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Synthesis, Characterization and Antimicrobial Evaluation of New *cis*-Bicyclo [3.3.0] octane-3,7-dione Derivatives

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NEWLY synthesized bicyclo[3.3.0]octane-3,7-dione derivatives were evaluated for their antimicrobial activity. These compounds were prepared from reactions of *cis*-bicyclo[3.3.0]octane-3,7-dione with stabilized phosphorus ylides, (2-oxovinylidene)triphenylphosphorane, tris(dialkylamino)phosphines, as well as with Lawesson's and Japanese reagents and their structures were confirmed on the basis of spectroscopic and elemental analyses.

Keywords: Octanedione, Phosphorus reagents, Antimicrobial activity.

Cis-Bicyclo[3.3.0]octane-3,7-dione (1) is composed of two fused symmetrical cyclopentanone units and it is easily prepared by the Wiess reaction [1-3]. It has several attractive features as a raw material for the synthesis of cyclopentanoid compounds, whether natural or non-natural [4-9]. Our work in organophosphorus chemistry [10-13], raised the interest in the synthesis of new olefinic and phosphorus compounds incorporating these significant units through the reaction of 1 with *N*-(triphenylphosphoranylidene) aniline (2a), cyclopenta-2,4-dien-1-ylidene(triphenyl)-λ^5-phosphane (2b), 2-(triphenylphosphanylidene) acetonitrile (2c), (dibromomethylene)triphenylphosphorane (2d), (2-oxovinyledene) triphenylphosphrane (2e), tris(dialkylamino) phosphines 3a,b as well as with Lawesson's and Japanese reagents 4a,b (Scheme 1). The aim of present study is to identify the preferred site of attack by these reagents on 1 and to synthesize new products with expected antimicrobial activity.

Results and Discussion

Chemistry

When dione 1 was refluxed with three mole equivalents of *N*-(triphenylphosphoranylidene) aniline (2a) in toluene 2h, a mixture of *N*,*N'*-(tetrahydropentalene-2,5(1*H*,3*H*)-diylidene)dianiline (6a) and 5-(phenylamino)-

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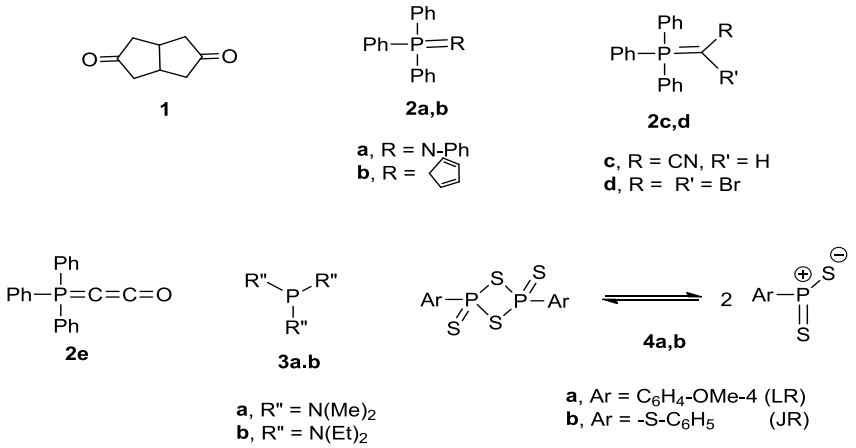
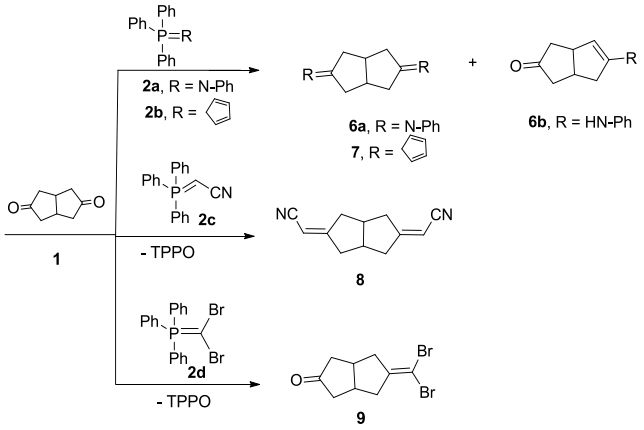
3,3a,6,6a-tetrahydropentalen-2(1*H*)-one (6b) was obtained. Triphenylphosphorane oxide (TPPO) was also isolated from the reaction medium and identified (Scheme 2). Moreover, when dione 1 was treated with two mole equivalents of ylide 2b in boiling toluene, 2,5-di(cyclopenta-2,4-dien-1-ylidene)octahydropentalene (7) [14] together with triphenylphosphane oxide (TPPO) were isolated and identified (Scheme 2).



Scheme 1

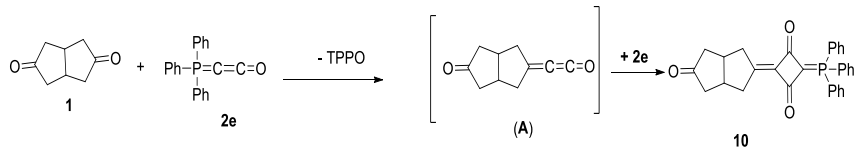


Scheme 2

Next, when dione 1 was refluxed with two mole equivalents of 2-(triphenylphosphoranylidene) acetonitrile (2c), in toluene 4h, tetrahydropentalene-2,5 (1*H*,3*H*)-diylidene)diacetonitrile (8) was isolated. Triphenylphosphorane oxide (TPPO) was also isolated from the reaction medium

and identified (Scheme 2). The structure of compound 8 was inferred from elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR, and MS data (*cf.* Experimental Section). Also, When 2d was allowed to react with one mole equivalent of 1 in dichloromethane at room temperature for 8h, 5-(dibromomethylene) hexahydropentalen-2(1*H*)-one (9) was obtained in good yield together with triphenylphosphorane oxide (Scheme 2).

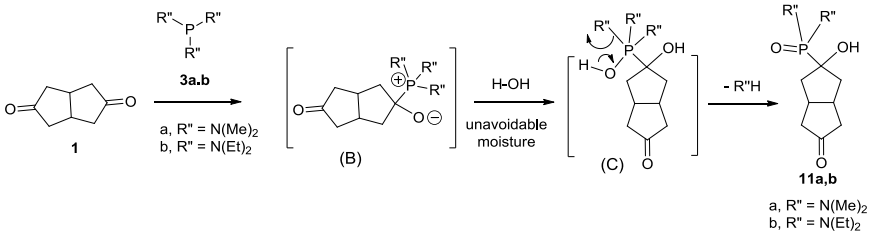
Also, the 4-(triphenylphosphoranylidene)cyclobutane-1,3-dione derivative (10) was obtained when two moles of phosphacumelene ylide (2e) were refluxed in dry toluene 8h with one mole of dione 1 (Scheme 3).



Scheme 3

A possible explanation for the formation of 2-(5-oxohexahydropentalen-2(1*H*)-ylidene)-4-(triphenylphosphoranylidene)cyclobutane-1,3-dione (10) is depicted in Scheme 3. This involves incipient attack of the carbanion center in the phosphacumelene centre 2e on the carbonyl group in 1 to give unstable oxaphosphetane [15-17] which decomposes to TPPO and the unstable ketene (A)[18]. A second ylide molecule of 2e is then added to the ketene to afford compound 10 in a crystalline form (Scheme 3). The structure of compound 10 was deduced from elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR, and MS data (*cf.* Experimental Section).

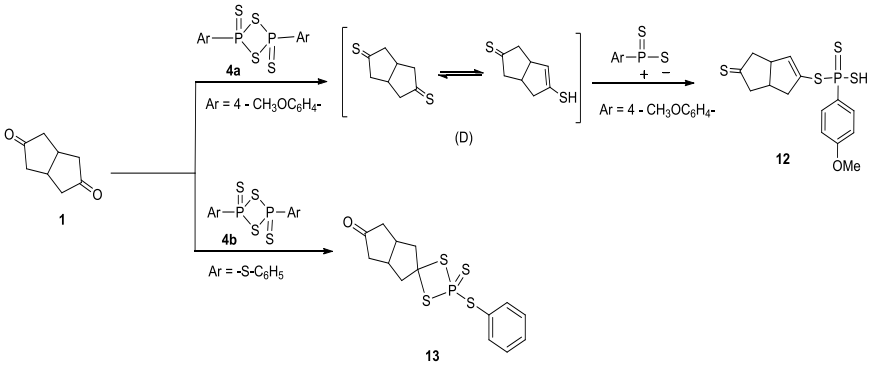
Furthermore, the behavior of dione 1 towards tris(dialkylamino)phosphines 3a,b was also examined in our study. We have found that 1 reacted with one mole equivalent of 3a or 3b in refluxing toluene for 12h to give 5-(bis(dialkylamino)phosphono)-5-hydroxyhexahydropentalen-2(1*H*)-one (11a,b, Scheme 4).



Scheme 4

The formation of the new phosphonate products 11a,b is based upon the conventional known mechanism [19-21] and their structures are designed with reference to their spectral data (*cf.* Experimental Section).

Moreover, the reaction of dione 1 towards bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide (4a, Lawesson's reagent) in dry toluene using 1:2 molar ratio at the reflux temperature was also studied, to give 5-thioxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl hydrogen (4-methoxyphenyl) phosphonotrithioate (12) in a 50% yield (Scheme 5). The structure of 12 was confirmed by analytical and spectroscopic data (*cf.* Experimental Section).



Scheme 5

Compound 12 gave correct elemental analysis and its IR spectrum showed peaks at 535 (P=S) [22], 1178 (P-C, aryl) [23], SH band at 2373, and CH aliphatic at 2954 cm^{-1} [24]. Its ^{1}H NMR showed signals at 3.76 (s, OCH_3), 2.36 (d, SH, exchangeable with D_2O). The ^{31}P NMR shift for compound 12 was δ = 19.7 ppm and the mass spectrum showed an ion peak at *m/z* = 372 [M^+] (Scheme 5). Formation of product 12 can be interpreted in terms of thionation [25] of compound 1 with LR to provide the intermediate (D). This step followed by addition of another molecule of LR *via* nucleophilic attack of the sulfur anion of the thio-octane on the electron deficient center in the monomeric species of 4a followed by migration of the proton to the electron rich center of the molecule (Scheme 5).

Moreover, when dione 1 was reacted with Japanese reagent 4b in refluxing toluene for 1h, the corresponding 2-(phenylthio)tetrahydro-1'*H*-spiro[[1,3,2] dithiaphosphetane-4,2'-pentalen]-5'(3'*H*)-one 2-sulfide (13) was obtained in a 40% yield (Scheme 5). The elemental microanalyses and spectroscopic data (IR, ^{1}H, ^{13}C, ^{31}P NMR, and MS data) agreed with structure of 13. Structure 13 was confirmed by the presence of one signal at 78.3 ppm (s) in its ^{31}P NMR spectrum. Moreover, ^{13}C NMR of it revealed the presence of signals at 22.8, 30.1, 37.2, 41.4 (4 CH_2), 51.1, 53.7 (2 CH), 128.7, 128.9, 135.9, 136.2 (aromatic C-H), 129.1 (d, $^{2}J_{CP}$ = 22.0 Hz, P-S-C-Ph), and at 218.0 (C=O).

Biological evaluation

Antimicrobial activity of six compounds were investigated, Table 1. The obtained results showed that compound 13 is the most active against both Gram positive and Gram negative bacteria. In addition, it exhibited moderate antifungal

activity against the *Candida albicans* reaching about 16% of the reference antibiotics [Nizo-arm (antifungal) and Cephradine (antimicrobial)]. In the same time, the starting material **1** showed no antimicrobial activity.

TABLE 1. The antibacterial and antifungal activities of some synthesized compounds.

Compound No.	Inhibition zone diameter mm/mg sample					
	Microorganism					
	Gram +ve bacteria		Gram -ve bacteria			Fungi
	B. cereus	*St. aureus*	*E. coli*	*P. aeruginose*	*Sa. typhimurium*	*C. Albicans*
1	0.0	0.0	0.0	0.0	0.0	0.0
8	11	10	10	15	10	10
9	13	15	11	15	9	10
10	15	12	12	12	10	12
12	10	0.0	8	12	0.0	0.0
13	**10**	**11**	**25**	**20**	**15**	**16**
Reference antibiotic.*	30	30	20	50	40	44

B.: Bacillus, St: Staphylococcus, E.: Escherichia, P.: Pseudomonas, Sa: Salmonella, C.: Candida.

**Reference antibiotics are Nizo-arm (antifungal) and Cephradine (antimicrobial)*

Based on these data, further experiments were done to determine the least inhibitor concentration (LTC) of compound **13** against all tested microorganisms in the range of 5*µ*L–25*µ*L. Table 2 represents the experimental results. LTC at 20*µ*L was found in case of *Bacillus cereus, Escherichia coli, Pseudomonas aeruginose, Salmonella typhimurium, and Candida albicans,* while LTC was found (only 15*µ*L) against *Staphylococcus aureus.* These results are of good biological and applicable values for antimicrobial pathogens research.

TABLE 2. The antibacterial and antifungal activities of compound 13 (LTC).

Concentration	Inhibition zone diameter mm/mg sample					
	Microorganism					
	Gram +ve bacteria		Gram -ve bacteria			Fungi
	B. cereus	*St. aureus*	*E. coli*	*P. Aeruginose*	*Sa. typhimurium*	*C.albicans*
5*µL*	8	15	8	7	5	12
10 *µL*	10	10	13	10	10	15
15 *µL*	10	22	15	12	15	18
20 *µL*	12	20	18	25	17	20
25 *µL*	11	20	15	22	15	20

Conclusion

From the results of the present investigation, it can be concluded that the reactions of dione 1 with different phosphorus reagents lead to different products,

depending on the nature of the phosphorus reagent as well as the stability of the intermediate. When dione 1 was reacted with pentavalent phosphorus reagents 2a-d, it yielded the alkylated products 6a,b, 7, 8 and 9 respectively. Moreover, dione 1 reacted with 2e to give cyclized derivative of dione 10. Moreover, when dione 1 was reacted with tris(dialkylamino)phosphines, it yielded (bis(dialkylamino)phosphono) hydroxyhexahydropentalen derivatives 11a,b. In addition, dione 1 reacted with thiating reagents 4a,b to give phosphonotrithioate 12 and spirodithiaphosphetane derivatives 13 respectively. According to antimicrobial evaluation, the most promising highly active compound is spirodithiaphosphetane derivative 13 against both Gram positive and Gram negative bacteria.

Materials and Methods

Experimental

Melting points were measured by means of an electrothermal melting points apparatus. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infrared Spectrometer Model 157. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO on a Jeol spectrometer at 500 and 125 MHz respectively and the chemical shifts were recorded in δ values relative to TMS as an internal reference. The ^{31}P NMR (200 MHz) spectra were recorded in $CDCl_3$ or DMSO on a Jeol-500 spectrometer. The mass spectra were recorded at 70eV with a Kratos MS equipment or Varian MAT311A Spectrometer. Elemental analyses were performed using the Elementar Varu EL-Germany Instrument. Their values agreed favorably with the calculated ones. The reported yields are of pure isolated materials obtained by column chromatography on silica gel 60 (Merk). Starting material **1** was prepared according to literature procedures [1-3].

Reaction of cis-Bicyclo [3.3.0] octane-3,7-dione (1) with N-(triphenylphosphoranylidene) aniline (2a)

A mixture of 2a (1.05g, 3 mmol) and dione 1 (0.14 g, 1 mmol) was refluxed for 2h in 30 ml dry toluene (the reaction was monitored by TLC). When the reaction was completed, the volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give products 6a and 6b. Triphenylphosphorane oxide (TPPO) was also isolated from the reaction medium and identified (mix M.p., MS).

N,N'-(tetrahydropentalene-2,5(1H,3H)-diylidene)dianiline (6a)

Eluent: petroleum ether (60-80°C)/ethyl acetate (95/5, *v/v*). Product 6a was separated as colorless crystals in 20% yield. M.P. 152-154°C. IR (KBr): $\tilde{\nu}$ = 1655 (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22, 2.31, 2.72, 2.78 (m, 8H, $4CH_2$), 2.54 (m, 2H, 2CH), 6.9–7.4 (m, 10H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.7–38.9 ($4CH_2$), 42.6 (2CH), 120.1–150.5 (aromatic CH), 179.1 (C=N-Ph) ppm. MS (EI 70 eV): *m/z* (%) = 286 [M-2H] (60), 211 [M^+-77] (20), 197 [M^+-91] (30). Anal. for $C_{20}H_{20}N_2$ (288.39): Calcd C, 83.30; H, 6.99; N, 9.71; Found: C, 83.60; H, 7.02; N, 9.91.

5-(Phenylamino)-3,3a,6,6a-tetrahydropentalen-2(1H)-one (6b)

Eluent: petroleum ether (60-80°C)/ethyl acetate (90/10, *v/v*). Product 6b was separated as colorless crystals in 40% yield. M.P. 238-240 °C. IR (KBr): $\tilde{\nu}$ = 3243 (NH), 1673 (C=O), 1612 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.58, 2.20, 2.33, 2.46, 2.76 (m, 6H, $3CH_2$), 2.40 (m, 1H, CH), 3.45 (m, 1H, CH), 5.90 (1H, =CH), 6.92–7.41 (m, 5H, H_{arom}), 8.63 (s, NH, exchangeable with D_2O) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.3, 45.1 (CH), 42.2, 44.8, 45.9 (CH_2), 104.6 (=CH), 153.1(=C-NH), 118.66–139.5 (aromatic carbon), 218 (C=O) ppm. MS (EI 70 eV): *m/z* (%) = 212 [M^+] (55), 136 [M-77] (20), 121 [M^+-92] (20). Anal. for $C_{14}H_{15}NO$ (213.28): Calcd C, 78.84; H, 7.09; N, 6.57; Found: C, 79.01; H, 7.23; N, 6.88.

Reaction of cis-Bicyclo[3.3.0]octane-3,7-dione (1) with cyclopenta-2,4-dien-1-ylidene(triphenyl)-λ^5-phosphane (2b)

A mixture of **2b** (0.64g, 2 mmol) and dione **1** (0.14 g, 1 mmol) was refluxed for 12h in 30 ml dry toluene. The volatile material was evaporated under reduced pressure. The residue was subjected to silica gel chromatography to give product **7**. Triphenylphosphorane oxide (TPPO) was also isolated from the reaction medium and identified (mix M.P., MS).

2,5-Di(cyclopenta-2,4-dien-1-ylidene)octahydropentalene (7)

Eluent: petroleum ether (60-80°C)/ethyl acetate (80/20, *v/v*). Product **7** was obtained as pale yellow crystals; in 20% yield. M.P. 128-130 °C. IR (KBr): $\tilde{\nu}$ = 1623 (C=C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24, 2.10 (m, 8H, $4CH_2$), 3.68 (m, 2H, CH), 6.21–6.22 (8H, cyclopentene) ppm.^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.6, 40.3 (CH_2), 43.7, 46.21 (CH), 118.1, 128.5 (cyclopentene), 163.2 (C=C) ppm. MS (EI 70 eV): *m/z* (%) = 234 [M^+] (45), 170 [M^+-64] (20). Anal. for $C_{18}H_{18}$ (234.34): Calcd C, 92.26; H, 7.74; Found: C, 92.36; H, 7.69. Compound **7** was characterized by comparing its m.p. as IR spectrum with those of a reference sample [14].

Reaction of cis-Bicyclo [3.3.0]octane-3,7-dione (1) with 2-(triphenyl-phosphanylidene) acetonitrile (2c)

A mixture of 2c (0.60g, 2mmol) and dione 1 (0.14 g, 1 mmol) was refluxed for 4h in 30 ml dry toluene to give product 8 which was precipitated during reflux. Triphenylphosphorane oxide (TPPO) was also isolated from the reaction medium and identified (mix m.p., MS).

2,2'-(Tetrahydropentalene-2,5(1H,3H)-diylidene)diacetonitrile (8)

Product **8** was separated as colorless crystals (methanol); in 40% yield. M.P. 238-240°C. IR (KBr): $\tilde{\nu}$ = 2363, 2235 (CN), 1612 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO): δ = 2.46 (m, 4H, $2CH_2$), 2.61 (m, 2H, 2CH), 3.32–3.56 (m, 4H, $2CH_2$), 5.90 (s, 2H, 2=CHCN) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 26.1–45.9 (CH_2, CH bicycloctane), 101.8 (*C*HCN), 117.5 (CN), 174.1 (*C*=CH-) ppm. MS (EI 70 eV): *m/z* (%) = 184 [M^+] (50). Anal. for $C_{12}H_{12}N_2$ (184.24): Calcd C, 78.23; H, 6.57; N, 15.21; Found: C, 78.25; H, 6.54; N, 15.25.

Reaction of cis-bicyclo[3.3.0] octane-3,7-dione (1) with (dibromomethylene) triphenylphosphorane (2d)

Triphenylphosphine (0.5 g, 0.1mol) was added to a well stirred solution of carbon tetrabromide (0.3 g, 0.05 ml) in DCM (3ml). When the solution became orange (*i.e.*2d is formed) [26], dione 1 (0.14 g, 0.001 mol) was added and the mixture was stirred at room temperature for 8h. After evaporation of the volatile material, the buff residual substance was chromatographed on silica gel column to give colorless product 9. Triphenylphosphane oxide (TPPO) was also isolated and identified.

5-(Dibromomethylene)hexahydropentalen-2(1H)-one (9)

Eluent: petroleum ether (60-80°C)/ethyl acetate (90/10, *v/v*). Product 9 was separated as colorless crystals; in 50% yield. M.P. 142-143°C. IR (KBr): $\tilde{\nu}$ = 1673 (C=O), 1622 (C=C), 626 (C-Br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.13 (m, 4H, $2CH_2$), 3.81–3.31 (m, 6H, $2CH_2$, 2CH) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 30.7–43.1 ($4CH_2$, 2CH), 77.2 (C- Br), 150.1 (C=C), 218 (C=O) ppm. MS (EI 70 eV): *m/z* (%) = 292 [M^+] (35), 292 [M^+] (35). Anal. for $C_9H_{10}Br_2O$ (293.98): Calcd C, 36.77; H, 3.43; Found: C, 36.80; H, 3.45.

Reaction of cis-bicyclo[3.3.0]octane-3,7-dione (1) with (2-oxovinylidene) triphenylphosphrane (2e)

A mixture of **2e** (0.60g, 2 mmol) and dione **1** (0.14 g, 1 mmol) was refluxed for 8h in 30 ml dry toluene. The volatile material was evaporated under reduced pressure. The residue was subjected to silica gel chromatograpy to give product **10**. Triphenylphosphorane oxide (TPPO) was also isolated from the reaction medium and identified (mix M.P., MS).

2-(5-Oxohexahydropentalen-2(1H)-ylidene)-4-(triphenylphosphoranylidene) cyclobutane-1,3-dione (10)

Eluent: petroleum ether (60-80°C)/ethyl acetate (50/50, *v/v*). Product 10 was separated as colorless crystals; in 60% yield. M.P. 108-110 °C. IR (KBr): $\tilde{\nu}$ = 1673 (C=O), 1623 (C=C), 1570 (C=P) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.74-2.44 (m, 10H, $4CH_2$, 2CH), 7.47–7.72 (m, 15H, aromatic) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1–43.9 ($4CH_2$), 46.7, 48.21 (2CH), 121.4 (d, J_{cp} = 135.2 Hz, C=P), 141.1, 210.1 (C=C), 130.6–157.5 (aromatic carbon), 198.8 (2C=O), 218 (C=O) ppm. $^{31}PNMR$ (125 MHz, $CDCl_3$): δ = 21.8 ppm [27,28]. MS (EI 70 eV): *m/z* = (%) 464 [M^+] (5), 202 [M-262] (100). Anal. for $C_{30}H_{25}O_3P$ (464.49): Calcd C, 77.57; H, 5.42; P, 6.67; Found: C, 77.51; H, 5.32; P, 6.60.

The reaction of cis-bicyclo[3.3.0]octane-3,7-dione (1) with tris(dialkylamino) phosphines 3a,b

General procedure

Tris(dialkylamino)phosphines 3a (or 3b) (1mmol) was added to a solution of compound 1 (1mmol) in dry toluene (30 mL), and the reaction mixture was refluxed for 12h (TLC). After evaporation of the volatile material under reduced

pressure, the residue was submitted to silica gel column chromatography to give the product 11a (or 11b).

5-(Bis(dimethylamino)phosphono)-5-hydroxyhexahydropentalen-2(1H)-one (11a)

Eluent: petroleum ether (60-80°C)/ethyl acetate (30/70, *v/v*). Product 11a was separated as yellow crystals; in 30% yield. M.P. 162-164 °C. IR (KBr): $\tilde{\nu}$ = 860, 1242 (P-($N(CH_3)_2$), 1325 (P=O), 1675 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21- 2.88 (m, 10H, 4 CH_2, 2CH), 2.99 (d, $^3J_{HP}$ = 11.10 Hz, 12H, 4 CH_3), 3.89 (s, 1H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8,29.7 (4 CH_2), 39.4 (2 CH), 51.2 (4 CH_3), 77.1 (C-OH), 220.2 (C=O) ppm. ^{31}P NMR (125 MHz, $CDCl_3$): *δ* = 23.8 ppm. MS (EI 70 eV): *m/z* (%) = 274 [M^+] (50). Anal. for $C_{12}H_{23}N_2O_3P$ (274.30): Calcd C, 52.54; H, 8.45; N, 10.21; P, 11.29; Found: C, 52.53; H, 8.39; N, 10.35; P, 11.32.

5-(Bis(diethylamino)phosphono)-5-hydroxyhexahydropentalen-2(1H)-one (11b)

Eluent: petroleum ether (60-80°C)/ethyl acetate (30/70, *v/v*). Product 11b is separated as yellow crystals; in 30% yield. M.P. 172-173 °C. IR (KBr): $\tilde{\nu}$ = 866, 1239 (P-($N(C_2H_5)_2$), 1328 (P=O), 1672 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, 12 H, 4 CH_3), 1.21- 2.87 (m, 10H, 4 CH_2, 2CH), 2.91 (q, $^3J_{HP}$ = 11.23 Hz, 8H, 4CH_2, ethyl), 3.89 (s, 1H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (4 CH_3), 22.8, 29.7 (4 CH_2), 39.4 (2 CH), 40.2 (4CH_2, ethyl), 75.1 (C-OH), 219.2 (C=O) ppm. ^{31}P NMR (125 MHz, $CDCl_3$): δ = 22.7 ppm. MS (EI 70 eV): *m/z* (%) = 330 [M^+] (50). Anal. for $C_{16}H_{31}N_2O_3P$ (330.40): Calcd C, 58.16; H, 9.46; N, 8.48; P, 9.37; Found: C, 58.18; H, 9.22; N, 8.40, P, 9.40.

The Reaction of Lawesson's Reagent 4a and / or Japanese Reagent 4b with cis-bicyclo[3.3.0]octane-3,7-dione (1)

General procedure

A mixture of 4a or 4b (2 mmol) and 0.14 g (1 mmol) of 1 was refluxed for 1h in dry toluene. The volatile material was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to afford products 12 and/or 13.

5-Thioxo-1,3a,4,5,6,6a-hexahydropentalen-2-yl hydrogen (4-methoxyphenyl) phosphonotrithioate (12).

Eluent: petroleum ether (60-80°C)/ethyl acetate (80/20, *v/v*). Product 12 was separated as colorless crystals in yield 50 %. M.P. 168-170 °C. IR (KBr) $\tilde{\nu}$ = 535 (P=S), 1178 (P-C, aryl), 1260 (C=S), 1600 (C=C), 2373 (SH), 2954 (OCH_3) cm^{-1}. ^1H NMR (500 MHz, DMSO) δ = 1.66, 1.92 (m, 6H, 3 CH_2), 2.36 (d, 1H, SH, exchangeable with D_2O), 3.74, 3.75 (m, 2H, 2 CH), 3.76. (s, 3H, OCH_3), 5.31 (d, 1H, =CH), 6.96–7.56 (2d, 4H, H_{arom}) ppm. ^{13}C NMR (125 MHz, DMSO): δ = 43.2, 52.4 (2 CH), 55.72 (OCH_3), 40.3, 60.7, 61.2 (3 CH_2), 125.1 (d, $^1J_{CP}$ = 115.3 Hz, P-C-Ph), 114.0, 132.9, 161.75 (aromatic C-H), 256.0 (C=S) ppm. ^{31}P NMR (200 MHz, DMSO): δ = 19.7 ppm; MS (EI 70 eV) = *m/z* (%) 372 [M^+] (60), 265 [M^+-107] (20), 170 [M^+-202] (15). Anal. for $C_{15}H_{17}OPS_4$

(372.53): Calcd C, 48.36; H, 4.60; P, 8.31; Found: C, 48.67; H, 4.93; P, 8.55.

2-(Phenylthio)tetrahydro-1'H-spiro[[1,3,2]dithiaphosphetane-4,2'-pentalen]-5'(3'H)-one 2-sulfide (13)

Eluent: petroleum ether (60-80°C)/ethyl acetate (80/20, *v/v*). Product **13** was obtained as colorless crystals in 40% yield. M.P. 161-162 °C. IR (KBr): $\tilde{\nu}$ = 627 (P=S), 1678 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.99, 2.12 (m, 8H, $4CH_2$), 2.36 (m, 2H, 2CH), 7.25–7.60 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8, 30.1, 37.2, 41.4 (4 CH_2), 51.1, 53.7 (2 CH), 128.7, 128.9, 135.9, 136.2 (aromatic C-H), 129.1 (d, $^2J_{CP}$ = 22.0 Hz, P-S-C-Ph), 218.0 (C=O) ppm; ^{31}P NMR (200 MHz, $CDCl_3$) δ = 78.3 ppm. MS (EI 70 eV) *m/z* (%) = 357 [M^+] (30), 280 [M^+-77] (50), 248 [M^+-109] (36). Anal. for $C_{14}H_{15}OPS_4$ (358.50): Calcd C, 46.90; H, 4.22; P, 8.64; Found: C, 47.00; H, 4.42; P, 8.66;

Biology

The antibacterial and antifungal activities were carried out in the Microbial Chemistry Department, National Research Centre, using the diffusion plate method [29-32] .

Antimicrobial assay

Preparation of microbial suspensions

A sterilized filter paper disc saturated with measured quantity (25 *μL*) of the sample (1 mg/mL final concentration) was placed on a plate (9cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (Dox's medium) which has been seeded with the spore suspension of the test organism. After incubation at 37 °C for 24h for bacteria (in case of fungi, at 25 °C for 72 h), the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in chloroform as a solvent.

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References

1. **Weiss, U. and Edwards, J. M.** A one-step synthesis of ketonic compounds of the pentalane, [3,3,3]- and [4,3,3]-propellane series. *Tetrahedron Lett.*, **9**, 4885-4887(1968).

2. **Bertz, S.H., Cook, J.M., Gawish, A. and Weiss, U.** Condensation of dimethyl 1,3-acetonedicarboxylate with 1,2-dicarbonyl compounds: cis-bicyclo [3.3.0]octane-3,7-diones .*Org Syn.*; **64**, 27-31(1990), ; *Coll.* **7**, 50-61(1986).

3. **Weiss, U.** Reactions of dicarbonyl compounds with dimethyl β-ketoglutarate V. Simple synthesis of tricyclo [6.3.0.$0^{1,5}$] undecane-3,7,9-trione, a novel cyclopentanoid compound. *Tetrahedron Lett.* **17**, 4549-4552(1976).

4. **Fu, X. and Cook, J. M.** The synthesis of polyquinanes and polyquinenes *via* the Wiess reaction. *Aldrichimica Acta*, **25**, 43-54(1992).

5. **Gupta, A.K., Fu, X. Snyder, L.P. and Cook, J.M.** General approach for the synthesis of polyquinenes via the Weiss reaction. *Tetrahedron*, **47**, 3665-3710(1991).

6. **Kubiak, G.** *Ph.D. Thesis*, University of Wisconsin- Milwaukee, Milwaukee, WI (1989).

7. **Belletire, J.L. and Adams, K.G.** Versatile diquinane intermediates. *Tetrahedron Lett.*, **24**, 5575-5576(1983) .

8. **Bertz, S.H.** The conversion of bicyclo[3.3.0]octane-3,7-dione to bicyclo[3.3.0]oct-1-ene-3,7-dione. Symmetry as a complicating factor in synthetic analysis. *Tetrahedron Lett.*, **24**, 5577-5580(1983).

9. **Sambasivarao, K., Kubiak, G., Lannoye, G. and Cook, J. M.** General approach to the synthesis of polyquinenes. 9. The monofunctionalization and alteration of the symmetry of the cis-bicyclo[3.3.0]octane-3,7-dione unit. *J. Org. Chem*., **53**, 5173-5175(1988).

10. **El-Sayed, N. F., Ewies, E. F., Boulos, L. S. and Mohram, M. E.** Synthesis of novel alkyl (dialkoxyphosphoryl)-1H-indole-3-yl) acetate, dialkoxyphosphoryl [2,3-b]indole-3-carboxylate and dialkyl methyl phosphonate derivatives using Wittig-Horner reagents and their antimicrobial activity. *Res. J. Pharm. Bio. Chem. Sci.*, **5**, 926-935(2014).

11. **Boulos, L.S., Ewies, E.F., Fahmy, A. F. M., and Mohram, M. E**. Synthesis of Some New Triphenylphosphanylidenes, Alkylphosphonates, and Heterocycles of Pyrazole Derivatives and Their Antimicrobial Activity. *Phosphorus, Sulfur and Silicon and The Related Elem*., **188**, 790-803(2013).

12. **El-Sayed, N. F., Ewies, E. F., El-Hussieny, M. and Boulos, L. S.** Synthesis of Novel pyrazole derivatives using organophosphorus, stibine and arsine reagents and their antitumor activity. *Z. Naturforsch. B*, **71**, 765-776(2016).

13. **Ewies, E. F., El-Sayed, N. F., Boulos, L. S. and Soliman, A. M.** Synthesis of novel 1,2-diphenylpyrrole derivatives using organophosphorus reagents and their antitumour activities. *J. Chem. Res.*, **38**, 325-330(2012).

14. **Erickson, M. S., Cronan, J. M. Jr., Garcia, J. G. and McLaughlin, M. L.** Syntheses of dipentafulvenes: Bichromophoric effects correlated with structure. *J. Org. Chem*., **57**, 2504-2508(1992).

15. **Maigali, S.S. Abdel-Malek, H.A. Soliman, F.M.** Reaction of camphorquinone derivatives with active phosphacumulenes and stabilized phosphonium ylides. *Egypt. J. Chem*., **53**, 315-327(2010).

16. **Bestmann, H. J., Schmid, G., Sandermeier, D. and Kisielowski, L.** Dimers of Ketenylidene- and *N*-Phenylketeniminylidene-triphenylphosphorane. *Angew. Chem. Int. Ed. Engl.*, **16**, 268-271(1977).

17. **Said, M.M., Maigali, S. S. and Soliman, F.M.** Chemistry of phosphorus ylides 17. reactions with phosphacumulenes X. The behaviour of phosphacumulenes towards o- and p quinones. Facile synthesis of cyclobutanedione derivatives. *Phosphorus Sulfur and Silicon and The Related Elem*., **108,** 41-49(1996).

18. **Bestmann, H.J., Schmid, G. and Wilhelm, E.** Tetrakis (phenylimino) cyclobutane (Tetrameric Phenyl Isocyanide). *Angew. Chem. Int. Ed. Engl.*, **19**, 136-137(1980).

19. **Bestmann, H. J.** Old and new ylid chemistry. *Pure Appl. Chem.*, **52**,771-779(1980).

20. **Ewies, E. F., El-Hussieny, M., El-Sayed, N. F., Ali, M. M. and Mahmoud, A. E.** Synthesis, characterization, and antitumor evaluation of 4-aminoximidofurazan derivatives. *Phosphorus, Sulfur, and Silicon and The Related Elem*. **191**, 1000-1008(2016).

21. **Ramalingam, S. and Kumar, P.** Synthesis of α-amino phosphonates by three component condensation of carbonyl compound, amine, and dialkyl phosphite using Yttria-zirconia based Lewis acid catalyst. *Catal. Lett.*, **125,** 315-319(2008).

22. **Bellamy L.J.** *"Infrared Spectra of Complex Molecules"* John Wiley & Sons, Academic Press, New York, vol. 1, 3rd ed. pp. 311-331(1975).

23. **Hesse, M., Meier, H. and Zeeh, B.** "*Spektroskopische Methoden in der Organischen Chemie*", Vol 1, Ch. 2, 64. (4th ed., Georg. Thieme Verlag, Stuttgart) (1991).

24. **Liu, H. L., Mao, H. Y., Xu, L., Zhang, H. Y., Hou, H. W., Wu, Q., Zhu, Y., Ye, B. X. and Yuan, L. J.** Four novel sulfur-rich complexes: syntheses, crystal structures of three nickel(II) and one cobalt(II) complex with derivatives of Lawesson's Reagent. *Polyhedron*, **23**, 1799-1804(2004).

25. **El-Barbary, A. A. Shabana, R. and Lawesson, S.-O.** Simple new routes to oximinophosphonodithioates, 1,3,5,2-oxathiazaphospholes and 1,3,2-thiazaphospholines from oximes and their derivatives. *Phosphorus, Sulfur and Silicon and The Related Elem*., **21**, 375-382(1985).

26. **Rabinowitz , R. and Marcus, R.** Ylid Intermediate in the Reaction of Triphenylphosphine with Carbon Tetrachloride. *J. Am. Chem. Soc.*, **84**, 1312-1313(1962).

27. **Maigali, S.S., Soliman, F.M. and Mohram, M.E.** Chemistry of Phosphorus Ylides. Part 36 Reactions of 2-Hydroxyisoindole-, Isoindoline-, and Indane-1,3-Dione With Stable and Active Phosphonium Ylides. *Phosphorus Sulfur and Silicon and The Related Elem*., **188**, 633(2013).

28. **Maigali, S. S., Abd-El-Maksoud, M. A., El-Hussieny, M., Soliman, F. M., Abdel-Aziz, M. S. and Shalaby, E. M.** Synthesis of antimicrobial agents from the reaction of aminoantipyrine, coumarin- and quinoline-carbaldehyde with phosphacumulene and phosphaallene ylides. *J. Chem. Res*., **38**, 754-761(2014).

29. **Grayer, R. J. and Harborne, J. B.** A survey of antifungal compound from higher plants, 1982–1993. *Phytochemistry*, **37**, 19-42(1994).

30. **Irob, O. N., Moo-Young, M. and Anderson, W. A.** Antimicrobial activity of Annatto (Bixaorellana) extract. *Inter. J. Pharm.*, **34**, 87-90(1996).

31. **Jawetz, E., Melnick, J.L. and Adelberg. E.A.** *Review of Medical Microbiology*: 186-191 (Lang Medical Publication, Los Altos, California) (1974).

32. **Muanza, D. N., Kim, B. W. Euler, K. L. and Williams, L.** Antibacterial and antifungal activities of nine medicinal plants from zaire. *Int. J. Pharmacog*., **32,** 337-345(1994).

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التشييد والتوصيف والتقييم المضاد للميكروبات لمشتقات جديدة من الأوكتان- ٧,٣- داي كيتون ثنائى الحلقة

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نظرا لأهمية مركب أوكتان ٧,٣ داى كيتون ثنائى الحلقة وجوده بنسبة كبيرة في كثير من مركبات السيكلوبينتانويد سواء الطبيعية أو المخلقة فقد هدف هذا البحث إلى تحضير وتوصيف مركبات عضوية فوسفورية جديدة ذات نشاط بيولوجي متوقع مشتقة من هذا المركب.

فعند تفاعل المادة البادئة مع أمثلة مختلفة من إيليدات الفوسفورالثابتة في مذيب الطولوين عند درجة الغليان فأدى إلى تكون المشتقات الأوليفينية لأوكتان ثنائي الحلقة مع خروج أكسيد ثلاثي فينيل الفوسفوران أما عند تفاعلها مع مثال من إيليدات الفوسفور النشطة تحت نفس ظروف التفاعل تم الحصول علي المشتق العضوي الفوسفوري لذات المركب. وعلي الجانب الآخر فقد تم الحصول علي مشتق ثنائي(ثنائي ألكيل فوسفينو) ٥-هيدروكسي أوكتان ثنائي الحلقة عند تفاعل مركب أوكتان ٧,٣ داى كيتون ثنائي الحلقة مع ثلاثي (ثنائي ألكيل أمينو) فوسفين. وأخيرا تم الحصول علي المشتقات الكبريتية للمركب البادئ عند تفاعله مع كل من كاشف لاوسن والكاشف الياباني في مذيب الطولوين عند درجة الغليان.

وقد تم التعرف علي التركيبات الكيميائية للمواد الجديدة بالوسائل الكيميائية والتحاليل الدقيقة للعناصر ودراسة طيف الاشعة تحت الحمراء وكذلك طيف الكتلة والرنين النووي المغناطيسي لذرات كلا من الهيدروجين والكربون والفوسفور.

وتم أيضا اختبار هذه المواد الجديدة معمليا كمضادات للبكتريا ومضادات للفطريات بالمقارنة بالأدوية المستخدمة في العلاج وهي البنسلين والنيزوآرم فوجد أن المركب الناتج من تفاعل المادة البادئة مع الكاشف الياباني الفوسفوروكبريتى

قد سجل نشاطا أعلى من نشاط الدواء المستخدم ضد البكتريا السالبه الجرام *E. coli* ونشاطا متوسطا ضد الفطريات.