tion for the receptor resistance to attack by organophosphorus drugs would lie in the unavailability of a free serine hydroxyl for phosphorylation. Some intriguing features of this hypothesis may be summarized as follows. The receptor would have its biochemical origin in the pool of AChE, a portion of which would be trapped in the membrane network and maintained in the acetylated form through a steady-state quantal discharge of ACh from the synaptic cleft. This would constitute a self-generating system, a phenomenon not uncommon in biochemistry (as is the case for instance for some of the catalytic intermediates of the tricarboxylic acid cycle). Assuming that some drugs could cause release of additional quantities of ACh[32] in addition to interacting directly with the receptors, more acetylated AChE could be made available with the result that steeper dose-response curves than expected would be observed as is often the case. Finally, the physico-chemical events following receptor stimulation might allow hydrolytic splitting of the acetyl group, thus accounting for desensitization. Reacetylation would be essential for sensitivity to reappear. It would be of considerable interest to attempt labeling of these receptors with radioactive acetyl groups and then study their turnover rate in the presence of various drugs.

It should be emphasized that the characteristics of the preceding speculation do not affect in any way the arguments forming the basis of the MPT.

(32) G. B. Koelle, *J. Pharm. Pharmacol.*, **14**, 65 (1962).

# 1-Aralkyl-4,4-dialkylpiperidines as Hypotensive Agents

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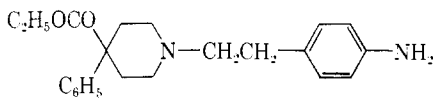
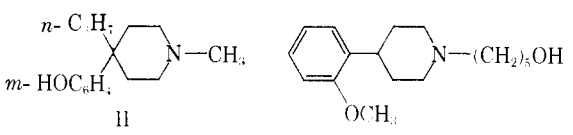
*Received June 1, 1964*

A large number of 1,4,4-trisubstituted piperidines have been synthesized by lithium aluminum hydride reduction of the corresponding glutarimides. Many of the piperidines are highly active as hypotensives when administered intraperitoneally to intact conscious rabbits. The most active compounds were 1-(3,4-diethoxyphenethyl)-4-methyl-4-*n*-hexylpiperidine hydrochloride and 1-(*p*-methoxyphenethyl)-4-spirocyclohexanepiperidine hydrochloride. Structure–activity relationships are discussed.

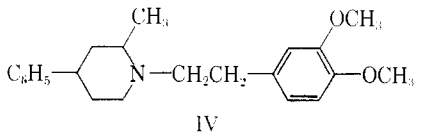
In recent years variations on the piperidine structure have been the subject of many investigations in addition to the earlier work which led to the introduction of 4-carboethoxy-1-methyl-4-phenylpiperidine (pethidine) as an analgesic. Other such compounds having potent analgesic activity have since been reported, *e.g.*, I[2] and II.[3] Hypotensive activity has also been demonstrated in this class, 1,2,2,6,6-pentamethylpiperidine (Pempidine) being the most prominent example. Other piperidines having hypotensive activity are III[4] and related compounds, while IV[5] has been reported to have neurosedative as well as hypotensive and antiemetic actions.



I

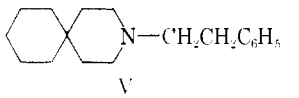


II III

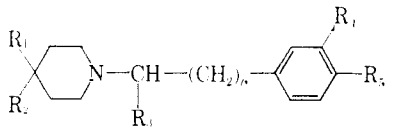


IV

It appeared that, with the exception of the pempidine category, a phenyl substituent at the 4-position was necessary for useful pharmacological activity. We had been engaged in a study of $\beta,\beta$-dialkylglutarimides[6] from which piperidines are easily obtained by lithium aluminum hydride reduction. The availability of a large number of glutaric acids, therefore, prompted our investigation of the effects of 4,4-dialkyl substitution in the piperidine ring with a variety of substituents on the nitrogen. Among the first compounds synthesized was 1-phenethyl-4-spirocyclohexanepiperidine (V). This was found to have negligible analgesic activity, but further screening showed interesting hypotensive action. Increased hypotensive activity resulted on introduction of a 1-methyl substituent into the side chain and encouraged further investigation of such compounds.



V



VI

This publication deals principally with the preparation and evaluation as hypotensives of piperidines

(1) To whom all inquiries should be addressed.

(2) J. Weijlard, P. Orahovats, A. Sullivan, G. Purdue, F. Heath, and K. Pfister, *J. Am. Chem. Soc.*, **78**, 2342 (1956).

(3) S. M. McElvain and D. H. Clemens, *ibid.*, **80**, 3915 (1958).

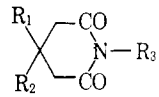
(4) U. S. Patent 2,891,066 (1959); J. Owen and T. Verhave, *J. Pharmacol. Exptl. Therap.*, **122**, 59 (1958).

(5) Eli Lilly and Co., Australian Patent 225,975 (1959).

(6) G. J. Handley, E. R. Nelson, and T. C. Somers, *Australian J. Chem.*, **13**, 129 (1960).

TABLE I

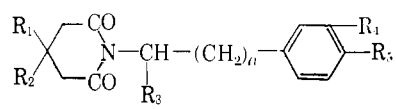
β-SUBSTITUTED GLUTARIMIDES



| $R_1$ | $R_2$ | $R_3$ | B.p. (mm.) or m.p., °C. | $n^{20}D$ | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | $i$-$C_3H_7$ | $CH_3$ | 98–100 (2.0), 36–39 | | $C_9H_{15}NO_2$ | 63.9 | 8.9 | 8.3 | 64.1 | 8.8 | 8.5 |
| $CH_3$ | $n$-$C_5H_{11}$ | $CH_2CH{=}CH_2$ | 166 (4.0) | 1.4790 | $C_{14}H_{23}NO_2$ | 70.9 | 9.8 | 5.9 | 71.2 | 9.7 | 6.0 |
| $CH_3$ | $n$-$C_6H_{13}$ | $(CH_2)_3OCH_3$ | 190–193 (4.5) | 1.4718 | $C_{16}H_{29}NO_2$ | 67.8 | 10.3 | 4.9 | 67.9 | 10.1 | 5.3 |
| $CH_3$ | $n$-$C_6H_{13}$ | $n$-$C_8H_{17}$ | 206 (3.0) | 1.4690 | $C_{20}H_{37}NO_2$ | 74.3 | 11.5 | 4.3 | 74.0 | 11.6 | 4.7 |
| $(CH_2)_5$ | | $C_2H_5$ | 142–145 (3.0), 33–36 | | $C_{12}H_{19}NO_2$ | 68.9 | 9.2 | 6.7 | 69.0 | 9.0 | 6.9 |
| $(CH_2)_5$ | | $n$-$C_3H_7$ | 138–140 (2.0) | 1.4961 | $C_{13}H_{21}NO_2$ | 69.9 | 9.5 | 6.3 | 69.3 | 9.3 | 6.1 |
| $(CH_2)_5$ | | $i$-$C_3H_7$ | 79–80 | | $C_{13}H_{21}NO_2$ | 69.9 | 9.5 | 6.3 | 70.2 | 9.4 | 6.4 |
| $(CH_2)_5$ | | $CH_2CH{=}CH_2$ | 134–138 (2.0) | 1.5092 | $C_{13}H_{19}NO_2$ | 70.6 | 8.7 | 6.3 | 70.2 | 8.5 | 6.3 |
| $(CH_2)_5$ | | $i$-$C_4H_9$ | 147–150 (1.0) | 1.4930 | $C_{14}H_{23}NO_2$ | 70.9 | 9.8 | 5.9 | 70.6 | 9.7 | 5.8 |
| $(CH_2)_5$ | | $i$-$C_5H_{11}$ | 146–148 (0.7) | 1.4915 | $C_{15}H_{25}NO_2$ | 71.7 | 10.0 | 5.6 | 71.6 | 10.0 | 5.6 |
| $(CH_2)_5$ | | $n$-$C_5H_{13}$ | 165–168 (1.5) | 1.4896 | $C_{16}H_{27}NO_2$ | 72.4 | 10.3 | 5.3 | 71.7 | 10.2 | 5.4 |
| $(CH_2)_6$ | | $C_6H_5$ | 169–170 | | $C_{16}H_{19}NO_2$ | 74.7 | 7.4 | 5.4 | 74.9 | 7.5 | 5.7 |
| $C_2H_5$ | $n$-$C_4H_9$ | H | 72 | | $C_{11}H_{19}NO_2$ | 67.0 | 9.7 | 7.1 | 67.3 | 9.7 | 7.4 |
| $C_2H_5$ | $CH_2CH(CH_3)C_2H_5$ | H | 63 | | $C_{12}H_{21}NO_2$ | 68.2 | 10.0 | 6.6 | 68.1 | 10.0 | 6.9 |

TABLE II

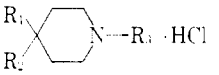
β-SUBSTITUTED GLUTARIMIDES



| $R_1$ | $R_2$ | $R_3$ | $n$ | $R_4$ | $R_5$ | B.p. (mm.) or m.p., °C. | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | $i$-$C_3H_7$ | H | 1 | H | H | 80–81 | $C_{16}H_{21}NO_2$ | 74.1 | 8.2 | 5.4 | 74.4 | 8.2 | 5.7 |
| $CH_3$ | $C_2H_5$ | H | 1 | H | H | 180 (1.0), 38–40 | $C_{16}H_{21}NO_2$ | 74.1 | 8.2 | 5.4 | 73.6 | 8.1 | 5.3 |
| $CH_3$ | $n$-$C_3H_7$ | H | 1 | H | H | 50–51 | $C_{17}H_{23}NO_2$ | 74.7 | 8.5 | 5.1 | 75.0 | 8.5 | 5.4 |
| $CH_3$ | $n$-$C_3H_7$ | $CH_3$ | 1 | H | H | 136–140 (1.0), 35–37 | $C_{18}H_{26}NO_2$ | 75.2 | 8.8 | 4.9 | 75.3 | 8.8 | 5.0 |
| $CH_3$ | $i$-$C_3H_7$ | H | 1 | H | H | 74–75 | $C_{17}H_{23}NO_2$ | 74.7 | 8.5 | 5.1 | 74.8 | 8.2 | 5.4 |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | H | H | 185–188 (1.0), 43–45 | $C_{18}H_{25}NO_2$ | 75.2 | 8.8 | 4.9 | 75.2 | 8.7 | 4.9 |
| $CH_3$ | $n$-$C_4H_9$ | $CH_3$ | 1 | H | H | 172 (0.8) | $C_{19}H_{27}NO_2$ | 75.7 | 9.0 | 4.7 | 75.8 | 9.2 | 4.8 |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | H | $OCH_3$ | 212 (2.0), 47–49 | $C_{19}H_{25}NO_3$ | 71.9 | 8.6 | 4.4 | 72.2 | 8.6 | 4.9 |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OCH_3$ | $OCH_3$ | 53–55 | $C_{20}H_{29}NO_4$ | 69.1 | 8.4 | 4.0 | 69.0 | 8.3 | 4.1 |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OCH_3$ | $OC_2H_5$ | 68–69 | $C_{21}H_{31}NO_4$ | 69.8 | 8.6 | 3.9 | 69.9 | 8.7 | 4.0 |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OC_2H_5$ | $OC_2H_5$ | 180–185 (1), 46–49 | $C_{22}H_{33}NO_4$ | 70.4 | 8.9 | 3.7 | 70.0 | 9.0 | 4.1 |
| $CH_3$ | $n$-$C_4H_9$ | H | 3 | H | H | 199–201 (3), 33–36 | $C_{20}H_{29}NO_2$ | 76.2 | 9.3 | 4.4 | 76.7 | 9.4 | 4.6 |
| $CH_3$ | $n$-$C_5H_{11}$ | H | 1 | H | H | 208–212 (3.5), 36–39 | $C_{19}H_{27}NO_2$ | 75.7 | 9.0 | 4.7 | 75.8 | 8.9 | 4.7 |
| $CH_3$ | $n$-$C_5H_{11}$ | H | 1 | $OCH_3$ | $OCH_3$ | 63–64 | $C_{21}H_{31}NO_4$ | 69.8 | 8.6 | 3.9 | 70.2 | 8.8 | 4.1 |
| $CH_3$ | $n$-$C_5H_{11}$ | $CH_3$ | 1 | H | H | 190 (2.0) | $C_{20}H_{29}NO_2$ | 76.2 | 9.3 | 4.4 | 75.8 | 9.2 | 5.0 |
| $C_2H_5$ | $CH_2CH(CH_3)C_2H_5$ | H | 1 | H | H | 217 (2.5) | $C_{20}H_{29}NO_2$ | 76.2 | 9.3 | 4.4 | 76.5 | 9.3 | 4.9 |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | H | H | 44–47 | $C_{20}H_{29}NO_2$ | 76.2 | 9.3 | 4.4 | 76.1 | 9.3 | 4.4 |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | H | $OCH_3$ | 63 | $C_{21}H_{31}NO_3$ | 73.0 | 9.1 | 4.1 | 73.2 | 9.1 | 4.0 |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OCH_3$ | $OCH_3$ | 63–64 | $C_{22}H_{33}NO_4$ | 70.4 | 8.9 | 3.7 | 70.7 | 8.8 | 4.0 |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OCH_2O$ | | 71 | $C_{21}H_{29}NO_4$ | 70.2 | 8.1 | 3.9 | 70.0 | 8.0 | 3.9 |
| $CH_3$ | $n$-$C_6H_{13}$ | $CH_3$ | 1 | H | H | 211 (4.5) | $C_{21}H_{31}NO_2$ | 76.6 | 9.5 | 4.3 | 76.4 | 9.4 | 4.8 |
| $CH_3$ | $i$-$C_6H_{13}$ | H | 1 | H | H | 64–65 | $C_{20}H_{29}NO_2$ | 76.2 | 9.3 | 4.4 | 76.4 | 9.5 | 4.5 |
| $CH_3$ | $i$-$C_6H_{13}$ | $CH_3$ | 1 | H | H | 204–206 (3.0) | $C_{21}H_{31}NO_2$ | 76.6 | 9.5 | 4.3 | 76.1 | 9.2 | 4.9 |
| $CH_3$ | $n$-$C_8H_{13}$ | H | 3 | H | H | 238–240 (6.0), 34–35 | $C_{22}H_{33}NO_2$ | 76.9 | 9.7 | 4.1 | 76.6 | 9.8 | 4.3 |
| $CH_3$ | $n$-$C_7H_{15}$ | H | 1 | H | H | 210–214 (1.5) | $C_{21}H_{31}NO_2$ | 76.6 | 9.5 | 4.3 | 76.4 | 9.4 | 4.5 |
| $CH_3$ | $n$-$C_7H_{15}$ | $CH_3$ | 1 | H | H | 200–202 (1.5) | $C_{22}H_{33}NO_2$ | 76.9 | 9.7 | 4.1 | 76.6 | 9.6 | 4.3 |
| $CH_3$ | $n$-$C_9H_{19}$ | H | 1 | H | H | 228 (4.0) | $C_{23}H_{35}NO_2$ | 77.3 | 9.9 | 3.9 | 77.2 | 9.9 | 4.1 |
| $C_2H_5$ | $CH_2CH(CH_3)C_2H_5$ | $CH_3$ | 1 | H | H | 191–194 (2.0) | $C_{21}H_{31}NO_2$ | 76.6 | 9.5 | 4.3 | 75.7 | 9.5 | 4.3 |
| $(CH_2)_4$ | | H | 1 | H | H | 66 | $C_{17}H_{21}NO_2$ | 75.2 | 7.8 | 5.2 | 75.5 | 8.1 | 5.3 |
| $(CH_2)_4$ | | H | 1 | $OCH_3$ | $OCH_3$ | 64–66 | $C_{19}H_{25}NO_4$ | 68.9 | 7.6 | 4.2 | 68.5 | 7.4 | 4.4 |
| $(CH_2)_4$ | | $CH_3$ | 1 | H | H | 182–184 (2), 39–42 | $C_{18}H_{23}NO_2$ | 75.8 | 8.1 | 4.9 | 75.9 | 8.0 | 5.3 |
| $(CH_2)_5$ | | H | 0 | H | H | 71–73 | $C_{17}H_{21}NO_2$ | 75.4 | 7.8 | 5.2 | 75.1 | 7.9 | 5.4 |
| $(CH_2)_5$ | | H | 1 | H | H | 80 | $C_{18}H_{23}NO_2$ | 75.8 | 8.1 | 4.9 | 76.3 | 8.2 | 4.8 |
| $(CH_2)_5$ | | H | 1 | H | $OCH_3$ | 62–64 | $C_{19}H_{25}NO_3$ | 73.4 | 7.7 | 4.3 | 73.8 | 8.2 | 4.1 |
| $(CH_2)_5$ | | H | 1 | $OCH_3$ | $OCH_3$ | 102–104 | $C_{20}H_{27}NO_4$ | 69.5 | 7.9 | 4.1 | 69.3 | 7.9 | 4.2 |
| $(CH_2)_6$ | | H | 1 | $OCH_3$ | $OC_2H_5$ | 91–93 | $C_{21}H_{29}NO_4$ | 70.2 | 8.1 | 3.9 | 70.3 | 8.2 | 4.1 |
| $(CH_2)_5$ | | H | 1 | $OCH_2O$ | | 89–91 | $C_{19}H_{23}NO_4$ | 70.4 | 6.8 | 4.1 | 69.7 | 6.9 | 4.4 |
| $(CH_2)_5$ | | $CH_3$ | 1 | H | H | 65–68 | $C_{19}H_{25}NO_2$ | 76.4 | 8.4 | 4.7 | 76.4 | 8.5 | 5.1 |
| $(CH_2)_5$ | | H | 3 | H | H | 90–91 | $C_{20}H_{27}NO_2$ | 76.6 | 8.7 | 4.5 | 77.2 | 8.7 | 4.5 |
| $(CH_2)_6$ | | H | 1 | H | H | 72–75 | $C_{19}H_{25}NO_2$ | 76.4 | 8.4 | 4.7 | 76.4 | 8.4 | 4.7 |

TABLE III

SUBSTITUTED PIPERIDINE SALTS



| $R_1$ | $R_2$ | $R_3$ | M.p., °C. | $n^{25}D$ of free base | Formula | Calcd., % C | H | N | Found, % C | H | N | Hypotensive activity[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | *i*-$C_3H_7$ | $CH_3$ | 152[b] | ... | $C_{15}H_{27}NO_7$[b] | 54.0 | 8.2 | 4.2 | 53.7 | 8.4 | 4.6 | 0 |
| $CH_3$ | $CH_3$ | $CH_3$ | 227[c] | ... | $C_{14}H_{20}N_4O_7$[d] | 47.2 | 5.7 | 15.8 | 47.7 | 5.5 | 15.6 | |
| $CH_3$ | *n*-$C_3H_7$ | H | 230–234[c] | ... | $C_9H_{20}ClN$ | 60.8 | 11.3 | 7.9 | 60.6 | 11.2 | 7.5 | |
| $CH_3$ | *i*-$C_3H_7$ | H | 277–282 dec.[c] | ... | $C_9H_{20}ClN$ | 60.8 | 11.3 | 7.9 | 60.8 | 11.4 | 7.2 | |
| $CH_3$ | *n*-$C_6H_{11}$ | H | 220[c] | ... | $C_{11}H_{24}ClN$ | 64.2 | 11.8 | 6.8 | 64.5 | 11.9 | 6.7 | 0 |
| $CH_3$ | *n*-$C_6H_{11}$ | $CH_2CH{=}CH_2$ | 185–186 | 1.4640 | $C_{14}H_{28}ClN$ | 68.4 | 11.5 | 5.7 | 68.3 | 11.4 | 5.7 | 0 |
| $CH_3$ | *n*-$C_6H_{13}$ | H | 221–222[c] | ... | $C_{12}H_{26}ClN$ | 65.6 | 11.9 | 6.4 | 66.0 | 11.6 | 6.4 | 0 |
| $CH_3$ | *n*-$C_6H_{13}$ | $(CH_2)_3OCH_3$ | 241 dec. | 1.4626 | $C_{16}H_{34}ClNO$ | 65.8 | 11.7 | 4.8 | 66.2 | 11.8 | 4.5 | |
| $CH_3$ | *n*-$C_6H_{13}$ | *n*-$C_8H_{17}$ | 268–270 | 1.4653 | $C_{20}H_{42}ClN$ | 72.4 | 12.8 | 4.2 | 72.6 | 12.8 | 4.3 | |
| $CH_3$ | *n*-$C_6H_{13}$ | $CH_2C(C_2H_5)H(CH_2)_3CH_3$ | 197–200 | 1.4608 | $C_{20}H_{42}ClN$ | 72.4 | 12.8 | 4.2 | 72.5 | 12.5 | 4.2 | 0 |
| $(CH_2)_4$ | | H | 258–259 | 1.4794 | $C_9H_{18}ClN$ | 61.5 | 10.3 | 8.0 | 61.3 | 10.4 | 7.8 | |
| $(CH_2)_5$ | | H | 228–229 | 1.4845 | $C_{10}H_{20}ClN$ | 63.3 | 10.6 | 7.4 | 63.5 | 10.5 | 7.2 | 0 |
| $(CH_2)_5$ | | $CH_3$ | 240–241 | 1.4811 | $C_{11}H_{22}ClN$ | 64.8 | 10.9 | 6.9 | 64.4 | 10.9 | 6.7 | |
| $(CH_2)_5$ | | $C_2H_5$ | 250 dec. | 1.4838 | $C_{12}H_{24}ClN$ | 66.2 | 11.1 | 6.4 | 66.4 | 11.0 | 6.2 | |
| $(CH_2)_5$ | | *n*-$C_3H_7$ | 266–267 dec. | 1.4835 | $C_{13}H_{26}ClN$ | 67.4 | 11.3 | 6.0 | 67.6 | 11.3 | 6.0 | + |
| $(CH_2)_5$ | | *i*-$C_3H_7$ | 285 dec. | 1.4840 | $C_{13}H_{26}ClN$ | 67.4 | 11.3 | 6.0 | 67.9 | 11.3 | 6.0 | ++ |
| $(CH_2)_5$ | | $CH_2CH{=}CH_2$ | 220–221 | 1.4934 | $C_{12}H_{24}ClN$ | 67.9 | 10.5 | 6.1 | 67.9 | 10.5 | 6.0 | 0 |
| $(CH_2)_5$ | | *i*-$C_4H_9$ | 290 dec. | 1.4768 | $C_{14}H_{28}ClN$ | 68.4 | 11.5 | 5.7 | 68.1 | 11.2 | 5.6 | 0 |
| $(CH_2)_5$ | | *i*-$C_5H_{11}$ | 320–325 dec. | 1.4815 | $C_{15}H_{30}ClN$ | 69.3 | 11.6 | 5.4 | 69.7 | 11.7 | 5.0 | 0 |
| $(CH_2)_5$ | | *n*-$C_6H_{13}$ | 305–310 dec. | 1.4800 | $C_{16}H_{32}ClN$ | 70.2 | 11.8 | 5.1 | 70.4 | 11.8 | 5.0 | + |
| $(CH_2)_5$ | | $C_6H_5$ | 208–212 | 1.5621 | $C_{16}H_{24}ClN$ | 72.3 | 9.1 | 5.3 | 72.5 | 8.9 | 5.0 | 0 |

[a] In rabbits, i.p. and/or i.v.: 0 = no noticeable action on blood pressure, + = variable activity with 10–15% fall in blood pressure obtained in about 50% of cases, ++ = 10–25% fall in about 75% of cases, +++ = 30–40% fall at higher doses in 75% of cases, ++++ = 50–60% fall obtained at higher doses with little variability shown in response and apparent existence of a dose–response curve. [b] Citrate. [c] Hygroscopic. [d] Picrate, m.p. 227°.

having the general structure VI where $R_1$ and $R_2$ are alkyl or spirocycloalkane; $R_3$ is H, $CH_3$, or $C_2H_5$; $n$ = 0, 1, 2, or 3; and $R_4$ and $R_5$ are H or alkoxy. Compounds having 1-alkyl and 1-phenyl substituents as well as many of the corresponding methiodide salts have also been synthesized.

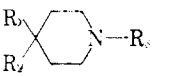
The $\beta,\beta$-dialkyl- and $\beta$-spirocycloalkaneglutaric acids, from which the required bases were derived, were obtained by acid hydrolysis of the $\alpha,\alpha'$-dicyano-$\beta$-substituted glutarimides.[7] Where the usual Guareschi reaction between the ketone, ethyl cyanoacetate, and ammonia failed to give the required imide as found with ethyl 2-methylbutyl ketone, the procedure described by McElvain and Clemens[3] for otherwise inaccessible alkyl aryl derivatives was employed successfully. This involves condensation of cyanoacetamide with the alkylidene cyanoacetate in the presence of sodium ethoxide.

Generally the glutaric anhydride was used in preference to the acid for condensation with the base, as reaction occurs more smoothly with the former and also conversion of the crude glutaric acid to the anhydride followed by distillation offered an easier method of purification. Reaction with the appropriate amine at 180–200° for several hours then gave the N-substituted glutarimide (Tables I and II), except that where $R_3$ in Table II is methyl, higher temperatures (to 350°) were necessary to complete the condensation. The method worked equally well for all alkyl and aralkylamines tried, yields of 70–90% being obtained, except in the case of *t*-butylamine where ring closure of the intermediate N-*t*-butyl-$\beta$-spirocyclohexaneglutaramic acid was apparently prevented by steric factors. Glutarimides having no N-substituent, required as intermediates to the secondary bases, were obtained by fusion of the anhydride with urea.

The piperidine bases were obtained in high yield (70–85%) by reduction in ether with lithium aluminum hydride. They were generally characterized as the hydrochloride salts (Tables III and IV). Phenolic derivatives of 1-phenylalkylpiperidines were derived from the corresponding alkoxy compounds, and the acetoxy compounds by acetylation of the phenols. In a few instances where the primary amine was less accessible than the alkyl halide, the required 1-substituted piperidine was prepared by alkylation of the secondary base. Methiodide salts (Tables V and VI) were obtained without difficulty by reaction in ether at room temperature for several days or by refluxing in acetone solution for 2–3 hr.

**Pharmacology and Structure–Activity Relations.**—After preliminary screening in mice, selected compounds were tested for hypotensive activity by intraperitoneal injection in intact conscious rabbits, measuring blood pressure in the auricular artery by use of the Grant Capsule. The initial dose used was generally the highest dose in mg./kg. which killed 0/5 mice acutely in preliminary screening. The tables give only a rough indication of hypotensive activities obtained, as the symbols refer only to intensity of action and largely ignore degree of toxicity and duration of action. Where relatively high activity appeared after intraperitoneal administration, the compound was tested further for oral activity in rabbits.

Some of the quaternary ammonium compounds had ganglion-blocking activity, but none of the tertiary bases showed this property. The mechanism by which the latter produce hypotensive action is still being studied, but our interest was concentrated on this class which seemed likely to produce a hypotensive drug lacking the undesirable side effects of the ganglion-blocking compounds.

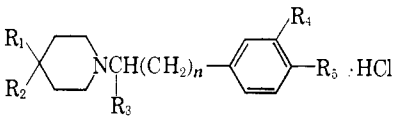


VII

(7) A. I. Vogel, *J. Chem. Soc.*, 1758 (1934).

TABLE IV

1-ARALKYLPIPERIDINE HYDROCHLORIDES



| $R_1$ | $R_2$ | $R_3$ | $n$ | $R_4$ | $R_5$ | $n^{20}D$ of free base | M.p., °C., HCl Salt | Formula | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N | Hypotensive activity[a] I.p. | Hypotensive activity[a] Oral |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | H | 1 | H | H | 1.5240 | 220–226[b] | | | | | | | | 0 | |
| H | $CH_3$ | $CH_3$ | 1 | H | H | 1.5261 | 207.5 | $C_{15}H_{24}ClN$ | 71.0 | 9.5 | 5.5 | 71.1 | 9.4 | 5.2 | 0 | |
| H | $i$-$C_3H_7$ | H | 1 | H | H | [c] | 270 dec. | $C_{16}H_{26}ClN$ | 71.8 | 9.8 | 5.2 | 71.7 | 9.7 | 5.1 | + | |
| $CH_3$ | $C_2H_5$ | H | 1 | H | H | 1.5175 | 315 dec. | $C_{16}H_{26}ClN$ | 71.7 | 9.8 | 5.2 | 71.7 | 9.7 | 5.1 | + | |
| $CH_3$ | $C_2H_5$ | $CH_3$ | 1 | H | H | 1.5136 | 266–270 | $C_{17}H_{28}ClN$ | 72.4 | 10.0 | 5.0 | 72.5 | 10.0 | 4.7 | ++[d] | |
| $CH_3$ | $n$-$C_3H_7$ | H | 1 | H | H | 1.5130 | 312–317 dec. | $C_{17}H_{28}ClN$ | 72.4 | 10.0 | 5.0 | 72.1 | 9.9 | 4.9 | 0 | |
| $CH_3$ | $n$-$C_3H_7$ | $CH_3$ | 1 | H | H | 1.5143 | 283 dec. | $C_{18}H_{30}ClN$ | 73.1 | 10.2 | 4.7 | 72.6 | 10.4 | 4.7 | +[d] | |
| $CH_3$ | $i$-$C_3H_7$ | H | 1 | H | H | [c] | 353 dec. | $C_{17}H_{26}ClN$ | 72.4 | 10.0 | 5.0 | 72.6 | 9.9 | 4.8 | ++ | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | H | H | 1.5100 | 285 dec. | $C_{18}H_{30}ClN$ | 73.1 | 10.2 | 4.7 | 72.8 | 9.8 | 4.9 | + | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | H | $OCH_3$ | 1.5158 | 289–291 dec. | $C_{19}H_{32}ClNO$ | 70.0 | 9.9 | 4.3 | 69.8 | 9.9 | 4.1 | 0 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OCH_3$ | $OCH_3$ | [c] | 265 dec. | $C_{20}H_{34}ClNO_2$ | 67.5 | 9.6 | 3.9 | 67.4 | 9.7 | 3.7 | 0 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OCH_3$ | $OC_2H_5$ | 1.5176 | 256 dec. | $C_{21}H_{36}ClNO_2$ | 68.2 | 9.8 | 3.8 | 67.7 | 9.7 | 3.6 | +++ | +++ |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OC_2H_5$ | $OC_2H_5$ | [c] | 257–258 | $C_{22}H_{38}ClNO_2$ | 68.8 | 10.0 | 3.7 | 69.1 | 9.9 | 3.8 | +++ | ++ |
| $CH_3$ | $n$-$C_4H_9$ | $CH_3$ | 1 | H | H | 1.5093 | 275–277 dec. | $C_{19}H_{32}ClN$ | 73.6 | 10.4 | 4.5 | 73.5 | 10.4 | 4.6 | 0 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 3 | H | H | ... | 254–257 | $C_{20}H_{34}ClN$ | 74.2 | 10.6 | 4.3 | 74.0 | 10.5 | 4.1 | 0 | |
| $CH_3$ | $n$-$C_5H_{11}$ | H | 1 | H | H | 1.5087 | 285 | $C_{19}H_{32}ClN$ | 73.6 | 10.4 | 4.5 | 74.0 | 10.5 | 4.8 | + | |
| $CH_3$ | $n$-$C_5H_{11}$ | H | 1 | $OCH_3$ | $OCH_3$ | 1.5200 | 258–260 dec. | $C_{21}H_{36}ClNO_2$ | 68.2 | 9.8 | 3.8 | 68.1 | 9.5 | 3.5 | 0 | |
| $CH_3$ | $n$-$C_6H_{11}$ | $CH_3$ | 1 | H | H | 1.5077 | 272 dec. | $C_{20}H_{34}ClN$ | 74.2 | 10.6 | 4.3 | 74.2 | 10.7 | 4.4 | ++ | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | H | H | 1.5056 | 283 | $C_{20}H_{34}ClN$ | 74.2 | 10.6 | 4.3 | 74.0 | 10.4 | 4.4 | +++ | ++ |
| $CH_3$ | $n$-$C_8H_{13}$ | $CH_3$ | 1 | H | H | 1.5017 | 255 | $C_{21}H_{36}ClN$ | 74.6 | 10.7 | 4.1 | 74.8 | 10.6 | 4.1 | +++ | ++ |
| $CH_3$ | $n$-$C_6H_{13}$ | $C_2H_5$ | 1 | H | H | 1.5028 | 216–219 | $C_{22}H_{38}ClN$ | 75.1 | 10.9 | 4.0 | 74.9 | 10.7 | 3.9 | ++[d] | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OCH_2O$ | | [c] | 274 | $C_{21}H_{34}ClNO_2$ | 68.6 | 9.3 | 3.8 | 68.7 | 9.4 | 3.7 | + | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | H | $OCH_3$ | 1.5106 | 285–287 | $C_{21}H_{36}ClNO$ | 71.3 | 10.3 | 4.0 | 71.7 | 10.0 | 3.6 | ++ | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OCH_3$ | $OCH_3$ | 1.5168 | 256–258 | $C_{22}H_{38}ClNO_2$ | 68.8 | 10.0 | 3.7 | 68.7 | 9.9 | 3.8 | ++ | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | OH | OH | [e] | 173–174 | $C_{20}H_{34}ClNO_2$ | 67.5 | 9.6 | 3.9 | 67.2 | 9.3 | 3.9 | 0 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OCOCH_3$ | $OCOCH_3$ | ... | 203 | $C_{24}H_{38}ClNO_4$ | 65.5 | 8.7 | 3.2 | 65.2 | 8.8 | 3.2 | +++ | ++ |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OC_2H_5$ | $OC_2H_5$ | [c] | 250–255 dec. | $C_{24}H_{42}ClNO_2$ | 70.0 | 10.3 | 3.4 | 69.8 | 9.9 | 3.2 | ++++ | 0 |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 2 | H | H | ... | 237–240 | $C_{21}H_{36}ClN$ | 74.6 | 10.7 | 4.1 | 74.1 | 10.6 | 3.9 | ++ | |
| $CH_3$ | $n$-$C_6H_{13}$ | $CH_3$ | 2 | H | H | 1.5020 | 209–212 | $C_{22}H_{38}ClN$ | 75.1 | 10.9 | 4.0 | 75.1 | 10.8 | 30.9 | +++ | ++ |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 3 | H | H | 1.5000 | 248–252 | $C_{22}H_{38}ClN$ | 75.1 | 10.9 | 4.0 | 75.0 | 10.5 | 3.8 | ++ | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 3 | H | $OCH_3$ | 1.5071 | 248–250 | $C_{23}H_{40}ClNO$ | 72.3 | 10.6 | 3.7 | 72.8 | 10.6 | 3.6 | +++ | ++ |
| $CH_3$ | $i$-$C_6H_{13}$ | H | 1 | H | H | 1.5043 | 295 dec. | $C_{20}H_{34}ClN$ | 74.2 | 10.6 | 4.3 | 74.3 | 10.6 | 3.9 | 0 | |
| $CH_3$ | $i$-$C_6H_{13}$ | $CH_3$ | 1 | H | H | 1.5035 | 294 dec. | $C_{21}H_{36}ClN$ | 74.6 | 10.7 | 4.1 | 75.2 | 11.0 | 3.8 | 0 | |
| $CH_3$ | $n$-$C_7H_{15}$ | H | 1 | H | H | 1.5065 | 285 | $C_{21}H_{36}ClN$ | 74.6 | 10.7 | 4.1 | 74.8 | 11.1 | 4.0 | +++[d] | + |
| $CH_3$ | $n$-$C_7H_{15}$ | $CH_3$ | 1 | H | H | 1.5041 | 255–258 dec. | $C_{22}H_{38}$ NCl | 75.1 | 10.9 | 4.0 | 75.3 | 10.6 | 3.8 | +++ | + |
| $CH_3$ | $n$-$C_9H_{19}$ | H | 1 | H | H | 1.5047 | 283–285 dec. | $C_{23}H_{40}ClN$ | 75.5 | 11.0 | 3.8 | 75.5 | 10.9 | 3.8 | 0 | |
| $C_2H_5$ | $CH_2C(CH_3)HC_2H_5$ | H | 1 | H | H | 1.5119 | 233–235 | $C_{20}H_{34}ClN$ | 74.2 | 10.6 | 4.3 | 73.8 | 10.2 | 4.2 | + | |
| $C_2H_5$ | $CH_2C(CH_3)HC_2H_5$ | $CH_3$ | 1 | H | H | ... | 218 | $C_{21}H_{36}ClN$ | 74.6 | 10.7 | 4.1 | 74.2 | 10.4 | 4.1 | ++ | |
| $(CH_2)_4$ | | H | 1 | H | H | 1.5268 | >310 | $C_{17}H_{26}ClN$ | 73.0 | 9.4 | 5.0 | 73.0 | 9.4 | 4.9 | ++ | |
| $(CH_2)_4$ | | $CH_3$ | 1 | H | H | 1.5276 | 275 dec. | $C_{18}H_{28}ClN$ | 73.6 | 9.6 | 4.8 | 73.7 | 9.8 | 4.6 | 0 | |
| $(CH_2)_4$ | | H | 1 | $OCH_3$ | $OCH_3$ | [c] | 261 dec. | $C_{19}H_{30}ClNO_2$ | 67.1 | 8.9 | 4.1 | 66.9 | 9.0 | 4.2 | ++ | |
| $(CH_2)_5$ | | H | 0 | H | H | 1.5350 | 259–260 | $C_{17}H_{26}ClN$ | 73.0 | 9.4 | 5.0 | 72.8 | 9.2 | 5.1 | 0 | |
| $(CH_2)_5$ | | $CH_3$ | 0 | H | H | ... | 281–284 dec. | $C_{18}H_{28}ClN$ | 73.6 | 9.6 | 4.8 | 73.5 | 9.6 | 4.5 | +[d] | |
| $(CH_2)_6$ | | $C_2H_5$ | 0 | H | H | 1.5306 | 295 dec. | $C_{19}H_{30}ClN$ | 74.1 | 9.8 | 4.6 | 74.1 | 9.7 | 4.5 | 0 | |
| $(CH_2)_6$ | | H | 1 | H | H | 1.5321 | 300 dec. | $C_{18}H_{28}ClN$ | 73.6 | 9.7 | 4.8 | 73.8 | 9.6 | 4.4 | ++ | |
| $(CH_2)_6$ | | H | 1 | H | OH | [f] | 235–241 | $C_{18}H_{28}ClNO$ | 69.8 | 9.1 | 4.5 | 69.4 | 9.0 | 4.3 | + | |
| $(CH_2)_5$ | | H | 1 | H | $OCH_3$ | 1.5368 | 295–298 | $C_{19}H_{30}ClNO$ | 70.5 | 9.3 | 4.3 | 70.5 | 9.2 | 4.4 | +++ | ++ |
| $(CH_2)_6$ | | H | 1 | H | $OCOCH_3$ | ... | 273–276 dec. | $C_{20}H_{30}ClNO_2$ | 68.3 | 8.6 | 4.0 | 68.6 | 8.6 | 4.1 | 0 | |
| $(CH_2)_6$ | | H | 1 | $OCH_3$ | $OCH_3$ | [g] | 265 dec. | $C_{20}H_{32}ClNO_2$ | 67.9 | 9.1 | 4.0 | 68.0 | 9.3 | 3.9 | 0 | |
| $(CH_2)_5$ | | H | 1 | $OCH_3$ | $OC_2H_5$ | [h] | 258–260 | $C_{21}H_{34}ClNO_2$ | 68.5 | 9.3 | 3.8 | 68.6 | 9.2 | 4.1 | ++ | |
| $(CH_2)_6$ | | H | 1 | $OCH_2O$ | | [c] | 305–308 dec. | $C_{19}H_{28}ClNO_2$ | 67.5 | 8.4 | 4.2 | 67.6 | 8.2 | 4.1 | +++ | + |
| $(CH_2)_5$ | | $CH_3$ | 1 | H | H | 1.5341[i] | 284–288 dec. | $C_{19}H_{30}ClN$ | 74.1 | 9.8 | 4.6 | 74.1 | 9.7 | 4.3 | ++ | ++ |
| $(CH_2)_5$ | | $CH_3$ | 1 | H | H | 1.5328[j] | 284–288 dec. | $C_{19}H_{30}ClN$ | 74.1 | 9.8 | 4.6 | 74.5 | 9.7 | 4.7 | ++ | ++ |
| $(CH_2)_5$ | | $CH_3$ | 1 | H | H | 1.5337 | 284–288 dec. | [k] | | | | | | | ++ | |
| $(CH_2)_5$ | | $C_2H_5$ | 1 | H | H | 1.5280 | 224–226 | $C_{20}H_{32}ClN$ | 74.6 | 10.0 | 4.4 | 74.7 | 10.1 | 4.2 | + | |
| $(CH_2)_5$ | | $CH_3$ | 1 | $OCH_3$ | $OCH_3$ | ... | 245 dec. | $C_{21}H_{34}ClNO_2$ | 68.6 | 9.3 | 3.8 | 68.5 | 9.3 | 3.9 | 0 | |
| $(CH_2)_6$ | | $CH_3$ | 1 | $OCH_2O$ | | [c] | 264–265 | $C_{20}H_{30}ClNO_2$ | 68.3 | 8.6 | 4.0 | 68.1 | 8.2 | 3.8 | 0 | |
| $(CH_2)_5$ | | H | 2 | H | H | 1.5279 | 259–261 | $C_{19}H_{30}ClN$ | 74.1 | 9.8 | 4.6 | 74.6 | 9.8 | 4.5 | + | |
| $(CH_2)_5$ | | $CH_3$ | 2 | H | H | 1.5278 | 198–204 | $C_{20}H_{32}ClN$ | 74.6 | 10.0 | 4.4 | 74.5 | 9.9 | 4.3 | +++[d] | |
| $(CH_2)_6$ | | H | 3 | H | H | 1.5261 | 253–254 | $C_{20}H_{32}ClN$ | 74.6 | 10.0 | 4.4 | 74.6 | 9.8 | 4.0 | +++ | ++ |
| $(CH_2)_6$ | | H | 3 | H | $OCH_3$ | 1.5279 | 235 | $C_{21}H_{34}ClNO$ | 71.7 | 9.7 | 4.0 | 71.8 | 10.1 | 3.8 | +++[d] | |
| $C(CH_3)H(CH_2)_4$ | | $CH_3$ | 1 | H | H | 1.5302 | 295–297 dec. | $C_{20}H_{32}ClN$ | 74.6 | 10.0 | 4.4 | 74.8 | 10.0 | 4.2 | 0 | |
| $(CH_2)_6$ | | H | 1 | H | H | 1.5377 | 299 dec. | $C_{19}H_{30}ClN$ | 74.1 | 9.8 | 4.6 | 74.2 | 9.6 | 4.3 | 0 | |
| $(CH_2)_6$ | | $CH_3$ | 1 | H | H | 1.5346 | 319–321 dec. | $C_{20}H_{32}ClN$ | 74.6 | 10.0 | 4.4 | 74.5 | 9.9 | 4.2 | + | |

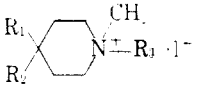
[a] In rabbits; for symbols see Table III, ref. *a*. [b] K. Kindler, [*Arch. Pharm.*, **265,** 389, 405 (1927)] gives m.p. 233°. [c] Crude base was not distilled. [d] Toxic or strong depressant effects at effective dose levels. [e] Base, m.p. 69–71°. [f] Base, m.p. 175–180°. [g] Base, m.p. 66–72°. [h] Base, m.p. 45–50°. [i] *dl*-Form. [j] *l*-Isomer, $[\alpha]^{45}D$ −16.6° (*c* 2.5, $H_2O$). [k] *d*-Isomer, $[\alpha]^{20}D$ +14.8° (*c* 2.5, $H_2O$).

The following general observations can be made about the relationship between activity and chemical structure in 1,4-substituted piperidines (VII): (a) secondary bases, where $R_3$ is H, are inactive; (b) tertiary bases having 1-alkyl substituents have little or no activity; and (c) good hypotensive activity is associated with the tertiary bases having phenylalkyl substituents on the nitrogen and fairly large alkyl substituents at the 4-position. The activity of one such compound was lost when the phenyl grouping was hydrogenated.

Most of the active compounds investigated have the general structure VIII where $R_1$ and $R_2$ are methyl,

TABLE V

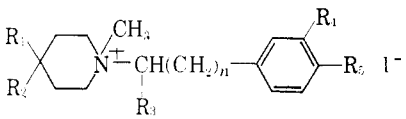
PIPERIDINE METHIODIDES



| $R_1$ | $R_2$ | R | M.p., °C. | Formula | Calcd., % | | | Found, % | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | C | H | N |
| $CH_3$ | $n$-$C_5H_{11}$ | $CH_2CH{=}CH_2$ | 126–127 | $C_{15}H_{30}IN$ | 51.3 | 8.6 | 4.0 | 51.1 | 8.6 | 3.7 |
| $CH_3$ | $n$-$C_6H_{13}$ | $CH_2C(C_2H_5)H(CH_2)_3CH_3$ | 222–223 | $C_{21}H_{44}IN$ | 57.7 | 10.1 | 3.2 | 58.1 | 10.0 | 3.1 |
| $CH_3$ | $n$-$C_6H_{13}$ | $n$-$C_8H_{17}$ | 262–265 | $C_{21}H_{44}IN$ | 57.7 | 10.1 | 3.2 | 57.6 | 10.0 | 3.1 |
| $(CH_2)_5$ | | $CH_3$ | 283 | $C_{12}H_{24}IN$ | 46.6 | 7.8 | 4.5 | 47.0 | 7.9 | 4.2 |
| $(CH_2)_5$ | | $C_2H_5$ | 206–208 | $C_{13}H_{26}IN$ | 48.3 | 8.1 | 4.3 | 48.7 | 7.8 | 3.9 |
| $(CH_2)_5$ | | $n$-$C_3H_7$ | 211–212 | $C_{14}H_{28}IN$ | 49.9 | 8.4 | 4.2 | 49.6 | 8.3 | 4.0 |
| $(CH_2)_5$ | | $i$-$C_3H_7$ | 273 dec. | $C_{14}H_{28}IN$ | 49.9 | 8.4 | 4.2 | 49.6 | 8.3 | 4.1 |
| $(CH_2)_5$ | | $CH_2CH{=}CH_2$ | 180–181 | $C_{14}H_{26}IN$ | 50.2 | 7.8 | 4.2 | 50.4 | 7.9 | 3.9 |
| $(CH_2)_5$ | | $i$-$C_4H_9$ | 226 dec. | $C_{15}H_{30}IN$ | 51.3 | 8.6 | 4.0 | 51.3 | 8.6 | 3.9 |
| $(CH_2)_5$ | | $i$-$C_5H_{11}$ | 240–241 dec. | $C_{16}H_{32}IN$ | 52.6 | 8.8 | 3.8 | 53.0 | 8.9 | 3.3 |
| $(CH_2)_5$ | | $n$-$C_6H_{13}$ | 217–218 | $C_{17}H_{34}IN$ | 53.8 | 9.0 | 3.7 | 53.8 | 9.0 | 3.4 |
| $(CH_2)_5$ | | $C_6H_5$ | 202–203 | $C_{17}H_{26}IN$ | 55.0 | 7.1 | 3.8 | 55.3 | 7.1 | 3.6 |

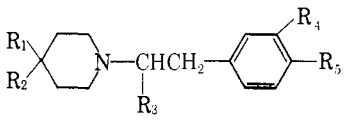
TABLE VI

1-ARALKYLPIPERIDINE METHIODIDES



| $R_1$ | $R_2$ | $R_3$ | $n$ | $R_4$ | $R_5$ | M.p., °C. | Formula | Calcd., % | | | Found, % | | | Hypotensive activity[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H | N | C | H | N | |
| H | H | H | 1 | H | H | 172–174[b] | | | | | | | | + |
| $CH_3$ | $C_2H_5$ | H | 1 | H | H | 187–191 | $C_{17}H_{28}IN$ | 54.7 | 7.6 | 3.8 | 54.8 | 7.5 | 3.3 | +++ |
| $CH_3$ | $C_2H_5$ | $CH_3$ | 1 | H | H | 195–197 | $C_{18}H_{30}IN$ | 55.8 | 7.8 | 3.6 | 55.6 | 7.8 | 3.5 | ++ |
| $CH_3$ | $n$-$C_3H_7$ | H | 1 | H | H | 197–198.5 | $C_{18}H_{30}IN$ | 55.8 | 7.8 | 3.6 | 55.8 | 7.4 | 3.4 | |
| $CH_3$ | $n$-$C_3H_7$ | $CH_3$ | 1 | H | H | 211–217 | $C_{19}H_{32}IN$ | 56.9 | 8.0 | 3.5 | 56.8 | 8.0 | 3.4 | |
| $CH_3$ | $i$-$C_3H_7$ | H | 1 | H | H | 215–217 | $C_{18}H_{30}IN$ | 55.8 | 7.8 | 3.6 | 56.0 | 7.5 | 3.6 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | H | H | 174–175 | $C_{19}H_{32}IN$ | 56.9 | 8.0 | 3.5 | 56.9 | 8.0 | 3.3 | + |
| $CH_3$ | $n$-$C_4H_9$ | $CH_3$ | 1 | H | H | 203–206 | $C_{20}H_{34}IN$ | 57.8 | 8.3 | 3.4 | 57.3 | 8.2 | 3.2 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | H | $OCH_3$ | 179–188 | $C_{20}H_{34}INO$ | 55.7 | 7.9 | 3.3 | 55.9 | 7.8 | 3.1 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OCH_3$ | $OCH_3$ | 204–207 | $C_{21}H_{36}INO_2$ | 54.7 | 7.9 | 3.0 | 54.7 | 7.8 | 3.1 | 0 |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OCH_3$ | $OC_2H_5$ | 165–174 | $C_{22}H_{38}INO_2$ | 55.6 | 8.1 | 3.0 | 55.9 | 8.1 | 2.9 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 1 | $OC_2H_5$ | $OC_2H_5$ | 226–227.5 | $C_{23}H_{40}INO_2$ | 56.4 | 8.2 | 2.9 | 56.5 | 8.2 | 2.6 | |
| $CH_3$ | $n$-$C_4H_9$ | H | 3 | H | H | 198–202.5 | $C_{21}H_{36}IN$ | 58.7 | 8.5 | 3.3 | 59.0 | 8.6 | 3.0 | |
| $CH_3$ | $n$-$C_5H_{11}$ | H | 1 | H | H | 177–178 | $C_{20}H_{34}IN$ | 57.8 | 8.3 | 3.4 | 58.2 | 8.4 | 3.4 | +++[c] |
| $CH_3$ | $n$-$C_5H_{11}$ | H | 1 | $OCH_3$ | $OCH_3$ | 203–205 | $C_{22}H_{38}INO_2$ | 55.6 | 8.1 | 2.9 | 55.9 | 8.3 | 2.5 | |
| $CH_3$ | $n$-$C_6H_{11}$ | $CH_3$ | 1 | H | H | 208–211 | $C_{21}H_{36}IN$ | 58.7 | 8.5 | 3.3 | 58.5 | 8.2 | 3.5 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | H | H | 214–215 | $C_{21}H_{36}IN$ | 58.7 | 8.5 | 3.3 | 58.3 | 8.4 | 3.2 | + |
| $CH_3$ | $n$-$C_6H_{13}$ | $CH_3$ | 1 | H | H | 211–215.5 | $C_{22}H_{38}IN$ | 59.6 | 8.6 | 3.2 | 59.7 | 8.7 | 3.1 | |
| $CH_3$ | $n$-$C_6H_{13}$ | $C_2H_5$ | 1 | H | H | 193–202 | $C_{23}H_{40}IN$ | 60.4 | 8.8 | 3.1 | 60.8 | 8.9 | 3.0 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | H | $OCH_3$ | 195–196 | $C_{22}H_{38}INO$ | 57.5 | 8.3 | 3.1 | 57.8 | 8.3 | 2.9 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OC_2H_5$ | $OC_2H_5$ | 230 dec. | $C_{26}H_{44}INO_2$ | 58.0 | 8.6 | 2.7 | 57.7 | 8.6 | 2.5 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 1 | $OCH_2O$ | | 202 | $C_{22}H_{36}INO_2$ | 55.8 | 7.7 | 3.0 | 55.5 | 7.5 | 2.9 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 2 | H | H | 181–184 | $C_{22}H_{38}IN$ | 59.6 | 8.6 | 3.2 | 59.7 | 8.7 | 3.0 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 3 | H | H | 217–218.5 | $C_{23}H_{40}IN$ | 60.4 | 8.8 | 3.1 | 60.2 | 8.7 | 2.9 | |
| $CH_3$ | $n$-$C_6H_{13}$ | H | 3 | H | $OCH_3$ | 213.5–214 | $C_{24}H_{42}INO$ | 59.1 | 8.7 | 2.9 | 59.4 | 8.7 | 2.7 | |
| $CH_3$ | $i$-$C_6H_{13}$ | H | 1 | H | H | 186–187.5 | $C_{22}H_{36}IN$ | 58.7 | 8.5 | 3.3 | 58.5 | 8.4 | 3.3 | |
| $CH_3$ | $n$-$C_7H_{15}$ | H | 1 | H | H | 197–202 | $C_{22}H_{38}IN$ | 59.6 | 8.6 | 3.2 | 59.6 | 8.6 | 2.9 | |
| $CH_3$ | $n$-$C_7H_{15}$ | $CH_3$ | 1 | H | H | 213–216 | $C_{23}H_{40}IN$ | 60.4 | 8.8 | 3.1 | 60.3 | 8.6 | 3.0 | |
| $CH_3$ | $n$-$C_9H_{19}$ | H | 1 | H | H | 205–208 | $C_{24}H_{42}IN$ | 61.0 | 9.0 | 3.0 | 61.4 | 8.9 | 3.1 | |
| $CH_3$ | $C_6H$ | H | 1 | H | H | 260 | $C_{21}H_{28}IN$ | 59.9 | 6.7 | 3.3 | 60.0 | 6.8 | 3.0 | + |
| $CH_3$ | $C_6H_5$ | $CH_3$ | 1 | H | H | 230 | $C_{22}H_{30}IN$ | 60.7 | 7.0 | 3.2 | 60.9 | 7.1 | 3.2 | 0 |
| $C_2H_5$ | $CH_2CH(CH_3)C_2H_5$ | H | 1 | H | H | 235[d] | $C_{21}H_{36}IN$ | 58.7 | 8.5 | 3.3 | 58.8 | 8.3 | 3.4 | ++ |
| $C_2H_5$ | $CH_2CH(CH_3)C_2H_5$ | $CH_3$ | 1 | H | H | 234–235 | $C_{22}H_{38}IN$ | 59.6 | 8.6 | 3.2 | 59.6 | 8.5 | 2.8 | |
| $(CH_2)_4$ | | H | 1 | H | H | 215 | $C_{18}H_{28}IN$ | 56.1 | 7.3 | 3.6 | 55.6 | 7.2 | 3.5 | ++ |
| $(CH_2)_4$ | | $CH_3$ | 1 | H | H | 221 | $C_{19}H_{30}IN$ | 57.1 | 7.6 | 3.5 | 56.8 | 7.7 | 3.8 | |
| $(CH_2)_5$ | | H | 0 | H | H | 241 dec. | $C_{18}H_{28}IN$ | 56.1 | 7.3 | 3.6 | 56.5 | 7.4 | 3.3 | 0 |
| $(CH_2)_5$ | | $CH_3$ | 0 | H | H | 180 dec. | $C_{19}H_{30}IN$ | 57.1 | 7.6 | 3.5 | 57.6 | 7.9 | 3.2 | |
| $(CH_2)_5$ | | $C_2H_5$ | 0 | H | H | 182.5–184 | $C_{20}H_{32}IN$ | 58.2 | 7.8 | 3.4 | 58.0 | 7.8 | 3.2 | |
| $(CH_2)_5$ | | H | 1 | H | H | 220 | $C_{19}H_{30}IN$ | 57.1 | 7.6 | 3.5 | 56.6 | 7.5 | 3.4 | |
| $(CH_2)_5$ | | $CH_3$ | 1 | H | H | 225–226 | $C_{20}H_{32}IN$ | 58.1 | 7.8 | 3.4 | 57.5 | 7.7 | 2.9 | + |
| $(CH_2)_5$ | | H | 1 | H | $OCH_3$ | 213–223 | $C_{20}H_{32}INO$ | 56.0 | 7.5 | 3.3 | 55.6 | 7.4 | 3.5 | |
| $(CH_2)_5$ | | H | 1 | $OCH_2O$ | | 230 | $C_{20}H_{30}INO_2$ | 54.2 | 6.8 | 3.2 | 54.0 | 6.8 | 2.7 | |
| $(CH_2)_5$ | | H | 1 | $OCH_3$ | $OCH_3$ | 235–236 | $C_{21}H_{34}INO_2$ | 54.9 | 7.5 | 3.1 | 54.8 | 7.4 | 3.0 | |
| $(CH_2)_5$ | | H | 1 | $OCH_3$ | $OC_2H_5$ | 212–213 | $C_{22}H_{36}INO_2$ | 55.8 | 7.7 | 3.0 | 55.6 | 7.6 | 2.9 | |
| $(CH_2)_5$ | | H | 2 | H | H | 180–182 | $C_{20}H_{32}IN$ | 58.1 | 7.8 | 3.4 | 58.1 | 7.8 | 3.1 | + |
| $(CH_2)_5$ | | $CH_3$ | 2 | H | H | 167.5–168.5 | $C_{21}H_{34}IN$ | 59.0 | 8.0 | 3.3 | 59.2 | 7.9 | 3.2 | |
| $(CH_2)_5$ | | H | 3 | H | H | 189–190.5 | $C_{21}H_{34}IN$ | 59.0 | 8.0 | 3.3 | 59.1 | 8.0 | 3.2 | +++ |
| $(CH_2)_5$ | | H | 3 | H | $OCH_3$ | 182–185.5 | $C_{22}H_{36}INO$ | 57.8 | 7.9 | 3.1 | 57.8 | 8.0 | 2.8 | |
| $(CH_2)_6$ | | H | 1 | H | H | 213.5–214.5 | $C_{20}H_{32}IN$ | 58.1 | 7.8 | 3.4 | 58.5 | 7.8 | 3.5 | |
| $(CH_2)_8$ | | $CH_3$ | 1 | H | H | 234–235 | $C_{21}H_{34}IN$ | 59.0 | 8.0 | 3.3 | 58.7 | 8.1 | 3.2 | |

[a] In rabbits, i.p.; for symbols see Table III, ref. 3. [b] C. T. Bahner, M. Fielden, L. Rives, and M. Pickens, *J. Am. Chem. Soc.*, **73**, 4455 (1951). [c] ++ activity orally in rabbits. [d] Softens from 207°.



VIII

$n$-hexyl, or 4-spirocyclohexane; $R_3$ is H or methyl; and $R_4$ and $R_5$ are H or alkoxy.

Many anomalous observations were made regarding the phenyl substituents $R_4$ and $R_5$. For example, introduction of a methylenedioxy group into 1-phenethyl-4-spirocyclohexanepiperidine ($R_3$ = H) at $R_4$ and $R_5$ increased activity markedly, but the same structural modification in the otherwise identical compound having $R_3$ = $CH_3$ resulted in slight hypertensive activity. Again, the activity of the former compound is abolished by introduction of $OCH_3$ groupings at $R_4$ and $R_5$, but the two compounds having, respectively, $OCH_3$ and $OC_2H_5$, or H and $OCH_3$ at $R_4$ and $R_5$ have activities similar to that of the parent compound. Similar anomalies were found among compounds having methyl $n$-hexyl substituents at the 4-position (Table IV). There is no apparent relation between activity and structure as far as substitution of the phenyl group is concerned.

Although all active compounds have fairly bulky 4-substituents, generally methyl and $n$-hexyl or spirocyclohexane, the limit is reached with methyl and $n$-nonyl, the compound 1-phenethyl-4-methyl-4-$n$-nonylpiperidine being inactive. High activity was, however, found when the desirable 4-substituents were retained and the phenylalkyl chain was lengthened. Thus 1-(1-methyl-3-phenylpropyl)-4-methyl-4-$n$-hexylpiperidine and 1-(4-phenylbutyl)-4-spirocyclohexanepiperidine are hypotensive when administered intraperitoneally or orally to the rabbit.

The $d$- and $l$-isomers of one active $dl$-compound were found to have activity identical with that of the $dl$-compound (Table IV). All other compounds having asymmetric centers were synthesized and screened as the $dl$-forms.

The suggestion[8] that the N-oxide derivative of a pharmacologically active base may retain activity of the base with reduced toxic side effects was investigated in one instance. The N-oxide of 1-phenethyl-4-spirocyclohexane was found to be without hypotensive activity.

## Experimental

Microanalyses were carried out by the University of Melbourne and C. S. I. R. O. Microanalytical Laboratory. Melting points were determined on a gas-heated Electrothermal apparatus and are uncorrected.

The following phenylalkylamine intermediates were either commercially available or were prepared by methods reported in the literature: benzylamine, 1-phenylethylamine, 1-phenylpropylamine, phenethylamine, 1-phenyl-2-propylamine (*dl*, *d*-, and *l*-), 1-benzylpropylamine, 3,4-dimethoxyphenethylamine, 3,4,5-trimethoxyphenethylamine, 1-(3,4-dimethoxyphenyl)-2-propylamine, 3,4-methylenedioxyphenethylamine, 1-(3,4-methylenedioxyphenyl)-2-propylamine, 1-phenyl-3-butylamine, and 4-phenylbutylamine.

*p*-Methoxyphenethylamine, 3-methoxy-4-ethoxyphenethylamine, and 3,4-diethoxyphenethylamine, previously reported in the literature, were synthesized by lithium aluminum hydride reduction of the corresponding $\beta$-nitrostyrenes, which were prepared according to the method of Gairaud and Lappin.[9] 4-(*p*-Methoxyphenyl)butylamine, obtained by lithium aluminum hydride reduction of $\gamma$-(*p*-methoxyphenyl)butyramide, has b.p. 146° (3 mm.), $n^{20}D$ 1.5208.

All phenylalkylamines having an asymmetric center, and the compounds derived from them, were prepared as the *dl*-forms unless otherwise stated.

The following examples are typical of the methods used for preparation of the compounds tabulated.

**N-Phenethyl-$\beta$-spirocyclohexaneglutarimide.**—$\beta$-Spirocyclohexaneglutaric anhydride (18.2 g., 0.1 mole) and phenethylamine (12.5 g., 0.103 mole) were mixed, and the mixture was heated at 190–210° for 3 hr. when evolution of water vapor ceased. The mix was cooled and macerated with water when the dark mass readily crystallized. The product was obtained as large colorless needles, m.p. 81–82° after two recrystallizations from petroleum ether (b.p. 55–95°), 21.5 g., 75% yield.

**1-Phenethyl-4-spirocyclohexanepiperidine Hydrochloride.**—An ethereal solution of the above glutarimide (14.3 g., 0.05 mole) was added with stirring over 15 min. to a slurry of lithium aluminum hydride (4.5 g., 0.13 mole) in 250 ml. of dry ether. The mixture was refluxed for 1 hr. and the complex then was decomposed by addition of moist ether and finally water. After filtration, the residue was washed thoroughly with ether and the solution was dried ($Na_2SO_4$). The solvent was removed and the residue was distilled to give 1-phenethyl-4-spirocyclohexanepiperidine as a colorless liquid, b.p. 174–176° (0.5 mm.) (11.0 g., 86% yield). The hydrochloride salt was prepared by treatment of an ethereal solution of the base with dry HCl. Recrystallization from ethanol-ether gave colorless needles, m.p. 300° dec.

**N-(1-Phenyl-2-propyl)-$\beta$-methyl-$\beta$-$n$-hexylglutarimide.**—$\beta$-Methyl-$\beta$-$n$-hexylglutaric anhydride (31.8 g., 0.15 mole) and 1-phenyl-2-propylamine (20.6 g., 0.153 mole) were mixed and heated together over a free flame to an internal temperature of 350°, maintaining this temperature for 15–20 min. when evolution of water vapor ceased. Distillation gave the product as a viscous liquid, b.p. 205–209° (5.0 mm.), 37.0 g., 75% yield.

**1-(3,4-Dimethoxyphenethyl)-4-spirocyclohexanepiperidine Methiodide.**—The free base (4.0 g.), obtained by hydride reduction of the corresponding glutarimide, was allowed to react with methyl iodide (4 ml.) in ethereal solution at room temperature. After several days the precipitate was filtered, washed with ether, and recrystallized from alcohol-ether to give pale yellow flakes, m.p. 235–236°, 85% yield.

***dl*-1-(1-Methyl-2-cyclohexylethyl)-4-spirocyclohexanepiperidine.**—1-(1-Phenyl-2-propyl)-4-spirocyclohexanepiperidine (5.4 g., 0.02 mole) was hydrogenated in acetic acid solution (100 ml.) using Adams' $PtO_2$ catalyst (0.2 g.) in a Parr low-pressure hydrogenator. Reduction began at 80° and was complete in 2 hr. After removal of catalyst, the solution was evaporated, the residue was made alkaline and extracted with ether. Treatment with HCl gave the hydrochloride salt which, after recrystallization from water containing a trace of HCl, was obtained as a colorless powder, m.p. 230–245°, 4.2 g., 67% yield.

*Anal.* Calcd. for $C_{19}H_{36}ClN$: C, 72.7; H, 11.6; N, 4.5. Found: C, 73.1; H, 11.3; N, 4.3.

***dl*-(1-phenyl-2-propyl)-4-spirocyclohexanepiperidine N-Oxide.**—The free base (5.4 g., 0.02 mole) was converted quantitatively to the crystalline N-oxide by mixing with 100 vol. of hydrogen peroxide (10 ml.) and 20 ml. of water. The N-oxide separated after a few minutes at room temperature. After air drying, the colorless product (5.7 g.) had m.p. 95–100° (with gas evolution above this temperature).

*Anal.* Calcd. for $C_{19}H_{29}NO$: C, 79.3; H, 10.2; N, 4.9. Found: C, 79.9; H, 10.3; N, 5.0.

The compound decomposed slowly to the piperidine base on storage at room temperature for several months.

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(8) C. C. Culvenor, *Rev. Pure Appl. Chem.*, **3**, 83 (1953).

(9) C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953).