activated ester was added to a solution of 1.34 g (5.0 mmol) of **1** and 0.84 g (10 mmol) of sodium bicarbonate in 40 ml of water. The mixture was allowed to stand at room temperature for 72 h and then concentrated to half volume at reduced pressure. The solution was acidified to pH 4 and then refrigerated overnight. The crude product was collected by filtration (2.14 g). Recrystallization from ethanol–water gave pure **11**: 1.01 g (42%); mp 137–139 °C; TLC, single spot by uv ($R_f$ 0.66), ninhydrin negative. Anal. ($C_{24}H_{29}N_3O_6S$) C, H, N.

***N*-(Carbobenzoxy-4-aminobutyryl)-*S*-(*p*-bromobenzyl)-L-cysteinylglycine (12).** A solution of 1.67 g (5.0 mmol) of the *N*-hydroxysuccinimide ester of **8** in 17 ml of dioxane was added to a solution of 1.74 g (5.0 mmol) of **2** and 0.84 mmol of sodium bicarbonate in 40 ml of water. The same reaction conditions and work-up as described above gave 2.41 g of crude **12**. Recrystallization from ethanol–water gave 1.1 g (40%) of pure **12**: mp 123–124 °C; TLC, single spot ($R_f$ 0.70), ninhydrin negative. Anal. ($C_{24}H_{28}N_3O_6SBr$) C, H, N.

***N*-(3-Aminopropionyl)-*S*-benzyl-L-cysteinylglycine (13).** In a dry flask protected from moisture, 1.0 g of glacial acetic acid saturated with hydrobromic acid was added to 473 mg (1 mmol) of **9**. The mixture was allowed to react 1 h or until bubbles were no longer produced. Dry ether (10 ml) was added and the mixture was refrigerated to crystallize as the salt. The solid was collected by filtration, quickly washed with fresh ether, and dissolved in 2 ml of 40% ethanol. The solution was neutralized with 1 N ammonium hydroxide and the solvent was removed at reduced pressure. The crude product was recrystallized from ethanol–water and gave pure **13**: yield 256 mg (75%); mp 190 °C dec; TLC, single spot by uv ($R_f$ 0.31), ninhydrin positive. Anal. ($C_{15}H_{21}N_3O_4S$) C, H, N.

***N*-(3-Aminopropionyl)-*S*-(*p*-bromobenzyl)-L-cysteinylglycine (14).** Following the same general procedure described for the preparation of **13**, 552 mg (1.0 mmol) of **10** gave 313 mg (75%) of pure **14** as a white solid: mp 218 °C darkens, 224–225 °C dec; TLC, single spot by uv, ninhydrin positive. Anal. ($C_{15}H_{20}N_3O_4SBr$) C, H, N.

***N*-(4-Aminobutyryl)-*S*-benzyl-L-cysteinylglycine (15).** Following the general procedure described above, 487 mg of **11** gave 163 mg (47%) of pure **15** as white solid from ethanol–water: mp 205–208 °C dec; TLC, single spot by uv ($R_f$ 0.30). Anal. ($C_{16}H_{23}N_3O_4S$) C, H, N.

***N*-(4-Aminobutyryl)-*S*-(*p*-bromobenzyl)-L-cysteinylglycine (16).** Following the above procedure, 283 mg (0.50 mmol) of **12** was deblocked and gave 130 mg (65%) of pure **16** after one recrystallization from ethanol–water: mp 194–197 °C dec; TLC, single spot by uv ($R_f$ 0.32), ninhydrin positive. Anal. ($C_{16}H_{22}N_3O_4SBr$) C, H, N.

**Enzyme Inhibition Studies.** A 40% methylglyoxal solution was purified and standardized as previously described.[2] Yeast glyoxalase I was obtained from Sigma Chemical Co. and was diluted to 20 μg/ml with 30% glycerin containing 0.1% bovine serum albumin. All enzymatic reactions were performed at 30 °C in 0.05 M phosphate buffer at pH 6.6. For each assay the cell contained 3.0-ml total volume and the rate of formation of product was followed by an increase in absorption at 240 nm using a Beckman Model 25 spectrophotometer. Methylglyoxal, reduced glutathione, inhibitor, and buffer were added to the cell and allowed to incubate for 3 min at 30 °C (to allow equilibration of hemimercaptal formation) before addition of enzyme. The concentration of hemimercaptal substrate, $CH_3COCHOH$-SG [SG = glutathione), at equilibrium was calculated from a quadratic equation using the dissociation constant, $3.1 \times 10^{-3}$ M, previously determined for the equilibrium reaction.[2] A computer program was used to determine the line of best fit by the method of least squares.

**Acknowledgment.** We are grateful to Jay Brownell for performing some of the experiments. This work was supported by Grant CA-10979 and Career Development Award CA-25258 from the National Cancer Institute, Department of Health, Education and Welfare.

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# Syntheses and Antiinflammatory and Hypnotic Activity of 5-Alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles. 4[1]

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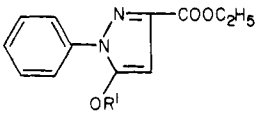
5-Alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles were prepared and tested for antiinflammatory and hypnotic activity. Four compounds showed antiinflammatory activity and three possessed hypnotic properties.

In a previous paper,[1] the authors reported the synthesis of 3-substituted 5-methoxy-1-phenylpyrazoles and the biological activity of these compounds. The result showed that 5-methoxypyrazoles containing the N-substituted

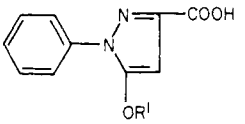
Table I. 5-Alkoxy-3-ethoxycarbonyl-1-phenylpyrazoles



| Compd | $R^1$ | Method | Recrystn solvent | Mp or bp (mm), °C | Yield, % | Formula[a] |
|---|---|---|---|---|---|---|
| 2 | Me | A | $Et_2O$-petr ether | 57-59 | 83 | $C_{13}H_{14}N_2O_3$ |
| | | | $Et_2O$ | 65-67 | | |
| 3 | Et | A | $C_6H_6$-petr ether | 85-87 | 75 | $C_{14}H_{16}N_2O_3$ |
| 4 | *n*-Pr | B | Petr ether | 61-63 | 85 | $C_{15}H_{18}N_2O_3$ |
| 5 | *i*-Pr | B | Oil | 169-171 (3) | 43 | $C_{15}H_{18}N_2O_3$ |
| 6 | *n*-Bu | C | Petr ether | 42-44 | 73 | $C_{16}H_{20}N_2O_3$ |
| 7 | *n*-Am | B | Petr ether | 43-45 | 70 | $C_{17}H_{22}N_2O_3$ |
| 8 | *i*-Am | B | Oil | 184 (2.5) | 75 | $C_{17}H_{22}N_2O_3$ |

[a] All compounds were analyzed for C, H, and N.

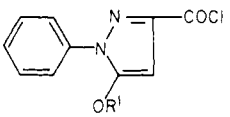
Table II. 5-Alkoxy-3-carboxy-1-phenylpyrazoles



| Compd | $R^1$ | Recrystn solvent | Mp, °C | Yield, % | Formula[a] |
|---|---|---|---|---|---|
| 9 | Me | EtOH | 172-174 | 78 | $C_{11}H_{10}N_2O_3$ |
| 10 | Et | EtOH | 150-151 | 57 | $C_{12}H_{12}N_2O_3$ |
| 11 | *n*-Pr | AcOEt-petr ether | 132-134 | 62 | $C_{13}H_{14}N_2O_3$ |
| 12 | *i*-Pr | $(i\text{-Pr})_2O$ | 130-132 | 65 | $C_{13}H_{14}N_2O_3$ |
| 13 | *n*-Bu | $Et_2O$-petr ether | 129-131 | 73 | $C_{14}H_{16}N_2O_3$ |
| 14 | *n*-Am | $Et_2O$-petr ether | 111-113 | 65 | $C_{15}H_{18}N_2O_3$ |
| 15 | *i*-Am | $Et_2O$-petr ether | 100-102 | 67 | $C_{15}H_{18}N_2O_3$ |

[a] All compounds were analyzed for C, H, and N.

Table III. 5-Alkoxy-3-chlorocarbonyl-1-phenylpyrazoles



| Compd[a] | $R^1$ | Recrystn solvent | Mp or bp (mm), °C | Yield, % |
|---|---|---|---|---|
| 16 | Me | $C_6H_6$ | 66-68 | 86 |
| 17 | Et | $C_6H_6$-petr ether | 61-63 | 93 |
| 18 | *n*-Pr | $C_6H_6$-petr ether | 54-56 | 88 |
| 19 | *i*-Pr | Oil | 156 (5) | 87 |
| 20 | *n*-Bu | Oil | 152 (3) | 92 |
| 21 | *n*-Am | Oil | 178 (2.5) | 85 |
| 22 | *i*-Am | Oil | 164 (2) | 80 |

[a] Elemental analysis of these compounds was generally omitted. Ir spectra of these compounds indicated the C=O absorption band at 1743-1760 $cm^{-1}$.

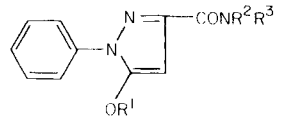
3-aminomethyl group have potent analgesic and antiinflammatory activity. The present paper describes the synthesis of 5-alkoxypyrazoles which have the N-substituted carbamoyl group instead of the aminomethyl group in the 3 position on the pyrazole ring and the effect of these compounds on the antiinflammatory and the hypnotic activity.

**Chemistry.** Starting material, 3-ethoxycarbonyl-5-hydroxy-1-phenylpyrazole (1), was prepared by condensation of diethyl oxalacetate with phenylhydrazine in xylene, followed by cyclization.[2] 5-Alkoxy-3-ethoxycarbonyl-1-phenylpyrazoles **2–8** were prepared by alkylation of **1** with alkyl halide or dialkyl sulfate in the presence of potassium carbonate or sodium ethoxide in the appropriate solvents.[3] 3-Ethoxycarbonyl-5-methoxy-1-phenylpyrazole (**2**) showed a double melting point, mp 57–59 and 65–67 °C. Acid chlorides **16–22** were obtained by treatment of either oxalyl chloride or thionyl chloride with carboxylic acids **9–15** which were prepared by hydrolysis of esters **2–8**. Condensation of the acid chloride with appropriate amines yielded amide compounds **23–62** (see Scheme I and Tables I–IV). Additionally, the reaction of the methylcarbamoyl derivative **43** with aminoethyl chlorides in the presence of sodium hydride in benzene gave ethylenediamine derivatives **63** and **64**. The 4-(2-hydroxyethyl)piperazino derivative **58** was also treated with either appropriate acid chloride or acid anhydride to give ester–amide compounds **65–67** (see Scheme II).

**Pharmacology and Results.** The antiinflammatory activities were tested according to the manner described by Winter et al.[4]

Groups of five male Wister strain rats (body weight 140–160 g) were used. Carrageenin (1%, 0.1 ml) was injected into the plantar surface of the rat's hind paw 30 min after administration of the test compound as a gum arabic suspension (100 mg/kg po).

Table IV. 5-Alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles. Structure and Activity

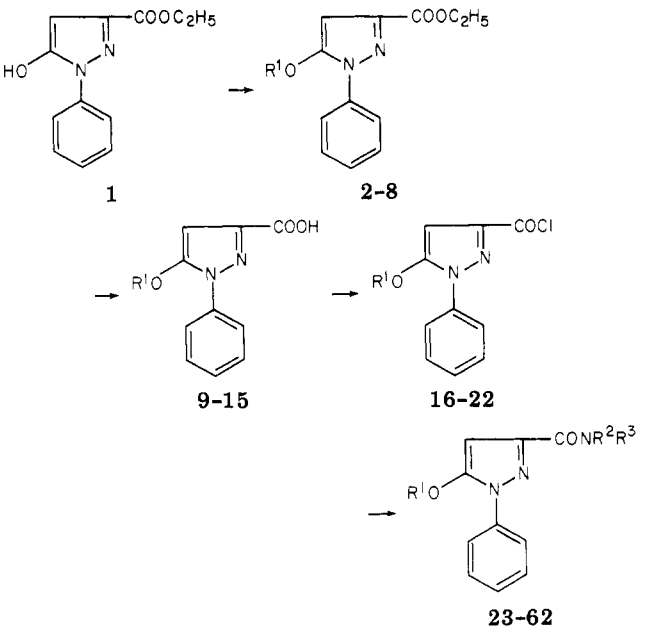



| Compd[a] | R¹ | NR²R³ | Recrystn solvent[b] | Mp or bp (mm), °C | Yield, % | Formula[c] | Antiinflam act. (100 mg/kg po), % inhibn[d] of edema (mean ± SE) |
|---|---|---|---|---|---|---|---|
| 23 | Me | $NH_2$ | A | 144-146 | 81 | $C_{11}H_{11}N_3O_2$ | 34.3 ± 5.8 |
| 24 | Me | NHMe | A-B | 113-115 | 74 | $C_{12}H_{13}N_3O_2$ | 57.9 ± 10.2 |
| 25 | Me | $NMe_2$ | A-C | 85-87 | 76 | $C_{13}H_{15}N_3O_2$ | 47.5 ± 10.1 |
| 26 | Me | NH-*n*-Bu | Oil | 197-198 (5) | 65 | $C_{15}H_{19}N_3O_2$ | 20.6 ± 6.4 |
| 27 | Me | N-*i*-$Pr_2$ | Oil | 186-187 (5) | 47 | $C_{17}H_{23}N_3O_2$ | 24.8 ± 4.9 |
| 28 | Me | c-$NC_4H_8$ | A-C | 121-123 | 78 | $C_{15}H_{17}N_3O_2$ | 29.2 ± 8.5 |
| 29 | Me | c-$NC_5H_{10}$ | Oil | 206-208 (4.5) | 84 | $C_{16}H_{19}N_3O_2$ | 28.2 ± 11.3 |
| 30 | Me | c-$N(CH_2CH_2)_2O$ | C-D | 75-77 | 80 | $C_{15}H_{17}N_3O_3$ | 73.8 ± 6.8 |
| 31 | Me | $NHCH_2CH_2NEt_2 \cdot C_4H_6O_6$[c] | E | 81-84 dec | 59 | $C_{17}H_{24}N_4O_2 \cdot C_4H_6O_6$[c] | 54.1 ± 7.0 |
| 32 | Me | c-$N(CH_2CH_2)_2NCH_3 \cdot HCl$ | D-F | 149-151 | 60 | $C_{16}H_{20}N_4O_2 \cdot HCl$ | 56.8 ± 7.3 |
| 33 | Me | c-$N(CH_2CH_2)_2NCH_2CH_2OH$ | A-C | 123-125 | 78 | $C_{17}H_{22}N_4O_3$ | 10.3 ± 4.6 |
| 34 | Me | $NHC_6H_4$-2-COOH | G-H | 256-259 dec | 80 | $C_{18}H_{15}N_3O_4$ | 24.1 ± 5.0 |
| 35 | Me | $NHC_6H_4$-3-$CF_3$ | C-I | 110-113 | 53 | $C_{18}H_{14}F_3N_3O_2$ | 20.9 ± 8.1 |
| 36 | Me | $N(Me)C_6H_4$-4-$CH_3$ | Oil | 215-222 (1-2) | 71 | $C_{19}H_{19}N_3O_2$ | 22.3 ± 4.4 |
| 37 | Et | $NMe_2$ | C-D | 96-98 | 76 | $C_{14}H_{17}N_3O_2$ | 65.8 ± 9.2 |
| 38 | Et | c-$N(CH_2CH_2)_2O$ | C-D | 74-76 | 62 | $C_{16}H_{19}N_3O_3$ | 35.4 ± 8.6 |
| 39 | *n*-Pr | $NMe_2$ | C-D | 83-85 | 75 | $C_{15}H_{19}N_3O_2$ | 26.2 ± 3.4 |
| 40 | *i*-Pr | $NMe_2$ | A-D | 110-112 | 76 | $C_{15}H_{19}N_3O_2$ | 43.9 ± 5.1 |
| 41 | *n*-Pr | c-$N(CH_2CH_2)_2O$ | C-D | 73-75 | 79 | $C_{17}H_{21}N_3O_3$ | 23.5 ± 6.0 |
| 42 | *n*-Bu | $NH_2$ | C-D | 106-108 | 78 | $C_{14}H_{17}N_3O_2$ | 26.5 ± 4.3 |
| 43 | *n*-Bu | NHMe | C-D | 70-71 | 83 | $C_{15}H_{19}N_3O_2$ | 65.0 ± 7.2 |
| 44 | *n*-Bu | NHEt | C-D | 63-65 | 85 | $C_{16}H_{21}N_3O_2$ | 0 |
| 45 | *n*-Bu | $NMe_2$ | C-D | 88-89 | 87 | $C_{16}H_{21}N_3O_2$ | 18.7 ± 2.0 |
| 46 | *n*-Bu | $NHCH_2CH{=}CH_2$ | Oil | 202-203 (3.5) | 78 | $C_{17}H_{21}N_3O_2$ | 4.4 ± 1.2 |
| 47 | *n*-Bu | NH-*n*-Pr | C-D | 38-40 | 73 | $C_{17}H_{23}N_3O_2$ | 51.2 ± 9.2 |
| 48 | *n*-Bu | $NHCH_2CH_2OH$ | C-D | 68-70 | 75 | $C_{16}H_{21}N_3O_3$ | 61.2 ± 11.0 |
| 49 | *n*-Bu | NH-*n*-Bu | C | 44-46 | 70 | $C_{18}H_{25}N_3O_2$ | 43.3 ± 6.5 |
| 50 | *n*-Bu | $NEt_2$ | C | 38-40 | 76 | $C_{18}H_{25}N_3O_2$ | 44.1 ± 8.5 |
| 51 | *n*-Bu | N-*i*-$Pr_2$ | Oil | 199-200 (5) | 62 | $C_{20}H_{29}N_3O_2$ | 15.8 ± 5.9 |
| 52 | *n*-Bu | c-$NC_4H_8$ | C-D | 88-90 | 85 | $C_{18}H_{23}N_3O_2$ | 17.6 ± 4.6 |
| 53 | *n*-Bu | c-$NC_5H_{10}$ | C-D | 49-51 | 82 | $C_{19}H_{25}N_3O_2$ | 15.6 ± 2.8 |
| 54 | *n*-Bu | c-$N(CH_2CH_2)_2O$ | C-D | 71-73 | 80 | $C_{18}H_{23}N_3O_3$ | 32.9 ± 6.6 |
| 55 | *n*-Bu | $NHCH_2CH_2NEt_2 \cdot C_4H_6O_6$[e] | H | 61-64 dec | 64 | $C_{20}H_{30}N_4O_2 \cdot C_4H_6O_6$[e] | 23.6 ± 5.1 |
| 56 | *n*-Bu | $NH(CH_2)_3NMe_2$ | C | 38-41 | 71 | $C_{19}H_{28}N_4O_2$ | 29.8 ± 3.6 |

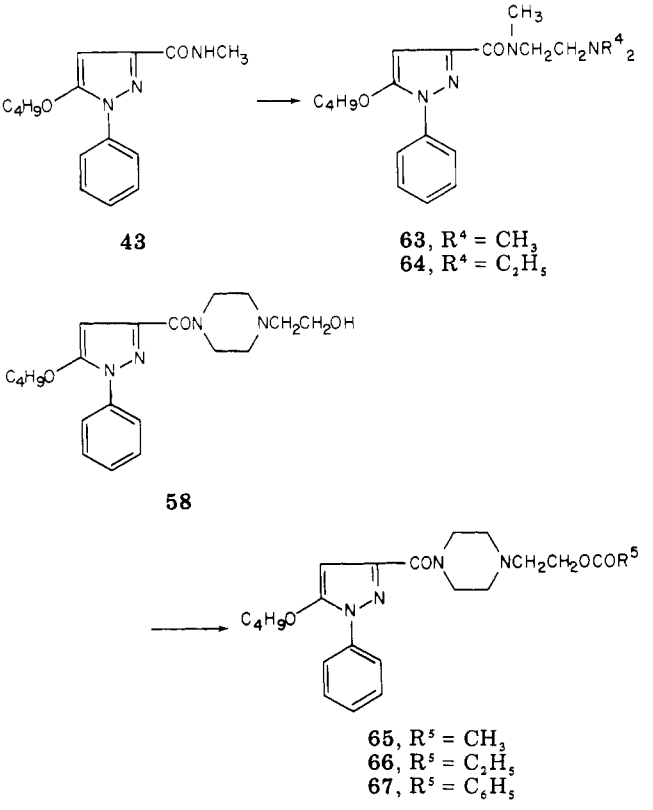
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 57 | *n*-Bu | c-N(CH$_2$CH$_2$)$_2$N-CH$_3$ | C | 78–79 | 71 | $C_{19}H_{26}N_4O_2$ | 32.3 ± 5.5 |
| 58 | *n*-Bu | c-N(CH$_2$CH$_2$)$_2$N-CH$_2$CH$_2$OH·HCl | D–F | 212–214 | 67 | $C_{20}H_{28}N_4O_3$·HCl | 41.3 ± 7.4 |
| 59 | *n*-Bu | NHC$_6$H$_4$-2-COOH | G | 211–212 | 78 | $C_{21}H_{21}N_3O_4$ | 0 |
| 60 | *n*-Bu | c-N(CH$_2$CH$_2$)$_2$N-C$_{14}$H$_{15}$N$_2$O$_2$ [f] | H | 195–196 | 41 | $C_{32}H_{38}N_6O_4$ | 0 |
| 61 | *n*-Am | NMe$_2$ | C | 68–70 | 84 | $C_{17}H_{23}N_3O_2$ | 20.0 ± 3.0 |
| 62 | *i*-Am | NMe$_2$ | C | 55–56 | 81 | $C_{17}H_{23}N_3O_2$ | 25.3 ± 4.8 |
| 63 | *n*-Bu | N(Me)CH$_2$CH$_2$NMe$_2$·C$_2$H$_2$O$_4$ [g] | D–F | 186–188 dec | 84 | $C_{19}H_{28}N_4O_2$·C$_2$H$_2$O$_4$ [g] | 28.2 ± 5.0 |
| 64 | *n*-Bu | N(Me)CH$_2$CH$_2$NEt$_2$·C$_2$H$_2$O$_4$ [g] | D–F | 141–143 | 79 | $C_{21}H_{32}N_4O_2$·C$_2$H$_2$O$_4$ [g] | 29.5 ± 5.4 |
| 65 | *n*-Bu | c-N(CH$_2$CH$_2$)$_2$N-CH$_2$CH$_2$OCOMe·HCl | D–F | 188–191 | 76 | $C_{22}H_{30}N_4O_4$·HCl | 43.9 ± 11.5 |
| 66 | *n*-Bu | c-N(CH$_2$CH$_2$)$_2$N-CH$_2$CH$_2$OCOEt·HCl | D–F | 199–202 dec | 73 | $C_{23}H_{32}N_4O_4$·HCl | 0 |
| 67 | *n*-Bu | c-N(CH$_2$CH$_2$)$_2$N-CH$_2$CH$_2$OCOC$_6$H$_5$ | D–G | 95–97 | 58 | $C_{27}H_{32}N_4O_4$ | 5.9 ± 1.2 |
| | Aminopyrine | | | | | | 66.0 ± 10.2 |
| | Phenylbutazone | | | | | | 54.5 ± 12.1 |

[a] Method of preparation: **23–33**, **35–58**, and **60–62**, D or E; **34** and **59**, F. [b] A, $C_6H_6$, *n*-pentane; C, petroleum ether; D, $Et_2O$; E, cyclohexane; F, MeOH; G, EtOH; E, AcOEt; I, $Me_2CO$. [c] All compounds were analyzed for C, H, and N. [d] Inhibitory effect on the swelling of rats hind paw induced by carrageenin; average of five rats. [e] Tartarate. [f] $C_{14}H_{15}N_2O_2$ is 5-*n*-butoxy-1-phenylpyrazolyl-3-carbonyl. [g] Oxalate.

Scheme I




Scheme II




The edema formation was measured 3 h after injection and compared with that of carrageenin alone and with the test compound for calculation of percent inhibition. The hypnotic activities were carried out using Pila's method[5] and determined as the effective case when the loss of righting reflex was observed more than 30 s within 60 min after intraperitoneal injection of the test compound (0.5% gum arabic suspension) using ddN male mice (body weight 18–20 g). Also these compounds were tested for acute toxicity in mice. The results of these tests are shown in Tables IV and V.

Of these compounds, 5-alkoxy-3-morpholinocarbonyl-1-phenylpyrazole, which has one or two carbons in the 5

Table V. Hypnotic Activity and Acute Toxicity of Selected Compounds in Mice

| Compd | $HD_{50}$,[a] mg/kg ip | $LD_{50}$,[a] po | Compd | $HD_{50}$,[a] mg/kg ip | $LD_{50}$,[a] po |
|---|---|---|---|---|---|
| **25** | 90.0 (78.3-104.0) | 385 (313-474) | **45** | 33.0 (30.6-35.6) | 460 (397-534) |
| **37** | 26.0 (19.7-34.3) | 330 (275-396) | **47** | 39.0 (30.5-49.9) | 650 (533-793) |
| **39** | 27.0 (21.5-31.9) | 320 (254-403) | **49** | 70.0 (58.8-83.3) | 370 (298-459) |
| **40** | 49.0 (40.5-59.3) | 525 (453-609) | **61** | 63.0 (53.4-74.3) | 420 (362-487) |
| **42** | 94.0 (81.7-108) | 360 (310-418) | **62** | 47.0 (36.2-61.1) | 350 (308-397) |
| **43** | 48.0 (41.0-56.2) | 325 (262-403) | Hexobarbital | 91.0 (88.8-93.3) | 745 (596-931) |
| **44** | 44.0 (38.3-50.6) | 400 (325-492) | | | |

[a] Numbers in parentheses indicate 95% confidence limits.

position on the pyrazole ring, showed excellent antiinflammatory activity. Compounds **37** and **43** exhibited marked activity except 5-alkoxypyrazole which has a 3-morpholinocarbonyl group in the 3 position on the pyrazole ring.

On observation of the hypnotic activities, when the alkyl group ($R^1$) in the 5 position on the pyrazole ring was fixed on *n*-Bu, compound **45**, which has NHMe as the substituent ($NR^2R^3$) in the 3 position on the pyrazole ring, exhibited the greatest activity. However, when $NR^2R^3$ was maintained as $NMe_2$, **37** and **39** exhibited potent hypnotic activity.

From the results, the effect of pyrazole derivatives containing bulky groups appears to be less active. Additional studies of pyrazole derivatives possessing the substituted phenyl group will be required.

## Experimental Section

All melting points were uncorrected. Ir spectra were measured on a Jasco Model IRG.

**5-Alkoxy-3-ethoxycarbonyl-1-phenylpyrazoles 2–8. Method A.** To a mixture of ethyl 3-ethoxycarbonyl-5-hydroxy-1-phenylpyrazole (1, 56 g), $K_2CO_3$ (53 g), and EtOH (200 ml) was added dropwise dialkyl sulfate (0.37 mol), and the mixture was refluxed for 7 h. After cooling, ice water (1.5 l.) was added to the reaction mixture. The crystals that separated were filtered and recrystallized from appropriate solvents.

**Method B.** A mixture of 1 (10 g), alkyl bromide (0.05 mol), $K_2CO_3$ (7 g), KI (0.5 g), and acetone (100 ml) was refluxed for 7 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether, and the ether was washed with 10% NaOH and then with $H_2O$, dried over $Na_2SO_4$, and evaporated. Either recrystallization from appropriate solvents or distillation in vacuo gave 5-alkoxy-3-ethoxycarbonyl-1-phenylpyrazoles.

**Method C.** A mixture of Na (3 g) in EtOH (200 ml), 1 (28 g), alkyl bromide (0.13 mol), and KI (3 g) was refluxed for 24 h. The reaction mixture was treated in the same manner as method B.

**5-Alkoxy-3-carboxy-1-phenylpyrazoles 9–15.** To a solution of KOH (12 g), $H_2O$ (60 ml), and MeOH (60 ml) was added the ester (0.1 mol), and the mixture was refluxed for 4 h. The reaction mixture was diluted with $H_2O$ (200 ml) and neutralized with 10% HCl. The crystals that separated were filtered and recrystallized from appropriate solvents.

**5-Alkoxy-3-chlorocarbonyl-1-phenylpyrazoles 16–22.** To a solution of 5-alkoxy-3-carboxy-1-phenylpyrazole (0.02 mol) in benzene (50 ml) was added dropwise oxalyl chloride (5.2 g), and the mixture was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was purified by an appropriate method. The results are shown in Table III.

**5-Alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles 23–62. Method D.** To a solution of amine (0.02 mol) in ether (30 ml) and 30% NaOH (10 ml) was added dropwise acid chloride (0.01 mol) in benzene, and the mixture was stirred for 1 h. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated. Either recrystallization from appropriate solvents or distillation in vacuo afforded the corresponding amides.

**Method E.** To a stirred solution of amine (0.015 mol) was added dropwise acid chloride (0.01 mol) in benzene under cooling, and the reaction mixture was stirred at room temperature for 2 h, and $H_2O$ added (1 ml). Stirring was continued for an additional 15 min. To the mixture was added $CHCl_3$ (30 ml), and the organic layer was washed with 10% HCl and with $H_2O$ to remove pyridine and dried over $Na_2SO_4$ to give crystals.

**Method F.** To a cooled solution of *o*-aminobenzoic acid (0.013 mol) in pyridine was added portionwise acid chloride (0.01 mol) with stirring, and the stirring was continued at room temperature for an additional 3 h. The reaction mixture was diluted with $H_2O$ (10 ml) and acidified with 5% HCl to give crystals. The crystals were filtered, washed with $H_2O$ and with hot $H_2O$, respectively, and recrystallized from appropriate solvents.

**5-*n*-Butoxy-*N*-(2-dimethylaminoethyl)-*N*-methylcarbamoylpyrazole (63).** To a solution of **43** (4 g) and dimethylaminoethyl chloride (2.5 g) in toluene (40 ml) was added 50% NaH (1.4 g), and the mixture was refluxed for 2 h. After cooling, the excess NaH was decomposed in the usual way. The organic layer was washed with $H_2O$ and extracted with 10% HCl. The aqueous layer was washed with ether, made alkaline with $Na_2CO_3$, and extracted with ether. The ether was dried over $Na_2SO_4$ and evaporated to afford an oil (4.2 g, 84%). Oxalate: colorless needles; mp 186–188 °C dec (from MeOH–ether). Anal. ($C_{19}H_{28}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

**5-*n*-Butoxy-*N*-(2-diethylaminoethyl)-*N*-methylcarbamoyl-1-phenylpyrazole (64).** The procedure was the same as that used for synthesis of **63** except that diethylaminoethyl chloride was used. A pale yellow oil was obtained in 79% yield. Oxalate: colorless needles; mp 141–143 °C (from MeOH–ether). Anal. ($C_{21}H_{32}N_4O_2 \cdot C_2H_2O_4$) C, H, N.

**3-[4-(2-Acetyloxyethyl)-1-piperazinyl]carbonyl-5-*n*-butoxy-1-phenylpyrazole (65).** A mixture of **58** (3 g), acetic anhydride (5 ml), and triethylamine (5 ml) was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in ether. The ether was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated to give a pale yellow oil (2.5 g, 76%): ir (film) 1739 (ester C=O) and 1629 $cm^{-1}$ (amide C=O). Hydrochloride: colorless leaflets; mp 188–191 °C (from MeOH–ether). Anal. ($C_{22}H_{30}N_4O_4 \cdot HCl$) C, H, N.

**5-*n*-Butoxy-3-[4-(2-propionyloxy)-1-piperazinyl]carbonyl-1-phenylpyrazole (66).** The procedure was the same as that used for synthesis of **65** except that propionic anhydride was used. A pale yellow oil was obtained in 73% yield. Hydrochloride: colorless leaflets; mp 199–202 °C dec (from MeOH–ether). Anal. ($C_{23}H_{32}N_4O_4 \cdot HCl$) C, H, N.

**3-[4-(2-Benzyloxyethyl)-1-piperazinyl]carbonyl-5-*n*-butoxy-1-phenylpyrazole (67).** To a cooled solution of **58** (2 g) in pyridine (10 ml) was added dropwise benzyl chloride (1 g) with stirring, and the mixture was stirred at room temperature for 2 h. After $H_2O$ (1 ml) was added to the reaction mixture, the stirring was continued for an additional 15 min. The reaction mixture was poured into $H_2O$ and extracted with $CHCl_3$. The organic layer was washed with $H_2O$ and dried over $Na_2SO_4$ to give an oil which crystallized on standing. The crystals were recrystallized from EtOH–petroleum ether to give colorless needles (1.5 g, 58%), mp 95–97 °C. Anal. ($C_{27}H_{32}N_4O_4$) C, H, N.

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# Ergoline Congeners as Potential Inhibitors of Prolactin Release. 3. Derivatives of 3-Phenylpiperidine

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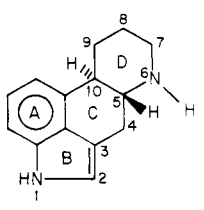
In a continuation of our attempts to elucidate the prolactin release inhibiting pharmacophore within the ergoline structure, we have prepared several derivatives of 3-phenylpiperidine. These congeners have been evaluated for inhibition of prolactin release in vivo and are for the most part inactive.

The ability of certain ergoline (1) derived compounds to inhibit the release of prolactin has been known and studied for some time.[1] The nidation-blocking action[2,3] as well as the lactation-inhibiting[4] and tumor-regression effects[5,6] of various ergoline derivatives are direct consequences of their prolactin release inhibiting activity. More recent findings have indicated that prolactin release is under the influence of a dopaminergic system in the brain.[7-9] Since potent dopaminergic activity has been demonstrated for several ergoline derivatives,[10,11] it is likely that these compounds inhibit prolactin release via an action on a dopaminergic system.[12]



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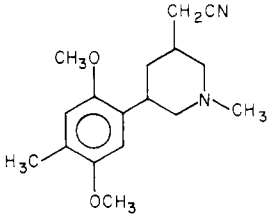

2

Examination of the ergoline structure reveals that the A and D rings comprise a 3-phenylpiperidine moiety. Derivatives of 3-phenylpiperidine have previously been prepared as analogues of ergoline derived compounds;[13-15] however, none of these have been evaluated for prolactin release inhibiting or dopaminergic activity. In a continuation of our efforts[16,17] to elucidate the smallest fragment within the ergoline structure that still retains prolactin release inhibiting activity, we have prepared several derivatives of 3-phenylpiperidine. In the design of potential prolactin release inhibitors several modifications of the basic 3-phenylpiperidine structure were desired: (1) a tertiary amine correlating with N-6 of ergoline, (2) an activated aromatic nucleus, and (3) a functional group that mimics the C-8 substituent of an ergoline derivative known to have prolactin release inhibiting activity. Congener **2** fulfills these criteria and now we report the synthesis and evaluation of this target compound and several intermediates for inhibition of prolactin release in vivo.

**Chemistry.** The synthetic sequence that was chosen for the preparation of **2** is shown in Scheme I. The 3-phenylpiperidine ring skeleton is formed by a Dieckmann cyclization of **9**, followed by appropriate alteration of the functional groups attached to the ring. This approach is somewhat similar to that used by Hohenlohe-Ochringen et al.[14] for their preparation of 3-phenylpiperidine derivatives. Although it is somewhat lengthy, this sequence was used since it permits the possibility of preparing congeners which have unsaturation in a position analogous to the unsaturation found in the D ring of some ergoline derivatives.

The unsaturated ester **8** was prepared from **3** in about 40% overall yield. Cyclization of **9** was accomplished with sodium hydride in benzene and initially gave **10** as a viscous oil. Interestingly, this oil showed four absorptions in the carbonyl region of the infrared spectrum (1620, 1660, 1720, and 1740 $cm^{-1}$) indicating the presence of both $\beta$-keto ester and hydrogen-bonded enol ester tautomers. After **10** was crystallized or converted to its crystalline hydrochloride salt, only the absorptions at 1620 and 1660 $cm^{-1}$ remained. Since the hydrogen-bonded enolized tautomer of **10** has only one asymmetric center, the tendency for **10** to exist predominantly in this form eliminated the need for a separation of diastereomers which might have been encountered at this stage.

Extraction of **10** from aqueous base into an organic solvent gave only a 75–83% recovery of this material. Improved yields were obtained from the Dieckmann cyclization when the hydrochloride salt of **10** was extracted from the work-up mixture into chloroform.

Treatment of **10** with sodium borohydride in ethanol gave **11**, which was presumed to be a mixture of isomers. Initial attempts to dehydrate **11** with $POCl_3$ in pyridine at steam bath temperature resulted in nearly complete loss of basic material; however, when the reaction was carried out at 5–10 °C a good yield of **12** was obtained.

Catalytic hydrogenation of **12** over 5% Pd/C proceeded to completion in several hours. Chromatographic analysis revealed that the product was a single diastereomer and a 220-MHz NMR spectrum (Morgan Schaffer Corp., Montreal, Canada) was in accord with the assignment of a cis-diequatorial arrangement of the substituents in **13**. This interpretation was confirmed by a computer-generated NMR spectrum. Entering chemical shift and coupling constant values from the 220-MHz NMR spectrum into a LAOCOON III program[18] in the format appropriate for *cis*-**13**, a splitting pattern for the piperidine protons was generated which was superimposable on the original spectrum.

Modification of the ester functional group proceeded without difficulty. It is assumed that the target compound **2** has the same cis-diequatorial arrangement of the C-3 and