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Fluorinated Analogs of DDT as Toxicants and DDT Synergists¹

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ABSTRACT

The insecticidal activities and ability to synergize DDT of 16 fluorine-containing structural analogs of DDT were determined.

Of the 2,2-difluoro-1,1-di-*p*-halophenyl derivatives of ethane, ethanol and ethyl acetate, the *p*-bromo- and *p*-chloro- compounds were about equally toxic to susceptible house flies (*Musca domestica* L.) and the *p*-fluoro-compounds were less toxic. The ethane, ethanol, and ethyl acetate derivatives decreased in toxicity in the order given. The fluorodiphenylethenes were not

significantly toxic to house flies.

Maximum synergistic activity with DDT occurred in those derivatives containing *p*-chloro- or bromo-groups, fluoro- being inferior in all cases. Synergistic activity varied with the nature of the group attached to the alpha carbon atom in the following order: OH > H > OCOCH₃. The fluorodiphenylethenes were the least active *p*-halophenyl synergists. The difluorodiphenyl compounds containing no halogen substituent in the benzene ring were devoid of synergistic activity.

The possibility of controlling DDT-resistant insects with compounds structurally related to DDT was emphasized by Summerford *et al.* (1951). They reported that 1,1-bis-(*p*-chlorophenyl)ethanol (DMC) and its 4,4'-difluoro-analog appreciably increased the toxicity of DDT to resistant house flies. Others (March *et al.* 1952; Speroni 1952; Tahori 1955; Nieman *et al.* 1956) have

shown that the most effective synergists of DDT are structurally related to it.

Tahori (1955) demonstrated that *p*-chloro- and *p*-bromo- substituted 2,2,2-trifluoro-1,1-diphenylethanols,

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ethanes and acetates are effective DDT synergists. Tahori found that 2,2,2-trifluoro-1,1-bis(*p*-chlorophenyl) ethanol was two to five times more effective than the corresponding non-fluorinated carbinol (DMC), and 1.5 times more effective than 1,1-bis(*p*-chlorophenyl)ethane.

In this study *p*-substituted 2,2-difluoro-1,1-diphenylethanol, their corresponding acetates and ethanes, and the monofluoroethenes were prepared (Bornstein *et al.* 1957) and tested for toxicity to susceptible house flies (*Musca domestica* L.) and for synergistic activity with DDT on resistant house flies.

EXPERIMENTAL.—The house flies used in this investigation were the National Association of Insecticide and Disinfectant Manufacturer's 1948 susceptible strain and the Orlando-Beltsville DDT-resistant strain. The larvae were reared on moist Purina dog pellets in a room held at 32° C. ± 1° and 50% R.H. ± 5%. Except for the period during which they were being treated with the test chemicals, adults were held at the same conditions and fed a water suspension of powdered milk. Adult females, 3 to 4 days old, were lightly anesthetized with carbon dioxide and treated topically with 1 μl. of an acetone solution of the test compound delivered from a micrometer driven syringe. Each compound was tested on 4 samples of 20 flies from each of 2 populations. When the test compounds were evaluated as synergists, they were mixed with DDT at the ratio of 5 parts DDT to 1 part test compound. Six dose levels of this mixture were applied. Dosage-mortality curves were obtained by plotting the toxicity data on log probability paper. LD 50 values were computed by slope determination of the response curves.

RESULTS AND DISCUSSION.—An LD 50 for DDT could not be obtained on resistant flies since 120 μg./fly was the

maximum amount practicable to deliver in 1 μl. of acetone. None of the analogs caused over 5% mortality to resistant flies when applied at 10 μg./fly.

The toxicities to house flies of the compounds alone and in combination with DDT are listed in table 1. Combinations of DDT and the test compounds were evaluated only on resistant flies since synergism of DDT has only been demonstrated with resistant strains (March *et al.* 1952).

The most toxic compounds to susceptible flies were those containing *p*-chloro- or *p*-bromo- substituents (table 1). In the 2,2-difluoro-1,1-di-*p*-halophenyl derivatives of ethane, ethanol and ethyl acetate, the *p*-chloro- and bromo- compounds had similar toxicities (1,2,3,5,6,7). The substitution of *p*-fluoro- groups (9,10,11) reduced toxicity when compared to chloro- and bromo-. The unsubstituted diphenyl derivatives (13,14,15,16) were not significantly toxic.

In the three *p*-halogen series, ethanols, ethanes, and ethyl acetates, the nature of the group attached to the alpha carbon atom affected insecticidal activity. The most toxic compounds within any halogen series were the ethanes (1,5,9). When the alpha hydrogen was replaced by hydroxyl to give the ethanol, toxicity was reduced (2,6,10). Toxicity decreased when the alpha hydroxyl group was acetylated (3,7,11). The ethenes (4,8,12) prepared by the dehydrofluorination of the ethanes had little toxicity.

Maximum synergistic activity with DDT generally occurred with the *p*-chloro- and *p*-bromo-substituted compounds, which were similar in activity. The *p*-fluoro- and the unsubstituted diphenyl derivatives were less active. The activities of the well known DDT synergists 1,1-bis(*p*-chlorophenyl)ethanol (DMC) (17), 1,1-bis(*p*-chloro-

Table 1.—Toxicity of analogs of DDT to susceptible house flies and DDT plus the analogs at a 5:1 ratio to resistant house flies.

| ANALOG | FORMULA | SUSCEPTIBLE | RESISTANT |
|---|--|-------------------------------------|--|
| | | Analog LD-50 (μg./fly) ^a | DDT Present in Mixture at LD-50 (μg./fly) ^b |
| 1. 2,2-Difluoro-1,1-bis-(<i>p</i> -chlorophenyl)ethane | (<i>p</i> -ClC ₆ H ₄) ₂ CHCHF ₂ | 2.5 | 0.70 |
| 2. 2,2-Difluoro-1,1-bis-(<i>p</i> -chlorophenyl)ethanol | (<i>p</i> -ClC ₆ H ₄) ₂ COHCHF ₂ | 3.7 | 0.62 |
| 3. 2,2-Difluoro-1,1-bis-(<i>p</i> -chlorophenyl)ethyl acetate | (<i>p</i> -ClC ₆ H ₄) ₂ C(O ₂ CCH ₃)CHF ₂ | 9.2 | 1.60 |
| 4. 2-Fluoro-1,1-bis-(<i>p</i> -chlorophenyl)ethene | (<i>p</i> -ClC ₆ H ₄) ₂ C=CHF | >10 (18) | 11.90 |
| 5. 2,2-Difluoro-1,1-bis-(<i>p</i> -bromophenyl)ethane | (<i>p</i> -BrC ₆ H ₄) ₂ CHCHF ₂ | 2.4 | 0.96 |
| 6. 2,2-Difluoro-1,1-bis-(<i>p</i> -bromophenyl)ethanol | (<i>p</i> -BrC ₆ H ₄) ₂ COHCHF ₂ | 4.8 | 0.71 |
| 7. 2,2-Difluoro-1,1-bis-(<i>p</i> -bromophenyl)ethyl acetate | (<i>p</i> -BrC ₆ H ₄) ₂ C(O ₂ CCH ₃)CHF ₂ | 9.3 | 1.70 |
| 8. 2-Fluoro-1,1-bis-(<i>p</i> -bromophenyl)ethene | (<i>p</i> -BrC ₆ H ₄) ₂ C=CHF | >10 (18) | 7.20 |
| 9. 2,2-Difluoro-1,1-bis-(<i>p</i> -fluorophenyl)ethane | (<i>p</i> -FC ₆ H ₄) ₂ CHCHF ₂ | 4.8 | 7.60 |
| 10. 2,2-Difluoro-1,1-bis-(<i>p</i> -fluorophenyl)ethanol | (<i>p</i> -FC ₆ H ₄) ₂ COHCHF ₂ | 6.7 | 3.48 |
| 11. 2,2-Difluoro-1,1-bis-(<i>p</i> -fluorophenyl)ethyl acetate | (<i>p</i> -FC ₆ H ₄) ₂ C(O ₂ CCH ₃)CHF ₂ | >10 (36) | 8.50 |
| 12. 2-Fluoro-1,1-bis-(<i>p</i> -fluorophenyl)ethene | (<i>p</i> -FC ₆ H ₄) ₂ C=CHF | >10 (17) | >12 (29) |
| 13. 2,2-Difluoro-1,1-diphenylethane | (C ₆ H ₅) ₂ CHCHF ₂ | >10 (24) | >12 (17) |
| 14. 2,2-Difluoro-1,1-diphenylethanol | (C ₆ H ₅) ₂ COHCHF ₂ | >10 (12) | >12 (24) |
| 15. 2,2-Difluoro-1,1-diphenylethyl acetate | (C ₆ H ₅) ₂ C(O ₂ CCH ₃)CHF ₂ | >10 (12) | >12 (10) |
| 16. 2-Fluoro-1,1-diphenylethene | (C ₆ H ₅) ₂ C=CHF | >10 (22) | >12 (8) |
| 17. 1,1-bis-(<i>p</i> -chlorophenyl)ethanol (DMC) | (<i>p</i> -ClC ₆ H ₄) ₂ COHCH ₃ | — | 3.70 |
| 18. 1,1-bis-(<i>p</i> -chlorophenyl)ethane | (<i>p</i> -ClC ₆ H ₄) ₂ CHCH ₃ | — | 1.60 |
| 19. 1,1-bis-(<i>p</i> -chlorophenyl)ethene | (<i>p</i> -ClC ₆ H ₄) ₂ C=CH ₂ | — | 4.4 |
| 20. 1,1-bis-(<i>p</i> -chlorophenyl)-2,2,2-trichloroethane (DDT) | (<i>p</i> -ClC ₆ H ₄) ₂ CHCCl ₃ | 0.35 | — |
| 21. Acetone | | 1 μl (3 ± 2) | 1 μl (3 ± 2) |

^a 10 μg. was maximum dose applied, resulting mortality in parentheses.

^b 12 g. was maximum dose applied, resulting mortality in parentheses.

phenyl)ethane (18) and 1,1-bis-(*p*-chlorophenyl)ethene (19) are listed for comparison.

The most active synergists were 2,2-difluoro-1,1-bis-(*p*-chlorophenyl)ethanol and 2,2-difluoro-1,1-bis-(*p*-bromophenyl)ethanol (2,6). Both of these compounds were superior to the non-fluorinated 1,1-bis-(*p*-chlorophenyl)ethanol, DMC (17). The *p*-chloro- and *p*-bromo-substituted diphenylethanes (1,5) were less active than the corresponding ethanols (2,6), but more active than 1,1-bis-(*p*-chlorophenyl)ethane (18). 2,2-difluoro-1,1-bis-(*p*-fluorophenyl)ethanol (10) is about one-fifth as active as the analogous chloro- and bromo-derivatives (2,6). This compound was slightly more effective than DMC (17) and was about one-half as active as 1,1-bis-(*p*-chlorophenyl)ethane (18). The *p*-fluoro-substituted ethane (9) was approximately one-tenth as active as the corresponding chloro-derivative (1) and the least active of the *p*-halophenylethanes. Furthermore, this compound was less than half as active as the corresponding ethanol (10).

The 2,2-difluoro-1,1-bis-(*p*-halophenyl)ethyl acetates showed the same activity pattern as the ethanols and ethanes, the *p*-chloro- (3) and *p*-bromo- (7) derivatives both being more active than the *p*-fluoro-compound (11). The chloro- and bromo- acetates (3,7) were about half as active as the parent ethanols (2,6) but were more active than DMC (17) or 1,1-bis-(*p*-chlorophenyl)ethane (18). The *p*-fluoro-substituted acetate (11) was about one-fifth as active as the corresponding chloro- and bromo-derivatives (3,7).

The *p*-halo-substituted diphenylethenes (4,8,12) were less active than the ethanols (2,6,10), acetates (3,7,11) and ethanes (1,5,9), from which they were derived. 2-Fluoro-1,1-bis-(*p*-chlorophenyl)ethene (4) was less active than 1,1-bis-(*p*-chlorophenyl)ethene (19). The *p*-fluoro-derivative (12) was considerably less active than the corresponding chloro- and bromo- compounds (4,8).

The insecticidal activities of these compounds containing fluorine on the terminal carbon atom resemble those found in DDT and its derivatives (containing chlorine on the terminal carbon). The most toxic compounds were the ethanes, whereas the corresponding ethanols were less active. Similarly, DDT is more toxic than its corresponding ethanol (Reuter & Ascher 1956). When the 2,2-difluoro-1,1-diphenylethanes are dehydrofluorinated, the resulting ethenes are almost devoid of insecticidal activity. This also follows the pattern of DDT, which is more active than its dehydrochlorinated analog (Sternberg *et al.* 1950).

Tahori (1955) evaluated a series of *p*-substituted 2,2,2-trifluoro-1,1-diphenylethanes, ethanols and ethyl acetates against *Musca vicina* Macq. He reported the *p*-chloro- and *p*-bromo-ethanes and ethanols to be of similar toxicities. However, in contrast to our results with diphenylethyl acetates, he reported that the trifluorodiphenylethyl acetates were similar in toxicity to the ethanes and ethanols. It is interesting to note that our series of ethenes had no significant toxicity, and were the least active synergistically. This was also the case with the acetates, which were less toxic and less active synergistically than the ethanes and ethanols.

In the *p*-chloro- and *p*-bromo-substituted difluorodiphenylethanol, a slight decrease in synergistic activity occurred when the hydroxyl group was replaced by hydro-

gen. This structure-activity correlation was more marked in the corresponding *p*-fluoro-substituted derivatives, where replacement of hydroxyl by hydrogen resulted in a large decrease in synergistic activity.

The similar synergistic activities of the various *p*-chloro- and *p*-bromo- derivatives within the same series is striking. In the ethanes, ethanols and acetates, the compounds containing *p*-chloro- or *p*-bromo- substituents were nearly equal in synergistic activity in every case. The fact that both chloro- or bromo- were equally good *p*-substituents contrasts with the decreased synergistic activity observed with the corresponding compounds carrying the smaller fluorine atom in the *p*-position.

Acetylation of the various ethanols resulted in a decrease in synergistic activity. It is possible that these acetates are not hydrolyzed rapidly by the house fly, for if they were, they would be expected to be as active as the ethanols.

The increase in synergistic activity obtained when fluorine is substituted for hydrogen on the terminal alkyl carbon is pronounced. For example, 2,2-difluoro substitution of 1,1-bis(*p*-chlorophenyl)ethanol (DMC)(17) and its corresponding ethane (18) increases synergistic activity. Tahori (1955) has reported a similar increase in synergistic activity with 2,2,2-trifluoro-substitution.

Fluorination of the side chain of 1,1-bis(*p*-chlorophenyl)ethene resulted in a decrease in synergistic activity (4,19). Similarly, March *et al.* (1952) reported that replacement of one side chain hydrogen by chlorine in the *p*-chloro-substituted diphenylethene series resulted in a decrease in synergistic activity. Consequently, it is evident that side chain halogenation of 1,1-bis-(*p*-chlorophenyl)ethene reduces synergistic activity.

The results of Tahori (1955), who evaluated the synergistic activities of trifluorodiphenylethanol, ethanes and acetates, were similar to those herein reported for the corresponding difluoro-compounds.

REFERENCES CITED

- Bornstein, J., M. S. Blum, and J. J. Pratt, Jr. 1957. DDT synergists. The synthesis and properties of some 2,2-difluoro-1,1-diarylethanol and 2-fluoro-1,1-diarylethenes. *Jour. Organ. Chem.* 22: 1210-13.
- March, R. B., R. L. Metcalf, and L. L. Lewallen. 1952. Synergists for DDT against insecticide resistant house flies. *Jour. Econ. Ent.* 45: 851-60.
- Nieman, M., A. Modiano, G. G. Mer, and R. Cevlich. 1956. Substituted benzenesulphonanilides as synergists for DDT. *Nature* 177: 800-1.
- Reuter, S., and K. R. S. Ascher. 1956. The action of di-(*p*-chlorophenyl)-trifluoromethylcarbinol on house flies. *Experientia* 12: 316-18.
- Speroni, G. 1952. Impiego de sinergici nell lotta contro la *Musca domestica* resistente agli insetticidi di contatto. *La Chimica e l'industria.* 34: 391-403.
- Sternburg, J., C. W. Kearns, and W. N. Bruce. 1950. Absorption and metabolism of DDT by resistant and susceptible house flies. *Jour. Econ. Ent.* 43: 214-9.
- Summerford, W. T., M. B. Geote, K. D. Quarterman and S. L. Schenk. 1951. The potentiation of DDT by several structurally related compounds. *Science* 114: 6-7.
- Tahori, A. S. 1955. Diaryl-trifluoromethylcarbinols as synergists for DDT against DDT-resistant house flies. *Jour. Econ. Ent.* 48: 638-42.