Zagazig J. Pharm. Sci., June 1995,
Vol. 4, No. 1, pp. 76- 83

ISSN 1110-5089

SYNTHESIS AND REACTIONS OF 1,2-[4,4'(BIS-1(2H)-PHTHALAZINOYL)] ETHANE

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ABSTRACT

Phthalic anhydride reacted with succinic acid in presence of potassium acetate to give compound **1** which reacted with two moles of hydrazine hydrate to give the new compound 1,2-[4,4' (bis-1(2H)-phthalazinoyl) ethane **2.** The behaviour of compound **2** towards different carbon electrophiles and carbon nucleophiles has been described.

INTRODUCTION

It is well known that phthalazinones are useful as remedies for arteriosclerosis[1] and thrombosis[2]. Furthermore they are used for development light sensetive material[3], inhibitory effects on platelet aggregation[4] and antihypertensive activity[5].

The present investigation deals with the synthesis of some new bis-phthalazinone derivatives and study their reactivity towards different reagents in the hope of obtaining some pharmacetical action as well.

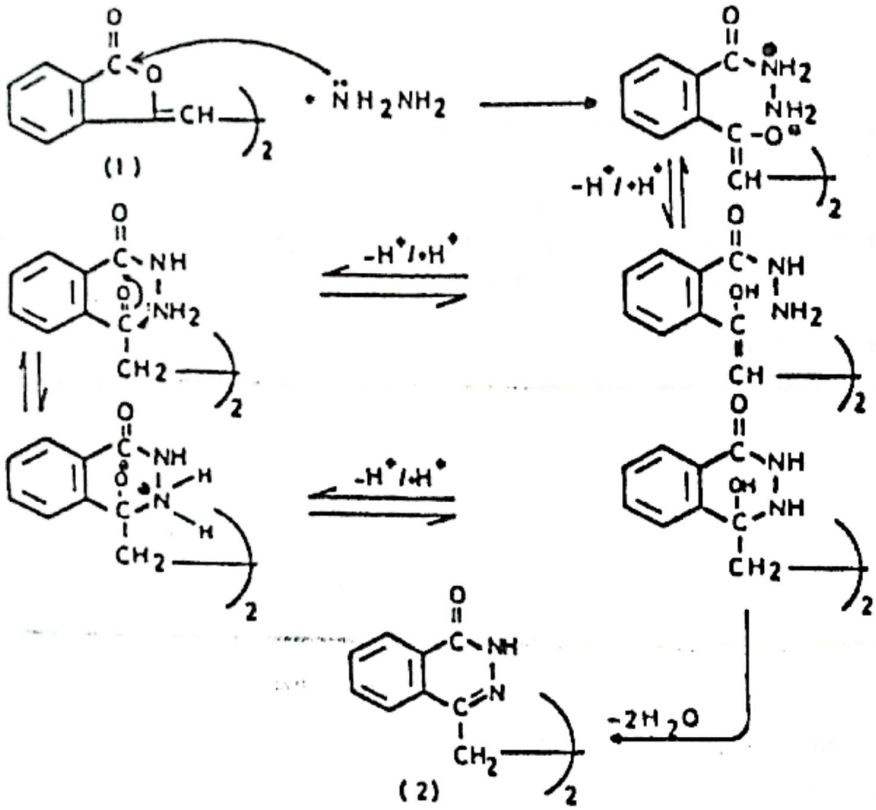
Phthalic anhydride reacted with succinic acid in the presence of dry potassium acetate at 220°C to give compound **1** which is well known in literature[6]. When compound **1** reacted with two moles of hydrazine hydrate in boiling butanol it yielded 1,2-[4,4' (bis-1(2H)-phthalazinoyl) ethane **2.** The reaction possibly takes place according to the mechanism suggested below (Scheme 1).

As a point of interest, thebis-phthalazinone derivative **2** exists in lactam, lactim tautomeric equilibrium. Thus in the absence of solvent or in the presence of a weakly polar solvent e.g. pyridine or non polar solvent e.g. xylene, it reacts with nucleophiles or electrophiles in the lactim form. Treatment of **2** with boiling acetic acid/acetic anhydride mixture led to the formation of 2,2'-(N-diacetyl) bis-phthalazinone derivative **3.** Condensation of **3** with aromatic aldehydes namely benzaldehyde, p-anisaldehyde, p-nitrobenzaldehyde or p-chlorobenzaldehyde in the presence of acetic acid/acetic anhydride mixture gave the corresponding 2,2'-(N-dicinnamoyl) bis-phthalazinone derivatives **4** a-d, respectively.

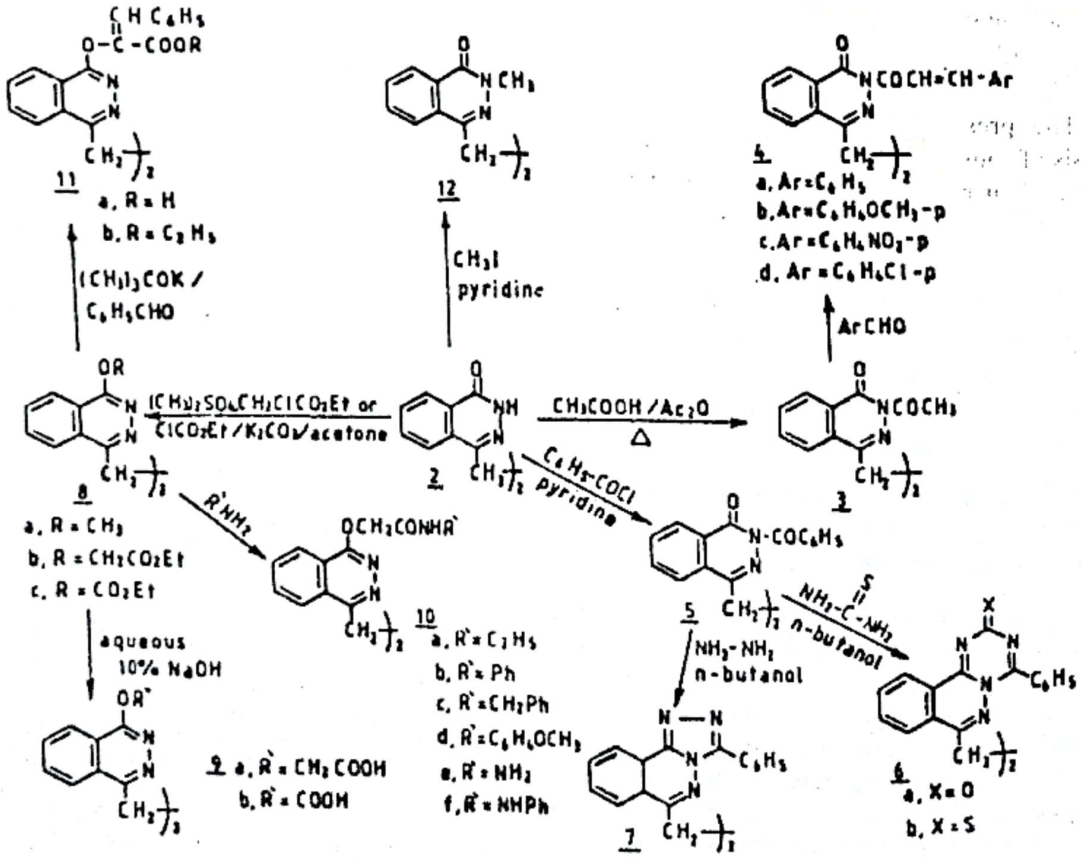
Treatment of bis-phthalazinone **2** with benzoyl chloride in the presence of pyridine led to the formation of 2,2'-(N-dibenzoyl) -bis-phthalazinone derivative **5.** The structure of **5** was confirmed chemically by the reaction with two moles of urea or thiourea in boiling n-butanol to form the triazino derivatives **6** a,b, respectively. Also, the addition of hydrazine hydrate to compound **5** in boiling butanol gave triazole derivative **7.**

The bis-phthalazinone **2** reacted with a variety of electrophilic reagents namely, dimethyl sulphate, ethyl chloroacetate or ethyl chloroformate in dry acetone using K_2CO_3 as a catalyst[7-9] to give 1,1'-(dimethoxy, diethoxy carbonylmethoxy or diethoxy carbonyl) -bis-phthalazine derivatives **8**a-c, respectively. No N-alkyl derivative was obtained by this method, and this may be due to the rapid interconversion of the lactam form to lactim form in the presence of dry acetone and K_2CO_3 which lead to the desired product. Hydrolysis of **8**b,c in alkaline medium gave the corresponding acid derivatives **9**a,b.

The behaviour of 1,1'-(diethoxycarbonylmethoxy)-bis-phthalazine derivative **8**b with primary amines or hydrazines namely, ethylamine,aniline, benzylamine, p-anisidine, piperidine, hydrazine hydrate and phenylhydrazine in boiling butanol afforded the corresponding N-aryl, N-alkylamide



Scheme 1



Scheme 2

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and hydrazide derivatives **10** a-g. Also the ester **8** b reacted with benzaldehyde in the presence of potassium tert-butoxide under the Stobbe condensation conditions affording the cinnamic acid derivative **11**a and a small amount of the Claisen product **11**b.

This reaction in analogous with the previous work of other co-workers[9-11]. The cinnamic ester derivative **11**b also converted to the cinnamic acid derivative **11** a upon hydrolysis with aqueous NaOH (10%).

The alkylation of **2** with methyl iodide in the presence of pyridine gave 2,2\'-(N-dimethyl-bis-phthalazinone) derivative **12.**

Antimicrobial Potentialities of the Experimental Organic Compounds:

Different synthesized organic compounds weretested for their antimicrobial activities against gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*E. coli* and *Pseudomonas aeruginosa*). Serial concentrations (20,40,60,80 and 100 ug/ml) of each compound were assayed against the test organisms using the cup-plate method. The results present in table (2) revealed that compounds No. (7,9), (IIa) and (IIb), were inactive versus the employed test-organisms. Compounds No. (2), (4c), (8a), (10b), (10e) and (10f), showed variable activities agaisnt gram-positive and gram-negative bacteria. Moreover, the results showed that, the magnitude of the antimicrobial activity of each compound was found to be directly proportional to the concentration of each compound.

EXPERIMENT

All melting points are uncorrected, IR(KBr discs) recorded on a unicam SP 1200 spectrophotometer. ^{1}H-NMR spectra (DMSO-d_6): varian EM-390-90 MHz, TMS as internal reference (chemical shift in δ scale). Microanalysis were carried out by Microanalytical centre, Cairo University.

Thin-layer plates were carried out using Merk Silica Gel 60 and U V. lamp (A425, 220-240 volts). The Rf's values were determined using the following systems:

System A: Chloroform, methanol, acetic acid, water. = (6:1.5:1.5:1)

System B: Chloroform, methanol = (7:3).

System C: Butanol, acetic acid, water.= (7:1.5:1.5).

Synthesis of 1,2-[4,4\' (bis-1(2H)-phthalazinoyl) ethane 2:

A mixture of compound **1** (0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol was refluxed for 2h, after cooling the solid obtained was filtered off and recrystallized from the suitablesolvent to give compound **2** (Table 2).

The IR-spectrum of 2 shows bands at 1670 (γC=O), 1610 (γC=N), 2800 (γCH_2) 1450 (γCH_2 bending vibration) and 3460 cm-1 (γNH). The ^{1}H-NMR shows signals at δ 2.7 (s,4H; CH_2 Ar), 7.3-8.2 (m, 8H; aromatic-H) and 8.6 (m, 2H; NH).

Reaction of bis-phthalazinone 2 with acetic anhydride/acetic acid mixture: Formation of 3:

A solution of bis-phthalazinone **2** (0.01 mole) in 50 ml mixture of acetic acid and acetic anhydride (1:1), was heated under reflux for 16h, the red crystals were filtered off after cooling and crystallized from the proper solvent to give **3** (Table 2). The IR-specrum reveals a strong absorption bands at 1650 (γC=O) and 1630 cm^{-1} (γC=N). ^{1}H-NMR shows signals at δ 2.3 (s, 6H; $COCH_3$), 2.7 (s, 4H; CH_2Ar) and 7.3-8.4 (m, 8H; aromatic-H).

Condensation of 2,2\'-(diacetyl)-bis-phthalazinone 3 with aromatic aldehyde: Formation of 4a-d:

A solution of **3** (0.01 mol) and the aromatic aldehyde namely benzaldehyde, p-anisaldehyde, P-nitrobenzaldehyide or P-chlorobenzaldehyde (0.02 mole) in 50 ml acetic acid/acetic anhydride mixture (1:1) was heated under reflux for 6 h. The reaction mixture was concentrated, cooled and the solid products separatedwere crystallized from the proper solvents to give 4a-d (Table 2).

The IR-spectra of 4a-d shows bands at 1670-1675 cm^{-1} (γC=O of amide and α , β unsaturated ketone). The ^{1}H-NMR of 4c shows signals at δ 2.6 (s, 4H; CH_2-) and 6.8-8.2 (m, 2OH; aromatic and olefinic-H).

Reaction of bis-phthalazinone 2 with benzoyl chloride: Formation of 5:

A mixture of 2 (0.01 mole) in 2 ml pyridine and benzoyle chloride (0.08 mole) was heated under reflux for 3 h. The cold reaction mixture was added

gradually with stirring to diluted hydrochloric acid, then the solid obtained was filtered off, washed with hot water, dried and crystallized from the suitable solvent to give **5** (Table 2).

The IR spectrum of 5 shows bands at 1610 and 1615 cm^{-1} (γC=O).

Reaction of 2,-2' (N-dibenzoyl)-bis-phthalazinone 5 with urea, thiourea and hydrazine hydrate: Formation of 6a-b, and 7:

A mixture of **5** (0.01 mole) and each of urea, thiourea or hydrazine hydrate (0.04 mole) in (80 ml) n-butanol was refluxed for 15 h. The products that separated after concentration and cooling were crystallized from the proper solvents to give 6a-b and 7.

The IR-spectra of 6a-b exhibit bands at 1630-1620 (γC=N), 1360 (γC=S) and 1710 cm^{-1} (γC=O).

The IR-spectra of 7 shows band at 1620 cm^{-1}(γC=N).

Reaction of 2 with dimethyl sulphate, ethyl chloroacetate or ethyl chloroformate: Formation of 8a-c:

Amixture of 2 (0.01 mole), anhydrous K_2CO_3 (0.08 mole) and each of, dimethyl sulphate, ethyl chloroacetate or ethyl chloroformate (0.02 mole) was refluxed in 100 ml dry acetone for 24 h. The excess acetone was removed by distillation, the reaction mixture was diluted with water and extracted with ether. The solid obtained was recrystallized from the proper solvents to give 8a-c (Table 2). The IR-spectra of 8b shows bands at 1755 (γC=O of ethoxy carbonyl) and 1630 cm^{-1} (γC=N).

^{1}H-NMR of **8a** shows signals at δ 2.6 (s, 4H; CH_2 Ar), 2.8 (s, 6H; OCH_3) and 7.2-8.4 (m, 8H; aromatic-H).

^{1}H-NMR of 8c shows signals at δ 1.1 (t, 6H; CH_3CH_2-) , 2.7 (s, 4H; CH_2-Ar), 4.3 (q, 4H; -CH_2CH_3) and 7.2-8.5 (m, 8H; aromatic-H).

Hydrolysis of 8b-c: Formation of acids 9a-b:

A mixture of the ester 9b or 9c (0.01 mole) in aqueous sodium hydroxide solution (10%, 10 ml for each 9 of ester) was refluxed for one h. The reaction mixture was acidified with dilute hydrochloric acid. The solid separated was filtered off, washed with water, dried and recrystallized from the proper solvents to give 9a-b (Table 2). The IR-spectra of 9a-b shows bands at 1690 (γC=O), 1640 (γC=N) and 3460 cm^{-1} (γOH). ^{1}HNMR of 8b shows signals at δ 2.7 (s, 4H; CH_2-), 7.2- 8.5 (m, 8H: arom-H) and 10.8 (br, 2H; COOH).

Reaction of the ester 8b with amines and hydrazines: Formation of 10a-f:

A solution of ester 8b (0.01 mole) and each of amines and hydrazines such as ethylamine, aniline, benzylamine, P-anisidine, hydrazine hydrate or phenylhydrazine (0.02 mole) was heated under reflux in 80 ml butanol for 4 h. The solids which separated on cooling were filtered, dried and recrystallized from the proper solvents to give **10**a-f (Table 2).

The IR of **10**a-f show band at 1650-1665 (γCO of amide), 1610-1620 (γC=N) and 3200-3400 cm^{-1} (γNH).

^{1}H-NMR of **10**b shows signals at δ 2.7 (s, 4H; CH_2-Ar) 5.2 (s, 4H; OCH_2CO), 6.1-6.3 (broad, 1H; NH) and 7.3-8.7 (m, 18H; arom-H).

^{1}H-NMR of 10e shows signals at δ 2.6 (s, 4H; CH_2-Ar), 5.1 (s, 4H; OCH_2CO), 6.3-6.6 (broad, 6H; $NH-NH_2$) and 7.3-8.4 (m, 8H; arom-H).

Reaction of 8b with benzaldehyde in presence of potassium t-butoxide: Formation of 11 a-b:

A mixture of 8b (0.01 mole) andbenzaldehyde (0.02 mole) was added in a course of 30 minutes to stirred boiling solution of potassium t-butoxide (prepared from potassium (0.22 g atom) and 70 ml t-butanol), the mixture was heated for 3 hr, and leaved overnight. The alcohol removed under reduced pressure, the residue was acidified with hydrochloric acid and extracted with ether.

The ethreal layer washed with aqueous sodium carbonate solution. The solid which were separated after evaporation of ether was crystallized from the proper solvent. Also, the solid which were found in aqueous layer were filtered off, washed with water and crystallized from the proper solvent to give **11**a-b (Table 2).

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Table 1: Antimicrobial activities of the experimental organic compounds using the Cup-plate method.

Test Organism	Conc. (ug/m)	Inhibition zone (mm)								
		2	4c	7	8a	9a	9b	10b	10e	10f
Staphylococcus aureus g+ve	20	7	-	-	8	-	-	-	8	-
	40	11	6	-	12	-	-	7	11	6
	60	12	9	-	15	-	-	19	14	9
	80	14	12	-	18	-	-	12	16	11
	100	18	16	-	20	-	-	14	19	13
Bacillus subtilis g+ve	20	7	9	-	7	-	-	8	-	-
	40	13	11	-	11	-	-	10	6	6
	60	15	13	-	13	-	-	13	9	9
	80	18	16	-	16	-	-	14	12	10
	100	22	19	-	19	-	-	16	15	13
E. coli g-ve	20	6	8	-	6	-	-	-	6	7
	40	10	11	-	8	-	-	6	9	8
	60	13	14	-	10	-	-	9	11	12
	80	16	16	-	13	-	-	11	13	14
	100	19	18	-	17	-	-	14	15	15
Pseudomonas aeruginosa g-ve	20	9	8	-	5	-	-	7	13	-
	40	11	11	-	8	-	-	10	15	6
	60	15	12	-	12	-	-	15	17	11
	80	17	14	-	16	-	-	17	18	15
	100	19	17	-	20	-	-	20	19	17

The IR-spectrum of **11a** shows band at 1715 (γ C=O), 1635 (γC=N), 1600 (γC=C) and 3400-3500 cm^{-1} (γ OH). The IR-spectrum of **11b** reveals bands at 1750 (γC=O), 1635 (γC=N) and 1600 cm^{-1} (γ C=C).

Reaction of bis-phthalazinone 2 with methyl Iodide: Formation of 12:

A mixture of bis-phthalazinone **2** (0.01 mole), pyridine (4 ml) and methyl iodide (0.08 mole) was heated on water-bath for 3h. The reaction mixture was cooled with cold dil. hydrochloric acid,the product obtained was filtered off, washed several times with hot water and recrystallized from the proper solvent to give **12** (Table 2).

IR-spectrum of **12** shows bands at 1690 (γC=O) and 1610 cm^{-1} (γC=N) . ^{1}H-NMR shows signals at δ 2.3 (s, 6H; CH_3-N), 2.7 (s, 4H; CH_2-) and 7.2 -8 .4 (m, 8H; arom-H).

Biological Activity:

Cup-plate technique was used for the determination of the antimicrobial activity. The samples were dissolved in dimethyl formamide (20% concentration) 0.1 ml of sample was allowed for use towards some gram positive and gram negative bacteria under aspectic conditions. The medium for cultivation of the test organisms was nutrient agar. bacteria were incubated at 30°C for 24h. and the diameters of the inhibition zones (in mm) were measured. The obtained results are summarized in Table (1).

Table 2: Physical data of compounds 2-12

Comp.	m.p °C	R_f system	Solvent yield%	Mol. formula Mol. wt.	Analysis found/req. C	H	N	S
2	320	0.74 (A)	Acetic acid 55	$C_{18}H_{14}N_4O_2$ 318.32	67.8 67.92	4.30 4.43	17.50 17.60	
3	285	0.68 (A)	Ethanol 55	$C_{22}H_{18}N_4O_4$ 402.39	65.40 65.67	4.40 4.50	13.70 13.92	
4a	241	-	Methanol 65	$C_{36}H_{26}N_4O_4$ 578.60	74.52 74.73	4.51 4.53	9.43 9.68	
4b	255	-	Ethanol 50	$C_{38}H_{30}N_4O_6$ 638.64	71.35 71.47	4.55 4.73	8.52 8.77	
4c	280	-	Methanol 50	$C_{36}H_{24}N_6O_8$ 668.59	64.52 64.67	3.41 3.61	12.41 12.57	
4d	261	-	Methanol 55	$C_{36}H_{24}N_4O_2$ 647.49	66.66 66.78	3.50 3.73	3.43 8.65	
5	285	0.67 (A)	Toulene 85	$C_{32}H_{22}N_4O_4$ 526.53	72.8 73.0	4.10 4..21	10.32 10.64	
6	185	-	Propanol 60	$C_{34}H_{22}N_8O_2$ 574.57	70.92 71.07	3.83 3.90	19.35 19.50	
6b	195	-	Xylene 45	$C_{34}H_{22}N_8O_2$ 606.70	67.33 67.31	3.51 3.65	18.40 18.47	10.42 10.57
7	283	-	Acetic acid 65	$C_{32}H_{22}N_8$ 518.55	73.98 74.12	4.13 4.27	21.40 21.61	
8a	299	0.64 (A)	Butanol 60	$C_{20}H_{18}N_4O_2$ 346.37	69.15 69.35	5.10 5.23	15.88 16.17	
8b	216	0.61 (A)	Butanol 65	$C_{26}H_{26}N_4O_6$ 490.48	63.50 63.67	5.32 5.34	11.22 11.42	
8c	211	- (A)	Butanol 60	$C_{24}H_{22}N_4O_6$ 462.43	62.33 62.34	4.61 4.79	12.06 12.12	

Table 2: cont.

Comp.	m.p °C	R_f system	Solvent yield%	Mol. formula Mol. wt.	Analysis found/req. C	H	N	S
9a	236	0.58 (C)	Benzene 60	$C_{22}H_{18}N_4O_6$ 434.39	60.73 60.83	4.12 4.17	12.82 12.90	
9b	231	0.59 (B)	Benzene 65	$C_{20}H_{14}N_4O_6$ 406.34	58.92 59.12	3.32 3.47	13.75 13.79	
10a	222	0.52 (C)	Ethanol 65	$C_{26}H_{28}N_6O_4$ 488.51	63.72 63.91	5.44 5.77	17.10 17.20	
10b	248	0.53 (B)	Propanol 60	$C_{34}H_{28}N_6O_4$ 584.62	69.63 69.86	4.61 4.82	14.24 14.37	
10c	241	0.50 (C)	Propanol 70	$C_{36}H_{32}N_6O_4$ 612.65	70.31 70.58	5.06 5.26	13.60 13.72	
10d	254	-	Propanol 60	$C_{36}H_{32}N_6O_6$ 644.65	66.80 67.07	4.83 5.00	12.91 13.04	
10e	281	0.57 (B)	Propanol 60	$C_{22}H_{22}N_8O_4$ 462.44	57.12 57.14	4.61 4..79	24.20 24.23	
10f	291	0.55 (C)	Propanol 55	$C_{34}H_{30}N_8O_4$ 614.63	66.44 66.30	4.92 4.70	18.23 18.00	
11a	151	-	Pet-Ether (80-100) 40	$C_{36}H_{26}N_4O_6$ 610.60	70.61 70.81	4.03 4.29	8.91 9.18	
11b	256	-	Toluene 45	$C_{40}H_{34}N_4O_6$ 666.70	71.90 72.06	5.14 5.14	8.12 8.40	
12	328	-	Propanol 80	$C_{20}H_{18}N_4O_2$ 346.37	69.31 69.35	5.22 5.23	16.03 16.17	

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تشييد وتفاعلات ١ ،٢- [٤،٤ ¯ - (بس- ١ (٢ H)- فثالذينويل)] إيثان

أحمد فؤاد الفرارجى - سمية الشيخ عبدالرحمن- عبدالفتاح زكريا هيكل - عصام عبدالغنى عبدالحليم - أحمد عبدالرازق شاهين

قسم الكيمياء - كلية العلوم - جامعة الزقازيق - مصر

يتفاعل حمض السكسينك مع أنهيدريد حمض الفثاليك لتكوين مشتق من الفثاليد الذي يتفاعل مع الهيدرازين هيدرات لتكوين البس-فثاليذينون.

وقد تمت دراسة تفاعلات مشتقات البس-فثاليذينون مع بعض الكواشف الالكتروفيلية والنيكلوفيلية مثل كبريتات ثنائي الميثيل وكلوروخلات الايثيل وكلوروفورمات الايثيل ليعطي مشتقات تتفاعل بدورها مع بعض الكواشف النتروجينية والاكسجينية مثل اليوريا والثيويوريا والهيدرازين هيدرات وأيضا مع بعض الكواشف النيكلوفيلية الكربونية تحت ظروف تفاعل مانيش وجريناره.

كما تم دراسة ظاهرة الإتزان الديناميكي الذي تتميز به نواة البس- فثاليذينون (لكتام-لكتيم) وقد تم إثبات تركيب المشتقات الجديدة المحضرة بالطرق الكيميائية وكذلك بالطرق الفيزيائية مثل التحاليل الدقيقة وطيف الأشعة تحت الحمراء والرنين النووي المغناطيسي.

وقد تمت دراسة القدرات الضد أحيائية لمشتقات البس-فثاليذينون ، وقد أوضحت النتائج أن مشتقاته لها تأثير مثبط علي نمو البكتريا سالبة - جرام وموجبة - جرام .