quitos. Experimental cross populations were tested not against larvae which had produced the parental adults, but against larvae from the parental colonies. Addition of adults from time to time to the breeding cages to ensure supplies of fresh eggs no doubt also contributed to variability. Although attempts were made to rear larvae under comparable conditions, the environment from pan to pan undoubtedly varied somewhat in food supply, temperature, and other factors which could affect the response to insecticides. Finally, one of the most important sources of error is the variability any assemblage of animals exhibits to a poison. Considering all these sources of experimental error, it is perhaps surprising that the results agree so closely as they do with the expected values, even though they cannot withstand statistical analysis. The writers believe that they merit notice as evidence that in the Philippine *C. fatigans* population, DDT resistance is probably due to selection for a single dominant gene.

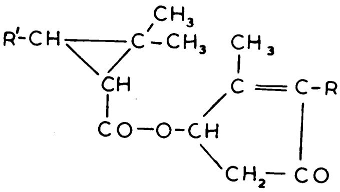
The Importance of Synthetic Pyrethroids *

by J. R. BUSVINE, *London School of Hygiene and Tropical Medicine, London, England*

The intensive research which finally elucidated the structure of the pyrethrins and cinerins in natural pyrethrum made possible the synthesis of a number of analogous compounds. This permitted investigation of the effect of variations of molecular form on toxicity, and led to production of some synthetic pyrethroid insecticides.

The relations between structure and toxicity have been well reviewed by Elliott.[a] In general, comparatively small changes in the main structure of the molecule lead to more or less complete loss of toxicity, suggesting that steric relations are important in the toxic action. Changes are possible in the unsaturated side-chain (R^2) of the keto-alcohol; and these have been exploited to produce the new synthetic insecticides allethrin, furethrin and cyclethrin. Recently, some experimental variations of the acid part of the molecule have revealed a promising compound, in which a phenyl group is substituted (at R^1) for the isobutylene group on the cyclopropane ring (Weiser [b]). (See accompanying figure.)

STRUCTURAL FORMULAE OF PYRETHROID INSECTICIDES



R^1	R^2	Name
$CH_3C{:}CH-$ CH_3	$CH{=}CH$ $-CH_2\quad CH{=}CH_2$	Pyrethrin I
$CH_3C{:}CH-$ CH_3	$CH{=}CH$ $-CH_2\quad CH_3$	Cinerin I
$CH_3C{:}CH-$ CH_3OOC	$CH{=}CH$ $-CH_2\quad CH{=}CH_2$	Pyrethrin II
$CH_3C{:}CH-$ CH_3OOC	$CH{=}CH$ $-CH_2\quad CH_3$	Cinerin II
$CH_3C{:}CH-$ CH_3	$CH{=}CH_2$ $-CH_2$	Allethrin
$CH_3C{:}CH-$ CH_3	$-CH-C{=}CH\quad CH$ $O-CH$	Furethrin
$CH_3C{:}CH-$ CH_3	$-CH-CH_2\quad CH$ CH_2CH_2	Cyclethrin
$CH\langle\begin{smallmatrix}CH=CH\\CH=CH\end{smallmatrix}\rangle C-$	$CH{=}CH_2$ $-CH_2$	Weiser's Compound XVI

The complexity of the subject is increased by the fact that both the acid and keto-alcohol components of pyrethroids can exist as *cis-* or *trans-*forms and as *dextro-* or *laevo-*rotatory forms, so that there are eight possible isomers. The relative toxicity of these to insects has been investigated, directly and indirectly, by Elliott et al.[c] and by Gersdorff & Mitlin.[d] These workers found that the (+) forms of the acid component conferred very much more activity than the (−) forms. It seems that the (+) forms of the keto-alcohol are also more insecticidal than the (−)

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[*] Revised version of note submitted to WHO Expert Committee on Insecticides, September 1959

[a] Elliott, M. (1954) *J. Sci. Food Agric.*, **11**, 505

[b] Weiser, J. (1958) *Vestn. čsl. Zool. Společ.*, **22**, 353

[c] Elliott, M. et al. (1950) *Ann. appl. Biol.*, **37**, 490

[d] Gersdorff, W. & Mitlin, N. (1953) *J. econ. Ent.*, **46**, 999

forms, though the difference is not so great. Finally, the *trans*-isomers are generally about twice as active as the *cis*-isomers. These differences are cumulative, so that (+) (+) *trans*-forms may be 150 or more times as insecticidal as the (−) (−) *cis*-isomers.

Natural pyrethrum contains (+) *trans* acids and (+) *cis* keto-alcohols, whereas the synthetic products are *cis-trans* racemic mixtures. From what has been said above, it will be evident that the double *dextro*-form in the natural product tends to make it more lethal to most insects than the synthetic materials.

Insecticidal value of synthetic pyrethroids

The published evidence of the relative insecticidal powers of natural and synthetic pyrethroids is very largely based on houseflies. Only allethrin has been more widely tested on other insects. This is a pity, because there is evidence that the relative values may change greatly with different insects (Elliott et al.[c]).

There is a further complication in the different results obtained by different authors. Thus, the potency of allethrin compared to natural pyrethrins has been reported as × 6 (Gersdorff[e]), × 1.2 (Stoddard & Dove[f]), × 1 (Moore[g]) and × 0.5 (Nash[h]). Some of these discrepancies may be due to the methods of measurement; others may be due to different proportions of isomers in the samples used.

Houseflies, however, are one of the few species for which approximate parity of allethrin has been claimed. For most other insects pyrethrins are more potent, as can be seen from the tabulation below:

	Potency of allethrin (pyrethrins = 1)	*Authors*
Cimex lectularius	0.56	Busvine & Nash[i]
Rhodnius prolixus	0.12	„
Pediculus humanus	0.24	„
Xenopsylla cheopis	0.17	„
Aëdes aegypti	0.38	„
Ornithodoros moubata	0.13	„
Aëdes aegypti (larvae)	0.4	Ginsburg[j]
Periplaneta americana	0.4	Bishopp[k]
Plutella maculipennis	1.8	Elliott et al.[c]
Macrosiphon solanifolu	0.06	„
Phaedon cochleariae	0.2	„
Oryzaephilus surinamensis	0.4	„

So far as the other synthetic compounds are concerned, there appear to be data only for houseflies. Furethrin was found to be about one-third as potent as allethrin by Gersdorff & Mitlin[l] but only 0.13 times as potent by Weiser.[b] Cyclethrin was found 0.6 times as potent as allethrin by Granett & Haynes[m] and 0.25 times by Weiser.[b] The only information about the new compound with the altered acid component was given by Weiser,[b] who found it to be 3.7 times as potent as allethrin, though less active for knock-down.

Combination with synergists

It is generally found that synergists are more effective in activating natural pyrethrins than in activating allethrin, at least with houseflies. However, the difference is not so pronounced with other synthetic pyrethroids. For example, the increase in potency of pyrethrins, allethrin and cyclethrin (synergized with sulfoxide) was 20, 3 and 8.5, respectively; and their relative potencies based on plain pyrethrins were 20, 8 and 12.5, respectively (Granett & Haynes[m]). Furethrin, too, seems to synergize more readily than allethrin (Incho & Ault[n]). It is also possible that this relationship may not hold with other insects. Thus, Nash[h] found that piperonyl butoxide actually synergized allethrin more (× 3) against bed-bugs than it did pyrethrins (× 2).

Persistence

Allethrin is more stable than natural pyrethrins, judged by bio-assay tests, either as oil films (Granett et al.;[o] Blacketh;[p] Busvine & Nash[i]) or as powder preparations (Goodwin-Bailey[q]). The difference, however, is not sensational; it does not represent a residual effectiveness of another order.

Resistance

Houseflies which had developed resistance to pyrethrins in the field in Sweden were found to be also resistant to allethrin in laboratory tests (Davies et al.[r]).

Practical considerations

Of the synthetic pyrethroids, only allethrin is manufactured on a large scale. The only manu-

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[e] Gersdorff, W. (1949) *J. econ. Ent.*, **42**, 532

[f] Stoddard, R. B. & Dove, W. E. (1949) *Soap*, **25**, No. 10, p. 118

[g] Moore, J. B. (1950) *J. econ. Ent.*, **43**, 207

[h] Nash, R. (1954) *Ann. appl. Biol.*, **41**, 652

[i] Busvine, J. R. & Nash, R. (1953) *Bull. ent. Res.*, **44**, 371

[j] Ginsburg, J. M. (1951) *Mosquito News*, **11**, 99

[k] Bishopp, F. C. (1950) *Agric. Chem.*, **5**, 22

[l] Gersdorff, W. & Mitlin, N. (1952) *J. econ. Ent.*, **45**, 849

[m] Granett, P. & Haynes, H. L. (1955) *J. econ. Ent.*, **48**, 409

[n] Incho, H. H. & Ault, A. K. (1954) *J. econ. Ent.*, **47**, 664

[o] Granett, P. et al. (1951) *J. econ. Ent.*, **44**, 552

[p] Blacketh, R. E. (1952) *J. Sci. Food Agric.*, **10**, 482

[q] Goodwin-Bailey, K. F. (1955) *Chem. Ind.*, p. 514

[r] Davies, M. et al. (1958) *Nature (Lond.)*, **182**, 1816

facturing plants appear to be in the United States of America, where synthetic substances are favoured by government policy in relation to self-sufficiency (in case of war, etc.). Some prices quoted recently were: allethrin, commercial grade (about 90%), $36 per pound; pyrethrins (20% concentrate, deodorized), $10.60 per pound (i.e., $53 per pound active principle). Allethrin is therefore cheaper, but not in proportion to the greater concentrations needed to compete with synergized pyrethrins for flies or with unsynergized pyrethrins for other insects. Only the discovery of a much more effective allethrin synergist or a reduction in price would make the synthetic insecticide seriously challenge the natural one, in normal circumstances (Goodwin-Bailey[q]). The complexity of the manufacturing process would seem to make a substantial price reduction unlikely.

Resistance to Pyrethrins*

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Resistance developed in the field

Pyrethrum resistance, at a level which appreciably affects control measures, has very rarely developed in the field. Indeed, there seem to be only two instances of this:

1. Strains of cockroaches collected from various parts of the United States of America were mostly found to possess low levels of pyrethrum resistance; but in one case, the level of resistance reached 13 or 30 times the normal level (the two figures refer to different test methods used by Keller et al.[a]). According to Spear (quoted by Brown[b]), this colony required substitution of sodium fluoride for field control.

2. Houseflies in Sweden, having become resistant to chlorinated-hydrocarbon insecticides and parathion, were controlled by synergized pyrethrum for about a year; but eventually the pyrethrum spray began to fail. Laboratory tests by Davies et al.[c] revealed a resistance of 11 to 14 times the normal to ordinary pyrethrins and 11 times to synergized pyrethrins.

It is noteworthy that both the cockroaches and the flies had developed resistance to other insecticides in the field prior to the discovery of the pyrethrin resistance. There are other records of pyrethrin resistance being discovered in the laboratory in strains taken from the field after developing resistance to chlorinated compounds. Thus, DDT-resistant flies from Torre in Pietra, Italy, were found to show a 5-fold pyrethrin resistance (Busvine[d]). Again, strains of resistant bed-bugs showed pyrethrin tolerance up to 10 times the normal. The level was roughly correlated with the DDT resistance, in different strains (Busvine[e]).

Whitehead[f] has found that a strain of the blue tick (*Boophilus decdoratus*) which was resistant to DDT was definitely resistant to pyrethrins (× 18), whereas other strains resistant to BHC or to BHC plus arsenite had a pyrethrin tolerance only 2 or 3 times the normal.

Lowered sensitivity of human body lice to pyrethrum powder was discovered in some instances in the very large surveys conducted by Wright & Brown[g] and Nicoli & Sautet[h]. In most cases the pyrethrin-tolerant lice showed some DDT resistance, but there was no correlation between the levels of resistance to the two types of insecticide.

Resistance developed in the laboratory

There are a few records of development of pyrethrum resistance in houseflies by selection on a normal colony. Thus, Decker & Bruce[i] reached a 20-fold and Harrison[j] a 5-fold increase. In both instances there was some raising of resistance to chlorinated-hydrocarbon insecticides.

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* Revised version of note submitted to WHO Expert Committee on Insecticides, September 1959.

[a] Keller, J. C. et al. (1956) *Pest Control*, **24**, 14

[b] Brown, A. W. A. (1958) *Insecticide resistance in arthropods*, Geneva (*World Health Organization: Monograph Series*, No. 38)

[c] Davies, M. et al. (1958) *Nature (Lond.)*, **182**, 1816

[d] Busvine, J. R. (1951) *Nature (Lond.)*, **168**, 193

[e] Busvine, J. R. (1958) *Bull. Wld Hlth Org.*, **19**, 1041

[f] Whitehead, G. B. (1959) *Nature (Lond.)*, **184**, 378

[g] Wright, J. W. & Brown (1957) *Bull. Wld Hlth Org.*, **16**, 9

[h] Nicoli, R. M. & Sautet (1955) *Monogr. Inst. nat. Hyg.*, **8**

[i] Decker, G. & Bruce (1952) *Amer. J. trop. Med. Hyg.*, **1**, 395

[j] Harrison, C. M. (1952) *Bull. ent. Res.*, **42**, 761