and llpc with an authentic sample. In both cases the reaction mixture consisted mostly of unreacted ester which masked the product in the initial investigation.

Experimental Section

Substituted *N*-Carbamoylpyrazinecarboxamides.—To 15 ml of dry DMF was added 1.2 g (0.02 mole) of urea. To the stirred solution cooled to −15° was added 1.0 g (0.02 mole) of NaH (50% in oil). The mixture was left to stir for 2 hr. To the cooled mixture was then added 0.005 mole of the pyrazinecarboxylate ester. The mixture was left to stir for 2 hr, and poured onto 40 g of ice–H_2O (acidified to pH 6 with HOAc). On standing a precipitate formed which was filtered and shown by tlc to contain starting ester and product. The product was isolated by liquid–liquid partition chromatography on a Celite column using a heptane–THF–MeOH–H_2O (150:100:10:5) solvent system. The yield of product was about 50 mg (4%) in both cases.

Acknowledgments.—We thank Mr. C. Pidacks and staff for the liquid–liquid partition chromatography.

N-Aryl-*N*-aroylamino Acid Derivatives

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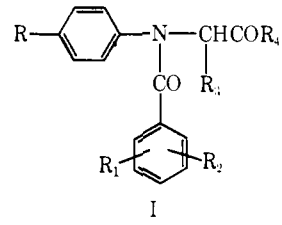
We have synthesized *N*-aryl-*N*-aroylamino acid derivatives of the general formula I. Recently, compounds of this type have been disclosed,[1] but only compounds



I

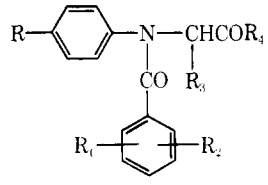
and analgetic activities were found in compounds **3**, **4**, and **5**.

Experimental Section[2]

Ethyl Esters of *N*-Aryl-*N*-aroylamino Acids. General Procedure.—A solution of 0.1 mole of the appropriate aroyl chloride[3] in 50 ml of dry PhH was added dropwise with stirring to a solution of 0.1 mole of the ethyl ester of the appropriate *N*-arylamino acid and 0.1 mole of NEt_3 in 200 ml of dry PhH. The reaction mixture was set aside at room temperature overnight and then filtered in order to remove the formed $NEt_3 \cdot HCl$. The filtrate was shaken with 0.5 *N* HCl, then with satd aq $NaHCO_3$, and, finally, with H_2O to neutral pH. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Generally, a gummy residue was obtained, which was directly converted into the acid derivative by hydrolysis (see below). In some cases, the ethyl esters were isolated and characterized (Table I).

***N*-Aryl-*N*-aroylamino Acids (I, R_4 = OH). General Procedure.**—EtOH (30–50 ml) was added to a mixture of 0.05 mole of the Et ester of the appropriate *N*-aryl-*N*-aroylamino acid in 150 ml of 0.5 *N* NaOH until a clear solution resulted. This solution was refluxed for 4 hr, shaken with Et_2O, and made acid by addition of 4 *N* HCl. The oily precipitate was extracted with Et_2O or EtOAc. The organic solution was washed (H_2O) and dried (Na_2SO_4). The residue obtained after evaporation of the

Table I



R	R_1	R_2	R_3	R_4	Mp, °C	Formula	Analyses[a]
H	H	H	Ph	OH	183–184	$C_{20}H_{17}NO_4$	C, H, N
CH_3O[b]	H	H	H	OH	125–126	$C_{16}H_{15}NO_4$	C, H, N
H[g]	H	4-Cl	H	OH	153–154	$C_{15}H_{12}ClNO_3$	C, H, N, Cl
Cl	H	4-Cl	H	OH	161–163	$C_{15}H_{11}Cl_2NO_3$	C, H, N, Cl
Cl[c]	H	H	H	OH	140–142	$C_{15}H_{12}ClNO_3$	C, H, N, Cl
H	H	2-Cl	H	OH	124–126	$C_{15}H_{12}ClNO_3$	C, H, N, Cl
C_2H_5O	H	2-OH	H	OH	137–138	$C_{17}H_{17}NO_5$	C, H, N
C_2H_5O	H	H	H	OH	92–93	$C_{17}H_{17}NO_4$	C, H, N
Cl[d]	H	2-Cl	H	OH	137–138	$C_{15}H_{11}Cl_2NO_3$	C, H, N, Cl
CH_3O	2-Cl	4-Cl	H	OH	172–174	$C_{16}H_{13}Cl_2NO_4$	C, H, N, Cl
$CH_3(CH_2)_6O$[e]	H	4-Cl	H	OH	115–116	$C_{22}H_{26}ClNO_4$	C, H, N, Cl
C_2H_5O[f]	H	H	CH_3	OH	128–129	$C_{18}H_{19}NO_4$	C, H, N
H	H	2-Cl	H	OC_2H_5	87–88	$C_{17}H_{16}ClNO_3$	C, H, N, Cl
CH_3O	H	2-Cl	H	OC_2H_5	97–98	$C_{18}H_{18}ClNO_4$	C, H, N, Cl
H	4-Cl	3-H_2NSO_2	H	OC_2H_5	113–115	$C_{17}H_{17}ClN_2O_5S$	C, H, N, Cl, S
C_2H_5O	4-Cl	3-H_2NSO_2	H	OC_2H_5	101–103	$C_{19}H_{21}ClN_2O_6S$	C, H, N, Cl, S
CH_3O	4-Cl	3-H_2NSO_2	H	OC_2H_5	123–124	$C_{18}H_{19}ClN_2O_6S$	C, H, N, Cl, S
CH_3O	H	4-Cl	H	$NH(CH_2)_5CH_3$	97–98	$C_{19}H_{21}ClN_2O_3$	C, H, N, Cl
C_2H_5O	H	4-Cl	H	$NH(CH_2)_2CH_3$	90–92	$C_{20}H_{23}ClN_2O_3$	C, H, N, Cl

[a] The analytical results obtained for the indicated elements are within ±0.3% of the theoretical values. [b] Compound **1**. [c] Compound **2**. [d] Compound **4**. [e] Compound **5**. [f] Compound **3**. [g] This is compound **28** in Table II of D. Evans, A. S. L. Mackintosh, and S. S. Szinai, *J. Med. Chem.*, **12**, 1006 (1969). They report mp 154–156°.

not yet described are now reported (Table I). Considerable choleretic activity was found in compounds **1**, **2**, and **3**. Moreover, meaningful diuretic

(1) Netherlands Application 6805246; SOGESPAR S.A. (1968).

(2) Melting points were determined in open capillary tubes and are uncorrected.

(3) In the preparation of *N*-*p*-ethoxyphenyl-*N*-salicyloylglycine *o*-acetoxybenzoylchloride was used.

solvent was crystallized from EtOAc or EtOAc–petr ether (bp 40–70°) a mixture. The yields were between 45–65%.

***N*-*n*-Propyl-*N'*-aryl-*N'*-(*p*-chloro)benzoylglycinamides [I, R_1 = $NH(CH_2)_2CH_3$]. General Procedure.**—The preparation of these compounds was carried out analogously to the Et esters of *N*-aryl-*N*-aroylamino acids, by allowing equimolar amounts of the appropriate *N*-*n*-propyl-*N'*-aryl glycinamide, Et_3N, and *p*-chlorobenzoyl chloride to react in dry PhH.

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Ferrocene Studies. V. Potential Medicinal Agents[1]

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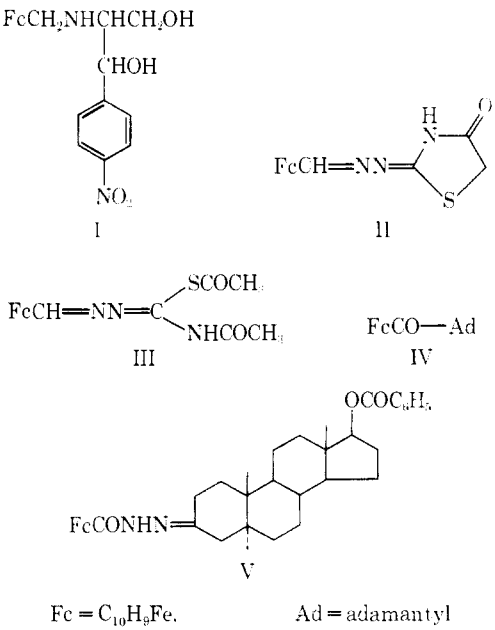
Despite the wide interest in ferrocene chemistry relatively few ferrocene derivatives have been tested for biological activities.[1a,2-5] This paper reports the preparation (see Experimental Section) of a number of new ferrocene derivatives which had no significant antibacterial, antifungal, or antiparasitic activity.



Fc = $C_{10}H_9Fe$. Ad = adamantyl

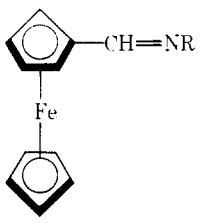
following manner. Equimolar quantities of ferrocenecarboxaldehyde and the reactants shown in Table I were dissolved in a minimum of abs EtOH and heated on a steam bath for a maximum of 30 min. After cooling to room temperature, the products shown in Table I were collected by filtration.

Condensation with D-Cycloserine.—A mixture of 5.0 g (0.05 mole) of D-cycloserine and 10.6 g (0.05 mole) of ferrocenecarboxaldehyde in 1200 ml of EtOH and 100 ml of MeOH was stirred at room temperature until all of the cycloserine dissolved. The solution was filtered and concentrated *in vacuo* to give the product indicated in Table I.

Condensation with D-(−)-*threo*-2-Amino-1-(*p*-nitrophenyl)-1,3-propanediol.—A mixture of 14.0 g (0.07 mole) of the amine, 15.0 g (0.07 mole) of ferrocenecarboxaldehyde, 0.05 g of *p*-toluenesulfonic acid, and 1200 ml of C_6H_6 was refluxed for 2 hr in a system containing a Dean–Stark trap. The solution was filtered hot and concentrated *in vacuo* to give the product indicated in Table I.

Preparation of I.—To a solution of 11.0 g of the above Schiff base in 500 ml of a 4:1 mixture of abs EtOH and dioxane was added 3.3 g of $NaBH_4$. After stirring at room temperature for

TABLE I



RNH2	Mp, °C[a,b]	Yield, %	Formula	Analyses[c,d]
Sulfanilamide	170–172[e]	73	$C_{17}H_{16}FeN_2O_2S$	C, H
Sulfaguanidine	245–246[e]	76	$C_{18}H_{18}FeN_4O_2S$	N, S
p-Sulfobenzoic acid *p*-hydrazide	196–198[e]	84	$C_{18}H_{16}FeN_2O_6S$	C, H
p-Toluenesulfonhydrazide	155–157	86	$C_{18}H_{18}FeN_2O_2S$	C, H
p-Toluenesulfonhydrazide[f]	185–186	93	$C_{19}H_{20}FeN_2O_2S$[f]	C, H
1-Hydrazinophthalazine·HCl	188–190	88	$C_{18}H_{19}ClFeN_4O$[g]	C, H, Cl, Fe, N
D-Cycloserine[h]	146–147	99	$C_{14}H_{14}FeN_2O_2$	C, H, N
D-(−)-*threo*-2-Amino-1-(*p*-nitrophenyl)-1,3-propanediol[h]	143–144	79	$C_{20}H_{20}FeN_2O_4$	C, H, N

[a] Recrystallized from EtOH unless otherwise noted. [b] Decomposition points, in most cases considerable darkening occurs before decomposition. [c] Within 0.3%. [d] Ir of all compounds were as expected. [e] Compound was not recrystallized. [f] Acetylferrocene used in place of ferrocenecarboxaldehyde. [g] Monohydrate of HCl salt. [h] Not prepared by the general procedure, see Experimental section for details.

Experimental Section[6]

Condensations with Ferrocenecarboxaldehyde.—Except as otherwise noted the compounds in Table I were prepared in the

(1) (a) Part IV, F. D. Popp and E. B. Moynahan, *J. Heterocycl. Chem.*, **7**, 351 (1970); (b) This work was supported in part by a research grant from The Norwich Pharmacal Co.

(2) J. L. Madinaveitia, *Brit. J. Pharmacol.*, **24**, 352 (1965).

(3) B. Loev and M. Flores, *J. Org. Chem.*, **26**, 3595 (1961).

(4) F. D. Popp, S. Roth, and J. Kirby, *J. Med. Chem.*, **6**, 83 (1963).

(5) D. M. Wiles and T. Suprunchuk, *Can. J. Chem.*, **46**, 1865 (1968).

(6) Analyses [by Spang Microanalytical Laboratory, Ann Arbor, Mich.] are within 0.3% unless otherwise noted. Mass spectra was by Morgan and Schaffer, Montreal, Canada. All melting points are taken in capillaries and are corrected. The infrared spectra of all compounds were as expected.