ther 1.5 hr, poured into $H_2O$, and extracted twice with $Et_2O$. The aq layer was acidified with aq HCl and the precipitated solid collected and dried. Recrystallization from $H_2O$–EtOH gave 21 g of the product (75%), mp 117–118°. *Anal.* ($C_{14}H_{16}O_5$) C, H.

**5,6-Dimethoxyindan-2-one (VII, R = H).**—VII (R = $CO_2Et$) (10 g) was heated at 100° with 20% $H_2SO_4$ (70 ml) for 2 hr. The solution was extracted with EtOAc and the organic phase washed with $H_2O$, dried, and concentrated *in vacuo*. The dark red residue was filtered through a Florisil column in $C_6H_6$, when removal of solvent and recrystallization from EtOH gave 6 g (83%) of product, mp 137–139°. *Anal.* ($C_{11}H_{12}O_3$) C, H.

**Spiro(5,6-dimethoxyindan)-2,5′-hydantoin (VIII).**—5,6-Dimethoxyindan-2-one (7 g), NaCN (3.6 g), and $(NH_4)_2CO_3$ (16.7 g) were heated in 40% EtOH (300 ml) for 3 hr at 60°. The temperature was maintained at 100° until unreacted $(NH_4)_2CO_3$ was removed, and allowed to cool when 4 g (42% yield) of the hydantoin, mp 298° dec was obtained. *Anal.* ($C_{13}H_{14}N_2O_4$) C, H, N.

**2-Amino-5,6-dimethoxyindan-2-carboxylic Acid (II, R = Me).**—A mixture of the hydantoin (VIII) (3.4 g) and $Ba(OH)_2$ (6 g) in $H_2O$ (50 ml) was refluxed for 24 hr, the hot solution filtered, and the filtrate boiled with $(NH_4)_2CO_3$ (2 g). The filtrate was concentrated *in vacuo* until crystallization occurred, and MeOH (100 ml) was added, when 2.5 g (82% yield) of the product, mp 299–300° dec was obtained. *Anal.* ($C_{12}H_{15}NO_4$)C, H, N.

**2-Amino-5,6-dihydroxyindan-2-carboxylic Acid Hydrobromide (II, R = H).**—The amino acid (II, R = Me) (1 g) in $CH_2Cl_2$ (30 ml) was treated at −70° with a solution of $BBr_3$ (0.5 g) in $CH_2Cl_2$ (10 ml) and cooled to −70°. The reaction mixture was allowed to reach room temp overnight, $H_2O$ (1 ml) added, and the dark brown solid filtered off. Treatment of the solid with charcoal in hot EtOH gave on concentration *in vacuo*, 0.7 g (57% yield) of the product, mp 250–254°. An analytical sample was recrystallized from EtOH–$Et_2O$, mp 260° dec. *Anal.* ($C_{10}H_{12}BrNO_4$)C, H, N, Br.

## Synthesis and Pharmacology of a Series of Substituted 2-Aminomethylpyrroles[1]

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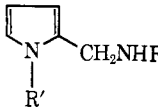
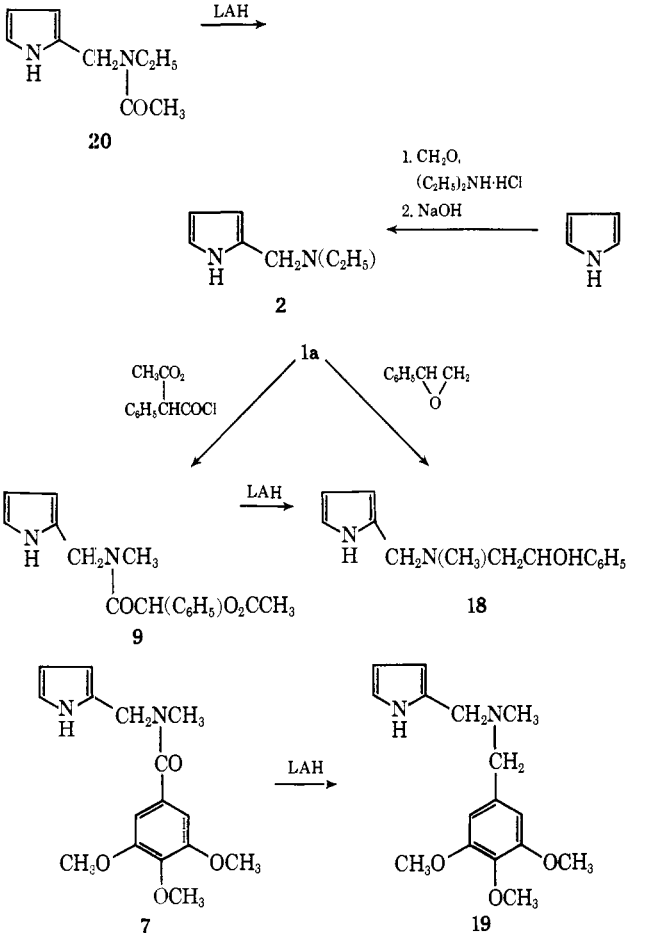
In a search for compounds which have an effect on the CNS, it was found that certain substituted 2-aminomethylpyrroles demonstrated a significant degree of depressant activity coupled with a relatively high $LD_{50}$. This note reports the compounds prepared in this area, in addition to their biological activity.

**Chemistry.**—The preparation of the necessary starting materials utilizing a Mannich reaction on pyrrole has been reported.[2] These substituted aminomethylpyrroles (**1a–d**) were treated with compounds having electrophilic groups (acid chlorides, acid anhydrides, isocyanates, isothiocyanates, etc.) giving in all cases the expected products (Table I).



| | R′ | R″ |
|---|---|---|
| 1a | H | $CH_3$ |
| 1b | H | $C_2H_5$ |
| 1c | H | $(CH_2)_2CH_3$ |
| 1d | $CH_3$ | $CH_3$ |

The LAH reduction of **20** resulted in the formation of the known compound 2[3] confirming the assigned structure. The direction of ring opening of styrene oxide when combined with **1a** was established by a LAH reduction of **9**, while the amide **7** using the same reducing agent was converted into the tertiary amine **19**.




**Pharmacology.**—A number of compounds prepared demonstrated a significant degree of CNS depressant activity (see Table I) in dose range studies in mice. The MLD (2000 mg/kg, po) and the minimal symptomatic dose (31 mg/kg, po) were determined for **20**. Phenobarbital when employed in dose range studies was found to have a minimal symptomatic dose of 15 mg/kg po.

In addition, the compounds reported in this paper were administered orally and screened for antihypertensive activity in renal hypertensive rats,[4] antiinflammatory activity in the carrageenin abscess test in rats[5] and analgetic activity in the phenylquinone-induced writhing test in mice.[6] There was no significant activity noted in these areas.

### Experimental Section

All compounds had ir spectra in agreement with their assigned structures and analyzed for C, H, and N within ±0.4 per cent of their theoretical values.

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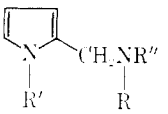
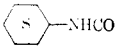
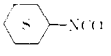
TABLE I



| No. | R | R′ | R″ | Pyrrole compd | Electrophile | Method[a] | Mp, °C | Recrystn solvent | % yield | Formula | Activity[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | $CH_3CO$ | H | $CH_3$ | 1a | $(CH_3CO)_2O$ | D | 74–76 | $Et_2O$ | 56 | $C_8H_{12}N_2O$ | + + |
| 4 | $C_6H_5CO$ | H | $CH_3$ | 1a | $C_6H_5COCl$ | A | 87–89 | $Et_2O$ | 59 | $C_{13}H_{14}N_2O$ | + + |
| 5 | *p*-$ClC_6H_4CO$ | H | $CH_3$ | 1a | *p*-$ClC_6H_4COCl$ | A | 146–147 | EtOH | 22 | $C_{13}H_{13}ClN_2O$ | − |
| 6 | *p*-$FC_6H_4CO$ | H | $CH_3$ | 1a | *p*-$FC_6H_4COCl$ | A | 141–143 | EtOH | 19 | $C_{13}H_{13}FN_2O$ | − |
| 7 | 3,4,5-$(CH_3O)_3C_6H_2CO$ | H | $CH_3$ | 1a | 3,4,5-$(CH_3O)_3C_6H_2COCl$ | A | 122–124 | EtOH | 76 | $C_{16}H_{20}N_2O_4$ | + |
| 8 | $C_6H_5CH_2CO$ | H | $CH_3$ | 1a | $C_6H_5CH_2COCl$ | A | 87–89 | EtOH | 20 | $C_{14}H_{16}N_2O$ | − |
| 9 | $(C_6H_5)_2(CH_3CO_2)CHCO$ | H | $CH_3$ | 1a | $(C_6H_5)_2(CH_3CO_2)CHCOCl$ | A | 117–119 | $Et_2O$–cyclohexane | 77 | $C_{28}H_{28}N_2O_5$ | − |
| 10 | $C_2H_5OCO$ | H | $CH_3$ | 1a | $C_2H_5OCOCl$ | A | Oil | | 31 | $C_9H_{14}N_2O_2$ | − + |
| 11 | *p*-$CH_3C_6H_4SO_2$ | H | $CH_3$ | 1a | *p*-$CH_3C_6H_4SO_2Cl$ | A | 86–88 | EtOH | 61 | $C_{13}H_{16}N_2O_2S$ | − |
| 12 | $C_6H_5NHCO$ | H | $CH_3$ | 1a | $C_6H_5NCO$ | B | 79–81 | $Et_2O$–petr ether | 48 | $C_{14}H_{15}N_3O$ | − − |
| 13 | $CH_3(CH_2)_4NHCO$ | H | $CH_3$ | 1a | $CH_3(CH_2)_4NCO$ | B | 43–45 | $Et_2O$–cyclohexane | 79 | $C_{13}H_{23}N_3O$ | + |
| 14 |  | H | $CH_3$ | 1a |  | B | 105–107 | $Et_2O$ | 67 | $C_{15}H_{21}N_3O$ | − |
| 15 | $C_6H_5NHCS$ | H | $CH_3$ | 1a | $C_6H_5NCS$ | B | 132–134 | | 86 | $C_{14}H_{15}N_3S$ | − |
| 16 | $CH_3(CH_2)_4NHCS$ | H | $CH_3$ | 1a | $CH_3(CH_2)_4NCS$ | B | 54–55 | $Et_2O$–petr ether | 51 | $C_{13}H_{23}N_3S$ | − |
| 17 | $H_2NCOCH_2CH_2$ | H | $CH_3$ | 1a | $CH_2{=}CHCONH_2$ O | C | 123–125 | EtOH | 55 | $C_{14}H_{17}N_3O$ | − |
| 18 | $C_6H_5CH(OH)CH_2$ | H | $CH_3$ | 1a | $C_6H_5CHCH_2$ | E, F | 72–74 | Cyclohexane | 1–20<br>2–67 | $C_{14}H_{15}N_3O$ | − |
| 19 | 3,4,5-$(CH_3O)_3C_6H_2CH_2$ | H | $CH_3$ | 1a | | E | 88–90 | EtOH | 56 | $C_{16}H_{22}N_2O_4$ | − |
| 20 | $CH_3CO$ | H | $C_2H_5$ | 1b | $(CH_3CO)_2O$ | D | 67–69 | | 75 | $C_9H_{14}N_2O$ | − + |
| 21 | $C_6H_5CO$ | H | $C_2H_5$ | 1b | $C_6H_5COCl$ | A | 58–60 | $Et_2O$–cyclohexane | 26 | $C_{14}H_{16}N_2O$ | − |
| 22 | $C_6H_5NHCO$ | H | $C_2H_5$ | 1b | $C_6H_5NCO$ | B | 87–89 | $Et_2O$ | 65 | $C_{14}H_{17}N_3O$ | − |
| 23 | $C_6H_5NHCS$ | H | $C_2H_5$ | 1b | $C_6H_5NCS$ | B | 96–98 | Petr ether | 100 | $C_{14}H_{17}N_3S$ | − − |
| 24 | *p*-$ClC_6H_4CO$ | H | $CH_3(CH_2)_2$ | 1c | *p*-$ClC_6H_4COCl$ | A | 59–61 | $Et_2O$–petr ether | 39 | $C_{13}H_{15}ClN_2O$ | − |
| 25 | $C_6H_5NHCO$ | H | $CH_3(CH_2)_2$ | 1c | $C_6H_5NCO$ | B | 123–125 | | 78 | $C_{13}H_{18}N_2O$ | − − |
| 26 | *p*-$ClC_6H_4CO$ | $CH_3$ | $CH_3$ | 1d | *p*-$ClC_6H_4COCl$ | A | 55–57 | Cyclohexane | 74 | $C_{14}H_{15}ClN_2O$ | − |
| 27 | *p*-$CH_3C_6H_4SO_2$ | $CH_3$ | $CH_3$ | 1d | *p*-$CH_3C_6H_4SO_2Cl$ | A | 117–119 | $(CH_3OCH_2)_2$ | 77 | $C_{14}H_{18}N_2O_2S$ | − |
| 28 | $C_6H_5NHCO$ | $CH_3$ | $CH_3$ | 1d | $C_6H_5NCO$ | B | 129–131 | EtOH–$Et_2O$ | 57 | $C_{14}H_{17}N_3O$ | − |

[a] Where oils or gums were obtained employing the listed methods, crystallization was induced by trituration with an appropriate organic solvent (usually petroleum ether, cyclohexane or ether). [b] CNS depressant activity (standard mouse dose range study): + = activity below 500 mg/kg po; ++ = activity below 250 mg/kg; − = inactive.

**Method A.**—To an ice-cooled and stirred solution of the pyrrole compd (0.1 mole), $Et_3N$ (0.3 mole), and $C_6H_6$ (300 ml), a solution of acid chloride (0.1 mole) in $C_6H_6$ (100 ml) was added dropwise over a 2-hr period. The reaction mixture was stirred for 6 hr and let stand overnight. The $Et_3N \cdot HCl$ formed was extracted from the $C_6H_6$ solution with $H_2O$ (200 ml). The organic layer was dried ($Na_2SO_4$) and filtered, followed by concentration under reduced pressure.

**Method B.**—A mixture of the pyrrole compd (0.05 mole) and the appropriate isocyanate (0.05 mole) or isothiocyanate (0.05 mole) in $C_6H_6$ (200 ml) was permitted to stand at room temp for 16 hr. The solvents were removed under reduced pressure.

**Method C.** A mixture of the pyrrole compd (0.1 mole) and the $\alpha,\beta$-unsaturated compd (0.1 mole) and $C_6H_6$ (300 ml) was stirred and refluxed for 10 hr. The reaction mixture was permitted to stand 16 hr at room temp during this period. Compd **17** was deposited while **18** was obtained as an oil after removing the solvent and purified by passing through a neutral silica column using EtOH as a solvent.

**Method D.**—To a cooled and stirred solution of the pyrrole compd (0.1 mole) dissolved in $C_6H_6$ (300 ml) under $N_2$, a solution of anhydride (0.1 mole) dissolved in $C_6H_6$ (200 ml) was added dropwise. After the addition was complete, the reaction was stirred for 12 hr, followed by extraction with two 100-ml portions of 10% aq NaOH and 100 ml of $H_2O$. The $C_6H_6$ layer was dried ($Na_2SO_4$), filtered, and concd under reduced pressure.

**Method E.**—To a cooled and stirred slurry of LAH (4 g) in THF (400 ml), a solution of the pyrrole compd (0.004 mole) dissolved in THF (200 ml) was added dropwise. After the addition was complete, the reaction mixture was refluxed for 5 hr. While cooling in an ice bath, the excess LAH was decomposed by the dropwise addition of a 10% NaOH solution (25 ml) and a satd $Na_2SO_4$ solution (25 ml). The reaction mixture was permitted to stir for 30 min followed by the addition of solid $Na_2SO_4$ (15 g). The reaction mixture was filtered and the filter cake washed several times with hot THF. The filtrate was dried ($Na_2SO_4$), filtered, and concd under reduced pressure.

**Method F.**—A solution of the pyrrole compd (0.1 mole), styrene oxide (0.1 mole) dissolved in $Et_2O$ (200 ml) was permitted to stand for 8 days at room temp. The $Et_2O$ was evaporated and the resulting oil (**18**) heated on the steam bath for 2 hr.

## A New Group of Anorexigenic Compounds

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The therapy of obesity is either based on reducing diets or on drugs which diminish the desire for food intake in excess of the energy expenditure—or most successfully—a combination of both. Anorexigenic agents presently in use are phenethylamine derivatives comprising the structural elements aryl-C-C-N[1-3] which show varying degrees of stimulation.

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