Synthesis of Pyridyloxadiazoles 2. 2-(Oxadiazolyl)pyridines and 2,6-*bis*(Oxadiazolyl)pyridines as Analogues of Pyridinolcarbamate

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Four 2-(oxadiazolyl)pyridines and three 2,6-*bis*(oxadiazolyl)pyridines, considered as potential analogues of pyridinolcarbamate (PC), were prepared and screened for antithrombotic activity against ADP- and collagen-induced platelet aggregation. All the compounds showed activity below the critical response expected for this category of drugs.

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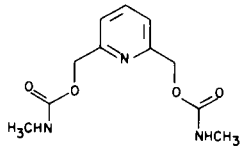
Pyridinolcarbamate (PC) (**1**) is a drug commonly used in Japan and many parts of the world for the prevention of atherogenesis and treatment of atherosclerotic disorders (3). In addition to its antiatherogenic action it is reported to have some antithrombotic activity as well (4-9). Biologically, a key step in these mechanisms appears to be the relaxation and reduced platelet adhesiveness resulting from the reduction of available Ca^{++} ions (10,11). The structure of PC suggested to us that at least in part, its mode of action could be explained by a possible interference with the free Ca^{++} ions as a result of a mild chelating activity. This idea resulted from the comparison of PC's structure with that of known host compounds (12, 13).

A research program designed to synthesize a series of 2,6-*bis*(oxadiazolyl)pyridine derivatives resembling PC structurally, and hopefully with an increased and more selective chelating activity, was initiated.

Physical properties, such as the hydrophobic/hydrophilic equilibrium (log P), were also considered important to resemble as much as possible those of PC. Measurement of its log P by the usual method in octanol/water (14) indicated that PC was quite hydrophilic. Its calculated log P value based on the additive character of partition coefficients (15) and using literature parameters (16) compared quite favorably with the measured value.



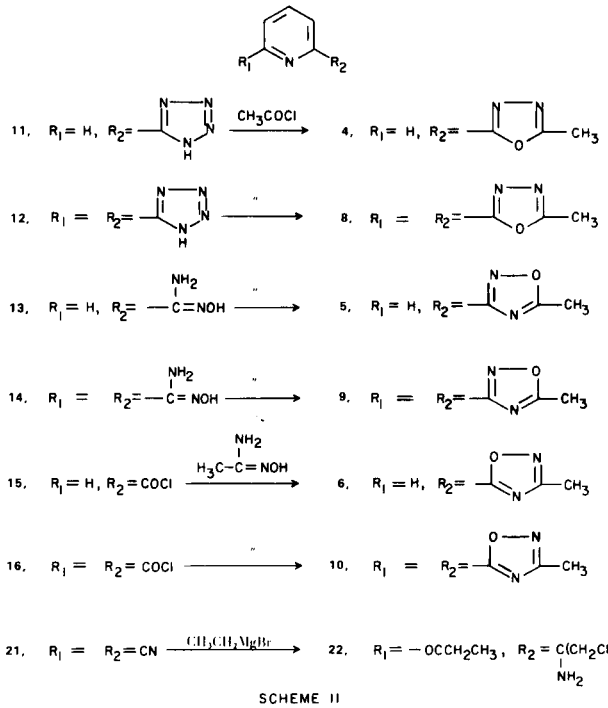
1

Calculated log P 0.35
Measured log P = 0.24 ± 0.05

The series of compounds synthetized is shown in Table I. Data on the log P values of these compounds are also shown and point out the differences between the several oxadiazole moieties. The two compounds that have log P values closest to that of PC are compounds **4** and **8**, while the others are somewhat more lipophilic. The log P values for the *bis* analogues were estimated from the experimental results obtained for the corresponding mono-substituted compounds. Structurally, the compounds presented a somewhat better chelating cavity than that of PC due to the presence of the five-member oxadiazole rings and offered several alternatives, depending on the rotation of the pyridine-oxadiazole single bond, to involve either nitrogen or oxygen as potential donors.

Synthesis of the final products generally involved a reaction between a suitable starting material and the appropriate acid chloride in refluxing pyridine (Scheme I).

SCHEME I



SCHEME II

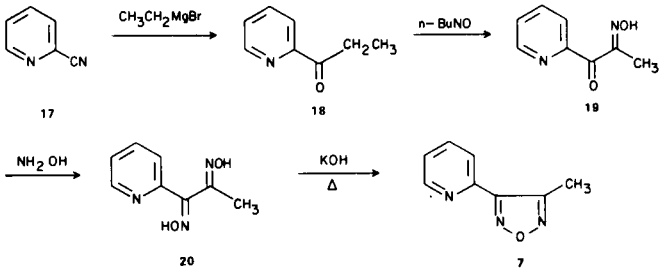
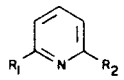
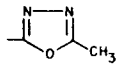
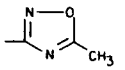
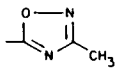
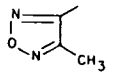
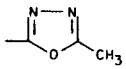
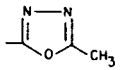
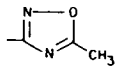
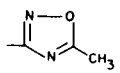
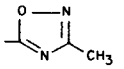
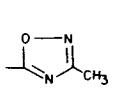


Table I

Physical Properties of *mono* and *bis*(oxadiazolyl)pyridines



Compound No.	R_1	R_2	Yield, %	Chromatographic System (SiO_2)	R_f	Crystallization Solvent	M.p., °C	Formula (a)	Calculated log P	Measured (c) log P
4		H	46	benzene-acetone (1:1)	0.37	ether	97-99	$C_8H_7N_3O$		0.46 ± 0.04
5		H	70	benzene-acetone (2:1)	0.38	benzene	88-89 (b)	$C_8H_7N_3O$		0.79 ± 0.04
6		H	10	chloroform-ethyl acetate (1:1)	0.37	sublimed	68-69	$C_8H_7N_3O$		0.89 ± 0.02
7		H	20	-----	-----	sublimed	37-38	$C_8H_7N_3O$		2.09 ± 0.1
8			14	benzene-acetone (1:1)	0.34	THF	194-196	$C_{11}H_9N_5O_2$	0.27	
9			51	benzene-acetone (1:1)	0.36	ethanol	180-181	$C_{11}H_9N_5O_2$	1.00	
10			45	chloroform-ethyl acetate (1:1)	0.36	ethanol	201-203	$C_{11}H_9N_5O_2$	1.15	

(a) Satisfactory analyses for C, H and H within ± 0.4% of the theoretical values were obtained for all compounds. (b) Lit. m.p. 87-88.5°. (c) Average of three determinations with standard deviations.

Almost invariably the compounds had to be purified by column chromatography from the dark reaction mixtures (see Table I). The only exception to this method was compound **7** which was made from dioxime **20** according to Scheme II. This approach, however, failed for the case of the corresponding *bis* analogue since the only product isolated from step one of the sequence, involving 2,6-dicyanopyridine and ethylmagnesium bromide in different molar ratios, was an oil identified as **22** by nmr spectroscopy but not further characterized (Scheme I).

The intensity of ADP- and collagen-induced aggregation was measured *in vitro* by the optical density method of Born (17). The standard drug used for comparison was aspirin at doses of 100 μg./ml. for the ADP-induced platelet aggregation and 10 μg./ml. for the collagen-induced aggregation, respectively. Test drugs were assayed at the same doses and the results were expressed as % inhibition of platelet aggregation. Aspirin at the doses indicated was 100% effective in both assays. Reduction of aggregation by more than 50% by test compounds added 2 minutes before the addition of either ADP or collagen denotes inhibition of platelet aggregation. Under these conditions PC was totally inactive and none of the 2,6-*bis*(oxadiazolyl)pyridines showed any significant inhibition of either ADP- or collagen-induced platelet aggregation. Only compound **8** which closely resembles PC in its log P value showed very marginal activity (15% inhibition) against ADP-induced platelet aggregation among the *bis*(oxadiazolyl)pyridines. In the monosubstituted series, however, compound **4**, which interestingly is also the more hydrophylic, showed a 45% inhibition against ADP-induced platelet aggregation and 37% inhibition against collagen-induced platelet aggregation. These values, however, fall below the expected criteria for an active compound.

EXPERIMENTAL

All chemical reagents are commercially available. They were purchased either from E. Merck or Aldrich Chemical Co. Melting points were determined by means of an Electrothermal capillary melting point apparatus; and they are uncorrected. A Perkin-Elmer model 727 infrared spectrophotometer was employed for ir spectra, using nujol mulls. A Varian Associates Model EM-360 analytical nmr spectrometer was used for nmr spectra of deuteriochloroform solutions with internal tetramethylsilane (δ 0.00) at ambient temperatures. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer, utilizing 1 cm path cells. Mass spectra were obtained in a Hitachi Perkin-Elmer RMU-6H instrument at 70 eV. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

2-(2-Pyridyl)-5-methyl-1,3,4-oxadiazole (**4**).

Starting with compound **11** (18) the synthesis of **4** was accomplished as reported earlier (19).

3-(2-Pyridyl)-5-methyl-1,2,4-oxadiazole (**5**) (20).

Starting with compound **13** (21) the synthesis of **5** was accomplished as reported earlier (19).

5-(2-Pyridyl)-3-methyl-1,2,4-oxadiazole (**6**).

Picolinic acid (2 g., 21.5 mmoles) was refluxed with 16 ml. of thionyl chloride for 30 minutes and the excess of reagent distilled off. Immediately after, 1.2 g. (16 mmoles) of acetamidoxime (22) dissolved in 18 ml. of dry pyridine was added and the mixture refluxed for 2 hours. A similar workup as before gave a crude mixture which was purified under the conditions described in Table I, affording compound **6** as white crystals; uv max (methanol): 240 nm (ε, 16,700), 275 nm (ε, 13,400); ir (nujol): 1560 cm^{-1} (broad); nmr (deuteriochloroform): δ 2.55 (s, 3), 7.70 (m, 1), 8.10 (m, 1), 8.40 (d, 1) and 9.15 (d, 1); ms: m/e 161 ($M^{+\cdot}$).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.61; H, 4.37; N, 26.07. Found: C, 59.58; H, 4.32; N, 25.93.

3-(2-Pyridyl)-4-methyl-1,2,5-oxadiazole (**7**).

A mixture of dioxime **20** (1.69 g., 9.43 mmoles), 12 g. of potassium hydroxide and 30 ml. of ethylene glycol was heated at 180-190° for 0.5 hours. After cooling, water was added and compound **7** precipitated as tan crystals. Following sublimation under vacuum, compound **7** was obtained as colorless needles; uv max (methanol): 240 nm (ε, 7,000), 269 nm (ε, 5,300); ir (nujol): 1600, 1580 and 1570 cm^{-1}; nmr (deuteriochloroform): δ 2.75 (s, 3), 7.40 (m, 1), 7.85 (m, 1), 8.20 (d, 1) and 8.75 (d, 1); ms: m/e 161 ($M^{+\cdot}$).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.61; H, 4.37; N, 26.07. Found: C, 59.50; H, 4.45; N, 26.14.

2,2'-(2,6-Pyridinediyl)*bis*(5-methyl-1,3,4-oxadiazole) (**8**).

In a similar fashion as for compound **4**, 3.2 g. (14.8 mmoles) of 5,5'-(2,6-Pyridinediyl)bistetrazole (**12**) (23) was reacted with 8.5 ml. of acetyl chloride. Similar workup as for compound **4** and purification of the crude mixture under the conditions described in Table I, afforded compound **8** as yellow crystals; uv max (methanol): 236 nm (ε, 23,000), 293 nm (ε, 9,700); ir (nujol): 1580, 1560 and 1540 cm^{-1}; nmr (deuteriochloroform): δ 2.70 (s, 6), 8.35 (m, 3); ms: m/e 243 ($M^{+\cdot}$).

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.31; H, 3.72; N, 28.79. Found: C, 54.35; H, 3.82; N, 28.70.

3,3'-(2,6-Pyridinediyl)*bis*(5-methyl-1,2,4-oxadiazole) (**9**).

Similarly as for compound **5**, 3.0 g. (15.3 mmoles) of Pyridine-2,6-diamidoxime (**14**) (24) was reacted with 3.27 ml. of acetyl chloride. Workup and purification of the product by column chromatography according to the conditions described in Table I afforded compound **9** as yellow crystals; uv max (methanol): 236 nm (ε, 9,700), 282 nm (ε, 7,500); ir (nujol): 1600 and 1500 cm^{-1}; nmr (deuteriochloroform): δ 2.55 (s, 6), 8.40 (m, 3); ms: m/e 243 ($M^{+\cdot}$).

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.31; H, 3.72; N, 28.79. Found: C, 54.07; H, 3.80; N, 28.68.

5,5-(2,6-Pyridinediyl)*bis*(3-methyl-1,2,4-oxadiazole) (**10**).

To a solution of 0.960 g. (12.9 mmoles) of acetamidoxime (22) in pyridine, 1.50 g. (7.35 mmoles) of 2,6-pyridinedicarboxylic acid chloride was added at room temperature. Following a similar workup as for compound **6**, the crude mixture was purified under the conditions described in Table I affording compound **10** as white crystals; uv max (methanol): 229 nm (ε, 21,200), 288 nm (ε, 10,200); ir (nujol): 1560 cm^{-1}; nmr (deuteriochloroform): δ 2.70 (s, 6), 8.20 (m, 3); ms: m/e 243 ($M^{+\cdot}$).

Anal. Calcd. for $C_{11}H_9N_5O_2$: C, 54.31; H, 3.72; N, 28.79. Found: C, 54.31; H, 3.78; N, 28.65.

1-(2-Pyridyl)-1,2-*bis*hydroxyiminopropane (**20**).

Hydrochloric acid gas was bubbled through a dry ether solution

of 3.21 g. (23.7 mmoles) of 2-propionylpyridine (**18**) (25) for several minutes. Dioxane was added to avoid precipitation of the insoluble hydrochloride salt. Immediately after, 2.4 g. (23 mmoles) of *n*-butyl nitrite was added dropwise under constant stirring. The dark orange solution was left for 15 minutes under hydrogen chloride gas and then left overnight at room temperature. The yellow solid formed was washed thoroughly with ether yielding 2.85 g. (60%) of the desired monoxime hydrochloride **19** which was immediately reacted wih equimolar amounts of hydroxylamine hydrochloride in refluxing ethanol for 3 hours. Evaporation of the solvent left an oily residue which solidified on standing giving 3 g. (95%) of the desired dioxime **20** as a hydrochloride salt. This salt was somewhat hygroscopic and consequently used immediately for the following reaction; ir (nujol): 3600-3200 (broad) and 1620 cm^{-1}; nmr (deuterium oxide): δ 2.30 (s, 3), 8.30 (t, 2) and 9.00 (m, 2).

This compound was not subjected to analysis but converted directly into compound **7**.

Partition Coefficients.

Each determination was done in at least triplicate at different volume ratios of octanol and water (14). The concentration of drug in the aqueous layer was determined spectrophotometrically.

Biological Assays.

All biological tests were performed by Panalbs, Inc., P. O. Box 81, Fayetteville, New York 13006.

REFERENCES AND NOTES

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(2) Present address: National Institutes of Health, National Cancer Institute, Building 37, Room 6D24, Bethesda, Maryland 20014.

(3) T. Shimamoto, T. Atsumi, Y. Yamashita, T. Motomiya, N, Isokane T. Ishioka, and A. Sakuna, *Am. Heart J.*, **79**, 5 (1970).

(4) H. Yamazaki, A. Kurai, and T. Shimamoto, *Thrombos. Diath. Haemorrh.*, **22**, 145 (1969).

(5) H. Yamazaki, T. Sano, T. Odakura, K. Takeuchi, T. Matsumura, S. Hosaki, and T. Shimamoto, *ibid.*, **26**, 251 (1971).

(6) H. Yamazaki, I. Kobayashi, and T. Shimamoto, *ibid.*, **24**, 438 (1960).

(7) H. Yamazaki, I. Kobayashi, T. Sano, and T. Shimamoto, *ibid.*, **29**, 490 (1973).

(8) T. Sano, H. Yamazaki, and T. Shimamoto, *ibid.*, **29**, 684 (1973).

(9) P. Didisheim, R. E. Sturm, and C. A. Owen, Jr., in "Experiments on Thrombosis and its Prevention. Current Concepts of Coagulation and Haemostasis", R. Losito and B. F. K. Longpre, Eds., Schattauer Verlag, Stuttgart-New York, N. Y., 1971, pp. 177.

(10) T. Shimamoto, in "Cardiovascular Disease. New Concepts in Diagnosis and Therapy", H. I. Russek, Ed., University Park Press, Baltimore, MD, 1974, pp. 361.

(11) T. Shimamoto, *Asian Med. J.*, **18**, 365 (1975).

(12) V. E. Weber and F. Vogtle, *Tetrahedron Letters*, 2415 (1975).

(13) M. Newcomb, G. W. Gokel, D. J. Cram, *J. Am. Chem. Soc.*, **96**, 6810 (1974).

(14) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).

(15) C. Hansch, in "Drug Design", Vol. I, E. J. Ariens, Ed., Academic Press, New Yrok and London, 1971, pp. 271.

(16) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 71, 525 (1971).

(17) G. V. R. Born, *Nature*, **194**, 927 (1962).

(18) W. J. van der Burg, *Rec. Trav. Chim.*, **74**, 257 (1955).

(19) V. E. Marquez, M. T. Di Parsia, and J. A. Kelley, *J. Heterocyclic Chem.*, **14**, 1427 (1977).

(20) W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, **32**, 2430 (1967).

(21) E. Bernasek, *ibid.*, **22**, 1263 (1957).

(22) R. Leaners, C. Moussebois, and F. Eloy, *Helv. Chim. Acta*, **45**, 441 (1962).

(23) J. M. Mc Manus and R. M. Herbst, *J. Org. Chem.*, **24**, 1462 (1959).

(24) G. A. Pearse, Jr., and J. Wisowaty, *J. Heterocyclic Chem.*, **10**, 647 (1973).

(25) K. B. Prasad and S. C. Shaw, *Chem. Ber.*, **98**, 2822 (1965).