Quaternary Indolylpyridinium Salts. Oral Hypoglycemic Agents

WILLIAM J. FANSHAWE, VICTOR J. BAUER, S. R. SAFIR,

Organic Chemical Research Section,

D. A. BLICKENS, AND S. J. RIGGI

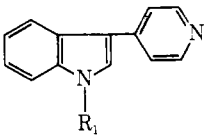
Department of Metabolic Chemotherapy, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received April 30, 1970

Quaternary pyrazolylpyridinium salts have been reported to be oral hypoglycemic agents in laboratory animals.[1a] Further studies demonstrated that hypoglycemic activity was retained when isoxazolyl,[1b] 1,2,4-oxadiazolyl,[1c] thiazolyl,[1d] and oxazolyl[1e] rings were substituted for the pyrazolyl moiety. Other quaternary pyridinium salts substituted with 1,2,4-triazolyl, 1,3,4-thiadiazolyl, tetrazolyl, and imidazolyl groups did not induce a hypoglycemic response in normal mice.[2] The pharmacological activity of one of the more interesting of these compounds, 1-methyl-4-(3-methyl-5-isoxazolyl)pyridinium chloride (**1**), has been described.[3a-c] To continue delineation of the structure–activity relationships of this series, we next considered benzazolyl groups as the substituent on the pyridinium ring, and as a first objective chose to examine the indolylpyridinium salts **2** and **3**.

The synthesis of **2**, as well as the position isomers **4** and **5**, was achieved by the Fischer indole route as described by Sugasawa, *et al.*[4] The reaction of 3-(4-pyridyl)indole[5] (**6**) with MeCl provided the desired pyridinium salt **3**. Oral administration of **2**, **4**, and **5** to mice did not elicit a hypoglycemic response, but **3** (Table II) produced a marked reduction in blood glucose levels of normal mice.

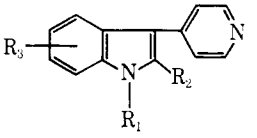
The synthesis of analogs of **3** was then undertaken to ascertain the effect of various substituents on the scope of the hypoglycemic activity. Quaternization of **6** with alkyl halides provided quaternary salts **7–11**, which are described in Table II. Reaction of the Na salt of **6** with alkyl halides afforded a group of 1-alkylated-3-(4-pyridyl)indoles (**12–14**), which were then converted into the pyridinium salts **15–19** (Table II).



12, $R_1 = CH_3$
13, $R_1 = CH_2{=}CHCH_2$
14, $R_1 = CH_2CH_2OC_2H_5$

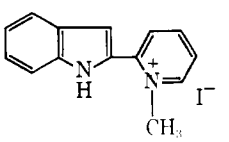
1-Methyl-2-(3-indolyl)pyridinium iodide (**20**), which had been prepared[6] from the reaction product of the indolyl Grignard reagent and 2-chloropyridine, was found inactive as a hypolgycemic agent. We utilized this general synthetic method to prepare the 3-(4-pyridyl)indoles **21–24**, which are described in Table I. Subsequent quaternization provided the pyridinium salts **25–28** described in Table II.

TABLE I
3-(4-PYRIDYL)INDOLES



Compd	R_1	R_2	R_3	Mp or bp, °C (mm)	Recrystn solvent	Formula[a]
12	CH_3	H	H	103–106	Hexane	$C_{14}H_{12}N_2$
13	$CH_2CH{=}CH_2$	H	H	82–84	Hexane	$C_{16}H_{14}N_2$
14	$CH_2CH_2OC_2H_5$	H	H	193–197 (0.08)		$C_{17}H_{18}N_2O$[b]
21	H	CH_3	H	185–187	CH_3CN	$C_{14}H_{12}N_2$
22	H	H	5-CH_3	220–223	$CHCl_3$	$C_{14}H_{12}N_2$
23	H	H	7-CH_3	223–226 dec	Me_2CO	$C_{14}H_{12}N_2$
24	H	H	5-F	198–201	$CHCl_3$	$C_{13}H_9FN_2$

[a] Compounds were analyzed for C, H, N, halogen. [b] A satisfactory elemental analysis was not obtained; characterized as the MeI salt **19**.



20

(1) (a) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. R. Boshart, *J. Med. Chem.*, **11**, 981 (1968); (b) V. J. Bauer, W. J. Fanshawe, H. P. Dalalian, and S. R. Safir, *ibid.*, **11**, 984 (1968); (c) W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 381 (1969); (d) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 891 (1969); (e) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 943 (1969).

(2) V. J. Bauer, G. E. Wiegand, W. J. Fanshawe, and S. R. Safir, *ibid.*, **12**, 944 (1969).

(3) (a) S. J. Riggi, D. A. Blickens, and C. R. Boshart, *Diabetes*, **17**, 646 (1968); (b) D. A. Blickens and S. J. Riggi, *Toxicol. Appl. Pharmacol.*, **14**, 393 (1969); (c) D. A. Blickens and S. J. Riggi, *Diabetes*, **18**, 612 (1969).

(4) S. Sugasawa, M. Terashima, and Y. Kanaoka, *Chem. Pharm. Bull.*, **4**, 16 (1956).

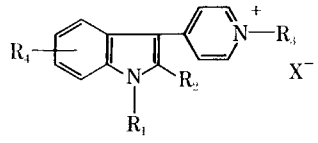
(5) D. Beck and K. Schenker, *Helv. Chim. Acta*, **51**, 260 (1968).

(6) J. C. Powers, *J. Org. Chem.*, **30**, 2534 (1965).

(7) Technical assistance of Mr. E. Locke, Mr. H. Siegriest, and Miss L. Will is greatly appreciated.

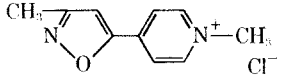
TABLE II

4-(3-INDOYL)PYRIDINIUM SALTS

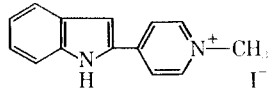


Compd	R_1	R_2	R_3	R_4	X^-	Mp, °C dec	Recrystn solvent	Formula[a]	% decrease in blood glucose[b] 0.5 mmole/kg	% decrease in blood glucose[b] 1.5 mmoles/kg	% decrease in blood glucose[b] Control
3	H	H	CH_3	H	Cl	251–255	*i*-PrOH hexane	$C_{14}H_{13}ClN_2$	37 ± 6[c]	50 ± 7[d]	10 ± 2
7	H	H	C_2H_5	H	I	251–253	EtOH	$C_{15}H_{15}IN_2$	36 ± 4	55 ± 12	−26 ± 10
8	H	H	$CH_2CH{=}CH_2$	H	Cl	216–219	EtOH hexane	$C_{16}H_{15}ClN_2$	33 ± 2	69 ± 15	9 ± 5
9	H	H	$CH_2C(CH_3){=}CH_2$	H	Cl	246–249	EtOH hexane	$C_{17}H_{17}ClN_2 \cdot 0.25H_2O$	30 ± 6	91 ± 1[e]	3 ± 2
10	H	H	CH_2– 	H	Br	195–197	CH_3CN	$C_{17}H_{17}BrN_2 \cdot 0.5H_2O$	24 ± 4	49 ± 12	−5 ± 6
11	H	H	$CH_2CH_2OC_2H_5$	H	Cl	165–169	*i*-PrOH	$C_{17}H_{19}ClN_2O \cdot 0.25H_2O$	21 ± 8	44 ± 13	6 ± 6
15	CH_3	H	CH_3	H	Cl	274–278	*i*-PrOH	$C_{15}H_{15}ClN_2$	9 ± 10	32 ± 10	−26 ± 10
16	CH_3	H	C_2H_5	H	I	229–231	MeOH	$C_{16}H_{17}IN_2$	24 ± 3	51 ± 19	6 ± 6
17	CH_3	H	$CH_2CH{=}CH_2$	H	Cl	235–238	*i*-PrOH hexane	$C_{17}H_{17}ClN_2 \cdot 0.25H_2O$	50 ± 12	85 ± 6[e]	3 ± 2
18	$CH_2CH{=}CH_2$	H	CH_3	H	I	209–212	EtOH	$C_{17}H_{17}IN_2$	11 ± 6	79 ± 12	5 ± 4
19	$CH_2CH_2OC_2H_5$	H	CH_3	H	I	120–122	EtOH	$C_{18}H_{21}IN_2O$	53 ± 13	85 ± 4	−1 ± 3
25	H	CH_3	CH_3	H	I	324–328	MeOH	$C_{15}H_{15}IN_2$	23 ± 4	35 ± 12	6 ± 3
26	H	H	CH_3	5-CH_3	I	260–263	MeOH	$C_{15}H_{15}IN_2 \cdot H_2O$	28 ± 7	42 ± 9	5 ± 9
27	H	H	CH_3	7-CH_3	I	249–251	EtOH	$C_{15}H_{15}IN_2$	38 ± 21[f]	63 ± 20	9 ± 5
28	H	H	CH_3	5-F	I	314–316	MeOH	$C_{14}H_{12}FIN_2$	37 ± 2	38 ± 3	6 ± 6

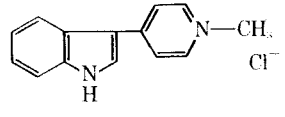
[a] Compounds were analyzed for C, H, N, halogen. [b] Values are means ± standard errors of 5 to 6 mice. Maximal reductions in blood glucose concentrations 3 to 5 hr after dosing are expressed as per cent decrease from predose values. Control animals were dosed orally with vehicle. An increase in blood glucose is indicated by a negative sign (−). Average predose blood glucose concentration for 51 control mice was 128 ± 3 mg %. [c] 0.2 mmole/kg. [d] 0.4 mmole/kg. [e] Determined on 3 mice. [f] Determined on 4 mice.



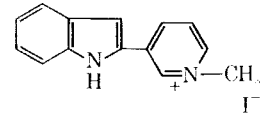
1



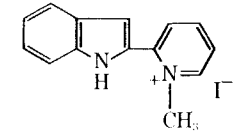
2



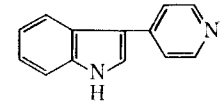
3



4



5



6

bulbar plexuses 3 to 5 hr after dosing were assayed[3b] for blood glucose using the method of Hoffman[8] as adapted for the Technicon AutoAnalyzer. All the indolylpyridinium salts in Table II produced a hypoglycemic effect. Blood glucose was maximally reduced 32–91% by these compounds.

Experimental Section[9]

1-Alkyl-3-(4-pyridyl)indoles.—To a stirred mixture of 1.25 g (0.029 mole) of NaH (55% dispersion in mineral oil) and 4.85 g (0.025 mole) of 3-(4-pyridyl)indole (**6**) in 20 ml of DMF was added a solution of 0.025 mole of the appropriate alkyl halide in 10 ml of DMF. This mixture was stirred at room temperature for 16 hr, and poured onto cracked ice. The mixture was acidified with dil HCl and washed with Et_2O. The aq solution was made basic with dil NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated under reduced pressure to the crude product which was purified by distillation and/or recrystallization. Compounds **12–14** were obtained by this procedure and are listed in Table I.

3-(4-Pyridyl)indoles.—To 0.02 mole of commercially available indole was added slowly 7.3 ml (0.022 mole) of 3 *M* ethereal MeMgBr. After gas evolution had subsided, a solution containing 0.03 mole of 4-chloropyridine in 20 ml of Et_2O was added to the mixture. This mixture was heated in a glass lined bomb at 160° for 20 hr. The reaction mixture was poured into a solution of 3 g of NH_4Cl in 150 ml of H_2O. The Et_2O phase was separated and the aq mixture was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to the crude products. Purification was accomplished by absorption chromatography (Al_2O_3) and/or recrystallization. Compounds **21–24** were obtained by this procedure, and are listed in Table I.

4-(3-Indolyl)pyridinium Salts.—The quaternary salts listed in Table II were prepared from the corresponding 3-(4-pyridyl)-indole bases listed in Table I by heating with an alkyl halide in a refluxing alcoholic solvent[2] or in a glass-lined bomb.[1c]

(8) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(9) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

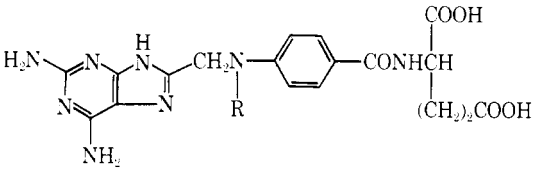
Folic Acid Analogs. II. *p*-{[(2,6-Diamino-8-purinyl)methyl]amino}-benzoyl-L-glutamic Acid and Related Compounds[1]

LOUIS T. WEINSTOCK, BERNARD F. GRABOWSKI, AND C. C. CHENG

Midwest Research Institute, Kansas City, Missouri 64110, and University of Missouri–Kansas City, Kansas City, Missouri 64110

Received February 6, 1970

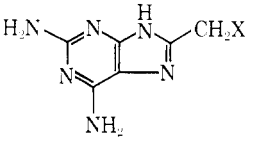
The biogenetic relationship between purines and pteridines has been described.[2] Since 2,6-diaminopurine, which inhibits the growth of leukemia,[3] is bound more tightly to dihydrofolic reductase than most pteridines,[4] and since the 2,6-diamniopurine analog of pteroic acid is more inhibitory to the growth of some bacteria than the parent 2,6-diaminopurine,[5] synthesis of the 2,6-diaminopurine congeners of aminopterin and methotrexate, Ia and Ib, was investigated.



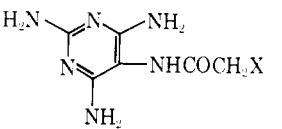
Ia, R = H
b, R = CH_3

A search of the literature revealed that, of the purine analogs synthesized in this group, the caffeine and the theophylline analogs of folic acid and pteroic acids have been reported.[3] These compounds were found to be without activity against the S-810, Ca-755, and L-1210 tumor systems.[6] The guanine[7] and 2,6-diaminopurine[5,8] analogs of pteroic acid as well as the 2,6-diaminopurine analog of homopteroic acid[8] were also prepared. The 2,6-diaminopurine derivatives were reported to be as inhibitory against dihydrofolic reductase as the parent 2,6-diaminopurine.[8]

Theoretically, two possible routes can be applied for the synthesis of compounds of this type. One utilizes the condensation of a 2,6-diamino-8-halomethylpurine with the appropriate *p*-aminobenzoyl compound; the other involves the reaction of 2,4,6-triamino-5-haloacetamidopyrimidine with the respective *p*-aminobenzoyl derivative with subsequent cyclization to the corresponding purine. Both routes were fruitful. Baker and Santi[8] prepared 2,6-diamino-8-hydroxymethylpurine (IIa) by the treatment of 2,4,5,6-tetraaminopyrimidine with glycolic acid. Attempted bromination of IIa by these investigators was not successful. This was also found to be true in our hands. Nevertheless, a procedure reported for the chlorination of 2-methyl-4-amino-5-hydroxymethylpyrimidine with thionyl chloride in dimethylformamide[9] was adopted for the chlorination of IIa. The resulting product IIb was then caused to react with appropriate *p*-aminobenzoyl derivatives to yield Ia, Ib, and related compounds.



IIa, X = OH
b, X = Cl
c, X = *p*-NHC_6H_4COOH



IIIa, X = Cl
b, X = *p*-NHC_6H_4COOH

Treatment of 2,4,5,6-tetraaminopyrimidine with chloroacetic acid followed by condensation of the resulting 5-chloroacetamidopyrimidine (IIIa) with *p*-aminobenzoic acid yielded IIIb. Cyclization of IIIb gave the diaminopurine analog of pteroic acid IIc.

(1) (a) This investigation was supported by Contract No. PH-43-65-64 with Chemotherapy, National Cancer Institute, of the National Institutes of Health, Public Health Service; (b) presented in part before the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969 (Medi 66).

(2) (a) A. Albert, *Biochem. J.*, **65**, 124 (1957); (b) E. Vieira and E. Shaw, *J. Biol. Chem.*, **236**, 2507 (1961); (c) F. Weygand, H. Simon, G. Dahms, M. Waldschmidt, H. J. Schliep, and H. Wacker, *Angew. Chem.*, **73**, 402 (1961); (d) W. S. McNutt, *J. Biol. Chem.*, **238**, 1116 (1963); (e) W. S. McNutt and S. P. Damle, *ibid.*, **239**, 4272 (1964); (f) A. W. Burg and G. M. Brown, *Biochim. Biophys. Acta*, **117**, 275 (1966); *J. Biol. Chem.*, **243**, 2349 (1968).

(3) J. H. Burchenal, A. Bendich, G. B. Brown, G. B. Elion, G. H. Hitchings, C. P. Rhodes, and C. C. Stock, *Cancer*, **2**, 119 (1949).

(4) S. F. Zakrzewski, *J. Biol. Chem.*, **238**, 1485 (1963).

(5) G. B. Elion, G. H. Hitchings, and H. VanderWerff, *ibid.*, **192**, 505 (1951).

(6) H. Zimmer and R. Atchley, *Arzneim. Forsch.*, **16**, 541 (1966).

(7) W. T. Caldwell and C.-S. Cheng, *J. Amer. Chem. Soc.*, **77**, 6631 (1955).

(8) B. R. Baker and D. V. Santi, *J. Heterocycl. Chem.*, **4**, 216 (1967).

(9) L. Suranyi and H. Wilk, German Patent, 1,150,987 (1963); *Chem. Abstr.*, **60**, 2971*b* (1964).