Antiinflammatory Fluoroalkanesulfonanilides. 3. Other Fluoroalkanesulfonamido Diaryl Systems[1]

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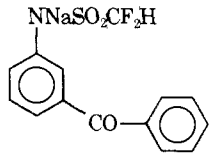
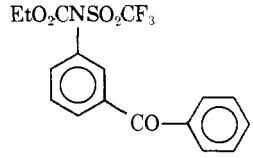
A series of isosteres of 3-benzoyltrifluoromethanesulfonanilide involving alternatives to the carbonyl linking group was synthesized and screened for antiinflammatory activity in the carrageenan rat paw edema test. The systems examined were of the type *m*-CF_3SO_2NH-C_6H_4-X-C_6H_5, where X was -CROH-, -CHR-, -CH(OH)CH_2-, -$COCH_2$-, -CH_2CO-, >C=CR_2, -CR=CH-, -C≡C-, -CH_2CH_2-, CONH-, -NR-, -O-, -$S(O)_n$- (n = 0, 1, 2), and carbon-carbon single bond. Many ortho and para derivatives were also tested. Several of these new trifluoromethanesulfonanilides proved equipotent with phenylbutazone. The effects on the anticarrageenan activity of both the nature and ring position of X are discussed.

The potent antiinflammatory activity of fluoroalkanesulfonamidobenzophenones has been discussed by Trancik, *et al.*,[2] and has led to selection of diflumidone and triflumidate for clinical testing.[3] This paper covers a portion of our continuing investigation of these novel systems and is concerned with the synthesis and evaluation of diaryl systems wherein the connecting link is a group other than carbonyl.



diflumidone sodium

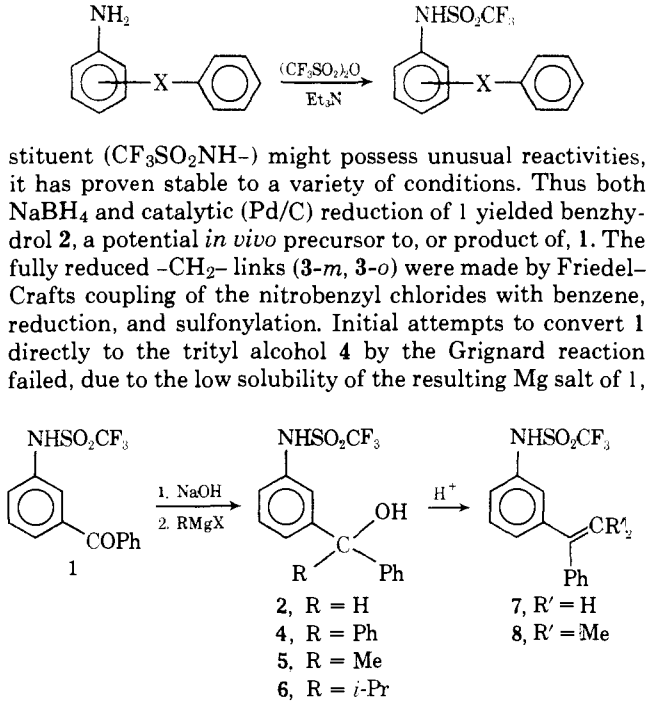


triflumidate

As pointed out by Scherrer[4a] and by Shen,[4b] many of the acidic nonsteroidal antiinflammatory agents are diaryl systems which can be fitted to a receptor site in which the acid-bearing ring lies flat on a surface and the second ring lies in a cavity. Thus a primary role of the linking group may be to sterically allow this fit, although the fact that only a limited number of active "link-type" isosteres of the arylacetic and *N*-phenylanthranilic acids have been reported probably reflects the importance of other factors (*e.g.*, effects on acidity and lipophilicity).

Our goals were new diaryl systems which would sterically mimic the benzophenones but, by virtue of different chemical natures, would possess different spectra of action, metabolism, and toxicity. We chose *m*-benzoyltrifluoromethanesulfonanilide (**1**) as our model. The initial studies[1] showed that, generally, antiinflammatory potency was highest for the CF_3SO_2- series (>CHF_2 > CH_2F ≫ CH_3), corresponding to the highest acidity and lipophilicity. (The apparent pK_a of **1** is 3.7; of diflumidone, 5.3 in 67% DMF-H_2O;[5] and the π value of CF_3SO_2NH- is 3.05.[6]) Our decision to work in the CF_3SO_2NHAr class was dictated in part by expectation that the electronic and lipophilic effects of new links would be leveled somewhat by the potent influence of this group, thus bettering the chances for links possessing only geometric similarity to the carbonyl group to be transported to the active site. Selection of the type and position of links was determined by their stereoelectronic relationship to the lead C=O link, by analogy with known antiinflammatory systems and with other biosteric changes, and by chemical feasibility.

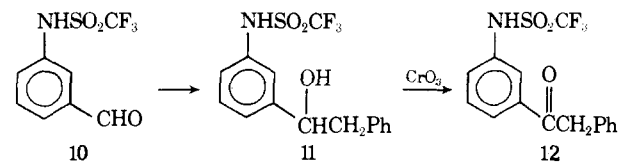
Chemistry. Many of these sulfonanilides were made by trifluoromethanesulfonylation of the appropriate aniline with $(CF_3SO_2)_2O$, the remainder by various transformations of these. Despite some concern that this unusual substituent (CF_3SO_2NH-) might possess unusual reactivities, it has proven stable to a variety of conditions. Thus both $NaBH_4$ and catalytic (Pd/C) reduction of **1** yielded benzhydrol **2**, a potential *in vivo* precursor to, or product of, **1**. The fully reduced -CH_2- links (**3**-*m*, **3**-*o*) were made by Friedel-Crafts coupling of the nitrobenzyl chlorides with benzene, reduction, and sulfonylation. Initial attempts to convert **1** directly to the trityl alcohol **4** by the Grignard reaction failed, due to the low solubility of the resulting Mg salt of **1**,



2, R = H
4, R = Ph
5, R = Me
6, R = *i*-Pr

7, R' = H
8, R' = Me

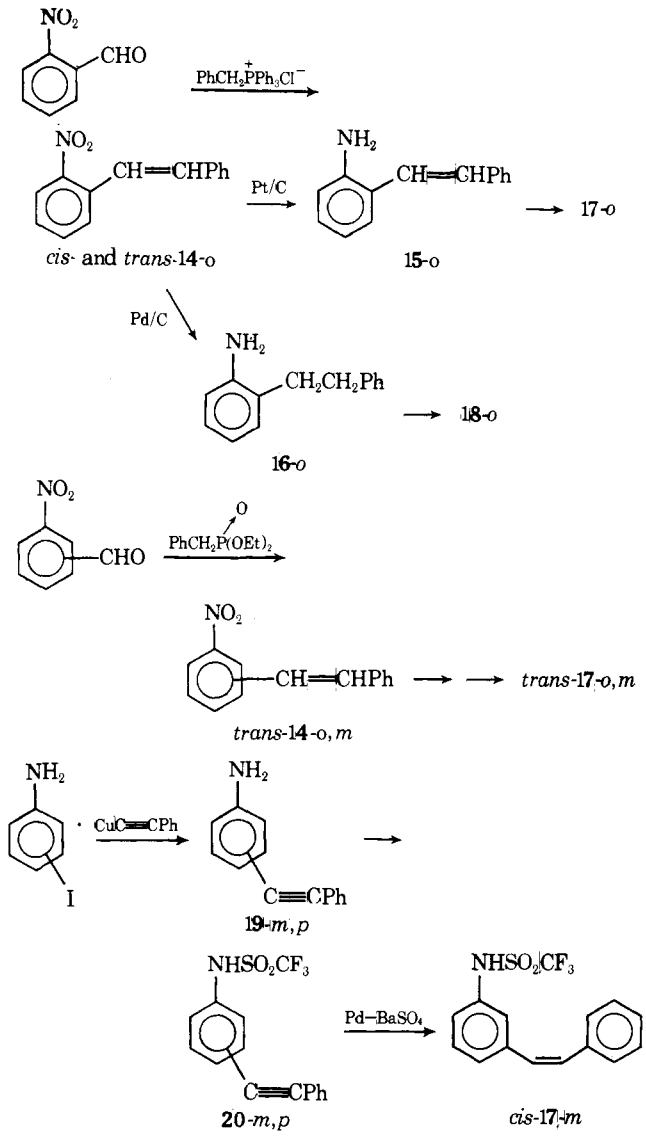
but the Na salt reacted smoothly in THF with PhMgBr and also with alkyl Grignards. Methylcarbinol **5** was dehydrated with H_2SO_4-HOAc to olefin **7**, a close isostere of benzophenone **1**, and reduced with HI-P to >CHMe-linked **9**. The good activity of **7** led to similar synthesis of **8**. A Grignard reaction on **10** gave **11**, converted by Jones oxidation to desoxybenzoin **12**, a homolog of **1**. The other desoxybenzoin isomer **13** was made from the aniline, synthesized through Friedel-Crafts reaction of *m*-nitrophenylacetyl chloride and benzene.



10 **11** **12**

Diverse routes were explored during synthesis of the *cis*- and *trans*-stilbenes (-CH=CH- link, **17**). Wittig reaction of *o*-nitrobenzaldehyde yielded the *o*-nitrostilbenes (**14**-*o*, *ca.* 2:1 cis:trans). Reduction with 5% Pt/C yielded the anilines (**15**-*o*), which were separable either as such or as the sulfonanilides (*cis*-**17**-*o* and *trans*-**17**-*o*). Reduction of **14**-*o* with 5% Pd/C proved nonselective, giving aminobibenzyl

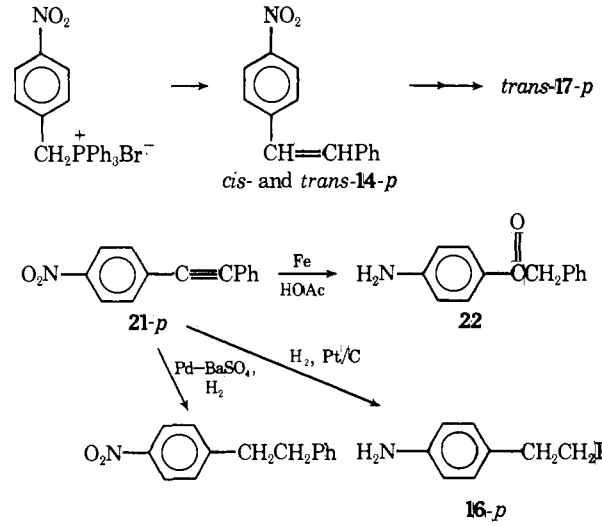
16-*o*. The phosphonate modification of the Wittig reaction was also used to prepare pure *trans*-14-*o* and, from *m*-nitrobenzaldehyde, *trans*-14-*m*. The latter was converted as above to *trans*-17-*m*. *cis*-17-*m* was made by Lindlar reduction of tolane **20**-*m*, in turn made by coupling of *m*-iodoaniline and CuC≡CPh to **19**-*m*.



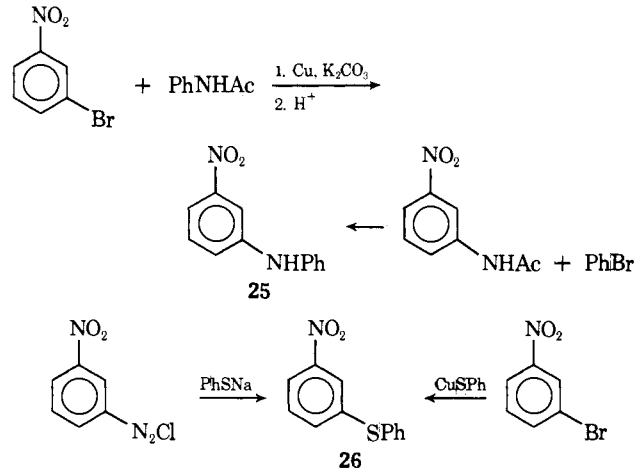
This route failed to give pure *cis*-17-*p* (overreduction to 18-*p*). Wittig reaction using the 4-nitrobenzylphosphonium salt gave 14-*p* (*ca.* 1:2 cis:trans), converted as above to afford only *trans*-17-*p* in pure form. Unaccountably poor yields in the synthesis of 19-*p* from *p*-iodoaniline[7] led to synthesis of nitrotolane (21-*p*). However, reduction of 21-*p* with Pt/C proved nonselective, yielding 16-*p*, while Lindlar reduction gave the saturated 4-nitrobibenzyl. (Similar selectivity has been reported in reduction of nitrobenzoate esters of acetylenic alcohols.)[8] An attempt to reduce 21-*p* with iron in HOAc to 19-*p* gave instead the acetanilide of hydrated product **22**. (These difficulties coupled with the low activity of the other *cis*-stilbenes led us to set aside this goal.) The meta and para isomers of 18 were made by Pd/C reduction of 14-*m*,*p*.

The Wittig sequence on *m*-nitroacetophenone gave primarily one isomer, converted to **23** (apparently trans). Carboxamide-linked **24** was notable for low solubility.

The intermediates for the NH (**27**), NMe (**28**), O (**31**),



OCH_2 (**32**), S (**33**), and σ-bond (**36**) linked series were readily accessible, excepting those for **27**-*m* and **33**-*m*. Amine **25**, the precursor to **27**-*m*, was unsuccessfully sought *via* the Ullmann reaction with aniline, but the apparently little-used Goldberg modification[9] using acetanilide gave it in excellent yield (independent of the degree of activation of the aryl bromide). The known[10] thiodiazo ether decomposition to **26** proved inferior to the coupling of CuSPh with *m*-bromonitrobenzene.[11]



Triflumidate is made by acylation of the Na salt of 1,[3] a reaction which is typical of most sulfonanilides we have studied. However, treatment of the Na salt of **27**-*o* with acid chlorides under identical conditions resulted in the link N-acylated isomers **29** and **30**. The position of acylation was indicated by the base solubility of **29** and **30**. In contrast, methylation of **27**-*o* does occur at the sulfonamide N, giving a product nonidentical with NMe-linked **28**.[12] These facts support the supposition that **27**-*o* acylates initially on the sulfonamido N and subsequent rearrangement affords the link N-acylated products. Oxidation of the sulfides **33** to **34** and **35** went readily. (Sulfone **35**-*m* was made *via* the Friedel–Crafts coupling route.)

Pharmacology. The primary screen was inhibition of

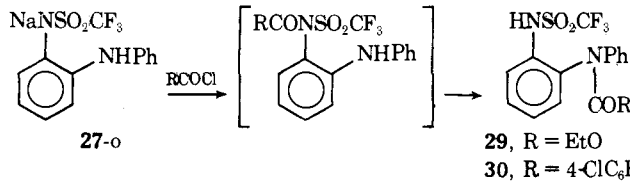
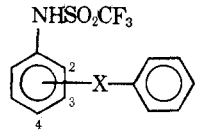


Table I



Compd no.	Link and position	Anticarrageenan rating[a]
1-*o*	2-C=O	+[b]
1-*m*	3-C=O	++++
1-*p*	4-C=O	±[b]
2	3-CHOH	++
3-*o*	2-CH_2	+
3-*m*	3-CH_2	+
4	3-C(OH)Ph	++
5	3-C(OH)Me	±[c]
7	3->C=CH_2	+++
8	3->C=CMe_2	+
9	3-CHMe	+
11	3-$CHOHCH_2$	+
12	3-$COCH_2$	±
13	3-CH_2CO	+
trans-17-*o*	2-	+++
cis-17-*o*	2-	+[c]
trans-17-*m*	3-	+++
cis-17-*m*	3- 	+[c]
trans-17-*p*	4-	+++
18-*o*	2-CH_2CH_2	±
18-*m*	3-CH_2CH_2	±
18-*p*	4-CH_2CH_2	±
20-*m*	3-C≡C	+
20-*p*	4-C≡C	+
23	3-CMe=CH	+
24	3-CONH	±
27-*o*	2-NH	+++
27-*m*	3-NH	+++[c]
27-*p*	4-NH	++
28	2-NMe	±
29	2-NCO_2Et	±[c]
30	2-$NCOC_6H_4$-4-Cl	±
31-*o*	2-O	++
31-*m*	3-O	+++
31-*p*	4-O	±
32	3-OCH_2	±
33-*o*	2-S	++
33-*m*	3-S	+++
33-*p*	4-S	±
34-*o*	2-SO	±
34-*m*	3-SO	+
34-*p*	4-SO	±
35-*o*	2-SO_2	±
35-*m*	3-SO_2	±
35-*p*	4-SO_2	+
36-*o*	2-σ bond	+
36-*m*	3-σ bond	+
36-*p*	4-σ bond	+

[a] ED_{35}: <5 mg/kg po, +++++ (indomethacin); 5–10, ++++ (diflumidone; 1); 11–25, +++ (phenylbutazone); 26–50, ++ (oxyphenbutazone); 51–150, + (aspirin); >150, ± (no significant activity at the screening dose of 100 mg/kg po). [b] Reference 2. [c] Triethylammonium salt.

carrageenan-induced edema of the rat's hind paw (modified).[13] Groups of ten female rats were used. Phenylbutazone (15 mg/kg) was included as a daily positive control, effecting 40 ± 5% inhibition of swelling. Maximum inhibition in this assay was 60–70%. The rating scheme is illustrated in footnote *a* of Table I and the screening results are listed in Table I.

Results

A surprising variety of linked compounds showed marked activity against carrageenan-induced edema, although none of these single-parameter analogs quite equalled our lead benzophenone (1) in potency. We have tested several of these new systems in other assays for antiinflammatory activity and have found good activity against uv-induced erythema of guinea pig skin and phenylquinone-induced writhing of mice, some activity in the adjuvant arthritis test, and none against cotton pellet granuloma. Although none tested has proven markedly different from diflumidone in acute therapeutic index, several were considered worthy of further synthetic follow-up (variations of the fluoroalkyl group and ring substituents, to be reported).

We hoped that the diversity of structures studied would lead to identification of the key features for transport and fit to the receptor site, but clearly no simple relationship exists between these changes and the biological activity. For instance, the most interesting compounds 1 (CO– link), **7** (C=CH_2), all *trans*-**17** (CH=CH), **27**-*o* and **27**-*m* (NH), **31**-*m* (O), and **33**-*m* (S) include both electron-donating and -attracting links. Sterically, all of these except the stilbenes (**17**) are similar flexible diaryl systems, but this is also true of most of the less active compounds. Certain correlations (and noncorrelations) do deserve comment.

The steric role of the link is important but not exclusively so. The linear links (biphenyls **36**, C≡C **20**) possess low activity, suggesting the requirement of a bent diaryl system. The two-atom links were generally uninteresting, possibly for reasons other than steric (see below), since an ortho two-atom-linked B ring can occupy the same site as a meta one-atom-linked B ring. The superior activity of the *trans*-stilbenes (**17**) is difficult to rationalize. Indeed, Dreiding models showed that in one noncoplanar conformation *cis*-**17**-*o* (and -*p*) could be superimposed on the *m*-benzoyl derivative 1. Our synthetic route to *cis*-**17**-*o* gave also the trans isomer, subsequently found to be far more active. The good activity of ortho and meta isomers is quite significant to the receptor site concept, as it indicates that the trough must extend to a considerable extent about the flat A ring. (This hypothetical receptor must already possess considerable flexibility to accommodate the variety of acidic groups (–$NHSO_2CF_3$, –CO_2H, –$CHRCO_2H$, –OCH_2CO_2H) and B-ring positions (ortho, meta, and para) which have been reported in antiinflammatory agents.[14]) Substitution on the link N of **27**-*o* (to **28**, **29**, and **30**) dramatically lowered the activity, suggesting adverse steric effects.

The role of electronic effects in the "sterically qualified" ortho and meta series is even less obvious. For the active derivatives, pK_a ranged from 3.7 to 4.6; for the less active, 2.9 to 4.8. All links involving tetrahedral carbon had low activity (**2–5**, **9**, **11–13**, **18**, **32**). The deleterious effect of this apparent electronic insulation is especially evident in **3** (CH_2), **11** ($COCH_2$), and **12** (CH_2CO). When these structures are contrasted with the highly active structures, the results suggest the need for π electrons in the link for good activity, possibly in allowing conjugation of the two rings (although coplanarity is sterically inconsistent with the trough concept), or in binding to some surface between the flat surface and trough.

We have not yet determined the partitioning of these compounds but have attempted to relate estimated lipophilicities and pK_a values to the antiinflammatory activity. A plot patterned after Craig's π–σ maps[15] hinted at some

optimal contour for high activity and justifies a more rigorous treatment when the necessary data are obtained.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover apparatus. Trifluoromethanesulfonic anhydride was obtained from the Chemical Division of the 3M Co. and redistilled to bp 78–81°. Reductions were accomplished in a Parr low-pressure apparatus at 40–50 psi.

Trifluoromethanesulfonylations. The aniline (0.10 mol) was dissolved in CH_2Cl_2 with 15 ml (0.107 mol) of Et_3N and, under N_2, 16.9 g (0.10 mol) of trifluoromethanesulfonic anhydride was added dropwise (very exothermic). The solvent was removed, under vacuum, excess aqueous NaOH added, and the mixture subjected to steam distillation until the Et_3N odor was no longer detectable. The basic solution was filtered through charcoal and acidified with HCl and the resulting oil or solid extracted with CH_2Cl_2. Purifications were effected by distillation, sublimation, chromatography, or multiple recrystallizations. Solvents frequently used included benzene (PhH), hexane (C_6H_{12}), petroleum ether (PE), trichloroethylene (TCE), and cyclohexane. Many of these sulfonanilides proved to be oils and were converted by treatment in *i*-PrOH–*i*-Pr_2O with excess Et_3N to their crystalline triethylammonium salts.

2-Benzoyltrifluoromethanesulfonanilide (1-*o*). Sulfonylation of 2-aminobenzophenone (19.7 g, 0.10 mol) yielded 1-*o* as a white solid (3.3 g, 10% mechanical loss) on acidification of the basic extract: mp 98–100°. *Anal.* ($C_{14}H_{10}F_3NO_3S$) C, H. Likewise, 4-aminobenzophenone (24.6 g, 0.125 mol) yielded 15.7 g (26%) of 1-*p*, a white solid: mp 136–137° (EtOH–H_2O). *Anal.* C, H.

3-(α-Hydroxybenzyl)trifluoromethanesulfonanilide (2). A solution of 16.5 g (0.05 mol) of 3-benzoyltrifluoromethanesulfonanilide (1) in 100 ml of MeOH was treated slowly at 0–5° with 2.0 g (0.052 mol) of $NaBH_4$ in 50 ml of 10% NaOH. The mixture was warmed to room temperature, decomposed with HCl–H_2O, and extracted with CH_2Cl_2 to give 17.3 g of a thick oil. Chromatography on alumina in benzene yielded seed crystals and, despite a strong tendency to oil out, 14.6 g (77%) of white **2** was obtained from benzene–cyclohexane: mp 67.5–69°. *Anal.* ($C_{14}H_{12}F_3NO_3S$) H, N; C: calcd, 50.8; found, 51.4. Catalytic hydrogenation (5% Pd/C in EtOH for 20 hr at room temperature) also converted 1 to **2**.

2-Benzyltrifluoromethanesulfonanilide (3-*o*). Friedel–Crafts reaction of 2-nitrobenzyl chloride (0.1 mol) with $AlCl_3$ (0.11 mol) in benzene yielded 2-nitrodiphenylmethane, bp 150° (0.5 mm) (17.6 g, 0.083 mol, 33%), which was reduced over Raney nickel in *ca.* 200 ml of EtOH to the aniline: mp 44°; 15.1 g (0.083 mol). This was sulfonylated to an oil, which was distilled at 140–160° (0.2 mm) to 6.5 g of 3-*o*, an oil (>90% pure by glc, 25% yield), from which crystalline 3-*o* was obtained: mp 55–56.5° (hexane). *Anal.* ($C_{14}H_{12}F_3NO_2S$) C, H, N. Isomer 3-*m* was made in an identical fashion: mp 39–40°. *Anal.* C, H.

3-(Diphenylhydroxymethyl)trifluoromethanesulfonanilide (4). A solution of 17.6 g (0.05 mol) of the sodium salt of 1 in *ca.* 50 ml of THF was added to the Grignard reagent from 7.85 g (0.05 mol) of bromobenzene and 1.62 g (0.05 mol) of Mg in THF. The resultant white slurry was stirred 3 hr. The THF was distilled out and the residue washed with 5% H_2SO_4, giving a sticky oil (21.0 g). Chromatography on Florisil yielded a solid (eluting with TCE and PhH) which was recrystallized to 7.8 g (38%) of 4: white solid; mp 108.5–109.5° (cyclohexane). *Anal.* ($C_{20}H_{16}F_3NO_3S$) C, H.

3-(1-Phenyl-1-hydroxyethyl)trifluoromethanesulfonanilide (5). In a fashion similar to 4, excess MeMgBr on the sodium salt of 1 (0.05 mol) in THF gave 15.9 g of thick brown oil. Of this, 6.5 g was treated with excess Et_3N in *i*-Pr_2O, giving the triethylammonium salt of 5, recrystallized from *i*-PrOH–*i*-Pr_2O to 2.83 g of a white solid: mp 124–126°. *Anal.* ($C_{15}H_{15}F_3NO_3S \cdot C_6H_{15}N$) C, H, N.

3-(α-Styryl)trifluoromethanesulfonanilide (7). Carbinol **5** was dehydrated by the method of Garbisch[16] by treating 11.0 g in HOAc with 12 ml of H_2SO_4 in 55 ml of HOAc for 2 min. Quenching in H_2O gave 7 as an oil. Distillation at 153° (0.2 mm) and recrystallization from PE gave a white solid: mp 38–41°; nmr in $CDCl_3$ showed CH_3 (τ 8.4, d, J = 7.2 Hz), CH (τ 5.8, q, $J \sim 7$ Hz), NH (τ 3.0), and ArH (τ 2.75). *Anal.* ($C_{15}H_{14}F_3NO_2S$) C, H, N.

3-(1-Phenyl-2-methylpropenyl)trifluoromethanesulfonanilide (8). In a fashion similar to 4, 35.1 g (0.1 mol) of the sodium salt of 1 was added to the solution from 13.5 g (0.11 mol) of *i*-PrBr and 2.4 g (0.1 mol) of Mg in THF. After heating 2 hr, the mixture was treated with dilute H_2SO_4 and extracted with CH_2Cl_2 to give 40.0 g of a thick oil, a mixture of the carbinol, and olefin 8. This was treated with 25 ml of H_2SO_4 in 100 ml of HOAc and quenched after 2 min, and the resulting oil distilled [bp 204–222° (0.2 mm)]. A fraction solidified and was recrystallized to an off-white solid: mp 74–77° (PE). *Anal.* ($C_{17}H_{16}F_3NO_2S$) H, N; C: calcd, 57.4; found, 56.8.

3-(1-Phenethyl)trifluoromethanesulfonanilide (9). Carbinol **5** (6.90 g, 0.02 mol) was heated with 20 ml of 55% HI, 2.48 g of red P, and 20 ml of HOAc at 100–110° for 3 hr. Filtration, water quenching, and distillation of the resulting oil gave 5.0 g of **9** (76%), bp 151° (0.27 mm), recrystallized from PE to a white solid: mp 38–41°; nmr in $CDCl_3$ showed CH_3 (τ 8.4, d, J = 7.2 Hz), CH (τ 5.8, q, $J \sim 7$ Hz), NH (τ 3.0, broad), and ArH (τ 2.75). *Anal.* ($C_{15}H_{14}F_3NO_2S$) C, H, N.

3-(2-Phenyl-1-hydroxyethyl)trifluoromethanesulfonanilide (11). Sodium 3-formyltrifluoromethanesulfonanilide (**10**),[17] mp 226–227°, was prepared from the free sulfonanilide with aqueous NaOH. This (13.1 g, 0.05 mol) was added in THF to a THF solution of benzylmagnesium chloride from 3.64 g (0.15 g-atom) of Mg and 19.0 g (0.15 mol) of benzyl chloride. Work-up with dilute H_2SO_4 gave a solid which was dissolved in dilute NaOH and reprecipitated with dilute HCl to 12.7 g of 11, a tan solid. Repeated recrystallization from PhH gave white rhomboids: mp 101.5–103.5°. *Anal.* ($C_{15}H_{14}F_3NO_3S$) C, H, N.

3′-(Trifluoromethanesulfonamido)-2-phenylacetophenone (12). Carbinol 11 (12.3 g, 0.036 mol) was treated in acetone with the Jones reagent from 2.9 g (0.029 mol) of CrO_3 and 4.5 g of H_2SO_4. After 0.5 hr, the solution was treated with *i*-PrOH and concentrated and the residue taken up in dilute NaOH. Acidification with dilute HCl gave 9.3 g of orange oil. Chromatography on alumina gave solid **12**, eluting with PhH and CH_2Cl_2, which was recrystallized from PhMe–cyclohexane to a white powder: mp 128.5–130°. *Anal.* ($C_{15}H_{12}F_3NO_3S$) C, H, N.

2-[3′-(Trifluoromethanesulfonamido)phenyl]acetophenone (13). A slurry of 73.2 g (0.55 mol) of $AlCl_3$ in 0.5 l. of PhH was treated with 101.2 g (0.53 mol) of 3-nitrophenylacetyl chloride at 55–60°. Work-up with ice–HCl gave 3-nitrodesoxybenzoin: yellow solid; mp 80–81° (EtOH); 38.4 g (30%). Reduction of 22.25 g (0.092 mol) with 25.8 g (0.46 mol) of Fe filings in HOAc at 100° for 3 hr gave a semisolid from which 10.8 g (55%) of 3-aminodesoxybenzoin was separated: mp 81–89°. This was sulfonylated, giving 8.8 g (28%) of **13** as white needles (PhH): mp 136–137.5°. *Anal.* ($C_{15}H_{12}F_3NO_3S$) C, H, N.

***cis*- and *trans*-2-(β-Styryl)trifluoromethanesulfonanilides (*cis*- and *trans*-17-*o*).** A solution of 3.0 g (0.13 g-atom) of Na in 100 ml of EtOH was treated with 38.9 g (0.10 mol) of benzyltriphenylphosphonium chloride and then with 16.0 g (0.106 mol) of 2-nitrobenzaldehyde. This was stirred overnight, quenched in water, and extracted with CH_2Cl_2 and the resulting oily solid was washed with CCl_4, leaving solid triphenylphosphine oxide. The CCl_4 was evaporated and the resulting oil was chromatographed on alumina with CCl_4, giving 22.95 g (94%) of an oil, a mixture of 2-nitrostilbenes (14). Nmr integration indicated *ca.* 70% cis (τ 3.77, AB, J = 12 Hz). Hydrogenation with 5% Pt/C in EtOH went slowly (24 hr) and yielded a mixture of a solid and oil, which was washed with CCl_4 to 4.7 g of solid, assumed to be *trans*-2-aminostilbene (**15**), and 12.25 g of mother liquors. The solid was sulfonylated to give 2.1 g (38%) of *trans*-17-*o*, mp 78–79.5° (TCE–C_6H_{12}). *Anal.* ($C_{15}H_{12}F_3NO_2S$) C, H, N. The mother liquors from the reduction were chromatographed on alumina with CCl_4 and the resulting 9.2 g of oil was sulfonylated. This product on alumina chromatography yielded 5.8 g of *cis*-17-*o* isomer (an oil, eluting with C_6H_{12} and CCl_4) and 2.7 g of the *trans*-17-*o* (eluting with PhH), mp 78–9.5°. The cis isomer yielded 5.64 g (28%) of white crystalline triethylammonium salt: mp 81.5–85°; nmr ($CDCl_3$) shows τ 3.2 (AB pattern, J = 12.5 Hz). The benzylphosphonate route (see *trans*-17-*m*, below) gave *trans*-17-*o*, identical by melting point and ir. *Anal.* ($C_{15}H_{12}F_3NO_2S \cdot C_6H_{15}N$) C, H, N.

***trans*-3-(β-Styryl)trifluoromethanesulfonanilide (*trans*-17-*m*).** A mixture of 15.1 g (0.1 mol) of 3-nitrobenzaldehyde, 22.8 g (0.10 mol) of diethyl benzylphosphonate, and 4.54 g (0.10 mol) of 58% NaH in glyme reacted vigorously and was then refluxed for 2 hr. Work-up gave 11.8 g (53%) of yellow *trans*-14-*m*: mp 103–107° (EtOH–H_2O); nmr ($CDCl_3$) shows vinyl CH at τ 2.9. Reduction of 15.7 g (0.07 mol) in EtOH with 5% Pt/C gave 8.8 g of yellow powder (mechanical loss), sulfonylated and eluted from alumina with PhH and recrystallized to 8.5 g (37%) of *trans*-17-*m*: white solid; mp 62–64° (PhH–C_6H_{12}). *Anal.* ($C_{15}H_{12}F_3NO_2S$) C, H, N.

***trans*-4-(β-Styryl)trifluoromethanesulfonanilide (*trans*-17-*p*).** 4-Nitrobenzyl bromide was converted to its triphenylphosphonium salt by heating on a steam bath with triphenylphosphine

in DMF overnight. This (24.0 g, 0.05 mol) was added to a solution of 1.5 g (0.065 g-atom) of Na in 100 ml of EtOH and the resulting maroon solution was treated with 7 ml (0.07 mol) of benzaldehyde. When the color had faded, the mixture was worked up to give 8.8 g (78%) of crude **14-*p***: yellow solid; mp 120–145°; nmr ($CDCl_3$) showed the cis AB pattern at τ 3.3 (J = 12 Hz). Integration indicated a trans/cis ratio of 2:1. Hydrogenation over 5% Pt/C in EtOH, sulfonylation, and chromatography yielded 7.0 g of tan *trans*-**17-*p***, recrystallized to white needles, mp 155–156.6° (PhH–C_6H_{12}), only a trace of a second product. *Anal.* ($C_{15}H_{12}F_3NO_2S$) C, H, N.

3-(Phenylethynyl)trifluoromethanesulfonanilide (20-*m*). A mixture of 22.0 g (0.10 mol) of 3-iodoaniline, 16.2 g (0.099 mol) of CuC≡CPh,[10] and 300 ml of pyridine was stirred at 125° under N_2 for 23 hr. Steam distillation left a dark oil, purified by elution from Florisil with TCE to 13.7 g (70%) of **19-*m***: mp 46.5–47.5° (PE); bp 154° (0.05 mm). *Anal.* ($C_{14}H_{11}N$) H; C: calcd, 87.0; found, 86.5. This was sulfonylated and reprecipitated from base to give 22.0 g of crude **20-*m***. Recrystallization gave a white solid: 13.6 g (60%); mp 92.5–94° (C_6H_{12}). *Anal.* ($C_{15}H_{10}F_3NO_2S$) H, N; C: calcd, 55.4; found, 55.9. This procedure also yielded the para isomer, **20-*p***: white solid; mp 123–124.5° (CCl_4–C_6H_{12}). *Anal.* C, H, N.

cis*-3-(β-Styryl)trifluoromethanesulfonanilide (*cis*-17-*m*).** Ethynyl derivative **20-*m (10.0 g, 0.031 mol) was hydrogenated in a Parr apparatus in 150 ml of MeOH over 0.3 g of 5% Pd–$BaSO_4$ and 0.3 g of quinoline. Chromatography on alumina of the resulting oil (eluting with CCl_4) gave *cis*-**17-*m*** as a tan oil, converted by Et_3N to 6.9 g (52%) of the triethylammonium salt: white needles (*i*-PrOH–*i*-Pr_2O); mp 63–65°. *Anal.* ($C_{15}H_{12}F_3NO_2S \cdot C_6H_{15}N$). This procedure on **20-*p*** yielded a mixture containing *cis*-**17-*p*** and **18-*p***.

Fe Reduction of 4-Nitrotolane (21-*p*). 4′-Amino-2-phenylacetophenone (22). A solution of 12.0 g (0.054 mol) of **21-*p***[10] (mp 116–8°) in 100 ml of HOAc at 100° was treated with 15.0 g (0.27 mol) of Fe powder and stirred overnight. Filtration, quenching, and extraction gave an acetanilide. The ir showed no C≡C. This was heated *ca.* 2 hr with aqueous NaOH and EtOH and quenched, and the resulting solid recrystallized to 3.5 g (31%) of a yellow solid: mp 140–142° (PhH); nmr (DMSO-d_6) supports the 4′-amino derivative **22**, CH_2 at τ 5.86, C_6H_5 at τ 2.75, 2′-ArH at τ 2.20, and 3′-ArH at τ 3.37 (J = 8.7 Hz). *Anal.* ($C_{14}H_{13}NO$) C, H, N.

Lindlar Reduction of 4-Nitrotolane (21-*p*). **21-*p*** (12.2 g, 0.055 mol) was hydrogenated in EtOH over 0.5 g of 5% Pd–$BaSO_4$ and 0.8 g of quinoline, taking up 2 equiv of H_2 in 20 hr. Work-up gave a yellow solid: bp 138° (0.15 mm); nmr ($CDCl_3$) clearly showed 4-nitrobibenzyl (–CH_2– at τ 7.1, ArH A_2B_2 at τ 2.15 and 2.9, and C_6H_5 at τ 3.02). A trial at 2 hr gave a mixture of the bibenzyl and the cis olefin.

2-(2-Phenethyl)trifluoromethanesulfonanilide (18-*o*). Crude **14-*o*** (from the Wittig procedure of **17-*o***, 0.1 mol scale) was hydrogenated over Raney nickel in ethanol to **16-*o***: 15.1 g (77%); tan liquid. Sulfonylation yielded 12.4 g (50%) of **18-*o***: a white solid; mp 62–64° (Hex–C_6H_{12}). *Anal.* ($C_{15}H_{14}F_3NO_2S$) C, H, N. Reduction of **14-*m*** and **14-*p*** over 5% Pd/C gave **18-*m*** (32%; white solid; mp 64.5–66°. *Anal.* C, H, N) and **18-*p*** (28%) [white solid; mp 71–73° (C_6H_{12}–PE). *Anal.* C, H, N].

3-(1-Phenyl-2-propenyl)trifluoromethanesulfonilide (23). 3-Nitroacetophenone and benzyltriphenylphosphonium chloride (0.1 mol each) were allowed to react as above to give 17.0 g of a yellow oil, hydrogenated over Pt/C in EtOH to give a solid, which was recrystallized from TCE–C_6H_{12} to 12.4 g (60%) of white solid, mp 84–108°. *Anal.* ($C_{15}H_{15}N$) H, N; C: calcd, 59.7; found, 60.3. The analysis indicates the desired amine, presumably cis–trans isomers. Sulfonylation of 11.0 g (0.053 mol) gave 16.4 g of oil, chromatographed on alumina to 4.2 g of oil (eluting with C_6H_{12}, CCl_4) and 9.0 g of solid (eluting with PhH, Et_2O). The oil yielded a broad melting point (86–98°) triethylammonium salt which analyzed correctly (C, H, N) and is therefore an isomeric mixture. The solid was recrystallized to white needles: mp 67–73° (C_6H_{12}); nmr indicates a single isomer, vinylic CH at τ 3.18. *Anal.* ($C_{16}H_{14}F_3NO_2S$) C, H.

3-Trifluoromethanesulfonamidobenzanilide (24). A slurry of 21.2 g (0.1 mol) of 3-aminobenzanilide in $CHCl_3$–CH_2Cl_2 was sulfonylated to 17.0 g (50%) of tan solid. Recrystallization from various solvents indicated solvent adsorption (PhMe, mp 115–116.5°; TCE, mp 142–145°; $CHCl_3$, mp 121–123°; $ClCH_2CH_2Cl$, mp 116–122°). All was recrystallized from PhMe and then HOAc–H_2O and dissolved in base. Acidification yielded 8.6 g of **24**: white solid; mp 142.5–144°. *Anal.* ($C_{14}H_{11}F_3N_2O_3S$) C, H, N.

3-Anilinotrifluoromethanesulfonanilide (27-*m*). A mixture of 20.2 g (0.10 mol) of 3-bromonitrobenzene, 13.5 g (0.10 mol) of acetanilide, 2 g of Cu dust, 1 g of KI, 13.8 g (0.10 mol) of K_2CO_3, and a catalytic amount (<0.1 g) of CuCl was stirred 22 hr at 180° (bath temperature) and steam distilled for 1.5 hr, and the residue was extracted into CH_2Cl_2. The resulting dark oil was heated on steam for 16 hr in 100 ml of 95% EtOH containing 30 ml of concentrated HCl. Addition of H_2O and cooling yielded 13.1 g (61%) of 3-nitrodiphenylamine (**25**): red needles; mp 104–107°.[9] [The alternative route, using 100 g (0.55 mol) of 3-nitroacetanilide and 172.8 g (1.1 mol) of bromobenzene, gave 86.1 g (73%) of **25**, mp 106–108°.]

Of this, 42.8 g (0.20 mol) was reduced in EtOH over Raney nickel, giving 24.8 g (57%) of 3-aminodiphenylamine, a dark oil. A portion was recrystallized to a grey solid, mp 63–66° (PhH–C_6H_{12}). Sulfonylation of 24.4 g (0.132 mol) gave, after reprecipitation from base and Florisil chromatography, 26.8 g (64%) of brown oil, eluted with PhH and Et_2O. The triethylammonium salt was made with excess Et_3N and recrystallized to off-white crystals, mp 106–110° (*i*-PrOH). *Anal.* ($C_{13}H_{11}F_3N_2O_2S \cdot C_6H_{15}N$) C, H, N.

2-(*N*-Methylanilino)trifluoromethanesulfonanilide (28). 2-Nitro-*N*-methyldiphenylamine [bp 145° (0.02 mm)] was prepared by stirring at 200° for 2 days a mixture of 0.3 mol of 2-chloronitrobenzene, 0.9 mol of *N*-methylaniline, and 0.35 mol of Na_2CO_3.[18] Reduction with Raney nickel in EtOH and distillation gave 2-amino-*N*-methyldiphenylamine, bp 135° (0.07 mm), in 40% overall yield.

Sulfonylation yielded **28** as a tan solid, mp 72–75° (PE). *Anal.* ($C_{14}H_{13}F_3N_2O_2S$) C, H, N.

2-(*N*-Ethoxycarbonylanilino)trifluoromethanesulfonanilide (29). A solution of 10.0 g (0.036 mol) of **27-*o*** in 100 ml of acetone was stirred 2 hr with 10.6 g (0.10 mol) of Na_2CO_3 and then heated to reflux and treated with 3.4 g (0.036 mol) of ethyl chloroformate. After 2 hr, the mixture was filtered and stripped to a maroon oil, soluble in water. Acidification and elution from alumina with PhH yielded 7.2 g (59%) of a red oil. The triethylammonium salt was recrystallized to a white powder, mp 80–85° (*i*-PrOH–*i*-Pr_2O). *Anal.* ($C_{16}H_{15}F_3N_2O_4S \cdot C_6H_{15}N$) C, H, N.

2-(*N*-4-Chlorobenzoylanilino)trifluoromethanesulfonanilide (30). In the same fashion, 10.0 g (0.036 mol) of **27-*o*** and 6.4 g (0.037 mol) of 4-chlorobenzoyl chloride yielded 9.8 g (60%) of **30**: base-soluble white solid; mp 170–171.5° (EtOH). *Anal.* ($C_{20}H_{14}ClF_3N_2O_3S$) C, H, N.

Phenoxytrifluoromethanesulfonanilide (31-*o,m,p*). Commercial meta and para anilines were used. The ortho derivative was made from 2-chloronitrobenzene and phenoxide in DMF, subsequently reducing with Raney nickel to mp 40–45°. Sulfonylation yielded **31-*o*** [white solid; mp 65–67.5° (TCE). *Anal.* ($C_{13}H_{10}F_3NO_3S$) C, H, N], **31-*m*** [tan oil; bp 140° (0.05 mm). *Anal.* C, H], and **31-*p*** [white solid; mp 78.5–80° (TCE–PE). *Anal.* C, H, N].

3-Benzyloxytrifluoromethanesulfonanilide (32). Commercial aniline yielded **32**: tan solid; mp 62–64° (C_6H_{12}). *Anal.* ($C_{14}H_{12}F_3NO_3S$) C, H.

Phenylthiotrifluoromethanesulfonanilide (33-*o,m,p*). CuSPh[11] was prepared from PhSH (1 mol) and commercial (0.5 mol) Cu_2O in 2 l. of refluxing 95% EtOH (18 hr). Of this, 17.3 g (0.10 mol) was heated with 3-bromonitrobenzene (20.2 g, 0.10 mol) in 100 ml of quinoline–30 ml of pyridine for 3 hr at 165–70°, giving a dark solution. The warm mixture was poured onto ice–HCl and extracted with CH_2Cl_2, and the oil distilled to 12.0 g (56%) of **26**, bp 169–175° (0.55 mm). Scale-up to 1.0 mol yielded 183.9 g (80%). Catalytic reduction with Raney nickel in Et_3N yielded 3-aminodiphenyl sulfide. Sulfonylation of 20.0 g (0.10 mol) yielded, on precipitation from base and distillation at 174° (0.15 mm), 22.7 g (68%) of **33-*m***. Recrystallization gave an off-white solid, mp 56.5–58.5° (TCE–C_6H_{12}). *Anal.* ($C_{13}H_{10}F_3NO_2S_2$) C, H, N.

2-Nitrodiphenyl sulfide was prepared from 2-chloronitrobenzene and benzenethiol in hot NaOH–EtOH (20% yield) and reduced with Raney nickel. The 4-nitro isomer was prepared in NaOH–DMF at 130° (54% yield). Sulfonylation yielded **33-*o*** [white solid; mp 41.5–44° (PhH–PE). *Anal.* C, H, N] and **33-*p*** [colorless liquid; bp 163° (0.5 mm). *Anal.* H, N; C: calcd, 46.8; found, 46.3].

3-Phenylsulfinyltrifluoromethanesulfonanilide (34-*m*). Diaryl sulfide **33-*m*** (16.66 g, 0.05 mol) was treated in 25 ml of acetone at −2° with 5.2 ml (0.051 mol) of 30% H_2O_2 in 15 ml of acetone over 1.5 hr. The mixture was concentrated to 17.3 g of thick oil and chromatographed on Florisil to 5.5 g (eluted with TCE) of unreacted **33-*m*** and 11.9 g (68%) (eluted with acetone) of **34-*m***. Recrystallization of the latter gave a white solid, mp 109.5–111° (TCE). Ir shows strong H bonding. *Anal.* ($C_{13}H_{10}F_3NO_3S_2$) C, H, N.

4-Phenylsulfinyltrifluoromethanesulfonanilide (34-*p*). A solution of 8.2 g (0.025 mol) of **33-*p***, 8.9 ml (0.025 mol) of 10% NaOH, and 5.3 g (0.025 mol) of $NaIO_4$ in 150 ml of H_2O was stirred 2 hr, filtered, and acidified. The product was extracted and recrystallized to 4.3 g (50%) of **34-*p***: off-white powder; mp 164–166° (*i*-PrOH–*i*-Pr_2O). *Anal.* ($C_{13}H_{10}F_3NO_3S_2$) C, H, N.

Similarly, **33-*o*** yielded **34-*o*** in 47% yield: a white solid; mp 128–130° (PhH–PE). *Anal.* C, H, N.

3-Phenylsulfonyltrifluoromethanesulfonanilide (35-*m*). 3-Nitrodiphenylsulfone was prepared from 3-nitrobenzenesulfonyl chloride (0.2 mol) and $AlCl_3$ (0.22 mol) in PhH in 55% yield: mp 77–79° (EtOH).[19] Catalytic reduction of 23.4 g (0.089 mol) over Raney nickel in EtOH and recrystallization yielded 12.4 g of tan aniline: mp 94.5–95° (PhH–cyclohexane). Sulfonylation and recrystallization gave 14.9 g (60%) of **35-*m***: white solid; mp 106–108° (TCE). *Anal.* ($C_{13}H_{10}F_3NO_4S_2$) C, H, N.

4-Phenylsulfonyltrifluoromethanesulfonanilide (35-*p*). A solution of 11.0 g (0.033 mol) of **33-*p*** and 10 ml (0.10 mol) of 30% H_2O_2 in HOAc was heated on steam for 5 hr, quenched, and extracted. Recrystallization gave **35-*p***: 7.0 g (58%) as a tan solid; mp 121–123° (TCE–cyclohexane). *Anal.* ($C_{13}H_{10}F_3NO_4S_2$) C, H, N. Likewise, **33-*o*** gave **35-*o***: off-white solid (56%); mp 87–89°. *Anal.* C, H, N.

Phenyltrifluoromethanesulfonanilide (36-*o,m,p*). The *o*- and *p*-aminobiphenyls and the *m*-nitrobiphenyl were obtained commercially and converted to **36-*o*** [white solid; mp 49–51° (C_6H_{12}). *Anal.* ($C_{13}H_{10}F_3NO_2S$) C, H, N], **36-*m*** [tan oil; bp 105–110° (0.1 mm). *Anal.* H; C: calcd, 51.8; found, 51.0], and **36-*p*** [white solid; mp 136–138° (C_6H_{12}). *Anal.* C, H].

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Antiallergic Activity of 4-Hydroxy-3-nitrocoumarins

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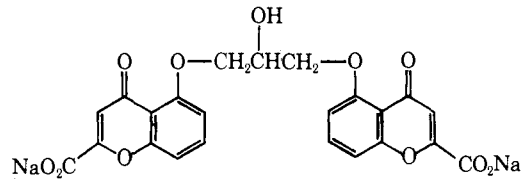
Twenty-four substituted 4-hydroxy-3-nitrocoumarins have been prepared by nitration of the corresponding 4-hydroxycoumarins. All were found to possess antiallergic activity as measured by the homocytotropic antibody–antigen induced passive cutaneous anaphylaxis reaction in the rat.

Disodium cromoglycate (**1**) is established as being of use in the treatment of some types of bronchial asthma.[1] It has been shown to inhibit the liberation of the mediators of immediate type allergic reactions initiated by reaginic antibody–antigen interactions.[2] It inhibits homologous passive cutaneous anaphylaxis (PCA) reactions in the rat induced by reaginic antibody and this reaction has been used as a routine screen for compounds with similar biological activity.[3,4] Some 2-nitroindan-1,3-diones (**2**) have shown greater activity than disodium cromoglycate as inhibitors of the rat PCA reaction[5] and as part of a continuing program on the investigation of compounds containing the 1,3-dicarbonyl-2-nitro moiety, we have prepared a series of 4-hydroxy-3-nitrocoumarins (**3**). We wish to report the synthesis and activities in the rat PCA test of some of these compounds.



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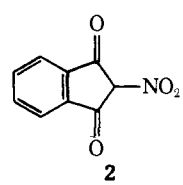

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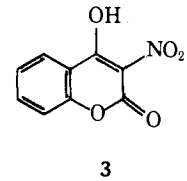

3

Chemistry. The synthesis of 4-hydroxycoumarins (**4**) has been extensively documented in the literature. In this study, two general routes have been employed, as shown in Scheme I, using readily available phenols (route A) or 2-hydroxyacetophenones (route B) as starting materials.

Route A. Reaction of a phenol with malonic acid using phosphorus oxychloride–zinc chloride as condensing agent, as described by Bose and Shah,[6] gave the 4-hydroxycoumarin (**4**) which is readily separated from the diphenyl malonate side product (**5**) by alkaline extraction. Other Lewis