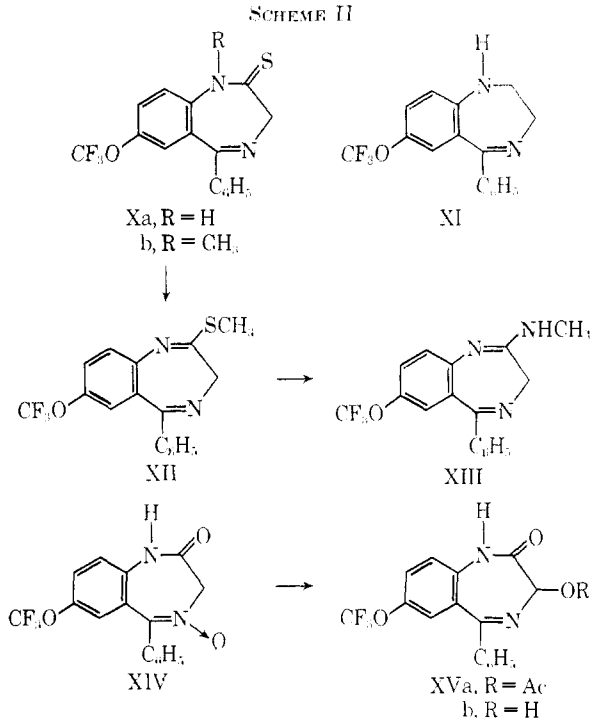
SCHEME II



Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Procedures used for the preparation of new compounds are indicated by the appropriate reference; when chromatography was required for the isolation of pure materials, as confirmed by thin layer chromatography, the details are summarized. All chromatography was conducted on a synthetic magnesia–silica gel adsorbent. The petroleum ether used was the fraction boiling at 30–60°. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

3-Phenyl-5-trifluoromethoxyanthranil (Va) was prepared by condensation of *p*-nitrophenyl trifluoromethyl ether[1b] with $PhCH_2CN$.[8,9] The product was eluted with petroleum ether–CH_2Cl_2 (3:1) and recrystallized (Me_2CO–H_2O) with difficulty; 20% yield, mp 87–89°. *Anal.* ($C_{14}H_8F_3NO_2$) C, H, N.

3-Phenyl-5-trifluoromethylthioanthranil (Vb).—Phenyl trifluoromethyl sulfide (34.5 g, 0.194 mole) was nitrated as described previously.[1b] Distillation of the crude product (28 g) with a spinning-band column gave 47% of a mixture of *o*- and *p*-nitrophenyl trifluoromethyl sulfides. Condensation of 15.3 g of this mixture with $PhCH_2CN$ was effected with methanolic KOH.[8,9] The product, isolated with ether, was dissolved in petroleum ether–CH_2Cl_2 (3:1) and chromatographed. The material eluted by petroleum ether–CH_2Cl_2 (3:1) was rechromatographed to furnish 7.34 g (36%) of yellow crystals. A sample recrystallized from MeOH–H_2O had mp 97–98°. *Anal.* ($C_{14}H_8F_3NOS$) C, H, N, S.

The remaining new compounds are given in Table II.

Acknowledgment.—Microanalyses were furnished by Mr. L. Brancone and his staff.

Sulfonylureas Having Diuretic Activity

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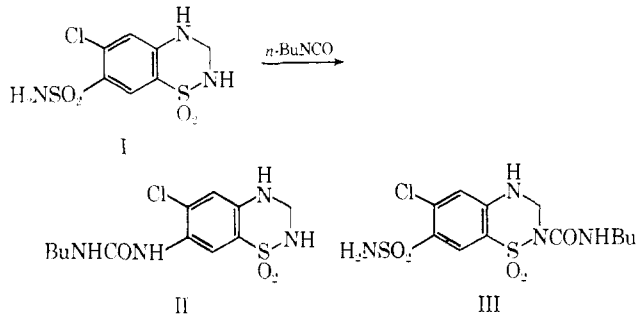
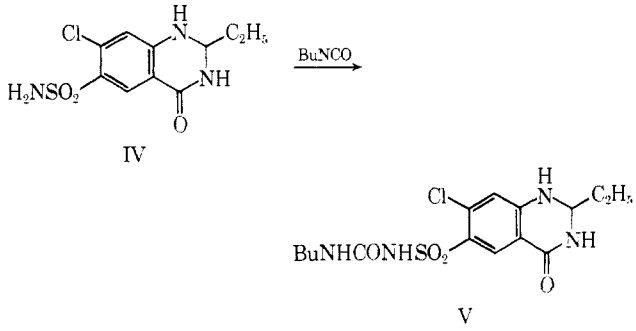
A patent[1] describing carbamoyl derivatives of 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides prompts us to report our own findings with such preparations because, at least in one instance, our results differ.

When we treated hydrochlorothiazide (I) with butyl isocyanate, a single product was obtained, mp 156–157°, to which we have assigned structure II. In the patent cited above, under reaction conditions essentially identical with those which we have employed, the product obtained had a melting point of 174° and was assigned structure III.



We have assigned structure II to our reaction product on the following basis: (a) it is reported that isocyanates do not react with N-substituted sulfonamides;[2] (b) the doublet at 2.95 and 3.05 μ in the ir spectra of I, characteristic of the unsubstituted 7-sulfamyl group, is no longer present in II; and (c) the related sulfamylquinazolone (IV), in which reaction at position II is unlikely, yields under comparable reaction conditions a monosulfonylurea derivative (V) of very similar structure to II. We are at a loss to explain the observed differences under what appears to be essentially identical reaction conditions.



Compound II was devoid of hypoglycemic activity in the guinea pig but showed a diuretic potency in rats essentially equivalent to that of hydrochlorothiazide, but with a somewhat better Na/K ratio.[3] Compound V was much less potent than II as a diuretic agent.

Experimental Section[4]

6-Chloro-3,4-dihydro-7-(N-butylcarbamoyl)sulfamyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—To a solution of 10.0 g (0.0336 mole) of 6-chloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4-benzothiazine 1,1-dioxide (I) in 34 ml (0.0336 mole) of 1 *N* NaOH and 34 ml of Me_2CO at 10°, was added 3.32 g (0.0336 mole) of *n*-butyl

(1) C. deStevens and L. H. Werner, U. S. Patent 3,252,975 (1966).

(2) F. Kurzer in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, p 495.

(3) We are indebted to Dr. A Maass and Dr. D. Walz and their staffs, of these laboratories, for the biological test results. For the diuretic assay, the procedure of V. D. Wiebelhaus, F. T. Brennan, and G. F. Sosnowski, *Fed. Proc.*, **19**, 364 (1960), was used; the hypoglycemic activity was determined using the procedure described in the paper by B. Loev, K. M. Snader, and D. T. Walz, *J. Med. Chem.*, **6**, 506 (1963).

(4) All melting points are corrected; ir spectra were taken as Nujol mulls on a Perkin-Elmer Model 137 Infracord.

isocyanate in an equal volume of acetone. After 3 hr at 25°, Me_2CO was removed *in vacuo* and the residual aqueous solution was acidified with dilute HCl to give a white solid. After several recrystallizations from MeOH-Et_2O, 2.0 g of pure product, mp 156–157° dec, and 9.2 g of impure white solid were obtained. Chromatography of the impure solid on 60–100 mesh Florisil using EtOAc as eluent gave unreacted I and an additional 4.0 g of pure product, mp 156–157° dec, ir singlet at 2.9 μ. *Anal.* ($C_{12}H_{17}ClN_4O_5S_2$) C, H, N.

7-Chloro-2-ethyl-6-(*n*-butylcarbamoyl)sulfamyl-1,3-dihydro-4(3H)-quinazolone (V).—7-Chloro-2-ethyl-6-sulfamyl-1,2-dihydro-4-quinazolone (IV, 8 g) was treated with 2.7 g of *n*-butyl isocyanate under the same conditions described above to give, after acidification of the aqueous solution, 8.2 g of crude product. It was purified by being put through a $NaHCO_3$–HCl treatment, then recrystallizing from EtOH, to give 4 g of product, mp 152° dec, ir singlet at 2.9 μ. *Anal.* ($C_{15}H_{21}ClN_4O_4S$) C, H, N.

Central Nervous System Depressants. VIII.[1] Pyrroles

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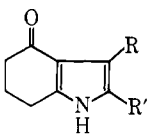
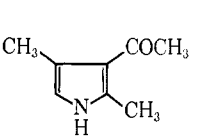
Recent interest in certain tetrahydro-4-oxoindoles[2] (I) and related pyrroles prompts us to report our work on some similar compounds. It was observed, in these laboratories, that many substituted pyrroles possessed marked CNS depressant properties in mice and rats. One of these, **3**, showed enough promise in animals that



I



3

it was studied in man as a muscle relaxant and tranquilizer. Unfortunately, side effects precluded doses large enough to observe its CNS effects. In attempts to obtain a better analog, a number of other ketopyrroles were prepared. However, none was markedly more potent than **3** in animals.

Table I lists pyrroles tested for their CNS depressant properties as observed in intact mice. Many of these are from commercial sources or are well known in the literature. Table II lists the new pyrroles which were prepared by modifications of the Knorr syntheses. Those of type I were prepared by reducing 1,3-cyclohexadione and an α-ketoxime with zinc and acetic acid, or were obtained by modification of an ester group in the primary Knorr product.

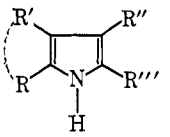
Experimental Section[3]

Ethyl 4,5,6,7-Tetrahydro-3-methyl-4-oxo-2-indolecarboxylate (**23**).—To a solution of 40.2 g (0.309 mole) of ethyl acetoacetate in 120 ml of AcOH was slowly added, with stirring and cooling in an ice bath, a solution of 246 g (0.335 mole) of $NaNO_2$ in 40 ml of H_2O at such a rate that the temperature remained below

(1) Paper VII of this series: R. B. Moffett, *J. Med. Chem.*, **7**, 446 (1964).

(2) (a) S. Hauptmann, H. Blume, G. Hartmann, D. Haendel, and P. Franke, *Z. Chem.*, **6**, 107 (1966); (b) K. Schoen, I. J. Pachter, and A. Rubin, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts M46; (c) M. J. Weiss, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967; (d) E. Bisagni, J. Marquet, J. Andre-Louisfert, A. Chentin, and F. Leinte, *Bull. Soc. Chim. France*, 2796 (1967).

TABLE I
PHARMACOLOGICAL ACTIVITY



No.	R	R′	R″	R‴	LD_{50},[a] mg/kg Mouse	LD_{50},[a] mg/kg Rat	Depression,[a] mg/kg Mouse	Depression,[a] mg/kg Rat	Motor act.,[b] mg/kg
1	CH_3	CH_2CH_3	CH_3	H	77		30		*c*
2	$COCH_3$	H	H	H	>1000				300
3	CH_3	$COCH_3$	CH_3	H	400	250	100	40	100[d]
4	CH_3	$COCH_3$	H	CH_3	553	225	100	70	30[e]
5	CH_3	$COCH_3$	CH_3	CH_3	233		100	70	40[f]
6	$COCH_3$	CH_3	CH_2CH_3	CH_3	767	400	<100	<100	70[g]
7	$COCH_3$	CH_3	$COCH_3$	CH_3	300	200		70	25
8	$COOCH_2CH_3$	CH_3	$COCH_3$	CH_3	1000		300		300
9	COOH	CH_3	$COCH_3$	CH_3	>1000		300	130	
10	$COCH_3$	CH_3	$COOCH_2CH_3$	CH_3	650		100	70	
11	$CONHCH_2C_6H_5$	CH_3	$COCH_3$	CH_3	300	>300	<300	130	50
12	CONH-3,4,5-$(OCH_3)_3C_6H_2$	CH_3	$COCH_3$	CH_3	>1000	>1000			
13	CH_3	CONH-3,4,5-$(OCH_3)_3C_6H_2$	CH_3	CH_3	>1000	>1000			
14	C_6H_5	H	H	H	533		<300		
15	COC_6H_5	H	H	H	767	750	100	*h*	225
16	CH_2COOH	H	H	C_6H_5	650		<300		
17	$CH_2CONHNH_2$	H	H	C_6H_5	1000		10		
18	C_6H_5	$COOCH_2CH_3$	CH_3	CH_3	>1000		300		
19		$-CH_2CH_2CH_2-$	$COCH_3$	CH_3	200		30		35
20		$-CH_2CH_2CH_2CO-$	$COCH_3$	H	233		100		
21[i]		$-CH_2CH_2CH_2CO-$	CH_3	CH_3	200		100		80
22		$-CH_2CH_2CH_2CO-$	CH_3	$COCH_3$	533		30	68	50
23		$-CH_2CH_2CH_2CO-$	CH_3	$COOCH_2CH_3$	1000				
24		$-CH_2CH_2CH_2CO-$	CH_3	COOH	>1000				

[a] For methodology see R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964), Table I, footnotes *a* and *b*. [b] For methodology see R. B. Moffett and P. H. Seay, *ibid.*, **2**, 229 (1960), Table I, footnote *c*. [c] Anticonvulsant activity. Dose protecting 50% of rats against supramaximal electroshock, 25 mg/kg ip. [d] Anticonvulsant activity. Dose protecting 50% of rats against supramaximal electroshock, 25 mg/kg ip. Muscle relaxant activity. Dose causing muscle paralysis in 50% of the mice, 115 mg/kg ip. [e] Anticonvulsant activity. Dose protecting 50% of rats against supramaximal electroshock, 20 mg/kg ip. [f] In spite of its depressant properties this compound showed about 50% increase in alert time in EEG studies. Anorexigenic effect in the dog: about 0.1 times as active as amphetamine. [g] Anticonvulsant activity. Dose protecting 50% of rats against supramaximal electroshock, 50 mg/kg. Sleep in rats at <250 mg/kg. [h] Sleep in rats at 500 mg/kg. [i] Footnote 2a.