarnine hydrochloride is used in medicine as a hemostatic agent [2].

The chemical properties and reactions of pseudobase **1** have been reviewed [3]. Many tetrahydroisoquinoline and phenylethylamine derivatives of **1** have been prepared, including alkaloids and their analogs.

We were interested in the transformation of cotarnine by 1,3-dimethylbarbituric acid (**2a**), which gave a Zwitter-ionic adduct (**3a**) and then formed 1,3-dimethyl-2,4,6-trioxoperhydropyrimidin-5-spiro-6′-[4′-methoxy-7′-(1,3-dimethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]-dioxolo[4,5-*g*]naphthalene (**4a**) [4]. The x-ray structure of **4a** and a hypothetical scheme of its formation have been discussed [5].

The goal of our work was to study similar reactions of cotarnine and the synthesis of new analogs of **4a**.

We found that the reaction of **1** with barbituric acids **2a-e** under forcing conditions (150-160°C) formed spirocyclic products **4a-e**. The reactions occurred through intermediate adducts **3a-e**, which were identified in the reaction mixtures by TLC and PMR. Pure standard **3a-e** were prepared as before [6]. In separate experiments, we showed that adding pure **3a-e** to the reaction (Scheme 1) gave the same final products **4a-e** in comparable yields (Table 1).

Thus, adducts **3a-e** acted as precursors for further spirocyclization that probably occurred as two combined reactions. In the first step, **3a-e** (relatively slowly) isomerized through **5** and **6** into intermediate amino derivatives **7**. In the second step, these intermediates (**7**) (rapidly) were deaminated by the starting CH-acids **2a-e** and converted into final products **4a-e**.

It was noted earlier that using triethylamine as the catalyst increased the yield of **4a** [5]. An analogous trend was observed for the reaction of **1** with 1,3-diethylbarbituric acid (**2b**), which produced **4b**. The yields of **4a** and **4b** under corresponding conditions were almost the same (Table 1). This indicated that the 1,3-dimethyl- and 1,3-diethyl-2,4,6-trioxopyrimidine moieties had almost the same reactivity in these conversions.

The reaction of **1** with unsubstituted barbituric acid (**2c**) was slightly more difficult. Adduct **3c** precipitated during the reaction and reacted more slowly (25 min) owing to the low solubility than its *N*,*N*-dialkyl derivatives **3a** and **3b** (8 min). Product **4c** was obtained in up to 13% yield. The reason for this was probably the reduced reactivity of intermediate **3c** and the instability of final product **4c** to hydrolysis and aminolysis side reactions. It is known that substituents on the N atoms increases markedly the hydrolytic stability of barbiturates [7].

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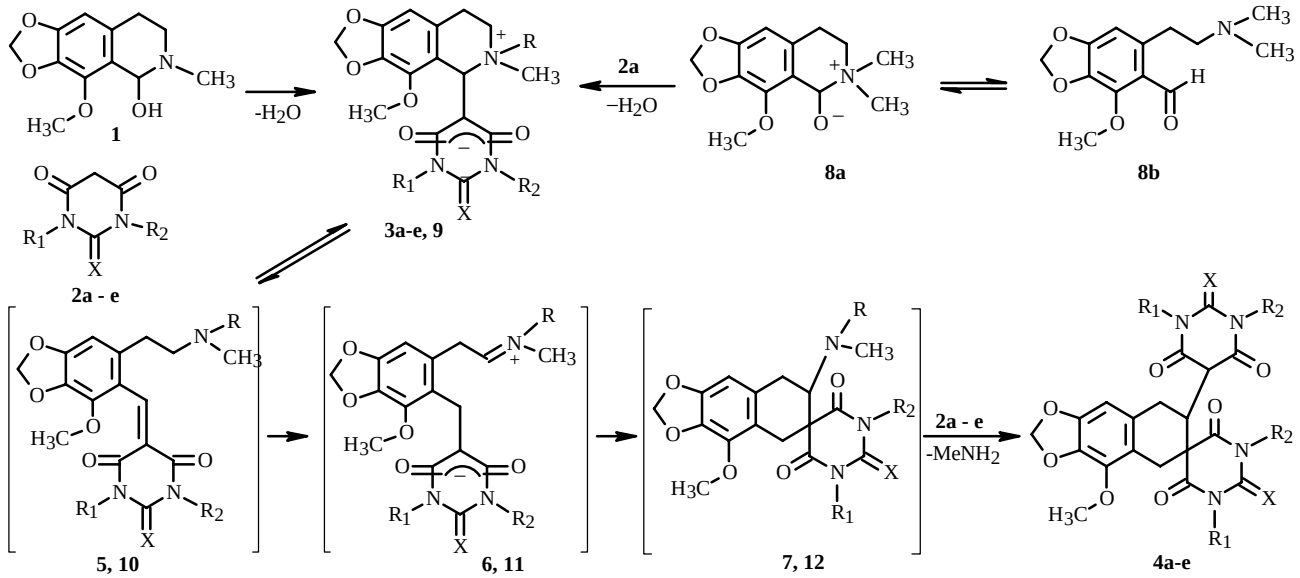
TABLE 1. Yield of Spirocyclic Derivatives **4a-e** from Reactions of Cotarnine (**1**) or Adducts **3a-e** with Acids **2a-e**

Starting material (ratio, mol)	Catalyst	Product	Yield, %
1 + 2a	-	**4a**	29
1 + 2a	NEt_3	**4a**	44
3a + 2a	NEt_3	**4a**	47
1 + 2b	-	**4b**	25
1 + 2b	NEt_3	**4b**	43
3b + 2b	NEt_3	**4b**	44
1 + 2c	-	**4c**	13
3c + 2c	-	**4c**	10
1 + 2d	-	**4d**	19
1 + 2e	-	**4e**	9



3a - e, 5, 6: R = H; **9 - 12:** R = R_1 = R_2 = CH_3

a: R_1 = R_2 = Me, X = O; **b:** R_1 = R_2 = Et, X = O; **c:** R_1 = R_2 = H, X = O; **d:** R_1 = Me, R_2 = H, X = O, **e:** R_1 = R_2 = Me, X = S

Scheme 1.

In a separate experiment it was shown that **4c** was converted by 50% in 10 min under the reaction conditions whereas its derivative **4a** lost only 2% under these same conditions. Adding triethylamine to the reaction mixture increased even further the rate of loss of **4c**.

The reaction of **1** with 1-methylbarbituric acid (**2d**) gave **4d** in 19% yield (Table 1). The reaction was also complicated by hydrolytic reactions.

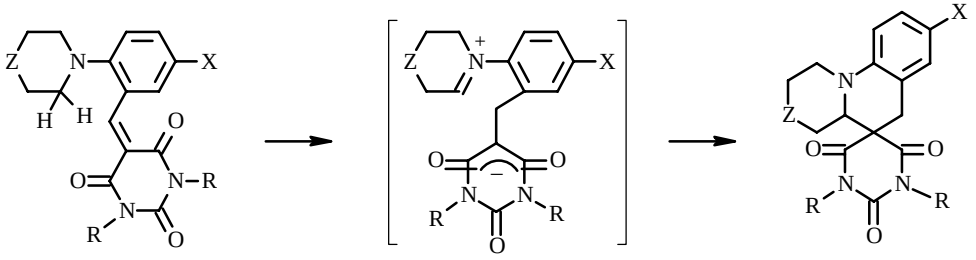
The reaction with 1,3-dimethyl-2-thiobarbituric acid (**2e**) went worst of all. Adduct **3e** was obtained quantitatively in the first step. However, it was converted further slowly and nonspecifically, with release of volatile sulfur compounds as side products. This feature and the low yield of spirocyclic thiobarbiturate **4e** indicated that the thioamide was unstable under the reaction conditions.

We studied the analogous reaction with *N*-methylcotarnine, a tautomeric system containing about 60% of the cyclic Zwitter-ionic form **8a** and up to 40% of the acyclic aldehyde form **8b** (see Experimental), as an example of a new substrate. Under the standard forcing conditions, the reaction with an excess of acid **2a** gave the expected known spirocyclic product **4a** (Scheme 1). Labile compounds **9** (26%) and **10** (16%), the contents of which were estimated from PMR spectra using the

characteristic resonances of the NCH and vinyl protons, were observed in the intermediate step in the product mixture at 20°C. Compound **9** gave the set of resonances ($CDCl_3$, δ, ppm) 3.16 (2H, t, $ArCH_2$), 3.23 (6H, s, 2NMe′), 3.39 (6H, s, NMe_2'), 3.82 (3H, s, OMe), 3.94 (2H, t, NCH_2), 5.42 (1H, s, NCH), 6.05 (2H, s, OCH_2O), 6.47 (1H, s, ArH) whereas the acyclic isomer **10** gave 2.91 (6H, s, NMe_2'), 3.00 (2H, t, $ArCH_2$), 3.17 (2H, t, NCH_2), 3.33 (6H, s, 2NMe), 3.86 (3H, s, OMe), 5.76 (2H, s, OCH_2O), 6.74 (1H, s, ArH), 8.21 (1H, s, =CH). Derivative **10** was an analog of intermediates **5** (Scheme 1) that could not be recorded earlier.

The observation of tautomeric intermediate **10** had fundamental significance for understanding the overall mechanism of such processes, primarily the hydrogen transfer mechanism from the NCH_2 group to C(1). (Such transfer is improbable in cyclic **9**.)

We propose that H^- transfer in **10** produced Zwitter-ion **11**, which cyclized into the spirocyclic intermediate **12**. Such a rearrangement is very similar to the T-reaction of 5-(*o*-dialkylaminobenzylidene)barbituric acids (**13**) that isomerize into spirocyclic derivatives **14** (Scheme 2) [8, 9].



13 **14**

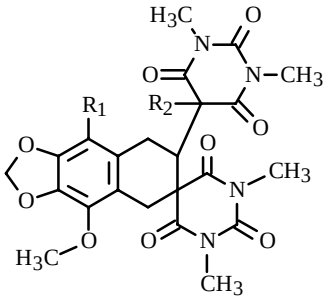
Scheme 2.

Cyclizations initiated by hydride loss from a NCH_2 group have been reviewed [10]. This type of conversion is known in heterocyclic chemistry as the *tert*-amino effect although such processes have not been described for the chemistry of natural compounds. The process shown in Scheme 1 is outside the scope of existing concepts of the *tert*-amino effect. The principle of the *tert*-amino effect did not include the possible formation of a ring without a N heteroatom whereas the isomerization of derivative **10** results in the closing of the carbocyclic system. The T-reaction of cotarnine adducts **3a-e** (Scheme 1) is even more unusual because the substrates, intermediates **5**, contain a secondary amino group whereas the *tert*-amino effect was known only for tertiary amines (anilines).

Considering these features, the rearrangement of the cotarnine and *N*-methylcotarnine adducts in Scheme 1 can be classified as a new type of T-reaction.

The properties and structures of spirocyclic derivatives **4a-e** are also interesting. These compounds are unexpectedly strong CH-acids. In particular, a pKa value of 1.10 was obtained for **4a** by spectrophotometry. This is 3.5 orders of magnitude greater than 1,3-dimethylbarbituric acid **2a** (pKa 4.65 [11]).

The chemical properties of spirocyclic CH-acids **4a-e** enable them to be used for further expansion of the range of this type of derivatives. For this, we carried out several reactions of **4a** with electrophilic reagents and prepared derivatives **15-21**.



15 - 21

15: R_1 = Br, R_2 = H; **16:** R_1 = R_2 = Br; **17:** R_1 = H, R_2 = Me

18: R_1 = H, R_2 = $CH_2CH{=}CH_2$; **19:** R_1 = H, R_2 = CH_2OH

20: R_1 = H, R_2 = CH_2NMe_2; **21:** R_1 = H, R_2 = CH_2CH_2(4-Py)

The electrophile was readily incorporated into the aromatic ring upon bromination of **4a**. The reaction of **4a** with an equivalent amount of Br_2 in acetic acid gave derivative **15**; with two equivalents of Br_2, dibromo derivative **16**.

In other examples, **4a** reacted with electrophilic reagents to form only the substitution products at the CH-acid atom C(5). Alkylation with methyliodide or allylbromide in the presence of triethylamine in $CHCl_3$ gave the corresponding alkyl derivatives **17** and **18** in moderate yield. The dimethylammonium salt of acid **4a** reacted with formaldehyde in water to form Mannich base **19**. For the trimethylammonium salt, hydroxymethyl derivative **20** was obtained. Addition of **4a** to 4-vinylpyridine in acetic acid gave Michael adduct **21** in practically quantitative yield.

Thus, it was demonstrated that CH-acid **4a** undergoes reactions characteristic of 5-monosubstituted barbituric acids [7]. This can be used to modify this interesting system.

In conclusion, we note again that we managed not only to open a new direction for modifying cotarnine but also to show that the *tert*-amino effect and T-reactions are possible in principle for natural compounds.

EXPERIMENTAL

PMR spectra were recorded on a Bruker AM-500 spectrometer at operating frequency 500 MHz; mass spectra, in an MX-1303 instrument with direct sample introduction into the ion source at 150°C and ionizing potential 70 eV. The purity of the products was monitored by TLC on Silufol UV-254 plates ($CHCl_3$:EtOAc, 5:1, or $CHCl_3$:EtOAc:CH_3CO_2H, 4:2:0.1), PMR spectra, and elemental analyses. Table 1 gives the yields for **4a-c**.

4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2*H*-1,3-methylenedioxy[4,5-*g*]isoquinolin-5-ol (cotarnine) (1) was isolated from cotarnine hydrochloride by the literature method [8].

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (4a). A solution of **2a** (4.68 g, 0.03 mol) in dimethylacetamide (15 mL) was stirred at 50°C, treated with cotarnine (**1**, 2.38 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol), refluxed at 155°C for 5 min, cooled, and treated with aqueous ammonia (5%, 50 mL). The precipitate was filtered off and washed with ammonia. The combined filtrate was acidified with conc. HCl. The resulting precipitate was separated and washed with water. The crude product was transferred to a flask, washed at 70°C with a mixture of ethanol (25 mL) and water (75 mL), and cooled. The precipitate was filtered off and washed with ethanol to afford **4a** (2.20 g), colorless crystals, mp 238-239°C (ethanol) (lit. [5] mp 234-235°C, CCl_4). The PMR, ^{13}C NMR, and mass spectra have been published [5].

Compound **4a** was prepared analogously from *N*-methylcotarnine (**8**, see below) and acid **2a**, yield 27%.

1,3-Diethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-diethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (4b) was prepared analogously to the aforementioned method from **1** and **2b**. Colorless crystals, $C_{27}H_{32}N_4O_9$, mp 188-190°C (ethanol).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.12 (3H, t, J = 7.1, CH_3), 1.17 (3H, t, J = 7.1, CH_3), 1.24 (6H, m, $2CH_3'$), 2.69 + 3.36 (1H each, dd, *ab*-system, J^1 = 15.5, 2H-8), 2.86 + 3.16 (1H each, d, J = 16.6, 2H-5), 3.50 (1H, m, J^1 = 5.9, H-7), 3.78 (4H, m, J = 7.1, $2NCH_2$), 3.85 (1H, d, J = 5.9, H-15), 3.91 (3H, s, OCH_3), 4.02 (4H, m, $2NCH_2$), 5.81 + 5.85 (1H each, d, *ab*-system, J = 1.5, OCH_2O), 6.24 (1H, s, ArH). Mass spectrum (*m*/*z*, *I*, %): 557 (5) $[M]^+$, 542 (8), 528 (3), 372 (100), 357 (17), 287 (4), 257 (11), 185 (6), 170 (5).

2,4,6-Trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (4c). Acid **2c** (3.84 g, 0.03 mol) was dissolved in dimethylacetamide (25 mL), treated at 50°C with **1** (2.38 g, 0.01 mol), stirred for 5 min to produce a suspension of adduct **3c**, heated to 150°C, stirred at this temperature for 20 min, cooled to 20°C, and treated with aqueous ammonia (2%, 75 mL). The resulting precipitate was separated, treated with HCl (20%, 20 mL), washed with water, and extracted again with aqueous ammonia (3%, 20 mL). The combined aqueous ammonia solution was acidified with AcOH and left for 30 min. The precipitate was separated. The solution was acidified with conc. HCl (20 mL) and left for 3 h at 10°C. The resulting crystals were filtered off, washed with water, and recrystallized from aqueous ethanol (50%) to afford **4c** (580 mg), colorless crystals, $C_{19}H_{16}N_4O_9$, mp 340-342°C.

PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.67 + 3.30 (1H each, dd, *ab*-system, J_1 = 14.2, 2H-8), 2.81 + 3.17 (1H each, d, J = 16.4, 2H-5), 3.50 (1H, m, J_1 = 5.9, H-7), 3.91 (3H, s, OCH_3), 3.93 (1H, d, J = 5.9, H-15), 5.85 + 5.86 (1H each, d,

ab-system, J = 1.5, OCH_2O), 6.32 (1H, s, ArH), 10.86 (1H, br.s, NH), 11.32 (2H, br.s, 2NH), 11.35 (1H, br.s, NH). Mass- spectrum (*m*/*z*, *I*, %): 444 (9) $[M]^+$, 316 (100), 287 (13), 273 (3), 231 (15), 205 (23), 127 (11).

The following compounds were prepared analogously from **1** and the appropriate acids **2d** and **2e**.

1-Methyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1-methyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (4d). A mixture of four diastereomers, colorless crystals, $C_{19}H_{16}N_4O_9$, mp 235-245°C (aqueous ethanol).

PMR spectrum of the main diastereomer ($CDCl_3$, δ, ppm, J/Hz): 2.63 + 3.28 (1H each, dd, *ab*-system, J_1 = 15.4, 2H-8), 2.90 + 3.16 (1H each, d, J = 17.2, 2H-5), 3.32 (3H, s, NCH_3), 3.37 (3H, s, NCH_3), 3.55 (1H, m, J_1 = 6.3, H-7), 3.81 (1H, d, J = 6.3, H-15), 3.94 (3H, s, OCH_3), 5.81-5.85 (1H each, d, *ab*-system, J = 1.5, OCH_2O), 6.27 (1H, s, ArH), 9.42 (1H, br.s, NH), 9.94 (1H, br.s, NH). Mass spectrum (*m*/*z*, *I*, %): 472 (9) $[M]^+$, 330 (100), 313 (17), 302 (2), 273 (3), 259 (5), 244 (6), 229 (11), 189 (2), 127 (5).

1,3-Dimethyl-2-thioxo-4,6-dioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-2-thioxo-4,6-dioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene (4e), light-yellow crystals, $C_{23}H_{24}N_4O_7S_2$, mp 155-169°C (aqueous ethanol).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.60 + 3.43 (1H each, m, *ab*-system, 2H-8), 2.71 + 3.22 (1H each, d, J = 17.1, 2H-5), 3.54 (1H, m, H-7), 3.57 (3H, s, NCH_3), 3.58 (3H, s, NCH_3), 3.63 (3H, s, NCH_3), 3.75 (3H, s, NCH_3), 3.87 (1H, d, J = 6.9, H-15), 3.92 (3H, s, OCH_3), 5.82 + 5.865 (1H each, d, *ab*-system, J = 1.5, OCH_2O), 6.30 (1H, s, ArH). Mass spectrum (*m*/*z*, *I*, %): 532 (20) $[M]^+$, 488 (3), 360 (100), 303 (16), 259 (33), 229 (25), 189 (5), 172 (40), 157 (19).

***N*-Methylcotarnine (8).** Cotarnine (**1**, 2.38 g, 0.01 mol) was dissolved in $CHCl_3$ (15 mL), treated with freshly distilled methyliodide (2.84 g, 0.02 mol), and left for 1 d at 20°C. The solvent was evaporated in vacuo. The crystalline solid was washed with ether and dried in vacuo. The product was dissolved in water (20 mL). The insoluble solid was filtered off. The filtrate was made basic with NaOH (0.5 g). The basic aqueous solution was extracted with CH_2Cl_2 (2 × 25 mL). The combined extracts were washed with water, dried over Na_2SO_4, and evaporated in vacuo to dryness to afford **8** (1.9 g, 77%), light-yellow crystals, $C_{13}H_{17}NO_4$, mp 154-156°C, a tautomeric mixture of **8a** and **8b**.

PMR spectrum ($CDCl_3$, δ, ppm): **8a** (60%) 3.37 (2H, m, CH_2Ar), 3.50 [6H, s, $+N(CH_3)_2$], 3.70 (2H, m, NCH_2), 4.03 (3H, s, OCH_3), 5.41 (1H, s, NCH), 5.87 (2H, s, OCH_2O), 6.31 (1H, s, ArH); **8b** (40%) 2.48 [6H, s, $N(CH_3)_2$], 2.87 (2H, m, NCH_2), 3.05 (2H, m, CH_2Ar), 4.11 (3H, s, OCH_3), 6.04 (2H, s, OCH_2O), 6.89 (1H, s, ArH), 10.32 (1H, s, CHO).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-8′-bromo-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (15). Compound **4a** (0.50 g, 0.001 mol) was dissolved in glacial acetic acid (25 mL), treated at 10°C over 10 min dropwise with bromine (0.16 g, 0.001 mol) in glacial acetic acid (5 mL), stirred for another 10 min, and diluted with water (70 mL). The resulting precipitate was separated, washed with water, and treated with aqueous ammonia (2%, 40 mL). The insoluble solid was separated. The aqueous ammonia solution was acidified with conc. HCl. The resulting crystals were filtered off, washed with water, and dried in air to afford **15** (0.44 g, 76%), colorless crystals, $C_{23}H_{23}BrN_4O_9$, mp 160-161°C (ethanol).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.82 + 3.15 (1H each, dd, *ab*-system, J_1 = 15.6, 2H-8), 2.87 + 3.25 (1H each, d, *ab*-system, J = 16.8, 2H-5), 3.18 (3H, s, NCH_3), 3.21 (3H, s, NCH_3), 3.33 (3H, s, NCH_3), 3.39 (3H, s, NCH_3), 3.49 (1H, m, J^1 = 6.0, H-7), 3.83 (1H, d, J = 6.0, H-15), 3.92 (3H, s, OCH_3), 5.92 + 5.95 (1H each, d, *ab*-system, J = 1.5, OCH_2O), 6.42 (1H, s, ArH).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-5-bromo-2,4,6-trioxoperhydropyrimidin-5-yl)-8′-bromo-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (16). A solution of **4a** (0.50 g, 0.001 mol) in glacial acetic acid (25 mL) was treated at 10°C over 10 min dropwise with bromine (0.32 g, 0.002 mol) in glacial acetic acid (5 mL), left for 40 min at room temperature, treated with water (several mL) until cloudy, and left at 10°C. The resulting crystals were separated; washed with water, aqueous ammonia (1%), and methanol; and dried in air to afford **16** (0.54 g, 82%), colorless crystals, $C_{23}H_{22}Br_2N_4O_9$, mp 230°C (dec., MeOH:AcOH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.79 + 3.31 (1H each, d, *ab*-system, J = 16.1, 2H-5), 3.18 (3H, s, NCH_3), 3.22 (3H, s, NCH_3), 3.25 (3H, s, NCH_3), 3.38 (3H, s, NCH_3), 3.70 (2H, m, J^1 = 9.0, 2H-8), 3.87 (3H, s, OCH_3), 3.91 (1H, dd, J^1 = 7.5, H-7), 5.98 (2H, s, OCH_2O).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3,5-trimethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (17). A solution of **4a** (0.50 g, 0.001 mol) in $CHCl_3$ (5 mL) was treated with freshly distilled triethylamine (0.101 g, 0.001 mol) and then methyliodide

(0.284 g, 0.002 mol), left for 3 d at room temperature, treated with $CHCl_3$ (15 mL), and organic layer was separated, washed with water, aqueous HCl (1%). The organic layer was dried over Na_2SO_4, and evaporated in vacuo to dryness. The solid was treated with hot hexane, washed with hexane, and dried in air to afford **17** (0.21 g, 41%), colorless crystals, $C_{24}H_{26}N_4O_9$, mp 231-233°C (CCl_4:hexane).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.53 (3H, s, CCH_3), 2.97 (2H, m, 2H-8), 2.99 + 3.26 (1H each, d, *ab*-system, J_1 = 16.0, 2H-5), 3.21 (6H, s, $2NCH_3$), 3.25 (3H, s, NCH_3), 3.31 (3H, s, NCH_3), 3.92 (3H, s, OCH_3), 5.83 + 5.86 (1H, d, *ab*-system, J = 1.5, OCH_2O), 6.36 (1H, s, ArH).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-5-allyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (18) was prepared by alkylation of **4a** with allylbromide using a method analogous to that above. Yield 48%, colorless crystals, $C_{26}H_{28}N_4O_9$, mp 219-221°C (CCl_4:hexane).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.71 + 2.86 (1H each, dd, *ab*-system, J_1 = 12.4, J_2 = 7.5, 2H-8), 2.98 (2H, d, J = 2.1, =CH$\underline{CH_2}$), 3.11 + 3.40 (1H each, d, *ab*-system, J = 15.6, 2H-5), 3.17 (3H, s, NCH_3), 3.21 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.32 (3H, s, NCH_3), 3.89 (3H, s, OCH_3), 5.04 (2H, m, J_1 = 14.0, $=CH_2$), 5.35 (1H, m, J_1 = 7.7, =CH), 5.84 + 5.86 (1H each, d, *ab*-system, J = 1.4, OCH_2O), 6.37 (1H, s, ArH).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-diemthyl-5-dimethylaminomethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (19). A solution of **4a** (0.50 g, 0.001 mol) in water (15 mL) with added aqueous dimethylamine (0.5 mL, 33%) was treated with aqueous formaldehyde (0.2 mL, 40%), refluxed for 5 h, and left overnight at room temperature. The resulting precipitate was separated, washed with water, and dried in air to afford **19** (0.28 g, 51%), colorless crystals, $C_{26}H_{31}N_5O_9$, mp 214-216°C.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.89 + 3.33 (1H each, d, *ab*-system, J = 16.2, 2H-5), 2.94 (2H, m, 2H-8), 2.80 (6H, s, NMe_2), 3.16 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.33 (3H, s, NCH_3), 3.36 (3H, s, NCH_3), 3.58 (1H, dd, J_1 = 11.3, H-7), 3.97 (3H, s, OCH_3), 5.84 + 5.85 (1H each, d, *ab*-system, J = 1.5, OCH_2O), 6.35 (1H, s, ArH).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-5-hydroxymethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (20). A solution of **4a** (0.50 g, 0.001 mol) in water (15 mL) with added alcoholic trimethylamine (25%, 0.5 mL) was treated with aqueous formaldehyde (0.4 mL, 40%), refluxed for 5 h, and left overnight at room temperature. The resulting precipitate was separated, washed with aqueous trimethylamine, and dried in air to afford **20** (0.34 g, 64%), colorless crystals, $C_{24}H_{26}N_4O_{10}$, mp 220°C (dec.).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.50-2.75 (3H, br.s, 2H-8 + OH), 3.14 (6H, s, $2NCH_3$), 3.22 (3H, s, NCH_3), 3.33 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 3.29 + 3.41 (1H each, d, *ab*-system, J = 13.0, HO$\underline{CH_2}$), 3.34 + 3.67 (1H each, d, *ab*-system, J = 14.6, 2H-5), 3.96 (3H, s, OCH_3), 4.07 (1H, dd, J_1 = 11.0, J_2 = 3.5, H-7), 5.85 + 5.92 (1H each, d, *ab*-system, J = 1.0, OCH_2O), 6.46 (1H, s, ArH).

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-{4′-methoxy-7′-(1,3-dimethyl-5-[2-(4-pyridyl)ethyl]-2,4,6-trioxoperhydropyrimidin-5-yl)-5′,6′,7′,8′-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene} (21). Compound **4a** (0.50 g, 0.001 mol) was dissolved with heating in glacial acetic acid (3 mL), treated with 4-vinylpyridine (0.115 g, 0.0011 mol), heated on a water bath for 30 min, and treated with water (10 mL). The precipitate was separated, washed with water and aqueous alcohol, and dried in a vacuum desiccator over KOH to afford **21** (0.57 g, 94%), colorless crystals, $C_{30}H_{31}N_5O_9$, mp 225-226°C (AcOH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.16-2.43 (4H, m, CH_2CH_2), 2.94 + 3.26 (1H each, d, *ab*-system, J = 15.5, 2H-5), 2.99 (2H, m, 2H-8), 3.18 (3H, s, NCH_3), 3.21 (3H, s, NCH_3), 3.28 (3H, s, NCH_3), 3.29 (3H, s, NCH_3), 3.37 (1H, dd, J_1 = 12.5, H-7), 3.92 (3H, s, OCH_3), 5.82 + 5.85 (1H each, d, *ab*-system, J = 1.5, OCH_2O), 6.33 (1H, s, ArH), 6.98 (2H, d, J = 5.8, 2PyH), 8.46 (2H, d, J = 5.8, 2PyH).

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