Synthesis of Some New (3-Benzazolylmethyl)aminodiphenyl Ethers as Potential Biologically Active Agents

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A series of 4-(3-benzazolylmethyl)aminodiphenyl ethers have been synthesized and evaluated for their biological activity. The compounds have been synthesized by the condensation of 4-aminodiphenyl ether with benzazoles, phthalimides, and 4-quinazolone in the presence of 40% formalin under Mannich conditions.

As reported earlier, substituted benzoxazoles especially those having a thione group at the second position exhibit antibacterial and antimicrobial activities (*1-3*). Further, quinazolone nucleus shows significant CNS depressant and antiviral activity (*4-8*).

Many Mannich bases have been reported to possess antibacterial (*9*) and anticonvulsant (*10*) properties. These observations led us to synthesize a series of the title compounds with a view to test them for their pharmacological properties.

All the synthesized compounds have been characterized by correct elemental analysis and IR and NMR spectra.

Experimental Section

All the melting points were taken in open capillaries in a liquid bath of concentrated sulfuric acid and are uncorrected. IR spectra were recorded on Perkin-Elmer Models 137 and 177 with KBr. NMR spectrum was recorded in $CDCl_3$ at 100 MHz (Me_4Si as internal reference).

II (*11*) was prepared by condensing phenols with 4-nitrochlorobenzene and subsequently reducing the 4-nitrodiphenyl ethers (I).

Benzazoles, phthalimide, 4-nitrophthalimide, and 4-quinazolone were obtained by known methods (*11*).

4-(3-Benzazolylmethyl)aminodiphenyl ethers (IV) were prepared as follows: Benzoxazolin-2-one (1.35 g, 0.01 mol) was suspended in 10 mL of methanol, 40% formalin (1 mL) and II (0.01 mol) were introduced with stirring. The contents were vigorously stirred for 10 min and then left at room temperature overnight. The product thus obtained was filtered, washed with

Table I. 4-(3-Benzazolylmethyl)aminodiphenyl Ethers (IV)

no.	R_1R_2N-	R	mp, °C	yield, %	antibacterial activity[a] against *B. subtilis*	antibacterial activity[a] against *S. lutea*
1	1-benzimidazolyl	CH_3	155-156	65	++	+
2	1-benzimidazolyl	F	144-145	60	+	+
3	2-methyl-benzimidazolyl	CH_3	158	55	-	-
4	2-methyl-benzimidazolyl	H	141-143	58	-	-
5	2-methyl-benzimidazolyl	F	145	52	+++	-
6	3-benzoxazolin-2-onyl	H	170	68	+	-
7	3-benzoxazolin-2-onyl	F	164	70	+	-
8	6-nitro-3-benzoxazolin-2-onyl	CH_3	155-156	71	++	+
9	6-nitro-3-benzoxazolin-2-onyl	F	171-172	65	-	-
10	3-benzoxazolin-2-thionyl	CH_3	173	50	+	-
11	3-benzoxazolin-2-thionyl	F	159-161	55	+	-
12	3-benzothiazolin-2-thionyl	CH_3	155-157	60	-	-
13	3-benzothiazolin-2-thionyl	F	98	58	++	+
14	1-benzotriazolyl	CH_3	143-145	52	+	-
15	1-benzotriazolyl	F	134-135	55	+	-
16	1-phthalimido	CH_3	225-227	75	-	+
17	1-phthalimido	F	165-166	72	-	-
18	4-nitro-1-phthalimido	CH_3	204	70	++	-
19	4-nitro-1-phthalimido	F	180-182	75	+	-
20	3-quinazolin-4-onyl	CH_3	134-135	65	+	+
21	3-quinazolin-4-onyl	F	212-215	62	++	-

[a] Key: - = no inhibition; +++ = inhibitory zone size >10 mm; ++ = inhibitory zone size 10-8 mm; + = inhibitory zone size 5-8 mm.

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methanol, and recrystallized from a suitable solvent.

The compounds thus obtained are listed in Table I.

NMR: **17**, δ 4.88 (CH_2), 6.40–7.82 (ArH and NH).

IR (cm^{-1}): **1**, 3230 (NH), 3040 (CH_2); **3**, 3050 (NH), 2800 (CH_2); **6**, 3350 (NH), 3000 (CH_2); **20**, 3300 (NH), 3000 (CH_2).

CNS Activity

Compounds **2**, **6**, **9**, **16**, and **19** were administered intraperitoneally at different dosages such as 200, 400, and 1000 mg to groups of 5, 4, and 4 mice, respectively. During gross observation, it was found that spontaneous motor activity and reactivity of the animals were increased.

ALD_{50} of compounds **2**, **16**, and **19** was >1000 mg/kg and for **6** and **9** it was 681 mg/kg.

The compounds did not show any protection against maximum electric shock (MES).

Antiviral Activity

Compounds **1**, **9**, **10**, **13**, **20**, and **21** were tested against the strains of vaccinia and Ranikhet disease viruses in vitro by a method reported earlier. The system taken was CAM culture of chick embryo; compound **10** showed an inhibition of 40% whereas the remaining compounds were inactive against these strains.

Antibacterial Activity

All the compounds (except **4**) of Table I were tested against the strains of *Bacillus subtilis* and *Sarcina lutea* by the Agar diffusion method (*12*). The results are recorded in Table I. Fifteen compounds showed inhibition against *B. subtilis* while six compounds were effective against *S. lutea*.

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Literature Cited

(1) Varma, R. S.; Nobles, W. L. *J. Pharm. Sci.* **1973**, *62*, 140.
(2) Varma, R. S.; Imam, S. A. *Indian J. Microbiol.* **1973**, *13*, 43.
(3) Varma, R. S.; Imam, S. A. *Def. Sci. J.* **1975**, *67*, 25.
(4) Gujral, M. L.; Saxena, P. N.; Tiwari, R. S. *Indian J. Med. Res.* **1955**, *43*, 637.
(5) Kacker, I. K.; Zaheer, S. H. *J. Indian Chem. Soc.* **1951**, *38*, 344.
(6) Zaheer, S. H.; Sidhu, G. S.; Sattur, P. B.; Seth, U. K. Symposium on CNS drugs. CSIR: New Delhi, 1966; 170.
(7) Jamamoto, M.; Morooka, S. *Japan Kokai Tokkyo Koho* **1974**, *110*, 681.
(8) Furman, R. H.; Howard, R. P.; Keaty, C. E. *Am. J. Med.* **1958**, *24*, 80.
(9) Kurihava Tonaburo et al. *Annu. Rep. Tokoku Coll. Pharm.* **1970**, *17*, 43; *Chem. Abstr.* **1971**, *75*, 110246r.
(10) Ram, V. J.; Pande, H. N. *J. Indian Chem. Soc.* **1974**, *51*, 634.
(11) Kapoor, Anup Ph.D. Thesis, 1978, Lucknow University.
(12) Varma, R. S.; Nobles, W. L. *J. Pharm. Sci.* **1968**, *57*, 1801.

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Selective Reaction of Isocyanates with the Amino Group of 2-Amino-2-methyl-1,3-propanediol

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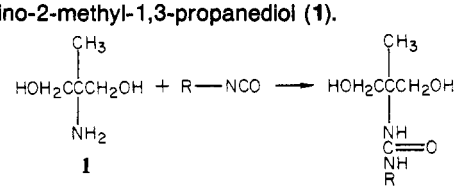
Isocyanates react very specifically with the amino group of 2-amino-2-methyl-1,3-propanediol. Five model compounds were made and identified with elemental analysis and IR, NMR, and mass spectra.

On the basis of information available from the literature,[1-3] a number of new urea derivatives have been synthesized by reacting model isocyanates very selectively with the amino group of 2-amino-2-methyl-1,3-propanediol (**1**).



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Analytical and proton chemical shift data of all the urea derivatives are listed in Table I. Infrared spectra of these compounds have no absorption at 5.8–5.9 μm characteristic of the urethane carbonyl and all of them have urea carbonyl absorption at 5.98–6.02 μm. C, H, and N analyses and the $(M + 1)^+$ peaks for all five compounds were as calculated.

Experimental Section

General Procedure. Isocyanates and 2-amino-2-methyl-1,3-propanediol were obtained from Eastman and Aldrich Chemical Co. Isocyanates were used as received. The diol was recrystallized twice from acetone.[4] Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded by using a Perkin-Elmer 521. Nuclear magnetic resonance spectra were obtained with a Varian EM 390 instrument, using tetramethylsilane as an internal standard and Me_2SO-d_6. Molecular weights were determined by chemical ionization mass spectrometer (Biospect) using methane as a reagent gas. Microanalysis were performed at American Cyanamid Co. of Bound Brook, N.J..

Synthesis of 2-Substituted-2-methyl-1,3-propanediol. Aqueous 2-propanol as Solvent. A 13-g sample (0.12 mol) of 2-amino-2-methyl-1,3-propanediol was dissolved in 40 mL of 70% aqueous 2-propanol and heated to gentle reflux. Isocyanate (0.10 mol) was added dropwise and then the mixture was refluxed for 30 min. Upon cooling of the mixture, the urea derivative precipitated, which was removed by filtration and recrystallized twice from aqueous 2-propanol.

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