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DICYANOVINYL- AND DICYANOALKYL-DIHYDRO-FUROBENZODIOXINS AND ANALOGOUS SUBSTANCES OF POTENTIAL CYTOSTATIC ACTIVITY

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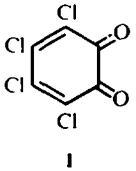
Abstract—The selective uncatalysed addition of tetrahalo-*o*-benzoquinones to the furyl residue of 2-vinylfurans to give the dihydrofurobenzodioxin adducts (**3a–e**), is described. In contrast to other 2-vinylfurans, ethyl furfurylidene cyanoacetate reacts with tetrachloro-*o*-benzoquinone (**1**) to give a diadduct **8**. The dihydrofurobenzodioxins (**7a–g**) are obtained by the action of **1** on the 2-alkylfurans (**6a–g**). The UV spectra of all the halogenated benzodioxin adducts are characterized by the presence of strong absorption in the 215 mμ region which is presumably the red shifted band I of benzene. The IR spectra of the dicyanovinyl- and dicyanoalkylfurans and their benzodioxin adducts are discussed.

DURING our studies on quinonoid compounds, evaluation of tetrachloro-*o*-benzoquinone (**1**) in tissue culture has revealed its cytostatic activity.* The compound proved to have retarding effect on tumor growth in mice infected with some strains such as Sarcoma 180, Adenosarcoma 755 and Lewis Lung Carcinoma.

These results prompted us to investigate its reactivity towards the known cytostatic compound,[1] furfurylidenemalononitrile (**2a**), in an attempt to obtain more biologically active products.



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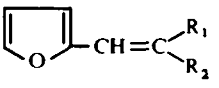

2a: $R_1 = R_2 = CN$
b: $R_1 = R_2 = COOEt$
c: $R_1 = H, R_2 = COOEt$
d: $R_1 = H, R_2 = CO \cdot Ph$
e: $R_1 = CN, R_2 = COOEt$

It is found that when tetrachloro-*o*-benzoquinone (**1**) is allowed to react with **2a** in boiling benzene it adds selectively to the 4:5-double bond of the furyl residue to give 2-(2′-dicyanovinyl)-4:5-dihydro-4:5-(tetrachloro-*o*-phenylenedioxy)-furan (**3a**) in good yield.* The bromo-analogue (**3b**) is similarly obtained by the action of tetrabromo-*o*-benzoquinone on **2a**.

It is known that tetrahalo-*o*-benzoquinones react with ethylenic compounds to give either regular Diels–Alder adducts of the type **4** or 1,4-dioxins like **3** where the α-

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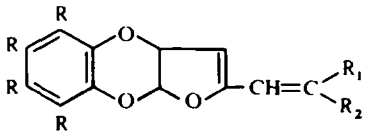
* Biological evaluation has been carried out by the Cancer Chemotherapy National Service Centre, Bethesda, U.S.A. to whom we are indebted

† Part of M.Sc. thesis, N. S. Girgis, Ain Shams University, 1968.



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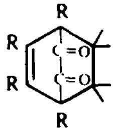
a: R = Cl, $R_1 = R_2$ = CN
b: R = Br, $R_1 = R_2$ = CN
c: R = Cl, $R_1 = R_2$ = COOEt
d: R = Cl, R_1 = H, R_2 = COOEt
e: R = Cl, R_1 = H, R_2 = CO·Ph

dicarbonyl moiety acts as a dienic component.[2,3] Structure **4** is excluded since the products do not give quinoxalines upon treatment with *o*-phenylenediamine as usually happens with *o*-diketones, and their IR spectra do not show $\nu_{C=O}$. When the products are heated above their m.ps they decompose affording the corresponding tetrahalo-*o*-benzoquinone together with **2a**.



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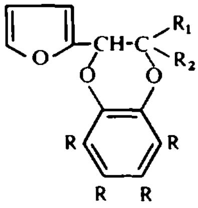

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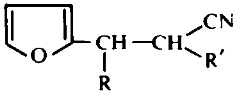
The two dioxins **3** or **5** could be possibly formed through quinone addition to **2a**. Discrimination between these two possible structures is accomplished by a study of the UV spectra of the products. Spectrum of **3a** shows K absorption (λ_{max} 315 mμ, ε_{max} 12,300, methanol) similar in nature to that of the parent substance **2a** (*cf* Table 1), suggesting the presence of the dicyanovinyl side chain and thus supporting the assigned structure **3**.

It is found also that **1** reacts in a similar manner with furfurylidenemalonic ester (**2b**), 2-furylacrylic ester (**2c**) and furfurylideneacetophenone (**2d**) to give the analogous dihydrofurobenzodioxin adducts (**3c–e**), respectively. The products do not form quinoxaline derivatives and exhibit absorption characteristics similar to **3a** (*cf* Table 1).

This enhanced dienophilic character exhibited by the isolated furan nucleus of this



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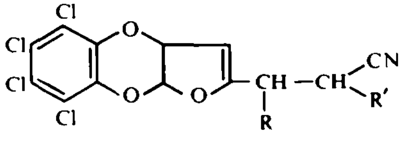

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a: R = Me, R′ = CN
b: R = Et, R′ = CN
c: R = iso-Bn, R′ = CN
d: R = Ph, R′ = CN
e: R = Me, R′ = COOEt
f: R = Et, R′ = COOEt
g: R = Ph, R′ = COOEt

TABLE 1

Compound	mμ		mμ	
	λ_{max}	ε_{max}	λ_{min}	ε_{min}
2a	240 345	3,100 27,600	275	600
3a	215 315	73,000 12,300	270	4000
3c	215 285	71,800 13,700	253	1500
3d	215 283	56,600 12,200	255	7500
2e	335	26,100	270	900
8	215 300	153,400* 4200	275	2100
6d	213	12,400		
7d	215 300	70,000 1800	275	300
6g	215 285	16,600 900	260	200
7g	215 295	60,700 1200	273	450
9	217 305	79,600 4000	275	600
Hexachlorobenzene	217 300	92,000 900	285	700
Pentachlorophenol	215 305	56,900 3800	275	1700
Tetrachlorocatechol	213 300	60,000 3600	280	1800
Trichlorophenol	296	300		

* This value is almost double that of the mono-adducts

open chain conjugated system is rather unusual since furan normally acts as a diene[4]* except when it is incorporated in a fused ring system such as benzofuran.[3]

The reactivity of the 4:5-double bond of the furyl nucleus towards quinone addition is further presented by the fact that the saturated analogues; dicyanoalkylfurans (**6a–d**) afford the analogous dihydrofurobenzodioxin adducts (**7a–d**) when they are allowed to react with tetrachloro-*o*-benzoquinone in boiling benzene. The products decompose into their generators when heated above their m.ps and lack $\nu_{C=O}$ in their IR spectra. The dicyanoalkylfurans (**6a–d**) are obtained by the action of the corresponding Grignard reagents on **2a** at 0–5°. Structure of the Grignard products is evidenced, beside combustion values, by the absence of ν_{NH} and $\nu_{C=O}$ in their IR

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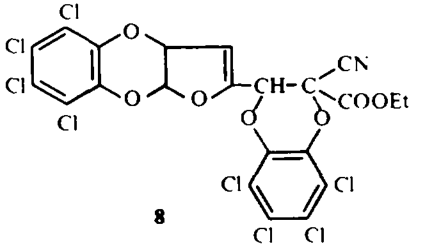
* The dienophilic character of an isolated furyl residue has been reported in one case in a regular Diels–Alder reaction in which furfural added to butadiene.[5] After reporting our communication,[1] in this connection, a further example has been noticed and the action of tetrachloro-*o*-benzoquinone on 2-methyl, 2-phenyl and 2,5-diphenyl furan has been described.[6] However, the selective addition of an *o*-quinone to an isolated furyl residue incorporated in an open chain highly conjugated molecule such as described in the present work has not been reported before.

spectra and thus excluding the possibility of 1,2-addition to the cyano groups. Their UV spectra show the K absorption of the furyl residue[7] (*cf* Table 1) and lack the electronic absorption suggestive of an α,β-unsaturated nitrile structure.

In contrast to the 2-vinylfurans (**2a–d**), it is found that ethyl furfurylidene cyanoacetate (**2e**) reacts with **1** under the same conditions to give the diadduct **8**, through the addition of the quinone to the double bonds of both the furyl residue and the vinyl side chain. This is rather unusual since it is known that *o*-quinones do not add to ethylenic double bonds of open chain α,β-unsaturated ketones, nitriles and esters. Structure of **8** is inferred from combustion values, its lack of colour and that upon pyrolysis it is decomposed into its generators. Its UV spectrum lack the presence of the K absorption due to the vinyl side chain and it does not give a quinoxaline with *o*-phenylenediamine. The saturated analogues (**6e–∂**) are also found to react with **1** to give the adducts **7e–∂** which have physical and chemical characteristics similar to **7a–d**. The saturated analogues **6e–∂** are obtained by the action of the corresponding Grignard reagents on **2e**. Their UV spectra are similar to **6a–d**.



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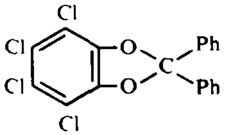

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All the foregoing halogenated furobenzodioxin adducts are characterized by exhibiting very strong absorption in the 215 mμ region of their UV spectra (*cf* Table 1). This absorption is also observed in the spectra of the halogenated benzodioxoles like **9**. The fully substituted benzenes; hexachlorobenzene, pentachlorophenol and tetrachlorocatechol are found also to show this strong absorption (*cf* Table 1) however, the less substituted trichlorophenol does not exhibit this λ_{max}. Apparently, this absorption might be due to the red shifted band I of benzene[8] which now appears in the near UV region through full substitution by auxochromes. As far as we are aware, nothing has been mentioned on the bathochromic shift of band I of benzene to the near UV region due to full substitution by auxochromes.[9] In this connection, use can be made of the presence of this absorption in the spectrophotometric determination of the active molluscicide and herbicide, pentachlorophenol, specially when admixed with the less potent trichlorophenol.

Stretching frequency bands due to nitrile absorption

It has been shown in this laboratory[10] that nitriles do not necessary show absorption in the 4·5 μ region characteristic of the cyano group, and that introduction of oxygenated or electronegative groups does not necessarily lead to quenching of the nitrile bands as previously reported by Kitson and Griffith.[11] Thus, it has been found, in this connection, that saturated malononitriles, in contrast to the unsaturated analogues and to malononitrile itself, do not show the stretching frequency band due to the nitrile absorption in their IR spectra.[10] This has been rationalized on the basis of free rotation of the carbon atom linked to the two cyano groups in the saturated analogues, in contrast to the unsaturated compounds. In the present investigation it is found that furfurylidenemalonotrile (**2a**) itself show strong absorption in the 4·5 μ region, whereas the saturated products (**6a–d**) lack this absorption. The IR spectra of the dihydrofurobenzodioxin adducts (**3a** and **b**), where the dicyanovinyl side chain is still present, show ν_C similar to that of **2a** whereas the dioxin adducts (**7a–d**), lack this absorption, resembling the parent saturated malononitriles (**6a–d**). These results confirm what has been previously reported in this connection[10] and might enhance a generalization in connection with the IR spectra of nitriles.

EXPERIMENTAL

M.ps were not corrected, Microanalyses were performed by the Microanalytical Lab., National Research Centre, Cairo, U.A.R. IR spectra were recorded by Perkin–Elmer Infracord Model 137. UV spectra were determined using a Carl Zeiss Spectrophotometer type PMQ II.

Preparation of vinyldihydrofurobenzodioxin adducts (**3a–e**). A soln of the 2-vinylfuran (0·01 mole) and the tetrahalo-*o*-benzoquinone (0·01 mole)* in dry benzene (20 ml) was refluxed for 6 hr. The soln was filtered while hot and the solvent was removed under reduced pressure. A few millilitres of MeOH was added to the oily red residue obtained, and left to stand for several hr. The separated crude crystalline solid was filtered off, washed with cold MeOH and recrystallized from the proper solvent to give the dihydrofurobenzodioxin as colourless crystals.

M.ps, yields, solvents of crystallization and combustion values of the products are shown in Table 2.

Reaction of tetrachloro-o-benzoquinone with ethyl furfurylidene cyanoacetate (**2e**). A soln of ethyl furfurylidene cyanoacetate (0·01 mole) and tetrachloro-*o*-benzoquinone (0·02 mole) in dry benzene (25 ml) was refluxed for 6 hr. The soln was filtered while hot, evaporated to dryness under reduced pressure, and left to cool. A few millilitres of dry ether was added to the dark red oily residue obtained and left to stand several hr. The separated product was filtered off, washed with ether and crystallized from benzene to give the diadduct **8** as colourless needles m.p. 231–232°, yield, 47%. (Found: C, 38·65; H, 1·36; N, 2·38; Cl, 39·84. $C_{22}H_9Cl_8NO_7$ requires: C, 38·65; H, 1·32; N, 2·05; Cl, 41·58%).

Reaction of tetrachloro-o-benzoquinone with 2-alkylfurans (**6a–d**). A soln of the 2-alkylfuran (0·02 mole) and tetrachloro-*o*-benzoquinone (0·02 mole) in dry benzene (30 ml) was heated under reflux for 6 hr. The soln was filtered while hot and the solvent was removed under reduced pressure. A few millilitres of MeOH was added to the dark red oily residue obtained, and left overnight. The separated crystalline mass was filtered off, washed with MeOH and crystallized from the proper solvent to give the dihydrofurobenzodioxin adduct as colourless crystals.

M.ps, solvents of crystallization, yields and analytical data of the products are shown in Table 2.

Pyrolysis of the furobenzodioxin adducts. The furobenzodioxin adduct (0·5 g) was heated above its m.p. under reduced pressure (oil pump) in a test tube shaped vessel fitted with a condenser. The compound melted with decomposition and a substance collected on the lower parts of the condenser. This was identified as the corresponding parent 2-vinyl- or 2-alkylfuran. The dark red residue which remained in the tube was extracted with n-hexane, filtered, concentrated and left to cool. The separated red product proved to be tetrachloro-*o*-benzoquinone (m.p. and mixed m.p.).

Reaction of dihydrofurobenzodioxin adducts with o*-phenylenediamine.* A soln of the dihydrofurobenzodioxin adduct (0·5 g) and *o*-phenylenediamine (0·2 g) in dry benzene (10 ml) was refluxed for 1 hr. The solvent was removed and a few millilitres of methanol was added to the residue. The separated solid proved to be unchanged adduct (0·45 g). The methanolic mother liquor was concentrated to a small bulk and cooled. The separated solid proved to be *o*-phenylenediamine (0·12 g).

Reaction of Grignard reagents with 2-vinylfurans. The 2-vinylfuran (0·04 mole) was added portionwise at 0–5° to a soln of the appropriate Grignard reagent (0·12 mole) (prepared from 0·12 atom Mg and 0·12 mole alkyl or aryl halide). A vigorous reaction occurred upon each addition. The mixture was then left at the reaction temp for 1 hr, then overnight at ambient temp. It was decomposed with ice and ammonium chloride and extracted with ether. The ethereal extract was washed with water, dried over Na_2SO_4, filtered

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* When 0·02 mole of the quinone was used, the same product was obtained in an almost equal yield.

TABLE 2

Dihydrofurobenzodioxin adduct	m.p °C	Yield %	Solvent of cryst	Formula		C%	H%	N%	Cl or Br%
3a	208-210	40	Benzene-cyclohexane	$C_{14}H_4Cl_4N_2O_3$	Found:	43·84	1·26	6·92	35·64
					requires:	43·70	1·03	7·17	36·41
3b	230–232	40	Benzene	$C_{14}H_4Br_4N_2O_3$	Found:	29·53	1·00	5·16	54·81
					requires:	29·04	0·70	4·92	56·33
3c	195–196	77	Benzene	$C_{18}H_{14}Cl_4O_7$	Found:	44·20	2·95		29·44
					requires:	44·62	2·89		29·33
3d	158–159	64·5	Benzene	$C_{15}H_{10}Cl_4O_5$	Found:	44·12	2·44		33·73
					requires:	43·69	2·43		34·46
3e	187–188	74	Benzene	$C_{19}H_{10}Cl_4O_4$	Found:	50·60	2·35		31·65
					requires:	51·35	2·25		31·98
7a	146 148	40	Benzene–n-hexane	$C_{15}H_8Cl_4N_2O_3$	Found:	44·39	2·36	7·00	34·30
					requires:	44·33	1·97	6·89	34·97
7b	166-168	34	Benzene–cyclohexane	$C_{16}H_{10}Cl_4N_2O_3$	Found:	46·26	2·41	6·92	33·02
					requires:	45·71	2·38	6·66	33·80
7c	195–196	32	Benzene–cyclohexane	$C_{18}H_{14}Cl_4N_2O_3$	Found:	48·21	3·34	6·45	32·46
					requires:	48·21	3·12	6·25	31·69
7d	168–169	33	Benzene cyclohexane	$C_{20}H_{10}Cl_4N_2O_3$	Found:	51·37	2·21	6·46	31·01
					requires:	51·34	2·13	5·98	30·34
7e	200 201	44·3	Benzene	$C_{17}H_{13}Cl_4NO_5$	Found:	44·86	2·69	3·73	30·60
					requires:	45·03	2·87	3·09	31·34
7f	147–148	40	Benzene-cyclohexane	$C_{18}H_{15}Cl_4NO_5$	Found:	46·81	3·70	3·17	30·60
					requires:	46·25	3·21	3·00	30·40
7g	158–159	40	Benzene-n-hexane	$C_{22}H_{15}Cl_4NO_5$	Found:	51·39	3·06	2·80	26·99
					requires:	51·26	2·91	2·72	27·57

TABLE 3

2-Alkylfuran	m.p., b.p. C°	Yield %	Solvent of cryst.	Formula		C%	H%	N%
6a	110/1 mm	80	—	$C_9H_8N_2O$	Found:	67·39	5·19	18·19
					requires:	67·50	5·00	17·50
6b	97/0·4 mm	75	—	$C_{10}H_{10}N_2O$	Found:	68·78	5·90	16·20
					requires:	68·96	5·81	16·09
6c	107/0·5 mm	81		$C_{12}H_{14}N_2O$	Found:			14·10
					requires:			13·88
6d	58–59	70	cyclohexane	$C_{14}H_{14}N_2O$	Found:	75·93	4·48	12·81
					requires:	75·33	4·93	12·55
6e	96/0·4 mm	81·5	—	$C_{11}H_{13}NO_3$	Found:	63·90	6·60	7·25
					requires:	63·75	6·32	6·76
6f	98/0·35 mm	80	—	$C_{12}H_{15}NO_3$	Found:	65·75	6·97	6·55
					requires:	65·14	6·83	6·33
6g	56–57	46	Methanol	$C_{16}H_{15}NO_3$	Found:	71·25	5·77	4·98
					requires:	71·36	5·61	5·2

and evaporated to dryness under reduced pressure. The oily products were distilled under reduced pressure whereas the solids were crystallized from the proper solvents.

M.ps, b.ps, yields and analytical data for the products are shown in Table 3.

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