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The Discovery of Bifenazate, a Novel Carbazate Acaricide

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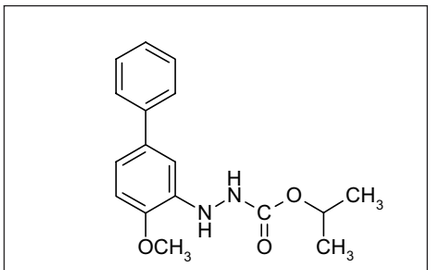
Abstract: A history of the discovery of the novel carbazate acaricide, bifenazate, is outlined. When a novel *ortho*-biphenyl substituted hydrazide compound showed acaricidal activity in the pesticide discovery screen, a small number of analogs were made to confirm and explore acaricidal effects. An *ortho*-biphenylcarbazate analog gave significantly greater acaricidal activity. Thereafter, several hundred structurally-diverse biphenyl-substituted carbazate analogs were synthesized and evaluated in a bioassay with the two-spotted spider mite (*Tetranychus urticae* Koch) in order to optimize the acaricidal activity. As a result of the optimization process, bifenazate, the analog with a methoxybiphenyl substituent to the terminal nitrogen atom of isopropyl carbazate, was selected for development and registration.

Keywords: Acaricide · Bifenazate · Carbazate · Discovery

Introduction

The two-spotted spider mite, *Tetranychus urticae* Koch, is one of the most important pest species in agricultural and ornamental crops worldwide [1]. Control of mites is a continual struggle because they possess the capacity to rapidly develop resistance to acaricides due to their high reproductive potential and their short life cycles. The reliance upon only a few effective acaricides has increased the likelihood of acaricide resistance problems. In several crops, both integrated pest-management programs (IPM) with beneficials and judicious use of acaricides to avoid resistance are practiced. An acaricide sub-group of the Insecticide Resistance Action Committee (IRAC) also addresses issues related to the optimal use of acaricide products. Selective acaricides with novel chemistries are highly toxic to phytophagous mites but have a wide margin of safety to non-target beneficial organisms. Such acaricides are favored by regulatory agencies and are also highly recommended by pest control advisors, modern growers and consumers. Acaricide discovery, which relies heavily on serendipity in the traditional screening approaches mainly conducted by agrochemical companies, has brought to the market a diverse range of chemical classes, often directed against novel biochemical and physiological targets [2]. The best of these have minimal effects on humans and the environment and are compatible with IPM for the crop systems in which they are used.

Bifenazate (Fig. 1) is a new type of acaricide belonging to the carbazate class. From among several hundred carbazate derivatives synthesized and evaluated for acaricidal activity in the early 1990s, the methoxybiphenyl-substituted carbazate (bifenazate) was selected for development [3]. In the USA, bifenazate was first approved and registered as a reduced-risk acaricide for the ornamental market and soon thereafter for crops such as apples, pears, peaches, plums, grapes, cotton, strawberries, and hops. Bifenazate is now under worldwide development for the selective control of spider mites in both agricultural and ornamental markets and is sold under the trade names 'Floramite', 'Acramite', and 'Mitekohne'. This report outlines a short history of its discovery.



bifenazate

Fig. 1. Structure of bifenazate

Discovery of the Lead Compound

Crompton research on acaricidal carbazates was initiated in 1990 when fungicidal phenylhydrazide compounds were discovered to have some acaricidal activity in the pesticide discovery screen. An *ortho*-biphenyl-substituted hydrazide **1** (Fig. 2) possessed a modest level of acaricidal activity (90% control of mites at 500 ppm). The activity of this compound was interesting because several phenylhydrazide compounds previously evaluated in the mite screen had not shown activity. We speculated that, in this case, the acaricidal activity was due to the presence of the *ortho*-biphenyl group. Furthermore, our earlier experience in screening oxadiazinone compounds had indicated that *ortho*-biphenyl substitution on a nitrogen atom in the ring

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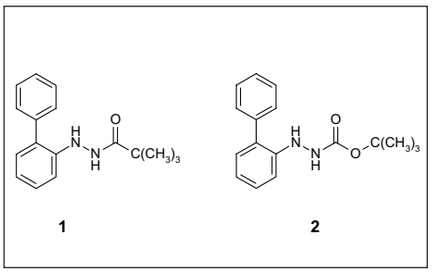
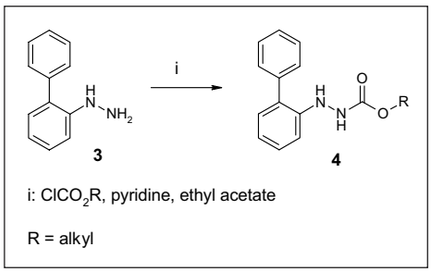


Fig. 2. Early hydrazide and carbazate hits



Scheme 1. Synthesis of *ortho*-biphenylcarbazates

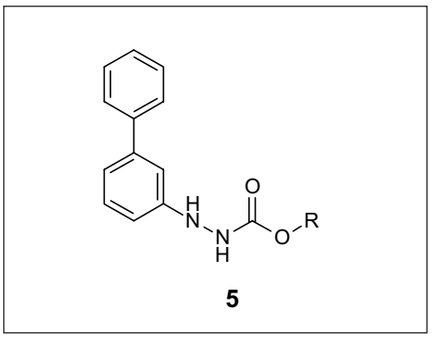


Fig. 3. *meta*-Biphenylcarbazates

system enhanced activity [4]. Therefore, we synthesized and evaluated a few structurally-diverse *ortho*-biphenyl-substituted hydrazine derivatives.

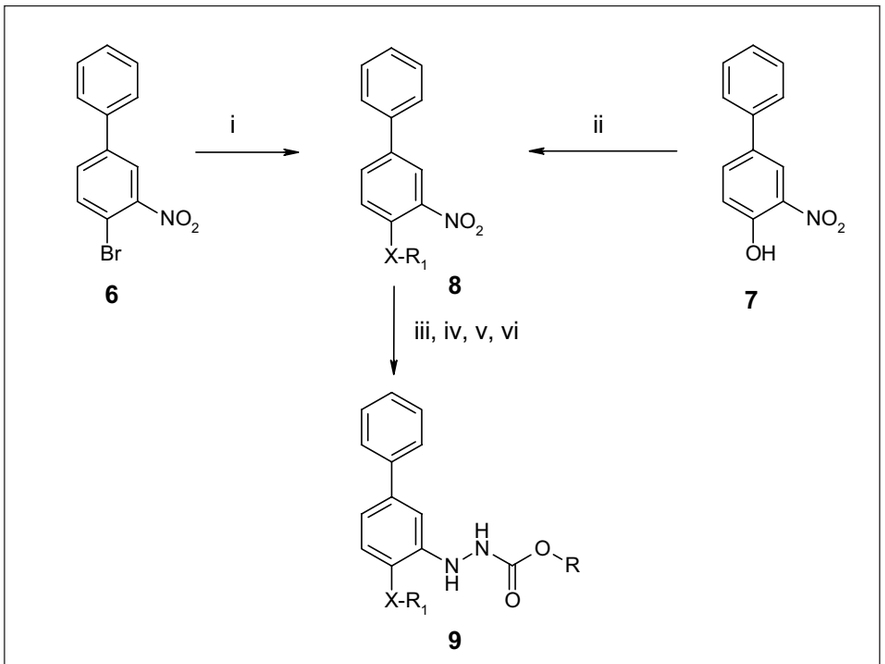
ortho-Biphenylcarbazate Analogs

The *ortho*-biphenylcarbazate analog **2** (Fig. 2), corresponding to the initial active *ortho*-biphenylhydrazide **1**, gave significantly greater acaricidal activity (96% control of mites at 100 ppm). Phenylcarbazates were reported to possess fungicidal activity [5] but biphenylcarbazates were not described in the literature. The improved level of mite control demonstrated by the *ortho*-biphenylcarbazate analog **2** depended on the presence of its biphenyl moiety. Therefore we synthesized and tested a variety of alkyl *ortho*-biphenylcarbazates. Alkyl *ortho*-biphenylcarbazates of the type **4** were synthesized by reaction of *ortho*-biphenylhydrazine **3**, readily prepared from commercially available *ortho*-biphenylamine by diazotization followed by $SnCl_2$ reduction, with alkyl chloroformates (Scheme 1) [6]. Optimal activity (80–100% control of mites at 100 ppm) in this series was obtained when the ester function consisted of a straight- or branched-chain alkyl group of three or four carbon atoms.

meta-Biphenylcarbazate Analogs

Isomeric alkyl *meta*-biphenylcarbazates **5** (Fig. 3) were synthesized from *meta*-biphenylhydrazine in a similar way to that for the *ortho*-biphenylcarbazates [7]. The acaricidal activities of alkyl *meta*-biphenylcarbazates paralleled their *ortho*-biphenyl-substituted counterparts with optimal acaricidal control of 80-100% at 100 ppm when the ester function consisted of three or four carbon length alkyl groups.

Additional modifications of the *meta*-biphenylcarbazate structure were explored by introducing different substituents oriented *para* to the pendant phenyl group as shown in Scheme 2. Two approaches were taken in preparing substituted *meta*-biphenylcarbazates **9**. In the first, we displaced the bromine atom in the commercially available compound **6** with the sodium salts of alkyl thiols or alkyl sulfinic acids, generating intermediates of the type **8** in which X = S or SO_2 and R_1 = alkyl. In the second, we alkylated the commercially available phenol **7** with alkyl halides, generating intermediates of type **8** in which X = O and R_1 = alkyl. Next, the nitro group in intermediate **8** was reduced to an amino group by tin chloride [8] and the resulting substituted *meta*-biphenylamine was converted into the carbazate **9** using the methods described for *ortho*-biphenylcarbazates. The structure–activity relationships for substituted *meta*-biphenylcarbazates are summarized in Fig. 4. Several carbazates of type **9** were more efficacious than the most active carbazates of type **4** or **5**. The most potent carbazates of type **9** were those with X = O, R = isopropyl, *sec*-butyl or *tert*-butyl and R_1 = methyl, ethyl or



Scheme 2. Synthesis of substituted *meta*-biphenylcarbazates

fluoroethyl. The best activity (100% control of mites at 25 ppm) was observed for the compound in which X = O, R = isopropyl and R_1 = methyl. By way of comparison to a commercial acaricide in the bioassay testing, this compound was five times as active as propargite and warranted development for the acaricide market. This compound became known as bifenazate.

Biphenyldiazene Analogs

Attention also focused on modifying the carbazate moiety by derivatization. One type of derivative that was prepared was the biphenyldiazene type **10** (Fig. 5). Biphenyldiazene analogs were synthesized by the method of Gaviraghi *et al.* [9], which involved a palladium-catalyzed oxidation of carbazates to diazenes. The acaricidal activities of the diazenes **10** were parallel to the corresponding carbazates from which they were made [10][11]. The best activity (100% control of mites at 25 ppm) was observed for the compound in which R = isopropyl, R_1 = phenyl and R_2 = methoxy. Although the activity of this compound was comparable to bifenazate, the compound was not as cost-effective.

Trifluoroacetylcarbazate Analogs

We also investigated modification of the biphenylcarbazates wherein a trifluoroacetyl group resided on one of the carbazate nitrogens (Fig. 6). Trifluoroacetylcarbazates **11** were prepared from the corresponding carbazates by reaction with trifluoroacetic anhydride [7]. The acaricidal activities of the trifluoroacetylcarbazates were generally parallel to those of the carbazates from which they were made. The best activity (100% control of mites at 25 ppm) was observed for the compound in which R = isopropyl, R_1 = phenyl and R_2 = methoxy. However, this compound did not perform as well as bifenazate under field conditions.

Conclusions

The observation that an *ortho*-biphenyl substitution imparted acaricidal activity in a hydrazide structure was exploited through synthesis of a variety of biphenylcarbazates and their diazene and trifluoroacetyl derivatives. Our optimization program led to identification of the first carbazate acaricide bifenazate.

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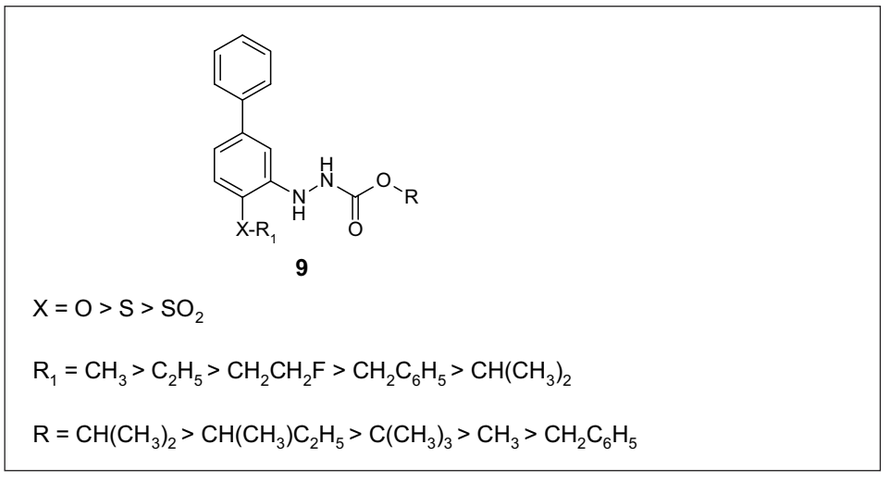

Fig. 4. Structure–activity relationships in substituted *meta*-biphenylcarbazates

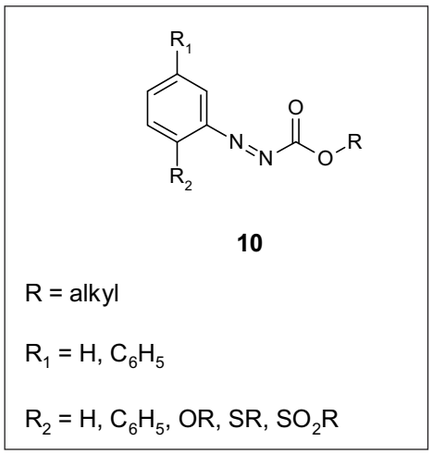

Fig. 5. Biphenyldiazenes

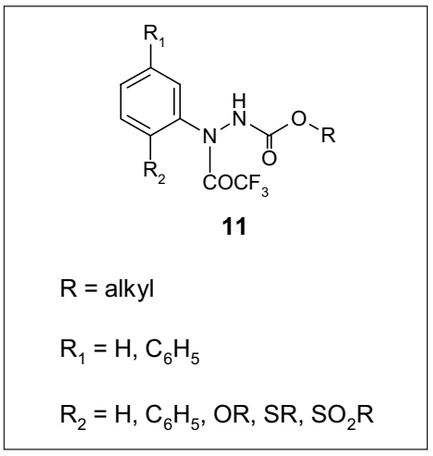

Fig. 6. Trifluoroacetylcarbazates

[1] H.R. Boland, 'World Catalogue of the Spider Mite Family (Acari: Tetranychidae)', Eds. H.R. Boland, J. Gutierrez, C.H.W. Flechtmann, Koninklijke Brill, NV, Leiden, **1998.**
[2] M.A. Dekeyser, R.G.H. Downer, *Pestic. Sci.* **1994**, *40*, 85.
[3] M.A. Dekeyser, P.T. McDonald, G.W. Angle Jr., R.C. Moore, *Proc. Brighton Crop Prot. Conf.- Pests Dis.* **1996,** *2*, 487.
[4] M.A. Dekeyser, D.M. Borth, R.C. Moore, A. Mishra, *J. Ag. Food Chem.* **1991**, *39*, 374.
[5] P.E. Frohberger, E. Urbschat, D. Mayer, K. Sasso (Bayer AG), DE 2223936, **1973**.
[6] M.A. Dekeyser, P.T. McDonald, G.W. Angle Jr., *J. Ag. Food Chem.* **1994**, *42*, 1358.
[7] M.A. Dekeyser, P.T. McDonald (Uniroyal), US 5367093, **1994**.
[8] F. Bellamy, K. Ou, *Tetrahedron Lett.* **1984**, *25*, 839.
[9] G. Gaviraghi, M. Pinza, G. Pifferi, *Synthesis* **1981**, *8*, 608.
[10] M.A. Dekeyser, P.T. McDonald (Uniroyal), US 5438123, **1995**.
[11] M.A. Dekeyser, P.T. McDonald, G.W. Angle Jr., *J. Ag. Food Chem.* **1995**, *43*, 1705.