TABLE I

No.	Compound	Yield, %[a]	Mp, °C[b]	Formula[c]	KB cell test, ED_{50},[d] μg/ml	Tumor wt— mg/kg	T/C	Lethality— mg/kg	Killed
1	1-(4-N-Ethyl-N-nitrosoamino-benzylidene)indene	53	123–124	$C_{18}H_{18}N_2O$		4 × 100[e]	0.56	4 × 400[e]	0/13
						500[f]	0.14		
						1250[f]	0.08	1250[f]	0/3
2	4-(4-N-Ethyl-N-nitroso-aminostyryl)quinoline	59	120.5–122.0	$C_{19}H_{17}N_3O$		4 × 100[e]	0.10	4 × 400[e]	1/6
						4 × 200[e]	0.02		
3	9-(4-N-Methyl-N-nitroso-aminobenzylidene)fluorene	73	145–146	$C_{21}H_{16}N_2O$	100	4 × 400[e]	0.90	4 × 400[e]	0/6
						1500[f]	1	1500[f]	0/3
4	1-(4-N-Methyl-N-nitroso-aminobenzylidene)indene	57	144–146	$C_{17}H_{14}N_2O$	35	59[f]	0.15	1500[f]	0/3
						240[f]	0.16		
						600[f]	0.07		
						4 × 400[e]	0.61	4 × 400[e]	0/6
5	2-N-Methyl-N-nitrosoamino-fluorene	51	120.5–122.0	$C_{14}H_{12}N_2O$		4 × 600[e]	0.8	4 × 600[e]	0/6
6	4-N-Methyl-N-nitrosoamino-stilbene	33	157	$C_{15}H_{14}N_2O$		4 × 400[g]	0.6	4 × 400[e]	0/6
7	4-(4-N-Methyl-N-nitroso-aminostyryl)quinoline	84	157–158	$C_{18}H_{15}N_3O$	66	30[f]	0.3	25[f]	1/2
						75[f]	0.15	75[f]	0/3
						4 × 100[e]	0.45	4 × 1000[e]	0/6
						4 × 1000[e]	0.09		

[a] Additional material could be recovered from the mother liquors. [b] Corrected for thermometer stem exposure; determined with Thiele tube. [c] Average of two analyses by Galbraith Laboratories. All compounds were analyzed for C, H. Analytical results obtained for those elements were within ±0.3% of the theoretical values. [d] Results of the standard *in vitro* KB tumor cell inhibition tests carried out under sponsorship of the Cancer Chemotherapy National Service Center at Southern Research Institute and A. D. Little Co. [e] We are grateful to CCNSC for screening tests against Walker 256, using four daily injections beginning 3 days after tumor implant, carried out at Battelle Memorial Institute. [f] We are grateful to Professor Alexander Haddow, Mr. J. E. Everett, and Mr. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was administered as a single intraperitoneal injection in arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor bearing animals were sacrificed approximately 8 days later and the average weights of tumors in treated and untreated hosts are reported as the ratio T/C.

New Compounds

DL-2-Indaneglycine and DL-β-Trimethylsilylalanine

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In a study of potential amino acid antagonists, DL-2-indaneglycine and DL-β-trimethylsilylalanine were prepared in order to determine the effect of the fused benzene ring upon the biological activity of known amino acid antagonists, cyclopentaneglycine and cyclopenteneglycine, and to determine whether or not a silicon-containing amino acid might exhibit antimetabolite activity. Neither of the compounds showed any growth-inhibiting properties in several different microorganisms. Steric effects of the large fused ring in the first case and the additional methyl group over that in leucine in the latter case may be responsible for the lack of biological activity of these compounds in binding appropriate enzymes.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected.

2-Bromoindane.—To 2-indanol[1,2] (20 g) in pyridine (3 ml) and 50 ml of $CHCl_3$ at −15° was added PBr_3 (16 ml) over a 30-min period. The reaction mixture was stirred for 2 hr at room temperature and extracted by addition of $CHCl_3$ (100 ml) and ice (100 g). The organic layer was washed with three 50-ml portions of H_2O, dried (Na_2SO_4), and distilled to give 10.9 g of a colorless liquid, bp 83–85° (4 mm), $n^{25}D$ 1.5817. *Anal.* (C_9H_9Br) C, H.

Ethyl α-Acetamido-α-cyano-2-indaneacetate.—To NaOEt, prepared from Na (1.4 g) and EtOH (50 ml), dried *in vacuo*, and suspended in DMSO (50 ml), a solution of ethyl acetamidocyanoacetate (10 g) in DMSO (50 ml) was added with vigorous stirring. 2-Bromoindane (10.5 g) was added dropwise over a 30-min period. The reaction mixture after stirring overnight was concentrated to 25 ml *in vacuo*, diluted with H_2O (100 ml), and extracted three times with 100 ml of Et_2O. The residue from evaporation of the solvent was recrystallized (EtOH–H_2O), then toluene) to yield 6.5 g of white flakes, mp 158–159°. *Anal.* ($C_{16}H_{18}N_2O_3$) C, H, N.

Ethyl α-Acetamido-α-cyano-β-trimethylsilylpropionate.—The above procedure was used to convert 10 g of bromomethyltrimethylsilane (Peninsular ChemResearch, Inc.) to the corresponding derivative of ethyl acetamidocyanoacetate. There was obtained 8.2 g of colorless crystals, mp 99–100°. *Anal.* ($C_{11}H_{20}N_2O_3Si$) C, H, N.

DL-2-Indaneglycine.—A solution of 2.0 g of ethyl α-acetamido-α-cyano-2-indaneacetate and 30 ml of 10% NaOH was refluxed for 12 hr and then acidified to pH 5 with concentrated HCl. A suspension of the resulting precipitate in 500 ml of H_2O was boiled and filtered, and the filtrate after cooling yielded fine crystalline plates. Recrystallization (H_2O) yielded 450 mg of white crystals, mp 323–325° dec. *Anal.* ($C_{11}H_{13}NO_2$) C, H, N. Tlc of this material showed only one purple spot after development with ninhydrin: R_f 0.67 (*n*-BuOH–AcOH–H_2O, 4:1:1), 0.76 (*t*-BuOH–2-butanone–H_2O–28% NH_4OH, 4:3:2:1), 0.85 (H_2O–MeOH, 1:1); pmr absorptions [D_2O, NaOD, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt internal standard], 2.72

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(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.

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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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