ANTI-INFLAMMATORY COMPOUNDS

PART I. THE ACTIVITY OF A SERIES OF NEW COMPOUNDS COMPARED WITH PHENYLBUTAZONE AND CORTISONE

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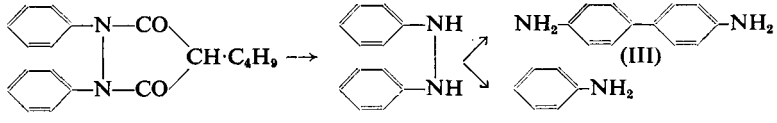
INTRODUCTION

SINCE the discovery by Hench[1] that cortisone and adrenocorticotrophic hormone possess the property of relieving rheumatoid arthritis and other inflammatory conditions, many workers have sought compounds which might simulate the action of these hormones. It has been shown that other substances possess anti-inflammatory properties and their mode of action is as yet unknown. Our interest in the production of compounds of this type arose from a consideration of the possible reasons for the toxicity of phenylbutazone, introduced by Wilhelmi[2]. This substance has been shown to have an outstanding anti-inflammatory activity but its use has been associated with a number of toxic side effects. At the time no evidence was available about the route by which the drug (I) was metabolised but it seemed possible that in the body the drug might be decomposed to form hydrazobenzene (II) and that this, or its rearrangement product, benzidine (III), or its disproportionation product, aniline (IV), might be responsible for the toxic effects of phenylbutazone.



(I) (II) (IV)

In an attempt therefore to obtain phenylbutazone derivatives with reduced toxicity, we planned to prepare a series of compounds which on similar decomposition would yield non-toxic derivatives of aniline, such as *p*-aminobenzoic acid and *p*-aminosalicylic acid. The above hypothesis is to be regarded solely as a theoretical possibility which provided some logical basis for the synthesis of the compounds described below. Burns *et al.*[3] investigated the metabolism of phenylbutazone but did not detect any of the possible decomposition products shown above.

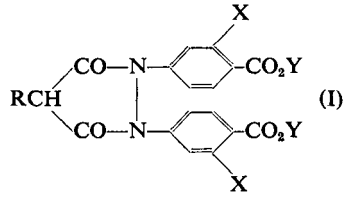
Whilst our work on phenylbutazone derivatives was in progress, the report by Lecompte *et al.*[4] came to our notice, in which the anti-inflammatory effect of cysteinamine was described. Moreover, Cornforth and Long[5,6] suggested that cortisone and the methionine antagonist, ethionine, desensitised the guinea-pig to the tuberculin reaction by their interference with glutathione production in the tissues. It therefore appeared desirable to investigate the anti-inflammatory activity of sulphur-containing

compounds related to cysteinamine and ethionine. The compounds studied in this work have, therefore, fallen into two categories, namely phenylbutazone derivatives and amino-sulphide derivatives.

CHEMISTRY

1. *Compounds Related to Phenylbutazone*

A series of compounds of general formula I,

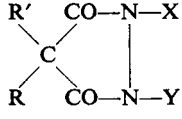


(I)

Where R = alkyl (methyl-hexyl)
X = H or OH
Y = alkyl or H

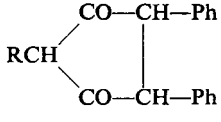
was prepared[7]. Furthermore, in order to study the effect on anti-inflammatory activity of small structural variations in the phenylbutazone molecule, the following types of compounds were studied:—

(*a*) A series of compounds of general formula II.

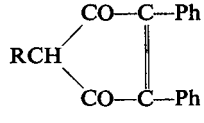


(II) (Phenylbutazone:—
R = $C_4H_9(n)$ R′ = H, X = Y = Ph.)

(*b*) A group of *cyclo*pentanediones (III) and cyclopentenediones (IV) derived from phenylbutazone by replacement of the ring nitrogens by carbon.



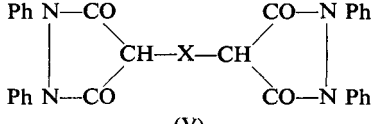
(III)



(IV)

(*c*) Acyclic compounds (compounds 342 and 423).

(*d*) Compounds of general formula V in which two pyrazolidine rings are linked by a carbon chain.



(V)

The compounds tested are given in detail in Table I.

TABLE I

ANTI-INFLAMMATORY ACTIVITY OF PHENYLBUTAZONE DERIVATIVES

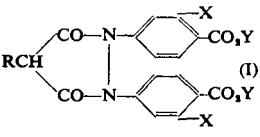
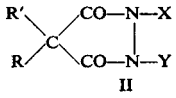
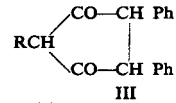
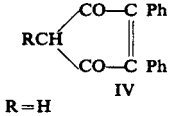
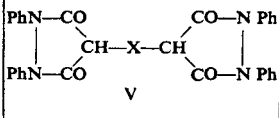
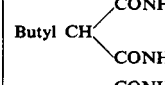
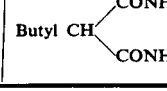
Ref. no.	Name	Formula	Anti-inflammatory activity in ultra-violet erythema test	
			Dose mg./kg.	Activity
		 (I)		
358	4-*n*-Butyl-1 : 2-di(4′-carboxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Butyl; X = Y = H	3 × 60	+
361	4-*n*-Butyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Butyl; X = OH; Y = H	3 × 60	−
389	4-*n*-Hexyl-1 : 2-di(4′-carboxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n* Hexyl; X = Y = H	3 × 300	−
390	4-*n*-Hexyl-1 : 2-di(4′-ethoxy-carbonylphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*-Hexyl; X = H; Y = Et	3 × 300	−
392	4-Ethyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = Et; X = OH; Y = H	3 × 50	−
393	4-*n*-Propyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Propyl; X = OH; Y = H	3 × 30	−
394	4-*n*-Propyl-1 : 2-di(4′-ethoxy-carbonyl-phenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Propyl; X = H; Y = Et	3 × 50	−
395	4-*n*-Propyl-1 : 2-di(4′-carboxy-phenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Propyl; X = Y = H	3 × 50	+
396	4-*iso*Propyl-1 : 2-di(4′-ethoxy-carbonylphenyl)pyrazolidine-3 : 5-dione	I. R = *iso*Propyl; X = H; Y = Et	3 × 50	−
397	4-Ethyl-1 : 2-di(4′-carboxyphenyl)-pyrazolidine-3 : 5-dione	I. R = Et; X = Y = H	3 × 50	−
398	4-*iso*Propyl-1 : 2-di(4′-carboxy-phenyl)-pyrazolidine-3 : 5-dione	I. R = *iso*Propyl; X = Y = H	3 × 50	−
404	4-*iso*Propyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Propyl; X = OH; Y = H	3 × 50	−
405	4-*n*-Hexyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Hexyl; X = OH; Y = H	3 × 50	−
406	4-Methyl-1 : 2-di(4′-methoxy-carbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = Y = Me; X = OH	3 × 30	−
407	4-Ethyl-1 : 2-di(4′-methoxycarbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = Et; X = OH; Y = Me	3 × 30	+
408	4-*n*-Propyl-1 : 2-di(4′-methoxy-carbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Propyl; X = OH; Y = Me	3 × 10	−
409	4-*iso*Propyl-1 : 2-di(4′-methoxy-carbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *iso*Propyl; X = OH; Y = Me	3 × 20	−
410	4-*n*-Butyl-1 : 2-di(4′-methoxy-carbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*Butyl; X = OH; Y = Me	3 × 50	++
411	4-*iso*Amyl-1 : 2-di(4′-methoxy-carbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *iso*Amyl; X = OH; Y = Me	3 × 50	−
412	4-*n*-Hexyl-1 : 2-di(4′-methoxy-carbonyl-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *n*-Hexyl; X = OH; Y = Me	3 × 20	−
421	4-Methyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = Me; X = OH; Y = H	3 × 4·5	−
422	4-*iso*-Amyl-1 : 2-di(4′-carboxy-3′-hydroxyphenyl)-pyrazolidine-3 : 5-dione	I. R = *iso*Amyl; X = OH; Y = H	3 × 5	−

TABLE I (*contd.*)

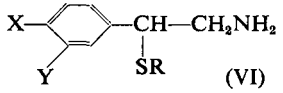
Ref. no.	Name	Formula	Anti-inflammatory activity in ultra-violet erythema test: Dose mg./kg.	Activity
		 II		
466	4-Allyl-1:2-diphenylpyrazolidine-3:5-dione[15]	II. R=C_6H_5; R′=H; X=Y=Ph	3 × 50	+++
482	4-*n*-Propyl-1:2-diphenylpyrazolidine-3:5-dione[15]	II. R=*n*Propyl; R′=H; X=Y=Ph	3 × 50	+++
343	4-*n*-Butyl-1-phenylpyrazolidine-3:5-dione	II. R=*n*Butyl; X=Ph; R′=Y=H	3 × 50	+
430	4-*n*-Butyl-1:2-di-*p*-tolylpyrazolidine-3:5-dione[15]	II. R=*n*-Butyl; R′=H; X=Y=p-$CH_3C_6H_4$–	3 × 50	+++
424	4-*n*-Butyl-4-methyl-1:2-diphenylpyrazolidine-3:5-dione	II. R=*n*-Butyl; R′=Me; X=Y=Ph	3 × 50	+
434	4-*n*-Butyl-4-methylpyrazolidine-3:5-dione	II. R=*n*Butyl; R′=Me; X=Y=H	3 × 50	–
		 III		
488	4:5-Diphenyl*cyclo*pentane-1:3-dione	III. R=H	3 × 10	–
486	2-*n*-Butyl-4:5-diphenyl*cyclo*pentane-1:3-dione	III. R=*n*Butyl	3 × 10	–
415	2:4:5-Triphenyl*cyclo*pentane-1:3-dione	III. R=Ph	3 × 50	–
491	2-*p*-Methoxyphenyl-4:5-diphenyl-*cyclo*pentane-1:3-dione	III. R=*p*-$MeOC_6H_4$–	3 × 50	–
		 IV		
487	4:5-Diphenyl*cyclo*pent-4-ene-1:3-dione	IV. R=H	3 × 10	–
485	2-*n*-Butyl-4:5-diphenyl*cyclo*pent-4-ene-1:3-dione	IV. R=*n*-Butyl	3 × 10	–
413	2:4:5-Triphenyl*cyclo*pent-4-ene-1,3-dione[16]	IV. R=Ph	3 × 50	–
490	2-*p*-Methoxyphenyl-4:5-diphenyl-*cyclo*pent-4-ene-1:3-dione	IV. R=p.$MeOC_6H_4$–	3 × 50	–
		 V		
489	4:4′-Methylenebis-(1:2-diphenylpyrazolidine-3:5-dione)	V. X=CH_2–	3 × 50	–
492	4:4′-Trimethylenebis-(1:2-diphenylpyrazolidine-3:5-dione)	V. X=-$(CH_2)_3$–	3 × 50	–
510	4:4′-Ethylidenebis-(1:2-diphenylpyrazolidine-3:5-dione)	V. X=$CH_3CH<$	3 × 30	–
342	*n*-Butylmalondianilide[17]		3 × 50	+
423	*n*-Butylmalondihydrazide[18]		3 × 50	–

Doses were determined by availability and toxicity of compound.

2. *Amino-sulphides*

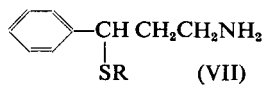
Reports on the anti-inflammatory action of cysteinamine, and our own work with ethionine suggested the preparation of some amino-sulphides for screening as potential anti-inflammatory agents.

The compounds prepared are given below, and their chemistry will be described elsewhere.



(VI)

516 R=CH_3; X=Y=H
522 R=C_2H_5; X=Y=H
523 R=C_2H_5; X=CH_3O; Y=H
524 R=C_3H_7(*iso*); X=Y=H
525 R=C_3H_7(*iso*); X=CH_3O; Y=H
526 R=C_3H_7(*n*); X=Y=H
532 R=C_3H_7(*n*); X=CH_3O; Y=H
550 R=C_2H_5; X=Y=CH_3O



(VII)

569 R=C_2H_5
571 R=C_3H_7(*iso*)

$RSCH_2CH_2CH_2NH_2$

(VIII)

575 R=C_2H_5

Experimental Methods

1. *Anti-inflammatory Activity*

The difficulty of inducing a clinical condition such as rheumatoid arthritis in experimental animals, together with the lack of real knowledge about the mechanism of anti-inflammatory activity, is reflected in the numerous methods suggested for screening possible anti-inflammatory compounds. Some of these have been recently enumerated by Wilhelmi and Currie[8] and additional methods have been described involving the production of granuloma by cotton pellets[9] or air pouches[10]. Three of these methods have been used to screen the compounds described above.

(*a*) Inhibition of the increase of capillary permeability by croton oil in the ear of the mouse[11], or by chloroform in the thoracic skin of the rat[4]. The former method was found difficult to manipulate and so was abandoned in favour of the latter. In this, 5 mg. of Pontamine Sky Blue was injected intraperitoneally into each rat exactly 2 hours before, and the drugs were injected intraperitoneally exactly 45 minutes before chloroform treatment. The experimental groups were compared with the control group for statistical significance. This is indicated in Table III by the sign, +.

(*b*) Inhibition of the production of inflammatory erythema by exposure of the depilated guinea-pig skin to ultra-violet light, using the Kromayer Lamp Model II and exposures of 20 or 30 seconds. Doses of test substances were given 45 minutes before, immediately before, and 30 minutes after, irradiation. This is a modification of the method used by Wilhelmi[2].

(*c*) Inhibition of the acute and chronic swelling of the rat's foot after the injection of 0·05 ml. of 10 per cent. mustard powder suspension[12]. This produces a gross œdema of the foot within thirty minutes (the "acute" stage) which slowly subsides by the next morning and which may reflect an increase in capillary permeability. During the days following, inflammatory tissue is laid down resulting in recurrence of swelling (the "chronic"

stage). The effect is measured daily for one week. The size of the foot before and after injection is measured by placing the foot on the platform of a dial micrometer and lowering the spring until very light contact is made with the surface of the most swollen point of the foot. The measurement of the normal foot is subtracted from each reading. The average percentage increase is compared with that of the control group, any difference being analysed for significance. Measurements are made after half an hour, and hourly for five hours after injection of mustard, then daily for the next five days. Doses are administered daily starting 3 days before the injection of mustard into the foot.

2. *Toxicity*

Acute and chronic toxicity of the compounds were determined by the usual methods in various species of experimental animals.

Results

1. *Phenylbutazone Derivatives*

(*a*) *Anti-inflammatory activity.* For the assay of the anti-inflammatory activity of phenylbutazone derivatives it was decided to use the guinea-pig erythema test in view of the work by Wilhelmi[2] who had shown that phenylbutazone displays marked activity with this type of test.

The results are given in Table I.

Phenylbutazone in a dose of 3 × 10 mg./kg. intraperitoneally was used as a standard in each test with a +++ result in each case. It is interesting to record that cortisone, administered as a micro-crystalline suspension of the acetate in total doses up to 50 mg. with single or repeated injections, showed no effect whatever in this test, suggesting that cortisone and phenylbutazone have a different mechanism of action in this particular test. Since compound 358 was of particular interest in view of its chemical structure, it was decided to carry out other tests on it. The results showed that the compound had a definite anti-inflammatory effect when assayed by the croton oil test at a dose of 500 mg./kg. intraperitoneally. The same substance also showed some degree of inhibitory effect against both types of swelling when assayed by the rat foot test at a dose of 400 mg./kg. intraperitoneally. On the other hand, only a doubtful effect was produced in this latter test when compound No. 358 was administered orally. In each of these tests, however, effective doses for phenylbutazone were close to the toxic range and the therapeutic index was, therefore, small. Toxicity tests on compound No. 358 demonstrated that it possessed a considerably lower toxicity and a higher therapeutic index than phenylbutazone.

(*b*) *Toxicity of Compound No.* 358. *Acute toxicity to mice.*

	LD50 in g./kg.		
	Oral	*Subcutaneous*	*Intraperitoneal*
Phenylbutazone	0·73	0·23	0·23
No. 358	>8·0	>8·0	>8·0

Chronic Toxicity

TABLE II

MAXIMUM TOLERATED DOSES OF PHENYLBUTAZONE AND COMPOUND NO. 358

Species	Phenylbutazone			Compound No. 358		
	Oral	Subcutaneous	Intra-muscular	Oral	Subcutaneous	Intra-muscular
Mouse ..	0·025 g./kg. (2 months)	0·01 g./kg. (2 months)	—	0·25 g./kg. (2 months)	0·063 g./kg. (2 months)	—
Rat ..	0·04 g./kg. (4 months)	—	0·016 g./kg. (5 months)	>0·5 g./kg. (4 months)	—	>0·1 g./kg. (5 months)
Guinea-pig	<0·012 g./kg. (4 months)	—	—	0·05 g./kg. (4 months)	—	—

2. *Amino-Sulphides.*

(*a*) *Anti-inflammatory action.* None of these compounds was found to be active by the guinea-pig erythema test. The results for the rat foot arthritis test and the chloroform patch test are given in Table III together with the acute toxicity figures for mice.

TABLE III

ANTI-INFLAMMATORY ACTIVITY OF AMINO-SULPHIDES

Ref. no.	Name	Anti-inflammatory activity				Acute toxicity to mice LD 50 mg./kg. intraperitoneal
		Dose mg./kg. intra-peritoneal	Rat foot test		Chloro-form patch	
			Acute	Chronic		
516	β-Methylthio-β-phenylethylamine hydrochloride	100	3/6	1/6	+	160
522	β-Ethylthio-β-phenylethylamine hydrochloride	50	5/6	2/6	+	97
523	β-Ethylthio-β-(4-methoxyphenyl)-ethylamine hydrochloride	100	2/6	0/6	+	220
524	β-*iso*Propylthio-β-phenylethylamine hydrochloride	50	4/6	0/5	+	140
525	β-*iso*Propylthio-β-(4-methoxy-phenyl)-ethylamine hydrochloride	50	2/6	0/5	+	140
526	β-Phenyl-β-propylthioethylamine hydrochloride	35	3/6	1/5	−	97
531	*N*-Dimethyl-β-phenyl-β-propylthio-ethylamine hydrochloride	75	3/6	0/6	−	160
532	β-(4-Methoxyphenyl)-β-propylthio-ethylamine hydrochloride	75	0/5	0/5	−	120
550	β-3:4-Dimethoxyphenyl-β-ethyl-thioethylamine hydrochloride	100	0/6	0/6		250
551	Di-(α-phenyl-β-aminoethyl) sulphide dihydrochloride	100	0/6	0/6		310
567	1-Ethylthio-1-phenyl*iso*propylamine hydrochloride (m.pt. 201 to 203°)	50	6/6	0/6		120
569	γ-Ethylthio-γ-phenylpropylamine hydrochloride	50	0/6	0/6	+	140
	Cysteinamine	50	3/5	0/6	+	>230
	Ethionine	100	4/6	5/5		

Note.—Scores in the rat foot test columns refer to the number of significant inhibitory results obtained over the experimental period.

It will be seen that only a small number of compounds showed activity and this was mainly confined to the inhibitory effect on the acute swelling. Ethionine appeared to be the most active of the compounds. It is also interesting to note that both cortisone and phenylbutazone had a very marked effect in this test in doses of 40 mg./kg. and 150 mg./kg. respectively, in distinction to the results quoted above with the guinea-pig

erythema test. However, the difference in action between cortisone and phenylbutazone is again illustrated by the results of the chloroform patch test, in which cortisone showed a high degree of activity and phenylbutazone only a low activity.

Discussion

The results reported here appear to fall into two divisions, namely those which relate chemical structure of the compounds to their anti-inflammatory activity and those which are of more purely physiological interest.

In the series of phenylbutazone derivatives, the results have shown that the basic structure has a high degree of specificity. Minor variations in the alkyl chain, for example, replacement of butyl by *n*-propyl (482), or by allyl (466), yield compounds with the same order of activity as phenylbutazone, but linking two diphenylpyrazolidinedione nuclei by an alkyl chain yields inactive compounds. This latter result may in part be explained by the fact that these bis compounds no longer give readily soluble neutral sodium salts. Replacement of the butyl group by H led to an inactive compound. Minor variations in the phenyl groups (430) likewise have little effect on activity but more radical substitution of the aromatic nuclei (formula I) yields compounds with a measurably smaller activity, although in these instances the toxicity also is reduced, and to an even greater extent. It is realised of course that this is in no way a proof of our original hypothesis, the validity of which can be tested only by comparative studies on the metabolism of phenylbutazone and its carboxy derivatives. Replacement of one of the phenyl groups by hydrogen led to a marked reduction in activity.

It appears that the enolisable 1 : 3-dioxo system is essential for activity, since on blocking this enolisation by substitution of the hydrogen on carbon atom 4 by methyl, activity was largely abolished. Replacement of both ring-nitrogens to give *cyclo*pentanedione or *cyclo*pentenedione derivatives (III, IV) yielded compounds which were completely inactive.

Investigation of compound No. 358 (4-*n*-butyl-1:2-di(4′-carboxyphenyl)-pyrazolidine-3 : 5-dione), in particular, suggested that it might be of clinical value and trials of its action in rheumatoid arthritis are now in progress.

With the series of amino-sulphides, our results are as yet not sufficiently numerous to justify any extensive deductions about structure-activity relationships. Ethionine, $C_2H_5S{\cdot}CH_2{\cdot}CH_2CH{\cdot}(NH_2){\cdot}COOH$, appears to be the most active compound so far tested with β-methylthio-, and β-ethylthio-β-phenylethylamine, probably the most active of this series of homologues.

Of the more purely biological implications of this work, perhaps the most interesting is the wide range of activity covered by the term "anti-inflammatory." A number of tests have been developed to detect this activity and the three methods employed in this investigation have yielded quite different results when used with cortisone and phenylbutazone. The former drug is known to have a marked anti-inflammatory effect in a number of clinical conditions, including rheumatoid arthritis, whilst the

latter appears to exert its anti-inflammatory effect mainly in rheumatic conditions. The comparative experimental effects of phenylbutazone and cortisone may be summarised.

Test	*Phenylbutazone*	*Cortisone*
Guinea-pig erythema	Active	Inactive
Rat foot arthritis	Active	Active
Rat chloroform patch	Low activity	High activity

It has been suggested that the beneficial action of phenylbutazone in rheumatoid arthritis is due solely to analgesia. However, using the technique previously described[13] we could demonstrate no analgesic activity in the rat, nor do the results above confirm this view of the mechanism of action of phenylbutazone.

A recent report[14] suggested that phenylbutazone had both a central and peripheral action and it is possible that cortisone may be acting only peripherally in those tests where differences were seen.

The anti-inflammatory activity of ethionine appears to parallel the observation by Cornforth and Long on the action of ethionine in inhibiting the tuberculin reaction. Ethionine is, of course, known to cause toxic effects in animals, due presumably to the metabolic disturbance produced by its antagonism to methionine, and it seems possible that the stress of this toxic effect may be responsible for the anti-inflammatory action. A more detailed investigation of this problem is now in progress.

Summary

1. A series of phenylbutazone derivatives has been tested for anti-inflammatory activity, using the guinea-pig erythema test, the rat foot arthritis test and the rat skin chloroform patch test.

2. The phenylbutazone structure shows a high degree of specificity; changes, other than minor ones, result in complete loss of activity.

3. None of the compounds tested was more active than phenylbutazone, but compound 358 (4-*n*-butyl-1:2-di(4′-carboxyphenyl)-pyrazolidine-3:5-dione) has a somewhat better therapeutic index.

4. A number of amino-sulphides was also shown to have some anti-inflammatory activity when tested by the rat foot test and the chloroform patch test but none was active by the guinea-pig erythema test. Similar differences are found between the actions of cortisone and phenylbutazone.

References

1. Hench, Kendall, Slocumb, Polley, *Proc. Mayo Clin.*, 1949, **24**, 181.
2. Wilhelmi, *Schweiz med. Wschr.*, 1949, **79**, 577.
3. Burns, Rose, Goodwin, Reichenthal, Horning, Brodie, *J. Pharmacol.*, 1955, **113**, 9.
4. Lecompte, Van Cauwenberge and Goblet, *C.R. Soc. Biol. Paris*, 1953, **147**, 1121.
5. Cornforth and Long, *Lancet*, 1953, **264**, 160.
6. Long, *ibid.*, 1954, **266**, 231.
7. Budziarek, Drain, Macrae, McLean, Newbold, Seymour, Spring and Stansfield, *J. Chem. Soc.*, in the press.
8. Wilhelmi and Currie, *Schweiz med. Wschr.*, 1954, **84**, 1315.
9. Meier, Schuber and Desaulles, *Experientia*, 1950, **6**, 469.

10. Selye, *J. Amer. med. Ass.*, 1953, **152**, 1207.
11. Wilhelmi, *Schweiz med. Wschr.*, 1950, **80**, 936.
12. Coutu, Gareau and Ducommun, *Rev. Canad. Biol.*, 1953, **12**, 40.
13. Bavin, Macrae, Seymour and Waterhouse, *J. Pharm. Pharmacol.*, 1952, **4**, 872.
14. Wilhelmi and Pulver, *Arzneimitt.-Forsch.*, 1955, **5**, 221.
15. Brit. Pat. 646,597 (J. R. Geigy, S.A.).
16. Koelsch and Wawzonek, *J. org. Chem.*, 1941, **6**, 684.
17. Dox and Yoder, *J. Amer. chem. Soc.*, 1922, **44**, 1578.
18. Blanhsma and de Graaf, *Rec. Trav. chim. Pays-Bas*, 1948, **57**, 3.

DISCUSSION

The paper was presented by MR. E. M. BAVIN.

MR. T. D. WHITTET (London) said that it would be useful if a less toxic derivative of phenylbutazone could be found. Cortisone and phenylbutazone each had their advantages and disadvantages. At his hospital the dose administered was that which gave reasonable remission with a minimum of side effects.

DR. R. F. TIMONEY (Dublin) said it appeared that compounds with the pyrazolidone structure showed greater activity than those with the cyclopentane structure, so it seemed that the activity of phenylbutazone lay in the former. When the *cyclo*pentanediol derivatives were formed, and replacement of the ring nitrogens by carbon effected, the activity of the compounds was lessened considerably.

The CHAIRMAN of the Session (DR. DAVIS) asked whether the effect of phenylbutazone was local or systemic. Cortisone and some of its derivatives were being used locally as anti-inflammatory agents with some success. Was there an association between the local and systemic effects of these compounds?

MR. E. M. BAVIN, in reply, said that the locus of action of the drugs was by no means settled. A recent German paper showed that cortisone and salicylates had both a central and peripheral action. That had been shown experimentally by measuring the response of drugs in animals. It seemed clear from the results that a dual action with cortisone was obtained. It might be that something similar would occur with phenylbutazone. As a means of trying to avoid side reactions blood levels of phenylbutazone could be determined, and American workers had shown that below a fairly sharp limit in the blood levels side reactions were unlikely. It was agreed that the specificity of the phenylbutazone molecule was a high one. It had been hoped that it would be possible to identify the activity with a particular grouping, but this had not been possible.