

(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.* ($C_8H_{15}NO_2Si$) C, H, N. Tlc of this material showed only one purple spot after development with ninhydrin: R_f 0.66 (n -BuOH–AcOH–H₂O, 4:1:1), 0.83 (t -BuOH–2-butanone–H₂O–28% NH₄OH, 4:3:2:1), 0.68 (MeOH); pmr absorptions [D₂O, 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 Acid¹

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Numerous literature references² describe the preparation of alkyl esters of lactic acid, but thus far no mention has been made of phenyl lactate. Wieland and Köppe³ 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 Section⁴

Reaction of O-Benzylactoyl Chloride with Phenol.—O-Benzylactoyl chloride was prepared⁵ from O-benzylactic acid in 79% yield, bp 94.5–95.5 (1.2–2.0 mm), n_D^{20} 1.5078. To 598 g (3.02 moles) of O-benzylactoyl 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-benzylactate, bp 143–148° (0.05–0.10 mm), n_D^{20} 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-benzylactate, 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 H₂ pressure of 2.8 kg/cm², 79.0 g (0.308 mole) of phenyl O-benzylactate, 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 C₆H₆ and dissolved in 600 ml of cold Et₂O. Some cloudiness formed which was removed by filtration. The total volume was brought to 1 l. by the addition of cold Et₂O. This solution was washed successively (100 ml each of ice-cold NaHCO₃, H₂O, and NaCl). The ether layer was dried (Na₂SO₄) 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_D^{20} 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 C₉H₁₀O₃: 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 CDCl₃ 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 Holtzman 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-dione¹ 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 Et₂O. The organic mixture was washed three times with equal volumes of H₂O 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. Ciaborn, *Ind. Eng. Chem.*, **32**, 692 (1940).

(3) T. Wieland and H. Köppe, *Ann.*, **581**, 1 (1953).

(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 \times 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 ₂ O	C, H
2-(N-Morpholino)ethyl	A	75	72	C ₂₂ H ₂₄ N ₂ O	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 ₃ O	C, H
3-Diethylamino-2-hydroxypropyl	A	55	65	C ₂₃ H ₂₈ N ₂ O	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	89	38	C ₂₁ H ₂₄ N ₂ O	C, H
Amino ^a		14	155 ^b	C ₁₆ H ₁₄ N ₂	C, H, N
2-Aminoethyl	C	73	78	C ₁₅ H ₁₅ N ₂	C, H
3-Aminopropyl	C	80	82	C ₁₉ H ₁₉ N ₂	C, H
4-Aminobutyl·HCl	C	23	143	C ₂₀ H ₂₂ N·HCl	C, H, Cl
2,3-Dihydroxypropyl	C	87	108	C ₁₅ H ₁₅ NO ₂	C, H
3-Hydroxypropyl	C	72	56	C ₁₉ H ₁₉ NO	C, H
2-Hydroxyethyl	C	75	105	C ₁₅ H ₁₅ NO	C, H
Acetamido	A	32	212 ^b	C ₁₈ H ₁₆ N ₂ O	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 $\pm 0.3\%$ 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 C₆H₆-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 N₂ for 3 hr at 160–170°. The cooled, amorphous reaction product was triturated with Et₂O 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 H₂O to which Na₂CO₃ was then added. The product was recrystallized from 5:1 C₆H₆-Et₂O.

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 H₂O, extracted once with C₆H₆, and then made strongly basic. The crude product separated as an oil and slowly solidified. Purification was accomplished by recrystallization from 3:1 C₆H₆-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

(1) F. J. Wolf, U. S. Patent, 2,473,931 (1949); *Chem. Abstr.*, **43**, 7042 (1949).

(2) B. R. Baker, F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Org. Chem.*, **18**, 178 (1953).

(3) M. L. Gujral, P. N. Saxena, and R. S. Tiwari, *Indian J. Med. Res.*, **43**, 637 (1955); *Chem. Abstr.*, **50**, 662 (1956).

(4) Br. Pawlewski, *Ber.*, **38**, 131 (1905).

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 acid⁶ 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 ₆ H ₅	98	298 dec	C ₁₄ H ₈ Br ₂ N ₂ OS
<i>o</i> -CH ₃ C ₆ H ₄	85	225	C ₁₅ H ₁₀ Br ₂ N ₂ OS
<i>m</i> -CH ₃ C ₆ H ₄	95	215	C ₁₅ H ₁₀ Br ₂ N ₂ OS
<i>p</i> -CH ₃ C ₆ H ₄	94	305 dec	C ₁₅ H ₁₀ Br ₂ N ₂ OS
<i>m</i> -ClC ₆ H ₄	90	218	C ₁₄ H ₇ Br ₂ ClN ₂ OS
<i>p</i> -ClC ₆ H ₄	98	207	C ₁₄ H ₇ Br ₂ ClN ₂ OS
<i>o</i> -OCH ₃ C ₆ H ₄	75	235	C ₁₅ H ₁₀ Br ₂ N ₂ O ₂ S
<i>p</i> -OCH ₃ C ₆ H ₄	87	228	C ₁₅ H ₁₀ Br ₂ N ₂ O ₂ S
<i>p</i> -OC ₂ H ₅ C ₆ H ₄	90	222	C ₁₆ H ₁₂ Br ₂ N ₂ O ₂ S
CH ₃	95	229	C ₉ H ₆ Br ₂ N ₂ OS
C ₂ H ₅	80	180	C ₁₀ H ₈ Br ₂ N ₂ OS
<i>n</i> -C ₄ H ₉	96	234	C ₁₂ H ₁₂ Br ₂ N ₂ OS
C ₆ H ₅ CH ₂	88	228	C ₁₅ H ₁₀ Br ₂ N ₂ OS

^a All compounds were analyzed for N, S, and the analytical results were within $\pm 0.3\%$ of the theoretical values.

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