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# Substituted α-Methylbenzyl and Tricyclic Arylalkyl Lactamimides as Inhibitors of Blood Platelet Aggregation

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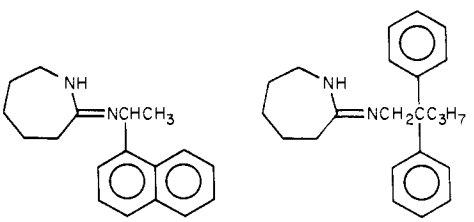
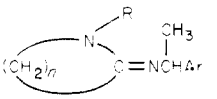
*N*-[1-(*p*-Phenoxyphenyl)ethyl]hexahydro-2*H*-azepin-2-imine hydrochloride (10) and *N*-[1-(2-dibenzothienyl)-ethyl]hexahydro-2*H*-azepin-2-imine hydrochloride (22) were found to inhibit in vitro aggregation of human blood platelets induced by ADP with minimal release of procoagulant platelet factor 3. The compounds were selected from a series of substituted α-methylbenzyl and tricyclic arylalkyl lactamimides that were free of hypoglycemic and diuretic effects. Compounds 10 and 22, as well as *N*-[1-(1-naphthyl)ethyl]hexahydro-2*H*-azepin-2-imine hydrochloride (I) and *N*-(2,2-diphenylpentyl)hexahydro-2*H*-azepin-2-imine hydrochloride (II), were evaluated for effects on ADP-induced platelet aggregation after repeated oral administration to guinea pigs. Compound II (RMI 12,366A) showed in vivo activity in this system 2 h after the last of four daily doses of 100 mg/kg po.

Naphthylalkyl lactamimides, especially I (RMI 7822A), were found earlier to inhibit adenosine diphosphate (ADP) and collagen-induced aggregation of human blood platelets.[1] Later it was found that I also has hypoglycemic and diuretic properties in rats.[2] We therefore set out to find lactamimides that inhibit platelet aggregation without causing hypoglycemia or diuresis. Compound II (RMI 12,366A), which was reported earlier,[2] meets these requirements. In this paper, we report preparation and evaluation of a series of substituted α-methylbenzyl lactamimides III, in which the substituent R is large and imparts lipophylic properties to the molecules, and tricyclic arylalkyl lactamimides IV. Compounds of this type inhibit aggregation of platelets but are free of hypoglycemic ef-




I II

Table I. Arylalkyl Lactamimides and Their Effect on Human Blood Platelets



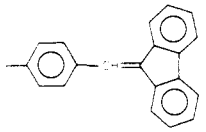
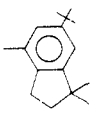
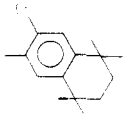
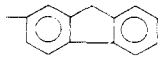
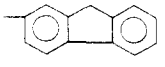
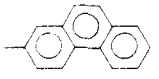
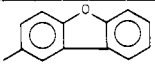
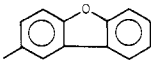
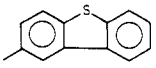
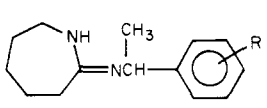
| No. | Ar | R | *n* | Mp, °C[a] | Yield, % | Mol formula[b] | Effects on human platelets[c] Concn, μg/ml | % inhibn of ADP-induced aggregation | % PF3 release |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $-C_6H_5$ | H | 5 | 245-247 | 41 | $C_{14}H_{20}N_2 \cdot HCl$ | 100 | 0 | |
| 2 | $-C_6H_4$-*p*-*n*-$C_{13}H_{27}$ | H | 5 | 183-185 | 81 | $C_{27}H_{46}N_2 \cdot HCl$ | 100 | 100 | |
| | | | | | | | 30 | 33 | |
| | | | | | | | 10 | 16 | |
| 3 | $-C_6H_4$-*p*-O-*n*-$C_{12}H_{25}$ | H | 5 | 186-188 dec | 81 | $C_{26}H_{44}N_2O \cdot HCl$ | 100 | 64 | |
| 4 | $-C_6H_4$-*p*-$C_6H_{11}$ | H | 5 | 245-247 | 64 | $C_{20}H_{30}N_2 \cdot HCl$ | 300 | | 0.62 |
| | | | | | | | 100 | 100 | 0.004 |
| | | | | | | | 30 | 31 | |
| | | | | | | | 10 | 9 | |
| 5 | $-C_6H_4$-*p*-$C_6H_5$ | H | 5 | 245-247 | 80 | $C_{20}H_{24}N_2 \cdot HCl$ | 300 | | 0.76 (2) |
| | | | | | | | 100 | 100 | 0.04 (2) |
| | | | | | | | 30 | 44 (2) | |
| | | | | | | | 10 | 0 (2) | |
| 6 | $-C_6H_4$-*p*-$CH_2CH_2C_6H_5$ | H | 5 | 230-232 | 76 | $C_{22}H_{28}N_2 \cdot HCl$ | 300 | | 0.91 (2) |
| | | | | | | | 100 | 78 (2) | 0.013 (2) |
| | | | | | | | 30 | 37 | 0.00 |
| | | | | | | | 10 | 8 | |
| 7 | $-C_6H_4$-*p*-$CH_2CH_2C_6H_5$ | Me | 3 | 87-89[d] | 32 | $C_{21}H_{26}N_2 \cdot HCl \cdot H_2O$ | 100 | 100 | |
| | | | | | | | 30 | 29 | |
| 8 | $-C_6H_4$-*p*-$CH{=}C(C_6H_5)_2$ | H | 5 | 219-221 | 55 | $C_{28}H_{30}N_2 \cdot HCl$ | 300 | | 2.30 |
| | | | | | | | 100 | 100 | 0.23 |
| | | | | | | | 30 | 21 (2) | |
| | | | | | | | 10 | 0 | |
| 9 |  | H | 5 | 266-268 dec | 59 | $C_{28}H_{28}N_2 \cdot HCl$ | 300 | | 0.42 |
| | | | | | | | 100 | 100 | 0.02 |
| | | | | | | | 30 | 38 | |
| | | | | | | | 10 | 6 | |
| 10 | $-C_6H_4$-*p*-$OC_6H_5$ | H | 5 | 210-212 dec | 68 (80) | $C_{20}H_{24}N_2O \cdot HCl$ | 300 | | 0.26 (2) |
| | | | | | | | 100 | 100 | 0.01 (2) |
| | | | | | | | 30 | 25 | |
| | | | | | | | 10 | 15 | |
| 11 | $-C_6H_4$-*o*-$OCH_2CH_2C_6H_5$ | H | 5 | 189-190 dec | 28 | $C_{22}H_{28}N_2O \cdot HCl$ | 100 | 81 | |
| | | | | | | | 30 | 30 | |
| | | | | | | | 10 | 11 | |
| 12 | $-C_6H_4$-*p*-$O(CH_2)_3C_6H_5$ | H | 5 | 202-205 | 76 | $C_{23}H_{30}N_2O \cdot HCl$ | 100 | 74 (2) | |
| 13 | $-C_6H_4$-*p*-$O(CH_2)_3$-$OC_6H_5$ | H | 5 | 162-164 | 58 | $C_{23}H_{30}N_2O_2 \cdot HCl$ | 100 | 100 | |
| | | | | | | | 30 | 14 | |
| | | | | | | | 10 | 0 | |
| 14 | $-C_6H_4$-*m*-$O(CH_2)_4$-$OC_6H_5$ | H | 3 | 136-138 dec[e] | 46 | $C_{22}H_{28}N_2O_2 \cdot HCl$ | 100 | 100 | |
| | | | | | | | 30 | 16 | |
| | | | | | | | 10 | 0 | |
| 15 |  | H | 5 | 257-258 dec | 65 | $C_{23}H_{36}N_2 \cdot HCl$ | 100 | 100 | |
| | | | | | | | 30 | 22 | |
| | | | | | | | 10 | 0 | |
| 16 |  | H | 5 | 247-248 dec[e] | 29 | $C_{24}H_{38}N_2 \cdot HCl$ | 100 | 77 | |
| 17 |  | H | 5 | 274-276 dec | 61 | $C_{21}H_{24}N_2 \cdot HCl$ | 300 | | 1.50 |
| | | | | | | | 100 | 100 | 0.06 |
| | | | | | | | 30 | 43 (2) | |
| | | | | | | | 10 | 0 | |
| 18 |  | H | 7 | 276-277 dec | 60 | $C_{23}H_{28}N_2 \cdot HCl$ | 100 | 100 (2) | |
| | | | | | | | 30 | 62 | |
| | | | | | | | 10 | 6 | |
| 19 |  | H | 5 | 262-264 dec | 72 | $C_{22}H_{24}N_2 \cdot HCl$ | 300 | | 2.60 |
| | | | | | | | 100 | 100 | 0.06 |
| | | | | | | | 30 | 43 (2) | |
| | | | | | | | 10 | 4 | |

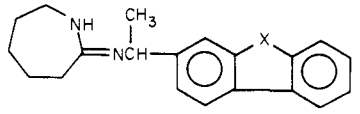
Table I (*Continued*)

| No. | Ar | R | n | Mp, °C[a] | Yield, % | Mol formula[b] | Effects on human platelets[c]: Concn, μg/ml | % inhibn of ADP-induced aggregation | % PF3 release |
|---|---|---|---|---|---|---|---|---|---|
| 20 |  | H | 3 | 188–191 dec | 44 | $C_{18}H_{18}N_2O\cdot HCl$ | 100 | 100 | |
| | | | | | | | 30 | 42 | |
| | | | | | | | 10 | 10 | |
| 21 |  | H | 5 | 304–306 dec[e] | 83 | $C_{20}H_{22}N_2O\cdot HCl$ | 100 | 67 | |
| 22 |  | H | 5 | 272–274 | 78 | $C_{20}H_{22}N_2S\cdot HCl$ | 300 | | 0.18 |
| | | | | | | | 100 | 100 | 0.013 |
| | | | | | | | 30 | 52 | |
| | | | | | | | 10 | 2 | |
| I[f] | See text | | | | | | 300 | | 0.037 |
| | | | | | | | 100 | 70 (2) | 0.003 |
| | | | | | | | 30 | 46 (2) | |
| | | | | | | | 10 | 0 (2) | |
| II[g] | See text | | | | | | 300 | | 0.130 |
| | | | | | | | 100 | 100 | |
| | | | | | | | 30 | 57 | |
| | | | | | | | 10 | 1 | |
| α-[*p*-(Fluoren-9-ylidenemethyl)phenyl]-2-piperidineethanol glycolate (RMI 10,393)[h] | | | | | | | 300 | | 0.747 (6) |
| | | | | | | | 100 | 99 (4) | 0.162 (6) |
| | | | | | | | 30 | 28 (6) | 0.003 (7) |
| | | | | | | | 10 | 1 (6) | |
| *N*-(2-Diethylaminoethyl)-*N*-(2-hydroxy-2-phenylethyl)2,5-dichloroaniline (AN 162)[i] | | | | | | | 300 | | 0.52 (42) |
| | | | | | | | 100 | 62 (118) | 0.10 (47) |
| | | | | | | | 30 | 10 (104) | |

[a] Compounds were recrystallized from methanol–acetone unless otherwise indicated. [b] All compounds were analyzed for C, H, and one other element. Analytical results obtained for these elements were within ±0.4% of the calculated values. [c] In vitro effect of test compound on the inhibition of platelet aggregation caused by ADP in human platelet-rich plasma. PF3 activity is given as percent of maximum. Number in parentheses indicates number of determinations. [d] Recrystallized from acetone. [e] Recrystallized from absolute ethanol. [f] Reference 1. [g] Reference 2. [h] References 11 and 12. [i] Reference 8.



III



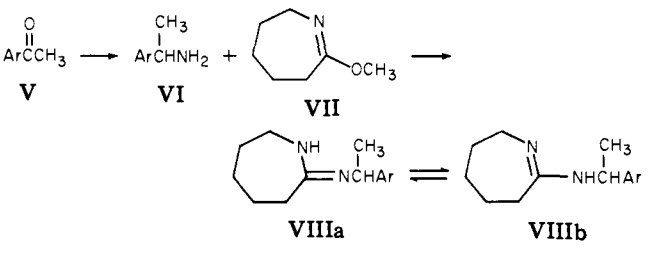
IV

fects. In vivo evaluation of a compound each of type III and IV, as well as of I and II, is also reported.

**Chemistry.** Compounds of type III and IV were prepared as shown in Scheme I. Primary amines VI were allowed to react with *O*-methylcaprolactim (VII)[3] by the method of Benson and Cairns[4] to give the lactamimides listed in Table I. These occur in two tautomeric forms VIIIa and VIIIb. The amines VI were prepared from aryl methyl ketones by Leuckart reaction and are listed in Table II. Representative examples of these reactions are given in the Experimental Section.

**Biological Evaluation.** The compounds listed in Table I were evaluated for inhibition of ADP-induced aggregation of human blood platelets by the method of Mustard et al.[5] and for release of platelet factor 3 (PF3) by the method of MacKenzie et al.[6] PF3 is a procoagulant factor and its release is an undesired property.[7] Because MacKenzie et al.[6] showed that PF3-like activity of 0.1–0.3% is caused by a normal breakfast, we adopted these values as our limit of acceptability. Data are given in the last three columns of Table I.

Scheme I



V VI VII

VIIIa VIIIb

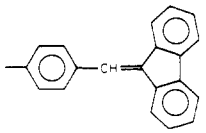
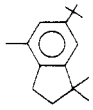
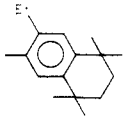
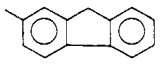
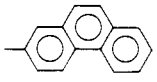
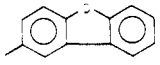
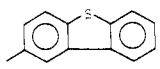
Compounds **10**, **22**, I, and II were evaluated in guinea pigs by the method of MacKenzie et al.[7,8] The test compounds were administered for 4 days and blood samples were obtained 2 h after the last dose and citrated platelet-rich plasma was isolated. The degree of aggregation induced by ADP was then determined in vitro and was compared to a value obtained at the same time from an untreated control group. Data are given in Table III.

Most compounds listed in Table I were evaluated for hypoglycemic activity by the method of Gerritsen and Dulin[9a] in fasted, glucose-primed rats at 100 mg/kg po and were found to be inactive.[9b] A representative number of compounds were also evaluated for diuretic activity in rats by the method of Lipschitz et al.[10a] and were found to have little or no activity.[10b]

## Discussion

The compounds shown in Table I all have an α-methyl group because it was shown earlier that this enhances activity.[1] It was also shown earlier that seven-membered lactam ring congeners had optimal activity with least effect on PF3 release and therefore only a few congeners with smaller or larger lactam rings were prepared. Compounds **2–7** are simple alkyl-, alkoxy-, cycloalkyl-, phenyl-, and phenethyl-substituted α-methylbenzyl lactamimides. Compounds **8** and **9** are triphenylethylene and benzylidenefluorene congeners that were prepared in analogy to α-[*p*-(fluoren-9-ylidenemethyl)phenyl]-2-piperidineethanol, reported earlier from our laboratories.[11,12] (For data see end of Table I.) Compounds **10–14** are phenoxy-,

Table II. Arylalkylamine Hydrochlorides

| No. | R | Mp (lit. mp), °C[a] | Yield, % | Mol formula[b] | ν max, cm$^{-1}$ |
|---|---|---|---|---|---|
| 23 | -$C_6H_4$-*p*-*n*-$C_{13}H_{27}$ | 110-112 | 10[c] | $C_{21}H_{35}N$·HCl | 2020 |
| 24 | -$C_6H_4$-*p*-O-*n*-$C_{12}H_{25}$ | 99-112[d] | 50 | $C_{20}H_{33}NO$·HCl | |
| 25 | -$C_6H_4$-*p*-$C_6H_{11}$ | 232-236 dec (253-254)[e] | | $C_{14}H_{19}N$·HCl | |
| 26 | -$C_6H_4$-*p*-$C_6H_5$ | 223-226 (224-226)[f] | | $C_{14}H_{13}N$·HCl | 2000 |
| 27 | -$C_6H_4$-*p*-$CH_2CH_2C_6H_5$ | 212-214 | 73 | $C_{16}H_{17}N$·HCl | 2010 |
| 28 | -$C_6H_4$-*p*-CH=$C(C_6H_5)_2$ | 241-245 | 46 | $C_{22}H_{19}N$·HCl | 2000 |
| 29 |  | 259-261 | 72 | $C_{22}H_{17}N$·HCl | 2010 |
| 30 | -$C_6H_4$-*p*-$OC_6H_5$ | 189-194 (180-181)[g] | 75 | $C_{14}H_{13}NO$·HCl | 2040 |
| 31 | -$C_6H_4$-*o*-$OCH_2CH_2C_6H_5$ | 120-133 dec | 43 | $C_{16}H_{17}NO$·HCl | 2040 |
| 32 | -$C_6H_4$-*p*-$O(CH_2)_3C_6H_5$ | 142-145 | 51[h] | $C_{17}H_{19}NO$·HCl | |
| 33 | -$C_6H_4$-*p*-$O(CH_2)_3OC_6H_5$ | 71-81 | | $C_{17}H_{19}NO_2$·HCl | |
| 34 | -$C_6H_4$-*m*-$O(CH_2)_4OC_6H_5$ | 79-81 dec | 39 | $C_{18}H_{21}NO_2$·HCl | 2000 |
| 35 |  | 254-255 dec | | $C_{17}H_{25}N$·HCl | |
| 36 |  | 261-263 dec | 22 | $C_{18}H_{27}N$·HCl | |
| 37 |  | 251-254 dec | 74 | $C_{15}H_{13}N$·HCl | 2000 |
| 38 |  | 266-267 | 60 | $C_{16}H_{13}N$·HCl[i] | 2010 |
| 39 |  | 213-218 (222-223)[j] | 63 | $C_{14}H_{11}NO$·HCl | |
| 40 |  | 281-283 dec | 60 | $C_{14}H_{11}NS$·HCl | 2040 |

[a] Recrystallized from *i*-PrOH-$H_2O$ unless otherwise indicated. [b] Microanalyses were not obtained for these compounds since products from the Leuckart reaction were found to generally contain small amounts of impurities, presumably secondary amines that were difficult to remove by recrystallization. Formation of lactamimides from these amines may be regarded as derivatization and therefore proof of structure. [c] In addition to product, 69% of the starting ketone was recovered. [d] For the base see Belgian Patent 596,509 (1961); *Chem. Abstr.*, 60, 16033 (1964). [e] A. de Rooker and P. de Radzitsky, *Bull. Soc. Chim. Belg.*, 72, 195 (1963). [f] A. de Rooker and P. de Radzitsky, *ibid.*, 73, 181 (1964). [g] J. H. Brown, C. K. Kim, D. Beauchamp, and G. Jennings, *J. Am. Chem. Soc.*, 58, 1808 (1936). [h] In addition to product, 45% of the starting ketone was recovered. [i] Anal. ($C_{16}H_{13}N$·HCl) C, H, Cl. [j] H. Gilman, P. T. Parker, J. C. Bailie, and G. E. Brown, *J. Am. Chem. Soc.*, 61, 2836 (1939).

phenylalkoxy-, and phenoxyalkoxy-substituted congeners. Compounds **15** and **16** are bicyclic and **17–22** tricyclic arylalkyl lactamimides.

A comparison of the data in Table I shows that the activity is broadly distributed throughout the series; this is all the more surprising if one considers that only gross structural variations are represented. It can be concluded from this finding that apart from the lactamimide function and the α-methyl-substituted carbon atom to which it is attached, almost any large lipophylic group will impart platelet aggregation inhibitory activity to this type of compound. Hypoglycemic activity, on the other hand, is associated with more definitive structural parameters (steric hindrance, α,α-diarylmethyl group) in lactamimides of generally lower molecular weight;[2,13-15] these compounds showed little or no effects on platelets.[2] Compounds with large, lipophilic groups showed a tendency to cause relatively high PF3 release or to possess PF3-like procoagulant activity. A similar observation was made earlier in another series.[7] Compounds **10** and **22** showed good activity with minimal release of PF3 and were selected for in vivo evaluation.

The effect of oral administration of compounds **10**, **22**, I, and II to guinea pigs over a period of 4 days on the degree of platelet aggregation induced by ADP is shown in Table III. Only one of the four compounds (II, RMI 12,366A) inhibited ADP-induced platelet aggregation in this test model at 100 mg/kg; aggregation induced by low levels of ADP was also inhibited at 30 mg/kg. At 300 mg/kg the animals died after administration of the third daily dose. Further pathologic–toxicologic evaluation is in progress. It is planned to evaluate II in additional antithrombotic test models for comparison with other platelet aggregation inhibitors.[16]

## Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer 521 instrument. NMR spectra were taken on a Varian Model A-60 instrument ($Me_4Si$ as internal standard). Where analyses are indicated only by symbols of the

Table III. Effect of Oral Administration to Guinea Pigs on in Vitro ADP-Induced Platelet Aggregation[a]

| No. | Daily dose (days), mg/kg po | No. of animals treated (control) | Concn of ADP, μg/ml of PRP | Inhibition of aggregation: Av ΔT (% ± SEM) Control | Av ΔT (% ± SEM) Treated | Av total response (cm² ± SEM) Control | Av total response (cm² ± SEM) Treated | % inhibn | p value |
|---|---|---|---|---|---|---|---|---|---|
| 10 | 30 (4) | 3 (6) | 0.45 | 28.3 ± 4.4 | 24.4 ± 4.9 | 9.3 ± 1.9 | 4.4 ± 2.6 | 53 | NS |
| | 30 (4) | 4 (6) | 0.80 | 62.8 ± 4.2 | 42.2 ± 7.1 | 13.0 ± 0.7 | 8.1 ± 1.7 | 38 | <0.05 |
| | 100 (4) | 4 (6) | 0.45 | 32.1 ± 6.6 | 17.7 ± 4.2 | 6.2 ± 1.6 | 4.4 ± 2.2 | 29 | NS |
| | 100 (4) | 4 (6) | 0.80 | 50.7 ± 6.0 | 49.0 ± 7.3 | 10.7 ± 1.3 | 9.8 ± 1.6 | 8 | NS |
| 22 | 30 (4) | 6 (6) | 0.45 | 20.0 ± 4.1 | 20.4 ± 3.7 | 28.7 ± 16.8 | 52.8 ± 21.4 | 0 | |
| | 30 (4) | 6 (6) | 0.80 | 41.4 ± 2.8 | 43.6 ± 3.4 | 10.8 ± 0.8 | 10.5 ± 1.1 | 3 | NS |
| | 100 (4) | 6 (6) | 0.45 | 24.2 ± 3.7 | 32.0 ± 4.5 | 2.2 ± 0.5 | 4.4 ± 1.6 | 0 | |
| | 100 (4) | 6 (6) | 0.80 | 43.8 ± 3.7 | 53.6 ± 7.0 | 9.1 ± 1.1 | 10.8 ± 1.6 | 0 | |
| I[b] | 30 (4) | 5 (6) | 0.45 | 8.5 ± 2.7 | 7.0 ± 2.9 | 0.45 ± 0.18 | 0.30 ± 0.14 | 33 | NS |
| | 30 (4) | 5 (6) | 0.80 | 25.5 ± 2.7 | 29.0 ± 3.8 | 4.6 ± 1.0 | 5.3 ± 1.6 | 0 | NS |
| | 100 (4) | 5 (6) | 0.45 | 5.2 ± 1.8 | 7.1 ± 3.7 | 0.20 ± 0.08 | 0.39 ± 0.27 | 0 | |
| | 100 (4) | 5 (6) | 0.80 | 17.5 ± 2.7 | 21.6 ± 2.9 | 1.73 ± 0.61 | 1.88 ± 0.54 | 0 | |
| II[c] | 10 (4) | 7 (8) | 0.40 | 18.6 ± 4.3 | 14.6 ± 5.6 | 30.3 ± 13.0 | 23.9 ± 15.0 | 21 | NS |
| | 10 (4) | 7 (8) | 0.80 | 44.9 ± 5.4 | 35.2 ± 4.4 | 106 ± 9.3 | 78.5 ± 14.0 | 26 | <0.2 |
| | 30 (4) | 3 (3) | 0.45 | 24.0 ± 3.0 | 19.7 ± 3.5 | 1.61 ± 0.5 | 1.41 ± 0.49 | 18 | NS |
| | 30 (4) | 3 (3) | 0.80 | 42.7 ± 1.4 | 35.3 ± 3.2 | 8.35 ± 1.3 | 7.10 ± 1.5 | 14 | NS |
| | 30 (4) | 8 (8) | 0.25 | 30.3 ± 7.0 | 21.2 ± 3.8 | 61.4 ± 22.5 | 22.7 ± 7.3 | 63 | 0.1 |
| | 30 (4) | 8 (8) | 0.35 | 34.6 ± 7.4 | 24.8 ± 4.3 | 70.2 ± 20.6 | 31.5 ± 8.9 | 55 | 0.1 |
| | 100 (4) | 3 (5) | 0.45 | 59.0 ± 6.8 | 34.3 ± 2.6 | 12.3 ± 2.1 | 3.6 ± 0.5 | 70 | <0.01 |
| | 100 (4) | 2 (2) | 0.80 | 83.6 ± 1.1 | 62.7 ± 2.7 | 18.7 ± 0.8 | 14.6 ± 0.7 | 20 | <0.01 |
| | 100 (1) | 8 (8) | 0.45 | 24.7 ± 7.9 | 21.4 ± 6.9 | 48.5 ± 22.0 | 42.1 ± 17.0 | 13 | NS |
| | 100 (1) | 8 (8) | 0.80 | 40.3 ± 5.2 | 36.0 ± 4.4 | 86.3 ± 12.0 | 76.4 ± 14.0 | 12 | NS |

[a] Compound administered for 4 days. Blood taken 2 h after the last dose. See Experimental Section and ref 8. [b] RMI 7822A; cf. ref 1. [c] RMI 12,366A; cf. ref 2.

elements, results obtained were within ±0.4% of theoretical values.

*N*-[1-(*p*-**Phenoxyphenyl)ethyl]hexahydro-2*H*-azepin-2-imine Hydrochloride (10).** A mixture of 200 g (0.944 mol) of *p*-phenoxyacetophenone and 239 g (3.78 mol) of $HCOONH_4$ was heated slowly to 160°. After the initial foaming had subsided, the temperature of the heating bath was raised to 185–190° and stirring was continued for 5 h. Upon cooling, the mixture was washed with $H_2O$, the washes were extracted with a small amount of $C_6H_6$, and the extract was added to the residue along with 250 ml of concentrated HCl. This mixture was heated on a steam bath for 4 h and cooled, and the product that precipitated was collected, washed with $(CH_3CH_2)_2O$, and recrystallized from $(CH_3)_2CHOH$–$H_2O$ to give 177.3 g (75%) of **30** (Table II). The ir (KBr) showed the weak, but characteristic primary amine hydrochloride band at 2040 $cm^{-1}$. The other compounds listed in Table II were prepared similarly.

To 177.3 g (0.71 mol) of **30** was added 180 ml (ca. 1.26 mol) of *O*-methylcaprolactim[3] and the mixture was stirred into a slurry and was allowed to stand at room temperature for 5 days. During the first 6 h, the mixture was stirred at frequent intervals and small portions of absolute $CH_3CH_2OH$ were added (300 ml total) to keep the mixture stirrable. When the mixture ceased to further solidify, it was cooled (-20°), and the solid was collected, washed with $(CH_3CH_2)_2O$, and recrystallized from $CH_3OH$–$CH_3COCH_3$ to give 176.0 g (72%) of **10** (Table I); a second crop of 18.4 g (8%) was recovered from the mother liquor.

Other compounds listed in Table I (with the exception of **7**) were similarly prepared, although generally at one-tenth the scale.

*N*-[1-(**2-Dibenzothienyl)ethyl]hexahydro-2*H*-azepin-2-imine Hydrochloride (22).** To a mixture of 368.6 g (2 mol) of dibenzothiophene and 533.4 g (4 mol) of anhydrous $AlCl_3$ under 2 l. of $CS_2$ at 0 to -10° was added dropwise over 2.5 h 157.0 g (2 mol) of $CH_3COCl$ at such a rate as to keep the temperature below 0°. Stirring was continued at 0 to -10° for 2 h. The mixture was then poured into 2 N HCl–ice, the $CS_2$ layer was separated, the aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed (2 N HCl, 1.9 N $Na_2CO_3$) and dried ($Na_2SO_4$). The solvent was evaporated and the residue was distilled to give 318.1 g, bp 164–238° (0.02 mm); NMR indicated that this material was predominantly the 2-acetyl isomer. Crystallization from 1.8 l. of $CH_3OH$ gave 121.4 g (28%): mp 105–109° (lit. mp 111–112°);[17] NMR ($CDCl_3$) δ 2.68 (s, 3), 7.3–8.3 (m, 6), 8.65–8.72 (m, 1).

A mixture of 121.4 g (0.536 mol) of 2-dibenzothienyl methyl ketone and 135.5 g (2.145 mol) of $HCOONH_4$ was heated to 185° for 6 h and in the manner described for **30**, 1-(2-dibenzothienyl)ethylamine hydrochloride (**40**) was isolated and recrystallized from 2-propanol–water: 84.1 g (60%); mp 281–283° dec; ir (KBr) 2040 $cm^{-1}$.

A mixture of 77.3 g (0.293 mol) of finely powdered **40** (hydrochloride salt) and 78 ml (ca. 0.54 mol) of *O*-methylcaprolactim was stirred to form a slurry. As the reaction mixture hardened, six 30-ml portions of absolute $C_2H_5OH$ were added during the first 6 h of standing at room temperature. After 5 days of standing and addition of another 200 ml of absolute $C_2H_5OH$ in portions, the mixture no longer solidified and the reaction was complete. The mixture was cooled (-20°), and the product was collected, washed with ether, and recrystallized twice from $CH_3OH$–$(CH_3)_2CO$ to give 76.5 g (71%) of **22** (Table I).

1-**Methyl**-*N*-[1-[*p*-(**phenylethyl)phenyl]ethyl]pyrrolidin-2-imine Hydrochloride Hydrate (7).** To 9.9 g (0.1 mol) of *N*-methylpyrrolidin-2-one in 200 ml of $C_6H_6$ was added dropwise 7.7 g (0.05 mol) of $POCl_3$. The mixture was stirred at room temperature for 4 h. To the resulting solution was added 13.1 g (0.05 mol) of **27** (hydrochloride salt). The mixture was stirred at room temperature for 1 h, and at the reflux temperature for 4 h, and was allowed to stand overnight. The resulting solution was transferred to a separatory funnel and was shaken with 200 ml of 2 N HCl. Three phases resulted. The two bottom layers were separated, washed with $C_6H_6$, made alkaline with 2 N NaOH, and extracted with ether. The extract gave 15.5 g of oil, to which 1 equiv of methanolic HCl was added. The product was crystallized and recrystallized three times from acetone to give 5.8 g (32%) of **7** (Table I).

1-[3-(**4-Phenoxybutoxy)phenyl]ethan-1-one.** A mixture of 59.3 g (0.437 mol) of 1-(3-hydroxyphenyl)ethan-1-one, 100 g (0.437 mol) of 4-phenoxybutyl bromide, and 60.2 g (0.437 mol) of $K_2CO_3$ in 500 ml of anhydrous acetone was stirred at reflux temperature for 18 h. The mixture was poured into water, the product was extracted into ether, the extract was washed ($H_2O$, 2 N $Na_2CO_3$, saturated NaCl solution) and dried ($Na_2SO_4$), and the solvent was evaporated. The product crystallized from 2-propanol to give 101.8 g (82%), mp 48–59°. A sample was recrystallized twice from 2-propanol to give the title compound, mp 60–61°. Anal. ($C_{18}H_{20}O_3$) C, H. 1-[4-(3-Phenoxypropoxy)phenyl]ethan-1-one, [mp 78–79°. Anal. ($C_{17}H_{18}O_3$) C, H], 1-[2-(2-phenylethoxy)-phenyl]ethan-1-one [mp 40–43°, bp 204–216° (2.6 mm). Anal. ($C_{16}H_{16}O_2$) C, H], and 1-[4-(3-phenylpropoxy)phenyl]ethan-1-one [mp 80–81° (no lit. mp given in abstract)][18] were similarly prepared in 70, 17, and 58% yield, respectively.

**Biological Methods. Blood Collection and Isolation of Plasma.** Whole blood was obtained from voluntary, experienced donors before breakfast. Donors were instructed to take no drugs, specifically aspirin, for 5 days before giving blood. No plasma was used that was lipidemic or, in a preliminary aggregation experiment, showed no second-phase aggregation (aspirin-like effect). Blood was collected by the two-syringe technique. It was decalcified with 3.8% sodium citrate solution, one part to nine parts of blood. The citrated blood was centrifuged at 100g for 10 min and citrated platelet-rich plasma (PRP) was isolated. The residue was recentrifuged at 1500g for 15 min to give platelet-poor plasma (PPP).

**Inhibition of ADP-Induced Platelet Aggregation.** Compounds were tested for inhibition of ADP-induced aggregation in a Bryston platelet aggregometer by the procedure of Mustard et al.[5] Human PRP was diluted with autologous PPP to 400000 platelets/mm$^3$. Saline was added to another aliquot of the same plasma sample to serve as control. After incubation for 20 min at 37°, ADP (2 μg/ml final concentration) was added to induce aggregation. The increase in light transmittance ($\Delta T$) through the plasma sample in the aggregometer, produced by platelet aggregating, was recorded. The maxima of the $\Delta T$ responses for control and test samples were then used to calculate percent inhibition of platelet aggregation by the test compound. More detail on the method and its variability is discussed elsewhere.[8]

**Platelet Factor 3 Activation.** Test compound solution was added to human citrated PRP and incubated at 37° for 20 min; a modified Stypven test was then performed. Plasma was diluted 1:10 for this modified test.[6]

**In Vivo Effect on in Vitro ADP-Induced Aggregation.**[8] Test compound was given to guinea pigs by a stomach tube at the indicated dose for 4 days. An untreated control group was maintained alongside. Blood was removed by heart pucture 2 h after the last dose and citrated PRP was isolated and adjusted for in vitro ADP-induced platelet aggregation. ADP was added at the concentration indicated in Table III. Max $\Delta T$ were obtained as described above. Total response was obtained by measuring the area between the aggregation curve and baseline transmittance for the 5-min period following ADP addition with a planimeter. Percent inhibition was calculated from the average total response of treated vs. control group.

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# Central Nervous System Active 5-Oxo-1,4,5,6,7,8-hexahydrocinnolines[1]

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Among a series of 5-oxo-1,4,5,6,7,8-hexahydrocinnolines examined for their CNS activity, 1-(2-diethylaminoethyl)-3-(*p*-fluorophenyl)-5-oxo-7,7-dimethyl-1,4,5,6,7,8-hexahydrocinnoline (**23**) and 1-(2-dimethylaminoethyl)-3-phenyl-5-oxo-7,7-dimethyl-1,4,5,6,7,8-hexahydrocinnoline (**27**) had sedative and anticonvulsant properties and were also active in tests used to characterize antidepressants. But their narrow safety margin precluded further follow-up studies. Derivatives **35–38** of 2-(ω-phenacyl)-3-hydrazino-5,5-dimethyl-2-cyclohexenone were active in tests used to characterize antidepressants and were weakly sedative but not anticonvulsant.

The multifactorial etiology of the depressive syndrome calls for "wide-spectrum antidepressants", encompassing depression-relieving, drive-enhancing, and anxiolytic effects.[2a] The pharmacological profile of maprotiline demonstrates such bipolar activity with both antidepressant as well as sedative tranquillizing properties.[2b] In the course of our continuing work on CNS-active drugs,[3] we encountered moderately interesting wide-spectrum activity in the CNS profile in a series of novel 5-oxo-1,-4,5,6,7,8-hexahydrocinnolines. We report briefly the results of our study of this series.

**Chemistry.** The title compounds **13–32** were synthesized in moderate to good yields from ketones **1–8** by reaction with appropriate hydrazines and are listed in Table I. The ketones became available from cyclohexane-1,3-diones by alkylation with phenacyl bromides