192. Synthesis of New 1,2,4-Trioxanes and their Antimalarial Activity

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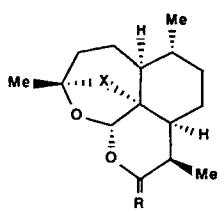
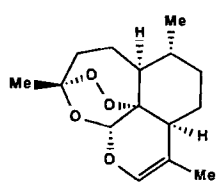
The three dihydronaphtho[1,2,4]trioxines **9–11** have been synthesized and two of them converted to the five carbamate and ester derivatives **12–16** (*Schemes 1* and *2*). The resulting new trioxanes together with two already known and ascaridole (**7**) were tested for antimalarial activity against the sensitive N strain of *Plasmodium berghei* in mice. On comparison with artemisinin (**1**) and dihydroartemisinin (**2**), modest activity was found. The four most active compounds were some 12–18 times less potent than **1**.

Introduction. – Artemisinin[1]) (**1**), dihydroartemisinin (**2**), and its derivatives are potent antimalarial agents [1]. Although these are sesquiterpene peroxides, the presence of the third O-atom in the same ring seems to be crucial. If one of the atoms of the peroxide group is removed, then the resulting deoxyartemisinin **3** has no antimalarial activity [2]. Other structural changes have profound consequences. The cleavage of any rings in artemisinin (**1**) [3] or the dehydration of dihydroartemisinin (**2**) to the olefin **4** destroys antimalarial activity [4]. Contrariwise, **2** is some ten times more active than **1** [5].



1 R = O, X = O–O
2 R = H, OH, X = O–O
3 R = O, X = O



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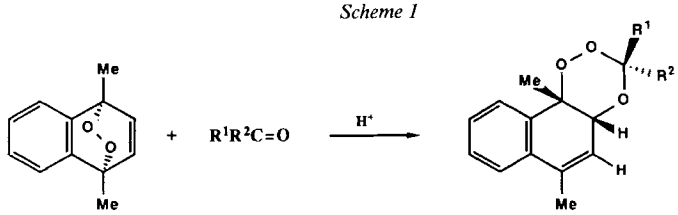
In the light of these observations, it seemed to us that simple trioxane derivatives [6] might be efficacious, if they could be rendered selectively toxic like the 4-aminoquinoline blood schizontocidal drugs [7] through their ability to accumulate in parasitized erythrocytes [8]. For example, chloroquine is concentrated into parasitized rodent erythrocytes

[1]) Artemisinin is also known as arteannuin and qinghaosu (QHS).

by factors of 600:1 compared to 14:1 for uninfected cells [9]. [^{3}H]Dihydroartemisinin is also concentrated, over 300 times, in erythrocytes infected by the *P. falciparum* parasite compared to a two-fold increase in uninfected erythrocytes [10] [11]. Furthermore, it appears that the uptake of dihydroartemisinin (**2**) and chloroquine by parasitized erythrocytes, and the cross-resistance of artemisinin (**1**) with certain blood schizontocidal drugs, despite their probably different modes of action [10] [12], may involve a common transport protein [13]. It may be supposed that this same protein could bind to the trioxane ring itself or to suitable substituents attached to it. We now describe the synthesis and *in vivo* testing of some 1,2,4-trioxanes bearing side chains attached to chloro and methoxyphenyl substituents, which in view of their known enhancement of antimalarial activity [14] might act as affinity groups.

Scheme 1



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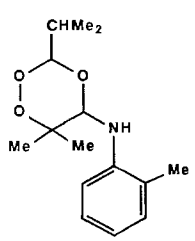
	R¹	R²
9a	CH_3	H
b	H	CH_3
10a	CH_2OH	H
b	H	CH_2OH
11a	$(CH_2)_6OH$	H
b	H	$(CH_2)_6OH$

Results and Discussion. – 3-Isopropyl-5-[(2′-methylphenyl)amino]-6,6-dimethyl-1,2,4-trioxane (**5**) [15], *trans*-perhydro-3,3-dimethylbenzo[*e*][1,2,4]trioxine (**6**) [16], and ascaridole (**7**) [17] were prepared according to literature procedures.

The dihydronaphtho[2,1-*e*][1,2,4]trioxines **9**–**11** were conveniently prepared by treating 1,4-dihydro-1,4-dimethyl-1,4-epidioxynaphthalene (**8**) with either acetaldehyde, hydroxyacetaldehyde, or 7-hydroxyheptanal in the presence of dilute sulfuric acid [18] [19] *(Scheme 1)*. Condensation created the *cis*-fused trioxane ring giving mixtures of the C(3) epimers (see **9a**/**b**, **10a**/**b**, and **11a**/**b**, resp.). Their configurations were easily identified by comparison with related compounds whose structures had been secured by X-ray [20].



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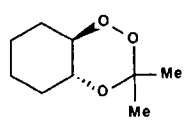

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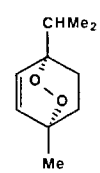

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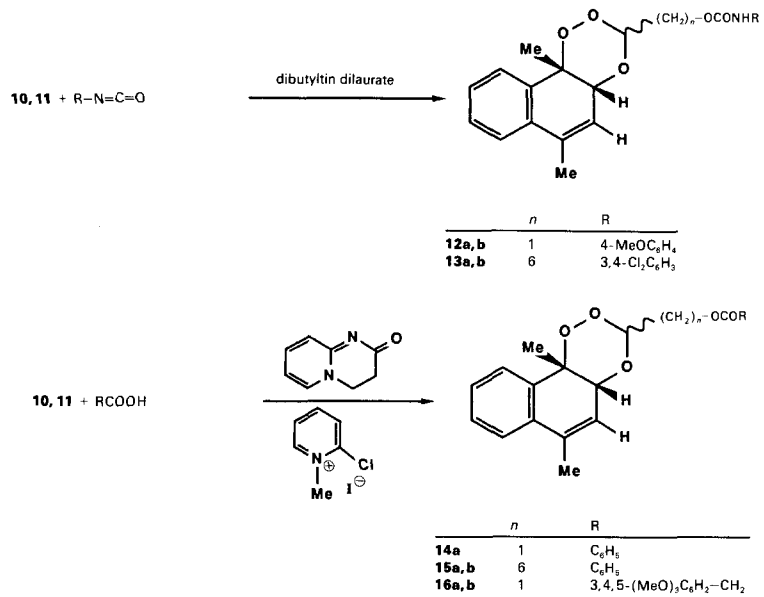
Esters and carbamates were chosen to attach the potential affinity groups since carboxylic acids and isocyanates are freely available. Unlike esters which are prone to enzymatic cleavage, carbamates are relatively inert to hydrolysis [21] and should have better chances of surviving to attack the erythrocyte. Carbamates **12** and **13** were prepared by reacting **10** and **11**, respectively, with 4-methoxyphenyl and 3,4-dichlorophenyl isocyanates using dibutyltin dilaurate as catalyst [22] *(Scheme 2)*. In each case, a pair of diastereoisomers was obtained.

Scheme 2



	n	R
12a,b	1	4-$MeOC_6H_4$
13a,b	6	3,4-$Cl_2C_6H_3$

	n	R
14a	1	C_6H_5
15a,b	6	C_6H_5
16a,b	1	3,4,5-$(MeO)_3C_6H_2$–CH_2

Esterifications of **10** and **11** with benzoic or (3,4,5-trimethoxyphenyl)acetic acid were most efficient when excess acid or base was avoided; the best yields were obtained by using 2-chloro-1-methylpyridinium iodide with 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one [23] (see **14**–**16**, *Scheme 2*).

The *'syn'* and *'anti'* diastereoisomers[2]) of **9**–**11** and the derivatives of **10** and **11** were distinguished by the ^{1}H-NMR signals for CH_3–C(10b) (1.25–1.33 and 1.79–1.97 ppm, resp.), H–C(4a) (4.09–4.20 and 4.44–4.48 ppm, resp.), and H–C(5) (5.92–5.97 and 5.77–5.85 ppm, resp.). The carbamates **12** did not exhibit the same pattern of differences owing to intramolecular chelation between the carbamic H-atom and the O(2) and O(4) atoms.

The parent trioxanes **9a,b** **10a,b**, and **11a,b** were formed in *'syn'/'anti'* ratios of 9:1, 2:1, and 4:1. These ratios are conserved in the carbamates **12a,b** and **13a,b** and the (trimethoxyphenyl)acetates **16a,b**. Acetates **16a,b** exist in solution essentially as enolates (^{1}H-NMR: 4 broad *d* at 5.22–5.32 ppm for the enolic vinyl protons due to the different *cis/trans* double bond geometries and *'syn'/'anti'* configurations). The remain-

[2]) The diastereoisomer with a *cis* relationship of the substituent at C(3) and the angular H-atom and CH_3 group is designated *'syn'*.

ing esters were obtained as the *'syn'* diastereoisomer for **14a** and in a *'syn'*/*'anti'* ratio of 6:1 for **15a/b**. Although aliphatic tertiary amines in CH_2Cl_2 generally cleave the peroxidic bond of C(3)-monosubstituted 1,2,4-trioxanes [24], a solution of **10** in $CDCl_3$ containing a 5-fold excess of Bu_3N was sufficiently stable for esterification to occur.

The aforementioned compounds were tested against the sensitive N-strain of *P. berghei* in mice *(Table)* [25]. None of the trioxanes, known or new, derivatized or not, displayed significant activity when compared to the standards artemisinin (**1**) and dihydroartemisinin (**2**). The most active trioxane is the known compound **6**, which unlike artemisinin and the remaining trioxanes, has a *trans*-fused bicyclic structure. The other known trioxane, the monocyclic 5-toluidino derivative **5**, is of comparable, low activity. Ascaridole (**7**) containing the peroxide function is inactive at the maximum tolerated dose.

Table. *Antimalarial Effects of Some 1,2,4-Trioxanes and Ascaridole* (**7**) *against N-Strain of* Plasmodium berghei *in Mice*[a])

Compd.[b])	ED_{50} (mean)	ED_{90} (mean)	Compd.[b])	ED_{50} (mean)	ED_{90} (mean)
1	2.5	5.4	**11**	42	540[d])
2	1.4	2.2	**12**	80	≫ 100
5	60	≫ 100	**13**	42	770
6	30	≫ 100	**14**	NA[e])	–
7	> MTD[c])	> MTD[c])	**15**	> 100	> 100
9	45	330	**16**	> 100	> 100
10	120	≫ 100			

[a]) Data from 4-day test [25].
[b]) Compounds were administered as a formulation in *Tween 80*/H_2O or 10% DMSO/H_2O (**14–16**).
[c]) MTD = maximum tolerated dose. The MTD (mg/kg × 4) was 10.
[d]) This value was interpolated graphically.
[e]) Not active.

Of the new trioxanes containing the dihydronaphthalene moiety, the derivatives **9–11** have activities which are about the same as those of the trioxanes **5** and **6**, with the longer side-chain derivative **11** performing the best. The inactivity of benzoates **14** and **15** may be due to the known poor metabolism of benzoic acid in mice infected with *P. berghei* [26]. The (trimethoxyphenyl)acetate **16** is equally inert. In contrast, the carbamates **12** and **13** show low activity. Although chloro and methoxy groups offer the greatest potential for increasing antimalarial activity in drugs such as dihydrotriazines and quinolines [14], in the present instance, the 4-methoxyphenyl derivative **12** is more active than its parent **10**, while the 3,4-dichlorophenyl analogue **13** only has the same activity as **11**.

Conclusions. – The present study shows that the attachment of potential affinity groups to simple 1,2,4-trioxanes confers no enhancement of antimalarial activity. Moreover, it appears that the 1,2,4-trioxane ring itself is a necessary, but not a sufficient condition to ensure significant activity. This conclusion has been reinforced by results recently obtained from the *in vitro* testing of tetrahydropyran-derived 1,2,4-trioxanes against *P. falciparum* clones [27]. Consequently, the relation between structure and activity, especially what is required beyond the trioxane entity, still needs to be defined.

Experimental Part

General. Chemicals for esterification were placed in *Schlenk* tubes in a dry box under dry N_2 and dry solvents transferred by syringe under a blanket of Ar. Initial purifications of products were effected by wide-bore (∅ 7 cm), short-column chromatography [28] using 230–400 mesh silica gel at 4°. Final purifications were accomplished by successive prep. TLC on several 20 × 20 cm × 20 mm silica gel F_{254} plates. The bands containing product were removed to short glass columns and extracted by flushing with CH_2Cl_2. Solvent was removed *in vacuo* first at 20 Torr then 0.5 Torr, taking care to prevent foaming, which otherwise made complete removal of solvent difficult. M.p. (uncorrected): *Büchi* apparatus. IR spectra: *Perkin-Elmer-681* spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra: *Bruker-WH-360* spectrometer; δ in ppm relative to internal TMS (= 0 ppm) and coupling constants J in Hz. MS: at 70 eV on a *CH-4 MAT* or *Finnigan GC/MS 4023* using the *INCOS* data system; *m/z* (% of the base peak). Microanalyses were performed by Dr. *H. J. Eder*, Service de Microbiochimie, Institut de Chimie Pharmaceutique, University of Geneva.

*(3*RS,*4a*SR,*10b*RS*)- and (3*RS,*4a*RS,*10b*SR*)-4a,10b-Dihydro-3,6,10b-trimethylnaphtho[2,1-e][1,2,4]trioxine* (**9a** and **9b**, resp.). To a soln. of 0.376 g (2 mmol) of 1,4-dihydro-1,4-dimethyl-1,4-epidioxynaphthalene [29] and 0.838 g (19 mmol) of acetaldehyde in 9 ml of nitromethane, 0.50 g of *Amberlyst 15* was added with stirring at r.t. After 15 h, the mixture was filtered through *Celite* and evaporated at 20 Torr. The resulting solid was purified by short-column chromatography: 0.439 g (94.6%) of colorless crystals. M.p. 93–97°. ^{1}H-NMR ($CDCl_3$; **9a/9b** 9:1, separable by HPLC [30]): major isomer **9a** *('syn')*: 1.18 (*d*, J = 6, Me–C(3)); 1.25 (*s*, Me–C(10b)); 2.17 (*d*, J = 1.6, Me–C(6)); 4.09 (*d*, J = 6.4, H–C(4a)); 5.48 (*q*, J = 6, H–C(3)); 5.92 (*dq*, J = 6.4, 1.6, H–C(5)); 7.20–7.45 (*m*, 3 arom. H); 7.69 (*d*, J = 7, 1 arom. H); minor isomer **9b** *('anti')*: 1.38 (*d*, J = 6, Me–C(3)); 1.97 (*s*, Me–C(10b)); 2.13 (*t*, J = 1.8, Me–C(6)); 4.44 (*quint.*, J = 1.8, H–C(4a)); 5.67 (*q*, J = 6, H–C(3)); 5.77 (*m*, H–C(5)); 7.26–7.43 (*m*, 3 arom. H); 7.63 (*d*, J = 8, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 100.94 (*d*, C(3) of **9a**); 96.26 (*d*, C(3) of **9b**). Anal. calc. for $C_{14}H_{16}O_3$ (232.30): C 72.38, H 6.96; found: C 72.43, H 6.92.

*(3*RS,*4a*SR,*10b*RS*)- and (3*RS,*4a*RS,*10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-methanol* (**10a** and **10b**, resp.). A soln. of 3.50 g (18.6 mmol) of 1,4-dihydro-1,4-dimethyl-1,4-epidioxynaphthalene and 5.00 g (83.3 mmol) of hydroxyacetaldehyde in 75 ml of THF was diluted with 18.5 ml of 3% *(v/v)* H_2SO_4/H_2O and stirred at r.t. for 20 h. The resulting soln. was added to 500 ml of H_2O and the mixture extracted with 7 × 100 ml of Et_2O. The combined Et_2O extracts were washed with 60 ml of sat. aq. $NaHCO_3$ soln., 2 × 60 ml of H_2O, and dried (Na_2SO_4). The solvent was evaporated initially at 20 Torr and then 0.01 Torr to yield 4.35 g (94.2%) of a pale yellow viscous oil, anal. pure. IR (neat): 3130–3650*s* (br.). ^{1}H-NMR ($CDCl_3$, **10a/10b** 2:1): **10a/10b**: 1.60–1.80 (br. *s*, OH); 7.28–7.45 (*m*, 3 arom. H); 7.56–7.73 (*m*, arom. H); major isomer **10a** *('syn')*: 1.28 (*s*, Me–C(10b)); 2.18 (*d*, J = 1.6, Me–C(6)); 3.47, 3.53 (2 *dd*, J = 12, 5, CH_2OH); 4.16 (*d*, J = 6.4, H–C(4a)); 5.49 (*t*, J = 5, H–C(3)); 5.95 (*d*, *q*, J = 6.4, 1.6, H–C(5)); minor isomer **10b** *('anti')*: 1.88 (*s*, Me–C(10b)); 2.15 (*d*, J = 1.8, Me–C(6)); 3.80 3.93 (2 *dd*, J = 12, 5, CH_2OH); 4.48 (*m*, H–C(4a)); 5.56 (*t*, J = 5, H–C(3)); 5.82 (*m*, H–C(5)). ^{13}C-NMR ($CDCl_3$): 102.81 (*d*, C(3) of **10a**); 98.54 (*d*, C(3) of **10b**). MS: 248 (8, M^+), 172 (23), 159 (100), 115 (20). Anal. calc. for $C_{14}H_{16}O_4$ (248.30): C 67.72, H 6.51; found: C 67.91, H 6.67.

*(3*RS,*4a*SR,*10b*RS*)- and (3*RS,*4a*RS,*10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-hexanol* (**11a** and **11b**, resp.). To a soln. of 12.1 g (106 mmol) of 7-hydroxyheptanal (prepared by the periodate oxidation of aleuritic acid [31]) in 85 ml of THF and 21 ml of 3% *(v/v)* H_2SO_4/H_2O was prepared by warming the originally inhomogeneous mixture in a water bath. After cooling, 4.00 g (21.2 mmol) of 1,4-dihydro-1,4-dimethyl-1,4-epidioxynaphthalene was added to the soln. and the mixture stirred at r.t. for 25 h. The org. solvent was evaporated at r.t. and the residue extracted with 3 × 200 ml Et_2O. The combined Et_2O extracts were washed with 2 × 25 ml of sat. aq. $NaHCO_3$ soln., 2 × 25 ml of H_2O and 4 × 25 ml of 30% $NaHSO_3$ soln. to remove aldehyde. Precipitated aldehyde $NaHSO_3$ addition product was dissolved by adding a little H_2O. The remaining org. layer was washed with 2 × 25 ml of H_2O, dried (Na_2SO_4), and evaporated to yield 4.73 g (73.9%) of a colorless oil, after purification by short-column chromatography. IR (neat): 3120–3660*s* (br.), 1646*w*, 1195*s*, 1087*s*, 753*s*. ^{1}H-NMR ($CDCl_3$, 0.122M; **11a/11b** 4:1): **11a/11b**: 0.83–1.83 (complex *m*, 4 CH_2, Me–C(10b), OH); 2.18 (*m*, Me–C(6)); 7.29–7.44 (*m*, 3 arom. H); 7.69 (*m*, 1 arom. H); major isomer **11a** *('syn')*: 1.44 (complex *m*, CH_2); 3.60, 3.65 (2 *t*, J = 6.4, CH_2OH); 4.09 (*d*, J = 6.4, H–C(4a)); 5.33 (*t*, J = 5.6, H–C(3)); 5.96 (*m*, H–C(5)); minor isomer **11b** *('anti')*: 1.51 (complex *m*, CH_2); 3.49, 3.51 (2 *t*, J = 6.4, CH_2OH); 4.47 (*m*, H–C(4a)); 5.52 (*t*, J = 5.6, H–C(3)); 5.80 (*s*, H–C(5)). MS: 318 (1.5, M^+), 172 (14.7), 159 (93.7), 115 (78.1), 87 (32.8), 31 (100). Anal. calc. for $C_{19}H_{26}O_4$ (318.45): C 71.67, H 8.23; found: C 71.41, H 8.30.

*(3*RS,*4a*SR,*10b*RS*)- and (3*RS,*4a*RS,*10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-methyl* N-*(4-Methoxyphenyl)carbamate* (**12a** and **12b**, resp.). A soln. of 0.84 g (5.6 mmol) of 4-methoxyphenyl isocyanate in 5 ml of dry CH_2Cl_2 was cooled to 4° and added to a soln. of 0.70 g (2.8 mmol) of **10** in 5 ml of

CH_2Cl_2 at 4°. Dibutyltin dilaurate (0.035 g, 0.056 mmol) was next added and the mixture stirred for 28 h. Fractionation by column chromatography (100 g of silica gel, MeOH/CH_2Cl_2 1:9) gave 0.84 g of impure product. Prep. TLC (3 plates, 3 successive elutions with CH_2Cl_2) furnished 0.53 g (47%) of a tan solid. IR (nujol): 3420–3220*m* (br.), 1740*m*, 1725*m*, 1712*m*, 1512*m*, 1218*m*, 1079*m*. ^{1}H-NMR ($CDCl_3$; **12a/12b** 2:1): **12a/12b**: 2.18 (*m*, Me–C(6)); 3.81 (2*s*, MeO); 5.62 (complex *m*, H–C(3)); 6.88 (*m*, 2 arom. H); 7.18–7.47 (complex *m*, 5 arom. H); 7.69 (*m*, 1 arom. H); indeterminate: 4.15 (complex *m*), 4.22 (*dd*, J = 6.6, 7.0), 4.45 (*dd*, J = 6.6, 11.6), 4.50 (br. *s*), 4.62 (*dd*, J = 4.6, 12.0; H–C(4a)); 3.95 (complex *m*), 4.15 (complex *m*; CH_2OH); major isomer **12a** (*'syn'*): 1.30 (*s*, Me–C(10b)); 5.97 (*m*, H–C(5)); 6.53 (br. *s*, NH); minor isomer **12b** (*'anti'*): 1.79 (*s*, Me–C(10b)); 5.85 (br. *s*, H–C(5)); 6.62 (br. *s*, NH). MS: no M^+, 384 (0.02), 209 (34), 172 (49), 159 (100), 149 (48), 134 (33), 115 (60). Anal. calc. for $C_{22}H_{23}NO_6$ (397.46): C 66.49, H 5.83, N 3.52; found: C 66.60, H 5.81, N 3.60.

*(3*RS*,4a*SR*,10b*RS*)- and (3*RS*,4a*RS*,10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-hexyl* N-*(3,4-Dichlorophenyl)carbamate* (**13a** and **13b**, resp.). A soln. of 0.74 g (3.9 mmol) of 3,4-dichlorophenyl isocyanate in 5 ml of dry CH_2Cl_2 was cooled to 4° and mixed with a soln. of 1.25 g (3.93 mmol) of **11** in 10 ml of CH_2Cl_2 at 4°. Dibutyltin dilaurate (0.15 g, 0.23 mmol) was added and the mixture stirred at 4° for 4 days. Fractionation by chromatography on 200 g of silica gel with CH_2Cl_2 yielded 0.21 g of solid. A further 1.20 g of crude oily product was obtained by eluting with 5% MeOH/CH_2Cl_2. Pure, partially crystallized, pale yellow oil (1.10 g, 55%) was obtained by prep. TLC (CH_2Cl_2, twice on 4 plates). IR (CCl_4): 3140–3560*m* (v. br.), 3440*m* (br.), 1743*s*, 1712 (sh), 1598*m*, 1580*m*, 1501*s*, 1203*s*, 1133*m*, 1089*m*. ^{1}H-NMR ($CDCl_3$; **13a/13b** 4:1): **13a/13b**: 1.10–1.80 (complex *m*, Me–C(10b), 4 CH_2); 2.15 (*m*, Me–C(6)); 4.12, 4.18 (2 *t*, J = 6, CH_2O); 7.15–7.44 (complex *m*, 5 arom. H); 7.58–7.73 (*m*, 2 arom. H); major isomer **13a** (*'syn'*): 1.44 (complex *m*, CH_2); 4.09 (*m*, H–C(4a)); 5.32 (*t*, J = 6.0, H–C(3)); 5.92 (*m*, H–C(5)); 6.61 (br. *s*, NH); minor isomer **13b** (*'anti'*): 1.51 (complex *m*, CH_2); 4.45 (*m*, H–C(4a)); 5.52 (*t*, J = 6.0, H–C(3)); 5.78 (br. *s*, H–C(5)); 6.64 (br. *s*, NH). MS: no M^+, 317 (4), 205 (23), 187 (21), 159 (100), 145 (17), 129 (17), 115 (32), 69 (73), 55 (48). Anal. calc. for $C_{26}H_{29}Cl_2NO_5$ (458.46): C 61.66, H 5.77, N 2.77, Cl 14.00; found: C 61.91, H 6.04, N 2.54, Cl 14.41.

*(3*RS*,4a*SR*,10b*RS*)- and (3*RS*,4a*RS*,10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-methyl Benzoate* (**14a**). A soln. of 0.50 g (3.4 mmol) of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one in 15 ml of dry CH_3CN was added to a soln. of 0.35 g (1.4 mmol) of **10**, 0.17 g (1.4 mmol) of benzoic acid, and 0.43 g (1.7 mmol) of 2-chloro-1-methylpyridinium iodide in 40 ml of dry CH_3CN under dry Ar. The mixture was stirred in the dark at r.t. for 6 h, then diluted with 40 ml of Et_2O. The insoluble residue was removed by filtration and dissolved in 30 ml of H_2O and 50 ml of Et_2O. The Et_2O layer was washed with 3 × 30 ml of H_2O, combined with the Et_2O filtrate and the org. solvent evaporated after drying (Na_2SO_4). Fractionation by prep. TLC (3 plates, CH_2Cl_2) gave **10** and 0.36 g (73%) of **14a** (*'syn'*) as a white, waxy solid. IR (neat): 1725*s*, 1601*w*, 1450*m*, 1270*s*, 1085*s*, 708*m*. ^{1}H-NMR ($CDCl_3$): 1.33 (*s*, Me–C(10b)); 2.20 (*d*, J = 1.6, Me–C(6)); 4.13 (*dd*, J = 5.8, 12.0, 1H, CH_2O); 4.20 (*d*, J = 6.4, H–C(4a)); 4.33 (*dd*, J = 3.4, 12.0, 1H, CH_2O); 5.74 (*dd*, J = 3.4, 5.8, H–C(3)); 5.97 (*m*, H–C(5)); 7.33–7.44 (complex *m*, 5 arom. H); 7.54 (*m*, 1 arom. H); 7.70 (*m*, 1 arom. H); 7.95 (*m*, 2 arom. H). MS: 352 (1, M^+), 159 (46), 146 (21), 105 (100), 77 (56). Anal. calc. for $C_{21}H_{20}O_5$ (352.41): C 71.58, H 5.72; found: C 71.44, H 5.68.

*(3*RS*,4a*SR*,10b*RS*)- and (3*RS*,4a*RS*,10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-hexyl Benzoate* (**15a** and **15b**, resp.). A soln. of 1.17 g (4.6 mmol) of 2-chloro-1-methylpyridinium iodide and 1.40 g (9.5 mmol) of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one in 20 ml of CH_3CN, prepared by warming in a water bath, was diluted at r.t. with a soln. of 0.50 g (4.1 mmol) of benzoic acid in 20 ml of CH_3CN and stirred for 20 min. Next, a soln. of 1.04 g (3.3 mmol) of **11** in 20 ml of CH_3CN was added and the mixture stirred at r.t. for 48 h. The solvent was evaporated, the residue dissolved in 50 ml of H_2O and 50 ml of Et_2O, the aqueous layer washed with 3 × 25 ml portions of Et_2O and the combined Et_2O phase washed with 3 × 20 ml sat. aq. NaCl soln. dried (Na_2SO_4), and evaporated. The product was fractionated by prep. TLC 4 (plates Et_2O petroleum ether 1:1): 0.51 g (36%) of yellow oil. Pure product was obtained by further prep. TLC of the product-containing bands using CH_2Cl_2/petroleum ether 1:1. IR (neat): 1718*s* (*d*), 1450*m*, 1313*m*, 1263*s*, 1110*s*, 1090*s*, 1068*m*, 1024*m*, 755*m*, 710*s*. ^{1}H-NMR ($CDCl_3$; **15a/15b** 6:1): **15a/15b**: 1.25–1.60 (complex *m*, Me–C(10b), 3 CH); 7.30–7.50 (*m*, 5 arom. H); 7.55 (*m*, 1 arom. H); 7.67 (*m*, 1 arom. H); 8.03 (*m*, 2 arom. H); major isomer **15a** (*'syn'*): 1.72 (*m*, CH_2); 2.15 (*m*, Me–C(6)); 4.16 (*d*, J = 6.6, H–C(4a)); 4.27 (*t*, J = 6.6, CH_2O); 5.32 (*t*, J = 5.4, H–C(3)); 5.93 (*m*, H–C(4a)); 4.27 (*t*, J = 6,6, CH_2O); 5.32 (*t*, J = 5.4, H–C(3)); 5.93 (*m*, H–C(5)); minor isomer **15b** (*'anti'*): 1.80 (*m*, CH_2); 1.98 (*s*, Me–C(6)); 4.45 (br. *s*, H–C(4a)); 4.33 (*t*, J = 6.6, CH_2O); 5.52 (*t*, J = 5.4, H–C(3)); 5.78 (br. *s*, H–C(5)). MS: no M^+, 188 (4), 172 (19), 156 (78), 145 (27), 123 (28), 115 (21), 105 (100), 91 (14), 77 (62), 68 (15), 55 (33); Anal. calc. for $C_{26}H_{30}O_5$ (422.56): C 73.91, H 7.16; found: C 73.65, H 7.44.

*(3*RS*,4a*SR*,10b*RS*)- and (3*RS*,4a*RS*,10b*SR*)-4a,10b-Dihydro-6,10b-dimethylnaphtho[2,1-e][1,2,4]trioxine-3-methyl (3,4,5-Trimethoxyphenyl)acetate* (**16a** and **16b**, resp.). The procedure for **14a** was applied to 0.50 g (2.0 mmol) of **10**, 0.47 g (2.1 mmol) of (3,4,5-trimethoxyphenyl)acetic acid, 0.62 g (4.8 mmol) of 2-chloro-1-methyl-

pyridinium iodide, and 0.71 g (4.8 mmol) of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one. The crude product was fractionated by column chromatography (135 g of silica gel Et_2O) and then by prep. TLC (3 plates, 3 × sequentially with Et_2O 30–60° petroleum ether 2:1 to give 0.511 g (56%) of a yellow oil. IR (neat): 3160–3680 (br. enol form), 1737*s*, 1590*s*, 1504*s*, 1461*s*, 1453*s*, 1421*s*, 1240*s*, 1126*s*, 1045*s*, 1003*s*. ^{1}H-NMR ($CDCl_3$; **16a/16b** 2:1): **16a/16b**: 2.16 (*m*, Me–C(6)); 3.59, 3.83, 3.86 (3 *s*, 3 MeO); 5.22 (br. *d*, J = 1.3), 5.25 (br. *d*, J = 1.3), 5.27 (br. *d*, J = 1.3), 5.32 (br. *d*, J = 1.6; O–C(OH) = C–*H*, *cis*/*trans* and *'syn'*/*'anti'* enol forms); 6.52 (*s*, 2 arom. H); 7.31–7.41 (complex *m*, 3 arom. H); 7.67 (*m*, 1 arom. H); major isomer **16a** (*'syn'*): 1.28 (*s*, Me–C(10b)); 3.95 (*m*, CH_2OCO); 4.14 (*d*, J = 6.4, H–C(4a)); 5.47 (*t*, J = 5.0, H–C(3)); 5.93 (complex *m*, H–C(5)); minor isomer **16b** (*'anti'*): 1.88 (*s*, Me–C(10b)); 4.52 (*m*, CH_2OCO); 4.47 (br. *s*, H–C(4a)); 5.54 (*t*, J = 4.2, H–C(3)); 5.80 (br. *s*, H–C(5)). MS: M^+, 266 (24), 181 (87), 159 (100), 172 (22), 145 (33), 128 (34), 115 (53), 91 (34), 77 (40). Anal. calc. for $C_{25}H_{28}O_8$ (456.53): C 65.78, H 6.18; found: C 66.00, H 6.02.

Blood Schizontocidal Test Protocol. Male, random-bred Swiss albino mice weighing 18–22 g were inoculated intravenously with 10^7 parasitized blood cells of N strain (Keyberg 173) *P. berghei*. Animals were then dosed subcutaneously once daily for 4 consecutive days beginning on the day of infection. Compounds were dissolved or suspended in sterile distilled H_2O with *Tween 80* except for **14–16** which were first dissolved in DMSO and subsequently diluted with H_2O. The parasitemia was determined on the day following the last treatment and the ED_{50} and ED_{90} *i.e.* 50% and 90% suppression of parasites when compared with untreated controls, estimated from a plot of log dose/probit activity.

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