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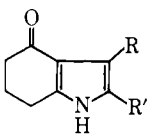
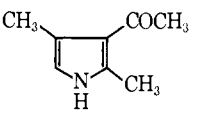
Recent interest in certain tetrahydro-4-oxoindoles[2] (I) and related pyrroles prompts us to report our work on some similar compounds. It was observed, in these laboratories, that many substituted pyrroles possessed marked CNS depressant properties in mice and rats. One of these, **3**, showed enough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

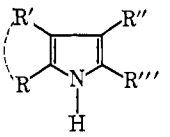
Experimental Section[3]

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-Lonisfert, A. Chentin, and F. Leinte, *Bull. Soc. Chim. France*, 2796 (1967).

TABLE I
PHARMACOLOGICAL ACTIVITY



No.	R	R′	R″	R‴	LD50,[a] mg/kg Mouse	LD50,[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.

TABLE II

CHEMICAL PROPERTIES

No. (from Table I)	Yield, %[a]	Mp, °C[b]	Crystn solvent	Formula[c]
11	58[e]	174–175	EtOH	$C_{16}H_{18}N_2O_2$
12	60[d]	201.5–203.5	MeOH	$C_{18}H_{22}N_2O_5$
13	43[e]	213.5–217	MeOH	$C_{17}H_{22}N_2O_5$
18	6.5[f]	109.5–111.5	EtOH–H_2O	$C_{13}H_{17}NO_2$
19	7.1[g]	209–210	Benzene–hexane	$C_{10}H_{13}NO$
20	66[e]	209–210	EtOH	$C_9H_{11}NO$
22	14.5[h]	171–172	MeOH	$C_{11}H_{13}NO_2$
23	25[e]	167–168	EtOH	$C_{12}H_{15}NO_3$
24	88[e]	273–274 dec	DMF–H_2O	$C_{10}H_{11}NO_3$

[a] Based on product melting not less than 2° below maximum obtained. [b] Footnote 3. [c] Prepared as described for **23** from acetoacetbenzylamide (in place of ethyl acetoacetate) and 2,4-pentanedione (in place of 1,3-cyclohexanedione). The solids did not dissolve, so 150 ml more of AcOH and 50 g more of Zn were added. [d] Prepared as described for **23** from acetoacet-3,4,5-trimethoxyanilide[4] (in place of ethyl acetoacetate) and 2,4-pentanedione (in place of 1,3-cyclohexanedione). The nitrosation reaction mixture became very thick and 300 ml more of AcOH and 150 ml more of H_2O was added. The crude product was crystallized from AcOH then from *i*-PrOH and finally from MeOH. [e] Preparation specifically described in the Experimental Section. [f] Prepared as described for **13** from ethyl benzoylacetate (in place of acetoacet-3,4,5-trimethoxyanilide). The crude product was extracted with ether, washed (H_2O), dried (Na_2SO_4), and distilled *in vacuo*. After removing unreacted ethyl benzoylacetate, solid was obtained which was recrystallized first from cyclohexane and then from 75% EtOH. [g] Prepared as described for **13** from 2,4-pentanedione (in place of acetoacet-3,4,5-trimethoxyanilide) and crude 1,2-cyclopentanedione monoxime [A. C. Cope, L. L. Estes, J. R. Emery, and A. C. Haven, *J. Am. Chem. Soc.*, **73**, 1199 (1951)] (in place of 2,3-butanedione 2-oxime). The crude product was recrystallized first from EtOH, with the aid of decolorizing charcoal, and then from benzene–hexane. [h] Prepared as described for **13** from cyclohexane-1,3-dione (in place of acetoacet-3,4,5-trimethoxyanilide) and 2,3,4-pentanetrione 3-monoxime (in place of 2,3-butanedione 2-oxime). [i] All compounds analyzed for C, H, N.

12°. After stirring at <12° for 3 hr and standing at room temperature overnight, a solution of 39 g (0.348 mole) of 1,3-cyclohexane dione in AcOH was added. Then 45 g of Zn dust was added at such a rate that the temperature did not rise above 60°. After stirring for 0.5 hr and refluxing for 3 hr the solution was separated from excess Zn and poured into 3 l. of ice water giving 40.9 g of yellow solid. This was recrystallized first from C_6H_6 and then from EtOH yielding 17.4 g of crystals, mp 167–168°.

4,5,6,7-Tetrahydro-3-methyl-4-oxo-2-indolecarboxylic Acid (24).—A solution of 21.2 g (0.096 mole) of the above ester and 10 g of NaOH in 100 ml of H_2O and 50 ml of EtOH was stirred under reflux for 8 hr, diluted with H_2O, and washed (Et_2O). The aqueous solution was acidified with HCl giving 18.1 g of acid which was recrystallized from DMF–H_2O yielding 16.25 g of crystals, mp 273–274° dec.

4,5,6,7-Tetrahydro-3-methyl-4-oxoindole (20).—Eleven grams (0.057 mole) of the above acid was heated with stirring in a Claisen flask in an oil bath at 266–270° until evolution of CO_2 ceased. The product was then distilled under high vacuum giving 6 g of white solid, mp 208–210°. Recrystallization from EtOH yielded 5.7 g of white crystals, mp 209–210°.

3′,4′,5′-Trimethoxy-2,4,5-trimethylpyrrole-3-carboxanilide (13).—To a solution of 26.7 g (0.1 mole) of acetoacet-3,4,5-trimethoxyanilide,[4] 13.6 g (0.1 mole) of $NaOAc.3H_2O$, and 10.1 g (0.1 mole) of 2,3-butanedione 2-oxime in 50 ml of AcOH was slowly added with stirring, during 10 min, 17.3 g (0.25 g-atom) of Zn dust. After stirring under reflux for 1.5 hr the mixture was poured into ice water giving 28.3 g of dark solid. This was recrystallized twice from MeOH, with the aid of decolorizing charcoal, yielding 13.4 g of tan crystals, mp 213.5–217°.

(3) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir spectra were obtained on all pure compounds and were in accordance with the proposed structure. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical.

(4) From Aldrich Chemical Co., Milwaukee, Wis.

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Some Analogs of 1-*p*-Chlorobenzyl-5-methylindole-3-acetic Acid

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Earlier we reported on the synthesis and biological properties of a series of 2-substituted 1-*p*-chlorobenzyl-5-methylindole-3-acetic acids.[1] Our interest in these compounds stemmed from the α-glycerophosphate dehydrogenase (GPDH) inhibitory activity of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid (**40**), an activity which might be of potential value in the chemotherapy of tumors.[1] Since none of the alterations which were made at the 2 position produced any over-all improvement in biological activity, it was decided to synthesize some related compounds having structural modifications at other locations in the molecule. These new compounds (**1**–**9**) and their properties are listed in Table I.

For the synthesis of 1-*p*-chlorobenzyl-2-ethylindole-3-acetic acid (**1**) and 1-*p*-chlorobenzyl-2-ethyl-6-methylindole-3-acetic acid (**2**), 2-ethylindole (**12**)[2] and 2-ethyl-6-methylindole (**13**)[2] were obtained by application of the Madalung[3a] reaction to propiono-*o*-toluidide (**10**)[4] and propiono-*p*-xylidide (**11**).[5] The acetic acid side chains were elaborated by means of the gramine[3b] sequence and the final products were obtained by hydrolysis after N-alkylation of the esters **20** and **21** with *p*-chlorobenzyl chloride. The experimental methods used for obtaining these compounds were essentially the same as those used earlier[1] for the synthesis of similar products. The intermediates obtained during the preparation of **1** and **2** are described in Table II.

An alternative route to **1**, wherein the nitrile **16** was alkylated with *p*-chlorobenzyl chloride to give 1-*p*-chlorobenzyl-2-ethylindole-3-acetonitrile (**16a**) which in turn was hydrolyzed to **1** with base, gave a lower over-all yield because of the low yield in the alkylation step.

Hydrogenolysis of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-acetic acid[1] in the presence of a Raney nickel catalyst gave 1-benzyl-2-ethyl-5-methylindole-3-acetic acid (**3**).

For the synthesis of 1-*p*-chlorobenzyl-2-ethyl-5-methylindole-3-glyoxylic acid (**4**) and its diethylamide

(1) E. Walton, C. H. Stammer, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *J. Med. Chem.*, **8**, 204 (1965).

(2) Prepared earlier in lower yield by a different method by R. Qadelet and M. Chastrette, *Compt. Rend.*, **249**, 1526 (1959).

(3) W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds," Vol. 8, A. Weisberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1954: (a) p 15; (b) p 62; (c) p 3.

(4) M. T. Dangyan, *Izv. Akad. Nauk Arm. SSR*, 3 (1944); *Chem. Abstr.*, **40**, 3410[3] (1946).

(5) C. V. Bowens and L. E. Smith, *J. Am. Chem. Soc.*, **62**, 3522 (1940).