Glycerides as Prodrugs. 3. Synthesis and Antiinflammatory Activity of [1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides (Indomethacin Glycerides)

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Mono-, bis-, and tris[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides and 1,3-dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides were synthesized and evaluated for antiinflammatory activity in the rat paw carrageenin edema assay. Three of the most active compounds (**4**, **18a**, and **18e**) were tested in the rat adjuvant arthritis model and found to be essentially equivalent in activity to indomethacin. On a molar basis, the acute gastric irritating properties of **18a** and **18e** were seven to eight times less than indomethacin, resulting in a 2.5- to 3-fold improvement in the ratio of antiedema activity to ulcerogenicity.

The observation that triglycerides in which aspirin is attached at the 2 position gave adequate blood levels of salicylate without causing gastric irritation[2,3] prompted us to investigate the analogous incorporation of other antiinflammatory agents. Indomethacin is one of the most useful of the antirheumatic drugs but has the disadvantage typical of these agents, i.e., that it may cause gastrointestinal ulceration and hemorrhage. In this paper, we report the synthesis and pharmacological properties of compounds in which indomethacin is part of a mono-, di-, or triglyceride.

Chemistry. The glycerides described in Table I were prepared by methods A to D (Schemes I–IV).

Method A. 1-Indomethacin monoglyceride (**4**) was obtained by the condensation of 2,2-dimethyl-1,3-dioxolane-4-methanol (**1**) with 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl chloride (**2**), followed by removal of the isopropylidene group with boric acid (Scheme I).

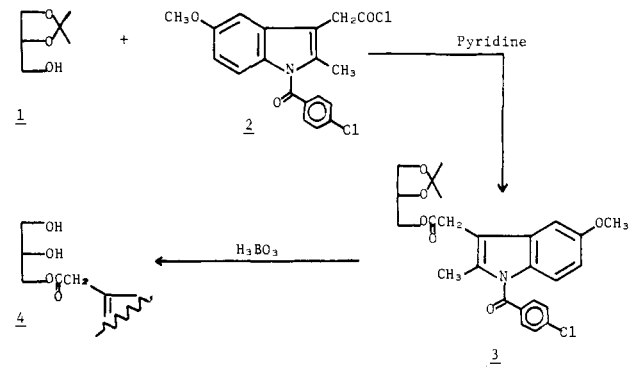
Method B. Condensation of 1,3-benzylideneglycerol (**6**) with **2**, followed by boric acid hydrolysis, yielded 2-indomethacin monoglyceride (**8**) as outlined in Scheme II.

Method C. The synthesis of 1,2-diindomethacin glyceride (**12**) is outlined in Scheme III. Compound **1** was reacted with β,β,β-trichloroethyl chlorocarbonate to give **9**, which gave **10** upon acid hydrolysis. Condensation of **10** with 2 mol of the acid chloride of indomethacin gave **11**. Reduction of **11** with zinc and acetic acid yielded the desired product **12**.

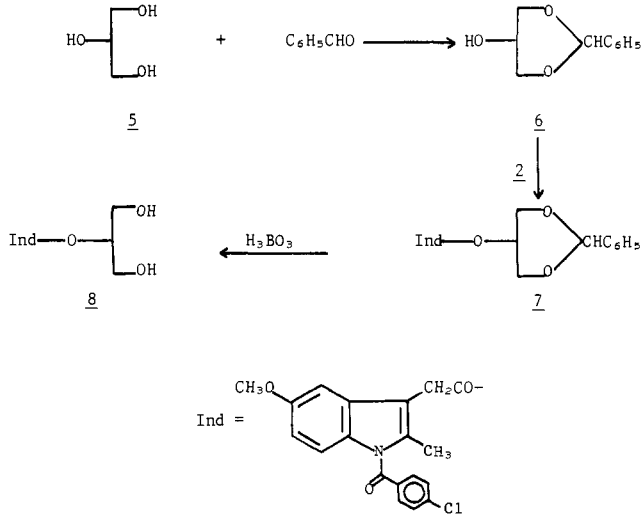
Method D. The preparation of 1,2,3-triindomethacin glyceride (**16**) is illustrated in Scheme IV. Condensation of 1,3-dihydroxyacetone (**13**) with 2 mol of **2**, followed by reduction of the carbonyl group with sodium borohydride, gave the corresponding 1,3-diglyceride **15** which was reacted with a 3rd mol of the acid chloride to give **16**.

The 1,3-dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides (**18**) described in Table

Scheme I



Scheme II

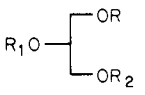


(1) Corresponding address: Abbott Laboratories, North Chicago, Ill. 60064.

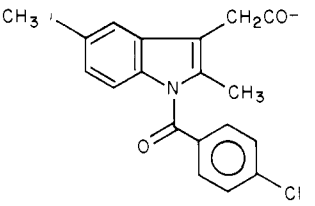
(2) For paper 1 of this series, see: Paris, G. Y.; Garmaise, D. L.; Cimon, D. G.; Swett, L.; Carter, G. W.; Young, P. *J. Med. Chem.* **1979**, *22*, 683. For paper 2 of this series, see: Paris, G. Y.; Garmaise, D. L.; Cimon, D. G., Swett, L.; Carter, G. W.; Young, P. *Ibid.* **1980**, *23*, under Notes in this issue.

(3) Carter, G. W.; Young, P. R.; Swett, L. R.; Paris, G. Y., submitted for publication in *Agents Actions*.

Table I. Physical and Antiinflammatory Data of Mono-, Bis-, and Tris[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides



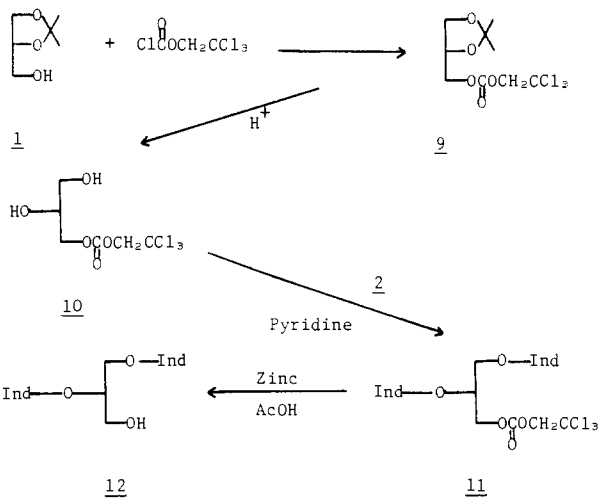
ind =



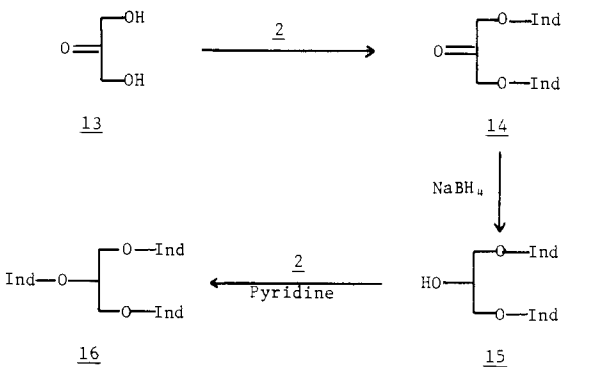
compd	R	R_1	R_2	mp, °C[a]	formula	anal.	method[b]	indomethacin, %	antiedema efficacy:[c] ED_{25},[d] μM/kg
4	ind	H	H	79-81	$C_{22}H_{22}ClNO_6$	C, H, Cl, N	A	83	5
8	H	ind	H	99-101	$C_{22}H_{22}ClNO_6$	H, N, O; C[e]	B	83	21
12	ind	ind	H	*f*	$C_{41}H_{36}Cl_2N_2O_9$	H, N; C[g]	C	92	31
15	ind	H	ind	*f*	$C_{41}H_{36}Cl_2N_2O_9$	H, N, O; C[h]	D	92	*i*
16	ind	ind	ind	123-124	$C_{60}H_{50}Cl_3N_3O_{12}$	C, H, Cl, N, O	D	96	*i*
indomethacin									5

[a] For more physical data, see Experimental Section. [b] Letters relate to the procedures given under Experimental Section. [c] Male Sprague-Dawley rats weighing 160-190 g were fasted overnight but allowed water ad libitum. Indomethacin and indomethacin glycerides were administered orally 2 h prior to the subplantar injection of 0.1 mL of 1.5% solution of carrageenin. Paw volumes were measured prior to and 3 h after injection by immersion in a mercury-containing vessel connected to a volumetric transducer and a polygraph. [d] ED_{25} refers to that dose of drug which inhibits paw swelling by 25% when compared to control (estimated by simultaneous linear-regression analysis). [e] C: calcd, 61.18; found, 60.42. [f] Amorphous material. [g] C: calcd, 63.82; found, 61.11. [h] C: calcd, 63.82; found, 62.19. [i] Compounds 15 and 16 were inactive at 26 and 18 μmol/kg, respectively.

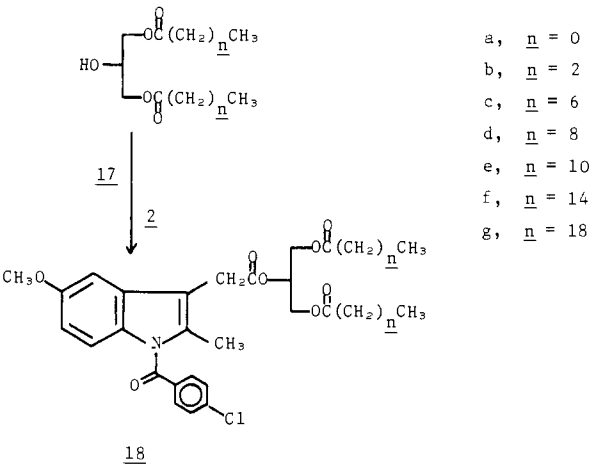
Scheme III



Scheme IV



Scheme V



a, n = 0
b, n = 2
c, n = 6
d, n = 8
e, n = 10
f, n = 14
g, n = 18

II were prepared by method E as outlined in Scheme V. 1,3-Dialkanoylglycerides (**17**) were obtained by the general procedure of Bentley and McCrae[4] and condensed with the acid chloride of indomethacin in the presence of a base to give the desired triglycerides (**18**). All compounds were characterized by NMR, IR, MS, and elemental analysis. Their physical properties are summarized in Table II.

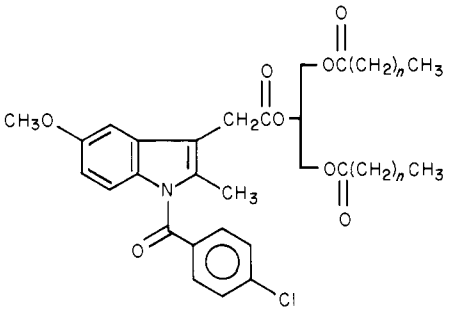
Pharmacology. Antiedema Efficacy and Ulcerogenicity. Compounds of Tables I and II were screened for antiinflammatory activity in the carrageenin rat paw edema assay, using a modification of the method described by Winter et al.[5] (see footnote *c* of Table I).

1. Rat Paw Edema Assay. It can be seen from Table I that compound **4** was as potent as indomethacin, compounds **8** and **12** were four to six times less potent, and compounds **15** and **16** were inactive.

The most active of the 1,3-dialkanoyl-2-indomethacin glycerides (**18a–g**) had approximately one-third to one-half

(4) Bentley, P. H.; McCrae, W. *J. Org. Chem.* **1970**, *35*, 2082.
(5) Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Exp. Biol. Med.* **1962**, *111*, 544.

Table II. 1,3-Dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides



no.	*n*	M_r	indomethacin, %	yield, %	physical form, mp[a]	formula[b]	MS (M^+)
18a	0	515.95	69	66	78-80	$C_{26}H_{26}ClNO_8$	515
18b	2	572.06	63	53	liquid	$C_{30}H_{34}ClNO_8$[c]	571
18c	6	684.27	52	51	liquid	$C_{38}H_{50}ClNO_8$[d]	683
18d	8	740.38	48	54	58-60	$C_{42}H_{58}ClNO_8$[e]	739
18e	10	796.46	45	54	51-52	$C_{46}H_{66}ClNO_8$[f]	795
18f	14	907.71	39	68	65-66	$C_{54}H_{82}ClNO_8$	907
18g	18	1020.92	35	83	70-72	$C_{62}H_{98}ClNO_8$	1019

[a] All solids were crystallized from petroleum ether (bp 30-60 °C). [b] Analyses for C, H, Cl, N, and O within ±0.4% of calculated values except where noted. [c] Anal. Calcd for $C_{30}H_{34}ClNO_8$: C, 62.99; H, 5.99; Cl, 6.20; N, 2.45; O, 22.37. Found: C, 62.35; H, 6.16; Cl, 5.97; N, 2.36; O, 23.04. [d] Anal. Calcd for $C_{38}H_{50}ClNO_8$: C, 66.70; H, 7.37; Cl, 5.18; N, 2.05; O, 18.71. Found: C, 66.09; H, 7.49; Cl, 5.40; N, 2.05; O, 18.97. [e] Anal. Calcd for $C_{42}H_{58}ClNO_8$: C, 68.14; H, 7.90; Cl, 4.79; N, 1.90; O, 17.29. Found: C, 67.67; H, 7.87; Cl, 4.99; N, 1.87; O, 17.60. [f] Anal. Calcd for $C_{46}H_{66}ClNO_8$: C, 69.72; H, 7.89; Cl, 4.47; N, 1.77; O, 16.15. Found: C, 68.98; H, 8.54; Cl, 4.32; N, 1.69; O, 15.92.

Table III. Antiedema Efficacy and Gastric Ulceration Caused by 1,3-Dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides

compd	antiedema efficacy: ED_{25}, μmol/kg	gastric irritation: UD_{50},[a] μmol/kg	therapeutic ratio: UD_{50}/ED_{25}
18a	14	67	5
18b	22		
18c	12		
18d	18		
18e	13	78	6
18f	23		
18g	38		
indomethacin	5	10	2

[a] UD_{50} refers to that dose which produced lesions in 50% of the treated animals. The ED_{25} values were estimated by linear regression.

the activity of indomethacin (Table III). The activity of 1,3-dilinoleoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (**19**; prepared by method E) was in the same range.

2. Gastric Irritation and Therapeutic Indices. We have previously reported[2,3] that the incorporation of aspirin or its cyclic analogue on the 2 position of a 1,3-dialkanoylglyceride reduced or eliminated the gastrointestinal irritation of aspirin. In studies investigating the antiedema activity of compounds **18a**, **18e**, and indomethacin, the rats' stomachs were also examined for the presence of gastric lesions (Table III) following the method described by Brodie and Hansen.[6] The doses which caused lesions in 50% of the animals (UD_{50}) were 67, 78, and 10 μmol/kg, respectively. Calculating the therapeutic indices (UD_{50}/ED_{25}) of the same products gave values of 5 and 6, respectively, compared to 2 for indomethacin. This represents a 2.5- to 3-fold improvement in the therapeutic index of indomethacin.

Table IV. Activity of 4, 18a, 18e, and Indomethacin vs. Adjuvant-Induced Arthritis

compd	dose, (μmol/kg)/day (days 14-25)	% inhibn of swelling	severity of involvement:[a,c] % change from control	body wt gain (days 1-25)
4	0.8	57	31	
	1.6	67	42	
	3.3	73	55	+[b]
	14.0	76	53	+
18a	0.8	43	25	
	1.6	50	28	
	3.3	72	55	+
	14.0	79	60	+
18e	1.4	30	30	
	2.8	70	41	
	5.6	63	53	+
	11.0	73	74	+
indomethacin	0.7	37	25	
	1.4	57	33	
	2.8	76	56	+
	7.0	75	74	+

[a] Four paws scored. [b] + = significant body weight gain. [c] Reference 8.

3. Rat Adjuvant Induced Arthritis.[7] Fourteen days after the subcutaneous injection of a microbacterial adjuvant into the tails of rats, the animals which showed definite disease involvement were selected for treatment. Compounds **4**, **18a**, **18e**, and indomethacin were administered orally at doses varying from 0.7 to 14.0 (μmol/kg)/day for 12 days. Antiinflammatory activity was evaluated following three criteria: the decrease in hind paw

(6) Brodie, D. A.; Hansen, H. M. *Gastroenterology* **1960**, *38*, 353.

(7) Glen, E. M.; Gray, J. *Am. J. Vet. Res.* **1965**, *26*, 1180.

(8) Pearson, C. M. *Proc. Soc. Exp. Biol. Med.* **1956**, *91*, 95.

volume as measured by mercury displacement, the subjective scoring of the overall severity of limb involvement, and the improvement of body weight gain as compared to diseased controls.

Compounds **4**, **18a**, and **18e** produced activity comparable to indomethacin when administered on a daily basis to adjuvant arthritic rats. The percent changes of hind paw edema and severity scores compared to control animals are presented in Table IV. Higher doses of the compounds also produced a significant improvement in body weight gain compared to diseased controls.

Conclusion

Therapeutic indices (UD_{50}/ED_{25}) which were calculated for the most active triglycerides showed only a 2.5- to 3-fold improvement in the therapeutic index of indomethacin compared to more than an 80-fold improvement with aspirin triglycerides.

In the rat adjuvant-induced arthritis model, the same triglycerides have shown essentially all the systemic activity associated with indomethacin incorporated in the molecule. Consistent with previously reported results for "aspirin triglycerides", "indomethacin triglycerides" produce a systemic antiinflammatory activity qualitatively similar to that of the parent drug. However, therapeutic indices (UD_{50}/ED_{25}) for the most active indomethacin triglycerides show less of an improvement than the most active aspirin triglyceride did over that of the parent drug. We believe that these results indicate that gastrointestinal damage due to indomethacin is mainly produced by systemically circulating drug, whereas damage caused by aspirin is primarily the result of local action on the gastric mucosa.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Department, Abbott Laboratories, North Chicago, Ill. IR, UV, and NMR spectra were in agreement with the assigned structures. NMR spectra were recorded with an EM 360 (Me_4Si). TLC's were performed on fluorescent silica gel GF plates and components were visualized by short- or long-wavelength UV fluorescence or by spraying with a saturated $KMnO_4$ solution.

Method A (Scheme I). 1-[1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (4). This product has been reported in the literature[9] without characterization. Compound **4** was prepared by the following method: 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl chloride (**2**; obtained by refluxing a solution of indomethacin and $SOCl_2$ in C_6H_6; 7.6 g, 0.02 mol) dissolved in 100 mL of THF (anhydrous and peroxide free) was added dropwise to a stirred solution of DL-isopropylideneglycerol (Solketal, Aldrich Chemical Co. Inc.; 2.64 g, 0.02 mol) in 100 mL of THF. Once the addition was completed, stirring was continued at room temperature for 16 h. The insoluble salt was removed by filtration and the filtrate was evaporated to dryness. The oily residue was treated with ether to remove the last traces of salt. Removal of solvent yielded crude **3** (8.1 g).

A part of the crude oil (6.5 g) was dissolved in 100 mL of triethyl borate and 2.4 g of dry H_3BO_3 was added. The reaction mixture was heated to 100 °C until a clear solution was obtained (10 min). Removal of the solvent under vacuum yielded an oil, which was heated to 100 °C under vacuum for 20 min. Upon cooling, a gummy residue was obtained. This residue was dissolved in 200 mL of a mixture of ether–H_2O (50:50), and the ethereal layer was decanted. The aqueous layer was extracted with 3 × 50 mL of ether. The combined ether extracts were dried over $MgSO_4$ and then evaporated to dryness.

The oily residue was purified by chromatography on a column of Florisil (220 g, impregnated with 10% w/w H_3BO_3). The column was washed successively with petroleum ether (bp 30–60), petroleum ether–Et_2O (50:50), and cyclohexane. Compound **4** was eluted from the column with cyclohexane–EtOAc (1:1). The chromatographed product was triturated with petroleum ether to give a solid: mp 79–81 °C; yield 4.1 g (69%); NMR ($CDCl_3$) δ 2.32 (s, 3 H, $NCCH_3$), 3.75 (s, 2 H, CH_2CO), 3.9 (s, 3 H, OCH_3), 3.8–4.2 (m, 4 H, 2 × CH_2O), 4.9 (m, 1 H, OCH), 6.6–7.7 (m, 7 H, 2 × Ph); MS *m/e* 431 (M^+).

Method B (Scheme II). 2-[1-(*p*-Chlorobenzoyl-5-methoxy-2-methylindole-3-acetyl]glyceride (8). 1,3-Benzylideneglycerol (**6**) was prepared by the method of Hibbert and Carter[10] from glycerol, benzaldehyde, and a catalytic amount of acid.

To a cold (0 °C) solution of **6** (4.83 g, 0.02 mol) in pyridine (60 mL) was added **2** (7.53 g, 0.021 mol). Stirring was continued for 1 h at 0 °C and then at room temperature for 17 h. The reaction mixture was treated with cold H_2O, extracted with $CHCl_3$, and dried over $MgSO_4$. Removal of the solvent gave a quantitative yield of crude **7** (10.6 g).

Crude **7** (10.4 g) was treated with 250 mL of triethyl borate and 2.6 g of H_3BO_3 as described for compound **3**, and the crude product was purified by column chromatography to give **8** in 22% yield: mp 99–101 °C; NMR ($CDCl_3$) δ 2.32 (s, 3 H, $NCCH_3$), 3.72 (s, 2 H, CH_2CO), 3.80 (s, 3 H, OCH_3), 3.9–4.45 (d, 4 H, 2 × CH_2O), 6.6–7.7 (m, 7 H, 2 × Ph); MS *m/e* 431 (M^+).

Method C (Scheme III). 1,2-Bis[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]-3-[[(β,β,β-trichloroethyl)oxy]carbonyl]glyceride (11). Compound **2** (15.4 g, 0.04 mol) dissolved in 75 mL of $CHCl_3$ was added at 0 °C to a suspension of [[(β,β,β-trichloroethyl)oxy]carbonyl]glycerol (**10**; 5.35 g, 0.02 mol) in pyridine (3.32 g) and $CHCl_3$ (75 mL). After 1 h, the cooling bath was removed and the reaction mixture was stirred at room temperature for 18 h. Ether (400 mL) was added to the reaction mixture. The organic layer was decanted and washed with H_2O (2 × 150 mL), 1% HCl (2 × 150 mL), H_2O (1 × 150 mL), 1% $NaHCO_3$ (2 × 150 mL), H_2O (2 × 150 mL), and brine (2 × 150 mL). The dried ether extracts (Na_2SO_4) were evaporated to dryness to yield an amorphous product, which was chromatographed on a Florisil (250 g) column with ether as eluent: yield 9.3 g (49%); MS *m/e* 741 (M^+).

1,2-Bis[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (12). Compound **11** was dissolved in 100 mL of ether, and 65 mL of HOAc (95%) was added. Zinc dust (15 g) was added to the cold stirred solution. The stirring was continued for 3 h, and ether (200 mL) was added to the reaction mixture. The insoluble material was filtered and washed with ether. The ether extracts were washed as previously described for **11** and dried over $MgSO_4$. Removal of the solvent yielded an oil, which was chromatographed on Florisil (110 g). Compound **12** was eluted with cyclohexane–EtOAc (3:1): yield 6.3 g (83%) of amorphous material; TLC R_f 0.33 (cyclohexane–EtOAc, 1:1); NMR ($CDCl_3$) δ 2.32 (s, 6 H, 2 × $NCCH_3$), 3.60 (s, 4 H, 2 × CH_2CO), 3.70 (s, 6 H, 2 × OCH_3), 4.4 (s, 4 H, 2 × CH_2O), 5.2 (m, 1 H, HCO), 6.6–7.7 (m, 14 H, 4 × Ph); MS *m/e* 770 (M^+).

Method D (Scheme IV). 1,3-Bis[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (15). A solution of **2** (31.60 g, 0.084 mol) in CH_2Cl_2 (400 mL) was added dropwise at 0–5 °C to a stirred solution of 1,3-dihydroxyacetone (**13**; 3.64 g, 0.040 mol) and pyridine (7.80 g, 0.112 mol) in 1 L of CH_2Cl_2. Following complete addition, stirring was continued for 17 h at room temperature. The salt was removed by filtration and the organic layer was washed with 3 × 300 mL of H_2O. Removal of the solvent yielded an oily residue, which was chromatographed on a column of Florisil (800 g). Compound **14** was eluted from the column with cyclohexane–EtOAc (20:80) and used without further purification in the next experiment: yield 13.6 g (44%).

Neutral sodium borohydride (0.97 g, 0.026 mol) was added portionwise to a solution of **14** (13.5 g, 0.0175 mol) in THF (200 mL), C_6H_6 (50 mL), and H_2O (14 mL) with stirring and cooling (0–5 °C). After the addition was completed (about 20 min), stirring was continued for 1 h at room temperature. The excess $NaBH_4$ was decomposed by slow addition of acetic acid (0.5 mL),

(9) Sherlock, M. H. South African Patent 6 802 186 (1968); *Chem. Abstr.* **1969**, *70*, P96617*a*.

(10) Hibbert, H.; Carter, N. M. *J. Am. Chem. Soc.* **1929**, *51*, 1601.

and the reaction was treated with 200 mL of $CHCl_3$. The organic layer was decanted and washed with 1% $NaHCO_3$ and H_2O. Removal of solvent yielded an oil, which was chromatographed on a Florisil column (200 g, acid-washed and impregnated with 10% boric acid, w/w) with cyclohexane–EtOAc, 3:1: yield 9 g (68%) of amorphous material; TLC R_f 0.41 (cyclohexane–EtOAc, 3:1); NMR ($CDCl_3$) δ 2.38 (s, 6 H, 2 × $NCCH_3$), 3.7 (s, 4 H, 2 × CH_2CO), 3.82 (s, 6 H, 2 × OCH_3), 4.15 (s, 4 H, 2 × CH_2O), 6.5–7.8 (m, 14 H, 4 × Ph); MS *m/e* 770 (M^+).

1,2,3-Tris[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (16). Compound **2** (4.14 g, 0.011 mol) was added to a solution of **15** (7.69 g, 0.01 mol) and pyridine (0.87 g, 0.011 mol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred for 4 days at room temperature. The insoluble material was filtered off and the organic layer washed with H_2O. Removal of the solvent yielded 1.7 g of solid (15%); mp 118–120 °C. This solid was chromatographed on a Florisil (200 g) column with cyclohexane–EtOAc (9:1 and then 8:2): TLC R_f 0.73 (cyclohexane–EtOAc, 1:1); mp 123–124 °C (after treatment with acetone); NMR ($CDCl_3$) δ 2.32 (s, 9 H, 3 × $NCCH_3$), 3.55 (s, 6 h, 3 × CH_2CO), 3.8 (s, 9 H, 3 × OCH_3), 4.2 (m, 4 H, 2 × CH_2O), 5.25 (d, 1 H, OCH), 6.5–7.8 (m, 21 H, 6 × Ph); MS *m/e* 1109 (M^+).

Method E (Scheme V). 1,3-Dialkanoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glycerides (18). General Procedure. Synthesis of the compounds in Table II is exemplified by the preparation of 1,3-dipalmitoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (**18f**).

1,3-Dipalmitoylglyceride (5.7 g, 0.010 mol) was dissolved in 50 mL of freshly distilled $CHCl_3$. Pyridine (0.95 g, 0.012 mol) and compound **2** (4.5 g, 0.011 mol) were added at once; the reaction mixture was stirred for 40 h at room temperature and treated with 100 mL of H_2O. The aqueous layer was decanted and extracted with 2 × 25 mL of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with 1% HCl and H_2O, dried over $MgSO_4$, and evaporated to dryness. The solid obtained was purified by chromatography on a Florisil column (180 g). Compound **18f** was eluted with petroleum ether–ether (50:50): yield 5.2 g (68%); mp 65–66 °C (after one crystallization from petroleum ether); NMR ($CDCl_3$) δ 2.40 (s, 3 H, $NCCH_3$), 3.7 (s, 2 H, CH_2CO), 3.82 (s, 3 H, OCH_3), 4.20 (m, 4 H, 2 × CH_2O), 5.3 (m, 1 H, OCH), 6.6–7.6 (m, 7 H, 2 × Ph); MS *m/e* 908 (M^+).

1,3-Dilinoleoyl-2-[1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl]glyceride (19). Compound **19** was prepared by the general procedure described for compounds **18**, using linoleic acid instead of the saturated fatty acids in positions 1 and 3. A viscous oil was obtained in 65% yield: NMR ($CDCl_3$) δ 2.40 (s, 3 H, $NCCH_3$), 3.7 (s, 2 H, CH_2CO), 3.85 (s, 3 H, OCH_3), 4.25 (m, 4 H, 2 × CH_2O), 5.4 (m, 8 H, 4 × CH=CH), 6.5–7.8 (m, 7 H, 2 × Ph); MS *m/e* 955 (M^+).

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Basic Antiinflammatory Compounds. N,N′,N″-Trisubstituted Guanidines

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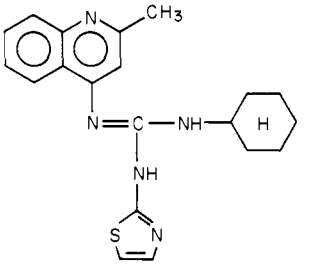
A variety of basic N,N′,N″-trisubstituted guanidines was prepared and tested for antiinflammatory activity. Compounds with a thiazolylguanidine moiety linked to the 4 position of the 2-methylquinoline ring exhibited fairly high antiinflammatory activity. Optimal activity was associated with the presence of *N*-cycloalkyl substituents on *N″*-4-(2-methylquinolyl)-*N′*-2-thiazolylguanidine. Pharmacological data on *N*-cyclohexyl-*N″*-4-(2-methylquinolyl)-*N′*-2-thiazolylguanidine (SR 1368, **44**) are presented and discussed.

The majority of clinically useful antiinflammatory agents are carboxylic acids, such as aroic, heteroaroic, arylalkanoic, and heteroarylalkanoic acids, and enolic acids. There are few examples of basic antiinflammatory compounds, among these, benzydamine[1,2] [1-benzyl-3-[3-(dimethylamino)propoxy]-1*H*-indazole]. Some amidine[3] and guanidine derivatives have been reported to exhibit antiinflammatory activity in animals, e.g., aminoguanidine[4] and trisubstituted[5] and tetrasubstituted[6] guanidines. During our investigations on biological activity of guanidine derivatives,[7] it was observed that certain thiazolyl-substituted guanidines containing other heteroaryl groups showed antiinflammatory activity. Variations in substituents around the guanidine moiety were made, and the results of pharmacological investigations eventually led to the selection of *N*-cyclohexyl-*N″*-4-(2-methylquinolyl)-*N′*-2-thiazolylguanidine (**44**, SR 1368) for further study.



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