dried and evaporated in vacuo. The crude hydroxy sulfone was dissolved in formic acid (7 mL, 97%) containing *p*-toluenesulfonic acid (0.10 g, 0.58 mmol) and heated at reflux temperature for 3 h. The cooled solution was poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL); the extract was dried, decolorized with charcoal, and evaporated in vacuo. Crystallization of the residue from ethyl acetate–hexane gave the sulfone acetic acid **80** (0.64 g, 86.5%), mp 162–163 °C.

***dl*-2-(10,11-Dihydrodibenzo[*b*,*f*]thiepin-2-yl)propionic Acid (77).** A solution of methyl 10,11-dihydrodibenzo[*b*,*f*]-thiepin-2-acetate (2.2 g, 7.75 mmol) in *tert*-butyl alcohol (15 mL) containing potassium *tert*-butoxide (0.87 g, 7.77 mmol) and diethyl carbonate (1.0 g, 8.5 mmol) was boiled under reflux for 12 h. Methyl iodide (1 mL) was added to the mixture and after a further 4 h at reflux temperature the cooled mixture was poured onto ice and concentrated hydrochloric acid (2 mL). The product was extracted into benzene (2 × 25 mL); the extract was washed with water, dried, and evaporated in vacuo. The residual oil was subjected to column chromatography on silica gel (25 g) using hexane–ethyl acetate (7:1) as the eluent. The oil (1.3 g) obtained on evaporation of the eluate was dissolved in methanol (25 mL) containing aqueous potassium hydroxide (2 mL, 50%) and heated at reflux temperature for 30 min. The cooled mixture was diluted with 1 N hydrochloric acid (100 mL) and extracted with benzene (2 × 25 mL). The extract was washed with water, dried, and evaporated in vacuo. The residual oil was dissolved in benzene (5 mL) containing dicyclohexylamine (1.0 g) whereupon the dicyclohexylammonium salt of 77 (1.2 g, 33%) crystallized. It was collected by filtration, washed with ether, and dried to give a solid, mp 142–143 °C.

## References and Notes


(1) Contribution No. 509 from the Syntex Institute of Organic Chemistry.
(2) (a) R. A. Scherrer and M. W. Whitehouse, Ed., "Antiinflammatory Agents. Chemistry and Pharmacology", Vol. I, Academic Press, New York, N.Y., 1974; (b) M. E. Rosenthale, *Annu. Rep. Med. Chem.*, **9**, 193–202 (1974); S. Wong, *ibid.*, **10**, 172–181 (1975).
(3) S. S. Adams, K. F. McCullough, and J. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, **178**, 115 (1969).
(4) L. Julou and J. C. Guyonnet, *J. Pharmacol.*, **2**, 259 (1971).
(5) A. Roszkowski, W. H. Rooks, A. J. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, **179**, 114 (1971).
(6) S. Wong, J. F. Gardocki, and T. P. Pruss, *J. Pharmacol. Exp. Ther.*, **185**, 127 (1973).
(7) K. Ueno, S. Kubo, H. Tagawa, T. Yoshioka, W. Tsukada, M. Taubokawa, H. Kojima, and A. Kasahara, *J. Med. Chem.*, **19**, 941 (1976).
(8) D. E. Aultz, G. C. Helsley, D. Hoffman, A. R. McFadden, H. B. Lassman, and J. C. Wilker, *J. Med. Chem.*, **20**, 66 (1977).
(9) Several patent filings on tricyclic acetic acids in this general area have also been made: e.g., (a) M. Nakanishi, T. Oe, and H. Maruyama, Japanese Patent 72 00 425 (1972); *Chem. Abstr.*, **76**, 126784w (1972); (b) F. Gadient, German Offen. 2 442 979 (1975); *Chem. Abstr.*, **83**, 43212b (1975).
(10) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, **42**, 3419 (1977), and references cited therein.
(11) G. A. Olah, "Friedel Crafts and Related Reactions", Vol. I, G. A. Olah, Ed., Interscience, London, 1963, pp 246–249.
(12) S. Dev, *J. Indian Chem. Soc.*, **32**, 255 (1955); A. Bhati and N. Kale, *Angew. Chem., Int. Ed. Engl.*, **6**, 1086 (1967).
(13) G. W. Smith, *J. Mol. Spectrosc.*, **12**, 146 (1964).
(14) These compounds were recently disclosed in the patent literature: K. Ueno and R. Dohmori, Japanese Kokai 77 83 591 (1977); *Chem. Abstr.*, **88**, 22872e (1978).
(15) J. P. Dunn, D. M. Green, P. H. Nelson, W. H. Rooks, A. Tomolonis, and K. G. Untch, *J. Med. Chem.*, **20**, 1557 (1977).
(16) D. E. Aultz, A. R. McFadden, and H. B. Lassman, *J. Med. Chem.*, **20**, 456 (1977).
(17) This test was conducted using a single dose of an aqueous solution of the sodium salts of **52** and **53**.
(18) D. V. Krishna Murthy and M. Kruseman-Aretz, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 622 (1978) (abstract no. 2363).
(19) R. Wegschneider and A. Lipschitz, *Monatsh. Chem.*, **21**, 787 (1900).
(20) A. Wohl, *Chem. Ber.*, **43**, 3474 (1910).
(21) R. Meyer and H. Wesche, *Chem. Ber.*, **50**, 444 (1917).
(22) H. Kaufmann and L. Weissel, *Justus Liebigs Ann. Chem.*, **393**, 10 (1912).
(23) M. A. Soderman and T. B. Johnson, *J. Am. Chem. Soc.*, **47**, 1393 (1925).
(24) L. S. Forney, *J. Org. Chem.*, **35**, 1695 (1970).
(25) J. A. Marshall and J. L. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).
(26) See also C. A. Winter, E. A. Riley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(27) R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950).
(28) C. W. Pearson, *Proc. Soc. Exp. Biol. Med.*, **91**, 95 (1956).
(29) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1958).


# 2-Pyrrolidinylideneureas, a New Class of Central Nervous System Agents†

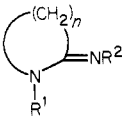

C. R. Rasmussen,* Joseph F. Gardocki, James N. Plampin, Barbara L. Twardzik, Brian E. Reynolds, Albert J. Molinari, Norman Schwartz, Walter W. Bennetts, Beth E. Price, and Janis Marakowski

*Departments of Chemical Research and Pharmacology, McNeil Laboratories, Fort Washington, Pennsylvania 19034.*

*Received April 26, 1978*


A series of *N*-aryl-*N'*-(1-methyl-2-pyrrolidinylidene)ureas was prepared and screened for pharmacological activity. Congeners possessing either phenyl or phenyl substituted with 4-nitro, 3-bromo, 3-chloro, 3-fluoro, and 3-methyl groups were found to demonstrate anxiolytic activity. 2,6-Disubstitution of the phenyl ring with methyl, chloro, and bromo imparted potent muscle-relaxant properties which appear to be centrally mediated. A significant separation of the anxiolytic and muscle-relaxant properties from other CNS activities, e.g., anticonvulsant, sedative, and hypnotic, was achieved.


Semicyclic amidines (lactamimides) 1 show a variety of pharmacologic activities, among which are hypoglycemic,[1a,b] antithrombotic,[1a] antianginal,[1c] and antiarrhythmic.[1c,d]



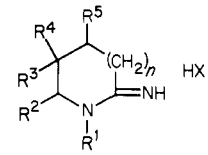

1

It became of interest to explore chemical modifications designed to lower the basicity of these substances and to submit the resulting compounds for broad pharmacological

† This paper is dedicated to the memory of our dear friend and consultant, the late Dr. Edward E. Smissman. Ed's long and fruitful association with these laboratories remains a cherished experience for us all.

0022-2623/78/1821-1044$01.00/0 

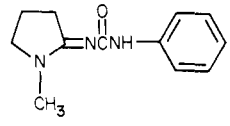
Table I. 2-Iminohexahydroazepines, -piperidine, and -pyrrolidines



| | n | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | formula | recrystn solvent[a] | % yield | mp, °C | analyses |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 0 | Me | H | H | H | H | $C_5H_{10}N_2 \cdot HBF_4$ | 2-P-E | 80-85 | 110.5-112.5 | C, H, N |
| | | | | | | | $C_5H_{10}N_2 \cdot HCl$ | 2-P | 82 | 186-189[b] | N |
| 5 | 0 | Et | H | H | H | H | $C_6H_{12}N_2 \cdot HCl$ | A[c] | 54 | 181-185 | H[d] |
| 6 | 0 | $n$-$C_4H_9$ | H | H | H | H | $C_8H_{16}N_2 \cdot C_6H_{13}NO_3S$[e] | A | 54 | 110-114.5 | C, H, N |
| 7 | 0 | $CH_2Ph$ | H | H | H | H | $C_{11}H_{14}N_2 \cdot HBF_4$ | 2-P-E | 76 | 112-114 | C, H, N |
| | | | | | | | $C_{11}H_{14}N_2 \cdot HCl$ | 2-P | | 203-204[f] | g |
| 8 | 0 | Me | Me | H | H | H | $C_6H_{12}N_2 \cdot HBF_4$ | 2-P-EA | 24 | 100-102 | C, H |
| 9 | 0 | Me | H | Me | Me | H | $C_7H_{14}N_2 \cdot C_6H_{13}NO_3S$[e] | A-E | 42 | (140) 143-145 | C, H, N |
| 10 | 0 | Me | H | Ph | H | H | $C_{11}H_{14}N_2 \cdot C_4H_4O_4$[h] | 2-P-E | 73 | (128-130) 131-133 | C, H, N |
| | | | | | | | $C_{11}H_{14}N_2 \cdot HBF_4$ | | 85[i] | 115-120 | C, H, N |
| 11 | 0 | Me | H | Ph | H | Me | $C_{12}H_{16}N_2 \cdot C_4H_4O_4$[h] | Et-E | 84 | 180-181 | C, H, N |
| | | | | | | | $C_{12}H_{16}N_2 \cdot HBF_4$ | | 86[i,j] | (96) 101-104 | C, H, N |
| 12 | 1 | Me | H | H | H | H | $C_6H_{12}N_2 \cdot HCl$ | 2-P | 33 | 135-140[k] | g |
| 13 | 2 | H | H | H | H | H | $C_6H_{12}N_2 \cdot HCl$ | Et-E | 83 | 161-163[l] | g |
| 14 | 2 | Me | H | H | H | H | $C_7H_{14}N_2 \cdot C_6H_{13}NO_3S$[e] | Et-E | 50 | 143-145 | C, H, N |

[a] For abbreviation legend, see footnote *a* in Table II. [b] Lit.[2] mp 186-188 °C. [c] Trituration. [d] C: calcd, 48.48; found, 48.04. [e] Cyclohexanesulfamic acid. [f] Lit.[2] mp 202-203 °C. [g] Not analyzed. [h] Fumaric acid. [i] Crude; TLC showed one spot. [j] $HBF_4$ salt appeared to be hygroscopic. [k] Lit.[2] mp 157 °C. [l] Lit. mp 159.5-160.5 °C: R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, 70, 2115 (1948).

screening. One change chosen for study is illustrated by *N*-(1-methyl-2-pyrrolidinylidene)-*N'*-phenylurea (**2**).



**2**

Urea **2**, when tested in the rat antianxiety assay, indicated activity at a minimum effective dose (MED) of 15 mg/kg ip. Because **2** represented a new structural entity to show this activity, we undertook a systematic study of substituent variation, the structure–activity relationships (SAR) of which constitute the subject of this paper.

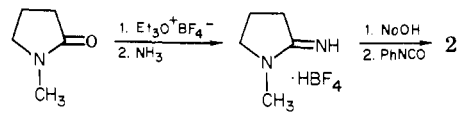
**Chemistry.** Synthesis of **2** and its congeners was straightforward as illustrated in Scheme I.

Intermediate 2-imino-1-methylpyrrolidine (**4**), previously prepared as the HCl salt in 32% yield,[2] was obtained in 80–85% yield when pyrrolidinone **3** was allowed to react with triethyloxonium tetrafluoroborate[3] followed by treatment with anhydrous ammonia. Amidine **4** was characterized as the previously unreported hydrotetrafluoroborate salt.[4] The other amidine starting materials (Table I), with the exception of **13**,[5] were prepared analogously.

Conversion of the amidine salts to their free bases was carried out in either benzene or toluene by the action of concentrated aqueous alkali. Dried solutions of these free bases, when treated with isocyanates, furnished the product ureas of Tables II and III. Occasionally, by-products were encountered.[6]

The subject ureas were found to be weak organic bases which were capable of forming crystalline salts with strong acids such as HCl and $H_2SO_4$. Several ureas were characterized in this manner.

Scheme I



**3** **4**

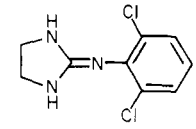
Two ureas, **83** and **84**, were prepared by reaction of carbamyl chlorides with **4** free base. In these cases, addition of triethylamine as a HCl scavenger was ineffective. The use of 2 equiv of base **4**, however, allowed reclamation of 1 equiv as **4**·HCl, followed by isolation of the desired product.

**Structure–Activity Relationships. A. Table II Ureas.** (1) 4-Substituted phenyl analogues **15–29**, in general, led to relatively weak central nervous system (CNS) activities characterized as depressant, muscle relaxant, and anticonvulsant. Exceptions were 4-nitrophenyl- (**16**) (Table IV) and 4-trifluoromethylphenyl- (**20**) ureas, each of which indicated good antianxiety activity along with significant sedative properties.

(2) 2-Substituted phenylureas **46–50** gave little CNS activity.

(3) 3-Substituted phenyl congeners bearing either methyl (**31**) or halo (**30, 33, 34**) indicated antianxiety activity of considerable interest. These compounds demonstrated a separation of anxiolytic properties from other CNS activities such as sedative, muscle relaxant, and anticonvulsant (Table IV and Pharmacological Results and Discussion). Other 3-substituents, ureas **35–44**, were of no interest. The lack of anxiolytic properties shown by 3-nitrophenyl (**45**) and 3-trifluorophenyl (**32**) analogues was unexpected in view of the fact that both 4-substituted congeners **16** and **20** were active.

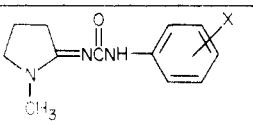
(4) 2,6-Disubstituted phenylureas, in particular. the 2,6-dichloro analogue **51**, were initially investigated as a probe toward uncovering possible antihypertensive agents in view of some structural similarities to the well-known antihypertensive agent, clonidine.



clonidine

Although of no interest as antihypertensive agents, this 2,6-disubstituted phenyl group of analogues was found to possess potent muscle-relaxant activity. The most active compounds were those with methyl (**52**), chloro (**51, 53**),

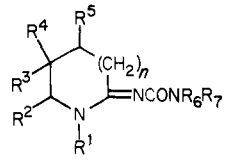
Table II. *N*-(1-Methyl-2-pyrrolidinylidene)-*N'*-(substituted phenyl)ureas



| no. | X | formula | mp, °C | recrystn solvent[a] | % yield[b] | analyses |
|---|---|---|---|---|---|---|
| 2 | H | $C_{12}H_{15}N_3O$ | 146-147.5 | M | 53[c] | C, H, N |
| 15 | 4-Cl | $C_{12}H_{14}ClN_3O$ | 142-144 | M | 61 | C, H |
| 16 | 4-$NO_2$ | $C_{12}H_{14}N_4O_3$ | 182-183 | A-M | 87 | C, H |
| 17 | 4-Me | $C_{13}H_{17}N_3O$ | 149-150 | A | 75 | C, H |
| 18 | 4-Br | $C_{12}H_{14}BrN_3O$ | 136-138 | 2-P-E | 75 | C, H |
| 19 | 4-F | $C_{12}H_{14}FN_3O$ | 115-116 | EA | 30 | C, H |
| 20 | 4-$CF_3$ | $C_{13}H_{14}F_3N_3O$ | 130-132.5 | EA-PE | 76 | C, H |
| 21 | 4-$OCH_2Ph$ | $C_{19}H_{21}N_3O_2$ | 140-142 | A | 75 | C, H |
| 22 | 4-OH[d] | $C_{12}H_{15}N_3O_2$ | 180-182 | M | 38 | C, H |
| 23 | 4-OEt | $C_{14}H_{19}N_3O_2$ | 147-148 | A | 63 | C, H |
| 24 | 4-SMe | $C_{13}H_{17}N_3OS$ | 141-144 | EA | 86 | C, H |
| 25 | 4-$CO_2Et$ | $C_{15}H_{19}N_3O_3$ | 181-183 | EA | 82 | C, H |
| 26 | 4-$SO_2Me$ | $C_{13}H_{17}N_3O_3S$ | 168-170 | EA | 89 | C, H |
| 27 | 4-OMe | $C_{13}H_{17}N_3O_2$ | 123-125 | CH-E | 42 | C, H |
| 28 | 4-*t*-$C_4H_9$ | $C_{16}H_{23}N_3O$ | 144-145 | CH-E | 48 | C, H |
| 29 | 4-$N(Me)_2$ | $C_{14}H_{20}N_4O$ | 138-139 | M-E | 79 | C, H |
| 30 | 3-Cl | $C_{12}H_{14}ClN_3O$ | 137-138 | M-E | 30 | C, H |
| 31 | 3-Me | $C_{13}H_{17}N_3O$ | 149-151 | A | 82 | C, H |
| 32 | 3-$CF_3$ | $C_{13}H_{14}F_3N_3O$ | 155-156.5 | A-PE | 46 | C, H |
| 33 | 3-Br | $C_{12}H_{14}BrN_3O$ | 138-140 | EA | 48 | C, H |
| 34 | 3-F | $C_{12}H_{14}FN_3O \cdot {}^3/_8H_2O$ | 142-143 | EA | 69 | C, H; $H_2O$[e] |
| 35 | 3-I | $C_{12}H_{14}IN_3O$ | 144-145 | A | 67 | C, H; I[f] |
| 36 | 3-OMe | $C_{13}H_{17}N_3O_2$ | 128-129.5 | A | 82 | C, H |
| 37 | 3-$SO_2F$ | $C_{12}H_{14}FN_3O_3S$ | 170-172 | EA | 73 | C, H |
| 38 | 3-COMe | $C_{14}H_{17}N_3O_2$ | 154-155.5 | A | 46 | C, H |
| 39 | 3-$CO_2Et$ | $C_{15}H_{19}N_3O_3$ | 124-125.5 | A | 40 | C, H |
| 40 | 3-SMe | $C_{13}H_{17}N_3OS$ | 110-111 | A | 45 | C, H |
| 41 | 3-CN | $C_{13}H_{14}N_4O$ | 145-147 | A | 45 | C, H |
| 42 | 3-SOMe[d] | $C_{13}H_{17}N_3O_2S$ | 133-134.5 | Et-E | 91 | C, H |
| 43 | 3-$SO_2Me$[d] | $C_{13}H_{17}N_3O_3S$ | 179-181 | Et (abs) | 86 | C, H |
| 44 | 3-*n*-$C_3H_7$ | $C_{15}H_{21}N_3O$ | 89-90 | CH-E | 39 | C, H |
| 45 | 3-$NO_2$ | $C_{12}H_{14}N_4O_3$ | 151.5-153 | THF-$H_2O$ | 79 | C, H, N |
| 46 | 2-Cl | $C_{12}H_{14}ClN_3O$ | 140-142 | M-E | 63 | C, H |
| 47 | 2-Me | $C_{13}H_{17}N_3O$ | 91-93 | E | 50 | C, H |
| 48 | 2-*i*-$C_3H_7$ | $C_{15}H_{21}N_3O \cdot HCl$ | 163-165 | Et | 57 | C, H |
| 49 | 2-OEt | $C_{14}H_{19}N_3O_2$ | 108-110 | A-EA | 48 | C, H |
| 50 | 2-$CF_3$ | $C_{13}H_{14}F_3N_3O$ | 177-179 | Et | 53 | C, H |
| 51 | 2,6-$Cl_2$ | $C_{12}H_{13}Cl_2N_3O$ | 134-136 | B-E | 60 | N |
| 52 | 2,6-$Me_2$ | $C_{14}H_{19}N_3O$ | 119-120 | EA-E | 84 | C, H |
| | | $C_{14}H_{19}N_3O \cdot HCl$ | 177-180 | 2-P-E | | C, H |
| | | $C_{14}H_{19}N_3O \cdot H_2SO_4$ | 160 dec | 2-P-E | 87 | C, H |
| 53 | 2-Cl-6-Me | $C_{13}H_{16}ClN_3O$ | 103-105.5 | A-PE | 69 | C, H |
| 54 | 2-Et-6-Me | $C_{15}H_{21}N_3O \cdot H_2SO_4$ | 243-245 | Et-E | 74 | C, H |
| 55 | 2,6-$Et_2$ | $C_{16}H_{23}N_3O$ | 71-73 | E-PE | 81 | C, H |
| 56 | 2,6-$Br_2$ | $C_{12}H_{13}Br_2N_3O$ | 115-117 | EA | 66 | C, H |
| 57 | 2,6-$(OMe)_2$ | $C_{14}H_{19}N_3O_3$ | 114-117 | EA-E | 59 | C, H |
| 58 | 2,6-$(i\text{-}C_3H_7)_2$ | $C_{18}H_{27}N_3O \cdot HCl$ | 192-193.5 | Et-E | 44 | C, H |
| 59 | 3,4-$(OMe)_2$ | $C_{14}H_{19}N_3O_3$ | 118-120 | M | 20 | C, H, N |
| 60 | 4-Cl-3-$CF_3$ | $C_{14}H_{13}ClF_3N_3O$ | 173-175 | EA | 77 | C, H |
| 61 | 3,5-$(CF_3)_2$ | $C_{14}H_{13}F_6N_3O$ | 165-166.5 | EA | 62 | C, H |
| 62 | 2,5-$Cl_2$ | $C_{12}H_{13}Cl_2N_3O$ | 148.5-150.5 | A | 83 | C, H |
| 63 | 3-Cl-4-F | $C_{12}H_{13}ClFN_3O$ | 158-160 | EA | 79 | C, H |
| 64 | 3,4-$(CN)_2$ | $C_{14}H_{13}N_5O$ | 203-205 dec | A | 71 | C, H, N |
| 65 | 3,5-$Cl_2$ | $C_{12}H_{13}Cl_2N_3O$ | 157-159 | EA | 31 | C, H |
| 66 | 3,4-$Cl_2$ | $C_{12}H_{13}Cl_2N_3O$ | 160-161 | A-$H_2O$ | 70 | C, H |
| 67 | 5-Cl-2-OMe | $C_{13}H_{16}ClN_3O_2$ | 161-163 | A | 31 | C, H |
| 68 | [g] | $C_{16}H_{17}N_3O$ | 148-149 | A | 78 | C, H |
| 69 | 4-$OCH_2Ph$-3-Cl | $C_{19}H_{20}ClN_3O_2$ | 115-117 | Et-E | 70 | C, H |
| 70 | 3-Cl-4-OH[d] | $C_{12}H_{14}ClN_3O_2$ | 194-196 | M | 53 | C, H |
| 71 | 2,4-$Cl_2$ | $C_{12}H_{13}Cl_2N_3O$ | 153-155 | MC-E | 35 | C, H |
| 72 | 4-Cl-2-$CF_3$ | $C_{13}H_{13}ClF_3N_3O$ | 134-135.5 | B-E | 71 | C, H |
| 73 | 3,4-$Me_2$ | $C_{14}H_{19}N_3O$ | 157-158 | CH-E | 44 | C, H |
| 74 | 2,4,6-$Br_3$ | $C_{12}H_{12}Br_3N_3O$ | 165-167.5 | A | 56 | C, H |
| 75 | 2,4,6-$Cl_3$ | $C_{12}H_{12}Cl_3N_3O$ | 160-162 | EA | 87 | C, H |
| 76 | 2,4,6-$Me_3$ | $C_{15}H_{21}N_3O$ | 121-123 | A | 55 | C, H |
| 77 | 3-Cl-2,6-$Me_2$ | $C_{14}H_{18}ClN_3O$ | 134-136 | M-E | 71 | C, H, N |
| 78 | 2,6-$Me_2$-4-$NMe_2$ | $C_{16}H_{24}N_4O \cdot {}^3/_8H_2O$ | 107.5-110.5 | E | 48 | C, H; $H_2O$[h] |

[a] A = acetone, B = benzene, CH = cyclohexane, E = ether, EA = ethyl acetate, Et = EtOH, H = hexane, M = MeOH, MC = $CH_2Cl_2$, 2-P = 2-PrOH, PE = petroleum ether (bp 40-60 °C). [b] Yields not maximized. [c] See ref 6. [d] See Experimental Section. [e] $H_2O$: calcd, 5.43; found, 5.49. [f] I: calcd, 36.98; found, 36.98. [g] α-Naphthyl. [h] $H_2O$: calcd, 2.29; found, 3.05.

Table III. 2-(Hexahydroazepinylidene)-, 2-(Piperidinylidene)-, and 2-(Pyrrolidinylidene)ureas



| no. | n | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | $R^7$ | formula | mp, °C | recrystn solvent[a] | % yield[b] | analyses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 79 | 0 | H[c] | H | H | H | H | H | Ph | $C_{11}H_{13}N_3O\cdot HCl$ | (205) 208-210 dec | Et | 20 | C, H |
| 82 | 0 | Me | H | H | H | H | H | COPh | $C_{13}H_{15}N_3O_2$ | 119-122 | A | 41 | C, H |
| 83 | 0 | Me | H | H | H | H | Me | Ph | $C_{13}H_{17}N_3O$ | 27.5-30[d] | H | 38 | H[e] |
| 84 | 0 | Me | H | H | H | H | Ph | Ph | $C_{18}H_{19}N_3O$ | 129-132 | EA | 77 | C, H |
| 85 | 0 | Me | H | H | H | H | H | $n$-$C_{12}H_{25}$ | $C_{18}H_{35}N_3O$ | 59-61 | A-EA | 46 | C, H |
| 86 | 0 | Me | H | H | H | H | H | $n$-$C_{18}H_{37}$ | $C_{24}H_{47}N_3O$ | 74-76 | A and M | 50 | C, H |
| 87 | 0 | Me | H | H | H | H | H | $c$-$C_6H_{11}$ | $C_{12}H_{21}N_3O$ | 110-112 | EA | 92 | C, H |
| 88 | 0 | Me | H | H | H | H | H | 1-adamantyl | $C_{16}H_{25}N_3O$ | 162-164 | A | 75 | C, H |
| 89 | 0 | Me | H | H | H | H | H | 2-furyl | $C_{10}H_{13}N_3O$ | 120-123 | A | 48 | C, H |
| 90 | 0 | Me | H | H | H | H | H | 2-thenyl | $C_{10}H_{13}N_3OS$ | 191-194 | A | >16 | C, H |
| 91 | 0 | Me | H | H | H | H | H | 3-pyridyl | $C_{11}H_{14}N_4O$ | 138-139.5 | A | 75 | C, H |
| 92 | 0 | Et | H | H | H | H | H | 3-ClPh | $C_{13}H_{16}ClN_3O$ | 122-124 | EA | 71 | C, H |
| 93 | 0 | $n$-$C_4H_9$ | H | H | H | H | H | 3-ClPh | $C_{15}H_{20}ClN_3O$ | 94-96 | EA | 71 | C, H |
| 94 | 0 | $CH_2Ph$ | H | H | H | H | H | 3-ClPh | $C_{18}H_{18}ClN_3O$ | 91-93 | A-PE | 75 | C, H |
| 95 | 0 | $CH_2Ph$ | H | H | H | H | H | 3-$CF_3$Ph | $C_{19}H_{18}F_3N_3O\cdot HCl$ | 164-165 | A-E | 89 | C, H |
| 96 | 0 | Me | Me | H | H | H | H | 3-ClPh | $C_{13}H_{16}ClN_3O$ | 129-130 | EA | 88 | C, H |
| 97 | 0 | Me | H | Me | Me | H | H | Ph | $C_{14}H_{19}N_3O$ | 120-123 | A-H | 20 | C, H, N |
| 98 | 0 | Me | H | Me | Me | H | H | 3-ClPh | $C_{14}H_{18}ClN_3O$ | 110-114 | B-H | 22 | C, H, N |
| 99 | 0 | Me | H | Ph | H | H | H | Ph | $C_{18}H_{19}N_3O$ | 125-128 | A-H | 38 | C, H, N |
| 100 | 0 | Me | H | Ph | H | H | H | 3-ClPh | $C_{18}H_{18}ClN_3O$ | 109-112 | A-H | 43 | C, H, N |
| 101 | 0 | Me | H | Ph | H | Me | H | Ph | $C_{19}H_{21}N_3O$ | 103-105 | MC-H | 52 | C, H |
| 102 | 0 | Me | H | Ph | H | Me | H | 3-ClPh | $C_{19}H_{20}ClN_3O$ | (63) 68-78 | MC-H | 57 | C, H, N |
| 103 | 0 | Et | H | H | H | H | H | 2,6-$Me_2$Ph | $C_{15}H_{21}N_3O$ | 121-123 | A | 34 | C, H |
| 104 | 0 | $n$-$C_4H_9$ | H | H | H | H | H | 2,6-$Me_2$Ph | $C_{17}H_{25}N_3O$ | 93-95 | EA | 72 | C, H |
| 105 | 0 | $CH_2Ph$ | H | H | H | H | H | 2,6-$Cl_2$Ph | $C_{18}H_{17}Cl_2N_3O$ | 121-123.5 | A-PE | 86 | C, H |
| 106 | 0 | $CH_2Ph$ | H | H | H | H | H | 2,6-$Me_2$Ph | $C_{20}H_{23}N_3O\cdot HCl$ | 185-195 dec | M | 73 | C, H |
| 107 | 0 | Me | Me | H | H | H | H | 2,6-$Me_2$Ph | $C_{15}H_{21}N_3O$ | 120-122 | EA | 85 | C, H |
| 108 | 0 | Me | H | Me | Me | H | H | 2,6-$Cl_2$Ph | $C_{14}H_{17}Cl_2N_3O$ | (130) 133-135 | B-H | 45 | C, H, N |
| 109 | 0 | Me | H | Me | Me | H | H | 2,6-$Me_2$Ph | $C_{16}H_{23}N_3O$ | 146-149 | A-H | 55 | C, H, N |
| 110 | 0 | Me | H | Ph | H | H | H | 2,6-$Cl_2$Ph | $C_{18}H_{17}Cl_2N_3O$ | 180-184 | Et | 29[f] | C, H, N |
| 111 | 0 | Me | H | Ph | H | H | H | 2,6-$Me_2$Ph | $C_{20}H_{23}N_3O$ | 148-151 | A | 45 | C, H, N |
| 112 | 0 | Me | H | Ph | H | Me | H | 2,6-$Cl_2$Ph | $C_{19}H_{19}Cl_2N_3O$ | (130) 133-136 | Et | 31 | C, H, N |
| 113 | 0 | Me | H | Ph | H | Me | H | 2,6-$Me_2$Ph | $C_{21}H_{25}N_3O$ | 137-140 | A-E-H | 81 | C, H, N |
| 114 | 1 | Me | H | H | H | H | H | Ph | $C_{13}H_{17}N_3O$ | 160-161 | A | 23 | C, H |
| 115 | 1 | Me | H | H | H | H | H | 4-$CF_3$Ph | $C_{14}H_{16}F_3N_3O$ | 154-155 | M | 33 | C, H |
| 116 | 2 | H | H | H | H | H | H | Ph | $C_{13}H_{17}N_3O$ | 132-134 | A | 57 | C, H |
| 117 | 2 | Me | H | H | H | H | H | Ph | $C_{14}H_{19}N_3O$ | 136-137 | EA | 45[g] | C, H |
| 118 | 2 | Me | H | H | H | H | H | 3-ClPh | $C_{14}H_{18}ClN_3O$ | 119-121 | A | 28 | C, H |
| 119 | 2 | H | H | H | H | H | H | 2,6-$Cl_2$Ph | $C_{13}H_{15}Cl_2N_3O$ | 183-185 | EA | 66 | C, H |
| 120 | 2 | H | H | H | H | H | H | 2,6-$Me_2$Ph | $C_{15}H_{21}N_3O$ | 216-217 dec | Et | 26 | C, H, N |
| 121 | 2 | Me | H | H | H | H | H | 2,6-$Cl_2$Ph | $C_{14}H_{17}Cl_2N_3O$ | 143-144 | A | 23 | C, H |
| 122 | 2 | Me | H | H | H | H | H | 2,6-$Me_2$Ph | $C_{16}H_{23}N_3O$ | 132-133 | A | 52 | C, H |

[a] See footnote *a*, Table II. [b] Yields not maximized. [c] See the Experimental Section. [d] Bp 30-42 °C (0.2-0.4 mm). [e] C: calcd, 67.50; found, 66.78, 67.02, 65.87. [f] A 16% yield of the isocyanate bis adduct was isolated. [g] A 10% yield of phenyl isocyanate bis adduct was also isolated.

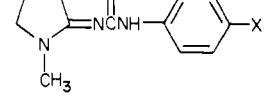
and bromo (**56**) as substituents. Introduction of ethyl (**54**, **55**), methoxy (**57**), and isopropyl (**58**) groups at these positions greatly reduced muscle-relaxant activity.

Ureas **51**–**56** represent a new class of centrally mediated skeletal muscle relaxants. As previously described for the anxiolytics, these agents also indicated a significant separation of muscle relaxant from other CNS activities such as sedative, hypnotic, anticonvulsant, and antianxiety. These compounds are compared with known muscle relaxants, chlorozoxazone, methocarbamol, and diazepam, in the Pharmacological Results and Discussion section and in Table V.

(5) Other variations of disubstituted phenyl gave congeners **59**–**73** which exhibited significantly reduced CNS properties. The only compound of this group worthy of mention is 3,5-bis(trifluoromethyl)phenylurea **61** which indicated anticonvulsant activity ca. one-fifth that of diphenylhydantoin sodium.

(6) 2,3,6- and 2,4,6-trisubstituted analogues **74**–**78** also showed muscle-relaxant activity but were less potent than ureas **51** and **52**.

**B. Thiourea Analogues.** Thioureas **80** and **81**, pre-



**80**, X = H
**81**, X = $NO_2$

pared for comparison with active anxiolytic ureas **2** and **16**, were essentially inactive in all CNS screens.

**C. Table III Ureas.** Removal of the pyrrolidine *N*-methyl group **79** converted the anxiolytic properties of **2** into weak muscle-relaxant activity.

Aroylurea **82**, urea nitrogen-substituted compounds **83** and **84**, and heteroaryl congeners **89**–**91** were of no pharmacological interest.

Dodecylurea **85** surprisingly demonstrated weak antianxiety activity at 25 mg/kg ip, but octadecyl- (**86**), cy-

clohexyl- (87), and adamantyl- (88) ureas did not.

*N*-Ethyl congener **92** (Table IV) was equipotent as an anxiolytic with **30** but appeared to have a larger sedative–hypnotic component.

Further modifications, at pyrrolidine nitrogen (**93–95** and **104–106**), ring expanded (**114–122**), and pyrrolidine substituted at various carbon atoms of the ring (**96–102** and **107–113**), furnished congeners which exhibited no CNS activity worthy of further study.

**Pharmacological Testing Results and Discussion.** Detailed individual CNS profiles were assigned to the subject ureas of Tables IV and V on the basis of their activity, or relative lack thereof, in the pentylenetetrazole infusion, strychnine infusion, and the supramaximal electroshock tests in mice. Because our compounds failed to show significant anticonvulsant activity, discussion of these tests is limited to those CNS profiles encompassing muscle-relaxant, sedative, and hypnotic activities.

Anxiolytic activity was assessed by the rat antianxiety assay.

Activity vs. pentylenetetrazole was primarily used to identify sedative (elevation of the pseudoconvulsive threshold), hypnotic (elevation of the persistent convulsant threshold), and sedative–hypnotic (elevation of both pseudo- and persistent-convulsive thresholds), as well as muscle relaxant (block of tonic extensor seizures), effects. Significant increases in the pseudo- and persistent-convulsive thresholds, along with a block of tonic seizures and lethality, are characteristic of the barbiturates (sedative–hypnotic) and benzodiazepines (anxiolytic, sedative–hypnotic, muscle relaxant, anticonvulsant). It is well-known that CNS activities, such as muscle relaxant, anticonvulsant, and sedative, are present at or near therapeutic doses along with the anxiolytic properties of the benzodiazepines, chlordiazepoxide (Table IV) and diazepam (Tables IV and V). Centrally acting muscle relaxants of the mephenesin class (mephenesin is regarded to be the classical standard for comparison), to which chlorzoxazone and methocarbamol belong, primarily block tonic extensor seizures, increase death volume, and produce a limited (1–15 min) delay of death (death time). In addition, these reference agents, at high doses, show an increase in the pseudoconvulsive threshold, which we interpret to indicate an overlying sedative component.

In the strychnine test, both centrally acting muscle relaxants and hypnotics cause an increase in the persistent convulsive threshold (block of tonic extensor seizures). Activity vs. convulsions caused by strychnine is regarded as a primary requisite for detecting centrally acting muscle relaxants. Chlorzoxazone, methocarbamol, and diazepam show significant activity in this test.

Block of the tonic extensor seizures elicited by the supramaximal electroshock test was used to furnish substantiation of centrally active muscle-relaxant activity. The reference compounds of Tables IV and V indicated significant activity in this test.

$LD_{50}/PD_{50}$ ratios were used to assess the presence, or absence, of barbiturate-like sedative–hypnotic activity. A compound with an $LD_{50}/PD_{50}$ ratio approaching unity was regarded not to be barbiturate-like.

$PD_{50}$/MED and $LD_{50}$/MED ratios provided evaluation of a given compound's therapeutic index (TI).

**A. Table IV Compounds. Anxiolytics. Antianxiety Activity.** All compounds exhibiting no activity at 25 mg/kg ip in the rat antianxiety procedure have been arbitrarily considered as inactive for the purpose of discussion.

Table IV. Anxiolytic Pyrrolidinylideneureas

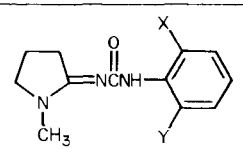


| no. | $R^1$ | $R^2$ | X | min active dose, mg/kg po, in the mouse: pentylenetetrazole[a,b] | strychnine[a,b] | electroshock[a,b] | $PD_{50}$,[a-c] mg/kg po, mouse | $LD_{50}$,[a-c] mg/kg po, mouse | $LD_{50}/PD_{50}$,[a] mouse | min active dose, mg/kg ip, in the rat: antianxiety[a,b] | TI[a,d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Me | H | H | 40 | 35 | >100 | 220 (195-249) | 215 (190-243) | 1.0 | 15 | 15 |
| 16 | Me | H | 4-$NO_2$ | 100 | >200 | >200 | ~1200 | 1310 (1065-1611) | ~1 | 15 | 80 |
| **30** | Me | H | 3-Cl | 32 | 50 | 142 | 950 (850-1064) | 1500 (1180-1910) | 1.6 | 15 | 63 |
| 31 | Me | H | 3-Me | 25 | >200 | 76 | 825 (737-924) | 850 (766-944) | 1.0 | 25 | 33 |
| 32 | Me | H | 3-$CF_3$ | 47 | 58 | 76 | >1000 | >1000 | | >25 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | Me | H | 3-Br | 52 | 58 | 180 | 1430 (1172-1744) | 1580 (1443-1730) | 1.1 | 25 | 57 |
| 34 | Me | H | 3-F | 38 | 210 | 200 | ~500 | 525 (451-612) | ~1 | 25 | 20 |
| 35 | Me | H | 3-I | 36 | 86 | 112 | >1000 | >1000 | | >25 | |
| 36 | Me | H | 3-OMe | 68 | 135 | 135 | 820 (685-985) | 1200 (980-1480) | 1.5 | >25 | |
| 92 | Et | H | 3-Cl | 60 | 137 | 200 | 1390 (1252-1543) | 1700 (1466-1972) | 1.2 | 15 | 58 |
| 96 | Me | Me | 3-Cl | 68 | 160 | 135 | 1307 (1071-1595) | ~1900 | 1.5 | >25 | |
| chlordiazepoxide | | | | 1.5[a] | 10 | 71 | 680 (579-795) | 990 (891-1098) | 1.5 | 2.5-5 | ~260 |
| diazepam | | | | 0.1[a] | 0.17 | 15 | 485 (300-775) | 535 (334-855) | 1.1 | 0.5-1.0 | ~485 |

[a] See Pharmacological Results and Discussion section. [b] See the Experimental Section for definitions of (1) minimum active dose for each test, (2) $PD_{50}$, and (3) $LD_{50}$. [c] Numbers in parentheses represent 95% confidence limits. [d] Therapeutic index (TI) = $PD_{50}$/minimum active dose in the antianxiety test.

Table V. Muscle-Relaxant Pyrrolidinylideneureas




| | | | min active dose, mg/kg po, in the mouse | | | | | | min active dose, mg/kg ip, in the rat | |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | X | Y | pentylenetetrazole[a,b] | strychnine[a,b] | electroshock[a,b] | $PD_{50}$,[a-c] mg/kg po, mouse | $LD_{50}$,[a-c] mg/kg po, mouse | $LD_{50}/PD_{50}$,[a] mouse | antianxiety[a,b] | TI[d] |
| 51 | Cl | Cl | 25 | 64 | 58 | 320 (258-406) | 565 (500-640) | 1.8 | >25 | 5 |
| 52 | Me | Me | 22 | 26 | 27 | 230 (192-276) | 320 (238-429) | 1.4 | >25 | 8.8 |
| 53 | Cl | Me | 28 | 52 | 43 | 232 (188-285) | 449 (359-561) | 1.9 | >25 | 4.5 |
| 54 | Et | Me | 20 | 96 | 36 | | 650 | | not tested | |
| 55 | Et | Et | 16 | 120 | 64 | 161 (115-225) | 370 (336-407) | 2.3 | >25 | 1.3 |
| 56 | Br | Br | 25 | 50 | 74 | 350 (271-452) | 560 (421-745) | 1.6 | >25 | 7 |
| 57 | OMe | OMe | 62 | >200 | 80 | 460 (391-541) | 650 (596-709) | 1.4 | >25 | |
| 58 | *i*-Pr | *i*-Pr | 180 | >200 | 165 | | ~260 | | not tested | |
| chlorzoxazone | | | 108 | 180 | 115 | 540 (400-729) | 1325 (1086-1617) | 2.5 | >25 | 3 |
| methocarbamol | | | 150 | 310 | 120 | 1050 (880-1250) | ~2000 | 1.9 | >25 | 3.4 |
| diazepam | | | 0.1 | 0.17 | 15 | 485 (300-775) | 535 (334-855) | 1.1 | 0.5-1.0 | 2900 |

[a] See footnote *a*, Table IV. [b] See footnote *b*, Table IV. [c] See footnote *c*, Table IV. [d] TI = $PD_{50}$/minimum active dose in the antistrychnine test.

Seven of the compounds of Table IV demonstrated significant anxiolytic activity by the method of Geller as modified by Margules and Stein.[7] The ip minimum active dose was 15 mg/kg for ureas **2**, **16**, **30**, and **92** and 25 mg/kg for congeners **31**, **33**, and **34**. Chlordiazepoxide was approximately three to six times more potent than the more active (15 mg/kg) group.

**Antipentylenetetrazole Activity.** All compounds in Table IV blocked the tonic extensor seizure, increased the death volume, and prolonged the death time to a limited degree. Their activity in this procedure was assigned to three categories: (a) those compounds, **34** and **35**, which only blocked the tonic extensor seizure; (b) those, **2**, **16**, **30–33**, and **36**, which at 25–200 mg/kg po increased the pseudoconvulsive threshold; and (c) those congeners which increased both the pseudo- and persistent-convulsive thresholds at 50–200 mg/kg po, viz. congeners **16** and **92**.

Chlordiazepoxide increased both pseudo- and persistent-convulsive thresholds, blocked tonic extensor seizures, and increased the death volume over the entire dose range tested (1–40 mg/kg). At 40 mg/kg chlordiazepoxide also blocked the convulsive and lethal effects of pentylenetetrazole. None of our compounds blocked these lethal effects.

Anxiolytic ureas **16** and **92** were qualitatively similar to chlordiazepoxide with regard to the presence of sedative–hypnotic activity along with antianxiety properties. 4-Nitrophenylurea **16**, at doses as low as 25 mg/kg, caused a significant (25%) elevation of the pseudoconvulsive threshold and, at 50 mg/kg, increased both the pseudo- and persistent-convulsive thresholds (73 and 45%, respectively). Urea **16** was the most potent congener to show this profile.

The most interesting anxiolytic was 3-chlorophenylurea **30**. Although urea **30** caused a block of tonic seizures at 32 mg/kg (twice the anxiolytic dose), no significant increase in the pseudoconvulsive threshold was observed at 100 mg/kg. At 200 mg/kg, however, **30** caused a significant rise (50%) in this threshold. Also, **30** demonstrated no elevation of the persistent-convulsive threshold at doses as high as 200 mg/kg. We have interpreted these results as having achieved a significant separation of anxiolytic activity from sedative and hypnotic components.

The Table IV ureas, in general, were significantly less active in both the strychnine and electroshock tests than in the pentylenetetrazole test, with the possible exceptions of analogues **32** and **33**.

Urea **30**, when evaluated on the basis of all the foregoing tests, could be described as a significantly less sedating anxiolytic agent than the benzodiazepines with, at best, weak muscle relaxant properties. Also, **30** appeared to be essentially devoid of anticonvulsant and hypnotic properties.

**$PD_{50}/LD_{50}$ and $PD_{50}$/MED Ratios.** The $LD_{50}/PD_{50}$ ratio of the Table IV ureas ranged from 1 to 1.6 compared to 1.5 and 1.1 for chlordiazepoxide and diazepam, respectively. A typical barbiturate, such as phenobarbital, demonstrates an $LD_{50}/PD_{50}$ ratio of ca. 3–4. Therefore, it can be presumed that neither the Table IV ureas nor the benzodiazepines are barbiturate-like in their profiles. Furthermore, all the active (15 mg/kg) anxiolytic compounds of Table IV, with the exception of **2**, would be expected to enjoy a wide margin of safety. However, our compounds, even though relatively safe, do not appear to have the margin of safety shown by the benzodiazepines. For example, urea **30** indicated a therapeutic index (TI) of ca. 60 [$PD_{50}$/MED (antianxiety)] whereas the TI values of chlordiazepoxide and diazepam were 260 and 485, respectively. It should be reemphasized, however, that the benzodiazepines show a pronounced sedative component in addition to muscle relaxant and anticonvulsant effects at or near doses required for anxiolytic effects. This evaluation has been amply substantiated in man. Conceptually, then, there should be a viable place in the physician's armamentarium for a nonsedating anxiolytic agent.

3-Chlorophenylurea **30**, because of its superior overall CNS profile was selected for further pharmacological and toxicological studies.

**B. Table V Compounds. Muscle Relaxants. Antipentylenetetrazole Activity.** The main effect of ureas **51–58** in this procedure was a block of extensor seizures with a limited (1–15 min) delay in the occurrence of death (death time) *without* accompanying increases in either the pseudo- or persistent-convulsive thresholds up to 200 mg/kg. These compounds, then, would be expected to be essentially devoid of sedative–hypnotic properties. Similarly, the known centrally acting muscle relaxants, chlorzoxazone and methocarbamol, also block tonic extensor seizures with prolonged death time. However, these reference compounds were also found to elevate the pseudoconvulsive threshold at high doses. Diazepam differed from the above-mentioned compounds in that it not only blocked the tonic extensor seizure, but also, with increasing doses (1–5 mg/kg po), elevated both the pseudo- and persistent-convulsive thresholds. At a dose of 5 mg/kg po, diazepam protected 70% of the mice treatment from the lethal effects of pentylenetetrazole. The Table V, ureas, like those of Table IV, did not protect the animals from these lethal effects. Compounds **51–53** and **56** were the most potent of the 2,6-disubstituted series. Congeners **57** and **58** were the least active members. Ureas **51–56** were found to be approximately four to seven times more potent than chlorzoxazone and methocarbamol and $^1/_{200}$–$^1/_{300}$th the potency of diazepam in this test. In particular, 2,6-dimethylphenylurea **52** was five and seven times more potent than chlorzoxazone and methocarbamol, respectively, and $^1/_{200}$th that of diazepam.

**Antistrychnine Activity.** All of the compounds except **57** and **58** were found to have significant activity (muscle relaxant) in this test and were significantly more potent than either chlorzoxazone or methocarbamol. Congener **52**, the most potent member of this series, was approximately six times more potent than chlorzoxazone and ten times more potent than methocarbamol. Urea **52** was about twice as potent as compounds **53** and **56** and $^1/_{150}$th that of diazepam.

**Antielectroshock Activity.** Compounds **51–58** were all effective agents for protection against supramaximal electroshock seizures in mice. All members of this series, except **58**, were more potent than either chlorzoxazone or methocarbamol. The most potent congeners (**52–54**) were approximately three to four times more potent than chlorzoxazone and methocarbamol and one-third to one-half that of diazepam. Urea **52** was the most potent member of our series.

**$PD_{50}/LD_{50}$ and $PD_{50}$/MED Ratios.** The $LD_{50}/PD_{50}$ ratio for the 2,6-disubstituted series ranged from 1.4 to 2.3. The ratios of diazepam, methocarbamol, and chlorzoxazone were found to be 1.1, 1.9, and 2.4, respectively. Of the most active muscle relaxant ureas (strychnine test), **51–53** and **56**, congener **52** had the best $LD_{50}/PD_{50}$ ratio (1.4).

Taking the $PD_{50}$ as an index of the overt depressant activity, the ratio of the $PD_{50}$ to the minimal active dose in each of the pentylenetetrazole and electroshock assays was calculated to be 10.5 and 8.5, respectively, for urea **52**.

The corresponding ratios determined for chlorzoxazone were 5 and 4.5; for methocarbamol 7 and 8.7; and for diazepam 485 and 36.

Of particular interest was the favorable ratio of the $PD_{50}$ to the minimal active dose in the strychnine assay (muscle relaxant activity). Here, the most potent congener **52** had the largest ratio (8.8), clearly indicating superiority over the remaining Table V ureas. The corresponding ratios for diazepam, chlorzoxazone, and methocarbamol were 2853, 3, and 3.4, respectively.

**Antianxiety Activity.** None of the Table V ureas was found to have anxiolytic activity at the highest dose tested (25 mg/kg).

**Summary.** Of the Table V compounds, 2,6-dimethylphenylurea **52**, based on the results of the foregoing tests, was found to have the best overall CNS profile for nonsedating muscle relaxation and safety. Urea **52**, as a result of more detailed pharmacological[8] and toxicological studies, was selected for clinical trials as a muscle relaxant. *N*-2,6-Dimethylphenyl-*N'*-(1-methyl-2-pyrrolidinylidene)urea (**52**) has been assigned the name xilobam (Chemical Abstracts Registry No. 50528-97-7) by the USAN Council on Drugs.

The principal differences among the Table IV, Table V, and reference compounds are the following. (1) Significant anxiolytic activity was observed in certain of the Table IV compounds, especially 3-chlorophenylurea **30**. The Table V ureas were not active. (2) The Table IV congeners appear to have significantly higher $LD_{50}$ and $PD_{50}$ values than the Table V compounds. We have assessed the relatively lower $LD_{50}$ and $PD_{50}$ of xilobam **52** (respiratory depression) as probably being a reflection of the potent muscle relaxant effect of this drug.[8] (3) The Table IV ureas show less, but still significant, separation from sedative properties than do the Table V compounds. (4) Both sets of active ureas show significantly cleaner activities than their respective reference compounds.

After this work was completed, a patent appeared which broadly disclosed ureas of the type reported herein.[9] This publication reported the subject ureas to be anthelmintic agents against hookworm. This activity was *not* detected for ureas **30** and xilobam **52**.[10]

Because certain of these compounds represent novel anxiolytics and muscle relaxants, further work is in progress.

## Experimental Section

**Pharmacological Methodology.** Anxiolytic activity in rats was determined according to the method of Geller,[7a] as modified by Margules and Stein,[7b] following five ip daily injections of the test compound. The minimum active dose in the antianxiety assay is defined as that dose which affects a significant increase in punished responses daily for 5 days.

The acute $PD_{50}$ and $LD_{50}$ were determined in mice following a single oral administration of the test compound over four and/or six dosage levels. The $PD_{50}$ is defined as that dose of the test compound in mice which produces a loss of righting reflex (LRR) for at least 1 min. The $LD_{50}$ is that dose of the test agent which produces a 50% lethality in mice. The $LD_{50}$ was calculated on the basis of mortality counts made at 7 days following the oral dosage regimen. The $PD_{50}$, $LD_{50}$, and 95% confidence limits were calculated according to the method of Litchfield and Wilcoxon.[11]

Antipentylenetetrazole and antistrychnine activities were tested in mice by the method of Orloff et al.,[12] as modified by Chen and Bohner.[13]

Antielectroshock activity in mice was determined according to Swinyard et al.[14]

The minimum active dose in the pentylenetetrazole and electroshock assays is defined as that dose, estimated graphically from a dose–response curve, which affects a significant 20% block of toxic seizures. The minimum effective dose in the strychnine assay, determined analogously, is defined as that dose which affects a significant 25% increase in the persistent-convulsive threshold.

**Chemistry.** Microanalyses were generally obtained from Scandinavian Microanalytical Laboratories, Herlev, Denmark. The results of these analyses, except where indicated, were within ±0.4% of theory. Melting points (uncorrected) were determined on a Thomas-Hoover apparatus. Spectral data were obtained as follows: $^1H$ NMR, in $Me_2SO$-$d_6$ or $CDCl_3$ with $Me_4Si$ as internal standard, on a Varian A-60A spectrometer; IR spectra, except where indicated, were taken in $CHCl_3$ on a Perkin-Elmer 521 grating instrument; UV spectra were obtained in either MeOH or MeCN on a Cary Model 14 recording spectrometer; and mass spectra (70 eV) were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. TLC systems usually employed for the ureas were silica gel GF with benzene–EtOAc (3:1) and benzene–ether–MeOH (2:4:0.5) as developing solvents.

**Starting Materials. I. Isocyanates.** Most of the isocyanates used in this work were commercially available from JaKem Industries, Eastman Kodak, and Aldrich Chemical Co. Isocyanates which are either new or were prepared by new methodology are reported herein.

**Procedure A.** These isocyanates were prepared from the corresponding anilines by the phosgene method of Inukai and Maki.[15]

**4-Benzyloxyphenyl isocyanate**: yield 92.5% from petroleum ether; mp 59–61.5 °C; IR 2280 $cm^{-1}$.

**Ethyl 3-Isocyanatobenzoate.** This ester, obtained as an oil, was dissolved in dry benzene, filtered (filter aid), and used directly to prepare urea **39**: IR (neat) 2270 and 1710 $cm^{-1}$.

**1-(3-Aminophenyl)-1-propanol.** A solution of 26.88 g (0.15 mol) of 3-nitropropiophenone in 500 mL of warm MeOH was divided into three equal portions. Each portion was placed in a 500-mL Parr bottle over 0.75 g of 10% Pd/C in MeOH. Hydrogenation at 60 psi for 30 min, according to the directions of Long and Schofield,[16] did not give the expected 3-aminopropiophenone but instead afforded the title amino alcohol: mp 68.5–71.5 °C; MS (70 eV) parent ion 151, calcd 151. Anal. Calcd for $C_9H_{13}NO$: C, 71.59; H, 8.67. Found: C, 71.14; H, 8.61.

**3-(1-Propyl)aniline.** The combined amino alcohol samples were dissolved in 110 mL of glacial HOAc containing 18.6 g of $H_2SO_4$ (98%) and 1.26 g of $H_2O$, and the recovered catalyst from the preceding procedure was reintroduced.[17] Hydrogenation at 60 psi for 4 h, followed by solvent removal in vacuo, basification with NaOH (10%), ether extraction, drying ($MgSO_4$), and solvent removal, gave 83% of the aniline (95% pure by GLC) which was converted directly to the isocyanate.

**3-(1-Propyl)phenyl isocyanate**: yield 81%; IR (neat) 2230 $cm^{-1}$; bp 54–56 °C (0.4 mm).

**4-Nitrophthalamide.** This compound has been reported in the literature;[18] however, no method of preparation or physical data were described.

To a warm solution of 40 g (0.21 mol) of 4-nitrophthalimide in 1 L of MeOH was added anhydrous $NH_3$ with cooling and stirring. After ca. 20 min, a granular solid separated. The $NH_3$ flow was stopped and the flask was allowed to stand in the ice–$H_2O$ bath for 15 min. The solid was filtered, washed with MeOH, and dried (70 °C) to afford 38.7 g (89%) of diamide of sufficient purity for the next step: IR (Nujol) 1670 $cm^{-1}$; mp 189–191 °C dec.

**4-Nitrophthalonitrile.** The procedure of Thurman was used.[19] A slurry of 46.15 g (0.22 mol) of 4-nitrophthalamide in 250 mL of dry DMF was cooled to −15 °C (ice–salt $H_2O$ bath) with stirring. Thionyl chloride, 115 g (0.96 mol), was added drop by drop over 45 min. Stirring was continued 4 h, during which time the cooling bath was allowed to warm to 0 °C. The homogeneous solution was poured with vigorous stirring onto excess ice–$H_2O$ and filtered *immediately*. If the product was not quickly filtered, a second crop of solid (mostly 4-nitrophthalimide by TLC) contaminated the product. The desired product was washed well with $H_2O$, dried, and recrystallized from acetone to give ca. 50% of pure material, mp 140–142 °C (lit.[18] mp 142 °C).

**4-Aminophthalonitrile.** To a suspension of 16.1 g (0.93 mol) of 4-nitrophthalonitrile in 350 mL of EtOH (95%) was added 1.5 g of Pd/C (10%). Hydrogenation was carried out on a Parr shaker at a starting pressure of 60 psi. After 45 min, $H_2$ uptake was complete. Workup and recrystallization from acetone–EtOH gave

9.9 g (75%) of pure aniline, mp 179–181 °C (lit.[18] mp 160–170 °C).

**3,4-Dicyanophenyl Isocyanate.** This isocyanate, prepared from the above aminodinitrile, was not isolated. Instead, it was dissolved in dry benzene and converted to urea **64**.

**3-Chloro-2,6-dimethylaniline.** Reduction of 2,4-dimethyl-3-nitrochlorobenzene, 122 g (0.66 mol), with 446.8 g (1.98 mol) of $SnCl_2 \cdot 2H_2O$ in 1.2 L of 12 N HCl,[20] containing 450 mL of glacial HOAc, below 40 °C, gave, after alkaline workup, 82 g (80%) of the aniline, bp 73–77 °C (0.45–0.5 mm) [lit.[21] bp 136–138 °C (17 mm)].

**3-Chloro-2,6-dimethylphenyl isocyanate**: yield 80%; bp 78–80 °C (0.6–0.7 mm); IR (neat) 2300 $cm^{-1}$.

**Procedure B.** Refluxing well-stirred benzene solutions of the appropriate benzoyl chloride in the presence of excess pulverized sodium azide until IR indicated the absence of acid chloride carbonyl absorption, according to the method of Inukai and Maki,[22] furnished the following isocyanates.

**2,6-Dimethoxyphenyl Isocyanate.** This compound was obtained in 74% yield: mp 32–35 °C; IR (Nujol) 2250 $cm^{-1}$, and partially decomposed upon recrystallization from petroleum ether (bp 40–60 °C). Reaction with **4** gave urea **57**.

**4-Trifluoromethylphenyl Isocyanate.** Solutions of this isocyanate were prepared in situ and used directly for synthesis of ureas **20** and **115**.

**Procedure C.** The method of Peck et al.[23] was the only satisfactory method for preparation of the two 4-dimethylaminophenyl isocyanates used in this work.

***N,N*,3,5-Tetramethylaniline.** This compound was prepared from trimethyl phosphate, 70 g (0.5 mol), and 90 g (0.75 mol) of 3,5-dimethylaniline according to the directions of Vogel.[24] The product, 88.5 g (74%), was sufficiently pure for the next step: NMR ($CDCl_3$) $\delta$ 2.8 [s, 6 H, $N(CH_3)_2$] and 2.3 (s, 6 H, $2CH_3$).

**4-Nitroso-*N,N*,3,5-tetramethylaniline.** To 51.3 g (0.34 mol) of *N,N*,3,5-tetramethylaniline was added 145 mL of concentrated HCl. After cooling to −10 °C, a solution of 24.8 g (0.34 mol) of $NaNO_2$ in 42 mL of $H_2O$ was added below the surface of the liquid with stirring over 45 min such that the temperature did not exceed 0 °C. The rate of addition was extremely sensitive ($NO_2$ fumes evolved easily). The addition should be carried out as slowly as practicable. After addition was complete, the mixture was allowed to stand 1 h, and the yellow crystalline salt was collected and washed with cold 6 N HCl. Conversion to the free base in $CH_2Cl_2$ with NaOH solution, drying ($K_2CO_3$), filtration, and solvent removal in vacuo gave a green-black solid: 28 g (46%); mp 93–100 °C. Two recrystallizations from benzene–hexane, followed by one from $Et_2O$, gave 21.9 g (36%) of pure material: mp 100–102 °C; UV (MeOH) 413 nm ($\epsilon$ 34 000), 327.5–342 br sh (1570), 279 sh (5200), 274 (5400), and 234 (4300); NMR ($CDCl_3$) $\delta$ 6.29 (s, 2 H, aromatic), 3.12 [s, 6 H, $N(CH_3)_2$], 2.64 (s, 6 H, $2CH_3$).

**2,6-Dimethyl-4-dimethylaminoaniline.** To a suspension of 500 mg of Pd/C (10%) in 95 mL of $H_2O$ and 5 mL of NaOH (10%) containing 7.8 g of $NaBH_4$ (0.21 mol), under $N_2$, was added 17.82 g (0.10 mol) of the nitrosoaniline in 250 mL of MeOH over 50 min.[25] The color changed rapidly from dark green to light yellow. The mixture was filtered (filter aid) and the filtrate treated with excess 12 N HCl. Removal of MeOH in vacuo, basification (NaOH), extraction with ether, drying ($K_2CO_3$), and solvent removal in vacuo furnished the crude aniline. Distillation at 0.4–0.5 mm gave 5.33 g (85%) of the aniline (95% pure by GLC): MS (70 eV) parent ion 164, calcd 164.

**2,6-Dimethyl-4-dimethylaminophenyl Isocyanate.** To a solution of a large excess of phosgene in 400 mL of toluene at −50 °C (dry ice–MeOH bath) was added 15.33 g (0.093 mol) of the aniline with rapid stirring.[23] The temperature was allowed to rise slowly over 3 h to 10 °C. The resulting thick slurry was heated to drive off excess phosgene (NaOH traps). When the boiling point temperature of toluene was attained, the solid gradually dissolved (HCl evolution). Heating under reflux overnight and cooling gave a solution of the isocyanate, a portion of which was used directly for the preparation of urea **78**. Removal of solvent in vacuo and recrystallization from MeOH (avoiding prolonged heating) gave pure isocyanate: mp 50–51 °C; IR (toluene) 2300 $cm^{-1}$.

**Procedure D.** The precursor benzoyl azides were synthesized from either their corresponding benzoyl chlorides and sodium azide or from acid hydrazides by the action of aqueous nitrous acid.[27] Those azides which were ether soluble were added drop by drop as dry ($MgSO_4$) solutions to boiling benzene or toluene such that ether flash distilled. Scrupulously dried, solid, ether-insoluble azides were decomposed in the same solvents. The isocyanates, thus prepared, were used directly for the preparation of ureas.

**3,4-Dimethoxyphenyl Isocyanate.** 3,4-Dimethoxybenzoyl azide[27] in ether, after decomposition, furnished crude isocyanate in 80% yield [IR (benzene) 2285 $cm^{-1}$] which was used to prepare urea **59**.

**4-Methanesulfonyl Isocyanate.** The solid azide, prepared from the acid chloride and aqueous $NaN_3$[26] (2 mol)–THF (followed by dilution with $H_2O$) and drying in vacuo, was obtained in 96% yield: mp 132–134 °C dec. The azide was decomposed in dry toluene and the solution was used to prepare urea **26**.

**4-*tert*-Butylphenyl Isocyanate.** The benzoyl azide was prepared as an ether solution over aqueous $NaN_3$. After drying and decomposition in refluxing benzene, this isocyanate furnished urea **28**.

**3-Cyanophenyl Isocyanate.** This compound, prepared analogously to that above as a toluene solution, gave urea **41**.

**4-Benzyloxy-3-chlorobenzoic Acid Hydrazide.** A solution of 32 g (0.11 mol) of ethyl 4-benzyloxy-3-chlorobenzoate and 20 mL of hydrazine (95%) in 25 mL of MeOH was stirred and heated under reflux for 8 h. Cooling afforded 29.4 g (97%) of the product, mp 168–171 °C. Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.73; N, 10.12. Found: C, 60.58; H, 4.79; N, 10.16.

**4-Benzyloxy-3-chlorobenzoyl Azide.** The above hydrazide, 27.6 g (0.1 mol), as a suspension in 500 mL of 1 N HCl at 0 °C was treated with a solution of $NaNO_2$ in 40 mL of $H_2O$ below 5 °C. After being stirred at 5 °C for 0.75 h, the solid was collected and dried: yield 27.8 g (97%); IR ($CHCl_3$) 2180 ($N_3$), 1695 $cm^{-1}$ (C=O).

**4-Benzyloxyphenyl-3-chlorophenyl Isocyanate.** The above dry azide, after refluxing 1 h in dry toluene, provided the title compound which was used to prepare urea **69**.

**II. Pyrrolidin-2-ones. 4,4-Dimethyl-2-pyrrolidinone.** A solution of 74.75 g (0.428 mol) of methyl 3,3-dimethyl-4-nitrobutyrate[28] in 700 mL of MeOH was hydrogenated over water-packed Raney nickel (W. R. Grace) on a Parr shaker overnight. After filtration and solvent removal in vacuo, the residue was taken up in xylene and heated under reflux for 4 h. Solvent removal and distillation furnished 40.83 g (85%) of product, bp 60–110 °C (0.5–1.0 mm) [lit.[29] bp 103 °C (4 mm)].

**1,4,4-Trimethyl-2-pyrrolidinone.** A solution of 40.83 g (0.362 mol) of the preceding lactam in 200 mL of dry benzene was added drop by drop to a stirred suspension of 17.38 g (0.362 mol) of NaH (50% dispersion in oil). After heating under reflux overnight, the suspension was cooled and 78.1 g (0.55 mol) of MeI was added. After heating under reflux for 4 h, the mixture was cooled and treated with 30 mL of $H_2O$. The separated aqueous layer was extracted with chloroform and the combined extracts were dried ($K_2CO_3$). Solvent removal in vacuo followed by distillation gave 41.0 g (89%) of the title compound, bp 75–80 °C (0.25 mm) [lit.[30] bp 160 °C (18 mm)].

**4-Phenyl-2-pyrrolidinone.** Hydrogenation of ethyl 3-phenyl-4-nitrobutyrate in ammoniacal ethanol followed by refluxing in xylene (vide supra) gave 5.65 g (70%) of pure product after recrystallization from benzene–petroleum ether: mp 74–76 °C (lit.[26] mp 75 °C).

**1-Methyl-4-phenyl-2-pyrrolidinone.** Methylation with methyl iodide, as described above, furnished the product in 60% yield: bp 128–135 °C (0.5 mm) [lit.[31] bp 139–140 °C (3 mm)].

**Ethyl 3-Cyano-2-methyl-3-phenylpropionate.** A solution of 117.14 g (1.0 mol) of phenylacetonitrile in 100 mL of dry DMF was added rapidly to a stirred suspension of 43.6 g (1.0 mol) of NaH (57% oil dispersion) in 900 mL of DMF which had been cooled to −20 °C under dry $N_2$. The mixture was gradually heated to 40 °C and maintained there for 1 h. After stirring at ambient temperatures for several hours, the mixture was recooled to 0 °C and treated with 253.4 g (1.4 mol) of ethyl 2-bromopropionate in 100 mL of DMF. After heating at 73 °C for 4 h, the resulting mixture was allowed to stir at room temperature overnight. Dilution with $H_2O$ (2.5 L), extraction with $Et_2O$, washing the combined extracts successively with $Na_2CO_3$ (10%) solution and $H_2O$, drying ($K_2CO_3$), and solvent removal in vacuo furnished the

crude product. Distillation gave 143 g (66%) of the cyano ester as a clear liquid, bp 110–130 °C (0.1–0.15 mm). GLC indicated 90% purity.

**3-Methyl-4-phenyl-2-pyrrolidinone.** A solution of 62.8 g (0.29 mol) of the above ester in 230 mL of absolute EtOH, containing 80 mL of $Et_3N$, was hydrogenated over Raney nickel as described above. Filtration followed by solvent removal in vacuo gave the crude lactam as a solid which was recrystallized from benzene–hexane. This solid, 41.72 g (82%), had a broad indefinite melting point.

**1,3-Dimethyl-4-phenyl-2-pyrrolidinone.** N-Methylation of the previously described lactam, 86.15 g (0.492 mol), with MeI, 115 g (0.8 mol), in the presence of NaH (50% dispersion in oil), 23.6 g (0.492 mol), in benzene, furnished 78.9 g (85%) of the product, bp 115–140 °C (0.3 mm).

**III. 2-Imino Heterocycles.** The general procedure for synthesis of the 2-imino-substituted heterocycles of Table I is illustrated by the following preparation.

**2-Imino-1-methylpyrrolidine Hydrotetrafluoroborate. A** solution of 2820 g (20 mol) of boron trifluoride etherate, in 10 L of anhydrous $Et_2O$ under dry $N_2$, was treated with 1390 g (14.6 mol) of epichlorohydrin. The addition was carried out with vigorous stirring (powerful motor equipped with a paddle stirrer) as rapidly as possible, maintaining a vigorous reflux. After the addition was completed, the mixture was stirred for 2.5 h. The ether was decanted from the resulting crystals and washed with 4 L of fresh anhydrous ether which was discarded. The crystals of triethyloxonium fluoborate were dissolved in 7 L of dry methylene chloride (molecular sieves) and 1460 g (14.6 mol) of 1-methyl-2-pyrrolidinone was added as rapidly as possible, maintaining a steady reflux. After the addition was complete, the mixture was stirred for 2 h at ambient temperatures. Then anhydrous ammonia was introduced for 3 h at a rate vigorous enough to cause initial reflux. The addition was carried out as rapidly as possible. Toward the end of the addition, the temperature of the mixture fell below 20 °C. The mixture was then allowed to stand overnight. After filtration from $NH_4BF_4$, the solvent was removed in vacuo and 2 L of *i*-PrOH and 500 mL of ether were added. Cooling gave 2331 g (85%) of the product which, after recrystallization from *i*-PrOH, melted at 110.5–112 °C.

The hydrotetrafluoroborate and HCl salts of the compounds of Table I were more desirable entities for conversion to their free bases (vide infra) than their corresponding organic acid salts which often emulsified.

**Procedures for the Preparation of the 2-(1-Substituted hexahydroazepinylidene)-, 2-(1-Substituted piperidinylidene)-, and 2-(1-Substituted pyrrolidinylidene)ureas of Tables II and III. I. Via Isocyanates.** A predetermined amount of the 2-imino heterocyclic salt (ca. 0.05 mol), generally in a slight stoichiometric excess, as a stirred suspension, with or without added $H_2O$ (generally not more than 1 mL), in toluene, benzene, etc., was treated with ca. 10–20 mL of commercial concentrated NaOH (50%). After stirring 2–3 min, the organic layer was decanted onto anhydrous $K_2CO_3$ and the aqueous layer was extracted twice with fresh solvent. The combined extracts, stoppered to prevent air moisture and $CO_2$ from entering (2-imino-1-methylpyrrolidine rapidly forms a crystalline carbonate salt), after drying 15–30 min, were rapidly filtered (suction) and *immediately* treated with solutions of the appropriate isocyanate in one portion with stirring under $N_2$ or Ar. The reactions were essentially complete in 15 min or less (TLC); however, stirring was generally carried out from 2 to 3 h.

Commercially available isocyanates were usually dissolved in dry pentane or benzene and filtered (filter aid) prior to use.

Those product ureas which separated from the reaction mixture were collected and washed with ether, to remove any residual isocyanate, and $H_2O$, to remove any unreacted 2-imino heterocycle. Often the reaction mother liquors, after a $H_2O$ wash and drying, afforded high-quality second crops which were combined with the first crops and recrystallized.

Solutions of ureas which did not crystallize from the reaction mixture were filtered (filter aid), if necessary, and the solvent was removed in vacuo. Trituration or dilution with ether and scratching gave the solid products. Those ureas which were not solids after ether treatment were converted to salts and purified.

Isocyanate bis-adduct by-products,[6] when encountered (TLC), were separated by fractional recrystallization. These by-products could be minimized by shortening reaction times and using freshly opened samples of isocyanate.

**II. Via Carbamoyl Chlorides. Reaction of 2-Imino-1-methylpyrrolidine (4) with *N*-Methyl-*N*-phenylcarbamoyl and *N*,*N*-Diphenylcarbamoyl Chlorides (Ureas 83 and 84).** A minimum of 2 mol of the free base 4 per mole of carbamoyl chloride was required. The second mole of 4 functioned as a HCl scavenger. The separated 4·HCl was easily reclaimed by filtration. The filtrate, following a $H_2O$ wash and drying, furnished the product ureas. Triethylamine was not effective as a scavenger.

**III. Via Isothiocyanates.** Thioureas 80 and 81. These products, obtained analogously from the appropriate isothiocyanate and free base 4, gave the following compounds.

***N*-(1-Methyl-2-pyrrolidinylidene)-*N'*-phenylthiourea**: mp 142–143.5 °C (from EtOAc in 64% yield); UV max (MeOH) 296 nm ($\epsilon$ 24 300). Anal. Calcd for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48. Found: C, 61.80; H, 6.55.

***N*-(1-Methyl-2-pyrrolidinylidene)-*N'*-(4-nitrophenyl)-thiourea:** mp 179–180.5 °C dec (from acetone in 73% yield); UV max (MeOH) 220 nm ($\epsilon$ 14 700), 256 (10 700), 332 sh (22 000), 357.5 (25 300). Anal. Calcd for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07. Found: C, 51.76; H, 5.12.

**IV. Via Other Ureas. *N*-(4-Hydroxyphenyl)-*N'*-(1-methyl-2-pyrrolidinylidene)urea (22).** To a solution of 11.16 g (0.034 mol) of urea 21 in 80 mL of glacial HOAc was added 0.68 g of 10% Pd/C. Hydrogenation at a starting pressure of 57 psi, followed by filtration, solvent removal in vacuo, and recrystallization, gave pure 22.

***N*-(3-Chloro-4-hydroxyphenyl)-*N'*-(1-methyl-2-pyrrolidinylidene)urea (70).** Hydrogenation of urea 69, 9.1 g (0.025 mol), was carried out in absolute EtOH as a suspension. Dilution with MeOH to effect solution, followed by appropriate workup, gave pure 70.

***N*-(1-Methyl-2-pyrrolidinylidene)-*N'*-(3-methylsulfinylphenyl)urea (42).** A mixture of urea 40, 7.89 g (0.03 mol), 75 mL of aqueous $NaIO_4$ (0.5 M), and 75 mL of MeOH was stirred overnight at room temperature. The precipitate was filtered and washed with $CHCl_3$. The filtrate was extracted with $CHCl_3$, the combined washings and extracts were dried ($K_2CO_3$), and the solvent was removed in vacuo. Urea 42, after recrystallization from MeOH, indicated a trace of impurity with $R_f$ identical with that of urea 43 (vide infra) [TLC Si GF, acetone–$CHCl_3$ (1:4)].

***N*-(1-Methyl-2-pyrrolidinylidene)-*N*-(3-methylsulfonylphenyl)urea (43).** Urea 40, 7.4 g (0.028 mol), in 50 mL of warm glacial HOAc, was treated with aqueous $KMnO_4$ (3%) until an excess was present. After being stirred at room temperature 15 min, excess $KMnO_4$ and $MnO_2$ were reduced with $NaHSO_3$ solution. Dilution with ice, basification with 5 N NaOH, extraction ($CHCl_3$), drying ($Na_2SO_4$), and solvent removal in vacuo gave urea 43.

***N*-Phenyl-*N'*-(2-pyrrolidinylidene)urea Hydrochloride (79).** This preparation is an adaptation of the method of Jentzsch and Seefelder.[32] To a solution of 1.70 g (0.02 mol) of dry pyrrolidin-2-one and 2.72 g (0.02 mol) of phenylurea in 25 mL of dry THF at 40 °C was added a solution of 2.5 g (0.025 mol) of phosgene in 25 mL of THF. After being stirred at room temperature overnight, the resulting solid was collected. A second crop of product was obtained by dilution of the mother liquors with $H_2O$ and separation of the solution from an insoluble oil (not characterized). Basification of the aqueous solution with $Na_2CO_3$ (10%) gave a crystalline free base which was converted to the HCl salt and combined with the first crop. Recrystallization from EtOH gave pure urea 79: MeOH max 263 nm ($\epsilon$ 22 300).[33]

**Acknowledgment.** We thank the Chemistry Analytical Group headed by Dr. Harold R. Almond, Jr., and the Psychopharmacology Section, headed by Dr. J. F. Gardocki, for their valuable contributions to this work.

## References and Notes

(1) (a) J. M. Grisar, G. P. Claxton, N. L. Wiech, R. W. Lucas, R. D. Mackenzie, and S. Goldstein, *J. Med. Chem.*, 16, 679, 885 (1973); (b) L. I. Barsky and W. L. Bencze, *ibid.*, 14, 40 (1971); (c) G. I. Poos, U.S. Patent 3 725 435 (April 3, 1973);

(d) C. R. Rasmussen, U.S. Patent 3876658 (April 8, 1975).
(2) R. Kwok and P. Pranc, *J. Org. Chem.*, **32**, 738 (1967).
(3) H. Meerwein, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 1080.
(4) After our findings, T. Kato, A. Takada, and T. Ueda, *Chem. Pharm. Bull.*, **20**, 901 (1972), published this method. These authors reported a 68% yield of **4** as the hydrochloride salt.
(5) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).
(6) The structures of these by-products have not yet been elucidated. However, we tentatively believe them to be related to those reported by R. Richter, *Chem. Ber.*, **101**, 3002 (1968).
(7) (a) I. Geller, "Psychosomatic Medicine", J. H. Nodine and J. H. Moyer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, p 267; (b) D. L. Margules and L. Stein, *Psychopharmacologia*, **13**, 74 (1968).
(8) J. F. Gardocki, W. E. Hageman, and T. P. Pruss, *Arch. Int. Pharmacodyn. Ther.*, in press.
(9) G. D. Diana, U.S. Patent 3717648 (Feb 20, 1973).
(10) H. D. McCurdy, Pitman-Moore, Inc., private communication.
(11) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(12) M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, *Proc. Soc. Exp. Biol. Med.*, **70**, 254 (1949).
(13) G. Chen and B. Bohner, *J. Pharmacol. Exp. Ther.*, 117, 142 (1956).
(14) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).
(15) K. Inukai and Y. Maki, *Kogyo Kagaku Zasshi*, **70**, 491 (1967); *Chem. Abstr.*, **68**, 2655 (1968).
(16) R. Long and K. Schofield, *J. Chem. Soc.*, 2066 (1953).
(17) This method is modeled after that of H. Oelschlager, *Chem. Ber.*, **89**, 2029 (1956).
(18) H. D. K. Drew and D. B. Kelly, *J. Chem. Soc.*, 639 (1941).
(19) J. C. Thurman, *Chem. Ind. (London)*, 752 (1964).
(20) R. L. Clark and A. A. Pessolano, *J. Am. Chem. Soc.*, **80**, 1657 (1958).
(21) H. E. Dadswell and J. Kenner, *J. Chem. Soc.*, 1102 (1927).
(22) K. Inukai and Y. Maki, *Kogyo Kagaku Zasshi*, **67**, 807 (1964); *Chem. Abstr.*, **61**, 9418 (1964).
(23) R. M. Peck, G. L. Miller, and H. J. Creech, *J. Am. Chem. Soc.*, **75**, 2364 (1953).
(24) A. I. Vogel, "Practical Organic Chemistry", 3rd ed, Longman, Green and Co., London, 1956, p 572.
(25) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).
(26) H. M. Singleton and W. R. Edwards, Jr., *J. Am. Chem. Soc.*, **60**, 540 (1938).
(27) J. G. Lombardino and C. F. Gerber, *J. Med. Chem.*, 7, 97 (1964).
(28) G. P. Pollini, A. Barco, and G. DeGiuli, *Synthesis*, 44 (1972).
(29) J. Colonge and J.-M. Pouchol, *Bull. Soc. Chim. Fr.*, 598 (1962).
(30) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc. C*, 2128 (1967).
(31) I. N. Kiseleva, M. M. Zobacheva, and V. V. Perekalin, *Zh. Org. Khim.*, **10**, 2224 (1974).
(32) W. Jentzsch and M. Seefelder, *Chem. Ber.*, **98**, 274 (1965).
(33) We have also prepared *N*-phenyl-*N'*-(2-pyrrolidinylidene)urea by reaction of 2-iminopyrrolidine (2-amino-1-pyrroline) with phenyl isocyanate and by hydrogenolysis of *N*-(1-benzyl-2-pyrrolidinylidene)-*N'*-phenylurea. The products of these reactions were identical.

# A New Warfarin Metabolite: Structure and Function

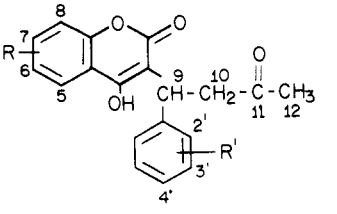
Michael J. Fasco, Paul P. Dymerski, J. David Wos, and Laurence S. Kaminsky*

*Division of Laboratories and Research, New York State Department of Health, Albany, New York 12201.*
*Received February 27, 1978*

The metabolism of the clinically utilized, anticoagulant warfarin [4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one] by rat liver microsomes has been investigated. The structure of a new warfarin metabolite [4-hydroxy-3-(3-oxo-1-phenyl-1-butenyl)-2*H*-1-benzopyran-2-one] (dehydrowarfarin) has been determined by mass spectral comparison with the chemically synthesized compound. The formation of dehydrowarfarin is catalyzed by cytochrome P-450 and is unusual in that the final product is effectively dehydrogenated warfarin.

Warfarin [4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one] (1) is a vitamin $K_1$ antagonist widely employed as a rodenticide and as a therapeutic drug for the treatment of such coagulation disorders as thrombophlebitis, pulmonary embolism, and myocardial infarction. Human[1] and rodent[2,3] resistance to warfarin has been encountered, however, and clinical complications have arisen as a consequence of its administration with other medications.[4,5]

The clinical and environmental importance of warfarin has prompted a number of investigations to determine its pharmacological and biological fate. The *R* and *S* optical enantiomers of warfarin have been resolved.[6] (*S*)-Warfarin is five to eight times more potent an anticoagulant than (*R*)-warfarin in both man[7-10] and the rat.[11-14] In man (*S*)-warfarin is metabolized faster than the *R* isomer, whereas in the rat (*R*)-warfarin is metabolized more rapidly.[12-14] These observations suggest that the rate of metabolism of the warfarin enantiomers is not solely responsible for their different hemorrhagic potencies. Barker et al.[15] found little unmetabolized warfarin in the urine of rats administered the drug but were able to identify four monohydroxylated metabolites (1a–**d**) as well as a cyclized



1, R = R' = H
1a, R = 6-OH; R' = H
1b, R = 7-OH; R' = H
1c, R = 8-OH; R' = H
1d, R = H; R' = 4'-OH

derivative, 2,3-dihydro-2-methyl-4-phenyl-5-oxo-4*H*-pyrano[3,2-*c*]-2*H*-benzopyran. Lewis and Trager[16] isolated a mixture of diastereoisomeric, aliphatic warfarin alcohols from the urine of human volunteers. Subsequent in vitro

0022-2623/78/1821-1054$01.00/0 