Experimental Section

When analyses are indicated, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Catalytic Hydrogenation of 6-Benzylmethylamino-4,4-diphenylheptan-3-one and Its 5-Methylhexan-3-one Isomer.—A mixture of the amino ketone **5a**[12] (20 g), 4 *N* HCl (20 ml), 10% Pd–C (2.5 g), and EtOH (400 ml) was shaken with H_2 at room temperature and pressure until gas uptake ceased. The filtered product was evaporated and the residual salt (11 g) gave the **pyrrolidine base 8**: bp 128–132° (0.5 mm) (8 g); mp 56–58° from EtOH; N–Me pmr characteristics in $CDCl_3$ (Hz from TMS), base 147 (singlet), HCl 176 (doublet J = 5 Hz). *Anal.* ($C_{20}H_{25}N$) C, H, N.

The same product, mp and mmp 56–58°, was obtained by shaking a mixture of the freshly distilled base (2.5 g) from 2-ethyl-4-methyl-3,3-diphenyl-Δ′-pyrroline hydriodide **9**,[9,10] 10% Pd–C (0.2 g), and EtOH (70 ml) with H_2 at 60°. The hydriodide **9** resisted hydrogenation under these conditions. The same reduction procedure applied to the benzylmethylamino ketone **7**[12] gave the 4-methylpyrrolidine isomer **10** as a **hydrochloride monohydrate**, mp 226–227° from EtOH–Et_2O. *Anal.* ($C_{26}C_{26}ClN\cdot H_2O$) C, H, N.

Debenzylation of 6-Benzylmethylamino-4,4-diphenylheptan-3-ol.—The benzylmethylaminomethadol **5b** (α isomer) was obtained as a hydrochloride, mp 188–190° (lit.[8] 178–179°) from EtCO–Et_2O, by treating the ketone **5a** with LAH. *Anal.* ($C_{27}H_{34}ClNO$) C, H, N. A mixture of the free base **5b** (6 g), 4 *N* HCl (6 ml), 10% Pd–C (1 g), and EtOH (120 ml) was shaken with H_2 and processed as described for the reduction of **5a**. The *sec*-amine reaction product **11b** was isolated as a **hydrochloride** (3 g): mp 183–185° from EtOH–Et_2O; N-Me pmr characteristics of HCl (Hz from TMS), 135 (triplet J = 5) in DMSO-d_6, 145 (triplet J = 5) in $CDCl_3$. The salt had a sharp ir absorption at 3400 cm^{-1} (ν_{OH}) and the base at 3280 cm^{-1} superimposed upon a broad shoulder between 3500 and 3100 cm^{-1} typical of methadols (ν_{OH} and ν_{NH}). *Anal.* ($C_{20}H_{28}ClNO$) C, H, N.

Hydrolysis of α-3-Acetoxy-6-cyanomethylamino-4,4-diphenylheptane.—A mixture of the N-cyanomethyl derivative **12** (15 g)[7] and 6% HCl in H_2O (300 ml) was heated under reflux for 12 hr, cooled, and extracted (Et_2O) to remove nonbasic products. The base (3.5 g) recovered from the aqueous phase as usual was treated with HBr–EtOH to give the *sec*-**amine 11b hydrobromide**, mp 206–207° from EtOH–Et_2O. *Anal.* ($C_{20}H_{28}BrNO$) C, H, N. The melting point of this salt was undepressed by the hydrobromide of the *sec*-amine derived from **5b**.

Pmr spectra were recorded on a Varian A-60 spectrometer with $CDCl_3$ or DMSO-d_6 as solvents and TMS as standard.

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Synthesis of Some Ureidodihydrofurans and Related Pyrimidones as Potential Antimalarials[1,2]

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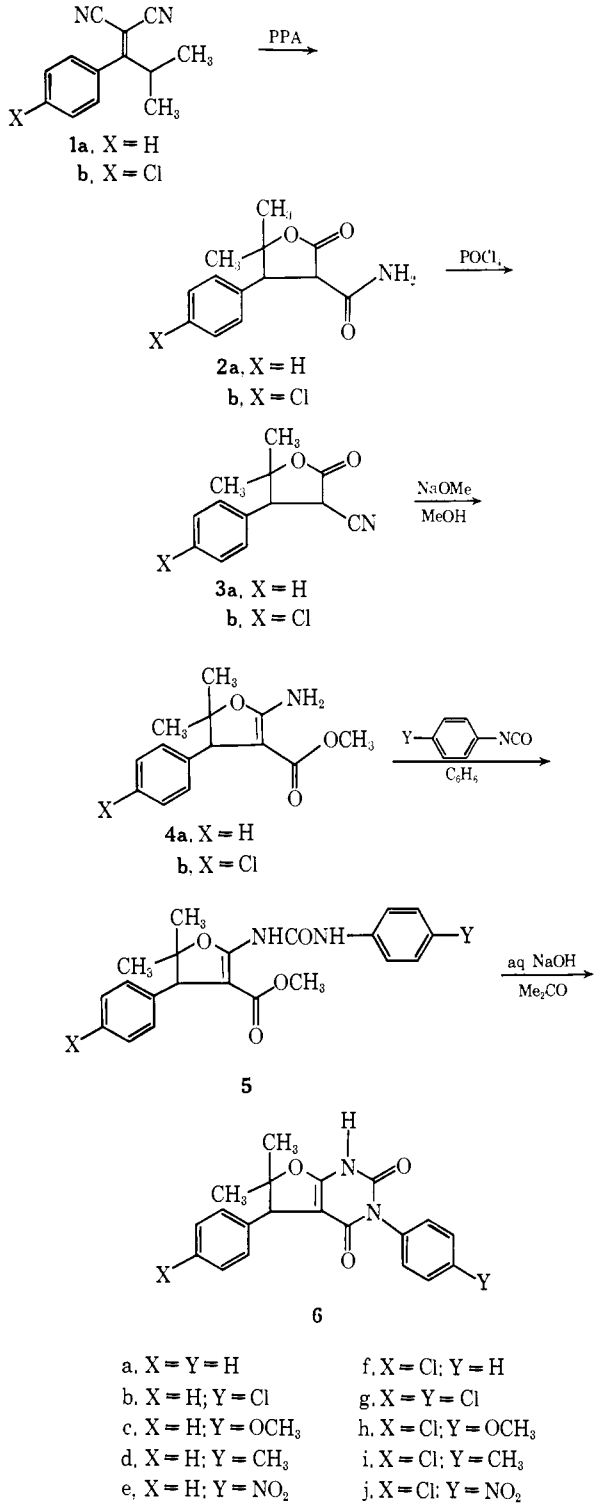
Extensive studies have been carried out in these laboratories concerning sulfuric acid cyclizations of ylidenemalonitriles derived from aryl- and alkyl-substituted aromatic ketones[3-6] leading to the formation of both indenone and indanone derivatives. Cyclization, however, of certain alkyl-substituted ylidenemalononitriles in polyphosphoric acid (PPA) leads to the formation of butyrolactones[7,8] which contain functional groups susceptible to metathesis. For example, cyclization of α-cyano-β-isopropylcinnamonitrile (**1a**) in hot PPA produces the lactone **2a** (see Chart I). It was envisioned that **2a** offered

CHART I



a, X = Y = H
b, X = H; Y = Cl
c, X = H; Y = OCH_3
d, X = H; Y = CH_3
e, X = H; Y = NO_2
f, X = Cl; Y = H
g, X = Y = Cl
h, X = Cl; Y = OCH_3
i, X = Cl; Y = CH_3
j, X = Cl; Y = NO_2

(1) Contribution No. 1640 from the Chemistry Laboratories of Indiana University.

(2) Taken in part from the thesis of R. L. E. submitted to the Graduate School of Indiana University in partial fulfillment of the requirements for the Ph.D. degree, May 1967.

(3) E. Campaigne and G. F. Bulbenko, *J. Org. Chem.*, **26**, 4703 (1961).

(4) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum, and D. R. Maulding, *ibid.*, **27**, 4428 (1962).

(5) E. Campaigne, D. R. Maulding, and W. L. Roelofs, *ibid.*, **29**, 1543 (1964).

(6) E. Campaigne and W. L. Roelofs, *ibid.*, **30**, 396 (1965).

(7) E. Campaigne and R. L. Ellis, *Chem. Commun.*, 141 (1966).

(8) E. Campaigne and R. L. Ellis, *J. Org. Chem.*, **32**, 2372 (1967).

versatility as a potential precursor toward a wide variety of pyrimidines with potential biological activity. This note represents one such study.

Discussion

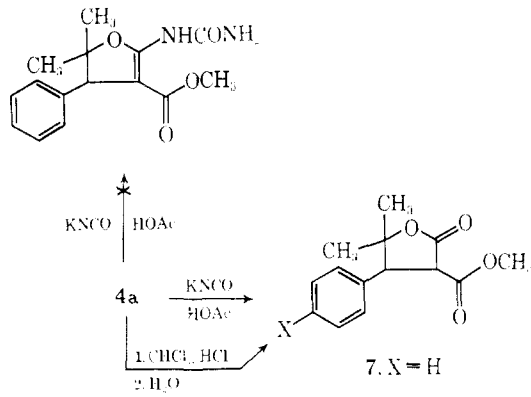
Since it has been reported that α-cyano-γ-lactones are capable of condensation with guanidine, urea, or thiourea[9] and are susceptible to rearrangement employing a sodium alkoxide salt[10] or concentrated NH_4OH[11] to yield 2-amino-3-carboalkoxydihydrofurans and 2-amino-3-carboxamidodihydrofurans, respectively, attempts were directed toward the preparation of α-cyanobutyrolactones of type **3**. Reaction of **2a** or **2b** with $POCl_3$[12] proceeded smoothly to yield **3a** or **3b**, but treatment with either dicyclohexylcarbodiimide[13] or toluenesulfonyl chloride in pyridine[14] returned only unreacted starting material.

The conversion of **3a** to **4a** must be carried out employing only a catalytic amount of alkoxide (see Experimental Section). Korte and Trautner[10] theorize that in the presence of 1 molar equiv of alkoxide ion, a shift of the equilibrium occurs toward the cyanolactone (from the amino ester) by formation of the conjugate anion of the cyanolactone. Surprisingly, the conversion of **3b** and **4b** was more refractory. Under identical conditions the latter cyanolactone required a longer reaction time (60–72 hr *vs.* 48 hr) to give satisfactory yields.

The first exploitation of condensing amines with organic isocyanates to generate a pyrimidine ring system *via* the initially formed ureas was by Breukink and Verkade[15] who reported the condensation of phenyl isocyanate and anthranilonitrile to generate an N-substituted quinazoline. Taylor and Ravindranathan[16] found that by employing phenyl isocyanate the same general reaction would occur under milder conditions. The synthesis of the unsubstituted quinazoline employing anthranilic acid and KCNO was reported by Lange and Sheibly.[17] When **4a** and **4b** were condensed with a series of *para*-substituted phenyl isocyanates the corresponding ureas (**5**) were isolated in good yields employing the conditions of Breukink and Verkade.[18] Disappointingly, condensation of **4a** with KCNO employing either 90% aqueous AcOH[18] or 1 molar equiv of KCNO and AcOH[17] did not produce the monosubstituted ureas as anticipated. It was theorized that the presence of AcOH resulted in rearrangement of **4a** to **7** *via* the imino ether derivative of **4a** followed by hydrolysis. This was verified by refluxing **4a** in chloroform with a trace of dry HCl followed by hydrolysis (see Chart II).

Cyclization of substituted ureas similar to **5** have been reported,[16,18] using strong bases such as alkoxide.

CHART II



Treatment of **5a** with a catalytic amount of NaOMe in MeOH afforded the desired compound **6a** in only 40% yield, along with starting material and decomposition products. The desired **6a** was isolated in a pure state only after column chromatography. Since the purification was tedious and the yield less than satisfactory, improved reaction conditions for the formation of **6a** were sought. Such variables as concentration of the alkoxide, the molar ratio of alkoxide, and time of reflux were explored but none of these proved fruitful. Treatment of **5** with 5% Me_2CO–H_2O–NaOH (sufficient to form a homogeneous solution) produced **6** in good to excellent yields of nearly pure product. The uv spectra of **5** and **6** are characteristic, and these are reported in Tables I and II. Disappointingly chlorination of **6a** with $POCl_3$ was unsuccessful and hence the desired aminopyrimidines were unobtainable by this route.

Pharmacology.—The above-described compounds were screened for potential antimalarial activity by the Walter Reed Army Institute of Research, using the procedure described by Osdene, Russell, and Rane.[19] We are indebted to Drs. Strube, Jacobus, and Sweeney for the results of these tests. None of the compounds submitted (**4b, 5a–j, 6a–d**) were considered active at the 640-mg/kg dose level.

Experimental Section

All melting points reported were obtained from a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Ir spectra were recorded with a Perkin-Elmer Model 137 or 137A Infracord. The uv spectra were recorded using either a Bausch and Lomb Model 505 or a Cary 14 spectrophotometer. The nmr spectra were recorded on a Varian Model A-60 spectrometer (Me_4Si as internal reference). All ir and nmr spectra are in agreement with the assigned structures.

α-Cyano-β-isopropylcinnamonitrile (1a) was prepared according to the method described by Campaigne, *et al.*,[4] in yields averaging about 92% based on consumed ketone; bp 118–120° (0.5 mm), mp 60°.

4-Chloro-α-cyano-β-isopropylcinnamonitrile (1b).—A mixture of 91 g (0.50 mole) 4-chloroisobutyrophenone,[20] 40 g (0.60 mole) of malononitrile, 5 g of NH_4OAc, and 15 ml of HOAc in 300 ml of dry C_6H_6 was refluxed for 8 hr while the azeotroped H_2O was collected in a Dean–Stark trap. At this time an additional portion of 6.6 g (0.1 mole) of malononitrile, 2 g of NH_4OAc, and 5 ml

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(19) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
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TABLE I

PHYSICAL CONSTANTS OF UREAS (5)

Urea	% yield	Mp, °C	Reflux period, hr	Recrystn solvent	Formula[c]	Uv[a] spectra λ_{max}, mμ	Uv[a] spectra $\epsilon \times 10^{-3}$
5a	93	150–152	16	95% EtOH	$C_{21}H_{22}N_2O_4$	208, 240, 286	39.2, 17.8, 34.0
b	97	167–169	16	95% EtOH	$C_{21}H_{21}ClN_2O_4$	207, 247, 287	39.8, 19.0, 33.8
c	82	150–152	16	95% EtOH	$C_{22}H_{24}N_2O_5$	207, 230, 252, 288	33.9, 15.85, 15.5, 31.7
d	91	158–159	16	95% EtOH	$C_{22}H_{24}N_2O_4$	207, 233, 288	42.3, 19.35, 31.6
e	91	192–194	8	EtOAc–cyclohexane	$C_{21}H_{21}N_3O_6$	207, 220 (s), 278, 327	32.3, 25.2, 14.6, 26.3
f	73[b]	171–173	16	C_6H_6	$C_{21}H_{21}ClN_2O_4$	207, 224, 241, 288	34.0, 19.2, 15.0, 32.0
g	74[b]	184–186	54	C_6H_6	$C_{21}H_{20}Cl_2N_2O_4$	208, 224, 250, 285	28.0, 15.2, 14.0, 27.0
h	63[b]	164–166	66	C_6H_6	$C_{22}H_{23}ClN_2O_5$	208, 224, 230 (s), 290	21.0, 18.8, 15.8, 20.0
i	71[b]	144–146	18	C_6H_6–hexane	$C_{22}H_{23}ClN_2O_4$	207, 223, 254, 289	31.0, 19.0, 15.5, 25.0
j	72[b]	137–140	52	C_6H_6	$C_{21}H_{20}ClN_3O_6$	208, 225, 274, 326	26.0, 21.5, 11.0, 23.0

[a] Spectra were recorded on a Bausch and Lomb 505 spectrometer in 95% EtOH. [b] Second crop of crystalline product was not attempted, while yields of **5a–e** are based on first and second crops. [c] All compounds gave a correct analysis for C, H, N.

TABLE II

PHYSICAL CONSTANTS OF PYRIMIDINE-2,4-DIONES (6)

Pyrimidine	% yield	Mp, °C	Reflux period, hr	Recrystn solvent	Formula[e]	Uv[a] spectra λ_{max}, mμ	Uv[a] spectra $\epsilon \times 10^{-3}$
6a	75	232.5–233.5	12[b]	$CHCl_3$	$C_{20}H_{18}N_2O_3$	213, 266	18.0, 16.7
b	92	248–250	12	95% EtOH	$C_{20}H_{17}ClN_2O_3$	210, 220, 268	19.3, 18.9, 15.6
c	87	226–228	12	95% EtOH	$C_{21}H_{20}N_2O_4$	208, 223, 267	26.2, 21.0, 16.0
d	77	229–231	12	c	$C_{22}H_{20}N_2O_3$	216, 264	23.0, 19.1
e	28[d]	217–219	24[d]	EtOAc	$C_{20}H_{17}N_3O_5$	208, 211, 267	24.5, 25.0, 18.2
f	82	214–216	18	EtOAc	$C_{20}H_{17}ClN_2O_3$	212 (s), 222, 265	16.2, 17.3, 9.1
g	50	247–249	18	95% EtOH	$C_{26}H_{16}Cl_2N_2O_3$	209, 223, 268	28.0, 27.0, 8.0
h	70	231–233	18	95% EtOH	$C_{21}H_{19}ClN_2O_4$	208, 225, 267	35.0, 32.0, 14.0
i	70	238–240	18	EtOAc	$C_{21}H_{19}ClN_2O_3$	209, 222, 267	34.0, 26.0, 11.0
j	33	269–271	4	95% EtOH	$C_2OH_{16}ClN_3O_5$	209, 218, 267	27.0, 27.0, 21.5

[a] Spectra were recorded on a Bausch and Lomb 505 spectrometer in 95% EtOH. [b] Compounds **6a–e** employed 10 ml of Me_2CO/g of urea while **6f–j** employed 4 ml of Me_2CO/g of urea. [c] Recrystallized from 95% EtOH and subsequently from $CHCl_3$ for an analytical sample. [d] Ring closure *via* NaOMe and MeOH. [e] All compounds gave a correct analysis for C, H, N.

of HOAc was added and refluxing was continued for an additional 10 hr. The cooled solution was washed (twice with H_2O, a 5% solution of $NaHCO_3$, H_2O), dried ($MgSO_4$), concentrated to an oil at reduced pressure, and distilled yielding 11 g of starting ketone. The remaining residue solidified on cooling and was recrystallized from 95% EtOH yielding 87 g (88% based on consumed ketone) of product, mp 76–78°. *Anal.* ($C_{13}H_{11}ClN_2$) C, H, N.

α-Carboxamido-β-(*p*-chlorophenyl)-γ,γ-dimethylbutyrolactone (2b).—A mixture of 50 g (0.216 mole) of **1b** and 500 g of PPA was heated with stirring for 6 hr at 100°. The mixture was then poured into 3 l. of H_2O and stirred for 2 hr and the solid product was filtered off. The product was taken up in EtOAc, dried ($MgSO_4$), and concentrated to approximately one-third its initial volume and hexane was added to induce crystallization. Recrystallization from EtOAc and hexane yielded 49 g (85%) of white crystalline product, mp 176–178°. *Anal.* ($C_{13}H_{14}ClNO_3$) C, H, N.

α-Cyano-β-phenyl-γ,γ-dimethylbutyrolactone (3a).—A solution of 23.3 g (0.10 mole) of **2a**[8] in 85 ml of $POCl_3$ was refluxed with stirring for 15–20 min in a 100° oil bath. The resulting solution was poured cautiously onto 1 kg of crushed ice with stirring. The solid which precipitated was extracted with C_6H_6 and the residual aqueous solution was saturated with NaCl and extracted with two smaller portions of C_6H_6. The combined organic extracts were washed (H_2O, 5% aqueous $NaHCO_3$, H_2O), dried ($MgSO_4$), treated with charcoal, and taken to dryness at reduced pressure. The resulting product was recrystallized from EtOAc and cyclohexane yielding 16.3 g (76%) of a colorless product, mp 175–176°. *Anal.* ($C_{13}H_{13}NO_2$) C, H, N.

α-Cyano-β-(*p*-chlorophenyl)-γ,γ-dimethylbutyrolactone (3b).—A mixture of 20 g (0.075 mole) of **2b** and 70 ml of $POCl_3$ was heated with stirring in a 100° oil bath for 1 hr. After cooling, the mixture was poured cautiously over 1 kg of crushed ice with stirring. The resulting solid was filtered, taken up in C_6H_6, dried ($MgSO_4$), and concentrated to one-third its initial volume and hexane was added to induce crystallization. After cooling, 18 g (96%) of white crystals were obtained, mp 129–130°. *Anal.* ($C_{13}H_{12}ClNO_2$) C, H, N.

2-Amino-3-carbomethoxy-4-phenyl-5,5-dimethyl-4,5-dihydrofuran (4a).—A mixture of 21.5 g (0.10 mole) of **3a** and 1.08 g (0.02 mole) of $NaOCH_3$ in 200 ml of anhydrous MeOH was refluxed for 48 hr. The cooled solution was neutralized carefully with HOAc to pH 6.5–7.0. The excess MeOH was then removed at reduced pressure, the residue was taken up in $CHCl_3$, washed (H_2O), and dried (Na_2SO_4), and $CHCl_3$ was removed. The resulting solid mass was recrystallized from EtOAc and cyclohexane giving 21 g (85%) of floculent needlelike crystals with mp 115–116°; uv max (95% EtOH) [mμ (ε)], 210 (7300), 269 (11,400), and 273 (11,500). *Anal.* ($C_{14}H_{17}NO_3$) C, H, N.

2-Amino-3-carbomethoxy-4-(*p*-chlorophenyl)-5,5-dimethyl-4,5-dihydrofuran (4b).—A mixture of 5 g (0.02 mole) of **3b** and 0.216 g (0.004 mole) of $NaOCH_3$ in 40 ml of anhydrous MeOH was refluxed for 60 hr. The homogeneous solution was cooled, neutralized with HOAc to pH 6.5–7.0, the excess MeOH was removed at reduced pressure, and the residue was taken up in $CHCl_3$. The organic solution was washed (H_2O), dried ($MgSO_4$), and concentrated at reduced pressure to yield a solid product which was recrystallized from EtOAc and hexane to yield 3.9 g (69%) of white crystals, mp 141–143°. *Anal.* ($C_{14}H_{16}ClNO_3$) C, H, N.

General Procedure for Ureido-4,5-dihydrofurans (5).—A solution of **4a** or **4b** and a 10% *M* excess of the aryl isocyanate in 8–10 ml of anhydrous C_6H_6/g of **5** was refluxed in a flame-dried, round-bottom flask with stirring (see Table I for reflux periods of individual compounds). After chilling in a refrigerator for 2–4 hr the precipitated products were collected by vacuum filtration, washed with a small portion of anhydrous C_6H_6, and dried. A second crop was obtained by concentration at reduced pressure to one-fourth the initial volume and chilling. The products were recrystallized as summarized in Table I.

General Procedure for 2,4-Dioxopyrimidines (6).[21]—A solution of 0.01 mole of **5** in 100 ml of 5% NaOH and Me_2CO was refluxed (see Table II for individual details), cooled to room temperature,

(21) Compound **6e** was not prepared by this general procedure.

and neutralized by dropwise addition of HOAc to pH 6–7. The precipitated product was collected by filtration, washed (H_2O), dried (P_2O_5) at reduced pressure, and recrystallized as summarized in Table II.

2,4-Dioxo-1H-3-(N-*p*-nitrophenyl)-5-phenyl-6,6-dimethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine (6e).—A solution of 3.85 g (0.0093 mole) of **5e** and 0.4 g (0.0075 mole) of $NaOCH_3$ in 150 ml of anhydrous MeOH was refluxed for 24 hr, concentrated at reduced pressure to one-tenth its initial volume, and hydrolyzed in H_2O (200 ml). The aqueous solution was neutralized by dropwise addition of HOAc causing the precipitation of a pale yellow solid which was subsequently collected by vacuum filtration, washed well (H_2O), dried (P_2O_5) at reduced pressure, and recrystallized twice from EtOAc affording 1.0 g (28%) of colorless crystals, mp 217–219°. *Anal.* ($C_{20}H_{17}N_3O_5$) C, H, N.

α-Carbomethoxy-β-phenyl-γ,γ-dimethylbutyrolactone (7).—A solution of 1.0 g (0.004 mole) of **4a** in 25 ml of $CHCl_3$ was refluxed for 10 hr with HCl gas bubbling through the solution continuously. After cooling to room temperature, the solution was washed (H_2O, 5% $NaHCO_3$, H_2O) and dried ($MgSO_4$). Concentration at reduced pressure yielded 970 mg of crude product which was recrystallized from 95% EtOH affording 790 mg (80%) of white crystalline product, mp 113.5–115°. *Anal.* ($C_{14}H_{16}O_4$) C, H.

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ω-Dithiolano Amino Acids[1]

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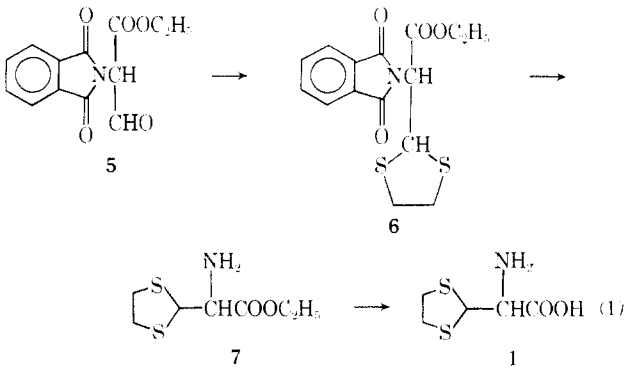
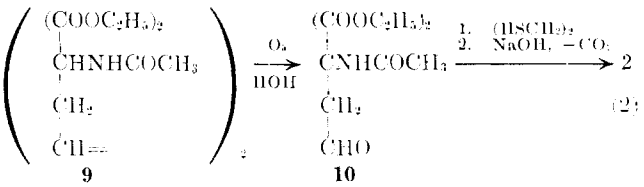
Many theories have been forwarded to explain the destructive action of ionizing radiation on the cell.[2] Although the chemical theories include a wide array of target molecules as the primary reaction in the cell, common agreement points to either a direct ionizing action on a cellular constituent or an indirect action mediated by peroxides formed in the cell. Based on the radioprotection afforded by cysteine and cysteamine many related aminothiols have been synthesized and examined. In this investigation interest was focused on the 1,3-dithiolane ring. The ease of chemical oxidation of this system to a disulfonyl would make it a likely candidate for radioprotection. Three 1,3-dithiolano amino acids were prepared for biological evaluation as radioprotective agents: 2-amino-2-[2-(1,3-dithiolano)]acetic (**1**), -propionic (**2**), and -butyric acids (**3**).

Ethyl phthalimidoacetate[3] (**4**) was treated with ethyl formate and NaOEt in xylene to give ethyl 2-phthalimidomalonaldehydate[4] (**5**). The 1,3-dithiolane derivative **6** was prepared by an HCl-catalyzed reaction of **5** with ethanedithiol. Hydrazine cleavage of **6** gave the intermediate amino ester **7** which was saponified by treatment with KOH in aqueous dioxane to give **1** (eq 1).

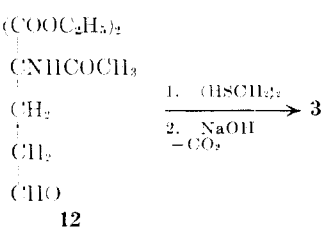


Unsuccessful approaches to the synthesis of the aldehyde **10** were made by alkylation of diethyl acetamidomalonate with chloroacetaldehyde diethyl acetal and through ozonolysis and reduction of diethyl allylacetamidomalonate (**8**). The synthesis of **2** (eq 2)



was accomplished *via* alkylation of diethyl acetamidomalonate using 1,4-dibromo-2-butene to give 1,1,6,6,-tetracarbethoxy-1,6-diacetamido-3-hexene (**9**).[5] Ozonolysis of **9** to **10** was followed by treatment with ethanedithiol to give the amido ester **11**. Alkaline saponification and decarboxylation in acid gave the intermediate amido acid; subsequent refluxing in 1 *M* H_2SO_4 yielded **2**.

Using the procedure of Warner and Moe[6] 4,4-dicarbethoxy-4-acetamidobutyraldehyde (**12**) was prepared. Treatment with ethanedithiol and HCl yielded the product 2-(3,3-dicarbethoxy-3-acetamidopropyl)-1,3-dithiolane (**13**); hydrolysis and decarboxylation of **13** proceeded with ease. Amide hydrolysis, unsuccessful using 2.5 *M* NaOH, was accomplished in 1 *M* H_2SO_4 to give 2-amino-4-[2-(1,3-dithiolano)]butyric acid (**3**).



Biological Results.—The radioprotective ability of 2-amino-2-[2-(1,3-dithiolano)]acetic acid (**1**) and 2-amino-4-[2-(1-3-dithiolano)]butyric acid (**3**) against radiation was tested in mice at Walter Reed Army Institute of Research. Neither of the compounds tested at 400 mg/kg afforded survival or protection in mice exposed to 950 R (cobalt-60, γ rays).

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