ethyl)-*m*-hydroxybenzyl Alcohol.—A soln of 0.50 g (1.62 mmoles) of the (+)-erythro benzoate·HCl in 50 ml of 10% NaOH soln was stirred at room temp for 1 hr, cooled in an ice–NaCl bath, and acidified with concd HCl. The ppt was filtered and dried to give 0.20 g (45.5%) of the benzamide of metaraminol: mp 125.5–127.0°, softens at 123.0°; identical with an authentic sample prepd from metaraminol by mmp, tlc (10% EtOH–PhH), ir, and nmr.

(αR,1*S*)- or (−)-*erythro*-α-(1-Aminoethyl-*m*-hydroxybenzyl Acetate (10d).—A soln of 5.3 g (0.025 mole) of (αR,1*S*)-(1-acetamidoethyl)-*m*-hydroxybenzyl alcohol in 3.8 ml of concd HCl and 150 ml of EtOH was heated at reflux for 1 hr. After concg reduced pressure, the residue was mixed with 100 ml of 50% C_6H_6–EtOH and reconcd. This process was repeated 4 times before the residue was dissolved in THF, filtered through a charcoal pad, and dild with Et_2O to give an oil. Since the oil failed to cryst from various solvents, it was dried under high vacuum to give the (−)-erythro acetate as a glass: mp 102° dec, sinters at 90°, $[\alpha]^{25}D$ − 34.5° (*c* 2, MeOH); nmr (D_2O), δ 1.28 (3, d, CH_3, J = 7 Hz), 2.27 (3, s, CH_3CO) 3.5–4.1 (1, m, CHN), 5.87 (1, d, CHO, J = 4 Hz), 6.8–7.5 (4, m, aromatic CH), weak absorption at δ 1.20 (d), 2.23 (s), 4.95 (d). *Anal.* ($C_{11}H_{15}NO_3 \cdot HCl \cdot 0.25H_2O$) C, H, N.

Acknowledgment.—The authors wish to thank K. B. Streeter, Y. C. Lee, and their staff for elemental analyses, W. R. McGaughran for the infrared and nmr spectra, and Dr. J. Wittick and his staff for the optical rotations. We are also indebted to Drs. M. L. Torchiana and C. C. Porter for the biological data.

Synthesis, Transformation, and General Pharmacologic Activity in 1,4-Benzodiazepine-3,5-diones[1]

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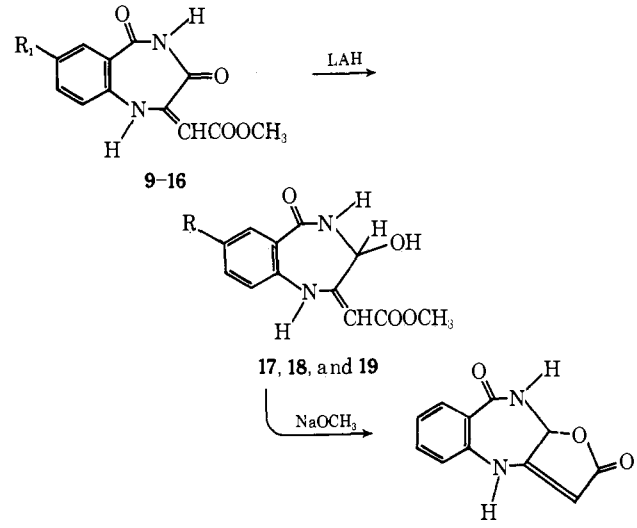
Received May 24, 1971

Although impressive potency was observed in 1,4-benzodiazepines possessing a lactam linkage[2] no syntheses or pharmacology have been reported for imide analogs. The original multistep synthesis of such 1,4-benzodiazepin-3,5-diones by Gartner[3] preceded any medicinal interest in the family and its complexity precludes its utility as a routine synthesis of this class. We have recently reported a facile direct cyclization of anthranilamide adducts of dimethyl acetylenedicarboxylate as a route to 2-carbomethoxymethylene-2*H*-1,4-benzodiazepin-3,5(1*H*,4*H*)-diones.[4] Herein we report an extension of this synthesis (**9**–**16**), some related transformations of the ring functions, and our results on the biological evaluation of this new class.

Hydride reduction, by inverse addition, reduced 3 of the benzodiazepinediones, (**9**, **11**, **12**) to their corresponding 3-OH analogs. Structural characterization of this hydroxybenzodiazepinone system has been reported elsewhere.[4] Treatment of the OH compound **17** with alcoholic alkoxide resulted in lactonization.



Biological Results.—The benzodiazepinediones (**10**–**16**) were tested in nonfasted albino rats (180–210 g), and the results were analyzed according to the methods of Malone and Carrano.[5] In general, all compds were nontoxic with no deaths observed up to 1000 mg/kg ip, except with **16** where death was observed at 1000 mg/kg at 48 hr postinjection. Compd **12** was tested only as high as 562 mg/kg and at this dosage showed some CNS depression which included decreased motor activity and body tone. Compd **14** was tested only at a maximum dose of 316 mg/kg.

Evaluation of **10**, **11**, **13**, **14**, **15**, and **16** in a CNS profile[6] resulted in no outstanding effects on pentylenetetrazole, strychnine, or maximal electroshock-induced convulsions. There was measurable, but not outstanding, antioxotremorine effects with all these compds at 200 mg/kg ip. Compd **10** did show a slight increase in hexobarbital sleep time and a slight protection of ACh writhing. In an anesthetized cat, **10** caused a fall in arterial blood pressure at 1–5 mg/kg iv, and potentiated the blood pressure response of norepinephrine and dimethylphenylpiperazinium (DMPP) at 1 and 25 mg/kg iv. Compd **11**, administered at 50 mg/kg ip, displayed no significant effects in the anesthetized cat. Compds **11**, **13**, **14**, and **16** showed a depression of weight gain which could indicate anorexigenic activity since the effect was delayed (*i.e.*, 24–48 hr postinjection) and no diarrhea or excessive urination was noted.

Compds **11** and **16** were tested in the isolated guinea pig ileum and had no outstanding effects at 10^{-4} *M* on the responses to ACh, histamine, serotonin, nicotine, or $BaCl_2$. Compds **11**, **14**, and **15** were tested in a combined antiinflammatory and analgetic test according

(1) Taken in part from the Ph.D. Thesis of T. F. L. (1968) and W. P. F. (1971) and the B.S. Honors thesis of H. W. S. (1970).

(2) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, "Drugs Affecting the Central Nervous System," A. Burger, Ed., M. Dekker, New York, N. Y., 1968, p 237.

(3) S. Gartner, *Justus Liebigs Ann. Chem.*, **332**, 226 (1904).

(4) N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.*, **33**, 3997 (1968).

(5) M. H. Malone and R. A. Carrano, "Hippocratic and Pharmacodynamic Screening," American Pharmaceutical Association Academy of Pharmaceutical Sciences, Symposium on Advances in Screening Methodology, Washington, D. C., November 1968.

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to previously described methods.[6] There was no significant activity.

Three of the intermediate dimethyl (2-carboxamidoanilino)fumarates (**1**, **3**, **4**) were also studied in the rat and found to possess only modest activity and low toxicity. No deaths occurred at doses up to 1000 mg/kg. Compds **1** and **4** produced slight CNS depression at doses from 100 to 1000 mg/kg with slight decrease in motor activity and body tone and a delayed (24–48 hr postinjection) decrease in body weight at the upper dose limit. Compd **3** had parallel CNS activity but displayed a greater effect on the autonomic nervous system. Marked reduction in pupil size was evident in the 100 to 1000 mg/kg dose range.

Compd **18**, a 3-hydroxybenzodiazepinone, was unavailable in sufficient quantity for rat screening and was evaluated ip in a modified Irwin neuropharmacological mouse profile at 300 mg/kg.[7] It was inactive except for slight reduction in spontaneous motor activity.

The lack of significant anticonvulsant and analgetic effects and the slight general pharmacologic activity in these compds could well be related to poor absorption. Necropsy at 48 hr postinjection with **11**, **12**, **13**, **14**, and **15** revealed the presence of unabsorbed drug in the abdominal cavity. Since significant cardiovascular effects were detected with **10** when administered iv, it is apparent that when absorption is bypassed, pharmacologic effects are observed.

Experimental Section

Combustion results reported in this work were provided by Dr. George I. Robertson, Microanalytical Laboratory, Florham Park, N. J. Melting points were obtained in capillaries in a Mel-Temp Apparatus and are reported uncorrected.

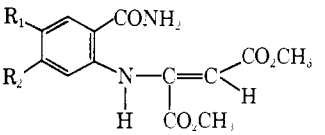
Anthranilamides.—The unsubstituted, 5-chloro-, 5-bromo-, 5-iodo-, and 5-methylanthranilamides were prepared by previously reported methods.[4,6] Oxidation of 5-methoxy-6-chloroisatin by the method of Adams and Snyder[8] gave the isatoic anhydride in 48% yield and this was treated with dil aq NH_3 according to the standard procedure.[9] The crude 4-chloro-5-methoxyanthranilamide (mp 173–175°) was obtained in 78% yield and was utilized directly without further purification. In a similar fashion from 5-fluoroisatin[10] the crude 5-fluoroanthranilamide (mp 146–149°) was obtd in 74% conversion. The phosgenation[11] of 5-methoxyanthranilic acid produced 5-methoxyisatoic anhydride which was converted by ammonolysis into 5-methoxyanthranilamide in 50% yield (mp 115–116° from MeOH). *Anal.* C, H, N.

Amide Adducts, Dimethyl (2-Carboxamidoanilino)fumarates.—A soln of 0.1 mole each of the required amide and dimethyl acetylenedicarboxylate was refluxed for 4 to 6 hr and concd *in vacuo*, and the pptd adduct was recrystd from MeOH. Yields and physical properties are reported in Table I.

Substituted 2-Carbomethoxymethylene-2*H*-1,4-benzodiazepine-3,5(1*H*,4*H*)-diones.—A soln of 0.07 mole of the amide adduct in Na-dried xylene was brought to reflux and treated with a catalytic quantity (approx 0.1 g) of NaOMe. MeOH was evolved during the 2-hr reflux and it was allowed to escape by employing an uncooled air condenser to reflux the xylene. The reaction medium was filtered hot and the yellow crystals which formed on chilling the xylene were filtered off, washed well with hexane, dried, and sublimed *in vacuo* to analytical purity (170–180°, 0.1 mm). Alternatively the crude product could be recrystd from xylene. Yields and properties are given in Table II.

3-Hydroxybenzodiazepinones.—The benzodiazepinedione (0.02 mole) was dissolved in 350–400 ml of previously dried and freshly distd THF. This soln was placed in an ice–salt bath and stirred until the temp was below 5°, a LAH (0.02 mole)–THF slurry was then added in small portions over 45 min. When the addn was completed, the ice bath was removed and the stirred soln was allowed to warm to ambient temp. Stirring was contd for an addl hr and the reaction was then quenched with moist Et_2O, and the solid ppt was allowed to settle. The solids were filtered off, and the filtrate was dried ($MgSO_4$). The collected solids

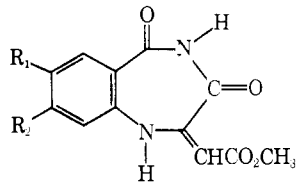
TABLE I
DIMETHYL (2-CARBOXAMIDOANILINO)FUMARATES



Compd	R_1	R_2	Mp, °C	Yield, %	Formula[a]
1	H	H	153–153.5	91	$C_{13}H_{14}N_2O_5$
2	F	H	160–161.5	91	$C_{13}H_{13}FN_2O_5$
3	Cl	H	156–158	84	$C_{13}H_{13}ClN_2O_5$
4	Br	H	162–164	71	$C_{13}H_{13}BrN_2O_5$
5	I	H	190–192	72	$C_{13}H_{13}IN_2O_5$
6	CH_3	H	134–135	84	$C_{14}H_{16}N_2O_5$
7	CH_3O	H	135–136	78	$C_{14}H_{16}N_2O_6$
8	CH_3O	Cl	158–162	75	$C_{14}H_{15}ClN_2O_6$

[a] Anal. C, H, N.

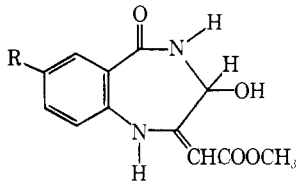
TABLE II
2-CARBOMETHOXYMETHYLENE-2*H*-1,4-BENZODIAZEPINE-3,5(1*H*,4*H*)-DIONES



Compd	R_1	R_2	Mp, °C	Yield, %	Formula[a]
9[b]	H	H	230–232	76	$C_{12}H_{10}N_2O_4$
10	F	H	224–227	79	$C_{12}H_9FN_2O_4$
11[b]	Cl	H	233–234	63	$C_{12}H_9ClN_2O_4$
12[b]	Br	H	239–240.5	81	$C_{12}H_9BrN_2O_4$
13	I	H	223–225	72	$C_{12}H_9IN_2O_4$
14[b]	CH_3	H	240–241.5	76	$C_{13}H_{12}N_2O_4$
15	CH_3O	H	199–200	87	$C_{13}H_{12}N_2O_5$
16	CH_3O	Cl	249–252	63	$C_{13}H_{11}ClN_2O_5$

[a] Anal. C, H, N (within ±0.4% of calcd values.) [b] Previously reported in ref 4.

TABLE III
3-HYDROXYBENZODIAZEPINONES



Compd	R	Mp, °C	Yield, %	Formula[a]
17	H	204–206	43	$C_{12}H_{12}N_2O_4$
18	Cl	219–221	54	$C_{12}H_{11}ClN_2O_4$
19	Br	216–219	44	$C_{12}H_{11}BrN_2O_4$

[a] Anal. C, H, N (within ±0.32% of theoretical values).

(7) S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Inc., Chicago, Ill., 1964. Testing carried out by Dr. Richard Matthews, Pharmakon Laboratories, Scranton, Pa.

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were washed repeatedly with hot THF to ext entrained product. The washings and the filtrate were combined and concd, and the resultant org solid was recrystd from MeOH. Yields and properties are reported in Table III.

Lactonization of the 3-Hydroxybenzodiazepinone.—A soln of 0.25 g (1.0 mmole) of **17** was prepd in 30 ml of anhyd MeOH contg 0.05 g of NaOMe. The reaction mixt was refluxed for 1.5 hr, chilled to 0°, and the pptd pale yellow crystals isolated by filtration. Addl product was obtd by concg the mother liquors. The crystals (0.17 g or 85%) were recrystd from DMSO–H_2O and exhaustively dried *in vacuo*, mp 264–266°. *Anal.* C, H, N.

Antispasmodic Agents. 2.[1] Syntheses and Pharmacological Activity of Ethyl 2-(ω-Aminoalkyl)-2-(3-methoxyphenyl)phenylacetates

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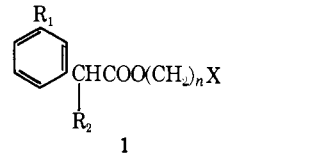
Received April 8, 1971

We have recently reported a series of aminoalkyl 3-substituted phenylacetates (**1**)[1] and now wish to describe the synthesis, and the antispasmodic and analgetic activity of ethyl 2-(aminoalkyl)-2-(3-methoxyphenyl)-phenylacetates and related compounds. Some 2-(aminoalkyl)-2,2-diphenylacetates have been reported by other investigators.[2–6]

2-(3-Methoxyphenyl)phenylacetic acid (**3**) was prepared by alkaline hydrolysis of 2-(3-methoxyphenyl)-phenylacetonitrile (**2**), which was obtained in good yield by benzyne reaction between 2-chloroanisole and phenylacetonitrile.[7,8] Ethyl 2-(aminoalkyl)-2-(3-methoxyphenyl)phenylacetates (**7a–7l**) were synthesized as follows; (A) condensation of the ester **4**, prepared from **1**, with aminoalkyl chlorides with the use of NaH;[9] and (B) condensation of ethyl 2-(4-bromobutyl)-2-(3-methoxyphenyl)phenylacetate (**5b**), prepared from **4**, with amines. In the latter method, condensation of ethyl 2-bromomethyl-2-(3-methoxyphenyl)phenylacetate (**5a**) with secondary amines gave only the starting material. The similar reaction of 2-chloromethyl-2-(3-methoxyphenyl)phenylacetonitrile (**6a**) with amines also resulted in failure.

Finally, the nitriles **8a–8c** and the alcohols **9a–9c** were synthesized in order to compare their pharmacological activities with those of ester analogs **7**. Condensation of **2** with aminoalkyl chloride afforded **9a,b**. The treatment of **6b** with dimethylamine gave **8c**. Reduction of **7** with LAH gave the corresponding alcohol **9**.

SCHEME I



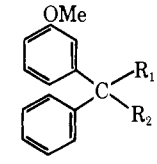
1

R_1 = OMe, OH, OAc

R_2 = H, Me, Et, CHMeEt, Ph

X = $N(Me)_2$, $N(Et)_2$, N□, N⬡, N⬡O

n = 2~3



2, R_1 = CN; R_2 = H

3, R_1 = COOH; R_2 = H

4, R_1 = COOEt; R_2 = H

5a, R_1 = COOEt; R_2 = CH_2Br

5b, R_1 = COOEt; R_2 = $(CH_2)_4Br$

6a, R_1 = CH_2Cl; R_2 = Cl

6b, R_1 = $(CH_2)_4Br$; R_2 = CN

Pharmacology.—Table I gave the results of screening for antispasmodic, anticholinergic, and analgetic activities. The compounds were tested by the Magnus[10] guinea pig ileum screen. The screening for analgetic activity was carried out by the hot plate method in mice. Although all the compounds were inferior to atropine sulfate in anticholinergic activity, the 3 compounds (**7b, 7c,** and **7k**) showed an antispasmodic effect similar to papaverine·HCl. Among them, 6 compounds (**7b,c,f,k,l,** and **9b**) showed analgetic activity; especially, in case of **7k,** the minimum effective dose was 25 mg/kg as shown in Table I.

Experimental Section[11]

Ethyl 2-(3-Methoxyphenyl)phenylacetate (4).—A mixt of 15 g of **3**, 100 ml of EtOH, and 2 ml of 98% H_2SO_4 was refluxed for 5 hr and evapd. The resulting residue was dild (H_2O) and extd (PhH). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The remaining residue was distd *in vacuo* to give 14.3 g (85%) of **4** as a pale yellowish oil: bp 162–164° (1.0 mm); ir (liq) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 1.12 (t, 3 H, CH_2CH_3), 3.53 (s, 3 H, OCH_3) 4.02 (q, 2 H, CH_2CH_3), 4.80 (s, 1 H, CH-COOEt), 6.42–7.16 (m, 9 H, ArH). *Anal.* ($C_{17}H_{18}O_3$) C, H.

Ethyl 2-Bromomethyl-2-(3-methoxyphenyl)phenylacetate (5a).—To a stirred soln of 14.4 g of CH_2Br_2 in 50 ml of dry DMF was added a soln of Na salt of **4** [prepd from 15 g of **4** and 2.9 g of NaH (50% suspension in mineral oil) in 50 ml of DMF]. After stirring for 3 hr at 70–80°, the mixt was poured into H_2O and extd (Et_2O). The ext was washed (H_2O), dried (Na_2SO_4), and evapd. The remaining residue was distd *in vacuo* to give 13.5 g (67.5%) of **5a** as a pale yellowish oil:[12] bp 188–189° (0.3 mm); ir (liq) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.17 (t, 3 H, CH_2CH_3), 3.68 (s, 3 H, OCH_3), 4.15 (s, 2 H, CH_2Br), 4.15 (q, CH_2CH_3), 6.60–7.40 (m, 9 H, ArH).

Ethyl 2-(4-Bromobutyl)-2-(3-methoxyphenyl)phenylacetate (5b).—To a stirred soln of 18 g of 1,4-dibromobutane in 50 ml of DMF was added in portions a soln of the Na salt of **4** [prepd

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(11) Melting points are uncorrected. Ir spectra were determined on a Shimazu spectrometer and nmr data on a JNM-MH-60 instrument (TMS).

(12) These samples were difficult to microanalyze because of comparatively low boiling points, but unambiguous structures rest on those of the following reaction products which were confirmed.