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# Triphenylpropylpiperazine Derivatives as New Potent Analgetic Substances

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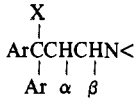
*Received June 18, 1971*

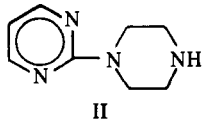
Sixty-four 1,4-disubstituted piperazines have been synthesized in which the 1 substituents are chiefly triphenylpropyl or *i*-Pr groups and the 4 substituents are pyrimidyl and its substituted derivatives, as well as closely related isosteric heterocycles, such as pyridazinyl, pyrazinyl, triazinyl, thiazolyl, and quinazolinyl. These compounds have a methadone-like structure and the most interesting one (**25**) shows good analgetic properties and seems to have a low dependence liability.

Many synthetic organic compounds with pronounced morphine-like activity have been described and among them, the diphenylpropylamines related to methadone. Up to now, several hundred of these compounds have been synthesized[1a] but no significant separation of analgesia and dependence liability has been demonstrated in that field. Nevertheless certain quantitative and time-effect differences have helped to make methadone the drug of choice, generally as a substitute for another opiate to minimize withdrawal symptoms. Thus we undertook a search for compounds structurally related to methadone with the structural requirements



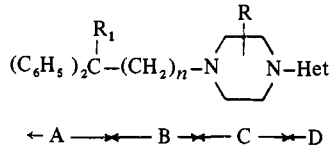
I

hoping to obtain compounds useful in the relief of pain, and, as far as possible, devoid of addicting properties and other undesirable effects. Generally, it is considered[1b] that the most active products are those in which X is an electronegative substituent taken from the following group listed in decreasing order of potency: CON<, COR, >CHOCOR, OCOR, CN, etc.... associated with the presence of a Me group in the $\alpha$ or $\beta$ position. The N substituent is a basic dialkylamino or cycloalkylamino group. The greatest activity is usually confined to the levo form of the $\beta$-branched compounds, the $\alpha$-branched one being nearly inactive. Our approach was influenced by 2 observations: (1) when we began an extensive research on vasodilatory piperazine derivatives[2] 10 years ago, we discovered a clear but not pronounced analgetic activity in one of them, the pyrimidylpiperazine II.



II

We therefore took this as a structural basis for the basic dialkylamino group in I, despite the fact that some authors[3,4] have pointed out a weak activity and high toxicity for piperazine derivatives structurally related to methadone; (2) a search of the literature revealed that the electronegative Ph group had rarely been employed as a third substituent X. Nevertheless, the triphenylpropylamine structure was included in the structure of spasmolytic substances studied by Swedish workers.[5] These findings prompted us to synthesize some compounds of the following formula:



III

To study the effect of appropriate changes on the activity of this class of compounds, structure III was divided into 4 portions and each one was varied selectively (See Tables II, III, and IV).

(a) In portion A, $R_1$ is more generally Ph optionally substituted by an alkoxy group. In 3 compounds (**9**, **11**, **12**) $R_1$ is H and in one $R_1$ is CN (**10**).

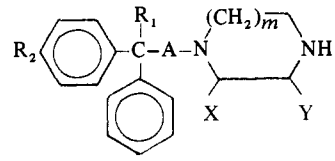
(b) In portion B, which is usually an unbranched $(CH_2)_n$ chain ($n$ = 2), we studied the influence of lengthening the chain as well as its $\alpha$ branching. Unfortunately we did not succeed in preparing the $\beta$-branched compound.†

(c) For the modification of portion C, we altered piperazine to 2-methylpiperazine, homopiperazine, and decahydroquinoxaline.

(d) In portion D, the pyrimidine group optionally substituted by various groups (See Table III), was replaced en-

†The reaction of the 1-methyl-3,3,3-triphenylpropyl *p*-toluenesulfonate with a monosubstituted piperazine failed and 4,4,4-triphenyl-2-butene was exclusively found as the Swedish workers have described it in the case of its condensation with morpholine.

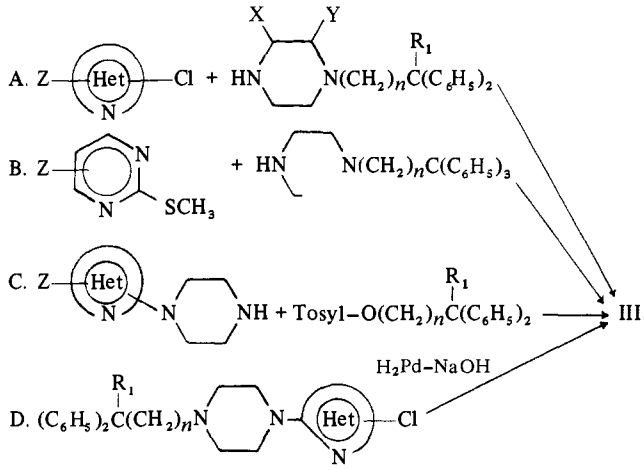
Table I

| No. | $R_1$ | $R_2$ | A | *m* | X | Y | Yield, % | Crystn[a] solvent | Bp (mm) or mp of amine or salt.[b] °C | Formula[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | |  | | | |
| 1 | H | H | $(CH_2)_2$ | 2 | H | H | 75.2 | | 162 (0.5) | $C_{19}H_{24}N_2$ |
| 2 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | H | H | 83 | AE | 129-130 K | $C_{25}H_{28}N_2 \cdot H_2O$ |
| 3 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | H | H | | AE | 183-185 cap | $C_{25}H_{28}N_2 \cdot 2HCl$ |
| 4 | $C_6H_5$ | H | $(CH_2)_3$ | 2 | H | H | 68[e] | | 195-200 (0.6) | |
| | | | | | | | | AE | 226-228 cap | $C_{26}H_{30}N_2 \cdot 2HCl \cdot 2H_2O$ |
| 5 | $C_6H_5$ | $OCH_3$ | $(CH_2)_2$ | 2 | H | H | 48.2 | AE | 225-230 (0.3) | $C_{26}H_{30}N_2O$ |
| 6 | $C_6H_5$ | H | $CH(CH_3)CH_2$ | 2 | H | H | 68.8 | AE | 205-210 (0.2) | $C_{26}H_{30}N_2$ |
| 7 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | $CH_3$ | H | 37.8[d] | AE | 190-193 (1) | |
| | | | | | | | | AE | 160 dec, cap | $C_{26}H_{30}N_2 \cdot 2HCl \cdot 2H_2O$ |
| 8 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | $(CH_2)_4$ | | 79 | | 225-230 (0.45) | |
| | | | | | | | | AE | 175-178 dec, MK | $C_{29}H_{34}N_2 \cdot 2HCl \cdot 0.5H_2O$ |

[a] AE, abs EtOH. [b] Uncor bp or mp, K, Kofler block; MK, Kofler hot stage microscope; cap, Mel-Temp capillary mp app. [c] All compounds have been analyzed for C, H, N with results (±0.4% limit), by means of a Perkin-Elmer Autoanalyser 240. [d] Prepd by alk hydrolysis of the 1-(3,3,3-triphenylpropyl)-2-methyl-4-carbethoxypiperazine, itself prepd from 1-carbethoxy-3-methylpiperazine by method C (See ref 2). [e] Prepd by analogy with ref 6 (See Experimental Section).

tirely by isosteric structures such as pyridazine, pyrazine, triazine, and thiazole.

**Chemistry.** The synthesis of these compounds was performed according to 4 general methods:

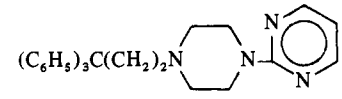



In method A, a substituted halogeno heterocycle was generally condensed with the appropriate N-monosubstituted piperazine in DMF in the presence of $K_2CO_3$. In method B, an appropriately substituted 2-methylthiopyrimidine was heated with an N-monosubstituted piperazine in equimolar proportion. In method C, a *p*-Ts ester was heated with an excess of an N-monosubstituted piperazine. In method D, the Cl atom of a 1-substituted 4-(chloropyridazinyl or *s*-triazinyl)piperazine was hydrogenolyzed under pressure over Pd/C.

**Structure-Activity Relationships (Table V).** The first few compounds studied in this series appeared to be powerful central analgetics. Their spectrum of activity together with numerous evident symptoms (Straub tail, antagonism to nalorphine, etc.) indicated that we were dealing with morphine-like properties.

We tried at first to establish the ideal chemical structure. Later, syntheses were conducted according to theories of antagonist-agonist interactions[7] as regards the analgetic receptor. Some derivatives behaved as antagonists to the other but were unfortunately devoid of any valuable agonistic activity of their own, pentazocine for example. Finally some members were selected and carefully studied for dependence liability, insofar as we could predict it from our animal studies. A brief account of the main facts emerging from this part of the work will be given.

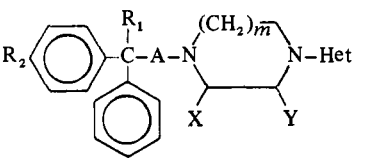
To explain rather complicated structure-activity relationships, it is useful to show the most interesting structure (i.e., **25**) and to summarize the way in which modifications in its 4 main parts (*cf.*, structure III) influence the activity.




25

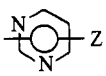
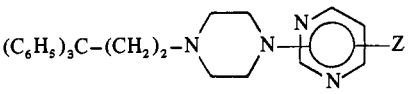
In part A, the presence of only 2 Ph groups in this part of the molecule with X = H or CN abolished the analgetic properties (**9**, **10**). Although the activity is not destroyed when D is pyrazinyl or pyridazinyl (**11**, **12**) it is still decreased. Clearly, the $(C_6H_5)_3C$ groups must be kept intact. In part B, the introduction of an additional $CH_2$ diminishes the activity, which is maintained but not increased when the chain is α branched (**15**, **16**, **18**) as in the isomethadone series. In part C, any modification of the piperazine ring is unfavorable (**19**, **20**, **21**, **22**). The most interesting part of structure III is D, where the kind of heterocyclic nucleus closely determines the activity, the order of the decreasing activity being: pyrazine (**62**) > pyrimidyl (**25**) > pyridyl (**56**) > pyridazinyl (**57**) > triazinyl inactive (**68**). Other N heterocycles were inactive. As far as the substitutions on the heterocyclic nucleus are concerned, Me or $Me_2$ in any position are not unfavorable (**27**, **28**, **29**, **63**, **67**), but 5 substitution on the pyrimidine ring was generally unproductive as shown in the inactive $Me_3$ (**30**) or $Me_2C_6H_5$ (**31**) derivatives. This holds also for **34-41** with 5-CN, OH substitutions which are inactive or only slightly active except for 4-EtO (**34**) and 5-$CO_2H$ (**35**) in which the activity is only diminished compared to **25**. Amino substitution is very favorable chiefly on the pyrimidine ring (**42**), but the $NH_2$

Table II

| No. | $R_1$ | $R_2$ | A | *m* | X | Y | Het | Method | Yield crystd, % | Crystn[a] solvent | Mp[b] of amine or salt, °C | Formula[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | |  | | | | | |
| 9 | H | H | $(CH_2)_2$ | 2 | H | H | 2-Pyrimidyl | A | 47.5 | AP | 111 K | $C_{23}H_{26}N_4$ |
| 10 | CN | H | $(CH_2)_2$ | 2 | H | H | 2-Pyrimidyl | *d* | 23.2 | AE | 113 K | $C_{24}H_{25}N_5$ |
| 11 | H | H | $(CH_2)_2$ | 2 | H | H | 3-Pyridazinyl | D[f] | 20 | C | 100–101 MK | $C_{23}H_{26}N_4$ |
| 12 | H | H | $(CH_2)_2$ | 2 | H | H | 2-Pyrazinyl | A | 18 | AE | 210–215 dec, MK | $C_{23}H_{26}N_4 \cdot 2HCl$ |
| 13 | $C_6H_5$ | $CH_3O$ | $(CH_2)_2$ | 2 | H | H | 2-Pyrimidyl | A | 38 | AE | 185–190 dec, cap | $C_{30}H_{32}N_4O \cdot 2CH_4O_3S$[g] |
| 14 | $C_6H_5$ | $C_6H_5$ | $(CH_2)_2$ | 2 | H | H | 2-Pyrimidyl | C | 59 | AE | 226–229 MK | $C_{38}H_{34}N_4 \cdot 2CH_4O_3S$[g] |
| 15 | $C_6H_5$ | H | $CH(CH_3)CH_2$[e] | 2 | H | H | 2-Pyrimidyl | A | 67.5 | AP | 170–174 MK | $C_{30}H_{32}N_4 \cdot 2CH_4O_3S$[g] |
| 16 | $C_6H_5$ | H | $(CH_2)_3$ | 2 | H | H | 2-Pyrimidyl | A | 69.7 | AP | 145 K | $C_{30}H_{32}N_4$ |
| 17 | $C_6H_5$ | H | $CH(CH_3)CH_2$[e] | 2 | H | H | 2-Pyrazinyl | A | 56 | AE | 165–168 MK | $C_{30}H_{32}N_4 \cdot 2CH_4O_3S$[g] |
| 18 | $C_6H_5$ | H | $CH_2CO$ | 2 | H | H | 2-Pyrimidyl | *d* | 78.4 | AcOH | 260 K | $C_{29}H_{28}N_4O$ |
| 19 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | $CH_3$ | H | 2-Pyrimidyl | A | | AP | 223–225 MK | $C_{30}H_{32}N_4 \cdot 2HCl \cdot 0.5H_2O$ |
| 20 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | H | $CH_3$ | 2-Pyrimidyl | C | 38 | AP | 194–196 MK | $C_{30}H_{32}N_4 \cdot 2HCl \cdot H_2O$ |
| 21 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | H | H | 2-Pyrimidyl | C | 24.2 | AM | 165–168 MK | $C_{30}H_{32}N_4 \cdot C_4H_4O_4 \cdot H_2O$[h] |
| 22 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | $(CH_2)_4$ | | 2-Pyrimidyl | A | 71.3 | AE | 161–162 K | $C_{33}H_{36}N_4 \cdot 0.5H_2O$ |
| 23 | $C_6H_5$ | H | $CH(CH_3)CH_2$[e] | 2 | H | H | 4-allylamino-2-pyrimidyl | A | 53.4 | AE | 147–149 MK | $C_{33}H_{37}N_5 \cdot 2HCl \cdot H_2O$ |
| 24 | $C_6H_5$ | H | $(CH_2)_2$ | 2 | $CH_3$ | H | 4-allylamino-2-pyrimidyl | A | 38.4 | AE | 168–170 MK | $C_{33}H_{37}N_5 \cdot 2HCl$ |

[a]AE, abs EtOH; AM, abs MeOH; AP, abs *i*-PrOH; C, cyclohexane. [b,c]See the corresponding footnotes in Table I. [d]See the Experimental Section. [e]Racemic form. [f]Hydrogenolysis performed without NaOH. [g]Bismethanesulfonate. [h]Neutral fumarate.

Table III

| No. |  | Method | Yield crystd, % | Crystn[a] solvent | Mp[b] of amine or salt, °C | Formula[c] |
|---|---|---|---|---|---|---|
| | | |  | | | |
| 25 | 2-Pyrimidyl | A | 64.7 | AE | 130 K | $C_{29}H_{30}N_4$ |
| 26 | 4-Pyrimidyl | A | 52 | E 70 | 64–66 K | $C_{29}H_{30}N_4 \cdot 2H_2O$ |
| 27 | 4-Methyl-2-pyrimidyl | A | 60 | AE | 128 K | $C_{30}H_{32}N_4$ |
| 28 | 4,6-Dimethyl-2-pyrimidyl | A | 69 | AE | 140 K | $C_{31}H_{34}N_4$ |
| 29 | 5,6-Dimethyl-2-pyrimidyl | A | 19.2 | AM | 211 K | $C_{31}H_{34}N_4 \cdot C_4H_4O_4$[i] |
| 30 | 4,5,6-Trimethyl-2-pyrimidyl | A | 33.3 | E 90 | 147 K | $C_{32}H_{36}N_4$ |
| 31 | 4,6-Dimethyl-5-phenyl-2-pyrimidyl | A | 58 | AE | 88–90 MK | $C_{37}H_{38}N_4$ |
| 32 | 4-Methoxy-2-pyrimidyl | A | 74.2 | AE | 125 K | $C_{30}H_{32}N_4O$ |
| 33 | 4-Hydroxy-2-pyrimidyl | *d* | 61.5 | AP | 176–180 MK | $C_{29}H_{30}N_4O \cdot 2HCl$ |
| 34 | 4-Ethoxy-5-carbethoxy-2-pyrimidyl | B | 20.6 | AE | 170–175 dec, MK | $C_{34}H_{38}N_4O_3 \cdot HCl$ |
| 35 | 4-Ethoxy-5-carboxy-2-pyrimidyl | *e* | 48.5 | AE | 222–224 cap | $C_{32}H_{34}N_4O_3$ |
| 36 | 5-Carbethoxy-2-pyrimidyl | B | 63 | AE | 117–118 MK | $C_{32}H_{34}N_4O_2$ |
| 37 | 5-Carboxy-2-pyrimidyl | *e* | 67 | D | 274–276 cap | $C_{30}H_{30}N_4O_2$ |
| 38 | 5-Dimethylcarbamido-2-pyrimidyl | *f* | 70.4 | AM | 155–157 MK | $C_{32}H_{35}N_5O$ |
| 39 | 5-Cyano-2-pyrimidyl | A | 36.2 | AP-EtOAc (50-50) | 168 K | $C_{30}H_{29}N_5$ |
| 40 | 5-Chloro-2-pyrimidyl | A | 75.6 | AE | 124 K | $C_{29}H_{29}ClN_4$ |
| 41 | 5-Dimethylsulfamido-2-pyrimidyl | A | 57.5 | DMF | 201 K | $C_{31}H_{35}N_5O_2S$ |
| 42 | 4-Amino-2-pyrimidyl | A | 30 | AE | 138–140 MK | $C_{29}H_{31}N_5$ |
| 43 | 2-Amino-4-pyrimidyl | A | 47 | AE | 188–190 MK | $C_{29}H_{31}N_5 \cdot 0.5H_2O$ |
| 44 | 4-Methylamino-2-pyrimidyl | A | 33 | AE | 151–153 MK | $C_{30}H_{33}N_5$ |
| 45 | 4-Dimethylamino-2-pyrimidyl | A | 58.5 | H | 115 (K) | $C_{31}H_{35}N_5$ |
| 46 | 4-Phenethylamino-2-pyrimidyl | A | 17.1 | AE | 265–267 dec, cap | $C_{37}H_{39}N_5 \cdot 2HCl$ |
| 47 | 4-Allylamino-2-pyrimidyl | A | 74 | AM | 156–158 MK | $C_{32}H_{35}N_5$ |
| 48 | 4-Cyclopropylmethylamino-2-pyrimidyl | A | 38 | AE | 195–200 dec, MK | $C_{33}H_{37}N_5 \cdot 2HCl \cdot 0.5H_2O$ |
| 49 | 4-(Cyclopenten-3-yl)amino-2-pyrimidyl | A | 60.5 | AP | 144–147 MK | $C_{34}H_{37}N_5$ |
| 50 | 4-Allylamino-5-amino-2-pyrimidyl | *g* | 43.5 | ACN | 150–152 cap | $C_{32}H_{36}N_6$ |
| 51 | 4-(3,3-Dimethylallylamino)-2-pyrimidyl | A | 21 | AE | 90 cap | $C_{34}H_{39}N_5 \cdot 2H_2O$ |
| 52 | 5-Dimethylaminomethyl-2-pyrimidyl | *h* | 35 | AE | 208–210 K | $C_{32}H_{37}N_5 \cdot 2C_4H_4O_4$[i] |
| 53 | 2-Quinazolyl | A | 32.8 | E 80 | 195–200 dec, MK | $C_{33}H_{32}N_4 \cdot C_4H_4O_4$[i] |
| 54 | 4-Quinazolyl | A | 26 | AM | 224–225 K | $C_{33}H_{32}N_4 \cdot 2HCl \cdot 2H_2O$ |
| 55 | 2-Methyl-4-quinazolyl | A | 79 | AE | 205–210 dec, MK | $C_{34}H_{34}N_4 \cdot C_4H_4O_4 \cdot 0.5H_2O$[i] |

[a]AE, abs EtOH; AM, abs MeOH; AP, abs *i*-PrOH; E 70, 70% EtOH; AcN, acetonitrile; D, diglyme; DMF, dimethyl formamide; H, *n*-hexane. For the others, see corresponding footnotes in Table II. [b,c]See the corresponding footnotes in Table I. [d]Prepd by hydrogenolysis of the corresponding 4-benzyloxy derivative. [e]Prepd in usual manner by alk hydrolysis of 34 and 36. [f]Prepd starting from 37. [g]Prepd by reduction of the corresponding 5-nitro derivative. [h]Prepd in the usual manner by reduction of 39 by means of LAH in THF (see the Experimental Section). [i]Neutral or acidic fumarate.

Table IV

| No. | Het | Method | Yield crystd, % | Crystn[a] solvent | Mp[b] of amine or salt, °C | Formula[c] |
|---|---|---|---|---|---|---|
| | $(C_6H_5)_3C-(CH_2)_2-N$ N–Het | | | | | |
| 56 | 2-Pyridyl | C | 51.9 | AcE | 148 K | $C_{30}H_{31}N_3$ |
| 57 | 3-Pyridazinyl | D | 81.7 | AE | 174–175 K | $C_{29}H_{30}N_4$ |
| 58 | 6-Methyl-3-pyridazinyl | A | 45.2 | AP | 179 K | $C_{30}H_{32}N_4$ |
| 59 | 6-Amino-3-pyridazinyl | A | 23.1 | B | 206–208 cap | $C_{29}H_{31}N_5$ |
| 60 | 6-Allylamino-3-pyridazinyl | A | 11 | AE | 175–178 MK | $C_{32}H_{35}N_5 \cdot 2HCl$ |
| 61 | 6-(3,3-Dimethylallylamino)-3-pyridazinyl | A | 42.2 | M 80 | 160–161 K | $C_{34}H_{39}N_5$ |
| 62 | 2-Pyrazinyl | A | 52.8 | AE | 148–150 MK | $C_{29}H_{30}N_4$ |
| 63 | 3,6-Dimethyl-2-pyrazinyl | C | 21.9 | AE | 195–200 dec, MK | $C_{33}H_{37}N_5 \cdot 2HCl \cdot 0.5H_2O$ |
| 64 | 3-Amino-2-pyrazinyl | C | 26 | AE | 182–185 MK | $C_{29}H_{31}N_5 \cdot 2CH_4O_3S \cdot H_2O$ |
| 65 | 6-Amino-2-pyrazinyl | A | 10 | AE | 242–244 cap | $C_{29}H_{31}N_5 \cdot 2CH_4O_3S$ |
| 66 | 6-Allylamino-2-pyrazinyl | A | 12 | AE | 250–255 dec, cap | $C_{32}H_{35}N_5 \cdot 2HCl \cdot 2H_2O$ |
| 67 | 6-Methyl-2-pyrazinyl | A | 57.5 | AE | 139 K | $C_{30}H_{32}N_4$ |
| 68 | 2-Triazinyl | D[d] | 10 | AM | 250–253 cap | $C_{28}H_{29}N_5 \cdot 2HCl \cdot H_2O$ |
| 69 | 4-Amino-2-triazinyl | D | 53.9 | AM | 166–169 cap | $C_{28}H_{30}N_6$ |
| 70 | 4,6-Diamino-2-triazinyl | A | 47 | AM | 340–346 cap | $C_{28}H_{31}N_7 \cdot 2CH_4O_3S$[e] |
| 71 | 4,6-Bis(allylamino)-2-triazinyl | A | 66.1 | C | 168–169 cap | $C_{34}H_{39}N_7$ |
| 72 | 2-Thiazolyl | A | 56.6 | AE | 160–162 MK | $C_{28}H_{29}N_3S \cdot 2CH_4O_3S$[e] |

[a] B, benzene; M 80, 80% MeOH. For the others, see the corresponding footnotes in Table II. [b,c] See the corresponding footnotes in Table I. [d] Hydrogenolysis performed without NaOH. [e] Bismethanesulfonate.

Table V

| No. | Toxicity, $LD_{50}$, mg/kg (mice) | Analgesia: Hot plate test, mg/kg ip or po | Analgesia: Phenylquinone writhing test, mg/kg sc or po | Carrageenin edema, mg/kg po |
|---|---|---|---|---|
| 11 | ≈125 ip | 10, 0<br>30, ++<br>50, +++ | 30, + | 20, 0 |
| 12 | ≈450 ip | 20, +<br>40, ++++ | 40, + | 40, 0 |
| 13 | >2000 po | 20, 0<br>40, ++ | 20, + | 40, 0 |
| 15 | >2000 po | 20, 0<br>30, +<br>40, ++++ | 100, +<br>200, + | 40, 0<br>80, 0 |
| 16 | >2000 po | 50, 0<br>100, ++ | 40, + | 20, 0 |
| 17 | ≈2000 po<br>≥400 ip | 20, +<br>40, ++ | 20, 0 | 20, 0<br>40, ++ |
| 25 | 501 ip<br>72 iv | $ED_{50}$<br>46.5 po, ++++<br>36 ip | $ED_{50}$<br>38 sc, ++++<br>6.5 po | 5, +<br>10, +++<br>20, ++++ |
| 27 | >2000 po | 100, 0 | 5, +<br>20, ++<br>40, +++ | 20, ++<br>30, +++ |
| 28 | >2000 po | 50, ++<br>100, ++++<br>200, ++++ | 10, +<br>40, ++++ | 20, ++<br>30, +++ |
| 29 | ≥2000 po | 40, ++<br>80, ++ | 40, ++ | 5, 0<br>10, +++<br>20, ++++ |
| 32 | >2000 po | 100, ++ | 40, + | 20, 0 |
| 33 | >2000 po | 20, 0<br>40, ++<br>80, ++ | 20, + | 40, 0<br>80, 0 |
| 34 | ≈1200 po | 50, +<br>100, +++ | 5, ++<br>20, +++ | 20, ++ |
| 35 | 2000 po | 50, ++<br>100, ++++ | 5, ++<br>20, ++++ | 20, 0<br>40, 0 |
| 42 | 188 ip | 10, ++<br>20, ++++ | 10, ++<br>20, ++ | 10, ++<br>20, ++++ |
| 44 | ≈100 ip | 10, +<br>20, + | 10, + | 10, ++ |
| 45 | ≈300 ip<br>>2000 po | 40, + | 20, + | 40, ++ |
| 47 | 461 ip<br>>2000 po | 25, 0<br>50, +<br>100, + | 20, +<br>40, ++ | 20, 0<br>40, 0 |
| 48 | >2000 po | 50, + | 40, 0<br>80, ++ | 20, 0 |
| 49 | >2000 po | 50, + | 40, ++ | 20, 0 |
| 56 | >2000 po | 20, +++ | 10, ++<br>20, +++ | 40, ++ |
| 57 | >2000 po | 50, +<br>100, +++ | 1, +<br>5, +++<br>10, +++ | 40, 0<br>80, ++ |
| 59 | ≈150 ip | 20, ++ | 10, 0 | 20, 0 |
| 60 | 2000 po | 100, ++++ | 40, 0 | 20, ++ |
| 62 | ≈200 ip<br>≈2000 po | 10, +++<br>25, ++++ | 10, 0<br>20, ++ | 20, + |
| 63 | ≈1000 po | 10, 0<br>25, ++++ | 1, 0<br>5, ++<br>20, ++++ | 20, + |
| 64 | ≈450 ip | 20, ++<br>40, +++ | 20, + | 20, + |
| 67 | >2000 po | 25, +<br>50, ++++ | 5, +++<br>10, +++ | 20, +++ |
| 69 | >2000 po | 50, +++ | 2.5, ++<br>10, +++ | 20, +++ |
| 71 | >2000 po | 50, 0 | 40, 0 | 20, 0 |
| 72 | ≈450 ip | 20, +<br>40, + | 40, ++ | 20, + |
| Morphine | sc 400<br>ip 300 | 16.5 sc, ++++ | 1 sc, ++ | sc 6, ++<br>8, ++++ |
| Codeine | ip 124<br>po 452 | 60 ip, ++++ | 5.6 sc, ++ | po 80, ++ |
| *d*-Propoxyphene | ip ≈150<br>po 300 | 37.2 sc,<br>65 po, ++++ | 7.5 sc, ++ | po 40, +++ |

group must be kept intact otherwise the activity decreases (44–52). Antagonistic properties to **25** and **42** are induced by N-substituting $NH_2$ in **42** with allyl (**47**) or cyclopropylmethyl (**48**). The appearance of antagonistic properties in these last 2 compounds, although limited enough inasmuch as **47** enhances the morphine effect, may be compared to a certain extent, with a more general antagonistic effect observed with the same kind of N substitutions in the morphine, morphinan, and benzomorphan series. Table VI points out the potency of the most interesting compounds by using 2 additional methods.[13,14] The second one, particularly, allows us to locate the level of analgetic activity by the animals' behavioral response, with peripheral, medullary, central, and cortical components. Antitussive properties[16] were also taken into account.

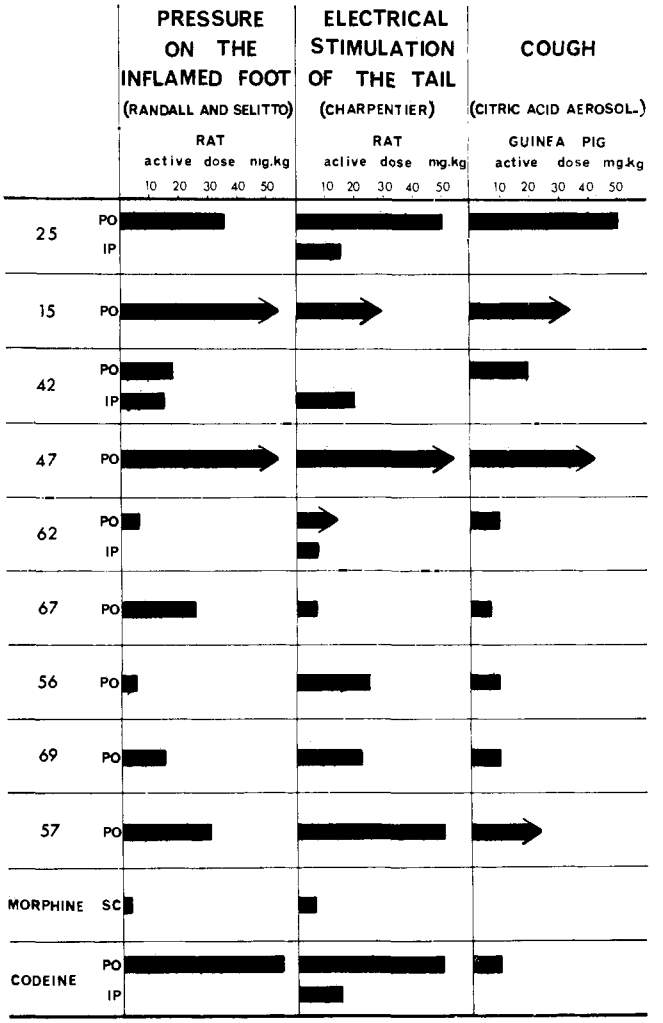
To conclude, 4 compounds (**25**, **62**, **57**, **47**) have been selected for extensive pharmacological studies. Compd **25** has an analgetic potency between that of morphine and codeine; it is almost devoid of respiratory depressant action and seems to have a low dependence liability, as judged by the appearance of a slight abstinence syndrome following withdrawal of the drug from tolerant animals and also by the fact that the animals never self-administered the compound in the course of selected experiments according to Kumar[8] (See Table VI).

Compd **62** is the most active in the series (as potent as morphine) but it induces bizarre behavioral effects after cessation of a 3-week treatment. The most striking withdrawal effect was fighting similar to that observed by Schneider[9] for apomorphine and LSD.

Compd **47** antagonized the actions of **25** and **62** while enhancing the morphine effect under the same conditions. Its analgetic potency is rather low but pentazocine is also inactive in the same tests, except in writhing tests where it is fairly active.[10]

Compd **57** behaves codeine-like and seems very similar to that drug in regard to potency, dependence liability, and general pharmacology.

Table VI




## Experimental Section‡

I. Pharmacological Methods. (a) Analgetic Activity. The analgetic activity was detd in mice by the modified hot plate test[11] and the phenylquinone writhing test.[12] The results were expressed according to the following scale: ++++, 100% inhibition or more; +++, 75%; ++, 50%; +, 25%.

Two methods were used in rats: those of Randall and Selitto[13] and Carroll and Lim modified by Charpentier.[14] The results are given as $ED_{50}$'s for the former method. For the latter the results are given as the dose which decreases by 50% the total response as far as the cry and biting the electrodes are concerned, inasmuch as only these 2 parameters are specifically modified by the central analgetic substances while both the jump and the escape are not modified except with toxic doses.

(b) Antiinflammatory Activity. Paw edema in the rat was produced with carrageenin according to Winter *et al.*[15] The data are given in a simplified form as follows: ++++, 50% inhibition or more; +++, 40%; ++, 30%; +, 20%.

(c) Antitussive Activity. Cough was induced in guinea pigs with a citric acid aerosol according to Charlier, *et al.*[16] The figures given represent $ED_{50}$'s.

II. Chemical Methods. (1) Substituted Halogenoheterocycles. The following compds were prepd according to lit. methods: 2-chloropyrimidine,[17] 4-chloropyrimidine,[18] 4-methoxy-2-chloropyrimidine,[19] 4-benzyloxy-2-chloropyrimidine,[2] 4-amino-2-chloro- and 2-amino-4-chloropyrimidine,[20] 4-methylamino-2-chloropyrimidine,[2] 4-dimethylamino-2-chloropyrimidine,[21] 4-methyl-2-chloropyrimidine,[22] 4,5-dimethyl-2-chloropyrimidine,[23] 4,6-dimethyl-2-chloropyrimidine,[24] 4,6-dimethyl-5-phenyl-2-chloropyrimidine,[25] 2,5-dichloropyrimidine,[26] 5-cyano-2-chloropyrimidine,[27] 4-chloro-5-carbethoxy-2-methylthiopyrimidine,[28] 5-chlorosulfonyl-2-chloropyrimidine,[29] 2-chloroquinazoline,[30] 4-chloroquinazoline, and 4-chloro-2-methylquinazoline,[31] 6-methyl-3-chloropyridazine,[32] 6-amino-3-chloropyridazine,[33] 3,6-dimethyl-2-chloropyrazine,[34] 3-amino-2-chloropyrazine,[35] 6-methyl-2-chloropyrazine,[36] 4-amino-2,6-dichlorotriazine, and 4,6-diamino-2-chlorotriazine,[37] 2-chlorothiazole,[38] 4,6-bis(allylamino)-2-chlorotriazine.[39]

The following compds were prepd in our laboratory: 4,5,6-trimethyl-2-chloropyrimidine (mp 93°); 4-phenethylamino-2-chloropyrimidine (mp 81°); 4-allylamino-2-chloropyrimidine (mp 169°); 4-cyclopropylmethylamino-2-chloropyrimidine hydrochloride (mp 218–219°); 4-(cyclopenten-2-ylamino)-2-chloropyrimidine hydrochloride (mp 125°); and 4-(3,3-dimethylallylamino)-2-chloropyrimidine (mp 177°); 4-allylamino-5-nitro-2-chloropyrimidine [mp (cap) 49°] (see ref 40); 5-dimethylsulfamido-2-chloropyrimidine (mp 121°) from the 5-chlorosulfonyl derivative and $Me_2NH$ in PhH; 6-allylamino-3-chloropyridazine (mp 107°) and 6-(3,3-dimethylallylamino)-3-chloropyridazine (mp 110°) from 3,6-dichloropyridazine and an EtOH soln of allylamine and 3,3-dimethylallylamine at 120°, respectively, in a stainless steel bomb. By the same method were prepd: 6-amino-2-chloropyrazine (mp 150°) and 6-allylamino-2-chloropyrazine hydrochloride (mp 110°). The others were obtd from commercial sources.

**5-Carbethoxy-2-methylthiopyrimidine** was obtd by heating under reflux 114 g (0.489 mole) of 4-chloro-5-carbethoxy-2-methylthiopyrimidine in a mixt of 912 ml of dioxan and 570 ml of $H_2O$ with 114 g of activated Zn powder: yield, 58 g (60%); colorless liquid; bp 99–100° (0.5 mm); $n^{25}D$ 1.5645. *Anal.* ($C_8H_{10}N_2O_2S$) C, H, N.

‡All melting and boiling points are uncorrected. Except otherwise mentioned, all the melting points in the experimental part were taken from a Kofler block. (See footnote *b*, Table II.) Where analysis are indicated only by symbols of the elements, analytical results were obtained within ±0.4% of the theoretical values.

5-Carbethoxy-4-ethoxy-2-methylthiopyrimidine was obtd in 82% yield from the same starting material in EtOH: bp 112–120° (0.5 mm); $n^{25}$D 1.546, mp 51° (petr ether). *Anal.* ($C_{10}H_{14}N_2O_3S$) C, H, N.

Toluenesulfonate Esters. The following esters were prepd according to ref 5: 1-methyl-1-*p*-toluenesulfonyl-3,3,3-triphenylpropane and 2-methyl-1-*p*-toluenesulfonyloxy-3,3,3-triphenylpropane. In the same manner were obtd 1-*p*-toluenesulfonyloxy-3,3-diphenylpropane [mp 60° (MeOH)] from 3,3-diphenylpropanol, bp 140–143° (0.7 mm), $n^{25}$D 1.581; 1-*p*-toluenesulfonyloxy-3-(4-biphenylyl)-3,3-diphenylpropane [mp 115° (EtOH)] from 3-(4-biphenylyl)-3,3-diphenylpropanol [mp 174° ($Et_2O$)]; 1-*p*-toluenesulfonyloxy-3,3,3-triphenylpropane [mp 119° (EtOH)] from 3,3,3-triphenylpropanol [mp 109–110° ($Et_2O$)]; 1-*p*-toluenesulfonyloxy-3-(4-methoxy phenyl)-3,3-diphenylpropane (oily) from 3-(4-methoxyphenyl)-3,3-diphenylpropanol, bp 225–230° (0.5 mm).

Monosubstituted Piperazines. All compds described in Table I except 4 were synthesized according to the following method.

1-(3,3,3-Triphenylpropyl)piperazine (2). A mixt of 150 g (0.338 mole) of 1-*p*-toluenesulfonyloxy-3,3,3-triphenylpropane and 331 g (3.84 moles) of anhyd piperazine was stirred under reflux at 140° for 6 hr. After cooling, the oily mixt was treated with $H_2O$ (1500 ml) and several times extd with $CHCl_3$. After removal of the solvent, the oily residue was distd and gave 100 g (83%) of pure product: bp 210° (0.2 mm); mp 130°.

Some hetero-substituted piperazine derivatives were synthesized according to the preceding procedure.

1-(3,6-Dimethyl-2-pyrazinyl)piperazine was prepd from 3,6-dimethyl-2-chloropyrazine and anhyd piperazine: yield 91%, bp 108–110° (0.6 mm); mp 73°. The dihydrochloride had mp 238–240° dec. *Anal.* ($C_{10}H_{16}N_4 \cdot 2HCl$) C, H, N.

1-(3-Amino-2-pyrazinyl)piperazine was prepd from 2-chloro-3-aminopyrazine (Aldrich) and anhyd piperazine: yield 50%; mp 162°. *Anal.* ($C_8H_{13}N_5$) C, H, N.

Other piperazine derivatives were prepd according to lit. methods: 1-(2-pyridyl)piperazine[41] and 1-(2-pyrimidyl)-2-methylpiperazine.[2]

1-(4,4,4-Triphenylbutyl)piperazine (4) was prepd by analogy with ref 6, by hydrolysis with 50% $H_2SO_4$ of the 1-(4,4,4-triphenylbutyl)-4-tosylpiperazine, mp 177° (MeOH), itself prepd from 4,4,4-triphenylbutylamine and *N,N*-bis(2-chloroethyl)-*p*-toluenesulfonamide, in diethylene glycol dimethyl ether (yield 50%).

1,4-Disubstituted Piperazines. Method A. 1-(3,3,3-Triphenylpropyl-4-(2-pyrimidyl)piperazine (25). A soln of 22.5 g (0.063 mole) of 1-(3,3,3-triphenylpropyl)piperazine and 6.6 g (0.057 mole) of 2-chloropyrimidine in 350 ml of DMF with 16 g (0.115 mole) of $K_2CO_3$ was stirred and heated at 140° for 9 hr. After cooling, the salt was filtered off, and the solvent was evapd to dryness *in vacuo*. The pasty residue was dissolved in 100 ml of anhyd EtOH and clarified with Darco. On cooling to 0°, the product crystd; it was filtered and washed with cold EtOH. After drying at 100° overnight *in vacuo*, 16 g (64.7 %) of colorless crystals was obtd (mp 130°). Bismethane sulfonate had mp 193–194° dec. *Anal.* ($C_{29}H_{30}N_4 \cdot 2HSO_3CH_3$) C, H, N.

Method B. 1-(3,3,3-Triphenylpropyl)-4-(5-carbethoxy-2-pyrimidyl)piperazine (36). A mixt of 59.5 g (0.167 mole) of 1-(3,3,3-triphenylpropyl)piperazine and 33 g (0.166 mole) of 5-carbethoxy-2-methylthiopyrimidine was stirred and heated at 200° for 12 hr. After cooling to 70°, the syrupy residue was treated with 300 ml of hot petr ether and the crystals were filtered off. The crude product (69 g) was recrystd twice from EtOH: yield, 53 g (63%); mp (MK) 117–118°.

Method C. 1-(3,3,3-Triphenylpropyl)-4-(2-pyridyl)piperazine (56). A mixt of 65 g (0.398 mole) of 1-(2-pyridyl)piperazine and 88 g (0.199 mole) of 1-*p*-toluenesulfonyloxy-3,3,3-triphenylpropane was stirred and heated at 135° for 11 hr. After cooling to 80°, the thick mixt was treated with $H_2O$ (400 ml) and $CHCl_3$ (250 ml), the aq layer was decanted and extd several times with $CHCl_3$, then discarded. The $CHCl_3$ layer was dried ($K_2CO_3$) and the solvent removed *in vacuo*. The cryst residue was dissolved in 400 ml of hot EtOH and cleared with Darco. After cooling, the crystals were filtered off and recrystd from 500 ml of EtOAc: yield, 45 g (51.9%); mp 148°.

Method D. 1-(3,3,3-Triphenylpropyl-4-(3-pyridazinyl)piperazine (57). A slurry of 14 g (0.0296 mole) of 1-(3,3,3-triphenylpropyl)-4-(6-chloro-3-pyridazinyl)piperazine [mp (cap) 197° (MeOH)] in 1 l. of MeOH was stirred at room temp under 6 kg/cm² of $H_2$ over 3 g of 5% Pd/C in the presence of 30 ml of 1 *N* NaOH. After 2 hr the theoretical quantity of $H_2$ was absorbed while the product went into soln. The catalyst was removed and the EtOH soln was concd. The crude product was dissolved in $CHCl_3$ and the soln was washed several times with $H_2O$. After removal of the solvent *in vacuo* the cryst residue (12 g) was dissolved in 150 ml of hot EtOH and cleared with Darco. On cooling to 0° the product crystd; it was filtered, washed with cold EtOH, and dried overnight in a vacuum desiccator: yield, 10.5 g (81.7%); mp 173°.

The starting material was prepd from a soln of equimolar quantities of 3,6-dichloropyridazine and 1-(3,3,3-triphenylpropyl)piperazine in MeOH, heated 12 hr under reflux, in the presence of $NaHCO_3$: yield, 82.6%. *Anal.* ($C_{29}H_{29}ClN_4$) C, H, N.

In the same manner were prepd the following starting materials: 1-(3,3-diphenylpropyl)-4-(6-chloro-3-pyridazinyl)piperazine (11), mp 120°, yield 50.4%; 1-(3,3-triphenylpropyl-4-(4,6-dichloro-2-*s*-triazinylpiperazine (68), mp 160°, yield 90%; and according to method A, 1-(3,3,3-triphenylpropyl)-4-(4-chloro-6-amino-2-*s*-triazinyl)piperazine (69), mp 200°, yield 60%.

Other Methods for the Preparation of 1,4-Disubstituted Piperazines (See Tables II and III). 1-(3,3-Diphenyl-3-cyanopropyl)-4-(2-pyrimidyl)piperazine (10). A slurry of 11.3 g (0.0585 mole) of diphenylacetonitrile and 2.3 g (0.0585 mole) of $NaNH_2$ in 75 ml of anhyd PhMe was stirred and heated under reflux for 1 hr. When the metallation was finished, a soln of 14 g (0.0617 mole) of 1-(2-chloroethyl)-4-(2-pyrimidyl)piperazine (mp 61°) in 30 ml of PhMe was added and the mixt was treated as above for 8 hr. After cooling, it was heated with $H_2O$ (50 ml) and then extd several times into 1 *N* $HSO_3Me$. The acid soln was made alk with excess $K_2CO_3$ and extd with $Et_2O$. After drying ($K_2CO_3$) of the exts and removal of the solvent *in vacuo* the residue (15 g) was dissolved in 50 ml of anhyd EtOH and the ice-cold soln was satd with HCl gas. The cryst product was filtered, washed with cold EtOH, and dried in a vacuum desiccator: yield 10.8 g of dihydrochloride; mp 178°. This salt was dissolved in 75 ml of $H_2O$, and the soln was rendered alk with excess $K_2CO_3$. The filtered crystals were recrystd from *i*-PrOH (25 ml): yield, 5.2 g (23.2%); mp 113°.

1-(3,3,3-Triphenylpropionyl)-4-(2-pyrimidyl)piperazine (18). A soln of 10 g (0.031 mole) of 3,3,3-triphenylpropionyl chloride (mp 130°) and 11.3 g (0.069 mole) of 1-(2-pyrimidyl)piperazine in 200 ml of anhyd xylene was stirred and heated under reflux for 3 hr. After cooling, the white crystals were filtered off and washed with $H_2O$, then recrystd from 105 ml of AcOH: yield, 10.9 g (78.4%); mp 260°. The starting chloride was obtained by chlorination of 3,3,3-triphenylpropionic acid[42] in excess $SOCl_2$.

1-(3,3,3-Triphenylpropyl)-4-(4-hydroxy-2-pyrimidyl)piperazine Dihydrochloride (33). A soln of 1-(3,3,3-triphenylpropyl)-4-(4-benzyloxy-2-pyrimidyl)piperazine dihydrochloride, mp (MK) 168–170°, in 600 ml of MeOH was stirred under 6 kg/cm² of $H_2$ over 2.5 g of 10% Pd/C. After 4 hr the theoretical quantity of $H_2$ was absorbed and the catalyst removed. The EtOH soln was concd *in vacuo* and the cryst residue was dissolved in 200 ml of hot *i*-PrOH and 10 ml of 4 *N* HCl. On cooling to 5°, the dihydrochloride crystd; it was filtered off and the crystals were washed with cold *i*-PrOH: yield, 8 g (61.5%); mp (MK) 176–180°. The starting material was prepd according to method A from 2-chloro-4-benzyloxypyrimidine: yield, 64%. *Anal.* ($C_{36}H_{36}N_4O \cdot 2HCl \cdot H_2O$) C, H, N.

1-(3,3,3-Triphenylpropyl)-4-(5-dimethylcarbamido-2-pyrimidyl)-piperazine (38). 1-(3,3,3-Triphenylpropyl)-4-(5-chlorocarbonyl-2-pyrimidyl)piperazine (15 g, 0.0281 mole) (mp 214°) was gradually added to a soln of 0.1124 mole of $Me_2NH$ in anhyd PhH at room temp. The mixt was heated under reflux for 1 hr. After cooling, it was treated with $H_2O$ (50 ml) and decanted. The organic portion was evapd *in vacuo* and the syrupy residue was dissolved in hot EtOH (50 ml). After cooling, the crystals were filtered off and washed with cold EtOH: yield, 10 g (70.4%); mp (MK) 155–157°. The starting chloride was prepd by chlorination of 37 in excess $SOCl_2$.

1-(3,3,3-Triphenylpropyl)-4-(4-allylamino-5-amino-2-pyrimidyl)-piperazine (50). A soln of 56 g (0.104 mole) of 1-(3,3,3-triphenylpropyl)-4-(4-allylamino-5-nitro-2-pyrimidyl)piperazine (mp 176°) in 3 l. of MeOH was stirred under 7 kg/cm² of $H_2$ over 20 g of Raney-Ni. After completion of the hydrogenation, the catalyst was removed and the solvent was evapd *in vacuo*. The resinous purple residue (45 g) was dissolved in anhyd MeOH (600 ml) and the soln satd with HCl gas. The crude dihydrochloride crystd, and after cooling was filtered off: yield, 42.5 g; mp (cap) 220–222°. It was dissolved in $H_2O$ (250 ml) and the base was pptd, with cooling to 0°, with 4 *N* NaOH (100 ml), collected on a filter, washed with $H_2O$, and dried in air. The crude product (31 g) was recrystd in MeCN (300 ml): yield, 23 g (43.5%); mp (cap) 150–152°. The starting material was prepd according to method A from 2-chloro-4-allylamino-5-nitropyrimidine: yield 97%. *Anal.* ($C_{32}N_{34}N_6O_2$) C, H, N.

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# Bicyclic Mannich Bases. 1. Psychotropic Activity of 2-(4-Aryl-1-piperazinyl)bicyclo[3.3.1]nonan-9-ones and Derivatives


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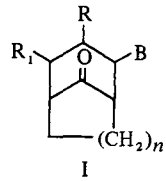
*Received September 7, 1971*


A series of 2-(4-aryl-1-piperazinyl)bicyclo[3.3.1]nonan-9-ones were synthesized and some of them were converted to the 9-phenyl-9-hydroxy derivatives. In most CNS models, 2-(4-phenyl-1-piperazinyl)-9-phenylbicyclo[3.3.1]nonan-9-ol (17) was found to exhibit an activity pattern similar to chlordiazepoxide.


It has been reported that 2-substituted-4-phenyl-1-piperazinylmethyl cycloalkanones possess analgetic and antiinflammatory activity in laboratory animals.[1] These findings prompted the synthesis of a number of analogous bicyclic Mannich bases having the general structure I where




I

R = H or lower alkyl, $R_1$ = H or Ph, $n$ = 1–3, and B = tertiary amino.

In initial general studies it was noted that 2-(4-phenyl-1-piperazinyl)bicyclo[3.3.1]nonan-9-one (4) had the property of inducing catalepsy in the rat. Since this effect is an indicator of potential tranquilizing activity, it was decided to further investigate this bicyclic structure where the 2-(4-aryl-1-piperazinyl) moiety is an integral part of the ring system. This paper is primarily concerned with the synthesis and CNS pharmacological properties of 2-(4-aryl-1-piperazinyl)-bicyclo[3.3.1]nonan-9-ones and derivatives thereof.

The compounds in Table I were prepared by the method of Stork and Landesman.[2] The fact that enamines derived from cyclohexanone and higher molecular weight amines reacted with acrolein in inert solvents to give crystalline 8a-amino-4a,5,6,7,8,8a-hexahydro-4*H*-1-benzopyrans (II) has been reported previously.[3] These intermediates could be isomerized to the bicyclic ketones by heating in DMF-$Et_3N$; it was later found that heating in 2-PrOH-$Et_3N$ resulted in cleaner isomerization of the intermediate.

In the case of the isomerization of II (B = 4-phenyl-1-piperazinyl; R = $R_1$ = H), we showed that the stereochemical results were formation of III and IV in a ratio of approximately 4:1.[3] These results are consistent with those reported by Dean, *et al.*,[4] who determined the stereochemistry of the amino ketones formed in the reaction of 1-morpholinocyclohexene with acrolein.