(sharp singlet, 4 protons), 6.68 (doublet, J = 6 cps, 1 proton), 6.83–7.50 (multiplet, 5 protons).

DL-β-**Trimethylsilylalanine.**—The above procedure was used to convert 2.0 g of ethyl α-acetamido-α-cyano-β-trimethylsilylpropionate to the corresponding alanine derivative except that the hydrolysis was carried out on a steam cone for 3 hr. There was obtained 450 mg of white crystalline material, mp 286–288°. *Anal.* ($C_6H_{15}NO_2Si$) C, H, N. Tlc of this material showed only one purple spot after development with ninhydrin: R_f 0.66 (*n*-BuOH–AcOH–H_2O, 4:1:1), 0.83 (*t*-BuOH–2-butanone–H_2O–28% NH_4OH, 4:3:2:1), 0.68 (MeOH); pmr absorptions [D_2O, NaOD, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt internal standard], 6.73 (triplet, J = 7 cps, 1 proton), 8.75–9.48 (multiplet, ABX system, 2 protons), 10.0 (broad singlet, 9 protons).

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Phenyl Ester of Lactic Acid[1]

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Numerous literature references[2] describe the preparation of alkyl esters of lactic acid, but thus far no mention has been made of phenyl lactate. Wieland and Köppe[3] prepared the corresponding thiophenyl ester by diazotization of alanylthiophenyl hydrochloride but were unable to obtain a satisfactory analysis for their product. We wish to report the synthesis of phenyl lactate by way of intermediates in which the lactic acid hydroxyl group is protected by benzylation. This compound has been tested at the Cancer Chemotherapy National Service Center in L1210 lymphoid leukemia at dose levels between 100 and 400 mg/kg and in Walker carcinosarcoma 256 (intramuscular) at a level of 400 mg/kg. It was found to be nontoxic and inactive in both systems.

Experimental Section[4]

Reaction of O-Benzyllactoyl Chloride with Phenol.—O-Benzyllactoyl chloride was prepared[5] from O-benzyllactic acid in 79% yield, bp 94.5–95.5 (1.2–2.0 mm), $n^{26}D$ 1.5078. To 598 g (3.02 moles) of O-benzyllactoyl chloride was added 284 g (3.02 moles) of phenol (Merck, reagent grade). The mixture was heated (bath temperature 70–80°) and stirred for 2 hr. After standing for 18 hr at room temperature, residual HCl was removed under vacuum and the product was distilled directly using a short-path distilling head. The first fraction, bp 35–91° (0.1–0.2 mm), consisted mainly of phenol (99 g). The distillation was halted and the head, condenser, and receivers were cleaned thoroughly. Upon resumption of distillation, there was obtained a forerun of 47 g, followed by the main fraction (326.5 g, 42%) of impure phenyl O-benzyllactate, bp 143–148° (0.05–0.10 mm), $n^{25}D$ 1.5385, sapon equiv 266 (calcd sapon equiv 256). Glpc showed two major components revealed as closely spaced peaks. The nmr spectrum showed two separate methyl group doublets of approximately equal intensity. The remaining peaks corresponded to the structure phenyl O-benzyllactate, as did the infrared spectrum. Analysis showed values for carbon to be approximately 1% high. Titration indicated 0.23 mequiv/g of free acid.

Phenyl Lactate.—Hydrogenolysis was performed at room temperature using an initial H_2 pressure of 2.8 kg/cm², 79.0 g (0.308 mole) of phenyl O-benzyllactate, 8 g of 5% Pd-C, and 800 ml of HOAc. After 18 hr of shaking, the hydrogen uptake amounted to 150% of the calculated amount, at which time the operation was halted. After filtration, the catalyst cake was washed with HOAc. The filtrate and washings were evaporated under vacuum, and the residual oil was dissolved in 400 ml of ether. Upon standing for 5 min, a grayish precipitate formed which was removed by filtration and the ether was then evaporated under vacuum. The product was flushed five times with C_6H_6 and dissolved in 600 ml of cold Et_2O. Some cloudiness formed which was removed by filtration. The total volume was brought to 1 l. by the addition of cold Et_2O. This solution was washed successively (100 ml each of ice-cold $NaHCO_3$, H_2O, and NaCl). The ether layer was dried (Na_2SO_4) and the solvent was removed to give 23.7 g of crude product. Distillation gave 7.74 g (15%) of product, bp 51–60.5° (0.005 mm), 55.0–56.0° (0.003 mm) (30-cm spinning band column), $n^{25}D$ 1.5085. The product solidified when stored at 5°, mp 30.0–30.5°; ir, uv, and nmr spectra were as expected.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; sapon equiv, 166. Found: C, 65.00; H, 6.04; sapon equiv, 172; free acid titration, 0.17 mequiv/g.

The phenyl ester linkage was found to be readily susceptible to hydrolysis, with phenol frequently present as a contaminant in distilled samples of phenyl lactate. Traces of phenol were readily detected by means of nmr spectroscopy, in which a doublet centered at 6.89 ppm (J = 3 cps) was confirmed as due to phenol by spiking of a $CDCl_3$ solution of pure phenyl lactate.

Analgetic Activity of 1-Substituted 2,5-Diphenylpyrroles

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The pharmacological screening of some 1-substituted 2,5-diphenylpyrroles (Table I) disclosed that those compounds in which the variable side chain contained the aminoethyl moiety produced complete analgesia at a dosage of 10 mg/kg when injected into Holtzmann rats. The animal's tails were completely insensitive to pinching or a hot lamp for 1.5 hr. The compounds included in this group were substituted with the 2-aminoethyl, 2-(N-morpholino)ethyl, 2-dimethylaminoethyl, and 2-(N′-methylpiperazino)ethyl groups. All of the pyrrole rings were synthesized from 1,4-diphenylbutane-1,4-dione[1] and the appropriately substituted amine by thermal condensation with or without a solvent.[2] Variations in the method of preparation are noted in the Experimental Section.

Experimental Section

Method A.—A mixture of 0.05 mole of 1,4-diphenyl-1,4-butanedione, 0.07 mole of the amine, and 100 ml of xylene was refluxed with stirring for 2 hr. The cooled mixture was poured into a 2-l. separatory funnel and diluted with 200 ml of Et_2O. The organic mixture was washed three times with equal volumes of H_2O after which it was extracted with 250 ml of 0.1 *N* HCl.

(1) Supported by Contract No. PH-43-62-479, Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service.

(2) For a review see: L. T. Smith and H. V. Claborn, *Ind. Eng. Chem.*, **32**, 692 (1940).

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(4) Melting points were obtained on a Thomas–Hoover Unimelt and are uncorrected. Microanalyses were performed by R. N. Boos and associates at Merck Sharp and Dohme Research Laboratories. The ir spectra were obtained on a Perkin-Elmer Model 137 recording spectrophotometer, the uv spectra by A. Kalowsky using a Cary Model 11 spectrophotometer. A Varian Associates A-60A instrument was used by R. C. Zerfing for recording nmr spectra (ppm downfield from TMS). Glpc was performed by W. E. Tait on a Barber-Coleman Model 10 gas chromatograph with a flame ionization detector using a 2 m × 6.4 mm glass column packed with 1% silicone fluid (DC QF1) on Gas Chrom Q support.

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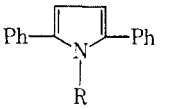
TABLE I
1-SUBSTITUTED 2,5-DIPHENYLPYRROLES



R	Method	Yield, %	Mp, °C	Formula	Analysis[c]
3-(N-Morpholino)propyl	A	40	78	$C_{23}H_{26}N_2O$	C, H
2-(N-Morpholino)ethyl	A	75	72	$C_{22}H_{24}N_2O$	C, H
3-Dimethylaminopropyl	A	38	48	$C_{21}H_{24}N_2$	C, H
2-Dimethylaminoethyl	A	68	54	$C_{20}H_{22}N_2$	C, H
2-(N-Methylpiperazino)ethyl	A	46	97	$C_{23}H_{27}N_3$	C, H
3-(N-Hydroxyethylpiperazino)propyl	A	35	92	$C_{25}H_{31}N_3O$	C, H
3-Diethylamino-2-hydroxypropyl	A	55	65	$C_{23}H_{28}N_2O$	C, H
4-Dimethylaminophenyl	B	82	216	$C_{24}H_{22}N_2$	C, H
3-N-Methyl-N-phenylaminopropyl	A	68	84	$C_{26}H_{26}N_2$	C, H, N
3-(2-Hydroxyethylamino)propyl	A	80	38	$C_{21}H_{24}N_2O$	C, H
Amino[a]		14	155[b]	$C_{16}H_{14}N_2$	C, H, N
2-Aminoethyl	C	73	78	$C_{18}H_{18}N_2$	C, H
3-Aminopropyl	C	80	82	$C_{19}H_{20}N_2$	C, H
4-Aminobutyl·HCl	C	23	143	$C_{20}H_{22}N\cdot HCl$	C, H, Cl
2,3-Dihydroxypropyl	C	87	108	$C_{19}H_{19}NO_2$	C, H
3-Hydroxypropyl	C	72	56	$C_{19}H_{19}NO$	C, H
2-Hydroxyethyl	C	75	105	$C_{18}H_{17}NO$	C, H
Acetamido	A	32	212[b]	$C_{18}H_{16}N_2O$	C, H, N

[a] Acidic hydrolysis. [b] The preparation of these compounds has been previously reported by H. Beyer, T. Pyl, and C. E. Volker, *Ann.*, **638**, 150 (1960), by a different method. They gave 214° as the melting point of the 1-amino compound and 137° for its acetyl derivative. [c] Compounds were analyzed for the elements indicated. The analytical results obtained for those elements were within ±0.3% of the theoretical values.

The crude product separated as an oil when the acidic extract was made basic with NaOH. Upon cooling, the oil solidified and was isolated by filtration. After being dried over KOH, the crude product was either sublimed at reduced pressure or recrystallized from 3:1 C_6H_6–hexane.

Method B.—A mixture of 0.05 mole of 1,4-diphenyl-1,4-butanedione and 0.08 mole of N,N-dimethyl-*p*-phenylenediamine was heated under N_2 for 3 hr at 160–170°. The cooled, amorphous reaction product was triturated with Et_2O and then filtered. The residue was dissolved in toluene and treated with 250 ml of 0.1 *N* HCl to give the crude product as the hydrochloride. The filtered amine hydrochloride was dissolved in hot H_2O to which Na_2CO_3 was then added. The product was recrystallized from 5:1 C_6H_6–Et_2O.

Method C.—A mixture of 0.05 mole of 1,4-diphenyl-1,4-butanedione, 0.25 mole of the amine, and 100 ml of ethylene glycol was refluxed for 2 hr. The cooled mixture was diluted with 500 ml of H_2O, extracted once with C_6H_6, and then made strongly basic. The crude product separated as an oil and slowly solidified. Purification was accomplished by recrystallization from 3:1 C_6H_6–hexane.

Some 6,8-Dibromo-S-substituted-2-mercapto-3-aryl- (or alkyl-) 4-quinazolones

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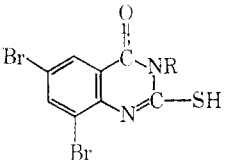
In view of the broad spectrum of biological activities associated with 4-quinazolones,[1-5] it seemed of interest to synthesize 6,8-dibromo-3-aryl- (or alkyl-) S-substituted-2-mercapto-4-quinazolones and evaluate them for their antimalarial activity. Their syntheses by condensation of 3,5-dibromoanthranilic acid[6] and aryl (or alkyl) isothiocyanates followed by alkylation with alkyl halides is reported in this communication. None of the compounds tested showed any chemotherapeutic activity in standard tests in chicks infected with *Plasmodium gallinaceum*.

Experimental Section

6,8-Dibromo-2-mercapto-3-phenyl-4-quinazolone.—A mixture of phenyl isothiocyanate (6.00 ml), 3,5-dibromoanthranilic acid

TABLE I
6,8-DIBROMO-2-MERCAPTO-3-ARYL- (OR ALKYL-) 4-QUINAZOLONES



R	% yield	Mp, °C	Formula[a]
C_6H_5	98	298 dec	$C_{14}H_8Br_2N_2OS$
o-$CH_3C_6H_4$	85	225	$C_{15}H_{10}Br_2N_2OS$
m-$CH_3C_6H_4$	95	215	$C_{15}H_{10}Br_2N_2OS$
p-$CH_3C_6H_4$	94	305 dec	$C_{15}H_{10}Br_2N_2OS$
m-ClC_6H_4	90	218	$C_{14}H_7Br_2ClN_2OS$
p-ClC_6H_4	98	207	$C_{14}H_7Br_2ClN_2OS$
o-$OCH_3C_6H_4$	75	235	$C_{15}H_{10}Br_2N_2O_2S$
p-$OCH_3C_6H_4$	87	228	$C_{15}H_{10}Br_2N_2O_2S$
p-$OC_2H_5C_6H_4$	90	222	$C_{16}H_{12}Br_2N_2O_2S$
CH_3	95	229	$C_9H_6Br_2N_2OS$
C_2H_5	80	180	$C_{10}H_8Br_2N_2OS$
n-C_4H_9	96	234	$C_{12}H_{12}Br_2N_2OS$
$C_6H_5CH_2$	88	228	$C_{15}H_{10}Br_2N_2OS$

[a] All compounds were analyzed for N, S, and the analytical results were within ±0.3% of the theoretical values.

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