3-[5-(3-Acetamidophenyl)-2-tetrazolyl]propionic Acid (29).—3-[5-(3-aminophenyl)-2-tetrazolyl]propionic acid (7 g, 0.03 mol) was stirred for 12 hr at room temp in 100 ml of an equivolume mixture of Ac_2O–AcOH. The pale yellow ppt was reprecipitated from $NaHCO_3$ and recrystd from EtOH to give 5 g (61%) of pale yellow crystals, mp 207°.

3-[5-(3-Phenylazophenyl)-2-tetrazolyl]propionic Acid (30).—To a solution of 7 g (0.03 mol) of 3-[5-(3-aminophenyl)-2-tetrazolyl]propionic acid in 75 ml of glacial AcOH was added 3.25 g (0.03 mol) of nitrosobenzene. After stirring at room temp for 16 hrs the ppt was collected and dried. Two recrystallizations from aq MeOH gave 5 g (52%) of red crystals, mp 155°.

3-(5-Phenyl-1-tetrazolyl)propionic Acid (44).—PCl_5 (51 g, 0.245 mol) was added portionwise to a solution of ethyl 3-benzamidopropionate (50 g, 0.232 mol) in 300 ml of dry C_6H_6. The solution was refluxed until the evolution of HCl ceased. After cooling, 100 g of a 13.4% solution of HN_3 in C_6H_6[17] was added. After stirring for 1 hr at 0° and 16 hr at reflux, HCl gas ceased to evolve. The solvent was removed under recuced pressure and the residue was hydrolyzed according to procedure 1. Two recrystallizations from H_2O gave 10.5 g (21%) of white plates, mp 146°. *Anal.* ($C_{10}H_{10}N_4O_2$) N.

2-Benzyl-5-tetrazolylacetic Acid (47).—Ethyl 5-tetrazolylacetate (36.5 g, 0.234 mol) was dissolved in 300 ml of abs EtOH containing 5.4 g (0.234 g-atom) of Na. To this was added, over a 15-min period, 29.6 g (0.234 mol) of $PhCH_2Cl$ in 50 ml of abs EtOH. After refluxing for 16 hr, the reaction mixture was filtered and concd *in vacuo* to give a yellow oil. Hydrolysis according to procedure **1** gave a waxy solid. Recrystallization from aq MeOH gave 14.4 g (28%) of pale yellow crystals, mp 154° dec. *Anal.* ($C_{10}H_{10}N_4O_2$) N; neut equiv, calcd 218; found 220.

Ethyl 3-[5-(4-chlorophenyl)-2-tetrazolyl]acrylate (48).—To a solution of 2 g (0.087 g-atom) of Na in 200 ml of abs EtOH was added 26 g (0.1 mol) of 5-(4-chlorophenyl)tetrazole and 11 g (0.11 mol) of ethyl propiolate. After refluxing 1 day under N_2, the solvent was removed under reduced pressure. The oily residue was stirred for 1 hr with 1 l. of 2% aq $NaHCO_3$. The undissolved yellow solid was recrystd first from EtOH and then from pentane to give 3 g (16%) of white needles, mp 121°, ir ($CHCl_3$) 1620 cm^{-1} (C=C), 1725 cm^{-1} (C=O). *Anal.* ($C_{12}H_{11}ClN_4O_2$) C, H, N.

(17) J. von Braun, *Justus Liebigs Ann. Chem.*, **490**, 100 (1931).

Synthesis and Screening for Antidepressant Activity of Some Aminoindanooxazolines, Aminoindanooxazines, and Aminoacenaphthoxazolines

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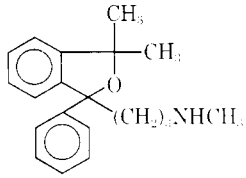
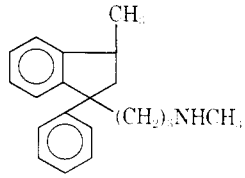
Some aminoindanooxazolines, aminoindanooxazines, and aminoacenaphthoxazolines having spatial orientations similar to those of the tricyclic drugs were synthesized and tested for potential antidepressant activity. None of the compounds were able to prevent reserpine-ptosis. Some of the compounds potentiated *d*-amphetamine toxicity and prolonged hexobarbital sleep time in mice.

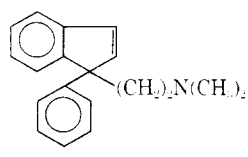
Basically substituted phenylpththalanes, indans, indenes, isochromanes, tetralines, isoindolines, indolines, tetrahydroisoquinolines, phthalimidines, oxindoles, dihydrobenzofurans, and dihydrobenzoxazines have been synthesized and screened for antidepressant activity.[1] Of these, the dihydrobenzofuran, indane, and indene derivatives (I, II, and III) have shown the most promise as potential antidepressant agents.[1,2]



I



II



III

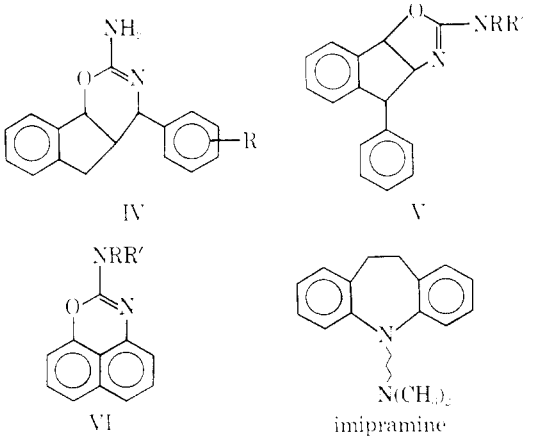
This paper reports the synthesis and testing as potential antidepressants of phenyl aminoindano-oxazines and oxazolines and aminoacenaphthoxazolines. These structures have the basic moiety fused onto either the indan nucleus (IV and V) or the acenaphthene nucleus (VI).

An examination of stereomodels showed that the angle between the two benzene rings in I, II, III, V, and imipramine is practically identical (110°) and that this results in the benzenoid-containing portion of these molecules being superimposable. Because indan is planar and rigid the C–C bond attaching the basic side chain to the ring is fixed at an angle of 55° to the ring. Because of N inversion, in imipramine the C–N bond attaching the basic side chain to the ring is either pseudoaxial or pseudoequatorial. In the former conformation the angle is similar to the phenylindans (~55°) and in the latter it is nearly in the same plane as one of the benzene rings. However, due to the flexibility of the propyl side chain the amino group of the phenylindans and imipramine can be made superimposable regardless of the configuration of the ring N in imipramine. In V the basic side chain is rigid and is not attached to the phenyl bearing carbon of indan as it is in II and III. Therefore, superimposition of N and the two phenyl rings of V and imipramine is restricted to one conformation of the imipramine side chain. In this conformation the three carbon atoms of the imipramine side chain also are superimposed on the three atoms of the oxazoline ring. Thus, it is likely that V would be able to interact with an imipramine receptor but that its structural requirement for interaction would be much more demanding. The divergence in structural similarity between imipramine and

(1) P. V. Petersen and I. Moeller-Nielson, *Antidepressant Drugs, Proc. Int. Symp. 1st. Milan 1966*, 217–21 (1967); *Chem. Abstr.*, **68**, 1724 (1968).

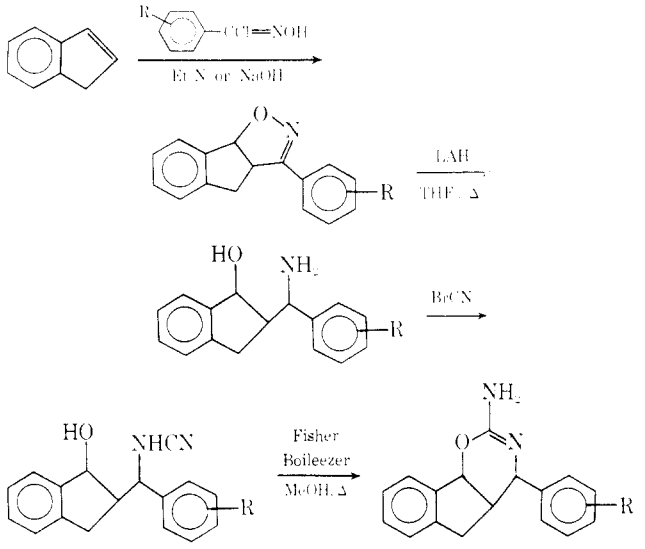
(2) J. H. Biel, *Ann. Rep. Med. Chem.*, 11 (1966); M. A. Davis, *ibid.*, 15–17 (1967).

IV and VI is great enough to preclude or at least make very doubtful the possibility of reaction at the same receptor.



Compounds of type IV were synthesized as shown in Scheme I. Indene was allowed to react with a benzo-

SCHEME I



nitrile oxide, which was generated *in situ* from the benzhydroximic chloride and base, to give the isoxazoline cycloaddition product. The isoxazolines were reductively cleaved with LAH in THF to the α-aminobenzylindanols. These were converted into the cyanamides by treatment with BrCN. The cyanamides were cyclized to the aminoindanooxazines by refluxing in MeOH in the presence of a few Fisher Boileezers.[3]

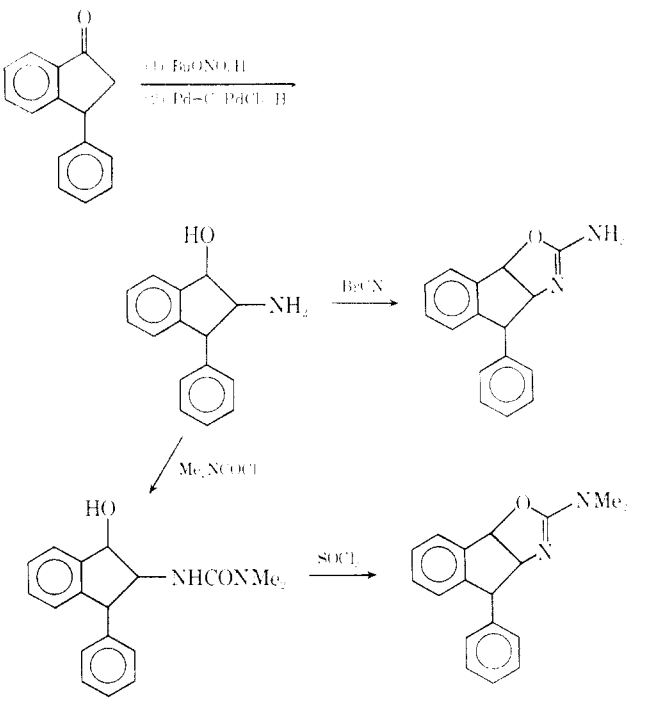
Compounds of type V were synthesized as shown in Scheme II. 3-Phenyl-1-indanone was treated with butyl nitrite in acid solution to give the isonitroso compound. This was calatytically hydrogenated to 2-amino-3-phenyl-1-indanol. The aminoindanol was cyclized with BrCN and it was converted into the urea *via* treatment with dimethylcarbamoyl chloride. The urea was cyclized to the dimethylaminoindanooxazoline with $SOCl_2$.

Compounds of type VI were synthesized similarly from acenaphthenequinone as shown in Scheme III.

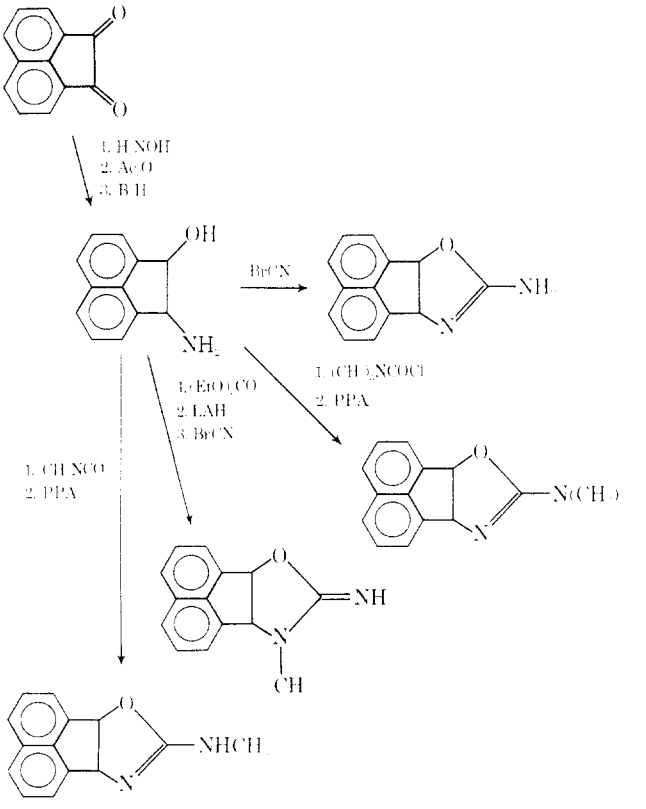
In all cases (types IV, V, and VI) the intermediate amino alcohol resulting from LAH cleavage of the is-

(3) Cyclization could also be induced thermally or by refluxing in MeOH in the presence of NaOAc but not as effectively as with boiling chips.

SCHEME II



SCHEME III



oxazoline or reduction of the isonitroso ketone is a mixture of the two diastereoisomeric reacemates [(*cis* (+) and (−)]. No attempt was made to separate either the diastereomers or the enantiomers but rather the mixture was used as such. The compounds of type IV, V, and VI are all *cis* (+) and (−) racemates. Results of pmr, ir, and elemental analyses substantiated assigned structure.

Pharmacology.—The ability of a compound to prevent reserpine-induced ptosis and to potentiate *d*-am-

phetamine toxicity in the mouse was used as an indication of antidepressant activity. The behavior of compounds of types IV, V, VI, related intermediates, and imipramine in these tests was determined. The results are recorded in Table I. The test methods are described in the Experimental Section.

None of the compounds were active in the reserpine ptosis test indicating that the rigidity of the basic side chain when it is part of a fused oxazoline or oxazine system does not meet the requirements of the imipramine receptor even though in the oxazoline case (type V) the benzenoid and the basic side chain are superimposable with their counterparts in one conformation of the imipramine molecule. Evidence that lack of activity is not due to the inability of an amino group of the type contained in compounds of types IV, V, and VI to interact with the imipramine receptor similarly to methylamino and dimethylamino is furnished by test results indicating that 2-amino-5-phenyloxazoline exhibits potent activity in the reserpine ptosis test.[4]

Many of the compounds of types IV, V, VI, and intermediates listed in Table I are active in the potentiation of amphetamine toxicity test. Compounds 6 and 9 are more potent than imipramine. They have ED_{50} values of 7.7 (5.7–10.5) mg/kg and 8.1 (5.7–11.5) mg/kg, respectively, and imipramine has an ED_{50} of 50 (30–83) mg/kg. Activity in this test is not as indicative of imipramine-like antidepressant activity as is activity in the reserpine ptosis test.

Most of these compounds are inactive or only moderately active in the hexobarbital sleep time test. An exception is 9 which prolongs hexobarbital sleep time greater than twofold at a dose of 17 mg/kg.

Experimental Section

Chemistry.—Melting points were determined in open capillary tubes using the Thomas-Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlaboratories, Indianapolis, Indiana. Where analyses are indicated by only symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Methods Used to Prepare the Compounds Listed in Table I. 3-(Substituted phenyl)-3a,8b-dihydro-4*H*-indeno[2,1-*d*]oxazoles.—To a stirred mixture of 46.5 g (0.3 mole) of benzhydroximic chloride, 34.8 g (0.3 mol) of indene, and 200 ml of $CHCl_3$ was added gradually 30 g (0.33 mol) of Et_3N. The mixture was stirred and heated at reflux temperature for 1 hr, cooled, washed (H_2O), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was recrystallized with the appropriate solvent.

2-(α-Amino-substituted benzyl)-1-indanols.—To a stirred suspension of 0.3 mol of $LiAlH_4$ in 200 ml of THF was added, dropwise, a solution of 0.15 mol of 3-phenyl-3a,8b-dihydro-4*H*-indeno[2,1-*d*]oxazole in 500 ml of THF. The mixture was stirred and heated at the reflux temperature for 18 hr, cooled, treated with a mixture of 30 ml of H_2O and 10 ml of THF, suction filtered, and the residue washed thoroughly with THF. The combined filtrate and wash solution were evaporated *in vacuo* and the residue was either crystallized or converted into the hydrochloride.

2-Amino-2,4a,5,9b-tetrahydro-4-phenylindeno[2,1-*e*]-1,3-oxazines.—A stirred ice-cooled mixture of 0.05 mol of 2-(α-amino-substituted benzyl)-1-indanol, 0.2 mol of NaOAc, and 200 ml of MeOH was treated, dropwise, with a solution of 0.05 mole of BrCN in 100 ml of MeOH. The mixture was stirred overnight at ambient temperature, treated with 30 ml of NH_4OH, and evaporated to dryness *in vacuo*. The residue was treated with 500 ml of $CHCl_3$ and 100 ml of H_2O. The layers were separated and the $CHCl_3$ layer washed (H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The crude cyanamide, obtained in this manner, was not purified, but rather was cyclized directly *via* 8-hr reflux in 150 ml of MeOH to which Fisher boiling granules had been added. After the 8-hr reflux the MeOH was evaporated *in vacuo* and the residue recrystallized.

2-Isonitroso-3-phenylindanone.—To a stirred solution of 85 g (0.44 mol) of 3-phenylindanone was added, over a 30-min period, 48 g (0.46 mol) of BuONO. After 15 min the solid product was suction filtered and washed (Et_2O) to give 81.7 g (84%), mp softens 203–205° and decomposes 212°. A sample recrystallized from EtOH melted at 210° dec.[5]

2-Amino-3-phenyl-1-indanol.—A mixture of 15 g of 2-isonitroso-3-phenylindanone, 3 g of Pd–C, 2 ml of 5% $PdCl_2$, 2 ml of concd HCl, and 20 ml of EtOH was hydrogenated for 18 hr at 2.1 kg/cm². The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was recrystallized from EtOH to give 12 g, mp 162–170°. The base liberated with NaOH melted at 160°.[6]

2-Amino-3a,8b-dihydro-4-phenyl-4*H*-indeno[2,1-*d*]oxazole Hydrochloride (12).—To a stirred mixture of 16.2 g (0.073 mol) of 2-amino-3-phenyl-1-indanol, 18 g of NaOAC, and 375 ml of MeOH maintained at 15–20° was added, over a 15-min period a solution of 8.5 g (0.080 mol) of BrCN in 15 ml of MeOH. The mixture was stirred at ambient temperature for 20 hr, concentrated *in vacuo*, treated with dilute NaOH solution, and extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with dilute HCl. The combined acidic extracts were decolorized with carbon, basified with NaOH solution, and extracted with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ solution was evaporated *in vacuo* and the residue (mp 190–195°) was converted into the hydrochloride with ethereal HCl.

***N*-(1-Hydroxy-3-phenyl-2-indanyl)-*N*′,*N*′-dimethylurea.**—To a stirred mixture of 10 g (0.045 mol) of 2-amino-3-phenyl-1-indanol, 20 ml of Et_3N, and 100 ml of CH_2Cl_2 kept under N_2 was added, over a 20-min period, a solution of 6.3 g (0.058 mol) of dimethylcarbamoyl chloride in 10 ml of CH_2Cl_2. The mixture was stirred and heated at the reflux temperature for 6 hr, cooled, treated with 300 ml of $CHCl_3$ and 100 ml of H_2O and the organic layer removed, washed (HCl, H_2O), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was recrystallized from aq MeOH to give 5.4 g (69%), mp 197–198°. *Anal.* ($C_{18}H_{20}N_2O_2$) C,H,N.

2-Dimethylamino-3a,8a-dihydro-4-phenyl-4*H*-indeno[2,1-*d*]-oxazole Hydrochloride (13).—To a stirred mixture of 5.4 g of *N*-(1-hydroxy-3-phenyl-2-indanyl)-*N*′,*N*′-dimethylurea and 75 ml of CH_2Cl_2 was added 2 ml of $SOCl_2$. The mixture was heated at the reflux temperature for 2 hr, concentrated *in vacuo*, and the residue extracted with H_2O. The H_2O extract was basified with NaOH solution and extracted with CH_2Cl_2. Evaporation *in vacuo* of the dried ($MgSO_4$) CH_2Cl_2 left a basic residue (mp 145–148°) which was dissolved in Et_2O and treated with ethereal HCl.

Acenaphthenequinone Oxime.—A mixture of 36 g (0.2 mol) of acenaphthenequinone, 14 g (0.02 mol) of $HONH_2 \cdot HCl$, and 2200 ml of pyridine was stirred at ambient temperature overnight, filtered to remove small amount of black solid, and concd *in vacuo*. The residue was triturated with H_2O and filtered to give 33 g of grey solid, mp 213–215° dec.[7]

***o*-Acetyloxime of Acenaphthenequinone.**—To a cooled, stirred mixture of 20 g (0.1 mol) of acenaphthenequinone oxime and 100 ml of pyridine was added, portionwise, 40 ml of Ac_2O. The mixture was stirred at ambient temperature overnight, cooled, and the precipitate suction filtered. The solid was washed with cold pyridine-C_6H_6, then with H_2O, and dried to give 17 g (83%), mp 185–187° (from PhMe). *Anal.* ($C_{14}H_9NO_3$) C,H,N.

2-Amino-1-acenaphthenol.—To a stirred, cooled mixture of 17 g (0.072 mol) of *O*-acetyloxime of acenaphthenequinone and 200 ml of THF was added, over a period of 20 min, 315 ml of a 1.0 *M* BH_3–THF solution. The stirred mixture was allowed to come to ambient temperature (1 hr), was heated at reflux temperature for 2 hr, and then allowed to stand overnight. The stirred mixture was treated with 45 ml of 50:50 THF–H_2O, 38 ml of 20% HCl, concd *in vacuo*, chilled, basified with aq NaOH, and extracted with $CHCl_3$ The dried ($MgSO_4$) $CHCl_3$ solution was evaporated *in vacuo* to give 12.9 g (97%), mp 107–111°; hydro-

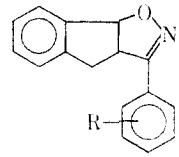
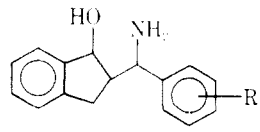
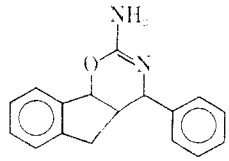
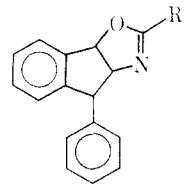
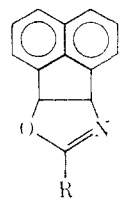
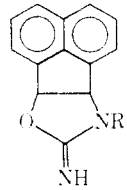
(4) In our reserpine-ptosis test 2-aminoindanooxazoline gave an ED_{50} of 12.2 (9.38–15.86).

(5) H. Richter and M. Schenck, German Patent 936,507 (1956); *Chem. Abstr.*, **53**, 2190 (1959).

(6) H. Richter and M. Schenck, German Patent 936,953 (1956); *Chem. Abstr.*, **53**, 2191 (1959).

(7) Francesconi and Pirrazoli, *Gazz. Chim. Ital.*, **33**, 42 (1903).

TABLE I

No.	R	Mp, °C[a]	Yield, %	Formula[e]	Mouse LD_{50}, mg/kg, ip	Screening Dose, mg/kg, ip	Potentiate *d*-amphet toxic[b]	Reserpine ptosis[c]	Hexobarbital sleep time[d]
		3-(Substituted phenyl)-3a,8b-dihydro-4*H*-indeno[2,1-*d*]oxazoles 							
1	H	134–135	36	$C_{16}H_{13}NO$	>1000	500	350 (175–700)	0/10	60/23
2	4-Cl	183–184	29	$C_{16}H_{12}ClNO$	>1000	500	1/10	0/10	49/23
3	4-CH_3	127–128	44	$C_{17}H_{15}NO$	>1000	500	148 (109–201)	0/10	79/32
4	2,4-Cl_2	113–114	43	$C_{16}H_{11}Cl_2NO$	>1000	500	125 (108–145)	0/10	112/32
		2-(α-Amino-substituted benzyl)-1-indanols 							
5	H	252–253	34	$C_{16}H_{17}NO \cdot HCl$	121	36	0/10	0/10	53/33
6	4-Cl	112–113	37	$C_{16}H_{16}ClNO$	147	44	7.7 (5.7–10.5)	0/10	76/33
7	4-CH_3	109.5–110	26	$C_{17}H_{19}NO$	147	44	1/10	0/10	53/34
8	2,4-Cl_2	103.5–104	49	$C_{16}H_{15}Cl_2NO$	147	44	2/10	0/10	64/34
		2-Amino-2,4a,5,9b-tetrahydro-4-phenylindeno[2,1-*e*]-1,3-oxazine 							
9	H	144–145	45	$C_{17}H_{16}N_2O$	56	17	8.1(5.7–11.5)	0/10	98/42
10	4-CH_3	150–151	65	$C_{18}H_{18}N_2O$	681	204	100 (43.4–230)	0/10	82/38
11	4-Cl	126–128	54	$C_{17}H_{15}ClN_2O$	681	204	2/10	0/10	40/26
		Substituted 2-Amino-3a,8b-dihydro-4-phenyl-4*H*-indeno[2,1-*d*]oxazoles 							
12	NH_2	214	28	$C_{16}H_{14}N_2O \cdot HCl$	147	44	7/10	0/10	40/26
13	$N(CH_3)_2$	168–169	18	$C_{18}H_{18}N_2O \cdot HCl$	68	20	4/10	0/10	52/39
		Substituted 8-Amino-6b,9a-dihydroacenaphth[1,2-*d*]oxazoles 							
14	NH_2	225	22	$C_{13}H_{16}N_2O \cdot HCl$	68	20	2/10	0/10	41/34
15	$NHCH_3$	214–215	39	$C_{14}H_{12}N_2O \cdot HCl$	56	17	3/10	0/10	51/39
16	$N(CH_3)_2$	146–147	80	$C_{15}H_{14}N_2O \cdot (CHCOOH)_2$	82	25	5/10	0/10	34/26
		Substituted 8-Imino-6b,9a-dihydroacenaphth[1,2-*d*]oxazoles 							
17	CH_3	247–248	89	$C_{14}H_{12}N_2O \cdot HCl$	56	17	1/10	1/10	51/39
18	Imipramine				95	53	50 (30–83)	35 (26–47)	95/27

[a] Recrystallization solvents EtOH, **9,15,16,17**; *i*-PrOH, **6,10**; MeOH–Et_2O, **12,13,14**; $CHCl_3$–hexane, **1**; $CHCl_2$, **2**; C_6H_6–hexane, **3**; Et_2O–hexane, **4**; EtOH–Et_2O, **5**; toluene, **7**; Et_2O, **8**; *i*-PrOH–hexane, **11**. [b] Results are expressed either as a ratio of number of mice dead to number of mice treated with screening dose, or as ED_{50} values (mg/kg) and their 95% confidence limits. [c] Results are expressed either as a ratio of number of mice protected to number of mice treated or as ED_{50} values (mg/kg) and their 95% confidence limits. [d] Results are expressed as a ratio of duration of sleeping times of treated group to the control group. [e] All compounds were analyzed for C, H, N.

chloride mp 295° dec (MeOH–Et_2O). *Anal.* ($C_{12}H_{11}NO \cdot HCl$)C, H, N.

8-Amino-6b,9a-dihydroacenaphth[1,2-*d*]oxazole Hydrochloride.—To a stirred, cooled (10°) mixture of 11.7 g (0.063 mol) of 2-amino-1-acenaphthenol, 15.6 g (0.19 mol) of NaOAc, and 125 ml of MeOH was added, over a period of 30 min, a solution of 7.4 g (0.068 mol) of BrCN in 10 ml of MeOH. The mixture was stirred at ambient temperature overnight, concd *in vacuo*, basified with aq NaOH, and extracted with $CHCl_3$. The dried (Na_2CO_3) $CHCl_3$ solution was evaporated *in vacuo* and the basic residue treated with ethereal HCl.

***N*-(2-Hydroxy-1-acenaphthenyl)-*N'*-methylurea.**—To a stirred, cooled (5°) solution of 10 g (0.54 mol) of 2-amino-1-acenaphthenol in 150 ml of CH_2Cl_2 was added a solution of 3.7 g (0.065 mol) of CH_3NCO in 5 ml of CH_2Cl_2. The mixture was stirred at ambient temperature overnight. The precipitate was suction filtered, washed with CH_2Cl_2–Et_2O, and recrystallized from EtOH to give 12.5 g (95%), mp 199–201°. *Anal.* ($C_{14}H_{16}N_2O_2$) C, H, N.

8-Methylamino-6b,9a-dihydroacenaphth[1,2-*d*]oxazole Hydrochloride.—A mixture of 8.9 g of *N*-(2-hydroxy-1-acenaphthenyl)-*N'*,*N'*-dimethylurea and 235 g of PPA was stirred at ambient temperature for 24 hr, poured into ice water, and filtered. The acid filtrate was chilled, basified with cold aq NaOH, and extracted with $CHCl_3$. The $CHCl_3$ was evaporated *in vacuo* and the residue was treated with dilute HCl and filtered. The acidic filtrate was again basified with NaOH solution and extracted with $CHCl_3$. After removal of $CHCl_3$, the basic residue was dissolved in ethanolic HCl and treated with Et_2O to precipitate the hydrochloride.

***N*-(2-Hydroxy-1-acenaphthenyl)-*N'*,*N'*-dimethylurea.**—To a stirred mixture of 10 g (0.054 mol) of 2-amino-1-acenaphthol, 10 ml of Et_3N, and 95 ml of CH_2Cl_2 kept under N_2 was added, over a period of 30 min, a solution of 7.6 g (0.070 mol) of dimethylcarbamoyl chloride in 10 ml of CH_2Cl_2. The mixture was stirred at ambient temperature for 17 hr, concd *in vacuo*, and the resulting solid recrystallized (C_6H_6) to give 10.3 g (75%), mp 125–145° (mixture of *cis* and *trans* isomers). *Anal.* ($C_{15}H_{16}N_2O_2$) C,H,N.

8-Dimethylamino-6b,9a-dihydroacenaphth[1,2-*d*]oxazole Maleate.—A mixture of 5.0 g of *N*-(2-hydroxy-1-acenaphthenyl)-*N'*,*N'*-dimethylurea and 155 g of PPA was stirred at ambient temperature for 18 hr, added to ice water, and the mixture filtered. The chilled, acidic filtrate was basified with cold NaOH solution and extracted with $CHCl_3$. The dried (Na_2CO_3) $CHCl_3$ extract was evaporated *in vacuo* and the basic residue recrystallized (C_6H_6) (mp 185–186°). The maleate was prepared in abs EtOH.

9,9a-Dihydroacenaphth[1,2-*d*]oxazol-8(6b*H*)-one.—A mixture of 20 g of 2-amino-1-acenaphthenol, 2 g of NaOMe, and 125 ml of $(EtO)_2CO$ was heated over a 1.5-hr period and 25 ml of EtOH–$(EtO)_2CO$ was allowed to distill. The chilled reaction mixture was suction filtered and the solid was washed with dilute HCl and recrystallized from EtOH (charcoal) to give 6.7 g (30%), mp 211–212°.

2-Methylamino-1-acenaphthenol.—The 9,9a-dihydroacenaphth[1,2-*d*]oxazol-8(6b*H*)-one (6.5 g) was reduced with 2.0 g of LAH in refluxing THF to 4.8 g (78%) of 2-methylamino-1-acenaphthenol, mp 114° (hexane–Et_2O). *Anal.* ($C_{13}H_{13}NO$) C,H,N.

6b,8,9,9a-Tetrahydro-8-imino-9-methylacenaphth[1,2-*d*]oxazole Hydrochloride.—2-Methylamino-1-acenaphthenol (4.5 g) in 70 ml of MeOH containing 6 g of NaOAc was treated with BrCN (2.6 g) at 5°. The stirred mixture was refluxed 1.5 hr, left at ambient temperature overnight, evaporated *in vacuo* and the residue suspended in dil NH_4OH and suction filtered. The basic residue was treated with EtOH–HCl to give the hydrochloride.

Pharmacology. Acute Toxicity in Mice.—Adult male mice, in groups of 4, were given the test compound, ip, using at least 3 dose levels, and observed for 24 hr. LD_{50} values were calculated by the method of Litchfield and Wilcoxon.[8]

Antagonism to Reserpine-Induced Ptosis in Mice.—Adult male mice were given test compound ip (this screening dose was *ca.* 0.3 LD_{50}) 30 min prior to a reserpine (5 mg/kg ip) challenge. Observation for ptosis was made 45 min after reserpine. Results are given as the ratio of number of mice protected to number of mice tested. When 6/10 or more mice were protected at this screening dose, additional tests were made to determine the ED_{50}. In these cases, the ED_{50} values and their 95% confidence limits (calculated according to the method of Litchfield and Wilcoxon[8]) are listed instead of the protection ratios.

Potentiation of Amphetamine Toxicity in Aggregated Mice.—Adult male mice, in groups of 10, were given test compound ip (0.3 LD_{50}), saline control, or amphetamine (5 mg/kg) "positive" control. All animals were dosed with amphetamine (5 mg/kg) 30 min later and aggregated by placement in cubic wire-mesh cages 16 cm on a side. They were then kept in a walk-in incubator (30°, for both noise and temperature control) for 5 hr at which time the dead were counted. If 3 or more were dead in the saline control group or 6 or less in the amphetamine control group the entire experiment was discounted arbitrarily. Results are given as a ratio of number of mice dead to number of mice in group. When 6/10 or more mice were found dead at the screening dose, additional tests were made to determine the ED_{50}. In these cases the ED_{50} values and their 95% confidence limits are listed instead of the lethality ratios.

Hexobarbital Sleep Time Test.—Adult male mice were injected ip with the test compound 30 min prior to the ip injection of 100 mg/kg of hexobarbital. The time in minutes between injection of the hexobarbital and the region of the righting reflex was taken as the duration of sleeping time. The results are expressed as a ratio of the treated group over the control group.

(8) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Chemotherapeutic Nitroheterocycles. 1.[1a] Substituted 2-(5-Nitro-2-furyl)pyrimidines

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A series of 5-substituted 2-(5-nitro-2-furyl)pyrimidines have been synthesized by reaction of 2-furamidine with α-substituted β-dimethylaminoacroleins and subsequent nitration of the furan ring. The derivatives were shown to be potent inhibitors of *Trichomonas vaginalis in vitro*. They also possess antibacterial activity; *in vivo* activity is reported.

Among antibacterial agents based on nitrofuran much attention has been paid to compounds in which the nitrofuran is directly attached to other heterocyclic systems.[2] At the outset of this work only a few papers were known in which nitrofurylpyrimidines were mentioned. Hull and Swain[3] synthesized some substituted 4-(5-nitro-2-furyl)-2-oxo-1.2.3.4-tetrahydropyrimidines. Howard[4] prepared 6-(5-nitro-2-furyl)-ura-

(1) (a) A preliminary report of part of this work was presented at the 6th International Congress of Chemotherapy, Tokyo, Aug 1969; (b) To whom inquiries should be addressed.

(2) K. Miura and H. K. Reckendorf, *Progr. Med. Chem.* **5**, 320 (1967).

(3) ICI, British Patent 868030, *Chem. Abstr.*, **56**, 1463 (1962).

(4) The Norwich Pharmacal Co., U.S. Patent 3121 083; *Chem. Abstr.*, **60**, 12027 (1964).