fixed concentration of dUMP used was 28 μM when either 5,10-CH_2-H_4PteGlu or 5,10-CH_2-H_4PteGlu$_5$ was used as variable substrate. The fixed concentration of 5,10-CH_2-H_4PteGlu was 600 μM when dUMP was used as variable substrate.

Registry No. **3a**, 107716-41-6; **3b**, 107716-42-7; **4**, 13726-52-8; **5**, 70280-70-5; **6**, 115827-03-7; **7**, 2378-95-2; **8a**, 107716-29-0; **8b**, 107716-30-3; **9a**, 107716-31-4; **9b**, 107716-32-5; **10**, 107745-48-2; **11**, 107716-34-7; **12**, 107716-33-6; **13**, 88543-89-9; **14a**, 107716-37-0; **14b**, 107716-38-1; PhCHO, 100-52-7; H_2CO, 50-00-0; ICH_2CH_2OH, 624-76-0; ethylene oxide, 75-21-8; 2,5-diamino-4-oxo-6-methylpyrimidine, 4214-86-2; thymidylate synthase, 9031-61-2.

Topical Nonsteroidal Antipsoriatic Agents. 2. 2,3-(Alkylidenedioxy)naphthalene Analogues of Lonapalene[1]

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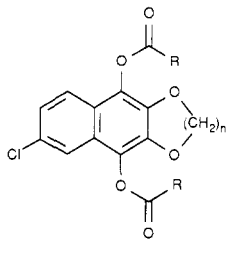
A series of 2,3-(alkylidenedioxy)naphthalene analogues (**5a–p**) of lonapalene (RS-43179, 1), a 5-lipoxygenase inhibitor currently under clinical investigation for the treatment of psoriasis, has been prepared and evaluated for topical inhibitory activity against arachidonic acid induced mouse ear edema. The results of these studies demonstrate that introduction of the fused 2,3-alkylidenedioxy ring, in place of the acyclic 2,3-dialkoxy substituent pattern characteristic of the previous series, caused a modest dimunition in overall potency within the series. These results suggest a potential steric intolerance for these extended planar analogues, in comparison with their 2,3-dialkoxy predecessors.

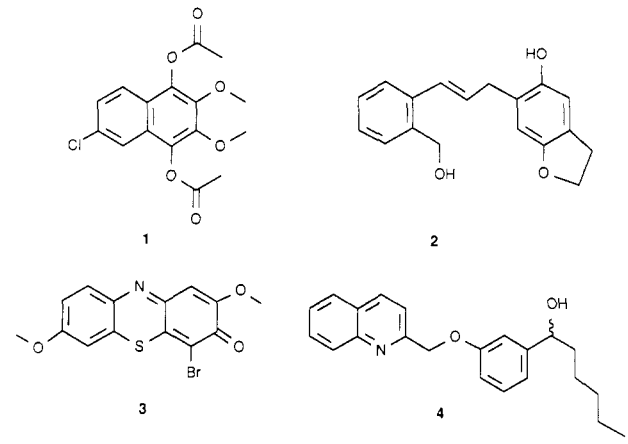
The regulation of abnormal arachidonic acid metabolism for the relief of chronic inflammatory or autoimmune conditons has been a prime target for pharmacological intervention in these disease states.[2-4] In particular, the development of 5-lipoxygenase (5-LO) inhibitors as therapeutic agents for diseases potentially caused or sustained by leukotriene B_4 (LTB_4) and other chemotactic lipoxygenase products has received increasing attention.[5] The viability of this approach has been most widely recognized in the treatment of psoriasis,[6] where elevated levels of arachidonic acid metabolites, especially the leukotrienes, have been detected.[7-10] A variety of compounds now identified as lipoxygenase (LO) or mixed cyclooxygenase–lipoxygenase (CO-LO) inhibitors are targeted for the topical or systemic treatment of psoriasis.[6]

Among 5-LO inhibitors with demonstrated topical activity (**2–4**,[11] Chart I), our interest has focused on lonapalene (**1**),[12] already shown to have clinical efficacy comparable to steroid therapy[13] and currently undergoing advanced clinical evaluation as a topical treatment for psoriasis. Previous structure–activity correlations related the activity of **1** and a series of close analogues in the arachidonic acid induced mouse ear edema assay to net lipophilicity and ease of ester hydrolysis.[12] In this study, a series of 2,3-(alkylidenedioxy)naphthalene lonapalene analogues (**5a–p**), distinguished by the incorporation of the 2,3-dialkoxy substituents into 5- to 7-membered rings, were prepared to investigate the effects of the introduction of

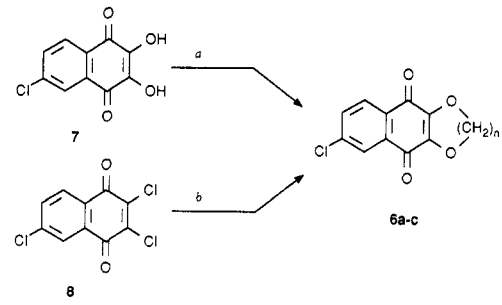


5a-p

Chart I



Scheme I[a]



[a] Reagents: a, $Br(CH_2)_nBr$/NaH/DMF; b, $HO(CH_2)_nOH$/NaH/DMF or no solvent.

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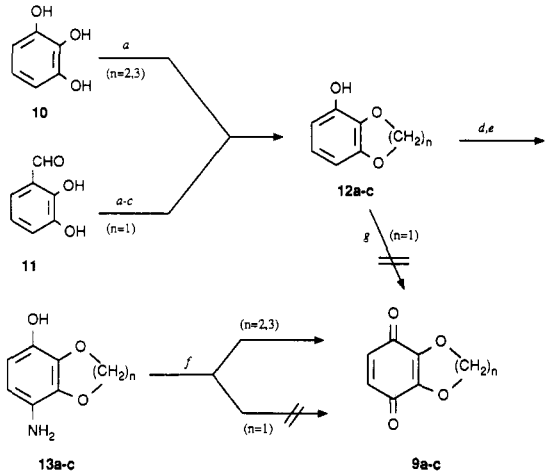
Scheme II[a]



[a] Reagents: a, $Br(CH_2)_nBr/K_2CO_3/DMF$; b, *m*-CPBA/CH_2Cl_2; c, 10% KOH/MeOH; d, diazotized sulfanilic acid/NaOH/H_2O; e, $Na_2S_2O_4$/NaOH/H_2O; f, $Na_2Cr_2O_7/H_2SO_4/H_2O$; g, $(KSO_3)_2NO/H_2O$.

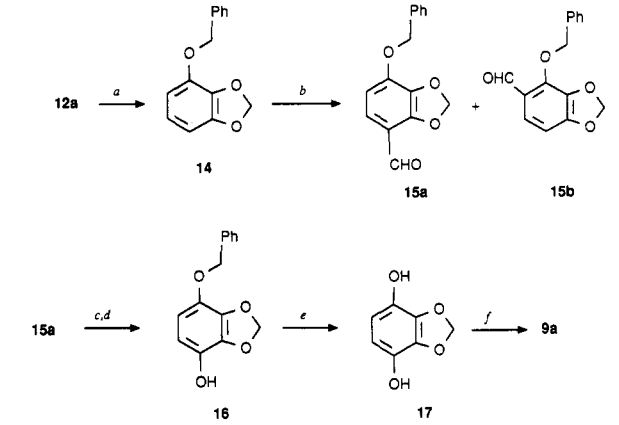
additional structural and/or sterically hindering rigidity while maintaining overall net isolipophilicity with the previous series.

Chemistry

Introduction of the 1,4-bis(acyloxy) functionality onto the naphthalene nucleus by reduction of the appropriate naphthoquinone precursor, followed by in situ acylation of the unstable hydroquinone intermediate, as precedented by our previous results,[12] was envisioned as the last step in the preparation of the ring-fused analogues **5a–p**. Synthesis of the requisite naphthoquinones (**6a–c**) for this transformation had been investigated previously (Scheme I),[14] but attempts to either cycloalkylate 6-chloroisonaphthazarin (**7**)[12] with the appropriate α,ω-dibromoalkane, or to use 2,3,6-trichloro-1,4-naphthoquinone (**8**)[12] for cyclization by double displacement with an α,ω-alkanediol, did not produce useful quantities of **6** for any ring size.

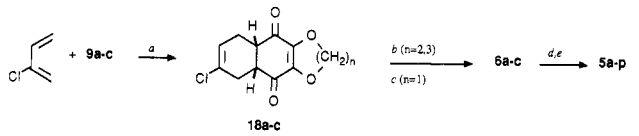
Investigations into alternative syntheses of 2,3-dialkoxy-1,4-naphthoquinones for the preparation of lonapalene (**1**) and analogues indicated that direct condensation of 2-chloro-1,3-butadiene (chloroprene) with an appropriately substituted 2,3-dialkoxy-1,4-benzoquinone, followed by the necessary adjustments in oxidation state, was a viable substitute for the more general route previously described.[15,16] To this end, synthesis of the required 2,3-(alkylidenedioxy)-1,4-benzoquinones (**9a–c**) was pursued via a route used for the preparation of 2,3-dimethoxy-1,4-benzoquinone (Scheme II).[17] The precursor phenols **12a–c**, prepared by literature methods[18–20] from either pyrogallol (**10**) or 2,3-dihydroxybenzaldehyde (**11**), were coupled with diazotized sulfanilic acid, and the resulting adduct was reduced with sodium dithionite to give the unstable aminophenols **13a–c**. Oxidation of the aminophenols with chromic acid afforded the corresponding quinones, but only in the cases where $n = 2$ or 3 (**9b,c**). Under even the mildest conditions possible for this transformation, 4-amino-2,3-(methylenedioxy)phenol (**13a**) decomposed, presumably by oxidative cleavage of the methylenedioxy ring. Attempts to circumvent this decomposition by direct oxidation of **12a** with Fremy's salt, as has been previously reported,[18] gave only negligible quantities of **9a**.

Scheme III[a]



[a] Reagents: a, $PhCH_2Br/K_2CO_3/DMF$; b, $PhN(CH_3)CHO/POCl_3/PhCl$; c, *m*-CPBA/CH_2Cl_2; d, 10% KOH/MeOH; e, H_2/Pd–C/THF; f, $(NH_4)_2Ce(NO_3)_6/CH_3CN$.

Scheme IV[a]



[a] Reagents: a, HOAc; b, $Na_2Cr_2O_7/H_2SO_4$; c, DDQ/$PhCH_3$/reflux; d, H_2/Pd–C/THF; e, RCO_2OCR/py/DMAP–THF.

An alternative approach that generated **9a** under conditions mild enough to avoid oxidative cleavage of the methylenedioxy ring was then investigated (Scheme III). Benzylation of **12a** provided **14**, which was subjected to Villsmeier–Haack formylation, as carried out with 2,3-(methylenedioxy)anisole,[21] to give a mixture of isomeric benzaldehydes, the desired **15a** and known **15b**,[22] separable

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Table I. Physical Data and Biological Evaluation of 2,3-(Alkylidenedioxy)naphthalene Analogues (**5a–p**) of Lonapalene (1)

compd	n	R	mp, °C	anal. (C, H, Cl)	% inhibn[a]	sig[b]
1					54[c]	+++
5a	1	CH_3	126–127	$C_{15}H_{11}ClO_6$	61	+++
5b	1	Et	138–139	$C_{17}H_{15}ClO_6$[d]	35	++
5c	1	*t*-Bu	189–190	$C_{21}H_{23}ClO_6$	−8	NS
5d	1	Ph	200–201	$C_{25}H_{15}ClO_6$[d]	10	NS
5e	2	CH_3	179–180	$C_{16}H_{13}ClO_6$	24	+
5f	2	Et	131–132	$C_{18}H_{17}ClO_6$	30	++
5g	2	*n*-Pr	108–109	$C_{20}H_{21}ClO_6$	26	+
5h	2	*i*-Pr	105–106	$C_{20}H_{21}ClO_6$	75	+++
5i	2	*t*-Bu	152–153	$C_{22}H_{25}ClO_6$	41	++
5j	2	Ph	199–200	$C_{26}H_{17}ClO_6$	*e*	
5k	3	CH_3	136–137	$C_{17}H_{15}ClO_6$	40	++
5l	3	Et	113–114	$C_{19}H_{19}ClO_6$	10	NS
5m	3	*n*-Pr	59–60	$C_{21}H_{23}ClO_6$	35	++
5n	3	*i*-Pr	106–107	$C_{21}H_{23}ClO_6$	27	+
5o	3	*t*-Bu	156–157	$C_{23}H_{27}ClO_6$	10	NS
5p	3	Ph	183–184	$C_{27}H_{19}ClO_6$	*e*	

[a] Percent inhibition (mean ± 3% SE, $n = 8$) of arachidonic acid induced mouse ear edema at 2 mg of total dose of test compound, as previously described in ref 12. [b] Statistical significance, p values as compared to positive control by Student's t test: +, 0.05; ++, 0.01; +++, 0.001; NS, not statistically significant, versus both positive (untreated edema) and negative (acetone vehicle) controls, in individual runs (four to six compounds per run) of the assay. [c] Data from ref 12. [d] Chlorine analysis not obtained. [e] Insufficiently soluble in acetone.

by chromatography. Baeyer–Villiger oxidation of the formyl residue of **15a**, followed by hydrolytic cleavage of the resulting formate ester, gave **16**. Hydrogenolytic cleavage of the benzyl ether, followed by oxidation of **17** by *brief* treatment with ceric ammonium nitrate in acetonitrile afforded the desired 2,3-(methylenedioxy)-1,4-benzoquinone (**9a**) in preparatively useful amounts.

Condensation of the benzoquinones **9a–c** with chloroprene (Scheme IV), followed by oxidation of the resulting Diels–Alder adducts, gave the desired 2,3-(alkylidenedioxy)-1,4-naphthoquinones (**6a–c**). Once again, however, the standard chromic acid oxidation[12] used for **18b** and **18c**, without adduct isolation, failed in the methylenedioxy series, prompting the use of DDQ in refluxing toluene or dichloromethane as oxidant. Finally, conversion of **6a–c** to the series of lonapalene analogues **6a–p** was carried out by the previously used procedure of catalytic reduction and in situ acylation.[12]

Biological Evaluation and Discussion

The lonapalene analogues (**5a–p**) were evaluated (Table I) in the arachidonic acid induced mouse ear edema model previously described by us[12,23] and others.[24,25] Despite recent reports to the contrary,[26] this bioassay was determined to be, and in our hands remains, predictive for the detection of the topical antiinflammatory activity of 5-LO inhibitors. The results generated by this assay have in general been useful for the qualitative comparison of potencies within a given series, but not for comparisons among different classes of compounds, likely due to absorption, lipophilicity, and lability differences possibly highlighted, or even induced, by the conditions of the assay. Since it was demonstrated previously[12] that compounds of this general type did not exhibit proinflammatory effects in the mouse ear and that 5-LO inhibitory activity was a time-dependent phenomenon, likely dependent on hydrolytic and/or enzymatic removal of one of the 1,4-ester groups, the analogues **5a–p** were not evaluated for either of these effects.

With these general findings in mind, the topical activity of compounds **5a–p** was moderately diminished overall, in comparison with the results previously obtained with lonapalene and analogues. In the present study, the activity was, however, spread over a somewhat wider range within each homologous series of esters. The simplest analogue structure, **5a**, exhibited activity comparable to that of **1**, but most other compounds were in general somewhat less active. Only these qualitative comparisons can be made, since these results are not derived from complete dose–response curves, but rather from single dose studies ($n = 8$). The structure–activity profile gleaned from the previous series of tetraoxygenated naphthalene derivatives, including **1**, suggested a dependence of topical activity in this assay on three parameters: net lipophilicity, hydrolytic lability of the 1,4-diester functionality, and the nature and position of the B-ring substituent(s). Since, in comparison with the previous set of lonapalene analogues,[12] compounds **5a–p** are essentially isolipophilic, possess the same range of 1,4-diester funtionalities, and maintain 6-chloro as the B-ring substituent, observed activity differences between **5a–p** and the analogues previously described should depend almost exclusively on the incorporation of the cyclic 2,3-dialkoxy substituents into the [2,3-*b*] dioxy ring. This linear tricyclic variation maintains the electronic character of the acyclic analogues, but introduces additional structural ridigity and steric barriers, interactions potentially either beneficial or detrimental to the inhibition of 5-LO by this class of molecules. The overall trend of lower activity seems to indicate that introduction of this structural modification is generally unfavorable, however. This is also reflected in the precursor naphthoquinone series, since 6-chloro-2,3-dimethoxy-1,4-naphthoquinone, the synthetic precursor to and the degradation product of **1**, demonstrated slight (30%) topical activity in this assay, whereas none of the ring-fused naphthoquinones (**6a–c**) related to **5a–p** were active topically (data not shown).

Conclusion

The general finding that a number of clinically useful antipsoriatic agents share the ability to inhibit 5-LO[27] and our own reports on the probable mechanism of action of **1**[28] and its clinical efficacy in psoriasis[13] indicate that in-

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hibition of 5-LO is a viable approach to the treatment of this disease. The nature and location of the interaction and resulting inhibiting of the tetraoxygenated naphthalene derivatives with the 5-LO enzyme remains, however, unknown. The putative naphthol structure[12] may function as an inhibitor by a reversible (spatial) or irreversible (redox) interaction at the active (peroxidation) site corresponding to C-5 of arachidonic acid. Reversible inhibition may occur by mimicking the hydroxyl of 15-hydroxyeicosatetraenoic acid (15-HETE), the product of 15-LO activity and a known inhibitor of 5-LO.[29] The restoration of defective 15-HETE biosynthesis to normal levels in the dermis to provide this endogenous 5-LO inhibitor has been proposed as a novel approach to the treatment of psoriasis[30] and has, in fact, been tested clinically by intralesional injection of 15-HETE.[31] Irreversible inhibition may be derived from an undetermined redox pathway involving the naphthol and 5-LO, resulting in a stabilized naphthol radical species and inactive enzyme. It seems clear from this series of molecular probes, however, that whatever the nature of interaction with 5-LO, introduction of the 2,3-alkylidenedioxy fusion is somewhat less favorable. Further work directed toward elucidation of the nature of the interaction(s) of the polyoxygenated naphthalenes with 5-LO, by synthesis of compounds with multiple oxygenation patterns on the naphthalene nucleus, by annulation of other ring systems in potentially favorable orientations, and by incorporation of functionality used in other classes of reported 5-LO inhibitors into hybridized structures, has been pursued and will be reported subsequently.

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtaind on either an EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instrument. Infrared spectra were recorded as KBr pellets with a Perkin-Elmer 237 grating spectrometer. Mass spectra were determined on an Atlas CH-7 instrument. All compounds exhibited NMR, IR, and mass spectral data consistent with the proposed structures. Elemental analyses were performed by either Atlantic Microlabs, Atlanta GA, or by the Analytical and Environmental Research Department, Syntex Research, on samples dried 24 h at ambient temperature and high vacuum. Results were within 0.4% of theoretical values, unless otherwise stated. Tetrahydrofuran (THF) was freshly distilled from sodium–benzophenone ketyl under nitrogen. *N*,*N*-Dimethylformamide (DMF) was freshly distilled from calcium hydride. Chloroprene was freshly distilled from a 50% xylene solution (Pfaltz and Bauer) before use in the Diels–Alder condensation reactions. Pyrogallol (**10**) and 2,3-dihydroxybenzaldehyde (**11**) (Aldrich Chemical Co.) were used in the literature preparations of compounds **12a–c**[18-20] and compound **9b**.[19] All organic extracts were dried over sodium sulfate prior to evaporation.

In vivo evaluation of topical antiinflammatory activity of compounds **6a–c** and **5a–p** in the arachidonic acid induced mouse ear edema model was carried out by methods previously described by us in studies on **1**.[12]

4-(Phenylmethoxy)-1,3-benzodioxole (14). A solution of **12a** (27.5 g 200 mmol) and benzyl bromide (35.5 mL, 300 mmol) in DMF (350 mL) was treated with K_2CO_3 (55 g, 400 mmol), and the resulting mixture was heated at 60 °C overnight. After cooling and filtration, the mixture was evaporated. The residue was dissolved in ethyl acetate (500 mL), and the organic solution was washed with 1 M HCl (3 × 250 mL) and brine (2 × 250 mL), then was dried, filtered, and evaporated. The residue was recrystallized from hexane to yield **14** (45.8 g, 200 mmol, 100%), mp 62–63 °C. Anal. ($C_{14}H_{12}O_3$) C, H.

4-Formyl-7-(phenylmethoxy)-1,3-benzodioxole (15a). A solution of **14** (45.8 g, 200 mmol) in chlorobenzene (50 mL) was added dropwise to a mixture of *N*-methylformanilide (34 g, 250 mmol) and $POCl_3$ (38.5 g, 250 mmol) in chlorobenzene (50 mL) maintained at −5 °C. When the addition was complete, the mixture was allowed to warm to room temperature. The reaction was then quenched by pouring onto ice, and the resulting mixture was stirred overnight and then was extracted with ethyl acetate (300 mL). The organic solution was washed with water (2 × 200 mL) and brine (2 × 200 mL), then was dried, filtered, and evaporated to give 47.9 g of crude product containing a mixture of isomers **15a** and **15b**. Chromatography of the residue over silica gel using 1:1 dichloromethane–hexane as eluant afforded isomers **15b** (8.78 g, 34 mmol, 17%), mp 70–71 °C (lit.[22] mp 70–71.5 °C), followed by **15a** (7.03 g, 27 mmol, 14%), mp 81–82 °C. Anal. ($C_{15}H_{12}O_4$) C, H.

4-Hydroxy-7-(phenylmethoxy)-1,3-benzodioxole (16). Solid *m*-chloroperbenzoic acid (19.5 g, 96 mmol) was added portionwise to a chilled solution of **15a** (16.4 g, 64 mmol) in dichloromethane (250 mL). After stirring at room temperature overnight, the mixture was evaporated, and the residue was dissolved in ethyl acetate (500 mL). The organic solution was washed with saturated $NaHCO_3$ (4 × 250 mL), water (2 × 250 mL), and brine (2 × 250 mL) and then was evaporated. The residue was dissolved in methanol (25 mL) and was treated with 10% KOH (50 mL) under nitrogen. The solution was then acidified and extracted with ether (300 mL). The organic solution was washed with water (2 × 250 mL) and brine (2 × 250 mL), then was dried, filtered, and evaporated to give **16** (15.2 g, 62.2 mmol, 97%), mp 95–96 °C.

1,3-Benzodioxole-4,7-dione (9a). A solution of **16** (12.16 g, 50 mmol) in THF (150 mL) was hydrogenated at atmospheric pressure over 10% Pd–C (0.3 g) overnight. The catalyst was removed by filtration, and the solution was evaporated. The residue containing **17** was dissolved in acetonitrile (500 mL), and the solution was treated with ceric ammonium nitrate (25 g, 46 mmol). After 5 min, the reaction was quenched with water, and the solution was extracted with ethyl acetate (500 mL). The organic solution was washed with water (3 × 300 mL) and brine (2 × 300 mL), then was dried, filtered, and evaporated. Chromatography of the residue over silica gel using dichloromethane as eluant afforded **9a** (4.92 g, 32.3 mmol, 64%) as a brick-red solid, mp 106–107 °C (lit.[18] mp 102 °C).

2,3-Dihydro-4*H*-1,5-benzo[*b*]dioxepin-6,9-dione (9c). Coupling of **12c**[20] with diazotized sulfanilic acid, followed by reduction of the adduct with aqueous sodium dithionite and oxidation of **13c** with chromic acid, by methods identical with those used for the preparation of **9b**,[17,19] afforded **9c**, mp 140.5–141.5 °C. Anal. ($C_9H_8O_4$) C, H.

6-Chloro-1,3-naphtho[2,3-*b*]dioxole-4,9-dione (6a). A solution of **9a** (4.92 g, 32 mmol) and chloroprene (5.0 mL, 54 mmol) in acetic acid (50 mL) was stirred in the dark at ambient temperature for 72 h. After addition of hexane (200 mL), the resulting precipitate of crude **18** (6.6 g) was collected by filtration and was air-dried protected from light. A mixture of crude **18** (1.1 g, 4.6 mmol) and DDQ (4.16 g, 18.3 mmol) in dry toluene (55 mL) was refluxed overnight. The reaction mixture was filtered while still warm, and the filtrate was evaporated to dryness. Chromatography of the residue over silica gel using dichloromethane as eluant afforded **6a** (0.75 g, 3.2 mmol, 69% from crude **18**), mp 235–236 °C. Anal. ($C_{11}H_5ClO_4$) C, H, Cl.

Scale-up of the oxidation reaction (23 mmol of crude **18**) and use of dichloromethane as solvent resulted in a 45% yield of **6a**.

7-Chloro-2,3-dihydro-1,4-naphtho[2,3-*b*]dioxane-5,10-dione (6b). A mixture of **9b** (17.14 g, 100 mmol) and chloroprene (13.3 g, 150 mmol) in acetic acid (100 mL) was stirred at ambient temperature for 90 h. The reaction mixture was then diluted with acetic acid (500 mL), and to it was added a solution dichromate (40 g, 134 mmol) in a mixture of sulfuric acid (2 mL) and water (25 mL). The mixture was heated at 60–70 °C for 2 h and then was cooled to room temperature and diluted with water (500 mL) to give an orange precipitate, which was collected by filtration, washed with water, and air-dried to yield **6b** (18.25 g, 73 mmol,

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73%), mp 279-280 °C. Anal. ($C_{12}H_7ClO_4$) C, H, Cl.

8-Chloro-2,3-dihydro-4*H*-1,5-naphtho[2,3-*b*]dioxepin-6,11-dione (6c). By the method described above for the preparation of **6b**, Diels-Alder condensation of **9c** (14.0 g, 77.7 mmol) with chloroprene (10.3 g, 116.6 mmol) in acetic acid, followed by aqueous dichromate oxidation, afforded **6c** (13.82 g, 52.2 mmol, 67%), mp 209-210 °C. Anal. ($C_{13}H_9ClO_4$) C, H, Cl.

6-Chloro-2,3-(alkylidenedioxy)-1,4-bis(acyloxy)-naphthalenes (5a-p). Reduction and acylation of **6a-c** by the methods described previously for the synthesis of **1** and analogues[12] gave **5a-p** in 75-90% yields. Physical data are reported in Table I.

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Registry No. 1, 91431-42-4; **5a**, 115943-32-3; **5b**, 115943-33-4; **5c**, 115943-34-5; **5d**, 115943-35-6; **5e**, 115943-36-7; **5f**, 115943-37-8; **5g**, 115943-38-9; **5h**, 115943-39-0; **5i**, 115943-40-3; **5j**, 115943-41-4; **5k**, 115943-42-5; **5l**, 115943-43-6; **5m**, 115943-44-7; **5n**, 115943-45-8; **5o**, 115943-46-9; **5p**, 115943-47-0; **6a**, 115943-48-1; **6b**, 115943-49-2; **6c**, 115943-50-5; **9a**, 86319-72-4; **9b**, 42965-39-9; **9c**, 115943-51-6; **14**, 115943-52-7; **15a**, 115943-53-8; **15b**, 82299-37-4; **16**, 115943-54-9; **17**, 86319-80-4; **18**, 115943-55-0; chloroprene, 126-99-8.

Inhibitors of Cyclic AMP Phosphodiesterase. 3. Synthesis and Biological Evaluation of Pyrido and Imidazolyl Analogues of 1,2,3,5-Tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline[1]

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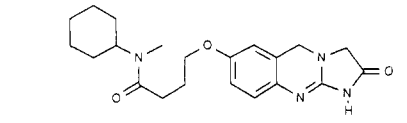
Hybridization of structural elements of 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline ring system common to the cyclic AMP (cAMP) phosphodiesterase (PDE) inhibitors lixazinone (RS-82856, 1) and anagrelide (3) with complementary features of other PDE inhibitor cardiotonic agents prompted the design and synthesis of the title compounds **7a-d**, **11**, **12**, and **13a,b**. The necessary features of these compounds were determined within the framework of the proposed active-site models for the high affinity form of cAMP PDE inhibited by cGMP (type IV). Evaluation of these targets, both in vitro as inhibitors of platelet or cardiac type IV PDE or in vivo as inotropic agents in the pentobarbital-anesthetized dog model of congestive heart failure, showed that these structure possessed negligibly enhanced activities over the parent heterocyclic system, and remained significantly inferior to **1** in all respects. This difference is ascribed to the absence of the *N*-cyclohexyl-*N*-methylbutyramidyl-4-oxy side chain of **1**. The proposal that the acidic lactam-type functionality, common to the type IV PDE inhibitor inotropic agents such as **4-6** and **8-10**, mimics the polarizable cyclic phosphate moiety of cAMP suggested that the side chain of **1** may function as an effective surrogate for selected characteristics of the adenine portion of cAMP. However, the results of this study show that incorporation of adenine-like hydrogen-bonding functionalities common to other type IV PDE inhibitors into the 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline system did not enhance activity to the levels observed for **1** and analogues. These observations, coupled with the kinetic pattern of inhibition of type IV PDE observed for **1** and analogues, suggest that access to a secondary, lipophilic-tolerant binding site, possibly coincident with the adenine binding domain, and adjacent to the catalytic ribose-phosphate binding site of platelet and cardiac type IV PDE, is responsible for the increased potency of these compounds.

The search for non-glycoside cardiotonic drugs for treating congestive heart failure has, of late, increasingly concentrated on the development of agents that raise myocardial levels of cyclic AMP (cAMP), either by receptor-mediated stimulation of adenylate cyclase or by direct inhibition of cAMP phosphodiesterase (PDE).[2,3] Within this latter class, a number of new agents displaying potent and specific inhibition of the cyclic GMP (cGMP) inhibited form (type IV) of cAMP PDE, the enzyme primarily responsible for cAMP turnover in myocardial tissue, have been examined as potential cardiotonic agents.[4-6] Our attention in this area has focused on lixazinone (RS-82856, **1**), a compound combining structural features of two potent inhibitors of type IV PDE, anagrelide (**2**) and cilostamide (**3**). We have previously reported the PDE inhibitory profile of **1** in comparison with its progenitors, and ascribed the observed enhancement of activity to the positionally specific attachment of the lipophilic *N*-cyclohexyl-*N*-methyl-4-oxybutyramide side chain of **3** onto



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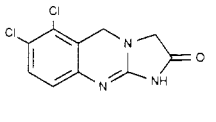

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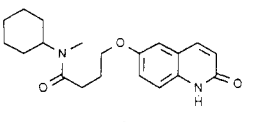

3

the 1,2,3,5-tetrahydro-2-oxoimidazo[2,1-*b*]quinazoline heterocycle of **2**.[7-9] The combination of potency and tissue

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