°C; $[\alpha]^{25}_D$ +169° (c 1.65, CH_3OH); IR ($CHCl_3$) 3540, 1710, 1635, 1590 cm^{-1}. Anal. ($C_{27}H_{34}O_{10}$) C, H.

Hydrolysis of 8β-Hydroxyverrucarin A (14). A solution of 100 mg (0.19 mmol) of **14** and 81 mg (1.9 mmol) of lithium hydroxide monohydrate in 5 mL of methanol was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo and the resulting residue was subjected to preparative TLC on silica gel (one 1-mm plate) with 20% methanol in dichloromethane as eluent to give 40 mg (74%) of 4β,8β,15-trihydroxy-12,13-epoxytrichothecene (**16**). Recrystallization from acetone–hexane provided an analytical sample of **16** which was identified by comparison (TLC behavior, mixture melting point, NMR spectra) with an authentic sample.[19] No effort was made to recover the other products of this reaction.

8-Oxoverrucarin A (17). To a mixture of 240 mg (2.4 mmol) of chromium trioxide and 1 mL of pyridine in 8 mL of dichloromethane was added 250 mg (0.48 mmol) of 8β-hydroxyverrucarin A (**14**). The reaction mixture was stirred for 1 h at room temperature, filtered, diluted to 20 mL with dichloromethane, and washed with three 10-mL portions of 5% hydrochloric acid. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Preparative TLC of the residue on silica gel (three 1-mm plates) with 5% methanol in dichloromethane as eluent yielded 203 mg (82%) of **17**, an analytical sample of which was obtained by recrystallization from dichloromethane–hexane: mp >300 °C; $[\alpha]^{25}_D$ +254° (c 1.68, $CHCl_3$); IR ($CHCl_3$) 3560, 1745, 1715, 1685, 1635, 1590 cm^{-1}. Anal. ($C_{27}H_{32}O_{10}$) C, H.

16-Oxoverrucarin A (18). A procedure similar to that described for the preparation of **17** provided, from 120 mg of 16-hydroxyverrucarin A (**15**), 75 mg (63%) of **18**: mp >300 °C; $[\alpha]^{28}_D$ +170° (c 4.28, $CHCl_3$); IR ($CHCl_3$) 3560, 1715, 1635, 1590 cm^{-1}. Anal. ($C_{27}H_{32}O_{10}$) C, H.

(18) Yagi, H.; Takker, D. R.; Hermandez, O.; Koreeda, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 1604.
(19) Kindly provided by Dr. James Schmidt, University of Virginia.

Reduction of 8-Oxoverrucarin A (17). A solution of 50 mg (0.10 mmol) of **17** in 0.65 mL of THF and 0.35 mL of absolute ethanol was cooled to −5 °C in an ice–water–sodium chloride bath. Sodium borohydride (11 mg, 0.29 mmol) was added in one portion and the mixture was stirred for 90 min with the temperature maintained between −5 and 0 °C. The mixture was then poured into 25 mL of water and extracted with three 25-mL portions of ethyl acetate. The combined organic layers were dried (magnesium sulfate) and concentrated in vacuo. Preparative TLC of the residue on silica gel (one 1-mm plate) with ethyl acetate as eluent afforded 28 mg (56%) of 8α-hydroxy-9,10-dihydroverrucarin A (**19**) and 18 mg (36%) of 8α-hydroxyverrucarin A (**20**).

Recrystallization from dichloromethane–hexane provided an analytical sample of **19**: mp >300 °C; $[\alpha]^{26}_D$ +141° (c 2.76, $CHCl_3$); IR ($CHCl_3$) 3520, 1715, 1635, 1590 cm^{-1}. Anal. ($C_{27}H_{36}O_{10}\cdot 0.5H_2O$) C, H.

Recrystallization from ethyl acetate–hexane provided an analytical sample of **20**: mp >300 °C; $[\alpha]^{28}_D$ +139° (c 2.94, Me_2SO); IR (KBr) 3460, 1710, 1635, 1590 cm^{-1}. Anal. ($C_{27}H_{34}O_{10}$) C, H.

When this reduction was carried out at −35 °C, **20** was isolated in 62% yield, **19** was isolated in 5% yield, and 7% of **17** was recovered unchanged.

Hydrolysis of 8α-Hydroxyverrucarin A (20). A procedure similar to that described for the hydrolysis of **14** gave, from 198 mg of **20**, 76 mg (70%) of 4β,8α,15-trihydroxy-12,13-epoxytrichothecene (**21**): mp 177–179 °C; $[\alpha]^{26}_D$ −71.3 °C (c 3.49, CH_3OH); IR (KBr) 3280. Anal. ($C_{15}H_{22}O_5$) C, H.

Acknowledgment. This investigation was supported by Grant CA 25967-01, awarded by the National Cancer Institute, DHEW, and by a Biomedical Research Board Grant, University of Maryland, made available through the U.S. Public Health Service. G.P.S. thanks the Gillette Corp. for a fellowship.

Supplementary Material Available: Full NMR data (Table II) for compounds **7**, **9–12**, **14**, **15**, and **17–21** (6 pages). Ordering information is given on any current masthead page.

1-[(Ethoxyamino)methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepins: A New Class of Antianaphylactic Agents

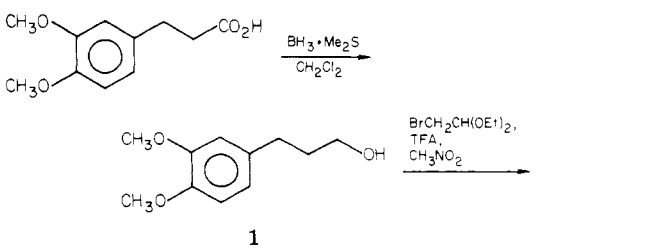
Ruth E. TenBrink,* John M. McCall, and Herbert G. Johnson

The Upjohn Company, Research Laboratories, Kalamazoo, Michigan 49001. *Received March 14, 1980*

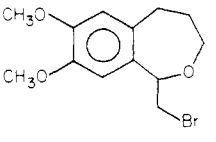
The synthesis and biological activity in the rat passive cutaneous anaphylaxis (PCA) test of a new class of compounds, 1-[(ethoxyamino)methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepins, are reported. These compounds are synthesized from the adduct of 1-(bromomethyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin and ethylene glycol or chloroethanol. The influence of the amine function on activity in the rat PCA is discussed. Aryl- or heteroarylpiperazines favor activity with this class of compounds.

In the past decade a number of compounds have been synthesized which inhibit the anaphylactic response in the rat passive cutaneous anaphylaxis (PCA) test. The prototype compound, disodium cromoglycate,[1] which is not absorbed orally, was followed by a number of orally active agents[2] which were identified by the rat PCA screen.[3] We now report a new class of compounds, the 1-ethoxy-1,3,4,5-tetrahydro-2-benzoxepins, which are active antiallergic agents.

Scheme I



1



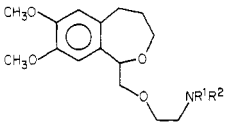
2

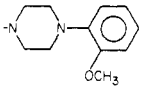
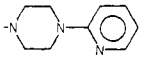
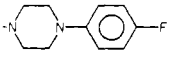
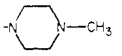
Chemistry. 1-(Bromomethyl)-1,3,4,5-tetrahydro-7,8-

(1) J. B. L. Howell and R. E. C. Altounyan, *Lancet*, **2**, 539 (1967); J. S. Cox, J. E. Beach, A. M. Blair, A. J. Clark, J. King, T. B. Lee, D. E. Loveday, G. F. Moss, T. S. Orr, J. T. Ritchie, and P. Shard, *Adv. Drug Res.*, **5**, 115 (1970).
(2) R. E. Giles and D. J. Herzing, *Annu. Rep. Med. Chem.*, **10**, 80 (1975); A. L. Oronsky and J. F. Wasley, *ibid.*, **11**, 51 (1975); A. L. Oronsky and J. F. Wasley, *ibid.*, **12**, 70 (1977); S. C. Bell and R. J. Capetola, *ibid.*, **13**, 51 (1978); S. C. Bell and R. J. Capetola, *ibid.*, **14**, 51 (1979).
(3) W. E. Brocklehurst, *Handb. Exp. Immunol.*, **21**, 1 (1973).

0022-2623/80/1823-1058$01.00/0

Table I



no.	NR^1R^2	yield, %	mp, °C	formula	% inhibn of rat PCA, oral dosing time (min) before challenge[c,d] 60	120
6a		82[a]	172-175	$C_{26}H_{35}N_2O_5 \cdot 2HCl \cdot H_2O$	100	20
6a		92[b]	75-85	$C_{24}H_{33}N_3O_4 \cdot HCl \cdot 2H_2O$	94	35
6c		62[b]	72-77	$C_{25}H_{33}N_2O_4 \cdot 2HCl$	52	0
6d	$-NHCH_2CH_2OH$	90[b]	118.5-119.5	$C_{17}H_{27}NO_5 \cdot C_6H_{13}NO_3S$	0	0
6e		92[b]	157.5-158.5	$C_{20}H_{32}N_2O_4 \cdot 2HCl \cdot 2H_2O$	0	0

[a] Isolated yields from 4. [b] Isolated yields from 5. [c] Dosage: po at 50 mg/kg. [d] 100% inhibition is obtained with disodium cromoglycate, 10 mg/kg iv, run as a standard. Replicate assays varied by 8% in 35 replicate assays.

dimethoxy-2-benzoxepin (2) is an intermediate in the synthesis of 1-(ethoxymethyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin. Compound 2 is novel and was prepared via an acid-catalyzed ring closure of 3-(3,4-dimethoxyphenyl)propanol (1) with bromoacetaldehyde diethyl acetal in nitromethane (Scheme I). A similar cyclization has been reported for the synthesis of 1-(bromomethyl)-6,7-dimethoxyisochroman.[4] The tetrahydrobenzoxepin forms with considerably more reluctance than the corresponding isochroman. Alcohol 1 was prepared by the borane–methyl sulfide reduction of 3-(3,4-dimethoxyphenyl)propionic acid.

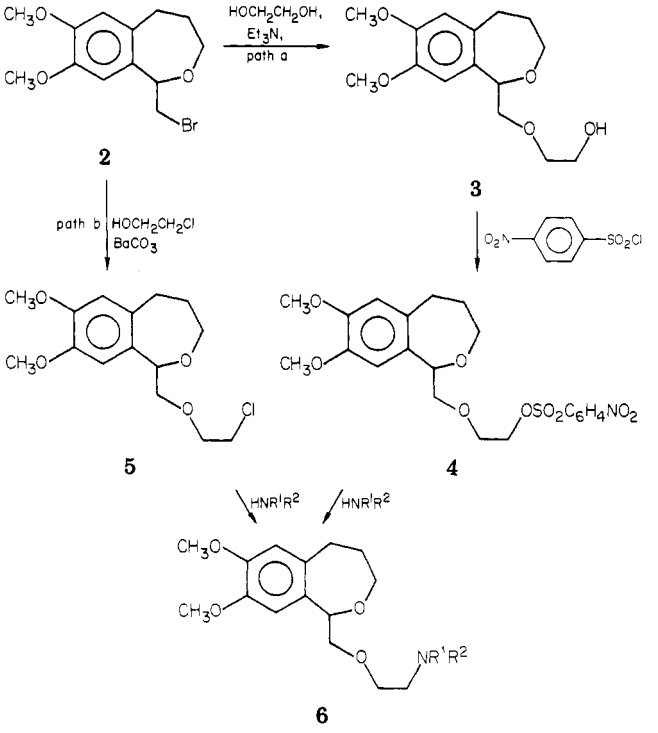
When the bromomethylbenzoxepin 2 was heated at 90–100 °C with an excess of ethylene glycol (path a), 3 was obtained in 89% yield (Scheme II). This displacement is surprisingly facile. Under similar reaction conditions, 1-(bromomethyl)-6,7-dimethoxyisochroman does not react. We believe that, in the case of the tetrahydrobenzoxepin, the displacement reaction is facilitated by both the participation of the π system of the dimethoxyphenyl ring and the greater conformational flexibility of the oxepin ring.

The *p*-nitrobenzenesulfonate of 3, when reacted with amines, gave the alkoxyamine compounds 6. In path b, 2 was heated at 70–90 °C with an excess of 2-chloroethanol and barium carbonate to give the chloroethoxy compound 5 in 41% yield. Treatment of 5 with a variety of amines gave the alkoxyamines 6.

Biological Results and Discussion. The title compounds were evaluated in the rat PCA test for their ability to inhibit the anaphylactic response. The results, listed in Table I, indicate that the arylpiperazine compounds **6a–c** show good activity, whereas the methylpiperazine **6e** and the ethanolamine **6d** were inactive. Thus, the aryl piperazine moiety is apparently a feature which favors activity in the rat PCA test for this series. The most active arylpiperazines (**6a** and **6b**) are the 2-pyridinyl and the 2-methoxyphenyl derivatives. We have not assigned a mechanism of action to the rat PCA activity. These compounds may act either by inhibition of mediator release or by antagonism of liberated mediators.

(4) T. A. Dobson and L. G. Humber, *J. Heterocycl. Chem.*, 12, 591 (1975).

Scheme II



Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian HFT80 spectrophotometer. Medium-pressure liquid chomatographies were run on EM silica gel 60 and EM RP2 silica gel.

3-(3,4-Dimethoxyphenyl)propyl Alcohol (1). To 50.0 g (0.280 mol) of 3-(3,4-dimethoxyphenyl)propionic acid in 300 mL of CH_2Cl_2 (cooled in an ice bath) was added dropwise 38 mL (0.30 mol) of 10 M borane–methyl sulfide complex. After gas evolution ceased, the ice bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then extracted with CH_2Cl_2, aqueous $NaHCO_3$, and then brine. The organic layer was filtered through Na_2SO_4 and taken to dryness to give 47.1 g (87%) of 1 as a clear liquid. This material was identical with known compound.[5]

1-(Bromomethyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin (2). A mixture of 20.0 g (0.104 mol) of 3-(3,4-dimethoxyphenyl)propyl alcohol, 39.0 mL (0.260 mol) of bromoacetaldehyde diethyl acetal, 8.0 mL (0.104 mol) of trifluoroacetic acid, and 300 mL of nitromethane was heated at 65 °C under a reflux condenser for 3.5 h. After cooling, the reaction mixture was extracted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was filtered through Na_2SO_4 and taken to dryness in vacuo.

The residue was chromatographed first on silica gel (CH_2Cl_2 eluent). The fractions containing product were then rechromatographed using 10% EtOAc–90% Skellysolve B as eluent to give 10.67 g (34%) of product, which solidified as a waxy solid after standing for several days. Anal. ($C_{13}H_{17}BrO_3$) C, H, Br.

1-[(2-Hydroxyethoxy)methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin (3). A mixture of 3.67 g (12.2 mmol) of **2**, 2.12 mL (12.2 mmol) of diisopropylethylamine, and 15 mL of ethylene glycol was heated at 100 °C for 7 h. The reaction mixture was then cooled and partitioned with CH_2Cl, H_2O, and brine. The organic layer was filtered through Na_2SO_4, taken to dryness, and chromatographed on silica gel using 2% MeOH–CH_2Cl_2 as eluent to give 3.06 g (89%) of product. The product, which crystallized upon standing, had mp 41–46 °C. Anal. ($C_{15}H_{22}O_5$) C, H.

***p*-Nitrobenzenesulfonate of 3 (4).** To a mixture of 3.00 g (10.6 mmol) of **3** and 1.63 mL (11.7 mmol) of triethylamine in toluene was added 2.59 g (11.7 mmol) of *p*-nitrobenzenesulfonyl chloride. The reaction mixture was stirred at room temperature for 1 h and then heated at 50 °C for 30 min. To this was added an additional 0.5 g of *p*-nitrobenzenesulfonyl chloride and 0.5 mL of Et_3N. After stirring at room temperature for 30 min, the reaction mixture was extracted with aqueous $NaHCO_3$ and brine. The organic layer was filtered through Na_2SO_4 and taken to dryness. Chromatography on silica gel using 1% MeOH–CH_2Cl_2 as eluent gave 1.56 g (32%) of product.

1-[(2-Chloroethoxy)methyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin (5). A mixture of 10.33 g (0.0343 mol) of **2**, 10 mL of 2-chloroethanol, and 6.77 g of barium carbonate was stirred at 90 °C for 46 h. The reaction mixture was then cooled, ethanol was added, and the solids were removed by filtration. The filtrate was taken to dryness in vacuo, and the resulting oil was extracted with CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was then taken to dryness and chromatographed on silica gel (10% EtOAc–Skellysolve B eluent) to give 4.18 g (41%) of product, mp 90–91 °C. Anal. ($C_{15}H_{21}ClO_4$) C; H: calcd, 7.04; found, 7.57.

1-(2-Methoxyphenyl)-4-[2-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)methoxy]ethyl]piperazine Dihydrochloride Hydrate (6a). A mixture of 0.50 g (1.07 mmol) of **4**, 0.22 g (1.07 mmol) of *o*-methoxyphenylpiperazine, 0.15 mL (1.07 mmol) of triethylamine, and 20 mL of THF was stirred at room temperature for 24 h. After removing the THF in vacuo, the reaction mixture was extracted with CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was filtered through Na_2SO_4, taken to dryness, and chromatographed on silica gel (3% MeOH–CH_2Cl_2 eluent) to give 0.40 g (82%) of product. The dihydrochloride monohydrate salt (mp 172–175 °C) was prepared with HCl/ether. Anal. ($C_{26}H_{35}N_2O_5 \cdot 2HCl \cdot H_2O$) C, H, N, Cl.

1-(2-Pyridinyl)-4-[2-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)methoxy]ethyl]piperazine Hydrochloride Dihydrate (6b). A mixture of 1.00 g (3.32 mmol) of **5** and 1.14 g (6.65 mmol) of 95% 1-(2-pyridinyl)piperazine was stirred at 90 °C for 20 h. Approximately 3 mL of toluene was then added and the reaction mixture was heated for an additional 28 h. After cooling, the reaction mixture was filtered (washing the solids with toluene), and the filtrate was washed with aqueous $NaHCO_3$ and brine. The organic layer was taken to dryness, and the residue was chromatographed on silica gel (3% MeOH/0.5% $NH_3 \cdot H_2O$/CH_2Cl_2 eluent) to give 1.30 g (92%) of product. The hydrochloride salt (dihydrate) (mp 75–85 °C) was prepared from HCl in EtOH. Anal. ($C_{24}H_{33}N_3O_4 \cdot HCl \cdot 2H_2O$) C, H, N.

1-(4-Fluorophenyl)-4-[2-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)methoxy]ethyl]piperazine Dihydrochloride (6c). A mixture of 1.27 g (4.42 mmol) of **5**, 1.52 g (8.44 mmol) of 1-(*p*-fluorophenyl)piperazine, and 3 mL of toluene was stirred at 90 °C for 18 h, after which the reaction mixture was extracted with CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was taken to dryness, and the residue was chromatographed on silica gel (2% MeOH/CH_2Cl_2 eluent) to give 1.16 g (62%) of an oil. The product was rechromatographed (2% MeOH/CH_2Cl_2) and the dihydrochloride salt (mp 72–77 °C) was prepared with HCl/Et_2O. Anal. ($C_{25}H_{33}N_2O_4 \cdot 2HCl$) C, H, N.

2-[[2-[(1,3,4,5-Tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)methoxy]ethyl]amino]ethanol Cyclohexylsulfamate Salt (6d). A mixture of 1.00 g (3.3 mmol) of **5** and an approximately tenfold excess of ethanolamine was stirred at 80 °C for 1 h and at room temperature overnight. The reaction mixture was then extracted with CH_2Cl_2 and H_2O, and the organic layer was taken to dryness. The crude product was chromatographed on RP2 silica gel with 4% MeOH/CH_2Cl_2 to give 0.96 g (90%) of product. The product was taken up in EtOAc, 1 equiv of cyclohexylsulfamic acid was added, and the mixture was warmed on a steam bath. A small amount of CH_2Cl_2/SSB was added. When the mixture cooled, 1.31 g of crystalline product, mp 118.5–119.5 °C, was obtained. Anal. ($C_{17}H_{22}NO_8 \cdot C_6H_{13}NO_3S$) C, H, N.

1-Methyl-4-[2-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)methoxy]ethyl]piperazine Dihydrochloride Dihydrate (6e). A mixture of 1.00 g (3.32 mmol) of **5**, 0.76 mL (6.8 mmol) of *N*-methylpiperzine, and 3 mL of benzene was heated at 80 °C for 24 h. After cooling, the mixture was extracted with CH_2Cl_2 and 10% NaOH. The organic layer was taken to dryness and the residue was chromatographed on RP2 silica gel (4% MeOH/CH_2Cl_2) to give 1.11 g (90%) of product. The dihydrochloride dihydrate salt, prepared from HCl/EtOH, was crystallized twice from CH_2Cl_2/EtOH to give 0.59 g of product, mp 157.5–158.5 °C. Anal. ($C_{22}H_{32}N_2O_4 \cdot 2HCl \cdot 2H_2O$) C, H, N, Cl.

Pharmacological Methods. Rat homocytotropic antibody was elicited to egg albumin (EA) by the injection of 0.5 mg of EA and 0.5 cm^3 of *H. pertussis* vaccine per rat. After 20–30 days, the serum was collected and frozen until use. The antibody was shown to be of the 72-h latency, heat-labile type 4.[6] Then 0.1 mL of an appropriate dilution of this serum was inoculated into the shaved dorsal surface of a 250-g Sprague–Dawley rat. Saline controls were run also. After 72 h, the rat was challenged iv with 2 mg of EA and 5 mg of Evans blue dye. In the case of drug-treated animals, the materials were given 5, 20, 60, and 120 min before challenge or the drugs given iv with antigen. Results were reported as the number of spots per animal (regardless of size) that were seen at four dilutions of serum. The control spots were compared to drug-treated spots, and a spot score was obtained (number of total spots divided by the number of animals). The percent inhibition of the PCA reaction was then calculated. For insoluble compounds orally, the material was suspendend in 0.25% carboxymethylcellulose in water. For soluble acids and iv administered drugs, the compound was solubilized in Tris buffer (w/w).

The significance of the difference between treated and control in this PCA test is significant. During repeat tests of the standard drug, disodium cromoglycate, the assay results for a given level of drug varied not more than 8% on 35 replicate assays.

(5) D. Nasipuri, R. Roy, and U. Rakshit, *J. Indian Chem. Soc.*, **37**, 369 (1960).

(6) J. Goose and A. M. J. N. Blair, *Immunology*, **16**, 749 (1969).