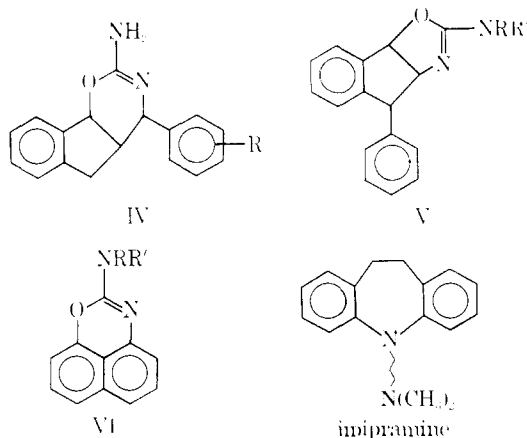
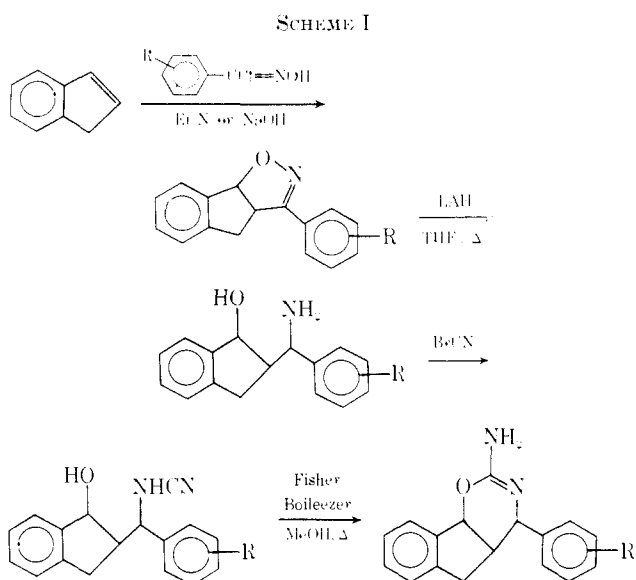


IV and VI is great enough to preclude or at least make very doubtful the possibility of reaction at the same receptor.



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



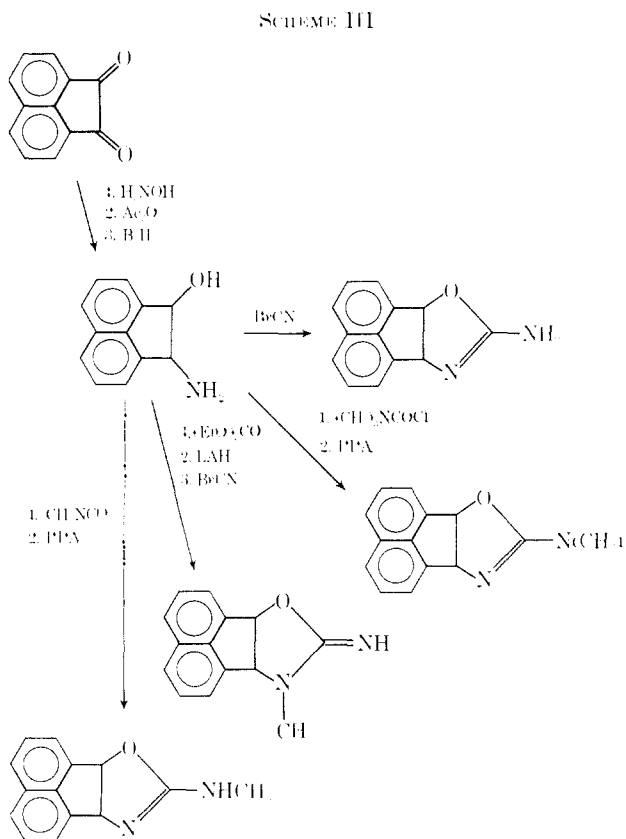
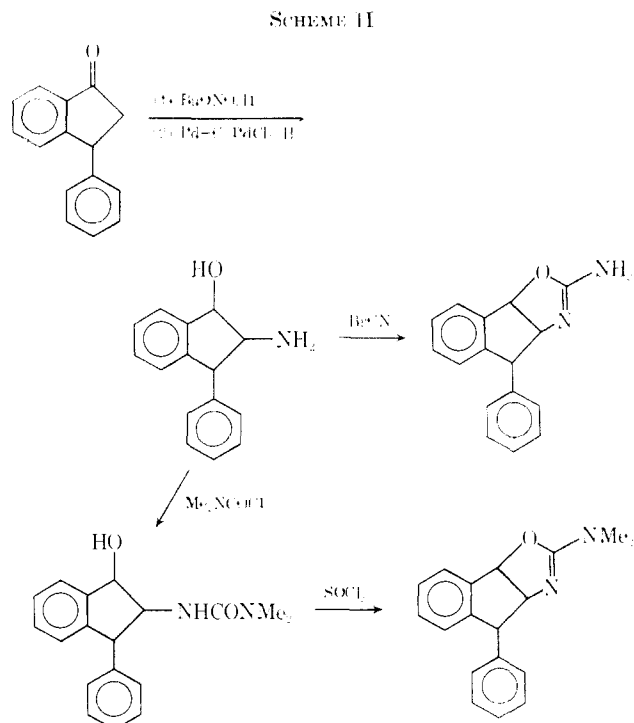
nitrile oxide, which was generated *in situ* from the benzhydroxamic chloride and base, to give the isoxazoline cycloaddition product. The isoxazolines were reductively cleaved with LAH in THF to the α -amino benzylindanols. These were converted into the cyanamides by treatment with BrCN. The cyanamides 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 catalytically 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 SOCl₂.

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.



oxazoline or reduction of the isonitroso ketone is a mixture of the two diastereoisomeric racemates [(*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 ED₅₀ values of 7.7 (5.7–10.5) mg/kg and 8.1 (5.7–11.5) mg/kg, respectively, and imipramine has an ED₅₀ 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 Micro Laboratories, Indianapolis, Indiana. Where analyses are indicated by only symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

Methods Used to Prepare the Compounds Listed in Table I. 3-(Substituted phenyl)-3a,8b-dihydro-4H-indeno[2,1-d]oxazoles.—To a stirred mixture of 46.5 g (0.3 mole) of benzhydroxamic chloride, 34.8 g (0.3 mol) of indene, and 200 ml of CHCl₃ was added gradually 30 g (0.33 mol) of Et₃N. The mixture was stirred and heated at reflux temperature for 1 hr, cooled, washed (H₂O), dried (MgSO₄), 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 LiAlH₄ in 200 ml of THF was added, dropwise, a solution of 0.15 mol of 3-phenyl-3a,8b-dihydro-4H-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 H₂O 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 NH₄OH, and evaporated to dryness *in vacuo*. The residue was treated with 500 ml of CHCl₃ and 100 ml of H₂O. The layers were separated and the CHCl₃ layer washed (H₂O), dried (MgSO₄), 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 (Et₂O) 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% PdCl₂, 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-4H-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 CHCl₃. The CHCl₃ solution was extracted with dilute HCl. The combined acidic extracts were decolorized with carbon, basified with NaOH solution, and extracted with CHCl₃. The dried (MgSO₄) CHCl₃ 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 Et₃N, and 100 ml of CH₂Cl₂ kept under N₂ was added, over a 20-min period, a solution of 6.3 g (0.058 mol) of dimethylcarbamoyl chloride in 10 ml of CH₂Cl₂. The mixture was stirred and heated at the reflux temperature for 6 hr, cooled, treated with 300 ml of CHCl₃ and 100 ml of H₂O and the organic layer removed, washed (HCl, H₂O), dried (MgSO₄), and evaporated *in vacuo*. The residue was recrystallized from aq MeOH to give 5.4 g (69%). *Anal.* (C₁₈H₂₀N₂O₂) C, H, N.

2-Dimethylamino-3a,8a-dihydro-4-phenyl-4H-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 CH₂Cl₂ was added 2 ml of SOCl₂. The mixture was heated at the reflux temperature for 2 hr, concentrated *in vacuo*, and the residue extracted with H₂O. The H₂O extract was basified with NaOH solution and extracted with CH₂Cl₂. Evaporation *in vacuo* of the dried (MgSO₄) CH₂Cl₂ left a basic residue (mp 145–148°) which was dissolved in Et₂O and treated with ethereal HCl.

Acenaphthenequinone Oxime.—A mixture of 36 g (0.2 mol) of acenaphthenequinone, 14 g (0.02 mol) of HONH₂·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 H₂O 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 Ac₂O. The mixture was stirred at ambient temperature overnight, cooled, and the precipitate suction filtered. The solid was washed with cold pyridine-C₆H₆, then with H₂O, and dried to give 17 g (83%), mp 185–187° (from PhMe). *Anal.* (C₁₄H₉NO₃) 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 BH₃-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-H₂O, 38 ml of 20% HCl, concd *in vacuo*, chilled, basified with aq NaOH, and extracted with CHCl₃. The dried (MgSO₄) CHCl₃ solution was evaporated *in vacuo* to give 12.9 g (97%), mp 107–111°; hydro-

(4) In our reserpine-ptosis test 2-aminoindano-oxazoline gave an ED₅₀ 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 ^c	Mouse ED ₅₀ , mg/kg, ip	Screening Dose, mg/kg, ip	Potentiate <i>d</i> -amphetamine ^b	Reserpine prosis ^c	Hexo-barbital sleep time ^d
3-(Substituted phenyl)-3a,8b-dihydro-4 <i>H</i> -indeno[2,1- <i>d</i>]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 ₂ NO	>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·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 ₁₄ Cl ₂ NO	147	44	2/10	0/10	64/34
2-Amino-2,4a,5,9b-tetrahydro-4-phenylindeno[2,1- <i>e</i>]-1,3-oxazine									
9	H	144-145	45	C ₁₇ H ₁₆ N ₂ O	56	17	8.1 (5.7-11.5)	0/10	98/42
10	4-CH ₃	150-151	65	C ₁₈ H ₁₈ N ₂ O	681	204	100 (43.4-230)	0/10	82/38
11	4-Cl	126-128	54	C ₁₇ H ₁₅ ClN ₂ O	681	204	2/10	0/10	40/26
Substituted 2-Amino-3a,8b-dihydro-4-phenyl-4 <i>H</i> -indeno[2,1- <i>d</i>]oxazoles									
12	NH ₂	214	28	C ₁₆ H ₁₄ N ₂ O·HCl	147	44	7/10	0/10	40/26
13	N(CH ₃) ₂	168-169	18	C ₁₈ H ₁₈ N ₂ O·HCl	68	20	4/10	0/10	52/39
Substituted 8-Amino-6b,9a-dihydroacenaphth[1,2- <i>d</i>]oxazoles									
14	NH ₂	225	22	C ₁₈ H ₁₆ N ₂ O·HCl	68	20	2/10	0/10	41/34
15	NHCH ₃	214-215	39	C ₁₉ H ₁₈ N ₂ O·HCl	56	17	3/10	0/10	51/39
16	N(CH ₃) ₂	146-147	80	C ₁₉ H ₁₈ N ₂ O·(CHCOOH) ₂	82	25	5/10	0/10	34/26
Substituted 8-Imino-6b,9a-dihydroacenaphth[1,2- <i>d</i>]oxazoles									
17	CH ₃	247-248	89	C ₁₉ H ₁₈ N ₂ O·HCl	56	17	1/10	1/10	51/39
18	Imipramine				95	53	50 (30-83)	35	95/27

^a Recrystallization solvents EtOH, **9,15,16,17**; *i*-PrOH, **6,10**; MeOH-Et₂O, **12,13,14**; CHCl₃-hexane, **1**; CHCl₂, **2**; C₆H₆-hexane, **3**; Et₂O-hexane, **4**; EtOH-Et₂O, **5**; toluene, **7**; Et₂O, **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 ED₅₀ 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 ED₅₀ 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-Et₂O). *Anal.* (C₁₂H₁₁NO·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 CHCl₃. The dried (Na₂CO₃) CHCl₃ 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 CH₂Cl₂ was added a solution of 3.7 g (0.065 mol) of CH₃NCO in 5 ml of CH₂Cl₂. The mixture was stirred at ambient temperature overnight. The precipitate was suction filtered, washed with CH₂Cl₂-Et₂O, and recrystallized from EtOH to give 12.5 g (95%), mp 199–201°. *Anal.* (C₁₄H₁₆N₂O₂) 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 CHCl₃. The CHCl₃ 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 CHCl₃. After removal of CHCl₃, the basic residue was dissolved in ethanolic HCl and treated with Et₂O 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 Et₃N, and 95 ml of CH₂Cl₂ kept under N₂ was added, over a period of 30 min, a solution of 7.6 g (0.070 mol) of dimethylcarbamoyl chloride in 10 ml of CH₂Cl₂. The mixture was stirred at ambient temperature for 17 hr, concd *in vacuo*, and the resulting solid recrystallized (C₆H₆) to give 10.3 g (75%), mp 125–145° (mixture of *cis* and *trans* isomers). *Anal.* (C₁₃H₁₆N₂O₂) 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 CHCl₃. The dried (Na₂CO₃) CHCl₃ extract was evaporated *in vacuo* and the basic residue recrystallized (C₆H₆) (mp 185–186°). The maleate was prepared in abs EtOH.

9,9a-Dihydroacenaphth[1,2-d]oxazol-8(6bH)-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(6bH)-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-Et₂O). *Anal.* (C₁₃H₁₃NO) 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 NH₄OH 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. LD₅₀ 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 LD₅₀) 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 ED₅₀. In these cases, the ED₅₀ values and their 95% confidence limits (calculated according to the method of Litchfield and Wilcoxon⁸) 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 LD₅₀), 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 ED₅₀. In these cases the ED₅₀ 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. I.^{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-furamide 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 nitrofurans much attention has been paid to compounds in which the nitrofurans are directly attached to other heterocyclic systems.² At the outset of this work only a few papers

were known in which nitrofurypyrimidines were mentioned. Hull and Swain³ synthesized some substituted 4-(5-nitro-2-furyl)-2-oxo-1,2,3,4-tetrahydropyrimidines. Howard⁴ 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).