or in D_2O using 4,4-dimethyl-4-silapentane-5-sulfonate as a standard. ^{13}C NMR spectra were taken of an IBM NR/80 spectrometer. Mass spectra were obtained on a Hewlett Packard 5985C GC/MS by the Northwestern University Analytical Service, Evanston, IL. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-6,7-DTN). The compound was prepared using the method of Cannon[5] or Horn,[6] mp 268–270 °C (lit.[7] mp 270–271 °C).

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (5). The compound was prepared as reported earlier.[2]

2,2′-Iminobis[1,2,3,4-tetrahydro-6,7-naphthalenediol] (6). The compound was prepared as reported earlier.[2]

2-[(5,6-Dihydroxy-1,2,3,4-tetrahydronaphthalenyl)imino]-1,2,3,4-tetrahydro-6,7-naphthalenediol (7). A mixture of 1.00 g (4.10 mmol) of A-6,7-DTN·HCl dimethyl ether, 0.850 g (4.10 mmol) of 5,6-dimethoxy-2-tetralone,[5] and 0.260 g (4.10 mmol) of sodium cyanoborohydride in 100 mL of methanol was stirred for 3 days under a nitrogen atmosphere. The solvent was removed, water was added, and extraction of the aqueous mixture with ethyl acetate afforded 7 tetramethyl ether. The product was taken up in methanol and the solution was saturated with hydrogen chloride. The solvent was removed on a rotary evaporator, and the resulting solid was crystallized from ethanol/water (10:1). The product was dissolved in 50 mL of 48% hydrobromic acid, and the solution was heated to reflux under a nitrogen atmosphere for 24 h. The acid was removed in vacuo, the resulting solid was dissolved in water, cleared with Norit, and filtered, and the water was removed in vacuo, leaving 0.200 g (11.6%) of light brown product: mp >300 °C; NMR (CD_3OD) δ 1.4–2.4 (m, 4 H), 2.4–3.0 (m, 8 H), 3.3–4.0 (m, 2 H), 6.2–6.4 (m, 4 H). The dicatechol proved to be too unstable to afford a correct combustion analysis: however, a correct C, H, N analysis was obtained for the HCl salt of the tetramethyl ether of 7: NMR (CD_3OD) δ 1.6–2.6 (m, 4 H), 2.6–3.2 (m, 8 H), 3.80 (s, 12 H), 6.62 (s, 2 H), 6.78 (s, 2 H).

2-[[2-(4-Hydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (8). The reductive amination of the protected A-6,7-DTN and *p*-methoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the trimethyl ether of 8 in 89% yield. Deblocking and workup as for 7 yielded 8 in 66% yield: mp 154–155 °C; NMR (CD_3OD) δ 1.61 (d, J = 6 Hz, 3 H), 1.81–2.91 (m, 2 H), 2.91–3.64 (m, 6 H), 3.64–4.31 (m, 2 H), 6.74–6.87 (m, 2 H), 7.04 (d, J = 8 Hz, 2 H), 7.41 (d, J = 8 Hz, 2 H). Anal. ($C_{19}H_{23}NO_4 \cdot 1H_2O \cdot 1.18HBr$) C, H, N, Br.

2-Amino-6-methoxy-1,2,3,4-tetrahydronaphthalene. A mixture of 5.50 g (31.3 mmol) of 6-methoxy-2-tetralone (Aldrich) and 2.61 g (31.3 mmol) of methoxylamine hydrochloride in 3.1 mL (31 mmol) of a 10 N solution of sodium hydroxide was heated to 70 °C for 18 h. The addition of water and extraction with ethyl acetate afforded the crude *o*-methyl oxime, which was dissolved in 50 mL of THF and, under a nitrogen atmosphere, was treated with 62 mL (62 mmol) of a 1 M solution of BH_3–THF complex. The solution was heated to reflux for 6 h and quenched with water. The addition of water and extraction with ethyl acetate afforded with crude tetralinamine. The product was dissolved in methanol, and the solution was saturated with hydrogen chloride. The solvent was removed, yielding 3.36 g (50.9%) of crude 2-amino-6-methoxy-1,2,3,4-tetrahydronaphthalene: NMR (CD_3OD) δ 1.5–2.5 (m, 2 H), 2.5–3.2 (m, 4 H), 3.2–3.6 (m, 1 H), 3.75 (s, 3 H), 6.6–7.4 (m, 3 H). The product was used without further purification.

2-[[2-(4-Hydroxyphenyl)-1-methylethyl]amino]-6-hydroxy-1,2,3,4-tetrahydronaphthalene (9). The reductive amination of 2-amino-6-methoxy-1,2,3,4-tetrahydronaphthalene and *p*-methoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the dimethyl ether of 9 in 22% yield. Deblocking and workup as for 7 afforded 9 in 49% yield: mp >300 °C; NMR (CD_3OD) δ 1.32 (d, J = 6 Hz, 3 H), 1.6–2.6 (m, 3 H), 2.6–3.2 (m, 5 H), 3.2–4.1 (m, 2 H), 6.4–7.3 (m, 7 H). Anal. ($C_{19}H_{23}NO_2 \cdot 0.8H_2O \cdot 1.15HBr$) C, H, N, Br, H_2O.

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-6-hydroxy-1,2,3,4-tetrahydronaphthalene (10). The reductive amination of 2-amino-6-methoxy-1,2,3,4-tetrahydronaphthalene and 3,4-dimethoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the trimethyl ether of 10 in 14% yield. Deblocking and workup as for 7 afforded 10 in 95% yield: mp >300 °C; NMR (CD_3OD) δ 1.27 (d, J = 6 Hz, 3 H), 1.5–2.5 (m, 3 H), 2.5–3.2 (m, 5 H), 3.2–3.9 (m, 2 H), 6.4–7.1 (m, 6 H). Anal. ($C_{19}H_{23}NO_3 \cdot 1.8H_2O \cdot 1.25HBr$) C, H, N, Br, H_2O.

4-[2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]ethyl]-1,2-benzenediol (11). The reductive amination of β-(3,4-dimethoxyphenyl)ethylamine (Aldrich) and 3,4-dimethoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the tetramethyl ether of 11 in 60% yield. Deblocking and workup as for 7 afforded 11 in 70% yield: mp 125 °C; NMR (D_2O) δ 1.33 (d, J = 6 Hz, 3 H), 2.5–3.7 (m, 7 H), 6.4–7.1 (m, 6 H). Anal. ($C_{17}H_{21}NO_4 \cdot 0.75H_2O \cdot 1.13HBr$) C, H, N, Br, H_2O.

4-[2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]ethyl]-1,2-dimethoxybenzene (12). The reductive amination of 3,4-bis(benzyloxy)phenethylamine hydrochloride (Aldrich) and 3,4-dimethoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt 13 in 65% yield. Hydrogenolysis of the HCl salt of 13 with Pd/C in ethanol at 40 psi of hydrogen with shaking using a Paar hydrogenator for 4 h afforded 12 in 70% yield: mp 212 °C; NMR (CD_3OD) δ 1.23 (d, J = 6 Hz, 3 H), 2.7–3.7 (m, 7 H), 3.78 (s, 6 H), 6.6–7.1 (m, 6 H). Anal. ($C_{19}H_{25}NO_4 \cdot HCl$) C, H, N.

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Nitro and Amino Derivatives of Lucanthone as Antitumor Agents

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A group of nitro and amino derivatives of lucanthone was prepared and tested for antitumor activity. Reaction of 1-chloro-4-methyl-7-nitrothioxanthenone and *N,N*-diethylethylenediamine gave the 7-amino analogue (11) directly, accompanied by 7-amino-1-chloro-4-methylthioxanthenone. The antitumor activity of 11 was inferior to that of lucanthone and 7-hydroxylucanthone. The most active compound in the series was the nitro compound 1. In the P-388 lymphocytic leukemia screen it showed a T/C = 178 at 200 mg/kg.

In a recent paper, reasons were given to support the hypothesis that hydroxylation of lucanthone at appropriate positions in the ring system might lead to compounds with enhanced antitumor activity.[1] It has been shown that

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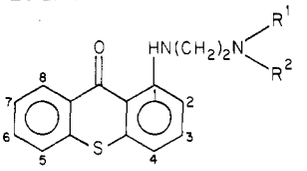
Table I. Chemical and Biological Data on Lucanthone Analogues



no.	ring substit	R^1	R^2	emp formula[a]	mp, °C	in vivo antitumor act. vs. P-388 lymphocytic leukemia[b] dose, mg/kg	T/C
1	4-NO_2	C_2H_5	C_2H_5	$C_{19}H_{21}N_3O_3S$	118-121	200	178
						100	145
						50	142
2	4-NH_2	C_2H_5	C_2H_5	$C_{19}H_{23}N_3OS$	105-107	200	125
						100	122
						50	107
3	4-NO_2	CH_3	CH_3	$C_{17}H_{17}N_3O_3S$	183-184	100	103
						50	143
						25	135
						12.5	114
4	4-NH_2	CH_3	CH_3	$C_{17}H_{19}N_3OS$	118-121	200	toxic[c]
						100	121
						50	100
5	4-NO_2	CH_2CH_2OH	H	$C_{17}H_{17}N_3O_4S$	160-163	50	120
						25	141
						12.5	133
6	4-NH_2	CH_2CH_2OH	H	$C_{17}H_{19}N_3O_2S$	184-187	100	129
						50	132
						25	120
11	7-NH_2, 4-CH_3	C_2H_5	C_2H_5	$C_{20}H_{25}N_3OS$	117-119	50	138
						25	103
						12.5	120
13	5-NH_2, 4-CH_3	C_2H_5	C_2H_5	$C_{20}H_{25}N_3OS \cdot H_2O$	76-90	200	123
						100	113
						50	100

[a] Analyses for C, H, and N for all compounds listed in Table I are within 0.4% of calculated values unless otherwise noted. [b] Standard NCI protocols were used as described in ref 5. The compounds were given once a day for 9 days. T/C = (treated animal survival time/control animal survival time) × 100. [c] Some deaths occurred in the animals medicated at this dose.

amino substitution in certain anthraquinones increases binding of a drug to DNA[2] and this in turn could lead to enhanced antitumor activity.[3] In view of the fact that introducing a 7-OH group in lucanthone resulted in increased antitumor activity, it seemed desirable to prepare and submit for biological evaluation a series of amino-substituted analogues of lucanthone.

A few 4-nitro- and 4-aminothioxanthenones were prepared from 1-chloro-4-nitrothioxanthenone.[4] Reaction with some ethylenediamines in refluxing ethanol gave the 4-nitrothioxanthenones **1**, **3**, and **5**, which on reduction gave the corresponding 4-amino compounds **2**, **4**, and **6** (Table I). The 7-amino analogue **11** was prepared as shown in Scheme I.

Ethyl 2-chloro-5-nitrobenzoate was condensed with 5-chloro-2-methylthiophenol to give the ester **8**, which was converted to the acid **9**. Cyclization with H_2SO_4 gave **10**, which on treatment with *N,N*-diethylethylenediamine in refluxing pyridine gave a mixture of the target amino compounds **11** and **12**, reduction of the nitro group having occurred under the conditions necessary to effect displacement of the chloro group.

Preparation of 1-chloro-4-methyl-5-nitrothioxanthenone from 2-[(5-chloro-2-methylphenyl)thio]-3-nitrobenzoic acid (**14**) failed in H_2SO_4 but succeeded via conversion to the acid chloride, followed by $AlCl_3$ cyclization. Displacement with *N,N*-diethylethylenediamine resulted in concomitant reduction of the nitro group to give the target 5-aminolucanthone (**13**) directly.

Biological Results

The antitumor evaluation was carried out by the NCI using the protocol discribed by Geran et al.[5] and the results are recorded in Table I. In contrast to 7-hydroxylucanthone (T/C = 188),[1] the corresponding 7-amino analogue (**11**) was less active than lucanthone. The 5-amino analogue, (**13**) was inactive. On the other hand, the 4-nitro compound (**1**) was fairly active (T/C = 178 at 200 mg/kg). Bioreduction of **2** to **5** cannot be the explanation of this result, since the corresponding 4-amino compound is inactive.

Experimental Section

Melting points were taken on a Laboratory Device Mel-Temp apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrometer. The NMR spectra were

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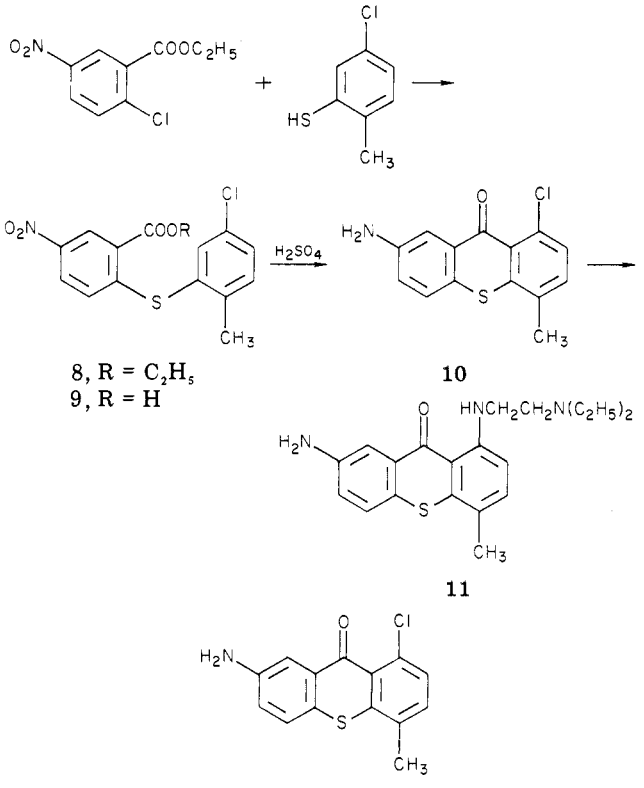
Scheme I



recorded on a Varian T-60A spectrometer in $CDCl_3$ and $(CD_3)_2SO$. Elementary analyses were determined by Instranal Laboratories, Rensselaer, NY, and Spang Microanalytical Laboratory, Eagle Harbor, MI.

1-[[2-(Diethylamino)ethyl]amino]-4-nitrothioxanthenone (1). A suspension of 12.5 g of 1-chloro-4-nitrothioxanthenone, 14 mL of *N,N*-diethylethylenediamine, and 175 mL of EtOH was refluxed for 20 h and worked up as usual to give 11.0 g of the crystalline base, mp 118–121 °C after crystallization from EtOH.

4-Amino-1-[[2-(diethylamino)ethyl]amino]thioxanthenone (2). A suspension of 7.0 g of the nitrothioxanthenone (1) in 80 mL of 90% EtOH, 4.5 g of Fe powder, and 1.9 mL of concentrated HCl was refluxed for 20 h. Then a solution of 1.0 g of Na_2CO_3 in 5 mL of H_2O was added, and the mixture was filtered hot (Celite). The filtrate was concentrated to a small volume, H_2O was added to the point of turbidity, and the solution was left overnight to give 4.0 g of crude amino compound, mp 99–100 °C. After recrystallization from aqueous EtOH it melted at 105–107 °C: yield 2.3 g.

1-[[2-(Dimethylamino)ethyl]amino]-4-nitrothioxanthenone (3). A suspension of 15.5 g of 1-chloro-4-nitrothioxanthenone[4] in 150 mL of EtOH and 10 mL of *N,N*-dimethylethylenediamine was refluxed with stirring for 20 h, cooled, and filtered. The filtrate was evaporated to dryness, and the residue was combined with the filtered solid. The combined solid material was dissolved in 50 mL of acetic acid. The solution was diluted with 150 mL of H_2O and filtered, and the filtrate was made alkaline. The crystalline base that separated was filtered, washed with H_2O, and dried: yield 15.5 g. After recrystallization from 2-methoxyethanol it melted at 183–184 °C.

4-Amino-1-[[2-(dimethylamino)ethyl]amino]thioxanthenone (4). A mixture of 4.47 g of the 4-nitro compound (3), 2.9 g of Fe, 1.2 mL of concentrated HCl, and 50 mL of 90% EtOH was stirred under reflux for 16 h. The mixture was made alkaline and filtered hot. The filtrate was concentrated to give a crystalline solid, which was dissolved in $CHCl_3$ and washed with Na_2CO_3 solution and H_2O. The organic layer was evaporated, and the solid residue was crystallized twice from ethanol: mp 118–121 °C; yield 2.0 g.

1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-4-nitrothioxanthenone (5). A suspension of 5.0 g of 1-chloro-4-nitrothioxanthenone, 4.0 mL of 2-(hydroxyethyl)ethylenediamine, and 50 mL of absolute EtOH was refluxed for 16 h. The cooled mixture was filtered, and the solid was suspended in 40 mL of boiling glacial acetic acid. The suspension was diluted with 120 mL of H_2O and filtered. The acid-insoluble fraction, mp 263–270 °C, weighed 3.2 g and was not investigated further.

The filtrate was made alkaline to give 2.1 g of the base, mp 157–161 °C. After recrystallization from EtOH, it melted at 160–163 °C.

4-Amino-1-[[2-[(2-hydroxyethyl)amino]ethyl]amino]thioxanthenone (6). A suspension of 4.0 g of the nitro compound (5), 2.50 g of Fe powder, 1.0 mL of concentrated HCl, and 45 mL of EtOH was stirred under reflux for 20 h. The hot solution was filtered (Celite). The filtrate, which deposited crystals on cooling, was reheated and made basic with 2.0 g of Na_2CO_3 dissolved in a minimum volume of H_2O. The cooled solution deposited 3.1 g of the desired base, mp 185–187 °C. After recrystallization from MeOH it melted at 184–187 °C.

Ethyl 2-[(5-Chloro-2-methylphenyl)thio]-5-nitrobenzoate (8). To a solution of 1.2 g of Na in 200 mL of absolute EtOH there was added 11.8 g of ethyl 2-chloro-5-nitrobenzoate, followed by 8.2 g of 5-chloro-2-methylthiophenol. The mixture was refluxed for 7 h and left overnight. The mixture was poured into ice–water and filtered. The solid was washed with H_2O, dried, and recrystallized from EtOH: yield 15.0 g; mp 90–92 °C.

7-Amino-1-[[1-(diethylamino)ethyl]amino]-4-methylthioxanthenone (11) and 7-Amino-1-chloro-4-methylthioxanthenone (12). A suspension of 15.0 g of the ester 8 in 100 mL of 5% KOH was heated under reflux until a clear solution was obtained. Then the solution was acidified with 6 N HCl while still warm and the solid that separated was filtered and dried: yield 11.1 g; mp 242–246 °C.

A solution of 9.5 g of the acid 9 and 55 mL of concentrated H_2SO_4 was stirred at 95 °C for 1.5 h and poured onto ice. The solid was filtered and dried: yield 8.2 g; mp 270–275 °C.

A suspension of 6.4 g of the crude 1-chloro-4-methyl-7-nitrothioxanthenone, 7.0 mL of *N,N*-diethylethylenediamine, and 6.0 mL of dry pyridine was refluxed for 48 h. The cooled mixture was diluted with H_2O, and then a solution of 6 g of KOH in 10 mL of H_2O was added. The cooled mixture was extracted with CH_2Cl_2, and the organic layer was extracted with 1 N HCl. The aqueous phase was made alkaline, and the material that separated was taken up in $CHCl_3$. The organic extract was washed with H_2O, dried, and evaporated to give 2.5 g of an impure solid. This was chromatographed on a column (65 g) of silica gel using $CHCl_3$ and $CHCl_3$–CH_3OH as the eluants.

The fraction that was eluted with $CHCl_3$ melted at 191–193 °C after recrystallization from EtOH. The NMR spectrum and elementary analysis indicated that this was 7-amino-1-chloro-4-methylthioxanthenone (12). Anal. ($C_{14}H_{10}ClNOS$) N.

The fraction that was eluted with $CHCl_3$–4% CH_3OH melted at 117–119 °C after crystallization from aqueous EtOH. This is compound 11: yield 1.5 g. Anal. ($C_{20}H_{25}N_3OS$) C, H, N.

Ethyl 2-[(5-Chloro-2-methylphenyl)thio]-3-nitrobenzoate. To a solution of 1.5 g of Na in 210 mL of absolute EtOH there was added 14.7 g of ethyl 2-chloro-3-nitrobenzoate and 10.2 g of 5-chloro-2-methylthiophenol. The mixture was stirred under reflux overnight and poured onto ice. The yellow oil which separated solidified. It was filtered and crystallized from EtOH: mp 63–65 °C; yield 13.6 g. After one more crystallization it melted at 67–69 °C. Anal. ($C_{16}H_{14}ClNO_2S$) C, H, N.

2-[(5-Chloro-2-methylphenyl)thio]-3-nitrobenzoic Acid (14). A suspension of 15.2 g of the above ester in 20 mL of EtOH and 80 mL of H_2O in which 6.4 g of KOH had been dissolved was refluxed for 5 h. The mixture was cooled and acidified with 6 N HCl. The acid that separated was washed with H_2O, dried, and crystallized from EtOH: yield 12.9 g; mp 207–209 °C. Anal. ($C_{14}H_{10}ClNO_4S$) C, H, N.

5-Amino-1-[[2-(diethylamino)ethyl]amino]-4-methylthioxanthenone (13). A suspension of 11.9 g of the nitro acid 14 in 7 mL of $SOCl_2$ and 44 mL of benzene was refluxed for 45 min. Excess $SOCl_2$ and benzene were removed in vacuo. The residue was dissolved in 45 mL of dry benzene, and to the stirred solution was added 7.0 g of $AlCl_3$ over a 30-min period. The mixture was heated under reflux for 90 min before being cooled and poured into iced, dilute HCl. The solid that separated was filtered, washed with H_2O, boiled with dilute NH_4OH, filtered, washed again with

H_2O, and dried. The yield of crude product, mp 260–320 °C, was 11.2 g.

A suspension of 5.0 g of the above thioxanthenone, 10 mL of *N,N*-diethylethylenediamine, and 8 mL of pyridine was heated under reflux for 36 h and worked up as in the case of the 7-amino analogue (11). The residue was chromatographed on 80 g of silica gel to give 2.4 g of the product, which was eluted with $CHCl_3$, mp 79–86 °C. After crystallization from EtOH and drying in air, the sample melted at 76–90 °C and appeared to be a hydrate. Anal. ($C_{20}H_{25}N_3OS \cdot H_2O$) C, H, N.

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1-Acyltriazoles as Antiinflammatory Agents

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Certain 1-acyl-3-phenyl-5-alkyltriazoles were synthesized and evaluated for antiinflammatory activity using the mouse active Arthus (MAA) reaction as the test system. Modification of the acyl group, 4-phenyl substituent, and alkyl group led to the selection of the most active member of this series, 1-acetyl-3-(4-chlorophenyl)-5-methyl-1,2,4-triazole (**3c**), for further evaluation as a novel nonacidic antiinflammatory agent.

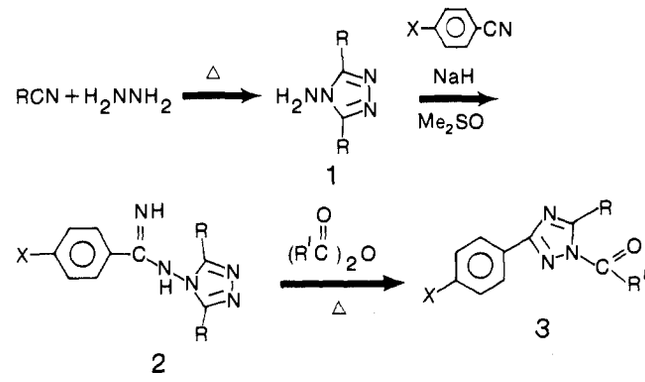
The development of an effective nonacidic antiinflammatory agent possessing an enhanced therapeutic ratio relative to the currently marketed acidic agents remains a major objective in drug research. In view of the current interest in such compounds, we report the discovery and selective antiinflammatory activity of the novel acyltriazole **3c** and certain close analogues.

In the course of a recent research program directed toward the synthesis of novel bioactive tricyclic heterocycles, 1-acetyl-3-(4-chlorophenyl)-5-methyl-1,2,4-triazole (**3c**) was synthesized[2] and evaluated in the mouse active Arthus (MAA) reaction. As a result of its oral antiinflammatory activity in this test system, a limited number of close analogues were prepared bearing variations of the 1-acyl, 5-alkyl, and 4-phenyl substituents.

The synthetic procedure used for their preparation is summarized in Scheme I and has been described previously.[2]

As indicated in Table I, four acyltriazoles (**3a,c,d,f**) possessed ID_{50} values of less than 500 mg/kg following oral administration in the MAA reaction, with compound **3c** being the most active of these. None of the intermediate *N*-aminotriazoles, **1** and **2**, exhibited appreciable activity in this test. On the basis of its potency in the MAA model, compound **3c** was selected for further evaluation.

Scheme I



Discussion

The biological data for **3c** are summarized in Table II along with the corresponding results obtained with a standard arylacetic acid antiinflammatory agent, ibuprofen. Comparison of these results indicates that **3c** possesses oral activity in the primary test system, i.e., mouse active Arthus (MAA), with an ID_{50} = 342 mg/kg and is approximately 10 times more potent when administered via the intraperitoneal route, i.e., ID_{50} = 37 mg/kg. In contrast, ibuprofen is less active, being unable to attain a 50% inhibition at these doses following either route of administration.

One of the major objectives of our antiinflammatory program has been the development of agents with selective profiles of activity, i.e., compounds which are active in test systems that represent immunological mechanisms believed to be involved in inflammatory diseases of man (Arthus reactions and adjuvant arthritis) and which possess little, if any, activity in animal models of inflammation that are nonspecific (e.g., carrageenin edema). Evaluation of **3c** in the carrageenin-induced edema test in the rat indicates it possesses such a selective profile, being inactive at doses at high as 150 mg/kg orally. Ibuprofen, on the other hand, is orally active in this animal model with an ID_{50} of 70 mg/kg. At a concentration of 1000 μM, **3c** had no inhibitory activity vs. thromboxane synthetase. Compound **3c** inhibits the systemic lesions of adjuvant-induced arthritis in the rat by 73% at an oral dose of 150 mg/kg. However, ibuprofen inhibits both the local and systemic lesions of adjuvant-induced arthritis at an oral dose of 60 mg/kg.

Comparison of the acute toxicity of **3c** and ibuprofen in the mouse indicates that the acyltriazole is much less toxic, with an oral LD_{50} of greater than 3200 mg/kg (vs. an LD_{50} of 1650 mg/kg for the acid). Thus, **3c** possesses a therapeutic ratio of greater than 9.3, based on the comparison of the LD_{50} to the ID_{50} in the MAA, while the corresponding value for ibuprofen is less than 2.1.

Conclusion

The preliminary data indicate that acyltriazole **3c** represents a new class of systemic antiinflammatory agents, possessing a selective profile of oral activity in the mouse active Arthus and adjuvant arthritis tests, a contrasting absence of activity in carrageenin-induced edema at oral doses as high as 150 mg/kg, coupled with a low degree of acute oral toxicity. This profile of activity is different from that possessed by the classical arylacetic acid type agents

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