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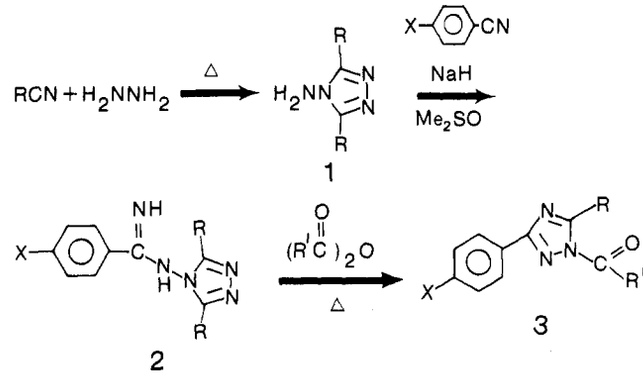
Certain 1-acyl-3-phenyl-5-alkyltriazoles were synthesized and evaluated for antiinflammatory activity using the mouse active Arthus (MAA) reaction as the test system. Modification of the acyl group, 4-phenyl substituent, and alkyl group led to the selection of the most active member of this series, 1-acetyl-3-(4-chlorophenyl)-5-methyl-1,2,4-triazole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

Scheme I



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.

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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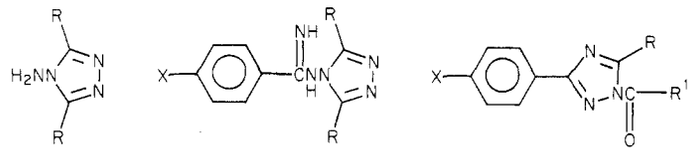
Table I. Chemical and Pharmacological Data on 1-Acyl-3-phenyl-5-alkyltriazoles and Intermediates



1a,b 2a-e 3a-g

no.	compound	R	R^1	X	mp, °C	yield, %	formula	anal.[a]	MAA: ID_{50}, mg/kg po
1a		CH_3			195-197	68	$C_4H_8N_4$	C, H, N	NT[b]
1b		C_2H_5			159-161	52	$C_6H_{12}N_4$	C, H, N	>600
2a		CH_3		H	299-301	71	$C_{11}H_{13}N_5$	C, H, N	>600
2b		CH_3		CH_3	311-312	82	$C_{12}H_{15}N_5 \cdot HCl$	C, H, N, Cl[c]	>600
2c		CH_3		Cl	310-312	80	$C_{11}H_{12}N_5Cl$	C, H, N, Cl	NT[b]
2d		CH_3		CF_3	277-278	88	$C_{12}H_{12}N_5F_3$	C, H, N, F	>600
2e		C_2H_5		Cl	284-285	51	$C_{13}H_{16}N_5Cl$	C, H, N, Cl	>600
3a		CH_3	CH_3	H	83-85	63	$C_{11}H_{11}N_3O$	C, H, N	439
3b		CH_3	CH_3	CH_3	103-104	83	$C_{12}H_{13}N_3O$	C, H, N	>600
3c		CH_3	CH_3	Cl	132-133	63	$C_{11}H_{10}N_3OCl$	C, H, N, Cl	342
3d		CH_3	CH_3	CF_3	101-102	38	$C_{12}H_{10}N_3OF_3$	C, H, N, F	411
3e		C_2H_5	CH_3	Cl	99-100	58	$C_{12}H_{12}N_3OCl$	C, H, N, Cl	543
3f		CH_3	C_2H_5	Cl	108-109	71	$C_{12}H_{12}N_3OCl$	C, H, N, Cl	408
3g		CH_3	Ph	Cl	115-116	70	$C_{16}H_{12}N_3OCl$	C, H, N, Cl	>600

[a] Analyses were within ±0.4% of the calculated value for the indicated elements. [b] Not tested. [c] Analyzed as the hydrochloride salt.

Table II. Profile of Biological Activity of 3c and of Ibuprofen

test	measurement	no. of animals per dose group	route of administration	dose, mg/kg	3c	ibuprofen
MAA	ID_{50},[a] mg/kg	6	po		342 (n = 3)	>600 (n = 2)
			ip		37	>150
	ID_{40},[a] mg/kg		po		175	386 (n = 4)
carrageenin-induced edema	ID_{50},[a] mg/kg	7	po		>150 (n = 3)	70 (n = 2)
adjuvant-induced arthritis	% inhibn local/systemic	10	po	30		30/30 (100)[b]
				37.5	18/7 (90)[b]	
				60		56/51 (100)[b]
				75	27/26 (90)[b]	
				120		65/57 (100)[b]
				150	21/73 (90)[b]	
acute toxicity in mice	LD_{50},[c] mg/kg	5	po		>3200	1650
			ip		600	490
therapeutic index	mouse LD_{50}/ mouse ID_{50} (MAA)		po		>9.35	<2.15

[a] ID_{50} (ID_{40}) is defined as the dose that produces a 50% (40%) inhibition of the reaction; value is the average of n ID_{50} (ID_{40}) determinations, where n = 1 unless otherwise indicated. [b] Percent survival; 0-10% mortality is normally observed in adjuvant control groups. [c] Mice observed for 8 days.

and suggests a new direction for future antiinflammatory research.

Experimental Section

Synthesis. Melting points were measured on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Microanalyses were obtained from the Squibb Analytical Department. IR and ^1H NMR spectra were obtained for all compounds and were consistent with the assigned structures. IR spectra were recorded on a Perkin-Elmer 621 spectrophotometer as KBr pellets, and the ^1H NMR spectra were obtained on a Perkin-Elmer R-12B spectrometer in $CDCl_3$ or Me_2SO-d_6. The following examples are general procedures.

4-Amino-3,5-dialkyltriazoles (1a,b). A mixture of 100 g (2 mol) of hydrazine hydrate and 1.8 mol of alkylnitrile was heated at 180 °C in an autoclave for 20 h. After the mixture cooled, the resulting solid was filtered off and recrystallized from 600 mL of ethyl acetate to yield 1.

***N*-(3,5-Dialkyl-4*H*-1,2,4-triazol-4-yl)benzenecarboximidamides (2a-e).** Sodium hydride (15.32 g, 364 mmol, 57% oil dispersion) was washed with ether (five times) in a sintered glass funnel to remove the oil. The free sodium hydride was washed, with a little Me_2SO, into a stirred suspension of 363 mmol of the appropriate benzonitrile and 363 mmol of 4-amino-3,5-dialkyltriazole (1) in 200 mL of Me_2SO (distilled from CaH_2 under vacuum). After the addition, the mixture was stirred in an ice bath for 1 h and then for 3 h at room temperature. The reaction mixture was poured into 2 L of ice–water and stirred for 15 min until the flocculent precipitate coagulated into a filterable state. The product was then filtered off, washed with water, and dried at 50 °C under vacuum overnight to yield crude 2. This material was suitable for use in the subsequent reaction.

The crude triazole (6.0 g) was digested with 2-propanol, filtered off, and dried to yield pure 2.

1-Acyl-1,2,4-triazoles (3a-g). A mixture of 254 mmol of 2 and 67 mL of anhydride in a 300-mL round-bottom flask equipped with a distillation head was heated to 170 °C in an oil bath. A solution formed from which acid distilled off in the first few minutes. The mixture was refluxed for 2.5 h, and the excess anhydride was removed under vaccum. The residue was triturated with 120 mL of water and filtered. The filter cake was dissolved in 1 L of hot 95% EtOH the mixture was filtered hot, and the product precipitated from the hot filtrate by the addition of 3 L of cold water. The product was filtered off, washed with water,

and dried at 80 °C under vacuum to yield 3. Pure **3g** was obtained by chromatography of the crude reaction mixture on silica gel (60–200 mesh) with ether/hexane (1:1).

Pharmacology. The carrageenin-induced edema, adjuvant-induced arthritis, and acute toxicity tests have been previously described.[3,4]

Mouse Active Arthus Test (MAA). The procedure used was based on that of Goldlust et al.[5] Male CD-1 mice (Charles River Breeding Laboratories), 19–21 g, were sensitized with an intraperitoneal injection of 0.5 mL of a 1:1 emulsion of Freund's complete adjuvant (DIFCO) containing 250 mg of bovine serum albumin (BSA) in saline. The mice were used for testing 5 to 6 weeks later. The skin of the back was shaved on the day before the experiment.

On the day of the experiment, test compounds were suspended with sterile 1% sodium carboxymethylcellulose in pyrogen-free saline (PFS). The test compound was administered orally to each mouse in a 0.5-mL volume 1 h before antigenic challenge, which consisted of an interdermal injection of 0.05 mL of 5 mg of BSA/mL of PFS into the skin of the back.

Three and one-half hours after antigenic challenge, the animals were sacrificed by exposure to carbon dioxide, and the lesions were excised using the acutal perimeter of the edema as a guide. The average lesion weights of groups receiving test compounds were compared with that of a control group, which received only vehicle, and the percent inhibition by test compounds was calculated. Dose–response curves were run for each compound, from which ID_{50} doses were calculated.

Acknowledgment. We thank The Squibb Analytical Section under the direction of Dr. Allen I. Cohen for microanalyses and spectra.

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Book Reviews

Oxygen and Life. Second BOC Priestley Conference. Sponsored by the BOC Gases Division Trust and Organized by The Royal Society of Chemistry and the University of Birmingham, September 15–18, 1980. The Royal Society of Chemistry, Burlington House, London. 1981. xii + 224 pp. 14.5 × 21 cm. £11.00.

This volume is a series of presentations by various established investigators on the biology, biochemistry, and toxicology of oxygen. Additionally, the Priestley Lecture by G. A. Soffen is included that relates to Mars and the role of oxygen and environment in organogenesis and life.

R. J. P. Williams presents an overview of oxygen and life, discussing the various biological catalysts, the chemistry and mechanism of action, and their wide range in the using of oxygen. This presentation provides the basis for the four main themes of this symposium. First, there are two papers by M. Calvin and A. Harriman, respectively, on photosynthesis and synthetic organometallic structures designed to mimic the chloroplast, using them as a basis for understanding the photoactivation process. The second section relates to the mechanism of oxygen toxicity and its critical importance, especially through the respiratory burst, in providing microbicidal oxidants. Of the three papers, the first, by J. A. Fee, is critical of the concept that oxygen toxicity stems from oxy radicals, such as superoxide. However, those by H. A. O. Hill/M. J. Okolow-Zubkowska and B. M. Babior discussing how oxygen is used by neutrophils do strongly favor oxidizing radicals as the source for the lethal effects observed. The paper by Babior would be of special interest and benefit to those nonbiologists, since the biological terms that are used are defined very clearly and succinctly. The third group of talks are concerned with various aspects of oxygen transport in biological systems. The extremes are the studies by C. A. McAuliffe in the use of small synthetic manganese–phosphine complexes on the one hand and high-molecular-weight hemocyanins by E. F. J. van Bruggen on the other. Two very intriguing papers in this section were by R. P. Geyer and by K. Yokoyama, T. Suyama, and R. Naito on the development and use of perfluorochemicals as blood substitutes by reason of their oxygen transporting capability. The last topic related to oxygen-utilizing enzymes. This section is more diverse and includes a talk by T. Ljones and T. Skotland on dopamine β-mono-oxygenase; two articles on cytochrome oxidase, one by K. J. Berry, M. J. Gunter, and K. S. Murray on synthetic models and a second by G. M. Clore on low temperature kinetic studies; and a paper by C. Greenwood on the importance of iron and copper metalloenzymes in protecting various living forms. Finally, there is an excellent article by O. Hayaishi on his outstanding contributions relating to indoleamine-2,3-dioxygenase and its requirement of the superoxide anion for metabolic activity.

This volume did not contain all of the presentations of the conference. Eight talks were not included. The great diversity of subject matter, only united by oxygen, might result in researchers having only limited interest in the entire volume. The work presented, however, is certainly most eminent.

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Fundamentals of Oncology. Second Edition. Revised and Expanded. By Henry C. Pitot. Marcel Dekker, New York. 1981. viii + 291 pp. 14 × 22 cm. $16.50.

This wide-ranging, yet remarkably compact, introduction to the subject of oncology forms the syllabus for a series of slide lectures presented annually at the University of Wisconsin Medical School by Professor Pitot and other faculty and staff of the McArdle Laboratory for Cancer Research. The first edition, issued in 1978, was so successful that a second edition had to follow almost immediately.

There are 13 chapters in this revised, slightly expanded edition, one more than in the original. After two introductory chapters devoted to an historical overview and exposition of general terminology and concepts, three chapters consider the physical, chemical, and biological factors currently regarded as being significant etiologic aspects of tumorigenesis. The next seven chapters deal with major aspects of the biochemistry and immunobiology of the cancer cell and with the pathogenesis and natural history of various types of tumors. Special emphasis is placed on host–tumor relationships and on the influence of nutritional, hormonal, and immunologic effects on the course of neoplastic disease. The final chapter, absent in the first edition, deals (rather briefly) with cancer chemotherapeutic principles, and there is a short epilogue in which the author attempts to predict the probable evolution of the field of oncology in the years ahead.

Each chapter has been updated to reflect newer discoveries that have been made since the first edition appeared. There is, for