Synthesis of Some 5-Substituted 10,11-Dihydrodibenz[b,f]azepines[1]

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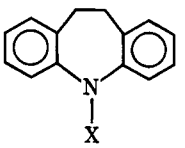
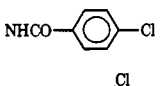
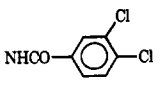
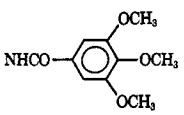
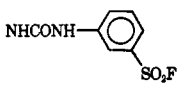
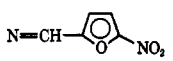
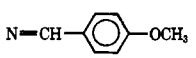
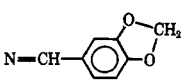
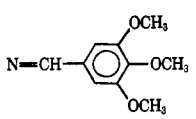
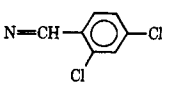
Recent observations of antimicrobial activity of arylhydrazides[2] and antimalarial activity of arylhydrazone derivatives[3] led us to prepare some hydrazide and hydrazone derivatives of 10,11-dihydrodibenz[b,f]azepine (1) which was prepared in two steps from 10,11-dihydrodibenz[b,f]azepine. Condensation of **1** with aryl acid chlorides or aryl aldehydes gives the corresponding hydrazides and hydrazones.

The compds listed in Table I were tested for antimalarial activity against *Plasmodium berghi* in mice and against *P. gallinaceum* in chicks and mosquitoes by the Walter Reed Army Institute of Research by previously described methods.[4] No significant activity was observed in these screens. The greatest increase in survival time for treated animals was 1.5 days for **3** and **4** in the chick screen.

TABLE I



No.	X	Mp, °C	% yield	Formula[a]	Recrystn solvent
1[b]	NH_2	52–53	65	$C_{14}H_{14}N_2$	Hexane
2		281–282	47	$C_{21}H_{17}Cl_2N_2O$	Me_2CO
3		271–272	87	$C_{21}H_{16}Cl_2N_2O$	Me_2CO
4		150–151	49	$C_{24}H_{24}N_2O_4$	Me_2CO
5		213–215 dec	95	$C_{21}H_{18}FN_3O_3S$	EtOH
6		145–147	78	$C_{19}H_{15}N_3O_3$	EtOH
7		143–144	74	$C_{22}H_{22}N_2O$	EtOH
8		127–129	70	$C_{22}H_{18}N_2O_2$	EtOH
9		150–151	67	$C_{24}H_{24}N_2O_3$	EtOH
10		107–109	81	$C_{21}H_{16}Cl_2N_2$	EtOH

[a] All compounds were analyzed for C, H, N and the anal results for these elements were within ±0.4% of the theor values. [b] Reported in British Patent 1,035,499; *Chem. Abstr.*, **65**, 12180 (1966).

and hydrazone derivatives of 10,11-dihydrodibenz-[b,f]azepine. Table I contains the compds which were prepared and screened for antimalarial and antimicrobial activity. The methods of synthesis of the title compds required 5*H*-amino-10,11-dihydrodibenz[b,f]azepine (**1**)

The title compds were also screened against several microorganisms which included the bacteria *Klebsiella sp.*, *Serratia marcescens*, *Enterobacter cloaca*, *Staphylococcus aureus*, and *Micrococcus sp.* The *in vitro* tests used included the paper disk–agar method and the method of measurement of turbidity caused by growth in a nutrient broth. Both of these methods were carried out essentially as previously described.[2] No significant activity was observed against these microorganisms. In the broth test **6** and **7** showed a slight

(1) We acknowledge the U. S. Army Medical Research and Development Command under Contract No. DAD17-68-C-8035 for partial support of this work. This is Contribution No. 921 from the Army Research Program on Malaria.

(2) N. H. Berner, R. S. Varma, and D. W. Boykin, Jr., *J. Med. Chem.*, **13**, 552 (1970).

(3) (a) J. R. DoAmaral, E. J. Blanz, Jr., and F. A. French, *ibid.*, **12**, 21 (1969); (b) W. T. Colwell, G. W. Chan, J. K. Horner, R. M. Parkhurst, and D. W. Henry, *ibid.*, **14**, 70 (1971).

(4) (a) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967); (b) E. J. Gerberg, L. T. Richard, and J. B. Poole, *Mosquito News*, **29**, 359 (1966).

inhibition of *Micrococcus* at the highest concn tested, 100 μg/ml.

Experimental Section

All melting points were observed on a Thomas-Hoover Uni-Melt and are uncorrected. Satisfactory ir spectra were recorded for all compds using a Perkin-Elmer Model 337 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

5*H*-Nitroso-10,11-dihydrodibenz[*b*,*f*]azepine.[5]—To a stirred solution of 5 g of 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine[6] in 50 ml of DMF was added 2 g of $NaNO_2$. The stirred mixt was maintained at 2–8° and 25 ml of 2 *N* HCl was added dropwise at such a rate that the temp did not rise above 8°. After addn was complete, the cooling bath was removed, and the mixt was stirred for 1 hr allowing it to come to room temp. The reaction mixt was poured into H_2O, allowed to stand until coagulation occurred, filtered, washed with H_2O, and dried; crude yield 5.4 g (94%), mp 109–111°. Recrystn from cyclohexane raised the mp to 113–115°. *Anal.* ($C_{14}H_{12}N_2O$) C, H, N.

5*H*-Amino-10,11-dihydrodibenz[*b*,*f*]azepine (1).[5]—To a stirred slurry of 0.44 g of LAH in 20 ml of Et_2O, cooled to 0° under N_2, a soln of 2.0 g of the nitroso compd in 15 ml of THF was added dropwise. After addn was complete, the mixt was allowed to warm to room temp then cautiously warmed to 30° (occasionally on warming, the reaction became quite exothermic and required further cooling), and maintained at that temp for 30 min. The reaction mixt was hydrolyzed and ext with Et_2O, and the Et_2O soln was dried ($CaSO_4$) and evapd, yielding 1.7 g (91%) of an oil. The oil was crystd from low-boiling petr ether, 1.4 g (82%); after repeated recrystn mp 52–53°.

Hydrazides.—In a typical procedure 1.0 g of **1**, 1.0 g of 3,4-dichlorobenzoyl chloride, and 50 ml of dry C_6H_6 were alternately warmed and agitated for 30–45 min. The reaction mixt was cooled, filtered, and washed with C_6H_6. The solid material was treated with charcoal in boiling MeCOEt. The mixt was filtered and evapd, and the residue was recrystd from Me_2CO; yield 1.6 g (87%), mp 271–272°.

Hydrazones.—In a typical procedure, 150 ml of dry PhMe, 1.33 g of **1**, and 1.20 g of 2,4-dichlorobenzaldehyde were refluxed in a flask fitted with a Dean–Stark apparatus for 2 hr. The reaction mixt was concd under reduced pressure, and the resulting oil was crystd from EtOH–Et_2O. Repeated recrystn from EtOH gave pure **10**; yield 1.75 g (81%), mp 107–109°.

Fluorosulfonylurea Derivative (5).—A mixt of **1** (1.0 g), *m*-fluorosulfonylphenyl isocyanate (0.95 g), and 75 ml of $CHCl_3$ was alternately warmed and agitated for 30–45 min. The reaction mixt was cooled, filtered, and washed with $CHCl_3$. Recrystn from EtOH produced pure **5**; yield 1.9 g, mp 213–215° dec.

(5) (a) C. Hanna and F. W. Schueler, *J. Amer. Chem. Soc.*, **74**, 3693 (1952); (b) F. W. Schueler and C. Hanna, *ibid.*, **73**, 4996 (1951); (c) *Cf.* footnote *b*, Table I.

(6) B. P. Das, R. W. Woodard, L. K. Whisenant, W. F. Winecoff, III, and D. W. Boykin, Jr., *J. Med. Chem.*, **13**, 979 (1970).

Analogs of Amphetamine. 6. 2,5-Dimethoxy-4-methyl- and 2,5-Dimethoxy-α,4-dimethylphenylalanines[1a]

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As a continuation of studying the effects of substitution on biological activities of amphetamine and 2,5-dimethoxy-4-methylamphetamine (DOM, STP), two amino acids, 2,5-dimethoxy-4-methylphenylalanine (**1**)[1b] and 2,5-dimethoxy-4,α-dimethylphenylalanine (**2**) were synthesized.

Heating a mixture of 2,5-dimethoxytolualdehyde, hippuric acid, and NaOAc afforded the oxazolone **3**, which was converted to the phenylpyruvic acid **4**. Compd **1** was obtained from **4** by the formation of the α-oxime **5** followed by catalytic reduction to generate the α-amino group. The phenylpyruvic acid **4** can be prepared from the 2-methyloxazolone **6**. Decomposition of **6** gave AcOH which can be easily removed from **4**. The disadvantage of this route was the low yield from the condensation of 2,5-dimethoxytolualdehyde with *N*-acetylglycine; in addition, **6** did not crystallize from solution and an extraction was, therefore, necessary. An attempt was made to prepare **1** from **3** *via* the α-benzamidophenylacrylic acid **7**. The benzoyl group of **8** was found to resist hydrolysis in either refluxing NaOH or H_2SO_4. Hydrolysis under pressure was not tried because of the awareness of a possible cleavage of the MeO group on the molecule.

For the synthesis of **2**, the substituted phenylacetone **5**[2] was converted to the hydantoin **8** by heating with $(NH_4)_2CO_3$ and KCN. Refluxing of **8** with aq Ba $(OH)_2$ then gave the α-methylphenylalanine **2**. Both **1** and **2** were further characterized by the *N*-benzoyl derivatives (**9** and **10**) and by the Me esters (**11** and **12**).

At a concn as high as 1×10^{-2} *M* neither **1** nor **2** inhibited DOPA decarboxylase in mouse brains, while α-methyldopa, a known inhibitor of the enzyme, had an I_{50} value of 3.3×10.4 *M*. Decarboxylation of **2** to DOM (STP) did not occur in brain, as demonstrated by the failure to detect DOM in either *in vitro* or *in vivo* studies.

Experimental Section[3]

4-(2,5-Dimethoxy-4-methylbenzylidene)-2-phenyl-5-oxazolone (3).—A mixt of 25 g (0.14 mole) of 2,5-dimethoxytolualdehyde, 37.4 g (0.21 mole) of hippuric acid, 34.4 g (0.42 mole) of NaOAc (anhyd), 100 ml of Ac_2O, and 80 ml of AcOH was heated on the steam bath for 45 min, during which period the mixt gradually turned orange. The resulting mixt was poured onto 1500 g of crushed ice, and the solid, upon standing overnight, was filtered: yield, 45.4 g; mp 204–205°. For purification, the product was recrystd from DMF at 100° to yield 25 g (55%) of bright orange solid, mp 210–211°. *Anal.* ($C_{19}H_{17}NO_4$) C, H, N.

4-(2,5-Dimethoxy-4-methylbenzylidene)-2-methyl-5-oxazolone (6).—A mixt of 9.0 g (50 mmoles) of 2,5-dimethoxytolualdehyde, 5.8 g (50 mmoles) of *N*-acetylglycine, 4.1 g (50 mmoles) of NaOAc, and 12.8 g (125 mmoles) of Ac_2O was warmed on the steam bath until a soln resulted. The soln was refluxed for 1 hr. After cooling 50 ml of H_2O was added, and the mixt was extd with 50 ml of $CHCl_3$. The ext was washed with H_2O (four 100-ml portions), dried (Na_2SO_4), and evapd to yield 14.0 g of gummy solid. Recrystn from EtOH gave 4.2 g (32%) of golden shining solid, mp 121–122°. *Anal.* ($C_{14}H_{15}NO_4$) C, H, N.

2,5-Dimethoxy-4-methylphenylpyruvic Acid (4). Method A. From 3.—A mixt of 18.3 g (0.57 mole) of **3** and 100 ml of 10% NaOH was refluxed for 10 hr, during that period the compd slowly dissolved and the orange color faded to yellow. A Na salt, which pptd upon cooling, was redissolved by the addn of 500 ml of H_2O. The soln was satd with SO_2 to yield 4.3 g of BzOH, mp 105–110°. After filtration, the soln was heated to boiling and 50 ml of concd HCl was added. On cooling, 9.8 g (72.5%) of yellow product pptd, mp 148–151°. Recrystn from 250 ml of $PhCH_3$

(1) (a) Previous paper of the series: B. T. Ho, V. Estevez, L. W. Tansey, L. F. Englert, P. J. Creaven, and W. M. McIsaac, *J. Med. Chem.*, **14**, 158 (1971); (b) after our paper was accepted, the synthesis of **1** was reported by K. Brewster and R. M. Pinder, *J. Med. Chem.*, **14**, 650 (1971).

(2) B. T. Ho and L. W. Tansey, *ibid.*, **14**, 156 (1971).

(3) Melting points were taken on a Mel-Temp apparatus and are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Ir spectra of all the compds were compatible with the assigned structures.