ACKNOWLEDGMENTS AND ADDRESSES

Received September 30, 1976, from the *Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ 85721.*

Accepted for publication December 7, 1976.

Supported in part by Contract N01-CM33750 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, education, and Welfare, Bethesda, MD 20014, and by the Elsa U. Pardee Foundation, Midland, Mich.

[x] To whom inquiries should be directed.

Anthelmintic Dihydroquinoxalino[2,3-*b*]quinoxalines

MICHAEL H. FISHER [x], AINO LUSI, and JOHN R. EGERTON

Abstract □ A series of dihydroquinoxalino[2,3-*b*]quinoxalines was synthesized and tested for anthelmintic activity in a model assay. The most promising compound, 5,12-diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline, was orally effective in sheep at a dose of 200 mg/kg against a broad range of helminths.

Keyphrases □ Quinoxalines, substituted—synthesized, anthelmintic activity evaluated □ Dihydroquinoxalino[2,3-*b*]quinoxalines, substituted—synthesized, anthelmintic activity evaluated □ Anthelmintic activity—evaluated in series of substituted dihydroquinoxalino[2,3-*b*]quinoxalines □ Structure–activity relationships—series of substituted dihydroquinoxalino[2,3-*b*]quinoxalines evaluated for anthelmintic activity

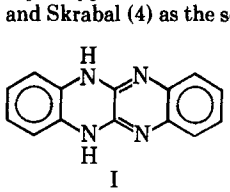
In the continuing search for anthelmintic agents of novel structure, dihydroquinoxalino[2,3-*b*]quinoxaline showed erratic but definite anthelmintic activity in a preliminary assay. Therefore, several analogs were synthesized and tested for anthelmintic efficacy.

RESULTS AND DISCUSSION

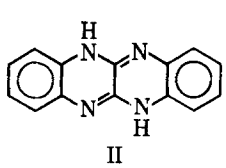
Fluoflavin was first prepared by Hinsberg and Pollak (1), who formulated the structure as 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (I). Since then, there has been considerable speculation as to whether the compound is more accurately represented by the tautomeric 5,11-dihydro structure, II. A spectroscopic study (2) indicated that the 5,12-dihydro structure, I, is the most probable, and it is used for fluoflavin derivatives in this report. Derivatives having substituents in the benzo rings also may have ambiguous structures; no attempt was made to establish their exact structures.

The new compounds prepared are listed in Tables I and II together with some previously described compounds. Synthetic procedures, generalized where possible, are described under *Experimental*. All derivatives were synthesized by reacting appropriately substituted 1,2-phenylenediamines with 2,3-dichloroquinoxalines over sodium carbonate in refluxing dimethylformamide (3) (Scheme I). Acylation was generally accomplished by long heating in a large excess of the anhydride. Alternatively, conventional acylation with the acyl halide in pyridine was possible.

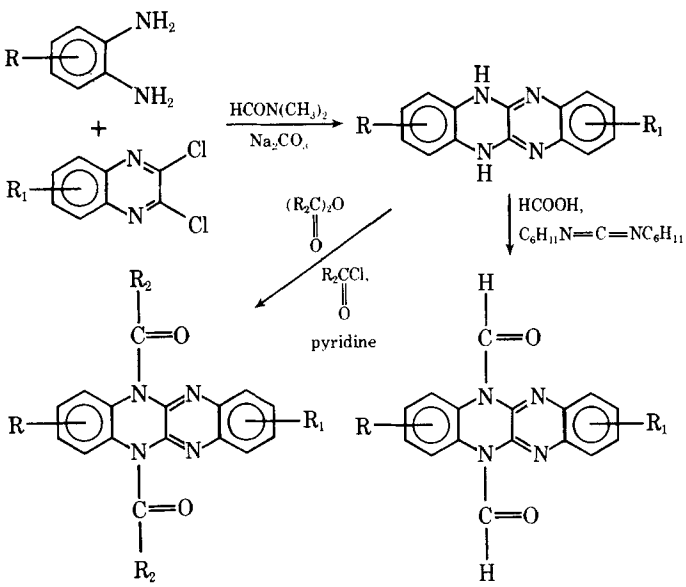
The diformyl derivative could only be prepared with 100% formic acid and *N,N'*-dicyclohexylcarbodiimide. Reduction of the nitro derivative (XXVIII) with hydrogen over palladium-on-carbon gave the amine (XXIX), which was acylated with methyl chloroformate to the carbamate (XXX). Oxidation of I with hydrogen peroxide in trifluoroacetic acid gave quinoxalino[2,3-*b*]quinoxaline 5,11-dioxide (XLIII), previously described by Kuhn and Skrabal (4) as the sole product isolated.



I



II



Scheme I

Biological results (the lowest oral doses demonstrating activity) are shown in Tables I and II. Compounds were tested for anthelmintic activity against *Trichostrongylus* in a standard laboratory animal model assay (5). The most potent compounds in the series, VIII–X, were lower acyl derivatives of the unsubstituted I.

The nonacylated compounds were all extremely insoluble; since I showed erratic but definite activity at 400 mg/kg, the main contribution of acylation was to achieve better absorption and distribution of the intrinsically active ring system. Acylation with groups larger than propionyl diminished activity, as did any of the ring substitutions tried. The aromatic analog (XLII) was inactive, but its bis(*N*-oxide) derivative (XLIII) was surprisingly among the most active compounds in the series. 5,12-Diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (IX) was selected as the most promising and evaluated for anthelmintic efficacy in sheep. At an oral dose of 200 mg/kg, it was effective against *Haemonchus contortus, Ostertagia circumcincta, Trichostrongylus axei, Trichostrongylus colubriformis,* and *Cooperia* sp.

EXPERIMENTAL[1]

Method A: 2-Methoxy-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (XXIII)—A suspension of 20.0 g (0.144 mole) of 4-methoxy-1,2-phenylenediamine, 28.8 g (0.144 mole) of 2,3-dichloroquinoxaline, and 15.3 g (0.144 mole) of sodium carbonate in 100 ml of dimethylformamide was refluxed for 5 hr and then cooled to room temperature. The product was filtered off and crystallized from acetic acid, 23.1 g (60.3%), mp >340°.

[1] Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected.

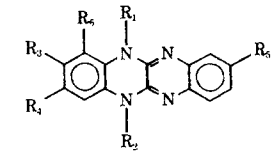


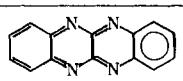
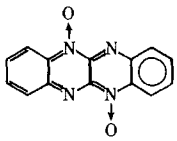
Table I—5,12-Dihydroquinoxalino[2,3-*b*]quinoxalines

Compound	R_1	R_2	R_3	R_4	R_5	R_6	Synthetic Method	Yield, %	Melting Point	Molecular Formula		Analysis, % Calc.	Analysis, % Found	Anthelmintic Activity[a], mg/kg
I	H	H	H	H	H	H	C[b]	—	>350°, >350° (1)	—	—	—	—	400
III	CH_3	H	H	H	H	H	D[c]	—	320°, 317–318° (2)	—	—	—	—	NA
IV	CH_3	CH_3	H	H	H	H	D	—	217°, 218–219° (2)	—	—	—	—	NA
V	C_6H_5	H	H	H	H	H	E[d]	—	323–327°	$C_{20}H_{14}N_4$	N	18.06	17.95	NA
VI	CH_3	$COCH_3$	H	H	H	H	D	—	190–191°, 190–191° (2)	—	—	—	—	NA
VII	C_6H_5	$COCH_3$	H	H	H	H	B	58	215–217°	$C_{22}H_{16}N_4O$	C H N	74.98 4.58 15.90	74.59 4.73 15.77	NA
VIII	CHO	CHO	H	H	H	H	—	37.9	225°	$C_{16}H_{10}N_4O_2$	C H N	66.21 3.45 19.31	66.15 3.27 19.14	100
IX	$COCH_3$	$COCH_3$	H	H	H	H	B	70	203–204°	$C_{18}H_{14}N_4O_2$	C H N	67.91 4.43 17.60	67.75 4.74 17.73	100
X	COC_2H_5	COC_2H_5	H	H	H	H	B	86	155°	$C_{20}H_{18}N_4O_2$	C H N	69.35 5.24 16.18	69.00 5.36 15.82	100
XI	CO-*n*-C_3H_7	CO-*n*-C_3H_7	H	H	H	H	B	55	144–145°	$C_{22}H_{22}N_4O_2$	C H N	70.57 5.92 14.96	70.30 6.04 15.08	400
XII	CO-iso-C_3H_7	CO-iso-C_3H_7	H	H	H	H	B	24	168–170°	$C_{22}H_{22}N_4O_2$	C H N	70.57 5.92 14.96	70.92 5.83 14.72	NA
XIII	COC_6H_5	COC_6H_5	H	H	H	H	—	12	219–220°	$C_{28}H_{18}N_4O_2$	C H N	76.01 4.10 12.66	75.81 4.36 12.57	400
XIV	$COOCH_3$	$COOCH_3$	H	H	H	H	B	20	151–152°	$C_{18}H_{14}N_4O_4$	C H N	61.71 4.03 16.00	61.44 4.10 15.88	200
XV	H	H	CH_3	H	H	H	A	56	350–360°	$C_{15}H_{12}N_4$	C H N	72.56 4.89 22.57	72.26 4.89 22.70	NA
XVI	$COCH_3$	$COCH_3$	CH_3	H	H	H	B	89	140–142°	$C_{19}H_{16}N_4O_2$	C H N	68.66 4.85 16.86	69.03 5.20 16.79	400
XVII	H	H	C_2H_5	H	H	H	A	30	340–345°	$C_{16}H_{14}N_4$	C H N	73.26 5.38 21.36	73.19 5.38 21.31	NA
XVIII	$COCH_3$	$COCH_3$	C_2H_5	H	H	H	B	66	160°	$C_{20}H_{18}N_4O_2$	C H N	69.35 5.24 16.18	69.53 5.39 16.22	NA
XIX	H	H	CF_3	H	H	H	A	76	300–307°	$C_{15}H_9F_3N_4$	C H N	59.61 3.00 18.57	59.47 3.18 18.53	NA
XX	$COCH_3$	$COCH_3$	CF_3	H	H	H	B	38	132–134°	$C_{19}H_{13}F_3N_4O_2$	C H N	59.23 3.14 14.74	59.64 3.17 14.79	NA

XXI	H	H	Cl	H	H	H	E	—	>350°, >350°(6)	—		—	—	NA
XXII	$COCH_3$	$COCH_3$	Cl	H	H	H	B	70	149–150°	$C_{18}H_{13}ClN_4O_2$	C	61.30	61.08	200
											H	3.72	4.03	
											N	15.88	15.64	
XXIII	H	H	OCH_3	H	H	H	A	60.3	>340°	$C_{15}H_{12}N_4O \cdot H_2O$	C	63.82	63.68	NA
											H	4.96	4.66	
											N	19.86	19.69	
XXIV	$COCH_3$	$COCH_3$	OCH_3	H	H	H	B	59	197–198°	$C_{19}H_{16}N_4O_3$	C	65.51	65.71	400
											H	4.63	4.73	
											N	16.08	16.01	
XXV	H	H	OC_2H_5	H	H	H	A	55	>350°	$C_{16}H_{14}N_4O$	C	69.05	69.21	NA
											H	5.07	4.89	
											N	20.13	20.01	
XXVI	$COCH_3$	$COCH_3$	OC_2H_5	H	H	H	B	85	148–151°	$C_{20}H_{18}N_4O_3$	C	66.28	66.14	NA
											H	5.01	5.15	
											N	15.46	15.56	
XXVII	H	H	NO_2	H	H	H	A	16	>350°	$C_{14}H_9N_5O_2$	C	60.20	59.83	NA
											H	3.25	3.31	
											N	25.08	25.33	
XXVIII	$COCH_3$	$COCH_3$	NO_2	H	H	H	B	57	139–141°	$C_{18}H_{13}N_5O_4$	C	59.50	59.43	NA
											H	3.61	3.94	
											N	19.28	19.49	
XXIX	$COCH_3$	$COCH_3$	NH_2	H	H	H	—	33	192–196°	$C_{18}H_{15}N_5O_2$	C	64.85	64.69	NA
											H	4.54	4.48	
											N	21.01	21.15	
XXX	$COCH_3$	$COCH_3$	$NHCOCH_3$	H	H	H	—	14	229–231°	$C_{20}H_{17}N_5O_4$	C	61.37	61.53	NA
											H	4.38	4.54	
											N	17.90	17.64	
XXXI	H	H	H	H	H	NO_2	A	77	>350°	$C_{14}H_9N_5O_2$	C	60.21	60.40	NA
											H	3.25	3.31	
											N	25.08	25.26	
XXXII	$COCH_3$	$COCH_3$	H	H	H	NO_2	B	30	165–168°	$C_{18}H_{13}N_5O_4$	C	59.30	59.35	NA
											H	3.58	3.20	
											N	19.28	19.89	
XXXIII	H	H	Cl	Cl	H	H	A	11	>350°	$C_{14}H_8Cl_2N_4$	C	55.46	55.15	NA
											H	2.66	2.60	
											N	18.48	18.20	
XXXIV	$COCH_3$	$COCH_3$	Cl	Cl	H	H	B	51	220–222°	$C_{18}H_{12}Cl_2N_4O_2$	C	55.83	55.47	NA
											H	3.12	3.15	
											Cl	18.31	18.66	
											N	14.47	14.29	
XXXV	H	H	CH_3	CH_3	H	H	A	68	350–355°	$C_{16}H_{14}N_4$	C	73.26	72.91	NA
											H	5.38	5.40	
											N	21.36	21.51	
XXXVI	$COCH_3$	$COCH_3$	CH_3	CH_3	H	H	B	89	199–203°	$C_{20}H_{18}N_4O_2$	C	69.35	69.43	NA
											H	5.24	5.25	
											N	16.18	16.24	
XXXVII	H	H	Cl	H	Cl	H	E	—	365°, >350° (6)	$C_{14}H_{18}Cl_2N_4$	C	55.46	55.26	NA
											H	2.66	2.60	
											Cl	23.39	23.39	
											N	18.48	18.61	
XXXVIII	$COCH_3$	$COCH_3$	Cl	H	Cl	H	B	55	150–153°	$C_{18}H_{12}Cl_2N_4O_2$	C	55.83	55.87	NA
											H	3.12	3.48	
											N	14.47	14.20	
XXXIX	H	H	NO_2	H	NO_2	H	A	71	>350°	$C_{14}H_8N_6O_4$	C	51.86	52.05	NA
											H	2.49	2.25	
											N	25.92	25.62	
XL	H	H	Cl	H	OCH_3	H	A	49	318–325°	$C_{15}H_{11}ClN_4O$	C	60.31	60.70	NA
											H	3.70	3.62	
											N	18.75	18.72	
XLI	$COCH_3$	$COCH_3$	Cl	H	OCH_3	H	B	95	165–170°	$C_{19}H_{15}ClN_4O_3$	C	59.61	59.93	400
											H	3.95	3.86	
											N	14.63	14.48	

[a] NA = not active at 400 mg/kg. [b] See Ref. 1. [c] See Ref. 2. [d] See Ref. 6. The melting point of V*a* was not given.

Table II—Quinoxalino[2,3-*b*]quinoxalines

Compound	Structure	Synthetic Method	Melting Point	Anthelmintic Activity[a], mg/kg
XLII		C[b]	>350°, >350° (1)	NA
XLIII[c]		F[d]	>350°	100

[a] NA = not active at 400 mg/kg. [b] See Ref. 1. [c] *Anal.*—Calc. for $C_{18}H_{18}N_4O_2$: C, 63.63; H, 3.05; N, 21.20. Found: C, 63.46; H, 3.00; N, 21.09. [d] See Ref. 4. The melting point was not given.

Method B: 5,12-Diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (IX)—A suspension of 1.0 g (0.004 mole) of I in 50 ml of acetic anhydride was refluxed for 20 hr until a clear solution was obtained. Excess acetic anhydride was evaporated, and the residue was crystallized from ethyl acetate, 0.95 g (70%), mp 203–204°.

5,12 - Diformyl -5,12- dihydroquinoxalino[2,3 - *b*]quinoxaline (VIII)—A mixture of 2.3 g (0.01 mole) of I, 0.94 g (0.02 mole) of 98–100% formic acid, and 4.12 g (0.020 mole) of *N,N'*-dicyclohexylcarbodiimide in 100 ml of dry dioxane was heated at 100° for 22 hr and then cooled. The dicyclohexylurea was filtered off, and the filtrate was evaporated. The residue was dissolved in benzene and filtered, and petroleum ether was added to the filtrate to crystallize the product, 1.1 g (37.9%), mp 225°.

5,12 - Dibenzoyl -5,12- dihydroquinoxalino[2,3 - *b*]quinoxaline (XIII)—A mixture of 1.0 g (0.004 mole) of I and 2 ml of benzoyl chloride in 10 ml of pyridine was allowed to stand at room temperature for 3 days. Addition of petroleum ether precipitated the product, which was crystallized from ethyl acetate, 0.23 g (12%), mp 219–220°.

8-Amino-5,12-diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (XXIX)—A suspension of 1.09 g (0.0030 mole) of 5,12-diacetyl-8-nitro-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (XXVIII) and 0.11 g of palladium-on-carbon in 50 ml of dimethoxyethane was reduced with hydrogen at 25 psi. After filtration and evaporation of the solvent, the residue was crystallized from a mixture of ethyl acetate and ether, 300 mg (33%), mp 192–196°.

Methyl *N*-(5,12-Diacetyl-5,12-dihydroquinoxalino[2,3-*b*]-quinoxalin-8-yl)carbamate (XXX)—A solution of 0.74 g (0.0022 mole) of XXIX in 12.5 ml of pyridine was acylated by treatment with 2 g of methyl chloroformate at room temperature for 90 hr. The product was precipitated by addition of water and crystallized from methylene chloride, 0.125 g (14%), mp 229–231°.

REFERENCES

(1) O. Hinsberg and J. Pollak, *Chem. Ber.*, **29**, 784 (1896).
(2) G. M. Badger and P. J. Nelson, *Aust. J. Chem.*, **16**, 445 (1963).
(3) G. Riedel and W. Deutschel, British pat. 971,048 (1964); through *Chem. Abstr.*, **62**, 1774 (1965).
(4) R. Kuhn and P. Skrabal, *Chem. Ber.*, **101**, 3913 (1968).
(5) J. E. Lynch and B. Nelson, *J. Parasitol.*, **45**, 659 (1969).
(6) F. Kehrmann and C. Bener, *Helv. Chim. Acta*, **8**, 20 (1925).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 12, 1976, from the *Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, NJ 07065.*

Accepted for publication December 1, 1976.

The authors thank Mr. R. N. Boos and associates for microanalyses.

[x] To whom inquiries should be directed.

Molecular Connectivity and Steric Parameters

WALLACE J. MURRAY

Abstract □ The possible relationship between molecular connectivity indexes, $^m\chi$, and E_s, a thermodynamically derived parameter used to estimate steric effects in organic reactions and sometimes used in biological structure–activity relationships, was investigated. The extended χ terms, $^2\chi$, $^3\chi$, and $^4\chi$, were correlated significantly to E_s (r = 0.961). Aralkyl esters deviated from the correlations, possibly due to intramolecular interactions.

Keyphrases □ Molecular connectivity indexes—relationship to E_s parameter used to estimate steric effects in organic reactions □ Steric parameters—E_s used to estimate steric effects in organic reactions correlated to molecular connectivity indexes □ Topological indexes—molecular connectivity indexes, relationship to E_s parameter used to estimate steric effects in organic reactions

The way atoms are connected to one another in a compound must ultimately influence the compound's physical and chemical properties. Changes in chemical structure most often lead to changes in biological activity. In correlating chemical structure and biological activity, statistical regression analyses, in which various physicochemical properties are used as surrogates for chemical structure, are used. These analyses have been called quantitative structure–activity relationships. The use of this term is unfortunate, since the properties of a molecule are not a description of the structure but rather are consequences of the structure. One is not relating structure to property but property to property. Norrington *et al.* (1) suggested the use of the term property–activity relationships to differentiate these methods from structure-based ones such as methods employing quantum mechanical calculations or the Free and Wilson approach (2).