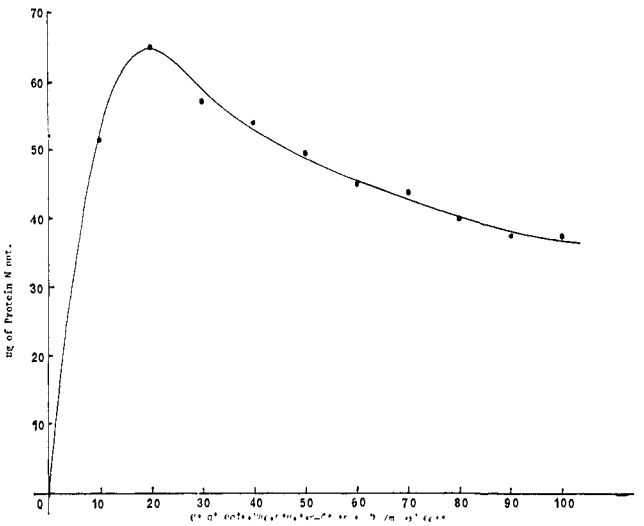

Figure 1.

Experimental Section

Melting points were taken with a Mel-Temp apparatus and are uncorrected.

Z-Phe-γ-*tert*-Bu-Glu-Ala-Gly-OMe (2).‡—To a soln of 15.1 g (27.6 mmole) of Z-Phe pentachlorophenyl ester in 200 ml of CH_2Cl_2 was added 10.5 g (27.6 mmoles) of γ-*tert*-Bu-Glu-Ala-Gly Me ester·HCl and 3.0 g (30 mmoles) of Et_3N. The mixt was stirred overnight at room temp and concd, and the product was dissolved in EtOAc, washed with 10% citric acid soln and H_2O, and then dried (Na_2SO_4) and concd *in vacuo* to give the product as an oil. This material was chromatog on a column of Silicar CC-7 using $CHCl_3$–EtOAc (1:1) as eluent, to give the fully blocked tetrapeptide; crystn from EtOAc–hexane yielded 13.5 g (78.5%): mp 183–185°, $[\alpha]^{24}D$ −12.5° (*c* 2.69, DMF). *Anal.* ($C_{32}H_{42}N_4O_9$) C, H, N.

Z-Phe-γ-*tert*-Bu-Glu-Ala-Gly Pentachlorophenyl Ester (3).—To a soln of 12.9 g (20.6 mmoles) of the fully blocked tetrapeptide **2** in 150 ml of MeOH was added 21 ml of 1 *N* NaOH and the soln was stirred for 90 min and then concd under reduced pressure. The residue was flooded with H_2O, acidified with 10% citric acid soln, and extd into EtOAc. The EtOAc soln was dried (Na_2SO_4) and concd under reduced pressure to give the tetrapeptide free acid as a solid; yield 12.6 g (100%). To this material in 90 ml of DMF was added 5.5 g (20.6 mmoles) of pentachlorophenol and 9.6 g (22.6 mmoles) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate. The mixt was stirred overnight at room temp. The reaction mixt was added to 400 ml of H_2O and the solid material was collected, washed with H_2O, and crystd from MeOH to yield 7.2 g (40.5%): mp 202–203°, $[\alpha]^{26}D$ −14.5° (*c* 5.59, DMF). *Anal.* ($C_{37}H_{39}Cl_5N_4O_9$) C, H, N.

Phe-γ-*tert*-Bu-Glu-Ala-Gly Pentachlorophenyl Ester·HCl (4).—A soln of 7.1 g (8.24 mmoles) of the tetrapeptide active ester **3** in 100 ml of MeOH was added to 0.8 g of 10% Pd/C. To this was added 8.25 ml of MeOH contg 0.30 g (8.24 mmoles) of dry HCl, and the mixt was hydrogenated for 2 hr. The reaction mixt was filtered, and the filtrate was concd to give a solid which was washed with Et_2O to yield 5.5 g (87.5%): mp 220°. $[\alpha]^{26}D$ 4.25° (*c* 4.7, DMF). *Anal.* ($C_{29}H_{34}Cl_6N_4O_7$) C, H, N.

Poly(Phe-Glu-Ala-Gly)Gly-*1*-^{14}C Et Ester (1).—To a soln of 1.0 mg of glycine-*1*-^{14}C Et ester·HCl (spec activity nCi/mmole) and 1.39 g (13.7 mmoles) of Et_3N in 5 ml of DMSO was added slowly a soln of 3.0 g (4.06 mmoles) of the polymerizing unit **4** in 34 ml of DMSO. The reaction mixt was shaken for 3 days at room temp and then centrifuged to yield the polymer which was washed with three 35-ml portions of H_2O and three 35-ml portions of Et_2O and dried to give the fully blocked polymer. This material was dissolved in 50 ml of 90% F_3CCO_2H and stirred for 50 min, and then concd under reduced pressure to yield the crude polypeptide **1**. This material was suspended in 40 ml of H_2O and dissolved by the addn of 4 *N* NaOH to pH 7.5. The soln was dialyzed against distd H_2O for 15 hr and then lyophilized to yield the Na salt of the polymer. This material was acidified to pH 2.5 with 6 *N* HCl in order to convert it to the free acid and dialyzed, with frequent changes of H_2O for 2 days. The free polypeptide **1** was obtained by lyophilization to yield 0.7 g (41%). *Anal.* ($C_{19}H_{24}N_4O_6 \cdot H_2O$) C, H, N.

Molecular Weight Determination.—A calibrated column of Sephadex G-50 (2.5 × 38.0 cm) was employed for the mol wt detn. Using 0.15 *M* NaCl as eluent, 4 mg of the Na salt of poly(Phe-Glu-Ala-Gly)Gly-*1*-^{14}C Et ester was passed through it and the polypeptide was eluted in a vol equiv to that corresponding to a mol wt of 1 × 10^4.

Immunochemical Results.—Two rabbits were treated at weekly intervals with 500 μg of poly(Phe-Glu-Ala-Gly)Gly-*1*-^{14}C Et ester **1**. The first 2 weeks they were injected intradermally using complete Freunds adjuvant as suspension medium and the 3rd week they were injected sc. The injection on the 4th week was done iv using buffered saline. Bleedings were conducted on the following week and the serum from one animal gave a precipitin reaction with polymer **1** as shown in Figure 1.

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‡ Z = benzyloxycarbonyl.

Synthesis and Reactions of Some Pyrrolidinediones

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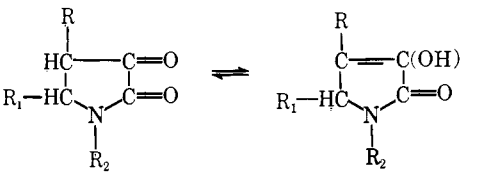
The present paper describes the synthesis and reactions of some new 2,3-, 2,4-, and 3,4-pyrrolidinediones. A number of 2,3-pyrrolidinediones are known,[1,2] and some of the new derivatives were found to possess an antimicrobial activity in preliminary screening tests. Their synthesis was carried out by the condensation of oxalacetic ester and phenylpyruvic acid and derivatives, as well as ethyl ethoxalylpropionate with different aldehydes and amines (Table I). The yields ranged from 30 to 60%.

SCHEME I



2,3-Pyrrolidinediones derived from phenylpyruvic acid failed to give a phenylhydrazone, an oxime, or an anil derivative and were recovered unchanged.

Attempts to prepare some 4-benzyl-2,3-pyrrolidinediones by the condensation of benzylpyruvic acid with different aldehydes and amines were unsuccessful. However, a 4-benzyl-2,3-pyrrolidinedione was prepared by condensing **2** with PhCHO in dil HCl soln to give the corresponding benzylidene derivative which was reduced with $NaBH_4$ to the required 4-benzyl-2,3-pyrrolidinedione.

(1) W. R. Vaughan and W. L. Meyer, *J. Org. Chem.*, **22**, 1560 (1957).
(2) P. L. Southwick and L. L. Seivard, *J. Amer. Chem. Soc.*, **71**, 2532 (1949); P. L. Southwick and R. T. Crouch, *ibid.*, **75**, 3413 (1953); P. L. Southwick, *J. Org. Chem.*, **21**, 1087 (1966).

TABLE I[l]

α-Keto acid or ester	Aldehyde	Amine	Time required at room temp for sepn of pyrrolidine-dione, hr	2,3-Pyrrolidine-dione	R	R_1	R_2	Mp, °C	Yield, %	Formula[k]
Oxalacetic ester	*p*-Nitrobenzaldehyde	*p*-Toluidine	24	1	$CO_2C_2H_5$	$C_6H_4NO_2$-*p*	$C_6H_4CH_3$-*p*	196–198[j]	32	$C_{20}H_{18}N_2O_6$
Oxalacetic ester	*p*-Nitrobenzaldehyde	2-Aminopyridine	24	2	$CO_2C_2H_5$	$C_6H_4NO_2$-*p*	C_5H_4N-α	186–187[j]	40	$C_{18}H_{15}N_3O_6$
Oxalacetic ester	*p*-Nitrobenzaldehyde	*p*-Chloroaniline	48	3	$CO_2C_2H_5$	$C_6H_4NO_2$-*p*	C_6H_4Cl-*p*	211–212	60	$C_{19}H_{15}ClN_2O_6$
Oxalacetic ester	*p*-Tolualdehyde	3-Aminopyridine	72	4	$CO_2C_2H_5$	$C_6H_4CH_3$-*p*	C_5H_4N-β	223–224[j]	36	$C_{19}H_{18}N_2O_4$
Oxalacetic ester	*p*-Tolualdehyde	2-Aminopyridine	24	5	$CO_2C_2H_5$	$C_6H_4CH_3$-*p*	C_5H_4N-α	195–196	30	$C_{19}H_{18}N_2O_4$
Oxalacetic ester	*o*-Vanillin	2-Aminopyridine	48	6	$CO_2C_2H_5$	$HOC_6H_3OCH_3$-*o,m*	C_5H_4N-α	190–191	54	$C_{19}H_{18}N_2O_8$
Oxalacetic ester	*p*-Chlorobenzaldehyde	2-Aminopyridine	24	7[a]	$CO_2C_2H_5$	C_6H_4Cl-*p*	C_5H_4N-α	213–214[j]	42	$C_{18}H_{15}ClN_2O_4$
Phenylpyruvic acid	Isobutyric aldehyde	Methylamine	72	8	C_6H_5	$(CH_3)_2CH$	CH_3	119–120	51	$C_{14}H_{17}NO_2$
Phenylpyruvic acid	Quinoline-4-aldehyde	Aniline	48	9	C_6H_5	C_9H_6N-4	C_6H_5	261–263	32	$C_{25}H_{18}N_2O_2$
Phenylpyruvic acid	Benzaldehyde	4-Aminopyridine	72	10	C_6H_5	C_6H_5	C_5H_4N-γ	277–278	31	$C_{21}H_{16}N_2O_2$
Phenylpyruvic acid	Veratraldehyde	Methylamine	72	11	C_6H_5	$C_6H_3(OCH_3)_2$-*m,p*	CH_3	186–187	30	$C_{19}H_{19}NO_4$
Phenylpyruvic acid	*m*-Methoxybenzaldehyde	*p*-Toluidine	18	12[b]	C_6H_5	$C_6H_4OCH_3$-*m*	$C_6H_4CH_3$-*p*	218–219	50	$C_{24}H_{21}NO_3$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*p*-Toluidine	6 days	13	C_6H_5	C_6H_4OH-*m*	$C_6H_4CH_3$-*p*	204–205	46	$C_{23}H_{19}NO_3$
Phenylpyruvic acid	*p*-Nitrobenzaldehyde	*p*-Bromoaniline	72	14	C_6H_5	$C_6H_4NO_2$-*p*	C_6H_4Br-*p*	226–227[j]	42	$C_{22}H_{15}BrN_2O_4$
Phenylpyruvic acid	*p*-Nitrobenzaldehyde	*p*-Aminoacetophenone	12	15	C_6H_5	$C_6H_4NO_2$-*p*	$C_6H_4COCH_3$-*p*	239–240	60	$C_{24}H_{18}N_2O_5$
Phenylpyruvic acid	Piperonal	*p*-Chloroaniline	4 days	16	C_6H_5	$C_6H_3(OCH_2O)$-3,4	C_6H_4Cl-*p*	231–232	40	$C_{23}H_{16}ClNO_4$
Phenylpyruvic acid	*p*-Nitrobenzaldehyde	*p*-Toluidine	18	17	C_6H_5	$C_6H_4NO_2$-*p*	$C_6H_4CH_3$-*p*	218–219	62	$C_{23}H_{18}N_2O_4$
Phenylpyruvic acid	*m*-Methoxybenzaldehyde	*p*-Aminoacetophenone	10 days	18	C_6H_5	$C_6H_4OCH_3$-*m*	$C_6H_4COCH_3$-*p*	212–213	54	$C_{25}H_{21}NO_4$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	2-Aminopyridine	Immediately	19	C_6H_5	C_6H_4OH-*m*	C_5H_4N-α	220	45	$C_{21}H_{16}N_2O_3$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*p*-Nitroaniline	24	20	C_6H_5	C_6H_4OH-*m*	$C_6H_4NO_2$-*p*	247–248[j]	32	$C_{22}H_{16}N_2O_5$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*m*-Nitroaniline	24	21	C_6H_5	C_6H_4OH-*m*	$C_6H_4NO_2$-*m*	234–235	26	$C_{22}H_{16}N_2O_5$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*p*-Chloroaniline	48	22[c]	C_6H_5	C_6H_4OH-*m*	C_6H_4Cl-*p*	201–202	34	$C_{22}H_{16}ClNO_3$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*p*-Bromoaniline	24	23	C_6H_5	C_6H_4OH-*m*	C_6H_4Br-*p*	212	36	$C_{22}H_{16}BrNO_3$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*p*-Toluidine	24	24[d]	C_6H_5	C_6H_4OH-*m*	$C_6H_4CH_3$-*p*	226–227	28	$C_{23}H_{19}NO_3$
Phenylpyruvic acid	*m*-Hydroxybenzaldehyde	*p*-Iodoaniline	72	25	C_6H_5	C_6H_4OH-*m*	C_6H_4I-*p*	238	26	$C_{22}H_{16}INO_3$
3,4-Dimethoxyphenylpyruvic acid	*p*-Nitrobenzaldehyde	*p*-Toluidine	22	26[e]	$C_6H_3(OCH_3)_2$-*m,p*	$C_6H_4NO_2$-*p*	$C_6H_4CH_3$-*p*	231–232	50	$C_{25}H_{22}N_2O_6$
3,4-Dimethoxyphenylpyruvic acid	*p*-Nitrobenzaldehyde	Aniline	14 days	27	$C_6H_3(OCH_3)_2$-*m,p*	$C_6H_4NO_2$-*p*	C_6H_5	204–205[j]	45	$C_{24}H_{20}N_2O_6$
3,4-Dimethoxyphenylpyruvic acid	*p*-Nitrobenzaldehyde	*p*-Chloroaniline	12 days	28	$C_6H_3(OCH_3)_2$-*m,p*	$C_6H_4NO_2$-*p*	C_6H_4Cl-*p*	227–228	37	$C_{24}H_{19}ClN_2O_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	*p*-Toluidine	3 days	29	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	$C_6H_4CH_3$-*p*	247–248	40	$C_{26}H_{25}NO_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	*p*-Iodoaniline	24	30	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	C_6H_4I-*p*	264[j]	25	$C_{25}H_{22}INO_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	*m*-Toluidine	72	31[f]	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	$C_6H_4CH_3$-*m*	237	20	$C_{26}H_{25}NO_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	2-Aminopyridine	Immediately	32	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	C_5H_4N-α	220	30	$C_{24}H_{22}N_2O_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	3,4-Dimethylaniline	72	33	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	$C_6H_3(CH_3)_2$-*m,p*	265	33	$C_{27}H_{27}NO_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	Methylamine	7 days	34	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	CH_3	245[j]	14	$C_{20}H_{21}NO_6$
3,4-Dimethoxyphenylpyruvic acid	*o*-Vanillin	*m*-Bromoaniline	72	35	$C_6H_3(OCH_3)_2$-*m,p*	$HOC_6H_3OCH_3$-*o,m*	C_6H_4Br-*m*	238	40	$C_{25}H_{22}BrNO_6$
3,4-Dimethoxyphenylpyruvic acid	Veratraldehyde	2-Aminopyridine	7 days	36	$C_6H_3(OCH_3)_2$-*m,p*	$C_6H_3(OCH_3)_2$-*m,p*	C_5H_4N-α	168	31	$C_{25}H_{24}N_2O_6$
3,4-Dimethoxyphenylpyruvic acid	*p*-Anisaldehyde	*p*-Chloroaniline	24	37	$C_6H_3(OCH_3)_2$-*m,p*	$C_6H_4OCH_3$-*p*	C_6H_4Cl-*p*	185	13	$C_{25}H_{22}ClNO_5$
3,4-Methylenedioxyphenylpyruvic acid	*o*-Vanillin	3,4-Dimethylaniline	24	38[g]	$C_6H_3(OCH_2O)$-3,4	$HOC_6H_3OCH_3$-*o,m*	$C_6H_3(CH_3)_2$-*m,p*	280[j]	22	$C_{26}H_{23}NO_6$
Benzoylpyruvic ester	*p*-Nitrobenzaldehyde	*p*-Toluidine	4 days	39[h]	COC_6H_5	$C_6H_4NO_2$-*p*	$C_6H_4CH_3$-*p*	249–250[j]	30	$C_{24}H_{18}N_2O_5$
Benzoylpyruvic ester	*p*-Nitrobenzaldehyde	2-Aminopyridine	4 days	40	COC_6H_5	$C_6H_4NO_2$-*p*	C_5H_4N-α	211–212[j]	38	$C_{22}H_{15}N_3O_5$
Benzoylpyruvic ester	*p*-Nitrobenzaldehyde	Aniline	48	41	COC_6H_5	$C_6H_4NO_2$-*p*	C_6H_5	245–246	45	$C_{23}H_{16}N_2O_5$
Benzoylpyruvic ester	*p*-Nitrobenzaldehyde	*p*-Aminoacetophenone	24	42	COC_6H_5	$C_6H_4NO_2$-*p*	$C_6H_4COCH_3$-*p*	264–265	30	$C_{25}H_{18}N_2O_6$
Benzoylpyruvic ester	*p*-Nitrobenzaldehyde	*p*-Chloroaniline	22	43	COC_6H_5	$C_6H_4NO_2$-*p*	C_6H_4Cl-*p*	237–238[j]	28	$C_{23}H_{15}ClN_2O_5$
Benzoylpyruvic ester	Benzaldehyde	*p*-Aminoacetophenone	18	44	COC_6H_5	C_6H_5	$C_6H_4COCH_3$-*p*	224–225	40	$C_{25}H_{19}NO_4$
Ethyl ethoxalylpropionate	*p*-Chlorobenzaldehyde	Aniline	20	45[i]	COC_6H_5	C_6H_4Cl-*p*	C_6H_5	150–151	57	$C_{20}H_{18}ClNO_4$
Ethyl ethoxalylpropionate	*p*-Nitrobenzaldehyde	2-Aminopyridine	22	46	COC_6H_5	$C_6H_4NO_2$-*p*	C_5H_4N-α	194–195	53	$C_{19}H_{17}N_3O_6$
Ethyl ethoxalylpropionate	*p*-Nitrobenzaldehyde	Aniline	24	47	COC_6H_5	$C_6H_4NO_2$-*p*	C_6H_5	248	52	$C_{20}H_{18}N_2O_6$
Ethyl ethoxalylpropionate	*o*-Nitrobenzaldehyde	*p*-Toluidine	24	48	COC_6H_5	$C_6H_4NO_2$-*o*	$C_6H_4CH_3$-*p*	165	58	$C_{21}H_{20}N_2O_6$
Ethyl ethoxalylpropionate	*m*-Nitrobenzaldehyde	*p*-Toluidine	24	49	COC_6H_5	$C_6H_4NO_2$-*m*	$C_6H_4CH_3$-*p*	235[j]	25	$C_{21}H_{20}N_2O_6$
Ethyl ethoxalylpropionate	*o*-Nitrobenzaldehyde	*m*-Toluidine	24	50	COC_6H_5	$C_6H_4NO_2$-*o*	$C_6H_4CH_3$-*m*	155	37	$C_{21}H_{20}N_2O_6$
Ethyl ethoxalylpropionate	Benzaldehyde	*m*-Nitroaniline	24	51	COC_6H_5	C_6H_5	$C_6H_4NO_2$-*m*	195	25	$C_{20}H_{18}N_2O_6$
Ethyl ethoxalylpropionate	*m*-Nitrobenzaldehyde	Aniline	24	52	COC_6H_5	$C_6H_4NO_2$-*m*	C_6H_5	162–164	21	$C_{20}H_{18}N_2O_6$

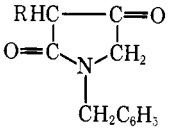
[a] λ_{max} (log ε) in MeOH, 285 (4.09), 325 (4.04). [b] 280 (3.82), 305 (3.9). [c] 285 (4.22), 307 (3.3). [d] 285 (4.15), 305 (4.18). [e] 270 (4.25), 280 (4.25), 320 (4.32). [f] 285 (4.09), 327 (4.4). [g] 285 (3.64), 330 (3.91). [h] 265 (4.22), 355 (4.15). [i] 295 (3.29). [j] Decomposition. [k] All analyses for C, H. [l] See Scheme I.

TABLE II

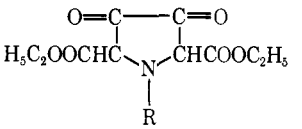
2,3-Dioxopyrrolidine	Derivative	Mp, °C	Solvent and shape of crystals	Formula[a]
1	Methyl ether	126–127	Aq EtOH	$C_{21}H_{20}N_2O_6$
2	Methyl ether	143–144	EtOH	$C_{19}H_{17}N_3O_6$
12	Methyl ether	125	EtOH	$C_{25}H_{23}NO_3$
23	Methyl ether	142–143	EtOAc–petr ether, plates	$C_{24}H_{20}NO_3Br$
4	Acetyl	224–225[b]	EtOH, white needles	$C_{21}H_{20}N_2O_5$
14	Acetyl	211–212	EtOH, white needles	$C_{24}H_{17}BrN_2O_5$
32	Acetyl	216	PhH–petr ether prisms	$C_{26}H_{24}N_2O_7$
37	Acetyl	234–235	EtOAc needles	$C_{27}H_{24}ClNO_3$
2	Benzoyl	194–195	EtOH	$C_{25}H_{19}N_3O_7$
15	Benzoyl	225–226	EtOH	$C_{31}H_{22}N_2O_6$
24	Benzoyl	215	PhH–petr ether needles	$C_{31}H_{22}N_2O_5$
20	Benzoyl	216–217	EtOAc, needles	$C_{36}H_{24}N_2O_7$
2	Quinoxaline	205–206	PhH	$C_{24}H_{19}N_5O_4$
7	Quinoxaline	263–264	AcOH, orange needles	$C_{24}H_{19}ClN_4O_2$
12	Quinoxaline	220–221[b]	EtOH, prisms	$C_{30}H_{25}N_3O$
23	Quinoxaline	277–278	MeOH, yellow needles	$C_{28}H_{20}BrN_3O$
38	Quinoxaline	262–263	MeOH, yellow needles	$C_{32}H_{27}N_3O_4$
6	2,3-Dinitrophenylhydrazone	241–242	AcOH	$C_{25}H_{22}N_6O_9$
48	Phenylhydrazone	172–173	MeOH, yellow prisms	$C_{27}H_{26}N_4O_5$
47	Phenylhydrazone	169–170	EtOAc–petr ether, yellow needles	$C_{26}H_{24}N_4O_5$
2	Oxime	249–250[b]	EtOH	$C_{18}H_{15}N_4O_6$
48	Oxime	122–123	EtOAc–petr ether needles	$C_{21}H_{21}N_3O_6$
47	Oxime	242–243	EtOH, prisms	$C_{20}H_{19}N_3O_6$
2	Anil	253–254	EtOH	$C_{24}H_{20}N_4O_5$
2	Carbethoxy to carbmethoxy	197–198[b]	PhH	$C_{17}H_{13}N_3O_6$

[a] All analyses for N. [b] Decomp.

Analogs of the 2,4-pyrrolidinediones described have been reported to be useful as sedatives and antispasmodics[3] and to possess an anticonvulsant activity.[4] 3,4-Pyrrolidinediones have been little investigated.



53, R = C_6H_5
54, R = $C_6H_3(OCH_2O)$ (3, 4)



55, R = C_6H_5
56, R = $C_6H_4CH_3$-*o*

In preliminary pharmacological testing a number of 2,3-pyrrolidinediones were tested against *Staphylococcus aureus* (resistant strain), *Klebsiella pneumoniae, Streptococcus aureus, Trichomonas foetus, Candida albicans, and T. mentagrophytes.*

4-Carbethoxy-5-(*p*-chlorophenyl)-1-phenyl-2,3-pyrrolidinedione[5] and the dione **2** were active against *T. foetus* in the *in vitro* screen to a dilution of 15–39 μg/ml while 4-carboxy-2-(*p*-chlorophenyl)-3-phenyl-7,8-benzo(*h*)quinoline[5] was active against *T. foetus* and *Streptococcus aureus* at 15–39 μg/ml. The other compds failed to show any appreciable antimicorbial activity.

Experimental Section

2,3-Pyrrolidinediones.—Equimolar quantities of the α-keto acid or ester, the aldehyde, and amine were dissolved in EtOH and the soln was refluxed for 40–45 min and then kept at room temp. The 2,3-pyrrolidinedione which sepd was filtered, washed with EtOH, and crystd usually from EtOH or AcOH (Table I).

The prepn of derivatives of 2,3-pyrrolidinediones such as Me ethers, Ac, Bz, and quinoxaline derivatives, oximes, 2,4-dinitrophenylhydrazones, and anils and the conversion of carbethoxy to carbmethoxy group was carried out as reported earlier.[6,7]

The diones obtd from oxalacetic ester, phenyl-, 3,4-dimethoxyphenyl-, and benzoylpyruvic acids give reddish, greenish, blueish green and blood red colorations, respectively, with $FeCl_3$. The ir spectra[2] of the diones exhibited bands between 1780 and 1765 cm^{-1} and between 1710 and 1720 cm^{-1}.

4-Benzylidene-1-α-pyridyl-5-*p*-nitrophenyl-2,3-pyrrolidinedione.—A mixt of **2** (3 g) and freshly distd PhCHO (2 g) was added to HCl (50 ml, 25%) contg some EtOH and the mixt was refluxed with stirring for 8 hr. After cooling for several hr, the solid which sepd was filtered (900 mg) and crystd from EtOH as pale yellow needles, mp 222–223°. *Anal.* ($C_{22}H_{15}N_3O_4$) C, H.

4-Benzyl-1-α-pyridyl-5-*p*-nitrophenyl-2,3-pyrrolidinedione.—The above dione (1 g) was added over a period of 10 min to a soln of $NaBH_4$ (110 mg) in EtOH (6 ml) and allowed to stand for 1 hr. After decompn the solvent was evapd under reduced pressure, leaving a white solid which was washed with H_2O and crystd from EtOH in colorless needles (120 mg), mp 213–214° dec. *Anal.* ($C_{22}H_{17}N_3O_4$) C, H, N.

2,4-Pyrrolidinediones.—Ethyl formate (0.108 mole) was dropped into a stirred and chilled suspension of NaOEt (0.1 mole) in Et_2O (100 ml) and stirred for 1 hr. (*N*-Phenacetyl)benzylaminoacetate (0.1 mole) was dropped in, and the mixt was stirred for 3 hr and allowed to warm to room temp. It was extd with H_2O and acidified to give **53**.[8]

Similarly, with *N*-3,4-methylenedioxyphenylbenzylaminoacetate, **54**, mp 226–227° from EtOH, was obtd. *Anal.* ($C_{18}H_{15}NO_4$) C, H.

3,4-Pyrrolidinediones.—A mixt of diethyl *N*-phenyldiglycolamidate (6.7 g) and diethyl oxalate (3.7 g) was added to NaOEt (1.5 g of Na in 50 ml of EtOH) and warmed gently when a vigorous reaction set in with the formation of a yellow disodium salt of **55**.

(3) German Patent 695,330; *Chem. Abstr.*, **35**, 3647 (1941); Swiss Patent 213,347; *Chem. Abstr.*, **36**, 4974 (1942); U. S. Patent 2,328,232; *Chem. Abstr.*, **38**, 753 (1944).

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After heating at 100° for 3–4 hr the salt was dissolved in cold H_2O and washed with Et_2O when **55** (7.5 g) sepd as yellow prisms. It was crystd from EtOH, mp 137–138°. *Anal.* ($C_{16}H_{17}NO_6$) C, H, N.

Similarly, condensation of diethyl *N*-*o*-tolyldiglycolamidate (3 g) and diethyl oxalate (1.85 g) gave **56** (1 g) on acidification of the soln of the Na salt. It was crystd from EtOH, mp 140–141°. *Anal.* ($C_{17}H_{19}NO_6$) C, H.

Acknowledgment.—We are grateful to Smith Kline & French Laboratories, Philadelphia, Pa., for carrying out the pharmacological testing of the compounds.

Preparation of Some Trimethylpentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8,11-dione Derivatives

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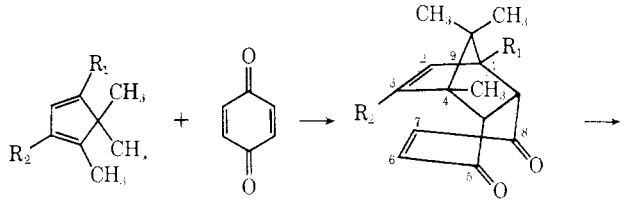
The prophylactic use of 1-aminoadamantane against Asian influenza in man has been described.[1] It appeared interesting to determine what other "cage" systems might combine a desirable size and shape with an unsubstituted amino function to produce structures having antiinfluenzal activity. The preparation of derivatives of the birdcage hydrocarbon,[2] homocubane[3] and noradamantane,[4] has already been reported from these laboratories. We now wish to report the preparation of amino derivatives of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione.

This cage system ($R_1 = R_2 = H$) was first prepared by Cookson and coworkers by the photocyclization of the Diels–Alder adduct of *p*-benzoquinone and cyclopentadiene.[5] In the present study, access to the cage system with an amino function was accomplished by using cyclopentadienes having a carboxyl group at the appropriate position in a reaction sequence paralleling that described by Cookson, *et al.* The resulting cage acid was converted to the amine in the last step.

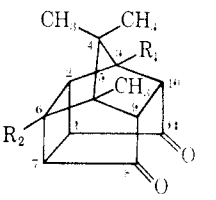
To obtain the 3-amino derivative of this system, the Me ester of α-camphylic acid[6] was condensed with *p*-benzoquinone to give the endo adduct **2a** which, upon uv irradiation in acetone, closed to the saturated diketone **3a**. Hydrolysis of **3a** with 48% HBr gave the free carboxylic acid **3b** which was converted to the amine **4a** *via* a modified Curtius reaction.[7]

Similarly, β-camphylic acid (**1b**)[6] was condensed with *p*-benzoquinone to give adduct **2b**. Irradiation of **2b** gave the cage acid **3c** which was characterized as the Et ester **3d**. This (**3c**) was converted, *via* the modified Curtius reaction, to the amine **4b**. The possibility that photolysis of **2a** and **2b** had resulted in dimerization[8] rather than intramolecular cyclization was ruled out by



1a, $R_1 = COOCH_3$; $R_2 = H$
1b, $R_1 = H$; $R_2 = COOH$

2a, $R_1 = COOCH_3$; $R_2 = H$
2b, $R_1 = H$; $R_2 = COOH$



3a, $R_1 = COOCH_3$; $R_2 = H$
3b, $R_1 = COOH$; $R_2 = H$
3c, $R_1 = H$; $R_2 = COOH$
3d, $R_1 = H$; $R_2 = COOC_2H_5$
4a, $R_1 = NH_2$; $R_2 = H$
4b, $R_1 = H$; $R_2 = NH_2$

determining the molecular weights (mass spectra) of the condensation products **3a** and **3c**.

Biological Activity.—The cage amines and several of the intermediates described were tested *in vitro* (plaque inhibition)[9] for antiinfluenza activity. The amines were also tested for activity against influenzal pneumonitis in mice.[10] Compds **2b, 4a,** and **4b** showed no activity *in vitro* against influenza A (WSN), parainfluenza 1 (Sendai), and influenza A_2 (Ann Arbor), but **3a** and **3c** had marginal activity against influenza A (WSN). Compd **4a** showed marginal activity against influenzal pneumonitis [influenza A_2 (Ann Arbor), well-tolerated dose in mice, 100 mg/kg; increase in per cent survival, 10%; increase in mean survival days, 1.4 days]. Compd **4b** was inactive against both influenza A_2 (Ann Arbor) and A_1 (swine) in mice.

Experimental Section

General.—Irradiation was carried out with a 250-W Hanovia medium-pressure Hg lamp in Pyrex apparatus. All mp (Thomas-Hoover apparatus) and bp are uncorrected.

Methyl 1,4,4a,5,8,8a-Hexahydro-4,9,9-trimethyl-5,8-dioxo-1,4-methanonaphthalene-1-carboxylate (2a).—Attempts to condense α-camphylic acid with *p*-benzoquinone returned only unreacted starting material. Consequently, the condensation was carried out using the Me ester. Methyl α-camphylate was prepd in 85% yield by methylation of α-camphylic acid[11] with CH_2N_2. A soln of 10.8 g (64 mmoles) of methyl α-camphylate and 7.0 g (64 mmoles) of recrystd *p*-benzoquinone in 130 ml of C_6H_6 was refluxed in the dark under N_2 for 22 hr. Upon removal of C_6H_6 *in vacuo*, the residual oil solidified. The crude product was crystd from aq MeOH to give 9.48 g (54%) of a yellow solid: mp 110–112°; nmr ($CDCl_3$), 0.82 (3 H, s), 1.02 (3 H, s), and 1.35 (3 H, s), CH_3 groups, 3.22 and 3.95 (2 H as AB quartet, J = 9 Hz), $C_{4a}H$ and $C_{8a}H$, 3.87 (1 H, s) OCH_3, 5.84 and 6.23 (2 H as AB quartet, J = 6 Hz), C_2H and C_3H, 6.63 (2 H, s) C_6H and C_7H. *Anal.* ($C_{16}H_{18}O_4$) C, H.

4,4,5-Trimethyl-8,11-dioxopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-3-carboxylic Acid (3b).—A soln of 1.9 g (6.94 mmoles) of adduct **2a** in 450 ml of EtOAc was irradiated for 24 hr under N_2. The colorless soln was concd *in vacuo* to a small vol to give

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(11) α-Camphylic acid can also be prepd from the β isomer by heating the latter at 175° for 15 hr in a closed system.