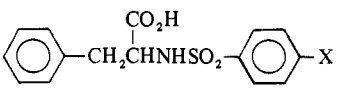
Table I. Physical Properties of 

No.	X	Configuration	% yield	Mp, °C	Recrystn solvent	$[\alpha]^{22}D$, deg	Formula	Analyses[a]
1	H	DL	58	115-117[b]	C_6H_6		$C_{15}H_{15}NO_4S$	C, H, N
2	H	D	58	130-132[c]	C_6H_6	+6.7 ($CHCl_3$)[c]	$C_{15}H_{15}NO_4S$	
3	H	L	68	131-133[d]	C_6H_6	-7.2 ($CHCl_3$)[d]	$C_{15}H_{15}NO_4S$	
4	F	DL	60	107-109	C_6H_6		$C_{15}H_{14}FNO_4S$	C, H, N, F
5	Cl	DL	77	138-140	EtOH-H_2O		$C_{15}H_{14}ClNO_4S$	C, H, N, Cl
6	Br	DL	64	165-166	EtOH-H_2O		$C_{15}H_{14}BrNO_4S$	C, H, N
7	Br	D	50	136-138	EtOH-H_2O	+18.3 (EtOH)	$C_{15}H_{14}BrNO_4S$	C, H, N
8	Br	L	60	137-139	EtOH-H_2O	-18.9 (EtOH)	$C_{15}H_{14}BrNO_4S$	C, H, N, Br[e]
9	OCH_3	DL	55	149-151	EtOH-H_2O		$C_{16}H_{17}NO_5S$	C, H, N
10	$NHCOCH_3$	DL	45	224-227[f]	EtOH-H_2O		$C_{17}H_{18}N_2O_5S$	

[a]Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [b]Lit.[12] mp 127-128°. [c]Lit.[13] mp 133°, $[\alpha]^{25}D$ +6.7° ($CHCl_3$). [d]Lit.[13] mp 133°, $[\alpha]^{25}D$ -7.0° ($CHCl_3$). [e]C: calcd, 46.89; found: 47.32; Br: calcd, 20.79; found: 21.29. [f]Lit.[14] mp 218-219°.

Table II

No.	% inhibition of heat-induced hemolysis (n)[a] Concn, M 10^{-3}	10^{-4}	10^{-5}	% inhibition of edema (n)[a] Dose, mg/kg 60	120	LD_{50}, mg/kg
1	34 (12)	31 (9)	18 (9)	18 (32)	19 (32)	820
2	35 (12)	29 (9)	27 (9)	32 (16)	35 (16)	850
3	17 (9)	0 (9)	0 (9)	0 (16)	0 (16)	
4	0 (9)	0 (9)	0 (9)	50 (16)	19 (16)	
5	65 (9)	0 (9)	0 (9)	37 (32)	31 (32)	
6	80 (15)	32 (15)	5 (9)	43 (32)	74 (32)	385
7	79 (18)	23 (18)	0 (9)	26 (16)	32 (16)	350
8	67 (9)	11 (9)	11 (9)	31 (16)	60 (16)	
9	29 (9)	48 (9)	0 (9)	10 (16)	35 (16)	
10	24 (9)	26 (9)	27 (9)	34 (16)	28 (16)	
Phenyl-butazone	75 (15)	50 (15)	11 (15)	34 (32)	52 (32)	336[b]

[a]n = No. of determinations per concn or dose level. [b]Ref 15.

to a pH of 2-3 and vigorously stirred. The resulting solid was collected, dried, and recrystallized from the appropriate solvent system.

Acknowledgments. The authors are indebted to Dr. J. H. Brown, Department of Pharmacology, L.S.U. Medical School, for valuable assistance and advice regarding the EMS assay.

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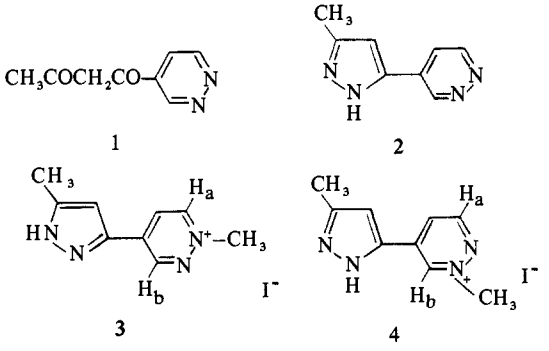
Quaternary 4- (and 5-) Azolylpyridazinium Salts. A New Class of Oral Hypoglycemic Agents

Gretchen E. Wiegand,* Victor J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965. *Received April 28, 1972*

An extensive series of quaternary azolylpyridinium salts including pyrazolyl,[1] isoxazolyl,[2-5] 1,2,4-oxadiazolyl,[6] thiazolyl,[7] oxazolyl,[8] thienyl, furyl, and pyrrolyl[9] derivatives has been found to display oral hypoglycemic activity in laboratory animals. We have also described[10] a number of azolylpyridinium salts which do not induce hypoglycemia. In order to delineate further the effect of structural changes on hypoglycemic activity, we have synthesized a series of quaternary salts in which the pyridinium group is replaced by pyridazinium and the five-membered heterocycle is chosen from those included in the active families listed above.

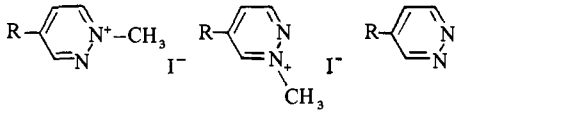
The pyrazolylpyridazinium salts **3** and **4** were prepared in a manner similar to that used for the pyrazolylpyridinium salts.[1] Thus, ethyl pyridazine-4-carboxylate[11] was condensed with Me_2CO to give the β diketone **1**, which was then allowed to react with N_2H_4 to provide the pyrazolylpyridazine **2**. Quaternization of **2** with MeI gave a separable mixture of the 4- and 5-pyrazolylpyridazinium salts



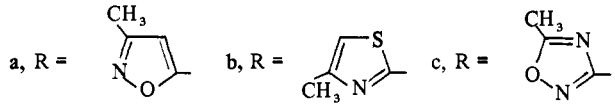
3 and **4**. The structural assignments are based upon pH-dependent uv spectra. In earlier work,[1] it was observed that

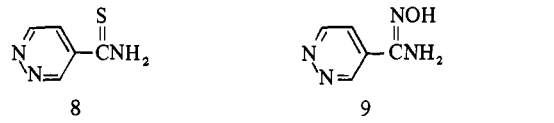
the uv max of 4-pyrazolylpyridinium salts undergo a pronounced bathochromic shift (302-365 mμ) on addition of base; a similar effect is seen for the 1-methyl-4-pyrazolylpyridazinium iodide **3** (322 mμ in MeOH, 375 mμ on addition of NaOH). In contrast, addition of base produces a smaller effect on the uv max of 3-pyrazolylpyridinium salts (262-290 mμ). The uv spectrum of the 1-methyl-5-pyrazolylpyridazinium salt **4** shows a similar absence of sensitivity to the addition of base (305-315 mμ). The nmr spectra of **3** and **4** confirm these structural assignments. The chemical shift of the pyridazinium proton H_a on the C adjacent to the quaternized N in **3** is displaced to lower field (δ 9.53) relative to its position in **4** (δ 9.41). Similarly, the chemical shift of H_b in **4** is displaced to lower field (δ 10.01) relative to its position in **3** (δ 9.75). This phenomenon occurs in all the azolylpyridazinium salts described herein and was used diagnostically to distinguish between isomeric structures.

The isoxazolylpyridazinium salts **5a** and **6a**, thiazolylpyridazinium salts **5b** and **6b**, and oxadiazolylpyridazinium salts **5c** and **6c** were prepared by procedures described for the respective azolylpyridinium salts.[2,6,7] Reaction of the β diketone **1** with NH_2OH gave the isoxazolylpyridazine 7a, which was treated with MeI to give a mixture of the quaternary salts **5a** and **6a**. Reaction of chloroacetone with **8**[12] gave the thiazolylpyridazine **7b**, which was treated with MeI to give a mixture of the salts **5b** and **6b**. Cyclodehydration of **9**[12] with Ac_2O gave the oxadiazolylpyridazine **7c** which was treated with MeI to give a mixture of the salts



5 **6** **7**





8 **9**

5c and **6c**. The mixtures of the salts **5** and **6** were purified by fractional crystallization to give the pure 1-methyl-4-azolylpyridazinium isomers **5a-c**. The 1-methyl-5-azolylpyridazinium salts **6a-c** thus obtained were contaminated with *ca.* 25% of the isomeric **5a-c**.

Hypoglycemic Activity.† Compounds were administered by gavage as suspensions in 0.5% aqueous carboxymethylcellulose to male CF-1-S mice (Carworth Farms, 25-30 g) at doses of 0.5-3.0 mmol/kg. Controls received vehicle only. All animals were allowed food *ad libitum* before dosing, after which they were fasted. Blood glucose concentration was determined before and 2-6 hr after dosing on samples (0.05 ml) from retrobulbar plexuses. The method of Hoffman,[13] as adapted to the Technicon AutoAnalyzer, was used to determine glucose concentration. With the exception of **6a-c**, compounds tested induced a hypoglycemic response (maximal reductions of 23-62% in blood glucose, Table I) similar to that observed in the azolylpyridinium salts.[1-9]

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

Table I. Hypoglycemic Effects of Azolylpyridazinium Salts

	% decrease in blood glucose,[a] mmol/kg				
Compd	0.5	1.0	1.5	3.0	Control
3	21 ± 4	14 ± 5	23 ± 7		4 ± 5
4	7 ± 11		33 ± 11	62 ± 9	19 ± 4
5a	22 ± 4		30 ± 5	16 ± 6	5 ± 9
5b	20 ± 9	14 ± 11	29 ± 6		13 ± 6
5c	34 ± 3	24 ± 4	19 ± 10		13 ± 6
6a	5 ± 6		20 ± 5	9 ± 4	6 ± 2
6b	20 ± 6	21 ± 9	28 ± 8		13 ± 6
6c	9 ± 9		9 ± 2	9 ± 5	6 ± 2

[a] Values are means ± standard errors of five or six mice and represent maximal reduction in blood glucose observed 2-6 hr after dosing expressed as per cent decrease from predose values. Average predose blood glucose concentration of 30 control mice was 142 ± 3 mg/100 ml. Phenformin (DBI, U. S. Vitamin) at 1.6 mmol/kg caused decreases in blood glucose of 18 ± 3, 40 ± 5, and 17 ± 7% (significantly different from control) at 1.5, 3.0, and 5.0 hr after dosing.

Experimental Section‡

1-(4-Pyridazinyl)-1,3-butanedione (1). A mixture of 7.7 g (0.05 mol) of ethyl pyridazine-4-carboxylate,[11] 8.4 g (0.15 mol) of Me_2CO, 3.6 g (0.067 mol) of NaOMe, and 85 ml of C_6H_6 was stirred and heated under reflux for 7 hr, H_2O was added, and the C_6H_6 layer was separated and washed with H_2O. The combined aqueous solution was washed with C_6H_6, acidified to pH 5 with dilute HCl, and extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and concentrated *in vacuo* to a yellow solid, which was recrystallized (H_2O) to give 2.4 g (30%) of pale yellow needles, mp 110-111°. *Anal.* ($C_8H_8N_2O_2$) C, H, N.

4-[3(5)-Methyl-5(3)-pyrazolyl]pyridazine (2). To 2.7 g (0.017 mol) of 1 was added slowly with stirring 10 ml of 100% hydrazine hydrate. The solution was stirred for 0.5 hr at room temperature, heated on a steam bath for 5 min, and stored at 5° for 48 hr. The precipitate was washed with H_2O and recrystallized (MeCN) to give 2.4 g (91%) of white crystalline solid, mp 183-184°. *Anal.* ($C_8H_8N_4$) C, H, N.

1-Methyl-4-[3(5)-methyl-5(3)-pyrazolyl]pyridazinium Iodide (3) and 1-Methyl-5-[3(5)-methyl-5(3)-pyrazolyl]pyridazinium Iodide (4). A solution of 0.65 g (4.0 mmol) of **2** and 1.5 ml of MeI in 30 ml of MeOH was stored at room temperature for 72 hr, concentrated to 20 ml, and cooled to give 0.35 g of yellow solid. Recrystallization from 15 ml of MeOH gave 0.25 g of **3** as a yellow crystalline solid: mp 233-234° dec; uv 322 mμ (ε 18,120); uv (MeOH, 0.1 *N* NaOH) 375 mμ (ε 20,800); nmr δ 4.93 (s, 3, N^+CH_2), 9.53 (d, 1, $J_{H_aH_c}$ = 6.3 cps, H_a), 9.75 (d, 1, $J_{H_bH_c}$ = 2.5 cps, H_b).

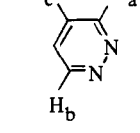
Anal. ($C_9H_{11}IN_4$) C, H, N; I: calcd, 42.0; found, 41.5.

The mother liquors were diluted with Et_2O to precipitate 0.63 g of yellow solid. Four recrystallizations (*i*-PrOH) afforded 35 mg of **4** as yellow crystalline solid: mp 232° dec; uv 305 mμ (ε 8460); uv (MeOH, 0.1 *N* NaOH) 315 mμ (ε 7850); nmr δ 4.71 (s, 3, N^+CH_3), 9.41 (d, 1, $J_{H_aH_c}$ = 5 cps, H_a), 10.01 (d, 1, $J_{H_bH_c}$ = 1 cps, H_b).

Anal. ($C_9H_{11}IN_4$) H, N; C: calcd, 35.8; found, 35.2; I: calcd, 42.0; found, 41.4.

4-(3-Methyl-5-isoxazolyl)pyridazine (7a). To a solution of 1.35 g (8.0 mmol) of 1 and 0.88 g (12.5 mmol) of $NH_2OH \cdot HCl$ in 15 ml of EtOH and 25 ml of H_2O was added 0.88 g (12.5 mmol) of Na_2CO_3. The solution was heated under reflux for 12 hr, diluted with H_2O, and extracted with C_6H_6. The C_6H_6 solution was dried ($MgSO_4$) and concentrated to a solid residue which was recrystal-

‡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 were within ±0.4% of the theoretical values. Uv spectra were recorded with a Cary 11 spectrophotometer and nmr spectra were determined in D_2O (Me_4Si) with a Varian A-60 spectrometer by Mr. W. Fulmor and staff. Only those signals in the nmr spectra which are pertinent to determination of structure and isomeric purity are reported. In all spectra H_a, H_b, and H_c refer to the pyridazine protons.



lized ($CHCl_3$–hexane) to give 1.0 g (80%) of white crystals, mp 154–156°.

Anal. ($C_8H_7N_3O$) C, H, N.

1-Methyl-4-(3-methyl-5-isoxazolyl)pyridazinium Iodide (5a) and 1-Methyl-5-(3-methyl-5-isoxazolyl)pyridazinium Iodide (6a). A solution of 0.5 g (3.1 mmol) of **7a** and 10 ml of MeI in 20 ml of MeOH was stirred at room temperature for 48 hr. The solution was cooled and 0.2 g of deep orange solid was collected. Recrystallization (EtOH) gave **5a** as deep orange crystals: mp 210–211° dec; nmr δ 4.68 (s, 3, N^+CH_3), 7.47 (s, 1, =CH), 9.73 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 9.91 (d, 1, $J_{H_bH_c}$ = 2.5 cps, H_b).

Anal. ($C_9H_{10}IN_3O$) H, I, N; C: calcd, 35.7; found, 35.2.

Addition of Et_2O to the mother liquors gave 0.4 g of orange solid which was recrystallized (MeOH) several times to give 68 mg of orange crystals of **6a**:§ mp 166–167° dec; nmr δ 4.75 (s, 3, N^+CH_3), 7.33 (s, 1, =CH), 9.55 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 9.80 (broad m, 1, H_b).

Anal. ($C_9H_{10}IN_3O$) C, H, I, N.

4-(4-Methyl-2-thiazolyl)pyridazine (7b). A solution of 2.1 g (15.0 mmol) of **8**[12] and 1.9 g (20.0 mmol) of 1-chloro-2-propanone in 100 ml of EtOH was heated under reflux for 6 hr and concentrated *in vacuo*. The solid residue was dissolved in H_2O and the aqueous solution was made alkaline with 1 *N* NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to a brown solid which was recrystallized ($CHCl_3$–hexane) to give 0.4 g (15%) of **7b** as a yellow crystalline solid, mp 131–133°.

Anal. ($C_8H_7N_3S$) C, H, N; S: calcd, 18.1; found, 17.3.

1-Methyl-4-(4-methyl-2-thiazolyl)pyridazinium Iodide (5b) and 1-Methyl-5-(4-methyl-2-thiazolyl)pyridazinium Iodide (6b). A solution of 0.4 g (2.25 mmol) of **7b** and 1 ml of MeI in 15 ml of MeOH was stirred at room temperature for 48 hr, cooled, and filtered to give 0.28 g of red solid. Recrystallization (MeOH) gave 0.22 g of **5b** as deep red crystals: mp 220–222° dec; nmr δ 4.67 (s, 3, N^+CH_3), 7.79 (d, 1, *J* = 1 cps, =CH), 9.63 (d, 1, $J_{H_aH_c}$ = 6.5 cps, H_a), 9.87 (d, 1, $J_{H_bH_c}$ = 2.5 cps, H_b).

Anal. ($C_9H_{10}IN_3S$) C, H, I, N, S.

Addition of Et_2O to the mother liquors gave 0.4 g of orange solid which was recrystallized (twice MeOH, twice Me_2CO) to give 0.172 g of orange crystals of **6b**:§ mp 171° dec; nmr δ 4.75 (s, 3, N^+CH_3), 7.69 (d, 1, *J* = 1 cps, =CH), 9.50 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 9.87 (d, 1, $J_{H_bH_c}$ = 1 cps, H_b).

Anal. ($C_9H_{10}IN_3S$) C, H, I, N, S.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)pyridazine (7c). A solution of 0.7 g (5.0 mmol) of **9**[12] in 5 ml of Ac_2O was heated under reflux for 3 hr, concentrated *in vacuo* to an oil, and diluted with H_2O. The aqueous mixture was adjusted to pH 6 with dilute aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to a tan solid. Sublimation at 100–110° (13 mm) followed by recrystallization (hexane) gave 0.18 g (22%) of white crystals, mp 133–134°.

Anal. ($C_7H_6N_4O$) C, H, N.

1-Methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)pyridazinium Iodide (5c) and 1-Methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)pyridazinium Iodide (6c). A solution of 0.75 g (4.6 mmol) of **7c** and 1.5 ml of MeI in 30 ml of MeOH was stirred at room temperature for 72 hr and concentrated to dryness. The solid residue was taken up in 50 ml of boiling Me_2CO and cooled to give 0.33 g of red solid. Recrystallization (Me_2CO) gave 0.17 g of **5c** as deep red crystals: mp 186–187° dec; nmr δ 4.75 (s, 3, N^+CH_3), 9.83 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 10.0 (d, 1, $J_{H_bH_c}$ = 2 cps, H_b).

Anal. ($C_8H_9IN_4O$) C, H, I, N.

Addition of Et_2O to the mother liquors gave 0.5 g of brown solid which was recrystallized (EtOH–Et_2O) to 0.35 g of very hygroscopic crystals of **6c**:§ mp 126–127° dec; nmr δ 4.83 (s, 3, N^+CH_3), 9.60 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 10.3 (broad m, 1, H_b).

Anal. ($C_8H_9IN_4O \cdot H_2O$) C, N; H: calcd, 3.44; found, 2.84.

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§Analytical samples of **6a**, **6b**, and **6c** were found to contain about 25% of the isomeric **5a**, **5b**, and **5c**, respectively (3:1 relative integrated intensity of the nmr N^+CH_3 and =CH signals).

Synthesis of Some *cis*- and *trans*-2-(Substituted amino)cyclohexyl Phenyl Ketones†

J. C. Letton,‡ E. Maher, and J. E. Gearien*

Department of Medicinal Chemistry, College of Pharmacy, University of Illinois at the Medical Center, Chicago, Illinois.

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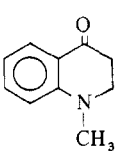
A number of β-amino ketones prepared in this laboratory have been shown to possess analgetic activity. When evaluated by the Hafner tail pinch method,[1] *N*-methyl-2,3-dihydro-4-quinolone (**1**) was found to have an ED_{50} of 250 mg/kg[2] while an open-chain analog, α,α-dimethyl-β-dimethylaminopropiophenone (**2**), was shown to have an ED_{50} of 35 mg/kg.[2] Since the possibility exists that the lower potency of the more rigid 1-methyl-2,3-dihydro-4-quinolone (**1**), might result from its inability to fit the receptor as readily as the open-chain analog (**2**), it was decided to study the biological activity of other β-amino ketones with the hope of ascertaining the stereochemical requirements for the analgetic activity of such compounds.



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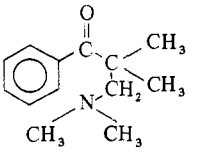

2

Among the compounds selected to study were the cis and trans isomers of a number of 2-(substituted amino)cyclohexyl substituted-phenyl ketones. In these compounds the spatial relationship between the amino and carbonyl groups, which appear to be necessary for analgetic activity,[3] is varied.

The cis isomers were prepd by the catalytic redn of the enamine of substituted 2-benzoylcyclohexanones (**3**) (Table I). The diketones **3** were allowed to react with amines in the presence of TsOH. The amine reacted exclusively with the carbonyl of the cyclohexanone ring to form the enamine **4**.

Infrared spectra of the diketones **3** showed peaks attributed to carbonyl absorption at approximately 1685 and 1710 cm^{-1}. The peak at 1685 cm^{-1} is attributed to the

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‡A portion of this study was abstracted from the dissertation of J. C. Letton submitted to the Graduate College of the University of Illinois at the Medical Center, Chicago, Ill., in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address, Kentucky State College, Frankfort, Ky.