contrast to the 2-benzyl series it appears that no additivity exists for the chain at the 1 position and the 5-$NO_2$ groups as far as analgesia is concerned since 1-substituted 5-nitro derivatives were less analgetic than their N-unsubstituted homologs.[1] Convulsant effects were constant in the series. 2-Aminopropylbenzimidazoles did not appear to give interesting biological results.

**Acknowledgments.**—The authors wish to thank the "Direction des Recherches et Moyens d'Essais" who have permitted this work to be done; we also thank Ciba Laboratories (Bâle) who kindly furnished a sample of etonitazene and J. Wylde for the English translation.

## 5-(Dimethylaminopropyl)-10,11-dihydro-5H-benzo[2,3]pyrido[6,7-*b*]azepine[1]

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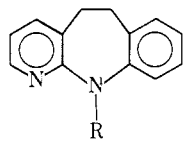
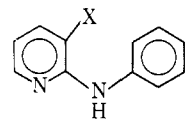
The title compound, Ib, was prepared to study the biological effects of isosteric substitution of a 2-pyridyl ring for a phenyl ring in the 10,11-dihydro-5H-dibenz-[*b*,*f*]azepine series of antidepressant agents. Our initial attempts at the synthesis of this heterocyclic



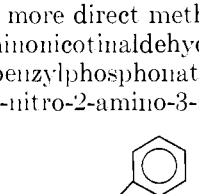
Ia, R = H
b, R = $(CH_2)_3N(CH_3)_2$



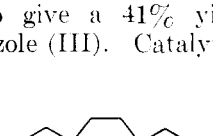
IIa, X = COOH
b, X = $CH_2OH$
c, X = $CH_2Cl$
d, X = $CH_2CN$
e, X = $CH_2OCH_3$

amine by homologation (IIb → IId) of the readily available 2-anilinonicotinic acid (IIa) followed by intramolecular cyclization were abandoned in favor of the present more direct method.

2-Aminonicotinaldehyde was condensed with ethyl *o*-nitrobenzylphosphonate[2] to give a 41% yield of *trans*-2′-nitro-2-amino-3-stibazole (III). Catalytic hy-



III



IV

drogenation of III in the presence of 5% Pd–C gave the diaminodihydrostilbazole IV which was converted to Ib by procedures previously described.[1] Compound Ib was isolated and characterized as the monohydrochloride and monomaleate salts.

In the attempted homologation sequence mentioned above, 2-anilinonicotinic acid (IIa) was converted by $LiAlH_4$ reduction into 3-(hydroxymethyl)-2-anilinopyridine (IIb). This compound on reaction with $SOCl_2$ gave the chloromethyl compound IIc. Attempts to convert IIc·HCl to the corresponding nitrile gave the alkoxy ethers as the major product.

Compound Ib[3] at oral doses of 1 and 3 mg/kg did not antagonize tetrabenazine-induced sedation in mice. The approximate $ED_{50}$ for this compound is between 5 and 10 mg/kg orally in mice, whereas the dibenzo compound has an oral $ED_{50}$ in the range of 1–3 mg/kg. At 30 mg/kg orally in the mouse, there was marked decrease in motor activity accompanied by tremors, twitches, and convulsions. The compound is lethal at 100 mg/kg.

These and our previously reported data demonstrate that substitution of one or both aromatic groups by pyridyl rings in the dibenzo[*b*,*f*]azepine series results in compounds having greater toxicity and lower antidepressant properties. However, these results are in contrast to similar substitutions in the dibenzo[*a*,*d*]cycloheptene series, which will be discussed in future communications from this laboratory.

### Experimental Section[4]

***trans*-2′-Nitro-2-amino-3-stilbazole (III).**—To a solution of ethyl *o*-nitrobenzylphosphonate[2] prepared from 27.1 g (0.125 mole) of *o*-nitrobenzyl bromide and 20.8 g (0.125 mole) of redistilled triethylphosphite was added, slowly, a suspension of 8.1 g of NaOMe in 40 ml of dry DMF at 0–5°. 2-Amino-3-pyridinealdehyde[5] (15.4 g, 0.125 mole) in 40 ml of DMF was added dropwise with stirring at 0 to −10°. After 15 min, the mixture was permitted to warm to room temperature and stirred for an additional 90 min. The dark brown reaction mixture was poured into 2 l. of ice water and allowed to crystallize overnight. The product was filtered, air dried, and recrystallized from *i*-$Pr_2O$ to give 12.5 g (41%) of product, mp 126–127°. *Anal.* ($C_{13}H_{11}N_3O_2$) C, H, N.

**2,2′-Diamino-3-phenethylpyridine (IV).**—A solution of 11.8 g of III in 250 ml of EtOH was reduced in a Parr hydrogenator at 50° in presence of 1 g of 5% Pd–C. After cooling, the catalyst was removed and the solution was concentrated *in vacuo* on the steam bath. The residue was recrystallized from a mixture of $CHCl_3$–hexane to give 8.2 g (78.5%) of product, mp 114–115°. *Anal.* ($C_{13}H_{15}N_3$) C, H, N.

**10,11-Dihydro-5H-benzo[2,3]pyrido[6,7-*b*]azepine (Ia).**—To a solution of 7.8 g (0.036 mole) of IV in 400 ml of EtOH, 85% $H_3PO_4$ was added dropwise until precipitation of the salt was complete. The phosphate salt was filtered, washed with anhydrous ether, air dried, transferred to a round-bottom flask, and heated at 250° (inner temperature) for 2 hr. After cooling the residue was suspended in $H_2O$, made basic with 50% NaOH, and extracted with $CHCl_3$. The solvent was removed and the residue was extracted several times with refluxing hexane (total 600 ml). Concentration of the combined hexane solutions gave the product (2.5 g, 37%) which was recrystallized several times from hexane; mp 96–97°. *Anal.* ($C_{13}H_{12}N_2$) C, H, N.

**5-(Dimethylaminopropyl)-10,11-dihydro-5H-benzo[2,3]pyrido-[6,7-*b*]azepine Hydrochloride (Ib).**—A solution of 5.9 g (0.03 mole) of Ia in 70 ml of anhydrous xylene was treated with 1.5 g of NaH (52.7% in mineral oil) and heated under reflux for 30 min. Dimethylaminopropyl chloride (4.0 g in 30 ml of xylene) was added dropwise and the mixture was heated with stirring for 14 hr. $H_2O$ was added, the product was extracted ($Et_2O$)

(1) For the first paper in this series see F. J. Villani, *J. Med. Chem.*, **10**, 497 (1967).

(2) R. J. Sundberg and T. Yamazaki, *J. Org. Chem.*, **32**, 290 (1967).

(3) We are indebted to Dr. Robert Taber of the Biological Division of the Schering Corp. for the biological data herein reported.

(4) Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were taken in a Thomas–Hoover melting point apparatus and are uncorrected. Spectral data, uv, ir, and nmr, and combustion elemental analyses were obtained by the Physical Analytical Department of the Schering Corp. and are in accord with the proposed structures.

(5) A. Albert and F. Reich, *J. Chem. Soc.*, 1370 (1960).

and dried ($Na_2SO_4$), and the solvent was removed. The residue was dissolved in $Et_2O$, and the product precipitated by the dropwise addition of ethereal HCl until acid was filtered, and recrystallized from 10% EtOH–EtOAc; yield 7.9 g (77%), mp 190–191°. *Anal.* ($C_{18}H_{23}N_3 \cdot HCl$) H, N; C: calcd, 67.99; found, 67.54.

The **Ib monomaleate salt** was formed in EtOAc and recrystallized from EtOAc–$Et_2O$, mp 89–90°. *Anal.* ($C_{18}H_{23}N_3 \cdot C_4H_4O_4$) C, H, N.

**3-(Hydroxymethyl)-2-anilinopyridine (IIb).**—A solution of 42.8 g (0.2 mole) of 2-anilinonicotinic acid[6] in 1 l. of anhydrous $Et_2O$ was added dropwise with stirring under reflux to 30 g of $LiAlH_4$ in 100 ml of $Et_2O$ and allowed to reflux for 20 hr. The product was isolated in the usual way to give 36 g (90%) of a yellow viscous oil bp 187–191° (1 mm). *Anal.* ($C_{12}H_{12}N_2O$) C, H. The **hydrochloride** salt after recrystallization from EtOH–$Et_2O$ had mp 189–190°. *Anal.* ($C_{12}H_{12}N_2O \cdot HCl$) H, N; C: calcd, 61.01; found, 61.44.

**3-(Chloromethyl)-2-anilinopyridine Hydrochloride (IIc).**—To a solution of 32 g (0.16 mole) of IIb in 600 ml of dry $CHCl_3$ was added dropwise 75 ml of purified $SOCl_2$ and the mixture was heated on the steam bath for 1 hr and allowed to cool overnight. The crystalline precipitate was filtered and recrystallized from EtOH–$Et_2O$ to give 30 g (75%) of product having mp 204–206°. *Anal.* ($C_{12}H_{11}N_2Cl \cdot HCl$) C, H, N.

**Attempted Preparation of IId.**—A solution of 7.8 g of KCN in 25 ml of $H_2O$ was added dropwise to a MeOH (100 ml) solution of 15.2 g (0.06 mole) of IIc·HCl, heated under reflux for 3 hr, and poured into $H_2O$. The aqueous solution was saturated with $K_2CO_3$ and extracted ($Et_2O$). After drying, the solvent was removed and the residue was distilled, bp 175–180° (3 mm), yield 7 g (47%). The product shows a strong band at 1080 $cm^{-1}$ characteristic of C–O–C stretching and is assigned structure IIe. *Anal.* ($C_{13}H_{14}N_2O$) C, H, N.

When acetone was substituted for MeOH in above reaction a product was obtained which contained minor amounts of nitrile as shown by a very weak band in the ir at 2250 $cm^{-1}$.

(6) S. Carboni, *Gazz. Chim. Ital.*, **85**, 1194 (1955).

## The Synthesis and Pharmacological Properties of Dibenz[*b*,*e*][1,4]oxazepin-11(5H)-ones

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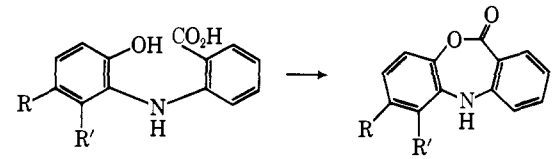
With the report of antiinflammatory activity of certain substituted anthranilic acid derivatives,[1] our attention was directed to the dibenz[*b*,*e*][1,4]oxazepin-11(5H)-one (I) ring system,[2] the rationale being that this system is a ring-closed analog of a hydroxy-substituted anthranilic acid derivative (II) and as such may possess significant antiinflammatory activity.

**Chemistry.**—The parent member of this system has been prepared by Gurien, *et al.*,[3] by a ring closure of N-(2-hydroxyphenyl)anthranilic acid (IIa) using thionyl chloride. The desired ring (Ia) was formed in low yield (15.7%) and was reported to be unstable when exposed to air, slowly reverting to the open-ring compound IIa. Similar stability problems were found in this laboratory when *p*-toluenesulfonic acid was used to effect ring closure. However, good yields of stable products[4] were obtained when dicyclohexylcarbodiimide was employed to bring about the ring closure (lactonization) of N-(2-hydroxyphenyl)anthranilic acid and related derivatives. It appears that traces of certain impurities will drastically effect the stability of this ring system.

The intermediate N-(2-hydroxyphenyl)anthranilic acids (IIa–d) were prepared from *o*-bromo- or *o*-chlorobenzoic acid and the appropriately substituted *o*-aminophenol by an Ullmann-type condensation. It was not necessary to purify these compounds completely prior to taking them on to the ring closure reaction. The assignment of structures I was based upon




II I

a, R = H; R′ = H
b, R = Cl; R′ = H
c, R = $CH_3$; R′ = H
d, R = $CH_3$; R′ = $CH_3$

elemental and ir analysis [$\nu_{max}^{Klbr}$ 1695–1710 (lactone) $cm^{-1}$].

**Biological Activity.**—Compounds IIa, Ia, Ic, and Id were tested for local antiinflammatory activity using a previously described method.[5] The compounds were triturated in a 2% sterile carrageenin solution. Female Sprague–Dawley rats obtained from Charles River Breeding Laboratories, weighing 60–80 g, were injected with 0.5 ml of the carrageenin mixture at the base of the tail. Twenty-four hours following the carrageenin injection, the rats were killed and the carrageenin-induced abscess was removed and weighed.

The four compounds (IIa, Ia, Ic, and Id) were found to possess significant local antiinflammatory activity. The minimal effective concentration established for each compound is summarized in Table I. Also included in this table is the minimal effective concentration obtained with mefenamic acid.

TABLE I
MINIMAL EFFECTIVE CONCENTRATIONS FOLLOWING LOCAL ADMINISTRATION

| Compd | % (w/v) conen in carrageenin |
|---|---|
| IIa | 2.7 |
| Ia | 0.03 |
| Ic | 0.1 |
| Id | 0.01 |
| Mefenamic acid | 0.003–0.01 |

### Experimental Section

When analyses are indicated, analytical results obtained for those elements were within ±0.4% of the theoretical values.

**N-(2-Hydroxyphenyl)anthranilic Acids (II).**—Potassium 2-chloro- or 2-bromobenzoate (1.0 mole) [prepared by adding a solution of KOH (1.0 mole, 56.1 g) in EtOH (300 ml) to a solution of 2-chloro- (1.0 mole, 156.6 g) or 2-bromobenzoic acid (1.0 mole, 201.0 g) in EtOH (500 ml) followed by the removal

(1) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *J. Pharmacol. Exptl. Therap.*, **138**, 405 (1962).

(2) This name is based upon IUPAC rules of nomenclature. Gurien, *et al.*,[3] gave the name dibenz[*b*,*e*][1,4]oxazepin-6(11H)-one in addition to a common name, depsazidone to the same compound.

(3) H. Gurien, D. H. Malarek, and A. I. Rachlin, *J. Heterocyclic Chem.*, **3**, 527 (1966).

(4) The compounds were stable when stored under normal shelf conditions exposed to light and air for over a 1-year period.

(5) S. Goldstein, R. DeMeo, I. Shemano, and J. M. Beiler, *Proc. Soc. Exptl. Biol. Med.*, **123**, 712 (1966).