Synthesis and Blood Pressure Lowering Activity of Benzylic Ethers of 2-Diethylaminoethanol and a Related Diamine

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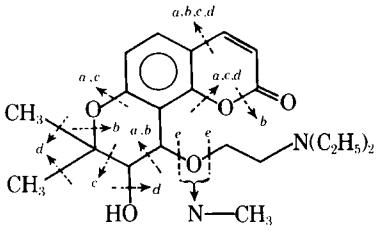
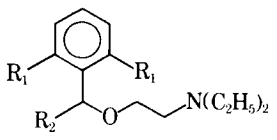
Abstract □ Based upon the unpublished finding that 3′-hydroxy-4′-(β-diethylaminoethoxy)-3′,4′-dihydroseselin possessed a potent blood pressure lowering effect in the cat at a dose of 1 mg/kg, the present study examined the activities of several related compounds. These compounds were derived by dissection of the parent compound to give four benzylic ethers of 2-diethylaminoethanol and a diamine, derived by replacing the ether oxygen of the parent compound with an N—CH_3 function. The simplest compounds were the benzyl and 2,6-dimethoxybenzyl ethers of the aminoalcohol. Closely related to the benzyl compound was a congener with a hydroxymethyl group on the benzylic carbon. The β-diethylaminoethyl ether of 4-chromanol was the most complex of the ethers. The blood pressure measurements were carried out on male cats and compared to papaverine hydrochloride as a standard. In all cases, the most potent blood pressure lowering activity resided in the parent compound, which was not greatly superior to the diamine but substantially more active than the other compounds.

Keyphrases □ 2-Diethylaminoethanol benzylic ethers and related diamine—synthesis, screened for blood pressure lowering activity □ Antihypertensive activity—synthesis and screening of 2-diethylaminoethanol benzylic ethers and related diamine

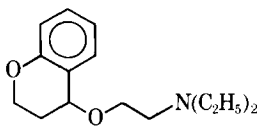
Gupta (1) prepared 3′-hydroxy-4′-(β-diethylaminoethoxy)-3′,4′-dihydroseselin (I*a*) in a search for water-soluble coronary vasodilators, since visnadin (I*b*), the parent compound, together with its closely



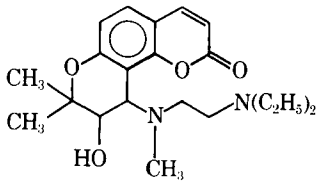
I*a*



II: $R_1 = R_2 = H$ (*a*)
III: $R_1 = OCH_3$; $R_2 = H$ (*b*)
IV: $R_1 = H$; $R_2 = CH_2OH$ (*c*)

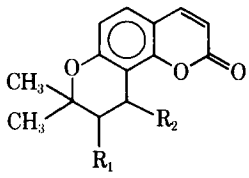


V: *d* to give the indicated structure



VI: *e* with substitution of N—CH_3 for O as indicated in I*a*

Scheme I



I*a*: R_1 = —OH, R_2 = —$OCH_2CH_2N(C_2H_5)_2$
I*b*: R_1 = —$OOCCH(CH_3)CH_2CH_3$, R_2 = —$OOCCH_3$
I*c*: R_1 = —$OOCCH_3$, R_2 = —$OOCC(CH_3)=CH-CH_3$
I*d*: R_1 = —$OOCCH_3$, R_2 = —$OOCCH_2CH(CH_3)_2$

related congeners pteryxin (I*c*) and suksdorfin (I*d*), were reputed (2, 3) to possess this interesting and potentially useful activity. Preliminary observations in these laboratories indicated that I*a* was lethal to rabbits and cats when administered in doses of 3–4 mg/kg iv. Further experimentation indicated that the cause of death was an acute blood pressure drop and that a dose of 1 mg/kg in the cat, while causing a significant blood pressure drop, was not lethal. Because of these observations, some of the simpler forms envisioned within the molecular structure of I*a* were proposed as candidates to determine whether significant activity could be generated in the structural modifications.

DISCUSSION

Consideration of the molecular structure of I*a* immediately suggested that its most important feature was that of being a benzylic ether of 2-diethylaminoethanol, since other compounds in which the ether function was replaced with a variety of acyloxy functions (*e.g.*, α-methylbutyroxy, angeloyloxy, and isovaleroxy) were without significant effect on the blood pressure at comparable dose levels. However, the necessity of the coumarin moiety as an activity-contributing part of I*a* had not been demonstrated, so the dissection of this moiety became the prime focus of this investigation.

The dissections employed are indicated in Scheme I, where the letters *a*, *b*, *etc.*, indicate the points of scission of I*a* and correlate with the numbers of the actual compounds prepared, *i.e.*, II, III, IV, V, and VI.

In II, the molecule has been stripped to the bare essentials of being a benzylic ether; in III, the simple benzylic ether has the oxygen functions of I*a* restored as methoxy groups. In IV, the hydroxy corresponding to that at the 3′-position of I*a* has been retained in a simple benzylic ether. The modification in V restores the benzopyran portion of I*a* (minus the *gem*-dimethyls). Compound VI represents the compound in which all of the elements of I*a* are kept intact except for the introduction of an N—CH_3 group in place of the ether oxygen, although one cannot be sure that the replacing group has the same steric orientation as the C-4′ group in I*a*.

Compound II was prepared by the method of Rericha *et al.* (4). Compound III was readily obtained by reduction of ethyl 2,6-dimethoxybenzoate to the corresponding alcohol with lithium aluminum hydride, followed by treatment of the sodium salt of the alcohol with 2-diethylaminoethyl chloride. 2-Phenyl-2-(β-diethylami-

noethoxy)ethanol (IV) was prepared by the method of Bottari and Macchia (5), which involved the interaction of the sodium salt of 2-diethylaminoethanol with ethyl-α-bromophenyl acetate, followed by lithium aluminum hydride reduction of the resulting product to give IV. The synthesis of V was accomplished by the alkylation of 4-chromanol with 2-diethylaminoethyl chloride. Compound VI was readily accessible from the reaction of Ic with *N,N*-diethyl-*N'*-methylethylenediamine, followed by acid hydrolysis.

Determination of the vasodepressor activity of Ia and the prepared compounds was made using cats as the test animal and papaverine hydrochloride as a standard. All blood pressure drops were compared to the standard drop in pressure achieved with papaverine. The order of vasodepressor activity determined in this manner was: Ia > VI >>> III > II > V > IV. It was clear that Ia and its close structural analog were virtually equivalent in activity and were both substantially superior to the others. Nevertheless, the fact that activity was evident in compounds without the coumarinic lactone feature suggests that additional studies might be desirable.

EXPERIMENTAL[1]

Synthesis—*3'-Hydroxy-4'-(β-diethylaminoethoxy)-3',4'-dihydroseselin (Ia)*—Pteryxin (Ic, 10 g, 0.025 mole) in tetrahydrofuran (40 ml) was treated with sodium amide (1.95 g, 0.05 mole), and the solution was stirred at room temperature for 1 hr. 2-Diethylaminoethanol (5.9 g, 0.05 mole) in tetrahydrofuran (5 ml) was added dropwise and the solution was stirred at room temperature for 2 hr. The contents then were diluted with water (1 liter) and acidified with sulfuric acid.

The aqueous acid solution was washed with ether and made alkaline with 10% aqueous sodium carbonate, and the precipitated base was thoroughly extracted with ether. The ethereal solution was washed with water, dried, and then evaporated to provide a brown oil. On standing in the refrigerator for a few days, the oil crystallized and was then recrystallized from ethanol–water to give white needles, mp 105–108°. The methiodide salt gave a melting point of 191–193°.

Anal.—Calc. for $C_{20}H_{27}NO_5 \cdot H_2O$: C, 63.30; H, 7.65; N, 3.69. Found: C, 63.60; H, 7.32; N, 3.59.

1-Benzyloxy-2-diethylaminoethane (II)—The synthesis was as described by Rericha *et al.* (4), bp 70–74°/0.1 mm [lit. (4) bp 72–76°/0.1 mm].

1-(2',6'-Dimethoxy)benzyloxy-2-diethylaminoethane (III)—2,6-Dimethoxybenzyl alcohol (0.5 g, 0.062 mole), prepared by lithium aluminum hydride reduction of ethyl 2,6-dimethoxybenzoate according to Hejno and Arnold (6), was treated with metallic sodium (1.43 g, 0.062 mole). A solution of 2-diethylaminoethyl chloride (8.5 g, 0.062 mole) in xylene (25 ml) was added dropwise to this solution, and the reaction mixture was refluxed for 12 hr; the contents then were diluted with water and extracted with aqueous 10% hydrochloric acid.

The acid extract was washed with ether, made alkaline with aqueous 10% sodium hydroxide, and extracted with ether to obtain the free base. The ethereal extract was washed with water, dried, filtered, and finally subjected to evaporation. The oily residue was distilled to obtain a product (7.6 g, 45.5%), bp 170–180°/2.5 mm.

The hydrochloride of the base, prepared by the use of ethereal hydrogen chloride, was recrystallized from ethyl acetate–ether to give an analytical sample, mp 98–99°.

Anal.—Calc. for $C_{15}H_{26}ClNO_3$: C, 59.30; H, 8.56; N, 5.26. Found: C, 59.20; H, 8.88; N, 5.59.

2-Phenyl-2-(β-diethylaminoethoxy)ethanol (IV)—Ethyl-α-bromophenyl acetate (19.5 g, 0.08 mole) was prepared according to the method of Narayanan and Martin (7), dissolved in anhydrous toluene (60 ml), and added dropwise to a solution of 2-diethylaminoethanol (10.6 g, 0.09 mole) in anhydrous toluene (25 ml), which had been pretreated with sodium (1.84 g, 0.08 mole) as in the preparation of III. The resultant mixture was refluxed for 2 hr with stirring, cooled, washed with water (50 ml), and extracted thoroughly with aqueous 10% hydrochloric acid. The combined acidic extract was washed with ether (50 ml) and made alkaline with 10% aqueous sodium hydroxide, and the free base was extracted into ether.

The ethereal extract was washed with water, dried, and evaporated to provide 4.6 g (20.7%) of an oil. The oil, after drying overnight in an evacuated desiccator over phosphorus pentoxide, was dissolved in anhydrous ether and added dropwise to a suspension of lithium aluminum hydride (0.7 g) in anhydrous ether. The reaction mixture was refluxed for 0.5 hr, cooled, and decomposed by the cautious addition of water. The organic phase was then dried and evaporated to dryness to yield a yellow oil (2.6 g, 66.6%). This oil was distilled under reduced pressure at bp 130–142°/2 mm [lit. (5) bp 135–140°/1.6 mm].

The hydrochloride salt was prepared by the addition of ethereal hydrogen chloride to a saturated solution of the free base in absolute alcohol. Recrystallization of the salt from acetone–ether yielded colorless crystals, mp 118–119°.

4-(β-Diethylaminoethoxy)chroman (V)—To a stirred suspension of sodium hydride (0.6 g of a 50% suspension in mineral oil) in anhydrous dimethylformamide (15 ml) under nitrogen was added dropwise a solution of 4-chromanol (1.6 g, 0.01 mole) in dimethylformamide (2 ml). The reaction mixture was stirred for 1 hr, and then a solution of 2-diethylaminoethyl chloride (2.7 g, 0.02 mole) in dimethylformamide (2 ml) was added dropwise (25 min). Stirring was continued at room temperature for 21 hr.

The mixture was poured into water and extracted with ether, and the ethereal extract was washed with water before being extracted with 10% aqueous hydrochloric acid (4 × 100 ml). The acidic extract was washed with ether and made alkaline with 20% ammonium hydroxide solution, and the free base was extracted with ether. The ethereal extract was washed with water and dried, and the ether was evaporated to obtain a pale-yellow oil (2 g, 76.9%). This oil was distilled at bp 115–120°/0.2 mm.

The picrolonate salt was prepared by mixing the free base (0.124 g) and picrolonic acid (0.132 g) in absolute ethanol to obtain large brown needles, mp 141–143° dec.

Anal.—Calc. for $C_{25}H_{31}N_5O_7$: C, 58.46; H, 6.08; N, 13.63. Found: C, 58.65; H, 6.27; N, 13.40.

3'-Hydroxy-4'-[methyl(N,N-diethylaminoethyl)amino]-3',4'-dihydroseselin (VI)—A mixture of visnadin (Ib, 19.5 g, 0.05 mole) in anhydrous benzene (250 ml) and *N*-methyl-2-diethylaminoethylenediamine (13 g) was refluxed for 19 hr. The solvent was removed under reduced pressure; the residue was extracted with 10% aqueous hydrochloric acid, alkalinized as before, and extracted with ether; and the ethereal extract was dried and evaporated to give 4 g of an oil. This oil was refluxed with sulfuric acid (20%, 30 ml) for 6 hr; after cooling, the reaction mixture was diluted with water and alkalinized with 20% ammonium hydroxide, and the free base was extracted into ether.

The ethereal extract was dried, concentrated to a small volume, and then treated with ethereal hydrogen chloride. The resulting salt (1.5 g) was chromatographed over neutral alumina (45 g), and

Table I—Blood Pressure Lowering Effects

Compound	Dose, mg/kg	Mean Blood Pressure Drop, mm/Hg	Percent Blood Pressure Drop[a]	Duration, min
Ia	0.5	43.3	72.0	5.0
	1.0	48.2	80.3	6.0
	2.0	74.0	123.0	10.0
II	1.0	17.0	28.3	4.0
	2.0	27.0	45.0	6.0
	3.0	40.0	66.6	9.0
III	1.0	18.0	30.0	3.5
	2.0	28.0	46.6	5.0
	3.0	48.0	80.0	5.5
IV	1.0	9.0	15.0	6.5
	2.0	16.0	26.6	10.0
	3.0	29.0	48.3	12.0
V	0.5	9.0	15.0	1.0
	1.0	15.0	25.0	2.0
VI	0.5	41.0	68.0	4.0
	1.0	48.0	80.0	7.0
	2.0	71.0	118.0	11.0

[a] Papaverine hydrochloride = 100.

[1] Melting points were determined in capillary tubes in a Thomas-Hoover melting-point apparatus and are uncorrected. NMR spectra were determined on a Varian A-60D instrument. Analysis were carried out by the Microanalytical Laboratory, School of Chemistry, University of Minnesota, Minneapolis, Minn., or by Schwarzkopf Laboratories, Woodside, N.Y. Anhydrous sodium sulfate was used to dry solvent extracts unless otherwise specified.

the free base was eluted with ethyl acetate. Reconversion of the free base to the hydrochloride salt with ethereal hydrogen chloride and recrystallization from acetone–ether provided pale-yellow crystals, mp 108–110° dec.

Anal.—Calc. for $C_{21}H_{32}Cl_2N_2O_4$: C, 56.37; H, 7.21; N, 6.26. Found: C, 56.53; H, 7.20; N, 6.11.

Pharmacology—The blood pressure lowering activities of the compounds studied were compared to papaverine hydrochloride, the standard, in three male cats weighing an average of 3 kg. The animals were anesthetized with pentobarbital sodium (30 mg/kg), with additional small doses being given as needed. The blood pressure was monitored continuously by a force transducer[2] connected to a polyethylene catheter placed in the femoral artery and coupled[3] to a recording polygraph[4] at a chart speed of 1 cm/min. The average blood pressures for the cats at the beginning and end of the experiments were 146 and 132 mm/Hg, respectively.

The compounds tested were simply dissolved in normal saline if they were in a salt form. If in the free base form, they were solubilized in the least amount of 0.02 *N* hydrochloric acid and made up to the normal saline concentration with appropriate amounts of sodium chloride and water. The compounds tested were injected as a bolus *via* a femoral venous catheter in doses ranging from 0.5 to 3 mg/kg, followed by a 3-ml saline flush. The results reported (Table I) for each dose are the results of three or more readings. The blood pressure was allowed to return to preinjection levels before additional injections were given.

The protocol for the administration of the several agents being tested was to administer them according to the Latin-square method, whereby each new animal preparation was tested with a different order of the agents. In addition, administration of papaverine hydrochloride at the beginning, during the course of, and at the end of the experiment indicated that the blood pressure was still normally responsive in each cat throughout the experiment. The drop in blood pressure by an average dose of 1.67 mg/kg of papaverine hydrochloride was 60 mm/Hg, and this value was assigned as a 100% drop in the blood pressure because increasing the dose failed to elicit a further drop. All compounds were rated as a percentage against the standard on this basis.

[2] Beckman 215071.
[3] Beckman 9853 coupler.
[4] Beckman R-411 dynograph.

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Cyanogen Condensations as a Route to 3-Amino-2-imino-1,3-benzothiazin-4-ones with CNS Depressant Potential

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Abstract □ Seven new 3-amino-2-imino-1,3-benzothiazin-4-ones, prepared from the condensation of cyanogen and 2-mercaptobenzhydrazides, were evaluated in a neuropharmacological mouse profile. CNS depression was observed in several members of the class.

Keyphrases □ 3-Amino-2-imino-1,3-benzothiazin-4-ones—synthesized and screened as CNS agents □ CNS agents, potential—synthesis and screening of seven 3-amino-2-imino-1,3-benzothiazin-4-ones □ 1,3-Benzothiazin-4-ones, 3-amino-2-imino—synthesized and screened as CNS agents

Recent interest in the synthesis and pharmacological properties of certain 1,3-benzothiazin-4-ones, particularly as central nervous system (CNS) agents with marked mydriatic activity (1–5), prompted this report on a new synthesis of some uniquely substituted analogs of this class and their biological activities. 2-Mercaptobenzhydrazides (I) and cyanogen (II) were found to undergo facile condensation, in 50–74% yield, to 3-amino-2-imino-3,4-dihydro-2*H*-1,3-benzothiazin-4-ones (III), a reaction that represents cyanogen acting as a one-carbon insertion unit to close a six-membered ring (Scheme I).

Previous examples are known in which cyanogen in heterocyclic syntheses completes a cycle by insertion of a single carbon (6), two carbons (7), or one carbon and a nitrogen (8). An earlier synthetic study with 2-mercaptobenzhydrazide reported its condensation with formaldehyde to form a seven-membered ring, but no biological testing data were provided on the resulting benzo-1,3,4-thiadiazepinone (9).

The benzothiazinone products, III*a*–III*c*, could be structurally distinguished from the equally plausible, and isomeric, seven-membered alternatives, IV*a*–IV*c*, by characteristic chemical reactions. Hydrolysis generated Compound VII, which possessed a free amino group as evidenced by formation of an anil, VIII. Furthermore, condensation of III*a* with phosgene and/or benzoyl chloride produced *s*-triazolo systems, which would have been impossible from the alternative structure, IV. In addition, the pendant amino on III*a* underwent facile anil formation with both *p*-nitro- and *p*-dimethylaminobenzaldehydes.

From a practical viewpoint, solutions of up to 5 *M* cyanogen in anhydrous tetrahydrofuran, stable to