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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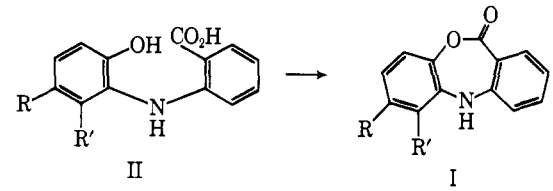
With the report of antiinflammatory activity of certain substituted anthranilic acid derivatives,[1] our attention was directed to the dibenz[*b*,*e*][1,4]oxazepin-11(5H)-one (I) ring system,[2] the rationale being that this system is a ring-closed analog of a hydroxy-substituted anthranilic acid derivative (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 [ν_{max}^{KBr} 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) concn 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).

of the solvent and the H_2O formed], the appropriately substituted 2-aminophenol (2.03 moles), and either *n*-BuOH or *n*-AmOH (500 ml) were heated together. When the temperature reached approximately 100°, Cu powder (1.0 g) was added, and the reaction mixture was refluxed for 30 min. After cooling, $NaHCO_3$ (25 g) and a saturated solution of $NaHCO_3$ (250 ml) was added followed by steam distillation until all organic solvent was removed. The dark residual material was filtered and the filtrate was acidified with 6 *N* HCl. A dark precipitate was formed. This mixture was heated to approximately 60° and the dark solid was filtered from the hot aqueous acidic suspension, washed (H_2O), dissolved in EtOH, and passed through a charcoal column to remove most of the color. After removal of the EtOH and extracting with C_6H_6, the products (IIa–d) were of sufficient purity to be carried on to the lactonization step.

Dibenz[*b*,*e*][1,4]oxazepin-11(5H)-one (Ia).—N-(2-Hydroxyphenyl)anthranilic acid (0.009 mole, 2.0 g), *p*-toluenesulfonic acid (0.5 g), and PhMe (200 ml) were refluxed together under N_2 with the H_2O formed being collected in a Dean–Stark receiver. After the theoretical amount of H_2O was collected, the cooled reaction mixture was extracted with saturated $NaHCO_3$, dried, filtered, and concentrated to dryness. The resulting solid was washed with cyclohexane yielding 1.0 g (53%) of Ia.

Dibenz[*b*,*e*][1,4]oxazepin-11(5H)-ones (I).—To a cooled solution of II (0.01 mole) in MeCN (300 ml), a solution of dicyclohexylcarbodiimide (0.012 mole) in MeCN (100 ml) was added slowly. After standing for 2 hr, the dicyclohexylurea formed was filtered off, and the filtrate was concentrated to dryness. The resultant yellow solids were recrystallized (C_6H_6) and analyzed for C, H, N: Ia ($C_{13}H_9NO_2$), yield 77%, mp 159–161°; Ib ($C_{13}H_8ClNO_2$), yield 47%, mp 236–238°; Ic ($C_{14}H_{11}NO_2$), yield 57%, mp 136–137°; Id ($C_{15}H_{13}NO_2$), yield 21%, mp 130–132.5°.

The Chemorelease of Norepinephrine from Mouse Hearts by Substituted Amphetamines[1]

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The chemorelease of norepinephrine from mouse hearts by a large number of sympathomimetic and related amines has been studied extensively by Daly, *et al.*[2] Their results showed that chemorelease of cardiac norepinephrine was strongly influenced by the nature and position of both ring and side-chain substituents.

As part of a long-range study of the effects of ring substituents on the psychopharmacological activity of substituted amphetamines,[3] the relative ability of some 25 of these compounds to release cardiac norepinephrine has been determined. The chemorelease of norepinephrine by a few of these amphetamines has previously been reported,[2] and results obtained in our study were in agreement within experimental error as shown in Table I.

Substituted amphetamines which were not available commercially were synthesized from the corresponding substituted benzaldehydes by the following route

TABLE I

CHEMORELEASE OF NOREPINEPHRINE-^{3}H FROM MOUSE HEARTS BY SUBSTITUTED AMPHETAMINES PREVIOUSLY REPORTED

Substituent(s)	Dose, mg/kg	Norepinephrine-^{3}H in heart, % of control: This study	Norepinephrine-^{3}H in heart, % of control: Previously reported[2]
None	10	58 (*dl*)	58 (*d*)
N-Methyl (*d* isomer)	10	57	62
3,4-Dihydroxy (*dl*)	5	45	39
4-Hydroxy (*dl*)	10	38	45
3,4-Dimethoxy (*dl*)	10	94	109
4-Chloro (*dl*)	10	77	71
3,4-Methylenedioxy (*dl*)	10	86	76

where R is substituted phenyl.

At a standard dose level of 10 mg/kg, the effectiveness of substituted amphetamines in chemorelease of cardiac norepinephrine divides these compounds into three groups: those with strong activity (release of 50% or more of the labeled norepinephrine), a group with moderate activity (release of 20 to 50% of the norepinephrine), and those with little or no activity (release of less than 20% of the norepinephrine). The norepinephrine releasing action of all amphetamines examined is summarized in Table II, tabulated in order of decreasing activity, and expressed in terms of per cent of labeled norepinephrine remaining in the heart compared with controls. The more active compounds were tried at lower dosages to obtain dose–response relationships.

The amphetamines with high activity include the 3-methyl,4-hydroxy,3-methoxy,4-fluoro,3,4-dihydroxy, and N-hydroxy derivatives as well as N-methylamphetamine and amphetamine itself. For all of these more active compounds, the effect of lower dosage was determined. In most cases, norepinephrine-releasing activity was negligible at a dose of 0.1 mg/kg, except for the 3-methoxy and 3,4-dihydroxy derivatives, which retained some activity even at a dose level of 0.1 mg/kg or less.

Methylation of the hydroxyl group in 4-hydroxyamphetamine to 4-methoxyamphetamine reduces the norepinephrine-releasing activity but does not abolish it as in the case of methylating the hydroxyl group in tyramine to 4-methoxyphenethylamine.[2] 3-Methoxyamphetamine exhibited an unexpectedly high activity for a methoxylated derivative.

Substituted amphetamines which retained moderate activity but were less active than unsubstituted amphetamine include 4-methoxy-, 3,4-dichloro-, 4-chloro-, and 3,5-dimethylamphetamines. Amphetamines with other indicated ring substituents failed to release norepinephrine from cardiac tissue.

Comparison of norepinephrine-releasing activity of amphetamines and β-phenethylamines with the same ring substituents shows that almost without exception the substituted amphetamines are more potent than the corresponding β-phenethylamines (Table III). However, substituents such as the hydroxyl group, which imparts greater activity to β-phenethylamine, do the same for amphetamine; this implies that in some instances the nature and position of the ring substit-

(1) This work was supported by Grant MH-11588 from the National Institute of Mental Health, U. S. Public Health Service.

(2) J. W. Daly, C. R. Creveling, and B. Witkop, *J. Med. Chem.*, **9**, 273 (1966); C. R. Creveling, J. W. Daly, and B. Witkop, *J. Pharmacol. Exptl. Therap.*, **158**, 46 (1967).

(3) J. R. Smythies, V. S. Johnston, R. J. Bradley, F. Benington, R. D. Morin, and L. C. Clark, Jr., *Nature*, **216**, 128 (1967).