II lists the compounds prepared by hydrolyzing the pyrimidine acetal.

To a 1.5 g. sample of III, dissolved in 20% sodium hydroxide, 50 ml. of 3% hydrogen peroxide was added and the mixture heated for 5 min. After cooling to 0°, it was acidified with hydrochloric acid and the resulting solids were collected by filtration and washed with cold water. Crystallization from ethanol–ether produced 90% of 4-(dimethoxy)methyl-2,6-dioxo-1-methylpyrimidine (IIIb), a white crystalline solid, m.p. 137° (cor.). The ultraviolet spectrum was consistent with the proposed structure.[14]

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.90; H, 5.98; N, 14.00.

Schiff Bases from Pyrimidine-4-carboxaldehydes.—These compounds were prepared by the interaction of the substituted and unsubstituted pyrimidine-4-carboxaldehyde with the appropriate amine. A solution of 0.01 mole of the aldehyde in a minimum amount of hot absolute ethanol was prepared. To this was added 0.01 mole of the amine and the mixture refluxed for 30 min. on a steam bath. The reaction mixture was placed in a refrigerator overnight, the product collected on a filter, and recrystallized from ethanol. The Schiff bases are shown in Table III.

Hydrazones from Pyrimidine-4-carboxaldehydes.—These derivatives were prepared by the interaction of the pyrimidine aldehydes with the appropriate hydrazine or hydrazide. To a solution of 0.01 mole of the aldehyde in a minimum amount of hot absolute ethanol or glacial acetic acid was added 0.01 mole of the hydrazine or hydrazide reagent dissolved in a minimum amount of the same solvent. The mixture was refluxed for 10 min. and then placed in a refrigerator overnight. The product was collected by filtration and recrystallized from ethanol or acetic acid. The hydrazones are shown in Table IV.

(14) According to D. Shugar and J. J. Fox (see ref. 6b) 3-methyluracil has λ_{max} 258.5 mμ (ε 7300) occurring between pH 3.0 and 7.2 and λ_{max} 218 mμ (ε 7060) at pH 12.0. The 1-methyluracil has λ_{max} 267.5 mμ (ε 9750) at pH 7.2 and λ_{max} 265 mμ (ε 7020) occurring between pH 12.0 and 14.0.

Acknowledgment.—We wish to thank Mr. Robert Morris for help in preparing some of the intermediate compounds required during the course of this work and to Mr. Carl W. Anderson for assistance in the screening tests. We are grateful to Dr. J. J. Fox and Dr. A. F. Hirsch, of the Sloan-Kettering Institute for Cancer Research, for their interest and suggestions on the ultraviolet studies.

The Synthesis and Antiinflammatory Activity of Some Derivatives of 1,3-Diphenylbarbituric Acid

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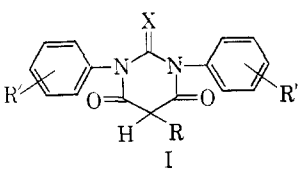
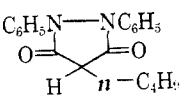
A series of 1,3-diphenylbarbituric acid derivatives has been prepared and evaluated for antiinflammatory activity. The compounds were found to be less toxic and less active than phenylbutazone by the testing procedures used. The most potent member of the series was 1,3-diphenyl-5-(3-methyl-2-butenyl)barbituric acid. Its activity compared quite favorably with that of phenylbutazone on parenteral administration but, when given orally, it proved active only at high dosages.

The recent communication by Scarborough and McKinney[1] describing the preparation and uricosuric activity of some substituted 1,3-diphenylbarbituric acids prompts us to report the results of a related investigation.

As part of a research program devoted to the synthesis and evaluation of organic compounds as potential antiinflammatory agents, it was of interest to us to examine a series of 1,3-diaryl-5-substituted barbituric and 2-thiobarbituric acids (I), whose relationship to phenylbutazone (II) is evident.



I



II

X = O or S
R = alkyl, cycloalkyl, aryl, alkenyl, aralkyl
R′ = H, CH_3, OCH_3

A search of the literature disclosed that, while there had been sporadic reports[2] on the preparation of N,N′-diarylbarbituric and 2-thiobarbituric acids, little interest had been shown in the 5-substituted analogs of these compounds. Whiteley[2a,b] reported the preparation of several compounds of structure I by means of the zinc–acetic acid reduction of the corresponding 5-alkylidene derivatives. Although we were able to obtain one compound (**19**, Table I) in good yield by this method, a more general and reliable procedure, and one which we used almost exclusively for the preparation of the compounds listed in Table I even though yields were low, proved to be the condensation of carbanilide or thiocarbanilide with substituted malonic acids in the presence of acetyl chloride.

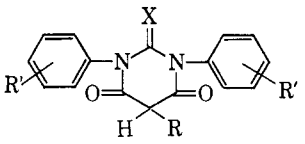
It has been reported[2c] that sodiomalonic ester and carbanilide or thiocarbanilide in absolute alcohol or benzene fail to form N,N′-disubstituted barbituric acid derivatives. We found that the desired reaction will occur under conditions of elevated temperature and succeeded in preparing 1,3-diphenyl-5-amylbarbituric acid (I, R = *n*-C_5H_{11}, R_1 = H, X = O) from the appropriate reactants in xylene at 140–145°. However, purification of the product proved troublesome, eventually requiring vacuum distillation to give a low yield of pure compound, and this procedure therefore received limited attention as a potential alternate route to I.

Pharmacology.—All of the compounds synthesized were evaluated for antinflammatory activity by means

(1) H. C. Scarborough and G. R. McKinney, *J. Med. Pharm. Chem.*, **5**, 175 (1962).

(2) (a) M. A. Whiteley, *J. Chem. Soc.*, **91**, 1330 (1907); (b) M. A. Whiteley and H. Mountain, *Proc. Chem. Soc.*, **25**, 121 (1909); (c) N. V. Koshkin, *Zh. Obshch. Khim.*, **5**, 1460 (1935); (d) I. N. D. Dass and S. Dutt, *Proc. Indian Acad. Sci.*, **8A**, 145 (1938).

TABLE I
SUBSTITUTED 1,3-DIARYLBARBITURIC ACIDS



Compd. no.	R	R′	X	M.p., °C.[a,b]	Time of heating, hr.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	n-C_4H_9	H	S	165.5–166.5	7	26	$C_{20}H_{20}N_2O_2S$[c]	68.15	68.11	5.72	5.66	7.95	7.97
2	n-C_4H_9	H	O	122–124[d]	15	24	$C_{20}H_{20}N_2O_3$	71.41	71.27	5.99	6.09	8.33	8.21
3	n-C_5H_{11}	H	S	175–176.5	6	38	$C_{21}H_{22}N_2O_2S$[e]	...	...	...	...	7.64	7.53
4	n-C_5H_{11}	H	O	168–170	17	20	$C_{21}H_{22}N_2O_3$	71.98	71.51	6.33	6.27	7.99	7.85
5	Allyl	H	O	151.5–152.5	16	28	$C_{19}H_{16}N_2O_3$	71.24	70.85	5.03	4.99	8.75	8.62
6	n-$C_{12}H_{25}$	H	S	104–106	8	25	$C_{26}H_{36}N_2O_2S$[f]	...	...	...	...	6.03	5.88
7	n-C_3H_7	H	O	150.5–151.5[g]	19	24	$C_{19}H_{18}N_2O_3$	70.79	71.11	5.63	5.72	8.69	8.69
8	i-C_3H_7	H	S	225–227[h]	9	39	$C_{19}H_{18}N_2O_2S$	67.43	67.48	5.36	5.29	8.28	8.08
9	n-$C_{12}H_{25}$	H	O	132 dec.	34	14	$C_{28}H_{36}N_2O_3$	...	...	...	...	6.25	6.00
10	i-C_3H_7	H	O	202–204	27	11	$C_{19}H_{18}N_2O_3$	70.79	71.24	5.63	5.65	8.69	8.61
11	Phenyl	H	O	261–262	8	22	$C_{22}H_{16}N_2O_3$	74.14	74.01	4.53	4.65	7.86	7.84
12	C_2H_5	H	O	141.5–142.5	15	18	$C_{18}H_{16}N_2O_3$	70.11	70.13	5.23	5.24	9.09	8.89
13	CH_3	H	O	199–201	14	21	$C_{17}H_{14}N_2O_3$	69.38	69.40	4.80	4.76	9.52	9.38
14	$(CH_3)_2$-C=CHCH$_2$—	H	O	117–118	14	13	$C_{21}H_{20}N_2O_3$	72.39	72.24	5.79	5.77	8.04	7.87
15	Cyclohexyl	H	O	223–224	15	10	$C_{22}H_{22}N_2O_3$	72.91	72.47	6.12	5.95	7.73	7.61
16	Cyclopentyl	H	O	217–218	19	9	$C_{21}H_{20}N_2O_3$	72.39	72.71	5.79	5.88	8.04	7.91
17	n-C_7H_{15}	H	O	135–137[i,j]	16	14	$C_{23}H_{26}N_2O_3$	72.99	73.28	6.93	6.88	7.40	7.34
18	n-C_8H_{13}	H	O	146–147.5	15	31	$C_{22}H_{24}N_2O_3$	72.50	72.32	6.64	6.72	7.69	7.76
19	Benzhydryl[k]	H	O	207–208[l,m]	k	64	$C_{29}H_{22}N_2O_3$	78.01	77.87	4.97	5.14	6.27	6.10
20	n-C_5H_{11}	p-CH_3O	O	143–145	20	7	$C_{23}H_{26}N_2O_4$	67.30	67.66	6.39	6.27	6.83	6.70
21	n-C_5H_{11}	m-CH_3	O	110–112[n]	12	17	$C_{23}H_{26}N_2O_3$	72.99	72.47	6.93	6.67	7.40	7.18

[a] Melting points were determined in a Thomas-Hoover "Uni-Melt" capillary melting point apparatus and are corrected. [b] The compounds were recrystallized from EtOH unless otherwise stated. [c] *Anal.* Calcd.: S, 9.10. Found: S, 9.06. [d] Lit.[1] m.p. 118–123°. [e] *Anal.* Calcd.: S, 8.75. Found: S, 8.41. [f] *Anal.* Calcd.: S, 6.90. Found: S, 6.52. [g] Lit.[1] m.p. 147–149°. [h] Lit.[2b] m.p. 237–240°. [i] Recrystallized from MeOH. [j] Lit.[1] m.p. 130–131°. [k] Prepared by reduction of the corresponding 5-diphenylmethylene derivative as described in the Experimental section. [l] Recrystallized from benzene–pet. ether. [m] Lit.[2a] m.p. 205–206°. [n] Recrystallized from MeOH–H_2O.

of the Randall–Selitto test[3] and the pleural effusion method.[4] The compounds were administered to rats at a maximum dosage of 200 mg./kg., I.P. Minimum effective doses[5] were established for those compounds found to be active. In general, these compounds were found to be less toxic and less active than phenylbutazone. The results of these evaluations appear in Table II.

Compounds **1**, **2**, **11**, **14**, and **17**, which were among those found active in the Randall–Selitto and/or pleural effusion methods, were further evaluated in rats by means of the cotton granuloma test[6] at a dose of 100 mg./kg./day, s.c., in sesame oil, for a period of 6 days.

Compound **14**, which appeared to be the most active member of the series based on the results obtained in both of the initial tests, also proved to be the only one which reduced granuloma weights in the cotton granuloma test. Phenylbutazone, in this test, was found to have a MED of 100–200 mg./kg./day, s.c. However, when the efficacy of **14** was evaluated by oral administration in the Randall–Selitto test, its MED (oral) was found to be between 500 and 1000 mg./kg.

(3) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

(4) D. E. Holtkamp, R. Wang, and M. Doggett, *Federation Proc.*, **17**, 379 (1958).

(5) MED is the lowest dose producing a significant ($P \leq 0.05$) antiinflammatory effect in the treated group of rats as compared to the control group. This dose was determined from a dose-response study using a logarithmic interval of 0.3. The number of rats per group was five in the Randall–Selitto test and six in the pleural effusion method.

(6) W. E. Dulin, *Proc. Soc. Exptl. Biol. Med.*, **90**, 115 (1955).

One of the major problems encountered in the evaluation of this series of compounds was the lack of

TABLE II
ANTIINFLAMMATORY ACTIVITY AND TOXICITY OF A SERIES OF SUBSTITUTED 1,3-DIARYLBARBITURIC ACIDS

Compound no.	LD_{50}, mg./kg., i.p.	MED, mg./kg., i.p.[a] Randall–Selitto	MED, mg./kg., i.p.[a] Pleural effusion
1	400	[b]	100
2	900	[b]	100–200
3	600	200	[b]
4	>1000	200	[b]
5	1000	[b]	[b]
6	400	[b]	200
7	600	[b]	[b]
8	>1000	200	100
9	500	200	[b]
10	750	[b]	[b]
11	500–1000	100	[b]
12	1000	200	[b]
13	>1000	100	[b]
14	500	50–100	100
15	>1000	200	[b]
16	>1000	[b]	[b]
17	>1000	50	[b]
18	>1000	[b]	[b]
19	>1000	[b]	200
20	>1000	200	[b]
21	>1000	[b]	[b]
Phenylbutazone	350	<50	50

[a] Administered as a suspension in 0.5% tragacanth. [b] No activity at 200 mg./kg., I.P.

complete absorption. In many cases, a significant amount of the injected compound could be found in the peritoneal cavity several hours after injection.

The compounds in this series did not exhibit hypnotic activity in the rat, even at doses approaching toxicity.

Experimental[7]

General Method for the Preparation of 1,3-Diaryl-5-substituted Barbituric and 2-Thiobarbituric Acids.—The substituted malonic acids used in this procedure were prepared by hydrolysis[8] of the corresponding diethyl esters and crystallization from benzene–petroleum ether. The substituted malonic esters, when not commercially available, were prepared by alkylation of diethyl malonate.[9]

The barbituric acid derivatives listed in Table I, with the exception of **19**, were prepared by the addition of a solution of 18 ml. (0.25 mole) of acetyl chloride in 25 ml. of anhydrous chloroform to a stirred mixture of 0.1 mole of the substituted malonic acid and 0.1 mole of the carbanilide in 500 ml. of anhydrous chloroform. The resulting mixture was stirred and refluxed[10] for 6 to 34 hr.,[11] cooled, and filtered to remove any unreacted carbanilide. The filtrate was concentrated under vacuum and the residue, which was slowly soluble in aqueous base, was stirred or shaken thoroughly with approximately 1 l. of 0.6 *M* sodium carbonate solution. The aqueous carbonate solution was washed with chloroform, filtered, and the filtrate acidified with 6 *N* hydrochloric acid to precipitate the product. When the product precipitated as an oil, it was isolated by extraction with chloroform.

1,3-Diphenyl-5-benzhydrylbarbituric Acid (19).—This compound was prepared by a modification of Whiteley's[2a] procedure. To a suspension of 8.4 g. (0.03 mole) of 1,3-diphenylbarbituric acid in 10 ml. of dry chloroform, there was added 12.1 g. (0.051 mole) of dichlorodiphenylmethane[12] and the mixture was swirled until it had become a homogeneous thick white suspension. The chloroform was then distilled, the mixture was placed in an oil bath, and the temperature was slowly raised to 200°. At 180°, the reaction mixture began to bubble and hydrogen chloride was evolved copiously. The mixture, which had become bright yellow, was kept at 200° for 2 hr., at which time the evolution of hydrogen chloride had almost ceased. After cooling, the reaction mixture was slurried with cold ethanol and the resulting suspension was filtered to yield 12.9 g. of bright yellow needles, m.p. 269–272°. Addition of excess ethanol to a filtered chloroform solution of this product gave 12.4 g. (93%) of bright yellow crystalline 1,3-diphenyl-5-diphenylmethylenebarbituric acid, m.p. 270.5–272°; lit.[2a] m.p. 264°. Reduction was effected when 6.0 g. of this product was boiled in acetic acid with its own weight of zinc dust until the solution had become colorless. The zinc dust was allowed to settle and the clear hot liquid was decanted into cold water to precipitate the reduction product as a white powder. Recrystallization from benzene–pet. ether gave 3.8 g. (64%) of large white prisms, m.p. 207–208°; lit.[2a] m.p. 205–206°.

An attempt to obtain this reduction product by use of catalytic hydrogenation (Pd/C, 10%) yielded only 1,3-diphenylbarbituric acid, the diphenylmethylene group having been cleaved.

Alternate Method for the Preparation of 1,3-Diphenyl-5-amylbarbituric Acid (4).—To an alcoholic solution of 0.11 mole of sodium ethoxide, prepared from 2.54 g. of sodium in 65 ml. of ethanol, there was added 21.2 g. (0.1 mole) of carbanilide and 23.0 g. (0.1 mole) of diethyl amylmalonate. As much of the ethanol as possible was removed by downward distillation and 50 ml. of dry xylene was added. The bath temperature was raised to 140–145°, any remaining ethanol being allowed to distill, and the reaction mixture was stirred at this temperature for 5 hr., the reaction being interrupted after 2 hr. for the addition of another 50-ml. portion of dry xylene. The mixture was then cooled and the xylene was extracted with a solution of 100 g. of sodium carbonate in 2 l. of water. The aqueous phase was washed with xylene, filtered, and acidified with 6 *N* hydrochloric acid to precipitate a solid which, when collected and recrystallized from ethanol, yielded 8.4 g. of a substance melting at 164–172°. When a second recrystallization, this time from methanol, failed to improve the melting point, the product was distilled *in vacuo*. The viscous oily product, b.p. 198–204° (0.1 mm.), on crystallization from ethanol, gave 3.8 g. (11%) of crystalline product, m.p. 167–169°, shown by mixture melting point and infrared spectrum to be identical with **4**.

Acknowledgment.—The authors are indebted to Dr. I. Shemano and his associates for the biological results reported, to Dr. S. Goldstein for his helpful suggestions and advice, and to Mr. Joseph P. Fabian for the infrared spectra.

(7) Nitrogen and sulfur analyses by Mr. Jerome Zalipsky of The National Drug Company. Carbon and hydrogen analyses by Dr. Alfred Bernhardt, Mülheim (Ruhr), Germany.

(8) C. S. Marvel and V. du Vigneaud, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 93.

(9) R. Adams and R. M. Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 250.

(10) In the preparation of the thio derivatives, the mixture was stirred at 51–55°; vigorous reflux caused a significant drop in yield.

(11) Reaction was allowed to continue until all, or virtually all, of the carbanilide had dissolved.

(12) H. Staudinger and H. Freudenberger, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 573.