Table V—Comparison of Dissolution-Rate Data of Meprobamate

Product[a]	Percent Remaining Undissolved,[b] min. 0	10	20	30	40	50	60	75	T_{90},[c] min.
A	100	—[d]	10.01	—	—	—	—	—	20.53
B	100	75.53	—	—	54.60	—	—	40.68	284.09
E	100	69.45	58.91	52.36	44.52	—	38.41	31.36	196.08
F	100	79.23	72.69	62.04	50.23	—	—	—	124.38
G	100	84.36	72.42	53.96	42.68	33.65	28.01	—	100.00

[a] See Table I for formulation. [b] Each point is the average of three determinations. [c] Apparent first-order rate process. [d] —, no experimental value at this time.

capsule formulation.

This observation leads one to believe that the primary granules formed from the normal disintegration of a tablet in an aqueous medium differ in some physical manner from the granules obtained by grinding up a tablet.

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Mechanism of Action of Salicylates VIII: Effect of Topical Application of Retinoic Acid on Wound-Healing Retardation Action of a Few Anti-Inflammatory Agents

K. H. LEE and THEODORE G. TONG

Abstract □ Oral administration of phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, or indomethacin, like salicylates or corticosteroids, retards skin wound healing in rats. The healing inhibitory action of any one of these anti-inflammatory agents can be reversed by local application of retinoic acid.

Keyphrases □ Retinoic acid, topical application—inhibition of wound-healing retardation of anti-inflammatory agents □ Anti-inflammatory agents, wound-healing retardation—retinoic acid inhibition □ Salicylates, wound-healing mechanism—analogy to other anti-inflammatory agents

Recently, it has been shown that oral administration of acetylsalicylic acid, sodium salicylate, or prednisone and topical application of salicylic acid or hydrocortisone in nonionic bases (NIB) retard skin wound healing in rats (1–3). The inhibitory action of these agents is, at least, partially attributed to their anti-inflammatory action since inflammation is an essential feature in healing. Salicylates also inhibit mucopolysaccharide synthesis, which is also an essential feature in wound healing (2). Intraperitoneal injection of retinol or topical application of retinoic acid can reverse the inhibitory action of these anti-inflammatory agents (2, 3).

Phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, and indomethacin are a few well-known anti-inflammatory agents. These agents, like salicylates, inhibit mucopolysaccharide synthesis (4). In the present study, it was found that all of these anti-inflammatory agents also retard wound healing, and topical application of retinoic acid can reverse the inhibitory action of these agents.

Table I—Retinoic Acid and Healing Retardation Action of a Few Anti-Inflammatory Agents[a]

Group	No. of Animals	Drugs Given		Mean Tensile Strength, g.	Percent Control
		Orally	Topically		
I	14	—	NIB	451 ± 9	100
II	9	Indomethacin, 4 mg./kg.	NIB	374 ± 9	83
III	14	Indomethacin, 4 mg./kg.	1% retinoic acid in NIB	433 ± 8	96
IV	7	Mefenamic acid, 20 mg./kg.	NIB	424 ± 9	94
V	16	Mefenamic acid, 40 mg./kg.	NIB	407 ± 7	90
VI	6	Mefenamic acid, 40 mg./kg.	1% retinoic acid in NIB	456 ± 10	101
VII	8	Flufenamic acid, 40 mg./kg.	NIB	398 ± 10	88
VIII	6	Flufenamic acid, 40 mg./kg.	1% retinoic acid in NIB	427 ± 7	95
IX	7	Phenylbutazone, 100 mg./kg.	NIB	403 ± 4	89
X	7	Phenylbutazone, 100 mg./kg.	1% retinoic acid in NIB	427 ± 9	95
XI	7	Oxyphenbutazone, 100 mg./kg.	NIB	385 ± 8	85
XII	6	Oxyphenbutazone, 100 mg./kg.	1% retinoic acid in NIB	439 ± 10	97

[a] The difference between the experiments and the controls is highly significant ($p < 0.01$, Student's t test) except Group IV animals receiving only 20 mg. of mefenamic acid/kg. ($p < 0.10$).

EXPERIMENTAL

Material and Drugs—The following materials and drugs were used in this study: retinoic acid,[1] phenylbutazone,[2] oxyphenbutazone,[2] mefenamic acid,[3] flufenamic acid,[3] indomethacin,[4] and NIB.[5] The strength of retinoic acid used was 1% in NIB. Methylcellulose USP[6] (400 cps.) was also used.

Administration of Drugs—All drugs were fed to rats daily for 4 days through a short stomach tube (PE 160) connected to a blunt hypodermic needle (No. 17) attached to a 50-ml. syringe, starting 1 day before operation. Each drug was suspended in a 0.5% methylcellulose solution. One milliliter of the suspension was fed to each rat.

Application of Retinoic Acid in NIB—Retinoic acid in NIB was applied with gentle rubbing directly on the sutured wound right after wounding. The application was repeated, once a day, on the 1st and 2nd days of wounding. For the control, only NIB was applied.

Wound Procedure—Sprague-Dawley male rats, weighing 230–240 g., were anesthetized with ethyl ether in an open mask. The hair on the back was depilated with an electric clipper. One incision, 6 cm. in length, was made through the skin and cutaneous muscles at a distance about 1.5 cm. from the midline on each side. No ligatures were used. Bleeding usually ceased after a few minutes. The incisions were closed with continuous through-and-through sutures with stitches 0.5 cm. apart. Black silk surgical thread (No. 3–0) and a curved needle (No. 19) were used. The continuous suture was pulled tight enough to secure good adaptation of the wound edges. The wounds were left undressed.

Measurement of Healing—Tensile strength, the force required to open a healing skin wound, was used to measure healing. On the 7th day after wounding, the tensile strength of the wound was measured with a simple laboratory-made tensiometer as described previously (1).

[1] All *trans*, Sigma grade, type XX, a crystalline synthetic compound obtained from Sigma Chemical Co., St. Louis, Mo.
[2] Supplied by Dr. T. A. Terzakis, Geigy Pharmaceuticals, Division of Geigy Chemical Corp., Ardsley, N. Y.
[3] Supplied by Dr. C. V. Winder, Research Laboratories, Parke, Davis and Co., Ann Arbor, Mich.
[4] Supplied by Dr. W. B. Gall, Research Laboratories, Merck Sharp and Dohme, Division of Merck and Co., Inc., Rahway, N. J.
[5] Prepared by Pharmaceutical Technology Laboratory, San Francisco Medical Center, San Francisco, Calif.
[6] Dow Chemical Co., Midland, Mich.

RESULTS AND DISCUSSION

The results of the effect of phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, and indomethacin on skin wound healing in rats are summarized in Table I. The mean tensile strength of the healing wound of the control animals from Group I was 451 ± 9 g. These animals received only topical application of NIB. Group II animals received 4 mg. of indomethacin/kg. of body weight orally, and the mean tensile strength of the healing wound was reduced to 374 ± 9 g., which is 83% of the control. Group III animals were treated the same way as Group II except that 1% retinoic acid in NIB was applied to the wound once a day during the first 3 days of wounding. The mean tensile strength of Group III animals was increased to 433 ± 8 g. Group IV animals received 20 mg. mefenamic acid/kg. of body weight orally; the mean tensile strength of these animals was 424 ± 9 g., which is not appreciably less than the control. An increased dosage of 40 mg. of mefenamic acid/kg. of body weight was used to feed Group V animals. The mean tensile strength of Group V animals was significantly reduced to 407 ± 7 g. Group VI animals received the same treatment as Group V animals except that retinoic acid was topically applied to the wound as described for Group III animals. The mean tensile strength of Group VI animals was increased to 436 ± 10 g. Group VII animals received 40 mg. of flufenamic acid/kg. of body weight, and the mean tensile strength was reduced to 398 ± 10 g. The reversal of wound-healing retardation action of flufenamic acid by local application of retinoic acid was demonstrated by the increase of mean tensile strength in Group VIII animals. Group IX animals received 100 mg. of phenylbutazone, and Group XI animals received a dosage of 100 mg. of oxyphenbutazone. The mean tensile strengths of Groups IX and XI were reduced to 403 ± 4 and 385 ± 8 g., respectively. Groups X and XII demonstrated that the local application of retinoic acid reverses the wound-healing inhibitory action of phenylbutazone and oxyphenbutazone.

Inflammation and mucopolysaccharide synthesis are the two known essential features in wound healing. Phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, and indomethacin, like salicylates, prednisone, and hydrocortisone, are anti-inflammatory agents. They are also potent inhibitors to mucopolysaccharide synthesis at the site where uridine-5′-diphosphoglucose is oxidized to UDPGA, as reported recently (5). These anti-inflammatory agents, therefore, retard wound healing also by their anti-inflammation activity and their inhibitory action on mucopolysaccharide synthesis.

SUMMARY

The healing retardation action of anti-inflammatory agents, phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, and indomethacin, has been demonstrated in rats.

Topical application of retinoic acid can reverse the healing inhibitory action of these anti-inflammatory agents.

The mechanism of action of these agents has been discussed.

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New Compounds: Some Potential Chemotherapeutic Agents Derived from Aralkyl Ketones

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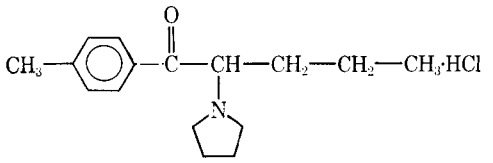
Abstract □ The Mannich reaction has been successfully applied to some aralkyl ketones, valerophenone and caprophenone, and their substituted derivatives in efforts to find efficient agents to be screened for possible CNS stimulant, analgesic, or antispasmodic activity. The aminoketones (Mannich bases) were converted to the γ-amino secondary alcohols by treatment with sodium borohydride. The synthesis of a series of γ-amino tertiary alcohols was achieved by the application of the Grignard reaction to the corresponding Mannich bases. The last section of the study involved the preparation of γ-amino alkyl esters from the corresponding secondary and tertiary alcohols.

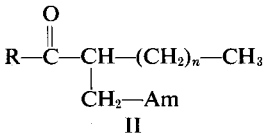
Keyphrases □ Chemotherapeutic agents—aralkyl ketone derivatives, synthesis □ Aralkyl ketone derivatives—synthesis, structure–activity relationships □ Mannich reaction—synthesis □ Grignard reaction—synthesis

The significant action of pyrovalerone hydrochloride (I) as a CNS stimulant has been reported (1):



I

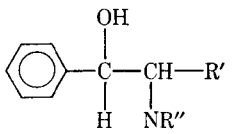
In view of this activity, the authors undertook the synthesis and study of aminoketones having the following structure (II):



II

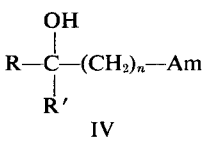
Am = substituted amino group
R = aryl group or substituted aryl group
n = 2,3

To investigate a possible structure–activity relationship, a number of analogs and derivatives were prepared. Recorded in the literature (2–5) are numerous ketonic Mannich bases prepared for pharmacological testing, such as antispasmodic, analgesic, local anesthetic, or chemotherapeutic agents. From the correlation of the chemical structure of these ketones with their antispasmodic activities, the following conclusions were drawn: (*a*) Activity is enhanced by the introduction of a phenyl group into the α-position of the propiophenones. (*b*) The piperidyl group was the most active amino group, while the morpholino group was the least active amino moiety. (*c*) Simple substituents in the *p*-position of the aromatic rings of the propiophenones decreased activity (5). Since some of the structural modifications in these various ketones had an effect on the physiological activity, the transformation of the ketones to the corresponding alcohols might possibly have a greater effect; also the amino alcohols are generally much more stable than the corresponding ketones (6). Lutz *et al.* (7) have reported the preparation and screening of 184 amino alcohols against avian malaria. The general structure (III) of the secondary alcohols is represented as follows:



III

These compounds included examples of 50 variations in the benzene nucleus and over 60 variations in the *N*,*N*-dialkyl groups on the nitrogen. The change in activity with variation in chemical structure led Denton *et al.* (8) to prepare more than 100 γ-amino tertiary alcohols; a majority of them have exhibited pharmacological activity. The general structure (IV) of the amino tertiary alcohols prepared by these workers is reported as follows:



IV