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# Chemistry of Phosphorus Ylides. Part 22 [1]. Effect of Newly Synthesized Niclosamide Mannich Bases, Phosphopyranones, Phosphoranylidenes, and Oxaphosphinin on Some Metabolic Aspects of *Biomphalaria Alexandrina**

**Fouad M. Soliman**†, **Medhat M. Said,** and **Soher S. Maigali**

Department of Pesticide Chemistry, National Research Centre, Dokki, Cairo, Egypt

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**Summary.** Niclosamide reacts with secondary amines and formaldehyde under the condition of *Mannich* reaction, to give new *Mannich* bases. The reaction of these niclosamide *Mannich* bases with active phosphacumulene ylides affords the corresponding phenyliminopyranone, pyranone, and pyranthione, respectively. When *Wittig* reaction was carried out on the pyranone, using *p*-nitrobenzaldehyde, a new arylidene and triphenylphosphine oxide were obtained. On the other hand, stabilized phosphonium ylides affect the transylidation of niclosamide *Mannich* bases to the corresponding phosphoranylidenes. When diphenylmethylenetriphenylphosphorane reacts with a niclosamide *Mannich* base, an oxaphosphinin was obtained. The molluscicidal potency of the newly synthesized derivatives against *Biomphalaria alexandrina* was studied, too.

**Keywords.** Niclosamide; Phosphonium ylides; Pyranone derivatives; Transylidation; Phosphoranylidenes; Oxaphosphinin; Molluscicidal potency.

## Introduction

Niclosamide [5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide] (**1**) is the active ingredient of bayluscide, which has been used as molluscicide of great significance in the last decade [2]. It is widely used in control programmes, and is still the molluscicide of choice [2], since it is effective against most aquatic snails and its activity persists for several months [3]. Due to its high activity at

* Dedicated to Professor Dr. *Hans Jurgen Bestmann* on the occasion of his 79th birthday

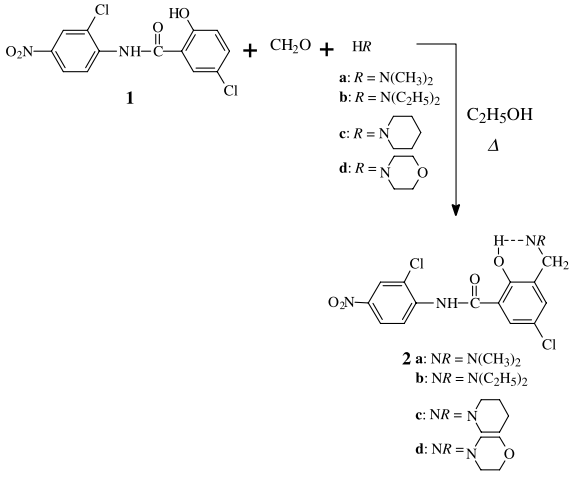
† Corresponding author. E-mail: solimanfma@hotmail.com

all stages of the snail life cycle [4], it has proved to be effective as molluscicidal [5], ovicidal [6], and anthelmintic agent [7]. Besides, niclosamide is introduced as an official drug in many pharmacopoeas [8]. Although certain algae, aquatic plants, are damaged, it does not adversely affect any economically important crop plants and shows no cumulative toxicity on animals [9].

Therefore, the present investigation has been aimed to synthesize new niclosamide *Mannich* base derivatives **2a**–**2d** and to react them with active nucleophilic phosphacumulene reagents, namely (*N*-phenyliminovinylidene)- (**3a**), (2-oxovinylidene)- (**3b**), and/or (2-thioxovinylidene)triphenylphosphorane (**3c**). These active phosphacumulene ylides are some of the most important phosphorus reagents, used for the synthesis of heterocyclic phosphorus compounds [10]. A comparative study on the behavior of the *Mannich* bases **2a**–**2d** towards the stabilized phosphonium ylides **8a**–**8f** or **12** and the iminophosphorane **14** has been performed, too.

## Results and Discussion

The *Mannich* reaction was carried out in neutral media using the bifunctional compound niclosamide (**1**) as substrate, formaldehyde and a base as the reagents. The bases employed were dimethyl-, diethylamine, piperidine, and morpholine. The *Mannich* bases produced **2a**–**2d** were isolated as yellow crystalline solid free bases. Only one product was isolated when either one or two mol-equivalents of the reagents were employed, which proves the presence of only one reactive centre. Absence of the OH absorption band in the IR of 5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxy-3-(dimethylaminomethyl)-benzamide (**2a**) is due to the presence of the intramolecular hydrogen bonding of the hydroxyl hydrogen with the basic nitrogen being a weak band which has been superimposed upon the NH absorption band near $\bar{\nu} = 3420\,\mathrm{cm}^{-1}$. The IR also shows the carbonyl amide at $1671\,\mathrm{cm}^{-1}$. The $^1$H NMR spectrum of compound **2a** shows bands at $\delta = 2.8$ ($2CH_3$, s), 4.2 ($CH_2$, s), 4.5 (NH, s) ppm exchangeable with $D_2O$. The aromatic protons appear at $\delta = 8.2$–$8.9$ (5H, aromatic, m) ppm. Moreover, the OH appears at $\delta = 15$ ppm

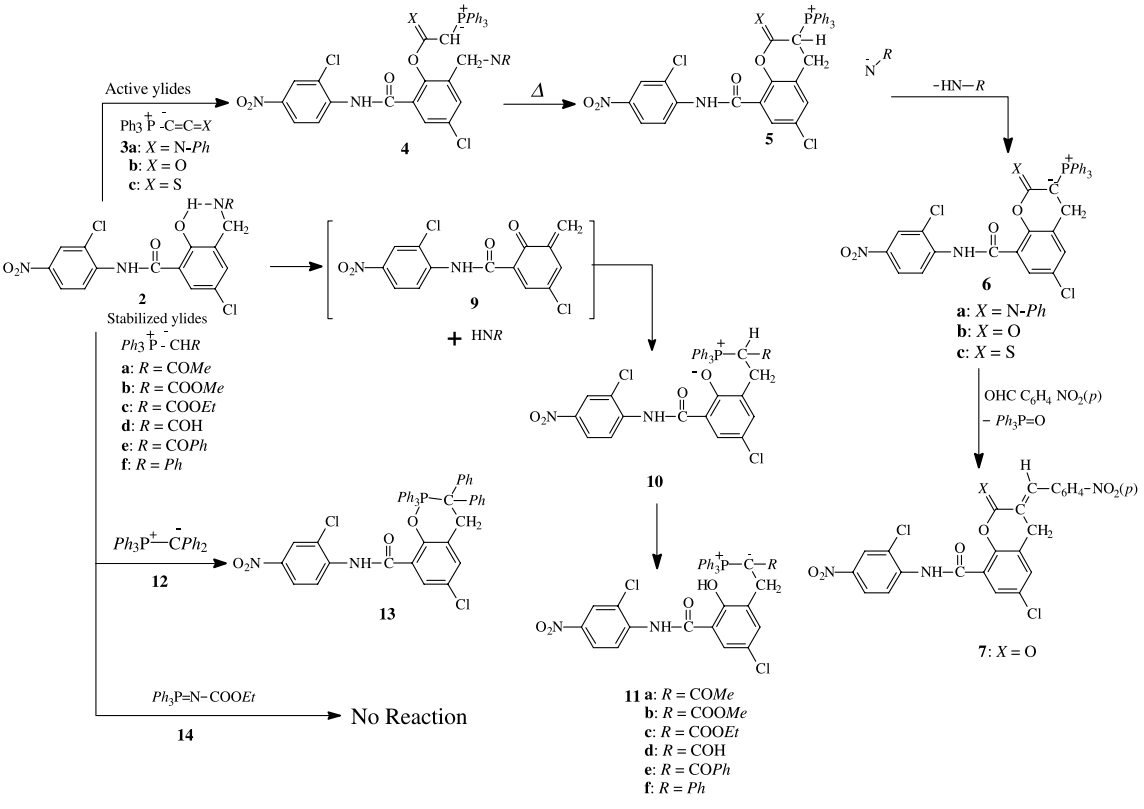



**Scheme 1**

(exchangeable with $D_2O$). Presence of carbonyl amide group in **2a** is also attested by a signal at $\delta = 169.72$ (C=O, NH) in its $^{13}C$ NMR spectrum, and in the mass spectrum $m/e$ is found at 384 ($M^+$) (Scheme 1).

When the active phosphacumulene ylides, namely, (*N*-phenyliminovinylidene)- (**3a**), (2-oxovinylidene)- (**3b**), and/or (2-thioxovinylidene)triphenylphosphorane (**3c**), reacted with niclosamide *Mannich* bases **2a**–**2d** in dry boiling toluene for 4 h, in case of **3a**, 6 h with **3b**, and for 8 h with **3c** by addition with cyclization, the corresponding phenyliminopyranone **6a**, pyranone **6b**, and thioxopyranone **6c** were formed. The structure of 6-chloro-*N*-(2-chloro-4-nitrophenyl)-3,4-dihydro-2-(phenylimino)-3-(triphenylphosphoranylidene)-2*H*-1-benzopyran-8-carboxamide (**6a**) was elucidated from elemental analysis and spectroscopic data. The $^1H$ NMR spectrum of **6a** shows signals at $\delta = 3.3$ ($CH_2$, d, due to P atom), 4.2 (NH, s) exchangeable with $D_2O$ and 7.3–8.3 (27H, aromatic, m) ppm. Its IR spectrum shows no OH absorption band which is exhibited by the *Mannich* bases **2**. Absorption bands are shown by compound **6a** at $\bar{\nu} = 3419$ (NH), 1674 (C=O, NH), 1610 (P=C) [11], and 1436 (P-aryl) $cm^{-1}$ [12]. The $^{31}P$ NMR of **6a** recordes a signal at $\delta = 16.82$ ppm, which supports the phosphoranylidene structure [13]. In the MS of **6a** the $m/e = 716$ ($M^+$) (Scheme 2).

Compounds **6a**–**6c** are equally obtained, irrespective whether one or two mol-equivalents of the phosphacumulenes **3a**–**3c** are used.




**Scheme 2**

When the Wittig reaction was carried out on pyranone derivative **6b** using *p*-nitrobenzaldehyde in dry boiling toluene for 8 h, the new exocyclic olefin, 6-chloro-*N*-(2-chloro-4-nitrophenyl)-3,4-dihydro-3-[(nitrophenyl)methylene]-2-oxo-2*H*-1-benzopyran-8-carboxamide (**7**), and triphenylphosphine oxide were obtained. The IR of **7** shows strong absorption bands at $\bar{\nu} = 3419$ (NH), 1739 (C=O, pyran), 1674 (C=O, NH) $cm^{-1}$, and lacks the presence of a peak arround 1440 (P–C) $cm^{-1}$. Its $^1$H NMR spectrum exhibits signals at $\delta = 4.2$ (CH2, s), 4.6 (NH, s) exchangeable with $D_2O$. In the MS of 7 the $m/e = 514$ ($M^+$) (Scheme 2).

We have also found that the niclosamide *Mannich* bases **2a**–**2d** reacted with the stabilized methylenetriphenylphosphoranes, namely, acetyl- (**8a**), methoxycarbonyl- (**8b**), ethoxycarbonyl- (**8c**), formyl- (**8d**), or benzoyl-methylenetriphenylphosphorane (**8e**), in dry boiling toluene for 10 h to give yellow crystalline phosphoranylidenes **11a**–**11e**. Compounds **11a**–**11e** are equally obtained whether one or two mol-equivalents of the *Wittig* reagents **8** were used with respect to one mol-equivalent of **2**. On the other hand, compound **2** reacted with phenylmethylenetriphenylphosphorane (**8f**) in boiling ethanol for 5 h to give the phosphorane **11f**. The IR spectrum of 5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxy-3-[3-oxo-2-(triphenylphosphoranylidene)butyl]benzamide (**11a**) taken as an example reveals the presence of absorption bands at $\bar{\nu} = 3544$ (OH), 3468 (NH), 1672 (C=O, $OCH_3$), 1662 (C=O, NH), and 1448 (P-aryl) $cm^{-1}$. Its $^1$H NMR spectrum showed signals at $\delta = 2.03$ ($CH_3$, s), 3.3 ($CH_2$, d), 5.08 (NH, s), and 12.3 (OH) ppm exchangeable with $D_2O$ and the aromatic protons appeared at $\delta = 7.2$–$8.4$ (20H, aromatic, m) ppm. Furthermore signals at $\delta = 169.45$ and 166.56 ppm were observed in the $^{13}$C NMR spectrum which were attributed to the carbonyl group. Moreover, a signal at $\delta = +23.34$ was found in the $^{31}$P NMR of **11a** (Scheme 2).

In the same sense, diphenylmethylenetriphenylphosphorane (**12**) reacted with niclosamide *Mannich* bases **2** in ethanol to give the oxaphosphinin **13**. The elemental analysis, IR, $^1$H, $^{13}$C and $^{31}$P NMR data agree with structure **13**. A signal at $\delta = +21.66$ was observed in the $^{31}$P NMR spectrum of compound **13**, which is in accordance with the oxaphosphinin structure [14] (Scheme 2).

The reactions of phosphinimines are often analogous to those of phosphonium ylides. But in their activity iminophosphoranes are inferior to phosphin alkylenes [15]. We have found that niclosamide *Mannich* bases **2a**–**2d** are inactive against ethoxycarbonyltriphenylphosphinimine (**14**), even if the reactants were boiled in toluene for a long time, they were recovered practically unchanged.

## *Biological Evaluation of the Tested Compounds*

### *Materials*

*Snails*: Field collected *B. alexandrina* snails (6–8 mm in diameter) were used to test the molluscicidal potency of the tested chemicals, new *Mannich* bases and organophosphorus niclosamide derivatives **2a**–**2d**, **6a**–**6c**, **11a**–**11f**, and **13**. Snails were obtained from Abu-Rawash, Giza, Egypt and were maintained in the laboratory in glass aerated aquaria, filled with dechlorinated water and kept at 25°C, fed fresh lettuce leaves *adlib* and left for 45 days to ensure that they were free from infection.

*Chemicals*: The tested molluscicides, namely, niclosamide *Mannich* bases and niclosamide organophosphorus derivatives, were prepared as mentioned in the text.

It is well known that organophosphorus compounds are the most important group of pesticides due to their rapid metabolism, absence of accumulation in the organism of animals, decomposition in the soil, and low chronic toxicity [16]. The use of molluscicides has always been considered to be a major supportive procedure in integrated schistosomiasis control [2]. Among synthetic compounds, niclosamide (the active ingredient of bayluscide) is still the molluscicide of choice, being highly active at all stages of the snail life cycle, effective on the schistosome larvae, and not toxic to humans, domestic animals, and crops [17].

Therefore, the molluscicidal potency of the newly synthesized *Mannich* bases **2a**–**2d** and organophosphorus niclosamide derivatives **6a**–**6c**, **11a**–**11f**, and **13** against *Biomphalaria alexandrina* snails, which is the specific intermediate host to *Schistosoma mansoni*, was studied and compared with bayluscide. The results showed that all the newly synthesized niclosamide derivatives **2a**–**2d**, **6a**–**6c**, **11a**–**11f**, and **13** have molluscicidal potency against *B. alexandrina* snails but most of them recorded higher $LC_{50}$ values, except compound **11f** which showed a lower value ($LC_{50}$ of 0.0004 $g/dm^3$) compared to bayluscide ($LC_{50}$ of 0.0005 $g/dm^3$) [9].

The presence of an OH group in the ortho position of niclosamide (**1**) is responsible for its toxicity against *B. alexandrina* snails [18], due to the formation of an intramolecular hydrogen bond with the oxygen of the carbonyl group [18]. This hydrogen bond reduced the polarity of the carbonyl group by decreasing the partial negative charge on the oxygen atom of this group. This in turn increases the chance of bonding with aminoacids of snail proteins most of which are enzymes.

The variable reported molluscicidal activity of the tested newly synthesized compounds could be explained on the basis that all of them still have the reactive

**Table 1.** Molluscicidal potency of the tested compounds against *B. alexandrina* snails

| Cmp. no. | $LC_5$ $g/dm^3$ | $LC_{10}$ $g/dm^3$ | $LC_{50}$ $g/dm^3$ | $LC_{90}$ $g/dm^3$ |
|---|---|---|---|---|
| **1** | – | – | 0.0005 | – |
| **2a** | 0.103 | 0.0106 | 0.0301 | 0.06 |
| **2b** | 0.0101 | 0.0106 | 0.0409 | 0.10 |
| **2c** | 0.009 | 0.0108 | 0.019 | 0.0293 |
| **2d** | 0.005 | 0.0101 | 0.030 | 0.08 |
| **6a** | 0.00098 | 0.0021 | 0.009 | 0.0303 |
| **6b** | 0.0022 | 0.0044 | 0.0077 | 0.021 |
| **6c** | 0.00097 | 0.0012 | 0.0041 | 0.007 |
| **11a** | 0.002 | 0.0036 | 0.0052 | 0.0076 |
| **11b** | 0.0104 | 0.0202 | 0.030 | 0.05 |
| **11c** | 0.006 | 0.0109 | 0.0208 | 0.0404 |
| **11e** | 0.0018 | 0.0021 | 0.0034 | 0.0056 |
| **11f** | 0.0009 | 0.00012 | 0.0004 | 0.0006 |
| **11d** | 0.0024 | 0.003 | 0.007 | 0.0098 |
| **13** | 0.0009 | 0.0009 | 0.0019 | 0.004 |

$LC_X$: The concentration at which X% of the populations died

groups of the niclosamide nucleus with different chemically reactive phosphorus moieties added, most of them are organophosphorus groups.

On the other hand, the biochemical investigation has been performed on snail metabolism. The most potent organophosphorus molluscicides **11f**, **11e**, **13**, and **6c**, showing $LC_{50}$ values between 0.0004–0.0041 $g/dm^3$ were selected for this study. We found that these four organophosphours niclosamide derivatives have an inhibitory effect on the most important glycolytic enzymes in tissue homogenates of *B. alexandrina* snails, as hexokinase (HK), pyruvate kinase (PK), and phosphoglucoisomerase (PGI). Although bayluscide showed a slightly higher inhibitory effect on hexokinase (HK) and glucose phosphate isomerase (PGI) compared to the organophosphorus derivatives **11f** and **13**, the four niclosamide derivatives **6c**, **11e**, **11f**, and **13** showed a remarkably higher inhibition rate of pyruvate kinase. Pyruvate kinase is an enzyme of critical importance for schistosome parasites, as homolactate fermenter within snail tissues [19].

Inhibition of hexokinase, pyruvate kinase, and glucose phosphate isomerase with the four tested compounds **6c**, **11e**, **11f**, and **13** and of hexokinase together with glucose phosphate isomerase only with bayluscide could be effective in decreasing the compatibility of *B. alexandrina* snails and hence *S. mansoni* infection.

It was found that the sublethal and less pollutant concentrations, $LC_5$ (1/10 of $LC_{50}$) were able to affect the compatibility of *B. alexandrina* to parasitic infection.

**Table 2.** Levels of hexokinase (HK), pyruvate kinase (PK), and glucose phosphate isomerase (PGI) in field collected, control and molluscicide-treated snails

| Snail group | Enzymes | HK | PK | PGI |
|---|---|---|---|---|
| Control | Mean ± S.D. | 9.8 ± 2.7 | 1.8 ± 0.62 | 1.47 ± 0.48 |
| **1**-Bayluscide treated | Mean ± S.D. | 3.9 ± 0.58 | 1.51 ± 0.52 | 0.89 ± 0.21 |
| | $P<$ | 0.01 | n.s. | 0.01 |
| | % change | 59.4 | 11.11 | 39.17 |
| **6c**-Treated | Mean ± S.D. | 2.6 ± 0.82 | 0.98 ± 0.138 | 1.27 ± 0.32 |
| | $P<$ | 0.001 | 0.01 | n.s. |
| | % change | 72.9 | 44.4 | 13.6 |
| **11e**-Treated | Mean ± S.D. | 8.0 ± 0.49 | 0.46 ± 0.08 | 1.29 ± 0.19 |
| | $P<$ | 0.05 | 0.001 | n.s. |
| | % change | 16.6 | 72.2 | 12.24 |
| **11f**-Treated | Mean ± S.D. | 3.7 ± 1.6 | 0.39 ± 0.29 | 1.19 ± 0.38 |
| | $P<$ | 0.01 | 0.01 | n.s. |
| | % change | 61.4 | 77.8 | 19.0 |
| **13**-Treated | Mean ± S.D. | 9.4 ± 0.32 | 0.304 ± 0.1 | 1.17 ± 0.42 |
| | $P<$ | n.s. | 0.001 | n.s. |
| | % change | 2.08 | 83.3 | 20.4 |

– Values are means ± S.D. of four independent experiments
– $P<0.05 \equiv$ significant, $P<0.01 \equiv$ highly significant, n.s. = no significance
– Enzymatic activities are expressed as mol/min/g tissue
– S.D. = Standard deviation
– % change = Percent change from control group

Snails treated with $LC_5$ of the four tested compounds **6c**, **11e**, **11f**, and **13** were metabolically disturbed and render less suitable for the development of the parasite (*S. mansoni* larvae) within snails tissue compared to bayluscide (**1**). This inspires more hope for their application in the intervention of schistosomiasis, especially, when used at their sublethal concentrations ($LC_5$).

## Conclusion

The reaction of the bifunctional *Mannich* base derivatives **2a**–**2d** with phosphacumulene ylides **3a**–**3c** represents a new approach to the construction of new heterocycles. These phosphonium ylides react only with the phenolic OH group rather than the NH group of the *Mannich* bases **2a**–**2d**, to give first the phosphonium ylides **4**, which are transformed into **5** by nucleophilic substitution of the dialkylamine anion. Elimination of the amine anion from **5** results in the formation of phenylimino-, oxo-, and thioxophosphoranylidene benzopyran carboxamide derivatives **6a**–**6c**. On the other hand, transylidation of niclosamide *Mannich* base derivatives **2a**–**2d**, using the stabilized methylenetriphenylphosphoranes **8a**–**8f** or **12**, results in the expulsion of the amine, with the formation of the unstable quinone-methylene **9**. The latter reacts with the phosphoranes **8** by nucleophilic addition to the methylene group giving the dipolar adduct **10**. The *R* moiety in **10**, which is electron withdrawing in nature, would stabilize formation of the new alkylated phosphoranylidene benzamide derivatives **11** *via* migration of the $\alpha$-proton to the electron rich centre of the molecule. Moreover, the quinone-methylene **9** affords directly the oxaphosphinin **13**, in case, when diphenylmethylenetriphenylphosphorane (**12**) reacts with niclosamide *Mannich* bases **2**. No reaction was observed when the iminophosphorane **14** was allowed to react with niclosamide *Mannich* bases **2** under different reaction conditions.

## Experimental

All melting points are uncorrected. The solvents were dried and distilled. Reactions were carried out under nitrogen atmosphere. Elemental analyses were carried out at the "Microanalysis Department", National Research Centre; their results were in agreement with the calculated values. The IR spectra were measured in KBr on a Perkin-Elmer infracord Spectrometer Model 157 (Grating). The $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Spectrometer at 90 (22.5) MHz, using *TMS* as an internal reference. $^{31}P$ NMR spectra were run, relative to external $H_3PO_4$ (85%), with a Varian FT-80 Spectrometer at 36.5 MHz, mass Spectra were obtained on a Varian MATCH-4B instrument.

### *Mannich Reaction on Niclosamide (5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide; **1**)*

*General Procedure*: An aqueous solution of formaldehyde (40%, 0.01 mol) was added dropwise with stirring to niclosamide (**1**) [20] and the amine (0.011 mol) in about 40 $cm^3$ of ethanol while maintaining the temperature below 10°C. The reaction mixture was then boiled under reflux for 2 h and left overnight at room temperature. After removing the volatile materials under reduced pressure, the product was isolated and recrystallized from ethanol. When the above described procedure was

**Table 3.** Physical and analytical data for niclosamide *Mannich* bases **2a–2d**, phenyliminopyranone **6a**, pyranone **6b**, thioxopyranone **6c**, exocyclic olefin **7**, phosphoranylidenes **11a–11f**, and oxaphosphinin **13**

| Cpd. no. | Mol. Wt/g mol$^{-1}$ | Formula | Mp/°C | Yield/% | Solvent for crystallization |
|---|---|---|---|---|---|
| **2a** | 384 | $C_{16}H_{15}N_3O_4Cl_2$ | 228 | 92% | Ethanol |
| **2b** | 412 | $C_{18}H_{19}N_3O_4Cl_2$ | 340 | 90% | Ethanol |
| **2c** | 424 | $C_{19}H_{19}N_3O_4Cl_2$ | 232 | 87% | Ethanol |
| **2d** | 426 | $C_{18}H_{17}N_3O_5Cl_2$ | 300 | 95% | Ethanol |
| **6a** | 716 | $C_{40}H_{28}N_3O_4PCl_2$ | 244 | 87% | Chloroform/Pet.ether |
| **6b** | 641 | $C_{34}H_{23}N_2O_5PCl_2$ | 264 | 85% | Ethyl acetate/Pet.ether |
| **6c** | 657 | $C_{34}H_{23}N_2O_4SPCl_2$ | 252 | 83% | Chloroform/Pet.ether |
| **7** | 514 | $C_{23}H_{13}N_3O_7Cl_2$ | 214 | 38% | Chloroform/Light pet. |
| **11a** | 657 | $C_{35}H_{27}N_2O_5PCl_2$ | 220 | 79% | Ethyl acetate/*n*-Hexane |
| **11b** | 673 | $C_{35}H_{27}N_2O_6PCl_2$ | 228 | 80% | Acetone/*n*-hexane |
| **11c** | 657 | $C_{36}H_{29}N_2O_6PCl_2$ | 188 | 79% | Benzene/Pet.ether |
| **11d** | 643 | $C_{34}H_{25}N_2O_5PCl_2$ | 245 | 78% | Methylene chloride/*n*-Hexane |
| **11e** | 719 | $C_{40}H_{29}N_2O_5PCl_2$ | 186 | 82% | Chloroform/*n*-Hexane |
| **11f** | 703 | $C_{40}H_{29}N_2O_4PCl_2$ | 215 | 76% | Ethyl acetate/*n*-Hexane |
| **13** | 780 | $C_{46}H_{34}N_2O_4PCl_2$ | 205 | 74% | Methylene chloride/*n*-Hexane |

performed using two mol-equivalents of both the base and aqueous formaldehyde no change in the nature of the products was observed and the corresponding niclosamide *Mannich* bases **2a–2d** were obtained, respectively.

### *The Reaction of Niclosamide Mannich Base **2c** with Phosphacumulenes **3a–3c** Preparation of Phenyliminopyranone **4a**, Pyranone **4b**, and Thioxopyranone **4c***

*General Procedure*: To a solution of niclosamide *Mannich* base **2c** (0.01 mol) in 20 cm$^3$ of dry toluene, was added a solution of (*N*-phenyliminovinylidene)- (**3a**) [21], (2-oxovinylidene)- (**3b**) [22], and (2-thioxovinylidene)triphenylphosphorane (**3c**) [22] (0.011 mol) in 30 cm$^3$ of dry toluene. The reaction mixture was refluxed for 4 h when **3a** was used, 6 h in case of **3b**, and for 8 h with **3c**. After the solvent had been distilled off under reduced pressure, the residue was crystallized from the appropriate solvent. Yields, analytical and spectroscopic data are presented in Tables 3 and 4.

When the reaction was performed using one mol-equivalent of niclosamide *Mannich* base derivative **2d** and the phosphacumulenes **3a–3c**, the same phenyliminopyranone **6a**, pyranone **6b**, and thioxopyranone **6c** were obtained irrespective of the amine used.

When the reaction was repeated using one mol-equivalent of niclosamide *Mannich* base **2c** and two mol-equivalents of the phosphacumulenes **3a–3c**, the same products **6a–6c** were isolated, too.

### *The Reaction of Pyranone **6b** with p-Nitrobenzaldehyde*

A mixture of the pyranone derivative **6b** (0.64 g, 0.001 mol) and *p*-nitrobenzaldehyde (0.17 g, 0.0011 mol) in dry toluene (20 cm$^3$) was refluxed for 8 h. Toluene was distilled off and the residue was crystallized from benzene to give the exocyclic olefin **7**, 6-chloro-*N*-(2-chloro-4-nitrophenyl)-3,4-dihydro-3-[(nitrophenyl)methylene]-2-oxo-2*H*-1-benzopyran-8-carboxamide (**7**) as pale greenish crystals.

The benzene filtrate yielded upon concentration and addition of *n*-hexane colourless crystals of triphenylphosphine oxide, mp and mixed mp 151°C [23] (62%).

**Table 4.** Spectroscopic data (IR & NMR) for compounds **2b–2d**, **6b–6c**, **11b–11f**, and **13**

| Cpd. no | IR: $\bar{\nu}/cm^{-1}$ | NMR: $\delta$/ppm | | |
|---|---|---|---|---|
| | | $^{1}$H NMR | $^{31}$P NMR | $^{13}$C NMR |
| **2b** | 3421 (NH), 1670 (C=O, amide) | 1.3 (t, 3H, $CH_2\underline{CH_3}$)<br>3.1 (s, 2H, $CH_2$)<br>4.3 (q, 2H, $\underline{CH_2}CH_3$)<br>4.5 (s, 1H, NH)<br>7.5–8.3 (m, 5H, Ar)<br>15 (s, 1H, OH) | – | 168.54 (C=O, amide) |
| **2c** | 3422 (NH), 1655 (C=O, amide) | 3.8 (s, 2H, $CH_2$)<br>4.1 (s, 1H, NH)<br>7.1–8.7 (m, 15H, Ar)<br>8.3 (s, 1H, OH) | – | – |
| **2d** | 3423 (NH), 1671 (C=O, amide) | 3.5 (s, 2H, $CH_2$)<br>4.4 (s, 1H, NH)<br>7.2–8.2 (m, 13H, Ar)<br>8.6 (s, 1H, OH) | – | – |
| **6b** | 3429 (NH), 1731 (C=O, pyran), 1645 (C=O, amide), 1439 (P-aryl) | 3.3 (d, 2H, $CH_2$)<br>5.3 (s, 1H, NH)<br>7.3–8.4 (m, 20H, Ar) | 21.26 | 165 (C=O, amide)<br>185 (C=O, pyran) |
| **6c** | 3427 (NH), 1635 (C=O, amide), 1439 (P-aryl), 1240 (C=S) | 3.21 (d, 2H, $CH_2$)<br>3.9 (s, 1H, NH)<br>7.2–8.4 (m, 20H, Ar) | 25.82 | – |
| **11b** | 3456 (OH), 3118 (NH), 1674 (C=O, ester), 1662 (C=O, amide), 1447 (P-aryl) | 2.7 (s, 3H, $OCH_3$)<br>3.8 (d, 2H, $CH_2$)<br>4.5 (s, 1H, NH)<br>7.0–8.4 (m, 20H, Ar)<br>12.1 (s, 1H, OH) | 21.55 | 165.72<br>163.52 (C=O) |
| **11c** | 3446 (OH), 2942 (NH), 1671 (C=O, ester), 1663 (C=O, amide), 1448 (P-aryl) | 2.4 (d, 2H, $CH_2$)<br>2.8 (t, 3H, $CH_2\underline{CH_3}$)<br>3.82 (q, 2H, $\underline{CH_2}CH_3$)<br>7.1–8.3 (m, 20H, Ar)<br>11.28 (s, 1H, OH) | 20.66 | – |
| **11d** | 3484 (OH), 3120 (NH), 1733 (CHO), 1661 (C=O, amide), 1447 (P-aryl) | 2.5 (d, 2H, $CH_2$)<br>4.3 (s, 1H, NH)<br>7.3–8.4 (m, 20H, Ar)<br>12 (s, 1H, OH) | 22.55 | – |
| **11e** | 3566 (OH), 3488 (NH), 1673 (C=O, ester), 1660 (C=O, NH), 1434 (P-aryl) | 2.33 (s, 1H, NH)<br>3.81 (d, 2H, $CH_2$)<br>7.3–8.2 (m, 25H, Ar)<br>11.9 (s, 1H, OH) | 22.23 | 183.25<br>168.62 (C=O) |
| **11f** | 3421 (OH), 2364 (NH), 1664 (C=O), 1436 (P-aryl) | 2.8 (d, 2H, $CH_2$)<br>4.7 (s, 1H, NH)<br>8.0 (s, 1H, OH)<br>7.2–8.1 (m, 25H, Ar) | 22.03 | 169.74 (C=O) |
| **13** | 3558 (NH), 1663 (C=O), 1447 (P-aryl) | 2.4 (d, 2H, $CH_2$)<br>4.1 (s, 1H, NH)<br>7.0–8.0 (m, 30H, Ar) | 21.66 | 169.73 (C=O) |

*The Reaction of Niclosamide Mannich Base **2c** with the Stabilized Phosphonium Ylides **8a–8e**. Preparation of the Phosphoranylidenes **11a–11e***

*General Procedure*: To a solution of niclosamide *Mannich* base **2c** (0.01 mol) in 20 $cm^3$ of dry toluene, was added a solution of the methylenetriphenylphosphoranes **8a–8e** [24–26] (0.01 mol) in 30 $cm^3$ of dry toluene and the reaction mixture was refluxed for 10 h. After the solvent was distilled off, the residue was crystallized from the appropriate solvents. Yields, analytical and spectroscopic data are presented in Tables 3 and 4.

*The Reaction of Niclosamide Mannich Base **2c** with Phenylmethylenetriphenylphosphorane (**8f**) and Diphenylmethylenetriphenylphosphorane (**12**). Synthesis of the Phosphoranylidene **11f** and Oxaphosphinin **13***

A solution of the *Wittig* reagents **8f** [27] or **12** [28] (0.01 mol) in 20 $cm^3$ of absolute ethanol was treated with 20 $cm^3$ of a 0.01 *M* solution of sodium ethoxide in ethanol with continuous stirring, where the orange colour of the phosphorane appeared immediately. The phosphorane solution was then added to a solution of the *Mannich* base **2c** in 30 $cm^3$ of absolute ethanol and the reaction mixture was stirred and boiled for 2 h at 25°C. Ethanol was distilled off under reduced pressure and the remaining precipitate was extracted with dry benzene. After the benzene extract had been concentrated, the phosphoranylidene **11f** and the oxaphosphinin **13** were precipitated. Yields, analytical and spectroscopic data are presented in Tables 3 and 4.

*Attempted Reaction of Niclosamide Mannich Base **2c** with Ethoxycarbonyltriphenylphosphinimine (**14**)*

No reaction was observed between the niclosamide Mannich base **2** and the phosphinimine **14** [29], even if the reactants were boiled in *THF* or toluene for a long time, they were recovered unchanged.

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