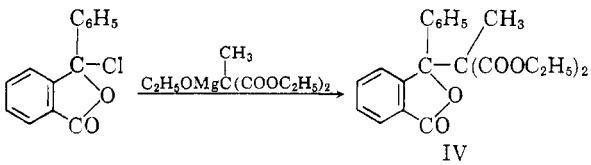
spectral analysis is in agreement with this structure.[6]

All attempts to hydrolyze IV to the malonic acid failed. Under both alkaline and acidic conditions either unchanged IV was recovered or *o*-benzoylbenzoic acid was obtained. The cleavage of IV under hydrolytic conditions stands in marked contrast to the ready hydrolysis of I to the malonic acid or to the half ester.[4]

It is also noteworthy that the ethoxymagnesium derivative of diethyl malonate reacts with the pseudo acid chloride of benzoylbenzoic acid by attack at the carbonyl group[4] to yield III whereas the ethoxymagnesium derivative of diethyl methylmalonate reacts by displacement of the chlorine atom to yield IV.



IV

EXPERIMENTAL[7]

Diethyl 3-phenylphthalidylmalonate, I_A. To a solution of 20 g. of diethyl malonate in 50 ml. of ether and 100 ml. of bis-2-ethoxyethyl ether was added 2.3 g. of sodium in small pieces. When solution was complete 24.0 g. of methyl *o*-benzoylbenzoate in 25 ml. of bis-2-ethoxyethyl ether was added, the ether distilled and the mixture refluxed for 6.5 hr. The cooled reaction mixture was poured on ice and dilute hydrochloric acid. The neutral fraction of the products was distilled to yield 14.0 g. of methyl *o*-benzoylbenzoate, b.p. b.p. 170–190° at 0.5 mm. and 12.0 g. of a yellow viscous product, b.p. 230–245° at 0.5 mm. On crystallization of the high boiling fraction from alcohol there was obtained 5.8 g. (16%) of colorless crystals of I_A, m.p. 95.0–98.6°. Recrystallization afforded a pure sample,[4] m.p. 100.4–101.8°.

In a similar experiment except that excess diethyl malonate was the solvent and the heating period was 7 hr. at 100±5° a smaller yield (10%) of I_A was obtained.

3-Phenylphthalidyl malonic acid, I_B. A small amount of I_A in aqueous ethanol was heated with a small excess of sodium hydroxide for 3 min. The reaction mixture was acidified with hydrochloric acid. This solution was allowed to evaporate to dryness and the solid residue was extracted with absolute alcohol. The filtered extracts were evaporated to dryness and the residue triturated with boiling benzene. The benzene-insoluble crystals were washed with water, collected, and dried to yield colorless crystals of I_B, m.p. 160° dec.[4]

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.4; H, 3.9. Found[8]: C, 65.1; 65.3; H, 4.0, 3.9.

3-Methyl-3-phenylphthalide. An authentic sample of 3-methyl-3-phenylphthalide, m.p. 76.8–78.0°, was prepared essentially as described.[9] The crude phthalide was purified by alkaline hydrolysis to remove a persistent impurity of methyl *o*-benzoylbenzoate. The pure phthalide had a strong carbonyl band at 5.65 μ.

On heating a small amount of I_B at 200–205° for 20 min. followed by vacuum distillation of the product, a good yield of 3-methyl-3-phenylphthalide, m.p. 76.8–78.0°, mixed melting point with above sample not depressed, was obtained. The infrared spectra were identical.

Diethyl 3-phenylphthalidylmethylmalonate, IV. A solution of the acid chloride prepared from 50.0 g. of *o*-benzoylbenzoic acid, prepared as described,[4] in 100 ml. of dry ether was added to the ethoxymagnesium salt of diethyl methylmalonate, prepared as described for diethyl malonate,[9] using 5.4 g. of magnesium and 38.0 g. of diethyl methylmalonate. The reaction mixture remained clear even after refluxing for 1 hr. or for longer periods up to 12 hr. The cooled mixture was treated with dilute hydrochloric acid and the products taken into ether-benzene. It was necessary to keep the separatory funnels used warm to prevent crystallization of the product. After washing with sodium carbonate solution, the ether-benzene solution was concentrated. The product, IV, was obtained in three crops, m.p. 103–107°, in 81–86% yield. The analytical sample, m.p. 106–107°, was obtained with little loss by recrystallization from alcohol.

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.1; H, 5.8. Found[8]: C, 68.9; H, 5.7.

Many attempts at hydrolysis of IV were made. These included among others the following: (a) heating at reflux with aqueous alcoholic sodium hydroxide for 1 hr.; (b) heating at reflux for 12 hr. in acetic acid containing a small amount of concentrated sulfuric acid; (c) refluxing in 88% formic acid for several hours; (d) refluxing acetic acid solutions containing large amounts of sulfuric acid; (e) holding a solution of 3.0 g. of IV in 25 ml. of acetic acid containing 5 ml. of 48% hydrobromic acid at 50 ± 5° for 33 days; (f) heating for various times with insufficient alkali for complete hydrolysis. The results of the above experiments are summarized as follows: (*a*) *o*-benzoylbenzoic acid in high yield; (b,c,e) recovery of almost all of IV unchanged; (d) recovery of IV (mainly) plus small amounts of *o*-benzoylbenzoic acid; (f) recovery of *o*-benzoylbenzoic acid and of IV.

One attempt at catalytic hydrogenation of IV in ethyl acetate over a rhodium-on-alumina catalyst at room temperature and 50 p.s.i. of hydrogen for 90 min. failed, as no uptake of hydrogen occurred and IV was recovered almost quantitatively.

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(6) I am indebted to Dr. Gideon Fraenkel for the NMR analysis. Significant features are the sharp unsplit CH_3 band at 8.362 τ units which indicates that the methyl group is on a carbon which has no hydrogen attached to an adjacent carbon. The fact that the ethyl groups are not equivalent indicates that freedom of rotation is restricted.

(7) All melting points are uncorrected.

(8) Microanalyses by the Galbraith Laboratories, Knoxville, Tenn.

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Synthesis of Potential Anticancer Agents. XIII. Alkyleniminoquinoxalines[1,2]

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The established anticancer activity of the ethylenimine (aziridine) group attributed to its "alkylating" action[3] prompted us to prepare a number of

(1) Previous paper in this series, R. C. Elderfield and T.-K. Liao, *J. Org. Chem.*, **26**, 4994 (1961).

(2) This work supported by a Research Grant (CY-2961) from the National Cancer Institute to The University of Michigan.

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TABLE I

ALKYLENIMINOQUINOXALINES

Compound	Substance	Starting Quinoxaline G.	Starting Quinoxaline Cpd.	Ml. of Imine and Triethylamine	Reaction Time and Temp. Hr.	Reaction Time and Temp. Temp.	Yield, G. (%)	Color and Appearance	Solvent[a]	M.P.	Analyses[b] Calcd. for	C	H	N
							2-Chloroquinoxalines							
III	3-*N*-Aziridino-	20	I	20 and 30[c]	72	25	15 (73)	Yellow needles	Pet. ether	101–102	$C_{10}H_8ClN_3$:	58.40	3.92	20.44
											Found:	58.93	3.89	20.59
IV	3-*N*-Pyrrolidino-	20	I	17 and 30[c]	72	25	20 (85)	Yellow thick needles	Pet. ether	93–94	$C_{12}H_{12}ClN_3$:	61.68	5.14	17.98
											Found:	61.80	5.30	17.91
V	3-*N*-Piperidino-	20	I	40 and 0[c]	72	25	21 (85)	Cream needles	Methanol	68.5	$C_{13}H_{14}ClN_3$:	63.11	5.65	16.96
											Found:	63.26	5.62	16.99
VI	3-*N*-Morpholino-	4.3	I	2.0 and 20	72	70	3.2 (60)	White needles	Ethanol	84.0	$C_{12}H_{12}ClN_3O$:	57.71	4.80	16.83
											Found:	57.72	4.68	16.64
VII	3-*N*-Hexamethylenimino-	50	I	25 and 150	3	100	60 (92)	Light yellow	Pet. ether	68.0–68.5	$C_{14}H_{16}ClN_3$:	64.24	6.11	16.00
											Found:	64.20	6.11	15.62
							2-Methylquinoxalines							
VIII	3-*N*-Pyrrolidino-	10	II	15 and 20	72	60	9.5 (80)	Red needles	Pet. ether[d]	108–109	$C_{13}H_{15}N_3$:	73.21	7.09	19.70
											Found:	73.07	6.94	19.87
IX	3-*N*-Piperidino-	2	II	5 and 5	72	60[e]	2.3 (90)	Orange beads	Pet. ether	55–56	$C_{14}H_{17}N_3$:	73.97	7.54	18.49
											Found:	74.09	7.37	18.43
X	3-*N*-Morpholino-	10	II	25 and 0	72	85	9.9 (78)	Red cubes	Pet. ether[d]	91–92	$C_{13}H_{15}N_3O$:	68.10	6.59	18.33
											Found:	68.36	6.71	18.72
XI	3-*N*-Hexamethylenimino	10	II	25 and 25	48	Reflux	8.8 (65)	Red-orange leaflets	Pet. ether	60	$C_{15}H_{19}N_3$:	74.68	7.88	17.43
											Found:	74.63	8.06	17.65
							2-*N*-Aziridinoquinoxalines							
XII	3-*N*-Pyrrolidino-	2	III	5 and 15	24	60	2.3 (100)	Stars	Pet. ether	56–57	$C_{14}H_{16}N_4$:	69.97	6.71	23.32
											Found:	69.20	7.94	23.11
XIII	3-*N*-Piperidino-	3	III	10 and 15	24	60	3.4 (92)	White needles	Ethanol	102	$C_{15}H_{18}N_4$:	70.83	7.13	22.03
											Found:	70.45	8.28	
XIV	3-*N*-Morpholino-	6	III	15 and 15	6	60	4.8 (65)	Yellow	Ethanol	125	$C_{14}H_{16}N_4O \cdot {}^1/_2H_2O$	62.90	7.16	20.96
											Found:	62.92	6.98	20.63
XV	3-*N*-Hexamethylenimino	7	III	15 and 10	4	Reflux	7.1 (100)	Yellow	Pet. ether	58	$C_{16}H_{20}N_4$:	71.61	7.51	20.88
											Found:	71.88	8.88	
							2-*N*-Pyrrolidinoquinoxalines							
XVI	3-*N*-Pyrrolidino-	10	I	20 and 30	72	60	11.8 (88)	Silver leaflets	Methanol	127	$C_{16}H_{20}N_4$:	71.61	7.51	20.88
											Found:	72.07	7.49	20.45
XVII	3-*N*-Piperidino	8	IV	20 and 20	24	60	7.4 (75)	Yellow needles	Ethanol	87	$C_{17}H_{22}N_4$:	72.30	7.55	19.84
											Found:	71.57	7.44	19.36
XVIII	3-*N*-Morpholino	1	VI	5 and 5	24	60	1.0 (91)	White needles	Ethanol	104	$C_{16}H_{20}N_4O$:	67.58	7.09	19.71
											Found:	67.08	7.08	19.65
XIX	3-*N*-Hexamethylenimino	8	VII	16 and 16	24	Reflux	74 (82)	Yellow cubes	Methanol	98	$C_{18}H_{24}N_4$:	72.94	8.16	18.90
											Found:	72.64	8.03	19.36

TABLE I (*Continued*)

Compound	Substance	Starting Quinoxaline G.	Starting Quinoxaline Cpd.	Ml. of Imine and Triethylamine	Reaction Time and Temp. Hr.	Reaction Time and Temp. Temp.	Yield, G. (%)	Color and Appearance	Solvent[a]	M.P.	Analyses[b] Calcd. for	C	H	N
							2-*N*-Piperidinoquinoxalines							
XX	3-*N*-Piperidino-	10	I	30 and 15	72	60	10.4 (70.3)	White needles	Ethanol	148	$C_{18}H_{24}N_4$:	72.94	8.16	18.90
											Found:	72.91	7.97	19.07
XXI	3-*N*-Morpholino-	1	VI	5 and 5	72	60	1.0 (83)	White needles	Ethanol	144	$C_{17}H_{22}N_4O$:	68.43	7.43	18.78
											Found:	68.48	7.48	18.93
XXII	3-*N*-Hexamethylenimino	8	VII	16 and 16	24	Reflux	7.6 (80)		Methanol	79	$C_{19}H_{26}N_4$:	73.51	8.44	18.05
											Found:	72.87	8.32	18.09
							2-*N*-Morpholinoquinoxalines							
XXIII	3-*N*-Morpholino-	10	I	30 and 30	72	Reflux	12 (80)	White needles	Ethyl acetate	225	$C_{14}H_{20}N_4O_2$:	63.98	6.71	18.65
											Found:	63.40	6.65	18.64
XXIV	3-*N*-Hexamethylenimino	8	VII	16 and 16	24	Reflux[f]	5.5 (57)	Lt. yel. cubes	Pet. ether–methanol	104–105	$C_{18}H_{24}N_4O$:	69.20	7.75	17.94
											Found:	69.30	7.82	18.02
							2-*N*-Hexamethyleniminoquinoxaline							
XXV	3-*N*-Hexamethylenimino	7	VII	20 and 25	24	Reflux[f]	—	Yellow cubes	Pet. ether	57	$C_{20}H_{28}N_4$:	74.07	8.61	17.22
											Found:	74.05	8.61	17.33

[a] When pet. ether boiling range is 40–60° unless otherwise noted. [b] Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. [c] Imine added over 10 min. to other reactants in 800 ml. ether. [d] 60–80° boiling range. [e] Crude product taken up in ether, dried, and recovered by evaporation. [f] Crude product taken up in chloroform, dried, and recovered by evaporation.

analogs of 2-N-ethyleniminoquinoxaline, e.g. 2-chloro-3-N-aziridinoquinoxaline (III), with a view to investigating the effect of the quinoxaline system as an adjunct to the aziridine system as well as an adjunct to homologous alkylenimino systems which are chemically stable under conditions which permit the aziridine system to serve in its alkylating role.

To this end 2,3-dichloroquinoxaline (I)[4] and 2-chloro-3-methylquinoxaline (II)[5] were prepared and used as primary starting materials for condensation with appropriate alkylenimines. The two active chlorines of I permitted the introduction of either one such substituent (III–VII) or two (similar or different) substituents (XII–XXV). Data are assembled in Table I.

In addition a quinoxaline carrying a nitrogen-mustard function was prepared by condensing 2-hydroxy-3-methylquinoxaline[6] with *p*-[*N,N-bis*-(2-chloroethyl)amino]benzaldehyde[7] to give 2-hydroxy - 3 - *p* - [*N,N* - *bis* - (2 - chloroethyl)amino]-styrylquinoxaline (XXVI).

It should be noted that for unaccountable reasons most of the aziridine-substituted compounds proved difficult to purify and invariably contained traces of water which could not be removed satisfactorily.

EXPERIMENTAL

The following general procedure served for the preparation of all but one of the compounds reported.

The appropriate alkylenimine was added to a mixture of the appropriate chloroquinoxaline and triethylamine (using ether as solvent for III, IV, and V and filtering off the triethylamine hydrochloride, evaporating ether from the filtrate, and adding water to the residue). The reaction mixture was stirred with water and the solid filtered off and recrystallized. In one case (IX) the product was extracted into ether and in two (XXIV and XXV) into chloroform; and after drying, filtering and removal of the organic solvent the residue was crystallized. External cooling during imine addition was necessary for XVI and XX. Data are summarized in Table 1.

2-Hydroxy-3-p-[*-N,N-bis(2-chloroethyl)amino*]*styrylquinoxaline* (XXVI). A mixture of 3 g. of 2-hydroxy-3-methylquinoxaline[6] and 4.5 g. of *p*-[*N,N-bis*-(2-chloroethyl)amino]-benzaldehyde[7] in 20 ml. of benzene containing 10 ml. of acetic anhydride was heated under reflux for 14 hr. The reaction mixture was evaporated under reduced pressure, and the dark gum was boiled with benzene and filtered hot. The shiny crimson residue crystallized from ethyl acetate as small needles, m.p. 215°: 3.1 g. (42%). If benzene is not used in the initial stage, intractable tars are obtained.

Anal. Calcd. for $C_{20}H_{19}ON_3Cl_2$: C, 61.85; H, 4.89; N, 10.82. Found: C, 61.43; H, 5.19; N, 10.75.

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The Geometrical Isomers of 1,5-Diphenylpentadiene-3-one

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Although 1,5-diphenylpentadiene-3-one (dibenzalacetone) has been known for many years, the geometrical isomerism of this compound has not been investigated. This note describes the preparation and characterization of the three possible isomers. The physical and spectral properties are reported and isomerization studies are described.

The preparation of 1,5-diphenylpentadiyne-3-one has been reported by Chauvelier.[1] This method was utilized except that 1,5-diphenylpentadiyne-3-ol was oxidized to 1,5-diphenylpentadiyne-3-one with manganese dioxide rather than with chromic acid. The chromic acid oxidation as described by Chauvelier gave benzoic acid as the only isolable product in our laboratory. The manganese dioxide oxidation gave almost quantitative yields of 1,5-diphenylpentadiyne-3-one in large runs.

Nightingale and Wadsworth[2] have reported the preparation of 1,5-diphenylpent-1-en-4-yn-3-one by the reaction of sodium phenylacetylene and cinnamic anhydride. Our crude yields approached those reported, but we obtained pure yields of only 5% by this method. The reaction of phenylacetylene-magnesium bromide with cinnamaldehyde gave 1,5-diphenylpent-1-en-4-yn-3-ol in 55% yield. The alcohol was oxidized to 1,5-diphenylpent-1-en-4-yn-3-one with Kiliani's reagent[3] or with manganese dioxide.

Hydrogenation of 1,5-diphenylpentadiyne-3-one and 1,5-diphenylpent-1-en-4-yn-3-one over Lindlar catalyst gave the *cis-cis* (I) and *cis-trans* (II) isomers, respectively. The *trans-trans* compound (III) was prepared by the method described in *Organic Syntheses*.[4] The properties of the three isomers are summarized in Table I.

TABLE I

PROPERTIES OF THE ISOMERS OF 1,5-DIPHENYLPENTADIENE-3-ONE

Isomer	M.P.	B.P.	λ_{max}	ϵ_{max}
cis-cis (I)	—	130/0.02 mm	287 mμ	11,000
cis-trans (II)	60	—	295 mμ	20,000
trans-trans (III)	111	—	330 mμ	34,300

The infrared absorption of the isomers confirms the structures that have been assigned. Both II

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