(+)-(1*R*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride [(*R*)-(+)-Tetrahydropapaveroline Hydrochloride] (4b·HCl). The above mother liquors, obtained from the treatment of tetrahydropapaverine with (−)-diacetone-2-keto-L-gulonic acid, were neutralized and resolved with (−)-di-*O*-*p*-toluoyl-*d*-tartaric acid in MeOH to afford 33% of (*R*)-(+)-*N*-norlaudanosine **(4a):** mp 98–99°; [α]D +28.4° ($CHCl_3$) [lit.[13] mp 97.5–98.5°, [α]D +26° ($CHCl_3$)].

In a manner similar to the procedure given for **3b**·HCl, **4a** was O-demethylated to give 77% of **4b**·HCl: mp 285–286°; [α]D +32.1°; identical in nmr and uv with **3b**·HCl; ORD and CD mirror images of **3b**·HCl. *Anal.* ($C_{16}H_{17}NO_4$·HCl) C, H, N.

(+)-(1*S*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide Hemihydrate [(*S*)-(+)-Laudanosoline Hydrobromide] (3d·HBr). Reductive alkylation of **3a** with CH_2O in the presence of Raney nickel afforded 78% of (*S*)-(+)-laudanosine **(3c):** mp 84–85°; [α]D +99.1° (EtOH) [lit.[17] mp 89°, [α]D +100°(EtOH)].

A solution of 6 g (16.8 mmoles) of **3c** in 60 ml of 48% HBr was refluxed for 3 hr and stored at 4° overnight. The crystals were filtered and dried to give 4.8 g (74%) of **3d**·HBr: mp 124–125°; [α]D +57.3°. An analytical specimen prepared from 24% HBr exhibited: mp 124–125°; [α]D +57.8°; nmr δ 2.60–3.60 (m, 3, CH_2) 2.75 (s, 3, NCH_3), 4.40 (m, 1, CH), 6.07–6.70 (m, 5, aromatic), 8.72 (b, 3, 3 OH), 8.92 (s, 1, OH), 9.90 (b, 1, N^+H); uv_{max} 230 nm (ε 11,200) (infl), 286 (6600); ORD (*c* 0.364, MeOH) $[\phi]_{600}$ +212°, $[\phi]_{589}$ +223°, $[\phi]_{299}$ +5510° (pk), $[\phi]_{283}$ −6300° (tr), $[\phi]_{244}$ +8925° (pk), and $[\phi]_{228}$ −10,500° (tr); CD (*c* 0.0095 *M*, MeOH) $[\theta]_{310}$ 0, $[\theta]_{292}$ +8610, $[\theta]_{258}$ +840, $[\theta]_{237}$ +19,110, $[\theta]_{222}$ +9240, $[\theta]_{212}$ +40,950, and $[\theta]_{220}$ +13,600. *Anal.* ($C_{17}H_{19}NO_4$·HBr·0.5H_2O) C, H, N.

(−)-(1*R*)-1-(3,4-Dihydroxybenzyl)-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide Hemihydrate [(*R*)-(−)-Laudanosoline Hydrobromide] (4d·HBr). Reductive methylation of **4a** afforded 75% of (*R*)-(−)-laudanosine **(4c):** mp 84–85°; [α]D −107.0° (EtOH) [lit.[17] mp 89°, [α]D −106° (EtOH)]. By the procedure given for the preparation of **1d**·HBr, O-demethylation of **4c** afforded 70% of **4d**·HBr: mp 124–125°; [α]D −57.3°; identical in nmr and uv with **3d**·HBr; ORD and CD mirror images of **3d**·HBr. *Anal.* ($C_{17}H_{19}NO_4$·HBr·0.5H_2O) C, H, N.

Conversion of (*S*)-(−)-Tetrahydropapaveroline Hydrochloride (3b·HCl) into (*S*)-(+)-Laudanosine (3c). A suspension of 500 mg (1.55 mmoles) of **3b**·HCl in 30 ml of MeOH was treated with CH_2N_2 according to the procedure given for the conversion of **1b** into **1c** to afford, after crystallization from ether, 350 mg (55%) of **3c**, identical in mmp, [α]D and nmr with **3c** obtained from **3a.**

Acknowledgments. We wish to thank the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, and Dr. V. Toome for the uv, ORD, and CD spectra.

References

(1) A. Brossi, A. Focella, and S. Teitel, *Helv. Chim. Acta,* **55,** 15 (1972) (paper 1).
(2) P. Holtz, K. Stock, and E. Westermann, *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.,* **248,** 387 (1964).
(3) P. V. Halushka and P. C. Hoffmann, *Biochem. Pharmacol.,* **17,** 1873 (1968).
(4) V. E. Davis and M. S. Walsh, *Science,* **167,** 1005 (1970).
(5) H. Yamanaka, M. S. Walsh, and V. E. Davis, *Nature (London),* **227,** 1143 (1970).
(6) G. Cohen and M. Collins, *Science,* **167,** 1749 (1970).
(7) T. L. Sourkes, *Nature (London),* **229,** 413 (1970).
(8) R. Heikkila, G. Cohen, and D. Dembiec, *J. Pharmacol. Exp. Ther.,* **179,** 250 (1971).
(9) A. M. Hjort, E. J. deBeer, and R. W. Fassett, *ibid.,* **62,** 195 (1938); D. W. Fassett and A. M. Hjort, *ibid.,* **63,** 253 (1938); A. M. Hjort, E. J. deBeer, J. S. Buck, and L. O. Randall, *ibid.,* **76,** 263 (1942).
(10) A. H. Beckett, *Fortschr. Arzneimittelforsch.,* 1,455 (1959).
(11) E. Späth, and F. Dengel, *Chem. Ber.,* **71,** 113 (1938).
(12) A. R. Battersby and T. P. Edwards, *J. Chem. Soc.,* 1214 (1960).
(13) A. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *ibid.,* 3600 (1964).
(14) K. Kakemi, *Yakugaku Zasshi,* **60,** 11 (1940).
(15) T. Reichstein and A. Grüssner, *Helv. Chim. Acta,* **17,** 311 (1934).
(16) H. Corrodi and E. Hardegger, *ibid.,* **39,** 889 (1956).
(17) A. Pictet and B. Athanesecu, *Chem. Ber.,* **33,** 2346 (1900).

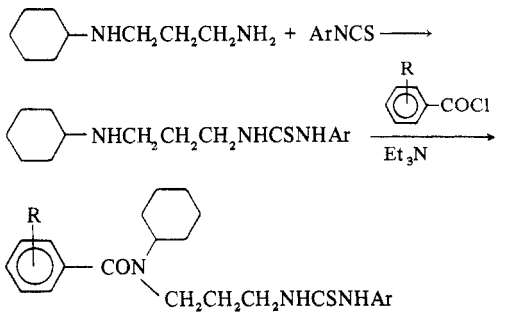
Anticonvulsant Activity of Nitrobenzamides and Their Inhibition of Nicotinamide-Adenine Dinucleotide Dependent Oxidations†

Surendra S. Parmar,* C. Dwivedi,‡ Basheer Ali,§ and R. S. Misra§

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow-3, India.
Received January 5, 1972

CNS-depressant properties exhibited by *N*-cyclohexylnitrobenzamides[1-3] prompted the synthesis of *N*-cyclohexyl-*N*-(1-aryl-3-propylthiocarbamido)nitrobenzamides. Anticonvulsant properties of these nitrobenzamides were investigated against pentylenetetrazol-induced seizures. Selective inhibitory effects of these nitrobenzamides were observed on nicotinamide-adenine dinucleotide (NAD) dependent oxidation of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and $NADH_2$ where NAD-independent oxidation of succinate was unaltered. Attempts were made to correlate the anticonvulsant activity of these nitrobenzamides with their enzyme inhibitory properties. The various nitrobenzamides were synthesized according to steps outlined in Scheme I.

Scheme I



Experimental Section

1-Aryl-3-(3-cyclohexylaminopropyl)thiocarbamides. 3-Cyclohexylaminopropylamine (0.02 mole) and suitable aryl isothiocyanates (0.02 mole) were mixed in 30 ml of dry PhH and warmed on a steam bath for 30 min. The reaction mixt was concd under reduced pressure. On cooling, the solid mass which sepd out was filtered, washed (H_2O, Et_2O), dried, and recrystd (EtOH). All compounds were characterized by their sharp melting points and elemental analyses (Table I).

***N*-Cyclohexyl-*N*-(1-aryl-3-propylthiocarbamido)nitrobenzamides.** Following the method of Roll[3] to a well-stirred and cooled mixt of 1-aryl-3-(3-cyclohexylaminopropyl)thiocarbamide (0.005 mole) and $(Et)_3N$ (0.005 mole) in 20 ml of DMF, an appropriate nitrobenzoyl chloride (0.005 mole) soln in 10 ml of DMF was added, and the mixt was stirred for 30 min. The crude product, which sepd out by the addition of ice water, was filtered, washed (H_2O), dried, and recrystd (EtOH-H_2O). These nitrobenzamides were characterized by their sharp melting points and elemental analyses (Table II).

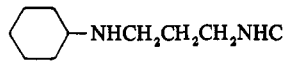
Biochemical Studies. Materials and Methods. Commercial chemicals were used in the present study. AMP, cytochrome *c*, α-ketoglutarate, and $NADH_2$ were obtained from Sigma Chemical Co., St. Louis, Mo., sodium β-hydroxybutyrate from Mann Research Laboratories Inc., New York, N. Y., sodium pyruvate from E. Merck, Darmstadt, and sodium succinate and other common chemicals were purchased from the British Drug House, Bombay.

Assay of Respiratory Activity of Rat Brain Homogenate. Res-

†This investigation was supported in part by financial assistance obtained from the Indian Council of Medical Research, New Delhi, and the Council of Scientific and Industrial Research, New Delhi.
‡Junior Research Fellow of I.C.M.R., New Delhi.
§Junior Research Fellow of C.S.I.R., New Delhi.

piratory activity was detd[4] by measuring O_2 consumption in the conventional Warburg manometric apparatus at 37° with air as the gas phase. Fresh brain homogenates of healthy albino rats equiv to 125 mg wet wt of brain were used in each flask. Homogenates were prepd in ice-cold 0.25 *M* sucrose. The reaction mixt in a final volume of 3 ml consisted of 20 m*M* Na_2HPO_4 buffer soln of pH 7.4, 6.7 m*M* $MgSO_4$, 1 m*M* AMP (Na salt), 33 m*M* KCl, and 500 μg of cytochrome *c*. The central well contained 0.2 ml of 20% KOH soln. The final concns of various substrates and nitrobenzamides used were 10 and 2 m*M*, respectively.

Table I. 1-Aryl-3-(3-cyclohexylaminopropyl)thiocarbamides



Ar	Mp,[a] °C	Yield, %	Molecular[b] formula
C_6H_5	126	84	$C_{16}H_{25}N_3S$
2-$CH_3C_6H_4$	131	66	$C_{17}H_{27}N_3S$
3-$CH_3C_6H_4$	123	78	$C_{17}H_{27}N_3S$
4-$CH_3C_6H_4$	147	85	$C_{17}H_{27}N_3S$
3,4-$(CH_3)_2C_6H_3$	117	70	$C_{18}H_{29}N_3S$
2-$OCH_3C_6H_4$	118	64	$C_{17}H_{27}N_3OS$
4-$OCH_3C_6H_4$	115	84	$C_{17}H_{27}N_3OS$

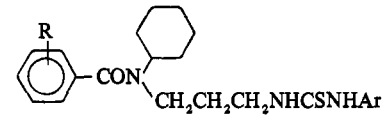
[a]Melting points were taken in open capillary tubes and are uncorrected. [b]All compounds were analyzed for C, H, and N and analyses were found within limits.

Anticonvulsant activity was detd[5] in albino mice of either sex weighing 25–30 g. Nitrobenzamides (100 mg/kg) were injected ip in 5% aqueous suspension of gum acacia to each group of 10 animals. Pentylenetetrazol (80 mg/kg) was injected sc 4 hr after the administration of nitrobenzamides. The occurrence of seizures was observed for the next 60 min. An episode of clonic spasm which persisted for at least 5 sec was considered a threshold convulsion. Animals not exhibiting even a threshold convulsion during 60 min were considered protected. Anticonvulsant activity was represented as per cent protection. The mortality was recorded after 24 hr to obtain an idea of the toxicity of these nitrobenzamides in pentylenetetrazol-treated animals.

Results and Discussion

The anticonvulsant activity exhibited by these nitrobenzamides at a dose of 100 mg/kg against pentylenetetraz-

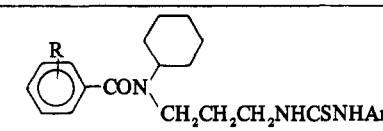
Table II. *N*-Cyclohexyl-*N*-(1-aryl-3-propylthiocarbamido)nitrobenzamides and Their Anticonvulsant Activity



No.	Ar	R	Mp,[a] °C	Yield, %	Molecular[b] formula	Protection,[c] %	Mortality,[d] %
1	C_6H_5	3-NO_2	148	62	$C_{23}H_{28}N_4O_3S$	40	0
2	2-$CH_3C_6H_4$	3-NO_2	162	52	$C_{24}H_{30}N_4O_3S$	40	10
3	3-$CH_3C_6H_4$	3-NO_2	168	56	$C_{24}H_{30}N_4O_3S$	60	20
4	4-$CH_3C_6H_4$	3-NO_2	186	60	$C_{24}H_{30}N_4O_3S$	40	20
5	3,4-$(CH_3)_2C_6H_3$	3-NO_2	149	58	$C_{25}H_{32}N_4O_3S$	40	10
6	2-$OCH_3C_6H_4$	3-NO_2	72	50	$C_{24}H_{30}N_4O_4S$	60	10
7	4-$OCH_3C_6H_4$	3-NO_2	146	60	$C_{24}H_{30}N_4O_4S$	40	0
8	C_6H_5	4-NO_2	182	64	$C_{23}H_{28}N_4O_3S$	40	50
9	2-$CH_3C_6H_4$	4-NO_2	187	55	$C_{24}H_{30}N_4O_3S$	30	40
10	3-$CH_3C_6H_4$	4-NO_2	198	58	$C_{24}H_{30}N_4O_3S$	60	40
11	4-$CH_3C_6H_4$	4-NO_2	194	65	$C_{24}H_{30}N_4O_3S$	20	40
12	3,4-$(CH_3)_2C_6H_3$	4-NO_2	167	60	$C_{25}H_{32}N_4O_3S$	20	40
13	2-$OCH_3C_6H_4$	4-NO_2	156	54	$C_{24}H_{30}N_4O_4S$	60	20
14	4-$OCH_3C_6H_4$	4-NO_2	138	62	$C_{24}H_{30}N_4O_4S$	40	50

[a,b]See footnotes to Table I. [c]Anticonvulsant activity is represented as per cent protection against pentylenetetrazol-induced seizures. [d]Toxicity represented as per cent deaths during the period of 24 hr of animals treated with pentylenetetrazol.

Table III. Effect of *N*-Cyclohexyl-*N*-(1-aryl-3-propylthiocarbamido)nitrobenzamides on the Oxidation of Different Substrates of Tricarboxylic Acid Cycle, $NADH_2$ and β-Hydroxybutyrate by Rat Brain Homogenate[a]



No.	Ar	R	Pyruvate	α-Keto-glutarate	β-Hydroxy-butyrate	$NADH_2$	Succinate
1	C_6H_5	3-NO_2	27.44 ± 0.98	23.84 ± 0.58	36.27 ± 0.65	34.91 ± 0.44	Nil
2	2-$CH_3C_6H_4$	3-NO_2	35.47 ± 0.85	28.75 ± 0.68	42.32 ± 0.85	38.28 ± 0.32	Nil
3	3-$CH_3C_6H_4$	3-NO_2	47.60 ± 1.80	40.21 ± 0.85	50.91 ± 0.88	49.98 ± 0.44	Nil
4	4-$CH_3C_6H_4$	3-NO_2	72.34 ± 1.85	74.46 ± 1.66	63.06 ± 1.25	71.36 ± 0.58	Nil
5	3,4-$(CH_3)_2C_6H_3$	3-NO_2	77.19 ± 2.01	77.15 ± 1.70	80.42 ± 1.50	80.36 ± 0.68	Nil
6	2-$OCH_3C_6H_4$	3-NO_2	46.33 ± 1.02	38.88 ± 1.02	44.29 ± 0.78	39.03 ± 0.50	Nil
7	4-$OCH_3C_6H_4$	3-NO_2	60.42 ± 1.22	61.94 ± 1.22	53.75 ± 0.81	60.10 ± 0.32	Nil
8	C_6H_5	4-NO_2	27.60 ± 0.75	37.47 ± 0.68	37.34 ± 0.75	25.43 ± 0.48	Nil
9	2-$CH_3C_6H_4$	4-NO_2	50.63 ± 0.68	54.03 ± 1.25	55.17 ± 1.25	48.46 ± 0.10	Nil
10	3-$CH_3C_6H_4$	4-NO_2	60.41 ± 0.99	55.67 ± 0.82	63.00 ± 0.77	59.61 ± 1.10	Nil
11	4-$CH_3C_6H_4$	4-NO_2	64.80 ± 1.54	65.80 ± 1.25	73.14 ± 0.78	72.70 ± 1.50	Nil
12	3,4-$(CH_3)_2C_6H_3$	4-NO_2	75.29 ± 1.75	75.46 ± 1.55	79.20 ± 0.80	76.95 ± 0.88	Nil
13	2-$OCH_3C_6H_4$	4-NO_2	38.62 ± 0.87	42.91 ± 0.85	42.00 ± 0.75	34.10 ± 0.76	Nil
14	4-$OCH_3C_6H_4$	4-NO_2	40.93 ± 0.65	48.99 ± 1.25	45.56 ± 0.68	41.77 ± 0.63	Nil

[a]Each experiment was done in duplicate. All values represent mean values of per cent inhibition with standard error (S.E.) calcd from 2 separate experiments. Inhibition was detd by the decrease in the O_2 uptake/125 mg wet wt of tissue per hr. All nitrobenzamides were used at a final concentration of 2 m*M*. Assay conditions are as indicated in the text.

ol-induced seizures are shown in Table II. All nitrobenzamides exhibited protection which ranged from 20 to 60%. Nitrobenzamides having 3-methylphenyl and 2-methoxyphenyl substituents (**3, 6, 10, 13**) at position 1 of the thiocarbamide moiety in both 3-nitro- as well as 4-nitrobenzamides were found to exhibit 60% protection against pentylenetetrazol-induced seizures. It is evident from Table II that all 3-nitrobenzamides elicited low mortalities after 24 hr in pentylenetetrazol-treated animals.

It is evident from Table III all nitrobenzamides were found to inhibit *in vitro* NAD-dependent oxidation of pyruvate, α-ketoglutarate, and β-hydroxybutyrate when they were incubated with rat brain homogenate. Selectivity of inhibition of respiratory activity was thus observed since NAD-independent oxidation of sodium succinate was found to remain unaltered. The ability of these nitrobenzamides to inhibit the oxidation of $NADH_2$ unlike anticonvulsant quinazolones[6,7] provides evidence regarding their possible inactivation of the process of electron transfer in the electron transport chain (ETC) by presumably acting at the site of transfer of electrons from $NADH_2$ to FAD.

The position of the nitro substituent at either the 3 or 4 position of the benzamide nucleus was found to have no significant effect on the biological properties of the compounds. On the other hand, substitutions at various positions of the benzamide and at position 1 of the thiocarbamide moiety have been found to play a definite role in influencing the ability of these compounds to inhibit oxidations of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and $NADH_2$. In all these nitrobenzamides presence of a 3,4-dimethylphenyl substituent was found to be most effective in producing inhibition of the oxidation of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and $NADH_2$ independently while an unsubstituted phenyl group was found to exhibit low inhibitory effect under similar experimental conditions. The greater effectiveness of 3-nitro- as well as 4-nitrobenzamides having 3-methylphenyl and 2-methoxyphenyl substituents at position 1 of the thiocarbamide moiety could not be reflected by their ability to selectively inhibit NAD-dependent oxidations. Introduction of a Me or MeO substituent in the phenyl moiety of the thiocarbamide part resulted in an increase in the degree of inhibition which was in the order of 4-substituted > 3-substituted > 2-substituted > unsubstituted. It was interesting to note that, in general, substitution of a MeO group (**6, 7, 13, 14**) for a Me group (**2, 4, 9, 11**) at position 2 or 4 of the phenyl nucleus attached at position 1 of the thiocarbamide moiety was found to decrease the inhibitory ability of almost all of these 3-nitro- and 4-nitrobenzamides (Table III). Inhibition, on the other hand, was found to increase by substitution of methoxy groups (**6**) in place of methyl substituents (**5**), which increase, however, remains unexplained on the basis of these observations. These studies, in spite of exhibiting selective inhibition of NAD-dependent oxidations, have failed to reveal a biochemical basis for anticonvulsant properties of these substituted nitrobenzamides.

Acknowledgments. The authors wish to express their thanks to Professor K. P. Bhargava and Dr. J. P. Barthwal for their advice and encouragement and to Dr. M. L. Dhar and Dr. Nitya Anand of the Central Drug Research Institute, Lucknow, for providing microanalysis facilities. Grateful acknowledgment is made to Professor B. D. Sanwal of the University of Toronto Medical School, Toronto, for his generous gift of research biochemicals.

References

(1) W. D. Roll, *J. Pharm. Sci.*, **57**, 1671 (1968).
(2) W. D. Roll, *J. Med. Chem.*, **13**, 303 (1970).
(3) W. D. Roll, *J. Pharm. Sci.*, **59**, 1838 (1970).
(4) R. S. Varma, B. Ali, S. S. Parmar, and W. L. Nobles, *J. Med. Chem.*, **13**, 147 (1970).
(5) S. S. Parmar, C. Dwivedi, A. Chaudhari, and T. K. Gupta, *ibid.*, **15**, 99 (1972).
(6) P. K. Seth and S. S. Parmar, *Can. J. Physiol. Pharmacol.*, **43**, 1019 (1965).
(7) S. S. Parmar and S. Nagar, *Jap. J. Pharmacol.*, **19**, 460 (1969).

Sudoxicam and Related N-Heterocyclic Carboxamides of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide. Potent Nonsteroidal Antiinflammatory Agents

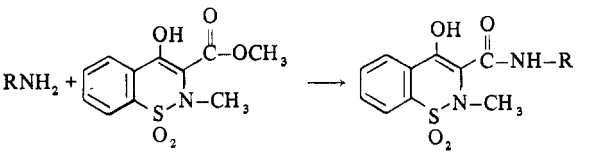
Joseph G. Lombardino* and Edward H. Wiseman

Pfizer Central Research, Pfizer, Inc., Groton, Connecticut 06340. *Received February 3, 1972*

Previous publications from these laboratories have described the antiinflammatory properties in animals of acidic heterocyclic compounds containing, as essential structural features, a relatively nonbasic nitrogen atom, a potentially enolic function, and a carboxamide substituent. Our initial reports described the antiinflammatory activity of the carboxanilides of 1,3-dioxoisoquinoline,[1,2] of 3-oxo-1,2-benzothiazine 1,1-dioxide,[3] and of 4-hydroxy-1,2-benzothiazine 1,1-dioxide.[4,5] These compounds generally exhibited potencies in the range of that of phenylbutazone. We report here the synthesis and biological properties of some N-heterocyclic carboxamides of the 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide system, some of which exhibit extended plasma half-lives in animals and man and antiinflammatory activity in animals exceeding that of indomethacin.

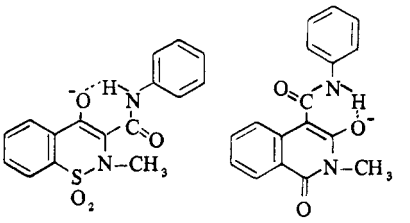
Discussion

The N-heterocyclic carboxamides were made in good yields from 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide[4] (I) and the ap-



I II

propriate heterocyclic amine in refluxing (18 hr) xylene solution. Infrared and nuclear magnetic resonance spectra of II indicated predominance of the enol rather than the



III IV

β-keto form. These N-heterocyclic carboxamides were generally more acidic ($pK_a \sim 5$-6 in 2:1 dioxane-H_2O) than the previously studied[4] N-aryl and N-alkyl carbox-