

stirred for 12 hr at room temperature. During the reaction period, if the temperature is allowed to exceed *ca.* 8°, the reaction goes exothermically out of control and the yields are drastically reduced. The reaction mixture was worked up by pouring into 1 l. of H₂O, filtered, washed with Et₂O, and dried. This material was sufficiently pure to proceed with the next step. Isoamyl formate can be used without a significant difference in yield, however, the product was consistently cleaner when isoamyl nitrite was used and, therefore, it is the reagent of choice. The yield was 112 g, mp 137–139°. Recrystallization from EtOH gave mp 142–143°.

***o,o'*-Diaminodibenzyls.**—In a typical reaction, 9 g of 2,2'-dinitro-4,4'-dichlorodibenzyl was suspended in 200 ml of EtOH and reduced with H₂ over PtO₂ (0.5 g) at *ca.* 3.15 kg/cm². When the theoretical amount of H₂ was absorbed, the reaction mixture was filtered. In order to isolate the diamine, the EtOH was evaporated under reduced pressure and the residue (6.6 g) was recrystallized from EtOH-hexane, mp 137–138°.

In normal synthetic sequence the filtered EtOH solution of diamine was treated with 15 ml of concd H₃PO₄ and the resulting diphosphate salt was filtered, washed with Et₂O, and dried *in vacuo* at 100°.

10,11-Dihydro-5*H*-dibenz[*b,f*]azepines.—In a typical example, 15 g of the dried diphosphate salt of 2,2'-diamino-4,4'-dichlorodibenzyl was heated at 280–300° in an open flask for 30 min, cooled, and extracted by refluxing with two 200-ml portions of C₆H₆. The C₆H₆ solution was washed with dilute HCl, H₂O and dried; the solvent was removed under vacuum. The yield of 3,7-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine was 5 g; mp 110–112°, recrystallization from hexane raised the mp to 113–114°.

5-Acetyl-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—A suspension of 2.1 g of 5-acetyl-3,7-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (prepared by the reaction of AcCl with 3,7-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine⁹) in 80 ml of CCl₄ and 1.2 g of NBS was stirred and irradiated with a 200-W sunlamp for 2 hr, the temperature being maintained at 60–65° (*cf.* ref 9). The reaction mixture was cooled and the precipitated succinimide was filtered. The filtrate was evaporated under reduced pressure and the resulting residue was triturated with hexane. The resulting solid was filtered and used in the next step without further purification.

5-Acetyl-10-azido-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—To a stirred solution of 7 g of 5-acetyl-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepine and 600 ml of Et₂O a solution of 5.5 g of NaN₃ in 25 ml of H₂O was added. The mixture was stirred for 16 hr at room temperature and the Et₂O layer was separated, washed, dried (CaSO₄), and Et₂O removed to yield 5.4 g of solid mp 128–131° dec; recrystallization from MeOH raised the mp to 132–133° dec. The 10-bromodichlorodihydrodibenz[*b,f*]azepines failed to react under the above conditions. The following was used to prepare the 10-azido derivatives for the dichloro series.

A solution of 2 g of 3,7-dichloro-5-acetyl-10-bromo-10,11-dihydro-5*H*-dibenz[*b,f*]azepine, 1.5 g of NaN₃, and 35 ml of MeOH was refluxed for 8 hr, cooled, poured into H₂O, and extracted with Et₂O. The Et₂O layer was washed with H₂O, dried, and evaporated under reduced pressure. The resulting gummy residue was dissolved in hexane-EtOH and after *ca.* 2 days at –10° crystals were obtained. Recrystallization from hexane gave a mp of 99–100° dec. The 10-azido compounds are *severe skin irritants* and should be handled accordingly. 5-Acetyl-10-azido-1,9-dichloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepine was used directly in the next step without purification.

10-Amino-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—A solution of 9 g of 5-acetyl-10-azido-10,11-dihydro-5*H*-dibenz[*b,f*]azepine, 4.5 g of NaBH₄, and 150 ml of *i*-PrOH was refluxed for 14 hr, cooled, poured into H₂O, and extracted with Et₂O. The Et₂O layer was washed (H₂O), dried (CaSO₄), and evaporated under reduced pressure. The residual material was purified by chromatography over Al₂O₃, the eluent C₆H₆-EtOH (99:1) gave the expected amine, yield 6 g, mp 95–98°. The amines apparently form stable solvates and must be fused *in vacuo* prior to combustion analyses.

5*H*-10,11-Dihydro-10-dibenz[*b,f*]azepinones (*cf.* Ref 10). A.—To a slurry of 19.5 g of NaOMe in 100 ml of DMSO at 140° was added a suspension of 12 g of 5-acetyl-10,11-dibromo-

10,11-5*H*-dihydrodibenz[*b,f*]azepine in 20 ml of DMSO. The temperature was maintained for 1.5 hr at 130–140° and the mixture was cooled, poured into H₂O, and extracted with Et₂O. The Et₂O was washed (H₂O), dried (CaSO₄), and evaporated under reduced pressure to yield a solid. The crude residue was not characterized; it is presumably 10-methoxy-5*H*-dibenz[*b,f*]azepine (*cf.* ref 11), however, it was used directly to prepare the 10-keto derivative and is referred to below as crude methoxy compound.

B.—The crude methoxy compound obtained from above was dissolved in 50 ml of dry xylene and 10 g of NaH (56% mineral oil dispersion) was added and the mixture was refluxed for 2 hr. To this solution 5 g of (Me)₂SO₄ in 20 ml of xylene was added dropwise, refluxing was continued for 14 hr. The solution was cooled, the excess NaH was decomposed with H₂O and it was extracted with Et₂O. The Et₂O layer was washed (H₂O), dried (CaSO₄), and evaporated *in vacuo*. The crude product was passed through an Al₂O₃ column and 3.5 g [mp 145–146° (lit.¹⁰ mp 145–146°)] of 5-methyl-10-methoxy-5*H*-dibenz[*b,f*]azepine was obtained.

C.—In a separate experiment, 2.4 g of crude methoxy compound from part A was refluxed with 75 ml of 2 *N* HCl for 1 hr; the mixture was cooled, extracted with C₆H₆, washed (H₂O), dried (CaSO₄) and the C₆H₆ removed under reduced pressure to yield 2 g of solid which on recrystallization from EtOH-Et₂O gave 5*H*-10,11-dihydro-10-dibenz[*b,f*]azepinone, mp 142–144°, lit.¹² mp 145–146°. 5-Methyl-10,11-dihydro-10-dibenz[*b,f*]azepinone (mp 103–104°, lit.¹⁰ mp 104°) was prepared from the corresponding 5*H*-methyl-10-methoxy compound by similar HCl hydrolysis.

D.—A solution of 2 g of crude 5*H*-keto compound (part C), 2 g of AcCl, and 25 ml of C₆H₆ was refluxed for 2.5 hr, cooled, and poured into H₂O. The C₆H₆ layer was washed (NaHCO₃), separated, and dried (CaSO₄). Evaporation of the C₆H₆ gave 1.3 g, mp 137–138°, of 5-acetyl-10,11-dihydro-5*H*-10-dibenz[*b,f*]azepinone (17). *Anal.* (C₁₈H₁₃NO₂) C, H.

10-Hydroxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepines.—The procedure outlined is typical for the preparation of the three 10-hydroxy compounds shown in Table II. A solution of 8 g of 5*H*-10,11-dihydro-10-dibenz[*b,f*]azepinone and 5 g of NaBH₄ in 40 ml of EtOH was stirred for 15 hr at room temperature. The EtOH was removed *in vacuo* and the solid was treated with H₂O and extracted with Et₂O. The Et₂O solution was washed (H₂O), dried (CaSO₄), and evaporated under reduced pressure. The residual oily mass was triturated with hexane and the resulting solid was crystallized from EtOH-hexane; yield 6 g; mp 106–107°.

Acknowledgments.—We are indebted to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck for the test results. We wish to thank Dr. Steck for helpful discussions.

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A New Class of 1,3-Benzoxazinones as Potential Central Nervous System Agents

NED D. HEINDEL AND LEE A. SCHAEFFER¹

Department of Chemistry, Lehigh University,
Bethlehem, Pennsylvania 18015

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Salicylic acid, salicylamide, and their derivatives constitute a widely used family of analgetics, antipyretics, and antirheumatic agents.² Numerous ana-

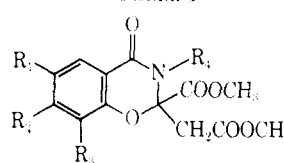
(1) (a) Taken in part from the M.S. Thesis of L. A. S., Lehigh University, 1969. (b) Supported by a grant (1 RO1MH-13562) from the National Institute of Mental Health.


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(9) W. Schindler and H. Blattner, *Helv. Chim. Acta*, **44**, 753 (1961).

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TABLE I



Compd	R ₁	R ₂	R ₃	R ₄	Yield, %	Formula	Mp, °C	Analysis
4	H	H	H	H	46	C ₁₃ H ₁₃ NO ₆	128.0–129.5	a
5	Br	H	Br	4-BrC ₆ H ₄	73	C ₁₉ H ₁₄ Br ₂ NO ₆	175.0–176.5	C, H, N
6	Br	H	H	H	53	C ₁₃ H ₁₂ BrNO ₆	156.5–158.0	a
7	Cl	H	H	H	45	C ₁₃ H ₁₂ ClNO ₆	158.5–160.0	a
8	CH ₃ O	H	H	H	44	C ₁₄ H ₁₅ NO ₇	168.5–169.5	C, H, N
9	H	H	H	C ₆ H ₅	93	C ₁₉ H ₁₇ NO ₆	170.5–172.5	a
10	I	H	I	4-IC ₆ H ₄	73	C ₁₉ H ₁₄ I ₂ NO ₆	187.0–188.0	C, H, I
11	I	H	I	C ₆ H ₅	61	C ₁₉ H ₁₅ I ₂ NO ₆	143.0–144.5	C, H, I
12	Cl	H	H	C ₆ H ₅	90	C ₁₉ H ₁₆ ClNO ₆	152.5–154.0	C, H, N
13	Br	H	Br	3-CF ₃ C ₆ H ₄	92	C ₂₀ H ₁₄ Br ₂ F ₃ NO ₆	139.0–140.5	C, H, N
14	H	H	H	4-BrC ₆ H ₄	76	C ₁₇ H ₁₆ BrNO ₆	107.0–110.0	C, H, N
15	H		H	H	10	C ₁₂ H ₁₀ NO ₆	150.5–152.0	a

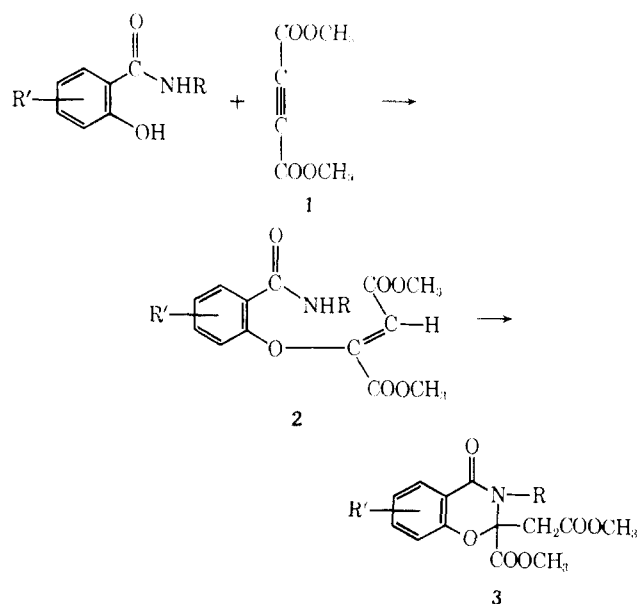
^a Preparation and properties are reported in ref 11.

logs have been synthesized involving alkylation at the phenolic OH and at the amidic N, esterification at the carbonyl, and substitution on the ring positions. The host of new materials does not appear to enhance significantly the properties of acetylsalicylic acid.

In the early 1950's attempts were made to incorporate the salicylamide moiety into a heterocyclic system. Horrom and Zaugg³ reported several 1,3-benzoxazinones with analgetic activity equal to that of salicylamide. Thomae⁴ and Kadatz⁵ studied the synthesis of 2-(β-chloroethyl)-2,3-dihydro-4*H*-1,3-benzoxazin-4-one and demonstrated it to be a more potent analgetic than the 2-phenylbenzoxazinone claimed previously.³ Baoli⁶ capitalized on the discovery of the 2-β-chloroethyl function as an enhancer of activity and prepared OH, Cl, and NH₂ ring-substituted analogs. Recently, Finkelstein and Chiang⁷ have reported analgetic activity in 2-(*p*-aminophenyl)-6-amino-2,3-dihydro-4*H*-1,3-benzoxazin-4-one.

Our recent work with acetylene esters as heterocyclic building blocks⁸ has shown that quinazolinones⁹ and benzothiazines¹⁰ can be prepared readily from *o*-amino- or *o*-mercaptobenzamides. In a similar fashion we have studied the mechanism of the condensation of *o*-hydroxybenzamides (salicylamides) and *o*-hydroxybenzanilides (salicylanilides) with dimethyl acetylenedicarboxylate (**1**) which leads to 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-ones.¹¹ We should like to comment, herein, on the synthetic generality of that reaction and on our studies of these benzoxazinones as potential CNS agents.

A variety of salicylamides and salicylanilides have been condensed with **1** in a direct base-catalyzed one-step process (see Table I) which produces high yields of the benzoxazinones. The presence of an *N*-aryl function (*i.e.*, a salicylanilide *vs.* a salicylamide) appears to enhance the yield of the ring closure product and is presumably a reflection of the greater "acidity" of the N-H proton in such systems. As was previously demonstrated in our mechanism study¹¹ a basic catalyst is required to effect both the OH to alkyne addition and the NH to vinyl ether addition since the reaction has been shown to proceed *via* these 2 discrete steps.



Since both steps are base catalyzed it was usually impossible to isolate any significant quantities of the adduct intermediates **2**. Invariably the salicylanilides proceeded directly to the cyclized heterocyclic product **3**. In one case (**2**, R = H; R' = 5-OMe) it was possible to isolate a sufficient quantity of the intermediate for screening and its CNS activity did not differ significantly from that of its heterocyclic

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analog **8**. A general procedure is described (see Experimental Section) which permits direct conversion of the *o*-hydroxyamides into the 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-ones.

Biological Activity.¹²—Compounds **4**, **5**, **6**, **7**, **8**, **10**, and **13** were evaluated for neuropharmacological activity in a modified Irwin mouse profile.¹³ Materials were administered ip in solution or suspension in H₂O-methyl cellulose to 4 mice. Benzoxazinones **4**, **6**, and **7** were inactive up to 1000 mg/kg. The methoxysalicylamide adduct (**2**, R = H; R' = 5-OMe) and its corresponding cyclized product **8** displayed slight depression at 300 mg/kg with marked writhing of the test animals observed in **8**.

The most significant activity, however, was observed in the halogenated benzoxazinones. Although the parent triiodosalicylanilide was exceedingly toxic, estimated LD₅₀ 75 mg/kg, it did exhibit significant depression and reduction of spontaneous motor activity at doses as low as 30 mg/kg. The corresponding triiodobenzoxazine **10**, was considerably less toxic, no deaths occurred at 300 mg/kg, and at this concentration the compounds displayed depression of alertness, reactivity, spontaneous motor activity, and muscle tone. Similar effects were observable in **5** at 1000 mg/kg and in **13** at 300 mg/kg.

Experimental Section¹⁴

Salicylamides and Salicylanilides.—Except as reported below these compounds were either commercial chemicals or were prepared by standard procedures available in the literature. 3,4',5-Tribromosalicylanilide was obtained as a manufacturer's sample from Sherwin-Williams Chemical Co., and 3,5-dibromo-3'-trifluoromethylsalicylanilide was similarly obtained from Pfister Chemical Co.

4'-Bromosalicylanilide was prepared by treating a solution of 0.05 mole of salicylic acid and 0.05 mole of *p*-bromoaniline in 113 ml of PhCl with 0.024 mole of PCl₃ followed by 0.002 mole of AlCl₃. The mixture was stirred at reflux for 6 hr until HCl evolution ceased, cooled to room temperature, treated cautiously with 50 ml of H₂O and Na₃PO₄ (hydrate) until a slightly alkaline pH was achieved. Exhaustive steam distillation left an involatile white solid which was filtered from the chilled aq medium and recrystd from MeOH to give 12.6 g (86%) of 4'-bromosalicylanilide, mp 176.5–178°. *Anal.* (C₁₃H₁₀BrNO₂) C, H, N.

5-Methoxysalicylamide was prepared in 92% yield by allowing 0.10 mole of methyl 5-methoxysalicylate to stand in 160 ml of NH₃-satd MeOH for 1 week in a refrigerator. Concentration *in vacuo* precipitated the amide which was purified by recrystallization from MeOH, mp 148–151°. *Anal.* (C₈H₉NO₃) C, H, N.

3,4',5-Triiodosalicylanilide and 3,5-diiodosalicylanilide¹⁵ were prepared by the ICl iodination of 0.05 mole of salicylanilide in 160 ml of HOAc. A solution of 0.16 mole of ICl in 45 ml of HOAc was added dropwise to the above solution over 40 min. The addition of 200 ml of cold H₂O precipitated a tan solid and (his mixture was heated to 75–90° with stirring for 1 hr, cooled to

room temperature and the ppt collected by filtration. Recrystallization from HOAc yielded 3,4',5-triiodosalicylanilide (mp 225–228°) in 23% yield. *Anal.* (C₁₃H₅I₃NO₂) N.

Dilution of the mother liquor yielded 45% of 3,5-diiodosalicylanilide, mp 165–168°, lit mp 173°. ¹⁵

Benzoxazinone Synthesis.—To a solution containing 30 mmoles of the appropriate *o*-hydroxyamide and 3 mmoles of NaOMe in 50 ml of anhyd MeOH was added 33 mmoles of dimethyl acetylenedicarboxylate. The addition was carried out dropwise over 0.5–1 hr and the mixture was then allowed to stir at ambient temperature for 24 hr. Concentration *in vacuo* precipitated the white crystalline products which were recrystd from MeOH to analytical purity. Yields and physical properties are reported in Table I.

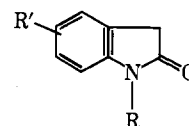
Substituted Oxindoles. III. Synthesis and Pharmacology of Some Substituted Oxindoles^{1a}

JOHN WALKER, ROY W. DAISLEY,^{1b} AND ARNOLD H. BECKETT

Pharmacy Department, Chelsea College of Science and Technology, University of London, London, S.W.3, England

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The compounds herein described were synthesized as part of a project complementary to an investigation of the alkaloids of various species of *Mitragyna*.² Certain investigators^{3–6} have reported interesting pharmacological activity, whereas other workers^{7,8} have found no significant activity among simple oxindole derivatives.



- 1**, R = H (a) R' = 4-OH; (b) R' = 5-OH; (c) R' = 6-OH;
 (d) R' = 7-OH; (e) R' = 4-MeO; (f) R' = 5-MeO;
2, R = CH₃ (g) R' = 6-MeO; (h) R' = 7-MeO
8, (a) R = *n*-Pr; R' = H; (b) R = *n*-Bu; R' = H
10, R = Et; R' = 5-OH
11a, R = Et; R' = 6-OH; (b) R = *n*-Pr; R' = 6-OH
12, R = Et; R' = 5-MeO
13, R = Et; R' = 6-MeO
19, R = H; (a) R' = 4-EtO; (b) R' = 4-*n*-PrO; (c) R = 4-*i*-PrO

Methods of preparation of compounds **1a–h** and **2a–h** have been described elsewhere.² The remaining compounds in this series were prepared by the routes shown in Schemes A and B. The appropriate substituted anilines **3a–c**, were acetylated and alkylated using NaH and the appropriate alkylating agent and deacetylated by refluxing with 50% H₂SO₄ to give the *N*-alkyl derivatives **5c–g** as oils. Reaction of these and the *N*-substituted anilines **6a,b** with ClCH₂COCl and pyridine in

(12) Testing was carried out by Dr. T. O. King, Bio/dynamics Inc., East Millstone, N. J., and by Dr. Richard J. Matthews, Pharmakon Laboratories, Scranton, Pa.

(13) S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Eds., Year Book Medical Publishers, Inc., Chicago, Ill., 1964.

(14) Melting points were obtained in capillaries in a Mel-Temp apparatus and are reported uncorrected. Elemental analyses were obtained from Dr. George I. Robertson, Microanalytical Laboratory, Florham Park, N. J., and where reported by the symbols of the elements are within ±0.3% of calculated values.

(15) Although the synthesis of these materials has been claimed in a patent, U. S. Patent 2,906,711; *Chem. Abstr.*, **54**, 3873 (1960), the details are insufficient to permit duplication of the method and a melting point is reported for only the 3,5-triiodosalicylanilide.

(1) (a) This work was carried out in part fulfilment of the requirements for the degree of Ph.D. of London University (R.W.D.); (b) Present address: School of Pharmacy, College of Technology, Brighton, Sussex, England.

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