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The Behaviour of Arylidene Barbituric Acid and Cyclohexadione Derivatives Towards Tris(dimethylamino)phosphine

N. R . Mohamed[1] , M. M. T. El-Saidi[1] , S. A. Abdel Aziz [2] , M. F. Zayed[1]

[1] National Research Center, Cairo, Egypt

[2] Agriculture Research Center, Cairo, Egypt

Tris(dimethylamino)phosphine **1** reacted with phenylarylidene barbituric acids **4** to yield the triaminophosphonium dipolar ion adduct **7**. 2-Arylidene-1,3-cyclohexanedione **5** and 2-Arylidene-5,5-dimethylcyclohaxane-1,3-diones **6** reacted with phosphine **1** to produce the dioxyxanthenes **10** and **12**, respectively. Structural assignments are based on analytical, chemical, and spectroscopic evidences. A mechanism is proposed to explain the formation of these compounds. The biological acitivity of the new synthesized compounds against *Aphis Craccivora*, a serious pest infecting many crops in Egypt, was studied.

(*Keywords*: Tris(dimethylamino)phosphine **1**, Barbituric acids **4**, Cyclohexanediones **5** & **6**, Phosphonium dipolar ions **7**, Dioxyxanthenes **10** & **12**, *Aphis Craccivora*)

compound **12a** showed a high activity and a moderate activity on *A. Craccivora*, respectively. The average mortality percent of *Aphids* calculated per concentration was given in Table-1.

Concentration (ppm)		% Mortality[a]	LC_{50}[b]	LC_{90}[c]
7a	250 125 62.5 31.25	80 70 60 30	50.97	415.36
12a	1000 500 250	80 60 30	391.75	2315

[a] Mortality death
[b] LC_{50} Lethal conc that killed 50%
[c] LC_{90} Lethal conc that killed 90%

Table-1

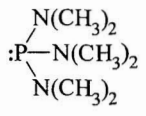
Experimental

All m.ps. were uncorrected. The appropriate precautions in handling moisture sensitive compounds were undertaken. tris(dimethyl-amino)phosphine **1**[22] was freshly distilled before use. Arylidene barbituric acid **4**, 2-arylidene-5,5-dimethyl-cyclohaxenesdiones **5** and 2-arylidene-1,3-cyclohaxenesdione **6** were recrystallized and dried before use.

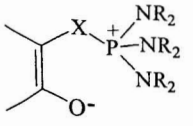
Introduction

The reaction of aminophosphines with *o*-quinones has been extensively studied[1]. However, attention has been devoted in the literature to the reactions of these phosphines since the synthesis of compounds having activity in the Leukaemia P 388 test system by the interaction of tris(dimethylamino) phosphine **1** with some *p*-quinones[2,3].

In view of these observations in connection with our interest in the synthesis of compounds of expected pesticidal activity and in continuation of our study on the reactions of aminophosphines with some *o*-quinone derivatives in which we obtained compounds having the phosphonium dipolar ion structure **2** and / or compounds having cyclic phospholene structure **3**[4,5], we have now investigated the reactions of tris(dimethylamino) phosphine **1** with arylidene barbituric acids **4**, 2-arylidene-1,3-cyclohexanedione **5** and 2-arylidene dimedones **6**. To the best of our knowledge no information about such work has appeared in the literature.



1



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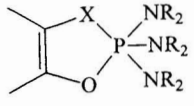
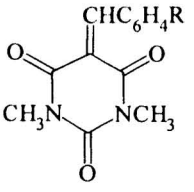
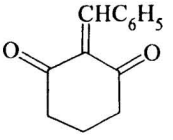


3

X = NH, NOH, $C(CN)_2$
R = CH_3



4a: R = H
b: R = Cl



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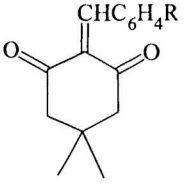
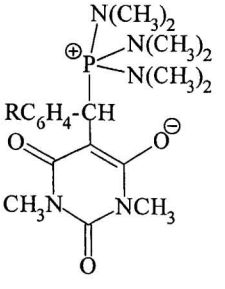


6a: R = H
b: R = Cl
c: $R = NO_2$

Results and Discussion

We have found that the reaction of tris(dimethylamino)phosphine **1** with benzylidene barbutric acid **4a** proceeded in benzene at room temperature to give chromatographically pure 1 : 1 adduct **7a**. Changing the reaction medium (using methylene chloride) or letting the reactants stand in the solvent for three days did not change the properties of the stable adduct. The triaminophosphonium dipolar ion structure **7a** is assigned to this adduct due to the following:



7a: R = H
b: R = Cl-*p*

a. This adduct is a colorless crystalline stable substance with sharp melting point.

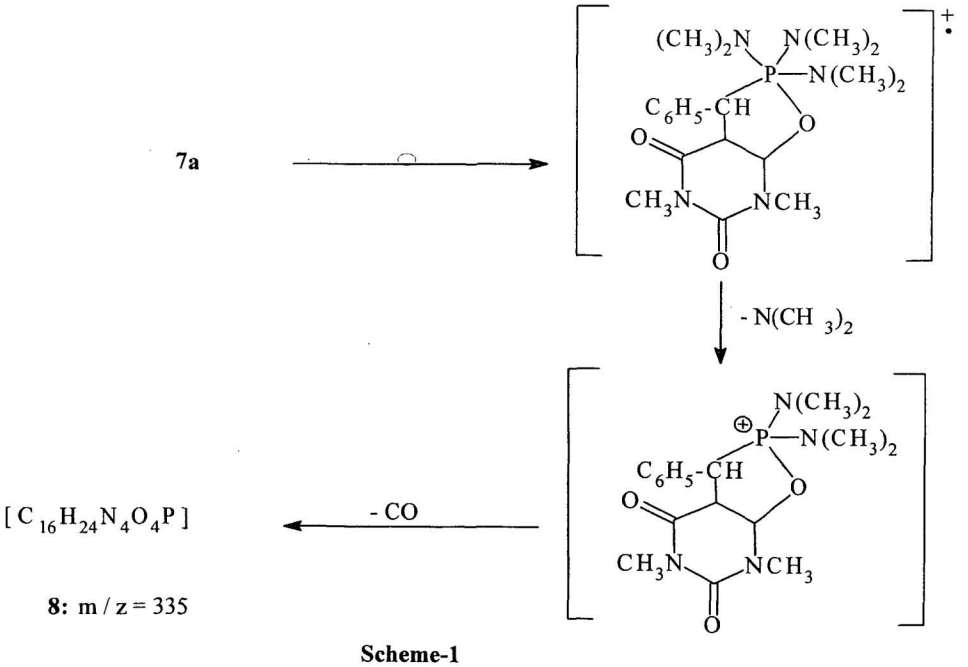
b. Elemental analysis of this adduct corresponds to $C_{19}H_{30}N_5O_3P$.

c. Adduct **7a** afforded phenyl arylidene barbituric acid **4a** and tris(dimethyl amino) phosphine **1** upon heating at its melting point under reduced pressure (pyrolysis).

Supplementary evidence for the assigned structure **7a** has been gained from MS, IR, ^{1}H NMR, and ^{31}P NMR data. In the MS of compounds **7a**, the molecular ion peak expected at m/z= 407 was not recorded. However, there are two prominent ion peaks at m/z= 244 (56 %) and at m/z=163 (29 %) corresponding to the starting **4a** and the aminophosphine **1**.This is in accordance with the result of thermolysis described above. Careful inspection of the MS of this compound indicated the presence of an ion peak at 335 (35 %) that corresponds to **8** (Scheme- 1). On the other hand, the molecular ion peak of compound 7a (m/z= 407) was recorded when utilizing the field ionization technique.

The ^{31}P NMR spectrum of this adduct has one signal at δ = +62.86 which indicates an open dipolar ion with quadruply connected phosphorus[1]. The ^{1}H NMR spectrum of **7a** showed a doublet centered at δ = 2.65 ppm (J_{HP} = 9 Hz) due to 18 H of the three magnetically equivalent dimethylamine groups. A singlet appeared at δ = 3.92 ppm due to the 6 H of the two NCH_3. The CH proton attached to phosphorus

appeared as a doublet centered at δ = 5.85 ppm (J_{HP} = 24 Hz). The aromatic protons appeared as two multilpets centered at δ = 7.15 and 7.32 ppm (5 H). The IR spectrum of this adduct revealed the presence of the enolate carbonyl absorption[6] at ν = 1488 cm^{-1}. The two bands at ν = 1324 cm^{-1} and at 844 cm^{-1} were attributed to the P-N$(CH_3)_2$ group. Moreover, the band at ν 1590 cm^{-1} (C=C) is consistent with the dipolar structure[6].

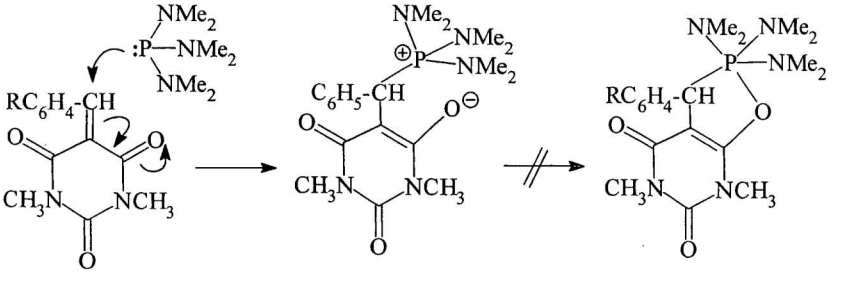


Scheme-1

Similarly, the reaction of compound **4b** with tris(dimethylamino)phosphine **1** proceeded in dry benzene at room temperature to give mainly 1 : 1 adduct of the aminophosphonium dipolar ion structure **7b**. This is based on analytical and

spectroscopic evidences (c.f. experimental part).

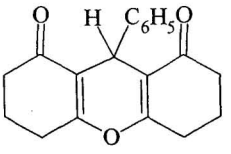
The formation of the dipolar ions **7** might arise by a known procedure[7,8] via the nucleophilic attack of the phosphorus atom of **1** on the arylidene carbon **4** (Scheme-2). Our results ruled out the possibility of the formation of compounds having the cyclic structure **9** since the latter would predict a negative value for the signal of the ^{31}P NMR corresponding to the phospholene structure[8,9] and would also predict a band in the IR spectrum ν= 1630 - 1690 cm^{-1} for the (C=C). Ramirez related the difficulty of **7** → **9** transformation of similar adducts to the considerable intramolecular overcrowding which is present in the triganol bipyramidal configuration of pentacovalent phosphorus compounds[9,10].



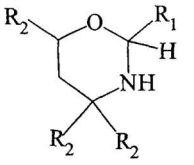
4 **7** **9**

Scheme-2

Next, we have investigated the behaviour of 2-benzylidene-1,3 cyclohexanedione **5** towards **1**. The reaction proceeded in benzene at room temperature whereby 1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroxanthene **10** was formed in a high yield (98 %).

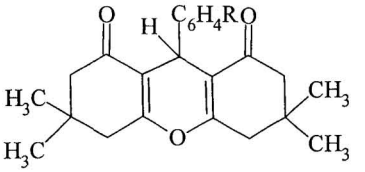


10



11: $R_1 = C_6H_5$, $R_2 = H$

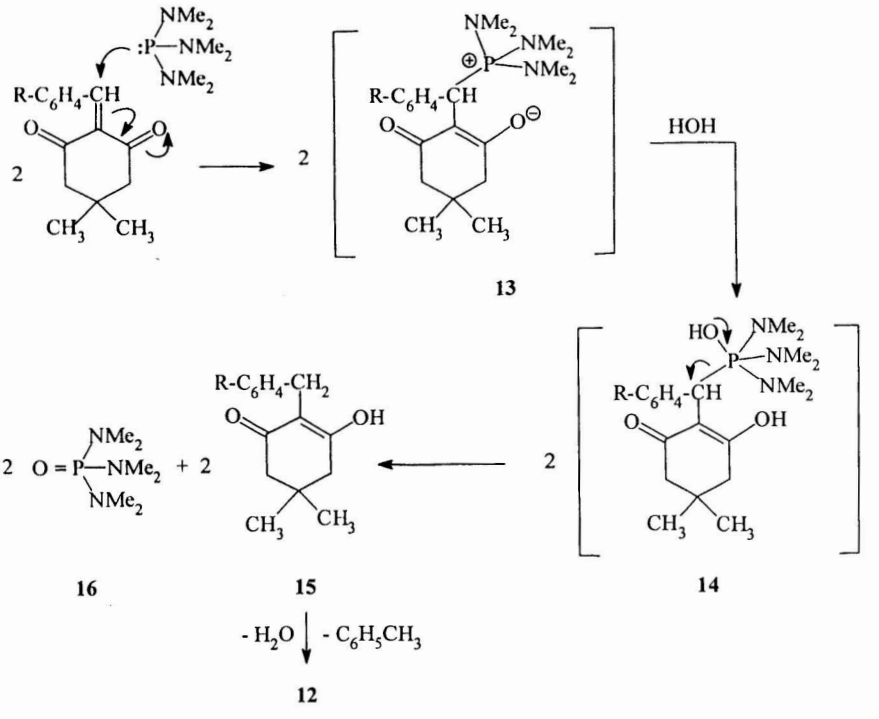
The structure of compound **10** was verified from analytical and spectroscopic evidences (c.f. experimental part). Moreover compound **10** was found identical (m.p. and mixed m.p.) with an authentic sample prepared by the reaction of 1,3-cyclohexanedione with 1,3-oxazinane **11**[11]. Similar xanthene derivatives were produced when 1,3-cyclohexanedione or methone (5,5-dimethyldihydro-resorcinol) reacted with aldehydes in the presence of base catalyst through a method for characterization of aldehydes[12,13]. Side reactions of these aldehydes, lack of convincing structural proofs for the products and suggestion of alternate structure for these products by other authors[14] prompted us to investigate the synthesis of some of these xanthene derivatives by this simple method i.e. via the reaction of some benzylidene derivatives with aminophosphine **1** utilizing 2-arylidene-5,5-dimethylcyclohexane-1,3-diones **6a-c** as starting materials whereby xanthenes **12a-c** were isolated and identified.



12a: R = H
b: R = Cl-*p*
c: R = NO_2-*p*

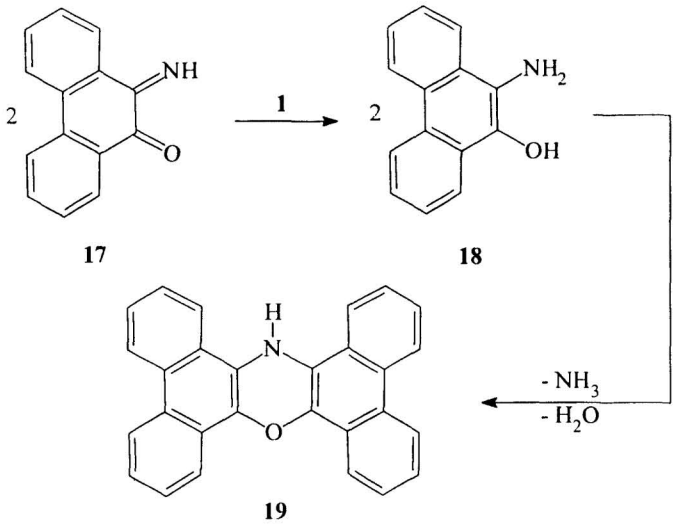
The structures of these compounds were verified using analytical and spectroscopic evidences (c.f. experimental part). A mechanism account for the formation of these compounds is depicted in Scheme-3.

It is probable that this reaction gives first the expected phosphonium dipolar ion **13**. This can add the elements of water that is unavoidably present in the medium yielding a transient intermediate **14**[15]. Charge delocalisation would cause phosphorus in this intermediate to act as a good leaving group[16], thereby producing **15** and hexamethylphosphono-amidate **16**. The formation of xanthene **12** was most probably due to the oxidative dimerization of **15** accelerated by the relatively high temperature at which the phosphonium ion **13** was generated[17]. Unstable phosphnium ions were previously noted to loose phosphoramidates and underwent several transformations[6,18].



Scheme-3

This recalls the formation of phenanthroxazine **19** produced from the reaction of phenanthrenequinonemonoimine **17** with aminophosphine **1** via 9-amino-10-phenanthrol **18**[4].



The stability of these adducts formed in the forementioned reactions could be explained in terms of the concept of " hard and soft bases " discussed by Pearson[19] and by Hudson[20, 21]. The arylidene carbon of **4** seems to be a softer acid than the arylidene carbon of **5** and **6**. Therefore, aminophosphine **1** which is a soft base attack **4** to produce a highly stable phosphonium dipolar ion **7**. On the other hand, **5** and **6** form relatively unstable phosphonium dipolar ions when attacked by the same soft base and decomposed to **15** and **16**.

The biological activity of the new synthesised compounds was studied. The test was carried out against *Aphis Craccivora* which is considered a serious pest infecting many crops in Egypt. The results indicated that compound **7a** and

The IR spectra were recorded in KBr with Pa 9712 IR spectrophotometer. The ^1H NMR spectra were run in $CDCl_3$ using TMS as an internal reference on a Varian EM-360 (60 MHz). The MS were taken on a Kratos (75 eV) Ms spectrometer. Elemental analyses were carried out by micro analytical center, Cairo University, Egypt.

The biological activity of the new compounds was tested against *Aphis Craccivora* (a serious pest infecting many crops in Egypt) at the laboratory of plant protection, Agriculture Research Center, Cairo, Egypt.

General Procedure:

To a solution of each of the arylidene derivatives[23] **4**, **5** or **6** (0.01 mole) in dry benzene (30 ml), tris(dimethylamino)phosphine (0.16 gm; 0.01 mole) was added. The reaction mixture was stirred for 1 hour and the mixture was left at room temperature for 3 hours whereby substantial mixture of products occurred as indicated by thin layer chromatography. The solid product formed was collected by filtration, dried and crystallized from a suitable solvent.

1-Tris[dimethylamino]benzylidene-3,5-dimethyl-6-oxy-2,4(3H,5H)-1-pyrimidene dione phosphobetain (7a) was formed as white crystals from toluene, **yield**: 95 % ; **mp**:195 - 196°C ; **IR** : 1488 (enolate carbonyl), 1324, 844 (P-N), 1590

(C=C) cm^{-1} ; **^{1}H NMR**: δ = 2.65 (d, 18H, $6CH_3$, J_{HP} = 9 Hz), 3.92 (s, 6H, $2CH_3$), 5.85 (d, 1H, CH, J_{HP} = 24 Hz), 7.15 & 7.32 (2m, 5H, aromatic protons) ; **^{31}P NMR**: δ = + 62.86; **MS**: m/z 407 (M^+), 244 (M^+ - $P(NMe_2)_3$, 56%), 163 ($P(NMe_2)_3$, 29%), 335 ($(C_{16}H_{24}N_4O_4P)^+$, 3.5%) ; **Found**: C, 56.18 ; H, 7.34 ; N, 17.19 ; P, 7.66. $C_{19}H_{30}N_5O_5P$. **Requires**: C, 56.02 ; H, 7.37 ; N, 17.19 ; P, 7.61 %.

1-Tris[dimethylamino]4-chlorobenzylidene-3,5-dimethyl-6-oxy-2,4(3H,5H)-1-pyrimidenedione phosphobetain (7b) was formed as white crystals from benzene, **yield**: 87 % ; **mp**: 213 - 214°C ; **IR** : 1488 (enolate carbonyl), 1324, 844 (P-N), 1586 (C=C) cm^{-1} ; **^{1}H NMR**: δ = 2.65 (d, 18H, $6CH_3$, J_{HP} = 9 Hz), 3.82 (s, 6H, $2CH_3$,), 5.85 (d, 1H, CH, J_{HP} = 24 Hz), 7.18 & 7.33 (2d, 4H, aromatic protons, J = 9 Hz, J_{AB} = 42 Hz) ; **MS**: m/z 441 (M^+), 278 ($(C_{16}H_{23}N_4O_2PCl)^+$, 57%), 163 ($P(NMe_2)_3$, 20.6%) ; **Found**: C, 51.60 ; H, 6.51 ; N, 15.80 ; P, 6.98. $C_{19}H_{29}N_5O_3PCl$. **Requires**: C, 51.64 ; H, 6.56 ; N, 15.85 ; P, 7.02 %.

1,8-dioxo-9-phenyl-1,2,3,4,5,6,7,8-octahydroxanthene (10) was formed as white crystals from benzene, **yield**: 98 % ; **mp**: 257 - 258°C (lit. mp. 255°C) ; **IR** : 1653 (C=O) cm^{-1} ; **^{1}H NMR**: δ = 1.95 (m, 4H, $2CH_2$), 2.28 (m, 4H, $2CH_2$), 2.55 (m, 4H, $2CH_2$), 4.75 (s, 1H, CH), 7.00 - 7.24 (m, 5H, aromatic protons) ; **MS**: m/z 294 (M^+, 89%), 277 ((M^+-17), 10.9%), 217 ((M^+-C_6H_5), 100%), 77 (C_6H_5, 5.44%) ; **Found**:

C, 77.50 ; H, 6.05. $C_{19}H_{18}O_3$. **Requires**: C, 77.55 ; H, 6.12 %.

1,8-dioxo-3,3,6,6-tetramethyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroxanthene (12a) was formed as white crystals from benzene, **yield**: 98 % ; **mp**: 206 - 207°C (lit. mp. 205°C)[11] ; **IR** : 1655 (C=O) cm^{-1} ; **^{1}H NMR**: δ = 0.93 (s, 6H, $2CH_3$), 1.04 (s, 6H, $2CH_3$), 2.13 (q, 4H, $2CH_2$)*, 2.40 (s, 4H, $2CH_2$), 4.68 (s, 1H, CH), 7.03 - 7.24 (m, 5H, aromatic protons) ; **MS**: m/z 350 (M^+, 89%), 333 ((M^+-OH), 4.16%), 273 ((M^+-C_6H_5), 100%), 77 (C_6H_5, 3.82%) ; **Found**: C, 78.80 ; H, 7.35. $C_{23}H_{26}O_3$. **Requires**: C, 78.85 ; H, 7.42 %.

* More lines than anticipated (quartet) due to ABX system resulted from the presence of carbonyl group adjacent to the methylene group[24].

1,8-dioxo-3,3,6,6-tetramethyl-9(*p*-chlorophenyl)-1,2,3,4,5,6,7,8-octahydro-xanthene (12b) was formed as white crystals from benzene, **yield**: 98 % ; **mp**: 227 - 228°C ; **IR** : 1653 (C=O) cm^{-1} ; **^{1}H NMR**: δ = 1.00 (s, 6H, $2CH_3$), 1.10 (s, 6H, $2CH_3$), 2.27 (q, 4H, $2CH_2$), 2.50 (s, 4H, $2CH_2$), 4.72 (s, 1H, CH), 7.26 (m, 4H, aromatic protons) ; **MS**: m/z 384 (M^+, 85%), 333 ((M^+-OH), 2.3%), 273 ((M^+-C_6H_4Cl), 100%), 111 (C_6H_4Cl 3.4%) ; **Found**: C, 71.70 ; H, 6.25. $C_{23}H_{25}O_3Cl$. **Requires**: C, 71.78 ; H, 6.29 %.

1,8-dioxo-3,3,6,6-tetramethyl-9(*p*-nitrophenyl)-1,2,3,4,5,6,7,8-octahydro-

xanthene (12c) was formed as yellow crystals from benzene, **yield**: 98 % ; **mp**: 212 - 213°C ; **IR** : 1664 (C=O) cm^{-1}; **^{1}H NMR**: δ = 0.87 (s, 6H, $2CH_3$), 1.01 (s, 6H, $2CH_3$), 2.06 (d, 2H, CH_2, J = 16 Hz), 2.26 (d, 2H, $2CH_2$, J = 16 Hz), 2.53 (s, 2H, CH_2), 2.55 (s, 2H, CH_2), 4.59 (s, 1H, CH), 7.44 (d, 2H, aromatic protons, J = 9 Hz), 8.09 (d, 2H, aromatic protons, J = 9 Hz) ; **MS**: m/z 395 (M^+, 100%), 378 ((M^+-OH), 68%), 273 ((M^+-$C_6H_4NO_2$), 76%) ; **Found**: C, 69.90 ; H, 6.40. $C_{23}H_{25}O_5N$. **Requires**: C, 69.87; H, 6.33 %.

Methods of Application of *A. Craccivora* :

Slide dip method which was developed by Voss (1961)[25] and later modified by Dittrich (1962)[26] was used in this study. Toxicants were prepared by dissolving 0.2 gm of each compounds in 10 ml acetone which were diluted by water 1 : 9 (this dilution by water did not cause any mortality in insects). *A.Craccivora* were transferred by the aid of a fine and three zero brush. Insects were first gently touched to withdraw their proboscis from leaves, then were transferred and affixed to double faced scotch tape tightly to slide on their dorsal part of the body. The slides were then dipped into the toxicant solution for 5 seconds and excess toxicant was taken off with filter paper. These individual adults were transferred to each slide. Each treatment was replicated 3 times realising 30 individuals per each concentration. The untreated check was maintained, using technique but the slides

were dipped in acetone. The slides were then put in a desiccator (63 - 73 RH) that was held in incubator 20°C for 2 hours before mortality counts were taken. Aphids unable to move normally were considered dead. The mortality counts were taken every 2 hours until 10 hours. The average percentages mortality were calculated (c.f. table-1, page 11).

References

1. Crutchfield M. M., Dungan C. H., Letcher J. H., Mark V., Van Wazer J. R. (1967), "*Topics in Phosphorous Chemistry*", Volume 5, John Wiley and Sons, New York.

2. Denny D. B., Pendse A. D. (1978), Phosphorus and Sulfur 5: 249.

3. Denny D. B., Felton S. M. (1968), J. Am. Chem. Soc. 90: 183.

4. Zayed M. F., El-Khoshnieh Y. O., Boulos L. S. (1991) Phosphorus, Sulfur and Silicon 62: 251.

5. Zayed M. F., El-Khoshnieh Y. O., Khir El-Din N., (1992), Egypt. J. Chem. 35: 515.

6. Ramirez F., Patwardhan A. V., Kugler H. J., Smith C. P. (1967), Tetrahedron 24: 2275.

7. Burgada R. (1964), C. R. Acad. Sci. 258: 4789; *ibid* (1967), Bull. Chem. Soc. Fr. 347:

8. Ramirez F. (1964), Pure Appl. Chem. 9: 337; *ibid* (1966), Bull. Chem. Soc. Fr. 2443:

9. Ramirez F., Patwardhan A. V., Kugler H. J., Smith C. P. (1967), J. Am. Chem. Soc. 89: 6276.

10. Hamilton W. C., LaPlaca S. J., Ramirez F. (1965), J. Am. Chem. Soc. 87: 127;

Hamilton W. C., LaPlaca S. J., Ramirez F., Smith C. P. (1967), *ibid* 89: 2268; Spartley R. D., Hamilton W. C., Ladell J. (1967), *ibid* 89: 2272

11. Singh K., Singh J., Singh H. (1996), Tetrahedron 52: 14273.

12. King F. E., Felton D. G. I. (1948), J. Chem. Soc. XX: 1371.

13. Horning E. C., Horning M. G. (1946), J. Org. Chem. 11: 95.

14. Chakravarti, Chattopadhyaya, Gosh. (1932), J. Indian Inst. Sci. A14: 141.

15. Ramirez F., Madon O. P., Smith C. P. (1965), J. Am. Chem. Soc. 87: 690.

16. Ramirez F., Bhatia S. B., Smith C. P. (1966), J. Org. Chem. 31: 4105.

17. Schonberg A., Awad W. I. (1947), J. Chem. Soc. 651.

18. Ramirez F., Gulati A. S., Smith C. P. (1967), J. Am. Chem. Soc. 89: 6283.

19. Pearson R. G. (1966), Science 151: 172; Pearson R. G., Songstad J. (1967), J. Am. Chem. Soc. 89: 1827.

20. Hudson R. F. (1965), "*Structure and Mechanism in Organic Chemistry*", Chapter 4 and 5, Academic Press, Inc. New York, N.Y.

21. Hudson R. F. (1962), Chimia 16: 173.

22. Burg A. B., Solta J. (1958), J. Am. Chem. Soc. 80: 1107; Van Wazer J. R., Callis C. F., Shoolery J. N., Jones R. C. (1956), *ibid* 78: 5715.

23. Saito K., Kambe S. Nakano Y. (1983), Synthesis 210.

24. Reisch J., Mahran M. R. (1977), Arch. Pharm. 310: 259; Grant P. K., Hills N. R. (1964), Aust. J. Chem. 17: 66; Cookson R. C., Grabb T. A., Frenkel J. J., Hudec M. J. (1966), Tetrahedron 7: 355.

25. Voss G., Azn. F. (1961), SchadlingsKunda, Jahrg 5: 76.

26. Dittrich J. (1962), J. Econ. Entomol. 55: 633.

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