Antiinflammatory Agents. I. 3-Benzoylfluoroalkanesulfonanilides

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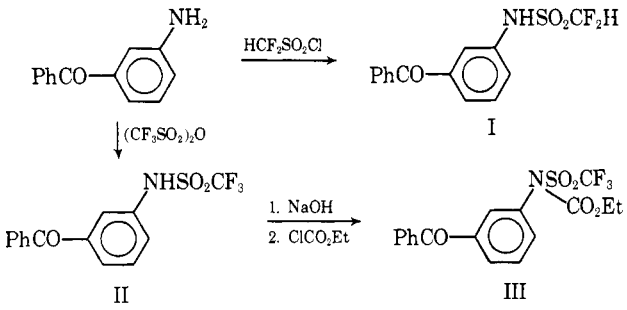
We wish to report two new classes of antiinflammatory agents, fluoroalkanesulfonanilides and N-acyl-substituted fluoroalkanesulfonanilides. These general classes were examined for antiinflammatory and allied pharmacological properties. A large number of compounds were screened and antiinflammatory activity was found generally in members of the series, but especially in the 3-benzoylfluoroalkanesulfonanilides. The high activity of two of the latter was coupled with a favorably low incidence of side effects in mice, rats, guinea pigs, dogs, and primates. These compounds are 3′-benzoyl-1,1-difluoromethanesulfonanilide (I) and ethyl *m*-benzoyl-N-(trifluoromethanesulfonyl)carbanilate (III).[1b]

Chemistry.—Compound I was synthesized by N-sulfonylation of 3-aminobenzophenone with difluoromethanesulfonyl chloride.[2] The sodium salt of I was prepared by precise titration with 1.000 *N* NaOH, removal of solvent *in vacuo*, and precipitation from a glyme–ether mixture. In similar fashion, 3-aminobenzophenone was treated with trifluoromethanesulfonic anhydride[3] to give II. Formation of the sodium salt of II with NaOH followed by reaction with ethyl chloroformate at room temperature gave III in good yield. The over-all sequence is outlined in Scheme I.

SCHEME I



Biological Activity.—The sodium salt of I and carbanilate III were compared to phenylbutazone in various standard antiinflammatory tests. Compound III was unusual in that it exhibited a delayed onset of activity in most tests. Consequently, results are expressed as values obtained at the time of peak activity, usually 4–6 hr after oral administration.

In the carrageenin rat paw edema test[4] (modified), ED_{50} potency values for I and III were approximately 1.5–2.0 and 1.0 times that for phenylbutazone, respectively. In uv erythema test[5] (modified), the ED_{40} values of I and III were approximately 2.2 and 4.7 times that of phenylbutazone. Both compounds were also approximately equipotent with phenylbutazone in the adjuvant arthritis test.[6] In addition, I displayed antipyretic activity and was active *vs.* bradykinin- and phenylquinone-induced writhing.

Acute, oral LD_{50} values for the sodium salt of I were 450 ± 26 mg/kg in male rats, 700 ± 37 mg/kg in the male mouse, and 720 ± 62 mg/kg in the female guinea pig. Comparable acute, oral LD_{50} values for III were 435 ± 57 mg/kg in the guinea pig, greater than 2000 mg/kg in the mouse, and 4700 ± 459 mg/kg in the rat.

Experimental Section[7]

3′-Benzoyl-1,1-difluoromethanesulfonanilide (I).—A solution of difluoromethanesulfonyl chloride (0.10 mole) in PhH (200 ml) was prepared according to Farrar[2] and added to a PhH solution of 3-aminobenzophenone (19.7 g, 0.10 mole) and pyridine (9.9 g, 0.125 mole). The mixture was heated to 50–55° for 72 hr, cooled, and extracted with 10% aqueous NaOH. The alkaline layer was washed with $CHCl_3$ several times and acidified with concentrated HCl. The product precipitated and was recrystallized from trichloroethylene–hexane to give 8.8 g (28%) of analytically pure I, mp 99–100.5°. *Anal.* ($C_{14}H_{11}F_2NO_3S$) C, H, N.

The Na salt of I was prepared by titrating a suspension of the sulfonanilide in H_2O with precisely an equimolar amount of 1.000 *N* NaOH. The aqueous solution was evaporated *in vacuo* and the dry salt was taken up in glyme. The glyme solution was dropped slowly into a tenfold excess of Et_2O with vigorous stirring. The white, crystalline, analytically pure salt was collected and dried *in vacuo*, mp 228–230° dec. *Anal.* ($C_{14}H_{10}F_2NNaO_3S$) C, H.

3′-Benzoyl-1,1,1-trifluoromethanesulfonanilide (II).—A mixture of 3-aminobenzophenone (59.8 g, 0.304 mole), Et_3N (50.4 ml), and $CHCl_3$ (400 ml) was stirred at 10–25° while trifluoromethanesulfonic anhydride was slowly added. The solution was stirred an additional 1 hr, washed with dilute HCl, and extracted with 10% NaOH. The alkaline extract was washed ($CHCl_3$), clarified with charcoal, and acidified to pH 1 with concentrated HCl. The product was collected by filtration, washed with copious amounts of H_2O, and dried. Recrystallization from hexane afforded 43.7 g (44%) of analytically pure II, mp 99–101°. *Anal.* ($C_{14}H_{10}F_3NO_3S$) C, H.

The Na salt of II was prepared as described for I, mp 290–292° dec. *Anal.* ($C_{14}H_9F_3NNaO_3S$) C, H.

Ethyl *m*-Benzoyl-N-(trifluoromethylsulfonyl)carbanilate (III).—Ethyl chloroformate (11.7 g, 0.107 mole), the Na salt of II (37.9 g, 0.108 mole), and MeAc (150 ml) were combined and stirred at 20–25° for 24 hr. The NaCl precipitate was removed by filtration and solvent was removed *in vacuo*. Two recrystallizations of the residual product from 95% EtOH afforded 33.3 g (78%) of analytically pure III, mp 131.5–132.5°. *Anal.* ($C_{17}H_{14}F_3NO_5S$) C, H, N.

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(1) (a) Contribution No. 573. (b) Diflumidone and triflumidate are approved generic names for I and III, respectively.

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(7) Melting points were obtained in open capillary tubes with the Thomas–Hoover Uni-Melt apparatus and are uncorrected. Analytical results where indicated by symbols of the elements were within ±0.2% of theoretical values. All spectra obtained (ir, nmr, uv) were in accordance with the proposed structures.