from IPO–MeOH gave 0.289 (48%) of anal. pure **38**, mp 263–265°. Anal. data are included in Table II.

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# Phenacylthioimidazolines and 3-Aryl-5,6-dihydroimidazo[2,1-*b*]thiazoles with Antidepressant Activity

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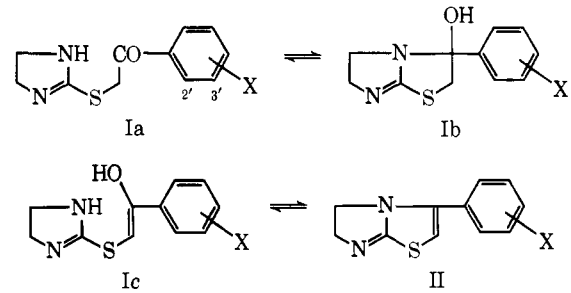
Some Ph-ring-substituted phenacylthioimidazolines are very potent antagonists of reserpine-induced hypothermia in mice. The proportion of open chain to cyclic carbinolamine tautomer depends on the type of substituent and possibly affects the activity. The 3-aryl-5,6-dihydroimidazo[2,1-*b*]thiazoles obtained by cyclodehydration are also active.

The reported antidepressant activity of 2-(3,4-dichlorophenoxymethyl)imidazoline[1] and an interest in imidazo[2,1-*b*]thiazoles, prompted us to prepare 2-(3,4-dichlorophenacylthio)imidazoline which proved to be exceptionally potent ($ED_{50}$ = 0.5 mg/kg) in the reserpine hypothermia test in mice. The effects on antireserpine activity of substitution in the Ph ring of phenacylthioimidazoline and the activity of the corresponding 5,6-dihydroimidazo[2,1-*b*]thiazoles obtained by cyclodehydration were investigated. A patent[2] describing some related compounds with antidepressant properties has become available since this work was started.




inhibitor of MAO and no anorectic, analgetic, analeptic, or CNS-depressant properties were found. The acute

TABLE I

$^1$H Nmr Results ($\tau$) for ArCOC($R^1R^2$)S(HN–N)

| Ar | $R^1$ | $R^2$ | Aromatic protons[a,b] | $-CH_2CO$[b,c] | $CH_2CH_2$[a] $+CH_2C(Ar)OH$ | Others | % keto form |
|---|---|---|---|---|---|---|---|
| 4-$MeOC_6H_4$ (HBr) | H | H | 1.77–3.05 (4) | 4.70 (1) | 5.53–6.50 | 6.05, 6.08 (MeO) | 50 |
| 4-$MeC_6H_4$ (HBr) | H | H | 1.88–2.83 (4) | 4.73 (0.8) | 5.50–6.83 | 7.68, 7.62 (Me) | 40 |
| $C_6H_5$ (HBr) | H | H | 1.67–2.62 (5) | 4.62 (0.54) | 5.28–6.62 | | 27 |
| $C_6H_5$ (base) | H | H | 2.27–2.80 (5) | | 5.83–7.27 | | 0 |
| 3-$ClC_6H_4$ (HBr) | H | H | 1.72–2.58 (4) | 4.63 (0.5) | 5.37–6.62 | | 23 |
| 4-$BrC_6H_4$ (HBr) | H | H | 1.97–2.55 (4) | 4.72 (0.42) | 5.45–6.63 | | 21 |
| 4-$ClC_6H_4$ (HBr) | H | H | 2.17–2.58 (4) | 4.63 (0.3) | 5.38–6.67 | | 15 |
| 4-$NO_2C_6H_4$ (HBr) | H | H | 2.33–2.98 (4) | 4.58 (0.07) | 5.20–6.63 | | 3 |
| $C_6H_5$ (HBr) | Me | H | 2.18–2.62 (5) | | 5.33–6.57 | 8.62[d] (Me) | 0 |
| $C_6H_5$ (HBr) | Me | Me | 2.17–2.55 (5) | | 5.45–6.33 | 8.38, 8.81 (Me) | 0 |

[a] Multiplet. [b] Number of protons is given in parentheses. [c] Singlet. [d] Doublet. $J$ = 7 Hz.

The most potent member of the series in the reserpine hypothermia test was **11** (I, X = 3′,4′-$Cl_2$, $ED_{50}$ = 0.5 mg/kg), and its pharmacology was investigated in some detail. The results suggest strong antidepressant activity with some stimulant properties at higher dose levels. The antidepressant properties were similar in several respects to those of imipramine, but the anticholinergic activity was weak. Compd **11** was not an oral toxicity was low and a 30-day subchronic toxicity test in rats showed no major ill effects. A preliminary teratogenic study in rats and rabbits was also negative.

The results shown in Tables III and IV indicate that monosubstitution in the 3′ or 4′ position of I with either electron-attracting or electron-donating groups usually gave compds which were more active than the unsubstituted compd (I, X = H, **7**), but the most active ones ($ED_{50}$ < 5 mg/kg) had electronegative substituents. Their activities, however, are not in the order of the Hammett $\sigma$ constants and the high activity of the

(1) C-P Chien and R. M. Kaplan, *Curr. Ther. Res. Clin. Exp.*, **11**, 471 (1969).

(2) Sandoz AG, German Patents 1,924,769; 1,938,674 (1970).

TABLE II
$R^1COCHBrR^2$

| $R^1$ | $R^2$ | % yield[a] | Time of reaction, hr | Lit. prepn |
|---|---|---|---|---|
| 2-$ClC_6H_4$ | H | 100 | 4 | *b* |
| 3-$ClC_6H_4$ | H | 52[c] | 4 | *d* |
| 4-$ClC_6H_4$ | H | 65[e] | 3 | *f* |
| 3,4-$Cl_2C_6H_3$ | H | *g* | | *h* |
| 2,4-$Cl_2C_6H_3$ | H | 100 | 4 | *i* |
| 2,5-$Cl_2C_6H_3$ | H | 100 | 4 | *j* |
| 2,4-$F_2C_6H_3$ | H | 90 | 4 | *k* |
| 2-$MeC_6H_4$ | H | 100 | 1 | *l* |
| 3-$MeC_6H_4$ | H | 100 | 2 | *f* |
| 2,5-$Me_2C_6H_3$ | H | 100 | 4 | *k* |
| 3,4-$Me_2C_6H_3$ | H | 100 | 1.5 | *f* |
| 2,4,6-$Me_3C_6H_2$ | H | 100 | 4 | *m* |
| 4-$CNC_6H_4$ | H | 100 | 2 | *k* |
| 2-$HO_2CC_6H_4$ | H | *g* | | *n* |
| 2,4-$(MeO)_2C_6H_3$ | H | 60[o] | 2 | *p* |
| 3,4-$(CH_2O_2)C_6H_3$ | H | 100 | 1 | *q* |
| 2-$HOC_6H_4$ | H | 56[r] | 4 | *s* |
| 3-$HOC_6H_4$ | H | 100 | 2 | *s, t* |
| 4-$HOC_6H_4$ | H | 100 | 1 | *s* |
| 2,6-$(HO)_2C_6H_3$ | H | 100 | 1 | *k* |
| 2-HO-4-$MeOC_6H_3$ | H | 100 | 2 | *u* |
| 3-HO-4-$MeOC_6H_3$[v] | H | 80 | 3 | *w* |
| 4-HO-3-$MeOC_6H_3$ | H | 100 | 1 | *x* |
| 4-HO-3-$ClC_6H_3$[y] | H | 100 | 1.5 | *k* |
| 4-HO-3-$MeC_6H_3$ | H | 100 | 1.5 | *k* |
| $C_6H_5$ | Me | 100 | 4 | *z* |
| $C_6H_5$ | Et | 100 | 4 | *aa* |
| 4-F-$C_6H_4$ | $CH_2CH_2Cl$ | *g* | | |
| α-Naphthyl | H | 100 | 4 | *bb* |
| β-Naphthyl | H | 100 | 4 | *bb* |
| 2-Furyl | H | 66 | 0.5 | *cc* |
| 2-Thienyl | H | 100 | 1 | *dd* |
| 2-Benzothiazolyl | H | 100 | 4 | *k* |

[a] As judged by wt of product, which was used directly on the subsequent reaction. [b] C. E. Vaslow and H. Moe, *J. Org. Chem.*, **25**, 1512 (1960). [c] Mp 41.5-42.5° (petr ether, bp 40–60°). [d] R. M. Laird and R. E. Parker, *J. Amer. Chem. Soc.*, **83**, 4277 (1961). [e] Mp 97.5–98.5° (petr ether, 80–100°). [f] M. I. Shevchuk and A. V. Dombrovski, *Zh. Obsch. Khim.*, **33**, 1135 (1963). [g] Prepd by lit. method. [h] R. Fuchs, *J. Amer. Chem. Soc.*, **78**, 5612 (1956). [i] G. L. Lukes and T. B. Williamson, U. S. Patent 3,184,379 (1965). [j] B. I. Stepanov and V. F. Traven, *Zh. Org. Khim.*, 1, 1896 (1965). [k] Not previously described. [l] D. Mercer, A. Robertson, and R. S. Cahn, *J. Chem. Soc.*, 997 (1935). [m] T. Kao and C. Miao, *J. Chin. Chem. Soc. (Taipei)*, **12**, 71 (1945). [n] S. Gabriel, *Ber.*, **40**, 72 (1907). [o] Impure product. [p] A. Blom and J. Tambor, *Ber.*, **38**, 3590 (1905); A. Sonn, *ibid.*, **52**, 926 (1919). [q] N. L. Drake and W. B. Tuemmler, *J. Amer. Chem. Soc.*, **77**, 1204 (1955). [r] Mp 44–45° (petr ether, bp 60–80°). [s] See ref 15. [t] S. J. Buchman, J. D. Pera, and F. W. Raths, German Patent 1,174,017 (1964). [u] K. B. Doifode and M. G. Marathey, *J. Org. Chem.*, **29**, 2025 (1964). [v] Prepn of starting acetophenone; A. Brossi, H. Gurien, A. I. Rachlin, and S. Tietel, *J. Org. Chem.*, **32**, 1269 (1967). [w] P. Pratesi, E. Grava, L. Lilla, A. LaManna, and L. Villa, *Farmaco Ed. Sci.*, **18**, 932 (1963). [z] B. Riegel and H. Wittcoff, *J. Amer. Chem. Soc.*, **68**, 1913 (1946). [y] Prepn of starting acetophenone, mp 110°; F. Krausz and R. Martin, *Bull. Soc. Chim. Fr.*, 2192 (1968). [z] See ref 14. [aa] A. Collet, *Bull. Soc. Chim. Fr.*, **15**, 1100 (1896); **17**, 76 (1897). [bb] C. B. Radcliffe, I. R. Sherwood, and W. F. Short, *J. Chem. Soc.*, 2293 (1931). [cc] E. B. Knott, *ibid.*, 1656 (1947). [dd] F. Kipnis, H. Soloway, and J. Ornfelt, *J. Amer. Chem. Soc.*, **71**, 10 (1949).

4′-amino derivative **27**, may be anomalous. 3′,4′-Disubstitution appears to give a further increase in activity but compds containing an OH or $CO_2H$ group in the Ph ring were inactive or weak. Replacement of the Ph ring by 2-naphthyl or 4-pyridyl also gave increased activity but other replacements of this type gave inactive compds.

The corresponding 5,6-dihydroimidazo[2,1-*b*]thiazoles II (Tables V and VI) were somewhat less active in nearly all cases, although they are still very potent by general standards, and the structure–activity relationships in this series are not the same. They were generally more toxic than the imidazolines, according to $LD_{50}$ values in mice.

The equilibrium between possible open-chain tautomers Ia and Ic and cyclic carbinolamine Ib (X = H) has been discussed previously with respect to ir spectra.[3] To see whether the position of this equilibrium is related to biological activity we have obtained a measure of the proportion of open-chain form from the integrated $^1H$ nmr signal for the $CH_2CO$ singlet at about $\tau$ 4.7 (Table I). The free bases lack C=O absorption in their ir spectra; they fail to give the relevant nmr signal and, since no evidence was found for an open-chain enol form such as Ic, the bases are assumed to exist entirely in the cyclic form Ib. These structures differ from those reported for a series of 2-phenacylthiobenzimidazoles[4] which exist solely in the keto form despite a variety of substituents in the Ph ring of the phenacyl group. The hydrobromides however, have a proportion of open-chain form Ib which varies according to the substituent X (Table I) and in the case of 4′ substituents is in the same order as the Hammett $\sigma$ constants, the most electronegative giving the smallest amount of open-chain form. The ir spectra of the salts in the solid state do not clearly show this relationship; the 4′-Br and 4′-CN compds absorb at 1675 $cm^{-1}$ whereas the 4′-Cl and 4′-$NO_2$ analogs do not absorb in the C=O region.

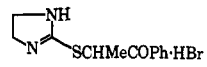
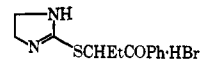
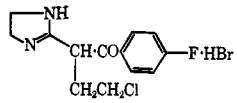
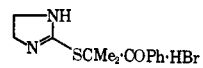
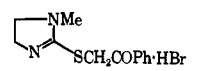
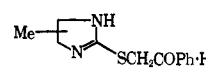
The nmr measurements suggest that outstanding biological activity ($ED_{50}$ < 5 mg/kg) is found in compds whose salts exist in soln as Ib to the extent of 75% or more, although on this basis alone the unsubstituted compd **7** should be more active. Also, as the equilibrium is related to the character of the substituent X, the effect on activity could be coincidental. The structure of norepinephrine, however, is more closely related to Ib than to Ia and interference with the action of norepinephrine may be responsible for the greater antireserpine activity of those compds which exist mainly as the Ib tautomer.

**Pharmacology.**—Compds were administered orally in 0.5% tragacanth suspension in the mouse and rat tests, control animals receiving the vehicle alone. In the cat behavior study[5] compds were given orally in gelatine capsules. Doses are always expressed as the free base. All compds were screened by the reserpine hypothermia test in mice as previously described.[5] The results are given in Tables III–VI.

The most active compd against reserpine (**11**, $ED_{50}$ = 0.5 mg/kg) was studied in more detail. Antidepressant activity was confirmed by its ability at 20 mg/kg to convert the behavior of tetrabenazine-treated rats from sedation to compulsive motor activity,[6] by potentiation at 25 mg/kg of the stimulant effects of DOPA in mice

(3) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).
(4) H. Alper and A. E. Alper, *ibid.*, **35**, 835 (1970).
(5) C. J. Sharpe, R. S. Shadbolt, G. R. Brown, A. Ashford, and J. W. Ross, *J. Med. Chem.*, in press.
(6) F. Sulser and F. Soroko, *Psychopharmacologia*, **8**, 191 (1965).

TABLE III

| No. | Structure | % yield | Mp, °C dec[a] | $\nu_{max}$[b] | Formula[c] | Reserpine[d] reversal |
|---|---|---|---|---|---|---|
| 1 |  | 74[e] | 165–175 s 238–239 | | $C_{12}H_{15}BrN_2OS$ | 1.8 |
| 2 |  | 85[f] | 214–215 | | $C_{13}H_{17}BrN_2OS$ | 0.8 |
| 3 |  | 65[g,h] | 221–222 | 1700 | | 1.1 |
| 4 |  | 7[i] | 222–228 | | $C_{13}H_{17}BrN_2OS$ | 10 |
| 5 |  | 80[j] | 158–159 | 1680 | | I |
| 6 |  | 91 | 143–144 | 1680 | $C_{12}H_{15}BrN_2OS$ | I |

[a] Mp were detd on a Büchi app and are cor. Phenacylthioimidazolinium salts often show a softening point (s) at which $H_2O$ is presumably lost, and then resolidify and melt again at the mp of the corresponding 3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazolium salt. [b] C=O absorption, ir spectra were recorded in Nujol on a Perkin-Elmer 237 spectrophotometer. [c] Where the formula is given compd analyzed for C, H, and N. [d] Figures denote $ED_{50}$ in mg/kg as defined under Pharmacology. I denotes no activity at a dose of 25 mg/kg. All doses are expressed as the free base. [e] Reaction time 2 hr. [f] Reaction time 48 hr. [g] Reaction time 16 hr. [h] See ref 2. [i] Heated under reflux 6 hr. [j] R. S. Shadbolt, *J. Chem. Soc.*, in press.

in which MAO was partially inhibited by iproniazid[7] and by enhancement of the agonist effects of norepinephrine on the isolated rat vas deferens.[8] The compd antagonized oxotremorine (0.2–0.4 mg/kg)-induced hypothermia ($ED_{50}$ = 2.3 mg/kg) and tremor ($ED_{50}$ = 7.9 mg/kg).[9] These effects suggest imipramine-like properties, although the anticholinergic activity was relatively weaker than that of imipramine against ACh-induced chromodacryorrhoea in rats. There was no inhibition of MAO activity at 10 mg/kg as assessed by potentiation of tryptamine convulsions in mice.[10]

Unlike the tricyclic antidepressants however, **11** at 50 mg/kg increased the motor activity of rats and mice and at 10 mg/kg caused the severe stereotyped reactions (as previously defined[5]) and mydriasis in cats and showed some antagonism of chlorpromazine hypothermia in mice. However, there was no marked anorectic activity in rats at 25 mg/kg and no analeptic action against pentobarbital lethality in mice. Although active in the phenylquinone writhing test, negative results in the mouse tail-clip, rat paw carrageenin edema, and guinea pig uv-erythema tests precluded strong analgetic or antiinflammatory properties. No CNS-depressant activity was observed in respect of pentylene-tetrazole convulsions,[11] potentiation of barbiturate hypnosis, or enhancement of pentobarbital anesthesia in mice.

The acute oral $LD_{50}$ in mice was 450 mg/kg. Daily dosing in rats at 50, 35, and 10 mg/kg for 30 days caused some stimulation but had no significant effects on body or organ wt nor on hematological profile. A dose of 60 mg/kg daily on days 6 to 15 of pregnancy caused neither toxicity nor abnormality of the rat fetus, but there appeared to be some increase in fetal toxicity in the rabbit.

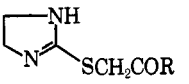
**Chemistry.**—2-Phenacylthioimidazolium salts (Tables III and IV) were prepared by treatment of 2-mercaptoimidazoline in acetone with $\alpha$-haloalkyl aryl ketones. Bromomethyl ketones were generally prepared by the action of $CuBr_2$ on the appropriate Me ketone. This reaction, previously used for selective $\alpha$-bromination of phenolic acetophenones,[12] has been extended to other acetophenones and heterocyclic Me ketones (Table II). The purity of the crude bromomethyl ketones was indicated by the generally good yields of I salts obtained from them (Tables III and IV). The bromination products of 2,6-$(OH)_2$ and 2,4-$(OMe)_2$ acetophenone were unsatisfactory in the subsequent reaction.

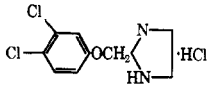
The reported dehydration of 2-phenacylthioimidazolium salts by heating in EtOH to give 3-aryl-5,6-dihydroimidazo[2,1-*b*]thiazolium salts[3,13] was confirmed in many cases, but electron-withdrawing substitution in the Ph ring (*e.g.*, I, X = 4′-CN, 2′,4′-$Cl_2$) necessitated either a longer reaction time or use of AcOH as solvent for dehydration to go to completion (Tables IV and VI). Although the dehydration of I, X = 4′-$NO_2$ hydrobromide, is reported,[3] we recovered it essentially unchanged after boiling for 2 hr in EtOH suspension. Steric factors also operate since I, X = 2′, 4′, 6′-$Me_3$ hydrobromide, was only partially dehydrated by boiling for 6 hr in EtOH suspension.

3-Hydroxy-3-methyl-2,3-dihydrothiazolo[3,2-*a*]benzimidazole, which exists in soln in equilibrium with the open-chain tautomer is reported to give the *O*-Ac deriv[14] but acetylation of 3-hydroxy-3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (100% Ib, X = H) gave the *N*-Ac derivative of the open-chain form.

(7) G. M. Everett, *Excerpta Med.*, 164 (1967).
(8) R. C. Urcillo and J. Jacobson, *J. Pharmacol. Exp. Ther.*, **148**, 247 (1965).
(9) P. S. J. Spencer, *Excerpta Med.*, 194 (1967).
(10) D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *ibid.*, **126**, 223 (1959).
(11) J. W. Bastian, W. E. Krause, S. A. Ridlon, and N. Ercoli, *ibid.*, **127**, 74 (1959).
(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, Vol. 1, p 161, Vol. 2, p 84.
(13) W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955).
(14) A. E. Alper and A. Taurens, *Can. J. Chem.*, **45**, 2903 (1967).

TABLE IV



| No. | R | Salt | % yield | Mp, °C dec[a] | $\nu_{max}$[b] | Formula[c] | Reserpine[d] reversal |
|---|---|---|---|---|---|---|---|
| 7 | $C_6H_5$ | HBr | 91[e] | 149 s, 251–253 | 1685 | | 10.8 |
| | | Base | | | | | |
| 8 | 2-$ClC_6H_4$ | HBr | 80 | 160–165 | 1710 | $C_{11}H_{12}BrClN_2OS$ | 15 |
| 9 | 3-$ClC_6H_4$ | HBr | 86 | 170–171 | 1685 | $C_{11}H_{12}BrClN_2OS$ | 1.2 |
| 10 | 4-$ClC_6H_4$ | HBr | 56 | 272–274 | | | 1.0 |
| 11 | 3,4-$Cl_2C_6H_3$ | HBr | 95 | 253–254 | 1685 | | |
| | | Base | | 156–158 | | $C_{11}H_{10}Cl_2N_2OS$ | 0.5 |
| 12 | 2,4-$Cl_2C_6H_3$ | HBr | 78 | 180 s, 251–252 | | $C_{11}H_{11}BrCl_2N_2OS$ | 5.1 |
| 13 | 2,5-$Cl_2C_6H_3$ | HBr | 77 | 173 s, 253–254 | | $C_{11}H_{11}BrCl_2N_2OS$ | 20 |
| 14 | 4-$BrC_6H_4$ | HBr | 87[e] | 299–302 | 1675 | | 1.0 |
| 15 | 2,4-$F_2C_6H_3$ | HBr | 67 | 242–244 | | $C_{11}H_{11}BrF_2N_2OS$ | 5.0 |
| 16 | 2-$MeC_6H_4$ | HBr | 81 | 178 s, 215 | 1670 | $C_{12}H_{13}BrN_2OS$ | I |
| 17 | 3-$MeC_6H_4$ | HBr | 72 | 158–159 | 1675 | $C_{12}H_{15}BrN_2OS$ | 9.4 |
| 18 | 4-$MeC_6H_4$ | HBr | 89 | 268–270 | 1670 | $C_{12}H_{15}BrN_2OS$ | 8.2 |
| 19 | 2,4-$Me_2C_6H_3$ | HCl | 50[f] | 170–171 | 1680 | | |
| | | Base | | 133–134 | | $C_{13}H_{16}N_2OS$ | *Ca.* 20 |
| 20 | 2,5-$Me_2C_6H_3$ | HBr | 78 | 174 s, 283–284 | 1680 | $C_{13}H_{17}BrN_2OS$ | I |
| 21 | 3,4-$Me_2C_6H_3$ | HBr | 72 | 170 s, 233–234 | 1675 | $C_{13}H_{17}BrN_2OS$ | 4.7 |
| 22 | 2,4,6-$Me_3C_6H_2$ | HBr | 58[f] | 242–243 | 1695 | $C_{14}H_{19}BrN_2OS$ | I |
| 23 | 4-$C_6H_5C_6H_4$ | HBr | 93[e] | 305–306 | 1670 | $C_{17}H_{15}BrN_2OS$ | I |
| 24 | 4-$CNC_6H_4$ | HBr | 78 | 307–308 | 1675 | $C_{12}H_{12}BrN_3OS$ | 3.7 |
| 25 | 4-$NO_2C_6H_4$ | HBr | 96[e] | 285.5–287 | | $C_{11}H_{12}BrN_3O_3S$ | 1.75 |
| | | Base | | 161.5–162 | | | |
| 26 | 2-$HO_2CC_6H_4$ | HBr | 60[f] | 300–301 | (1750) | $C_{12}H_{13}BrN_2O_3S$ | I |
| 27 | 4-$NH_2C_6H_4$ | HCl | 43[f] | 178 s, 247–249 | 1665 | $C_{11}H_{14}ClN_3OS$ | 3.6 |
| 28 | 3-$MeOC_6H_4$ | HBr | 85 | 214–215 | 1685 | $C_{12}H_{15}BrN_2SO_2$ | *Ca.* 29 |
| 29 | 4-$MeOC_6H_4$ | HBr | 80 | 242–243 | 1665 | $C_{12}H_{15}BrN_2SO_2$ | 7.4 |
| 30 | 3,4-$CH_2O_2C_6H_3$ | HBr | 78 | 255–256 | 1665 | | 3.7 |
| | | Base | | 155–156 | | $C_{12}H_{12}N_2O_3S$ | |
| 31 | 2-$HOC_6H_4$ | HBr | 89 | 248–249 | 1635 | $C_{11}H_{13}BrN_2O_2S$ | I |
| 32 | 3-$HOC_6H_4$ | HBr | 60 | 262–264 | 1675 | $C_{11}H_{13}BrN_2O_2S$ | I |
| 33 | 4-$HOC_6H_4$ | HBr | 68 | 312–315 | 1650 | $C_{11}H_{13}BrN_2O_2S$ | I |
| 34 | 2-HO-4-$MeOC_6H_3$ | HBr | 77 | 195 | 1625 | $C_{12}H_{15}BrN_2O_3S$ | 28 |
| 35 | 3-HO-4-$MeOC_6H_3$ | HBr | 76 | 257–258 | 1675 | $C_{12}H_{15}BrN_2O_3S$ | I |
| 36 | 4-HO-3-$MeOC_6H_3$ | HBr | 70 | 218–219 | 1665 | $C_{12}H_{15}BrN_2O_3S$ | I |
| 37 | 4-HO-3-$ClC_6H_3$ | HBr | 74 | 167 s, 222–223 | 1665 | $C_{11}H_{12}BrClN_2O_2S$ | I |
| 38 | 4-HO-3-$MeC_6H_3$ | HBr | 62 | 165 s, 217–218 | 1655 | $C_{12}H_{15}BrN_2O_2S$ | *Ca.* 25 |
| 39 | 1-Adamantyl | HBr | 69 | 323–324 | | $C_{15}H_{23}BrN_2OS$ | I |
| 40 | α-Naphthyl | HBr | 75 | 180 s, 267–269 | 1665 | $C_{15}H_{15}BrN_2OS$ | 18 |
| 41 | β-Naphthyl | HBr | 91 | 246–248 | 1680 | $C_{15}H_{15}BrN_2OS$ | 2.5 |
| 42 | 2-Furyl | HBr | 70 | 236–237 | 1665 | $C_9H_{11}BrN_2O_2S$ | I |
| 43 | 2-Thienyl | HBr | 67 | 241–243 | 1640 | $C_9H_{11}BrN_2OS_2$ | I |
| 44 | 2-Pyridyl | HBr | 38[g] | 165 s, 225–228 | 1675 | $C_{10}H_{12}BrN_3OS$ | I |
| 45 | 3-Pyridyl | HBr | 49[g] | 145–147 | | $C_{10}H_{12}BrN_3OS$ | I |
| 46 | 4-Pyridyl | HBr | 28[g] | 157–158 | | $C_{10}H_{12}BrN_3OS$ | 7.2 |
| 47 | 2-Benzothiazolyl | HBr | 72 | 305–307 | | $C_{12}H_{12}BrN_3OS_2$ | I |
|  | | | | | | | 5 |
| | Imipramine | | | | | | 6.2 |
| | Amphetamine | | | | | | 0.6 |
| | Nortriptyline | | | | | | 2.0 |

[a–d] See footnotes *a–d*, Table III. [e] See ref 3. [f] Reaction time 16 hr. [g] See details in Experimental Section.

## Experimental Section

Nmr spectra were recorded on a Varian A60 instrument in DMSO-$d_4$ ($Me_4Si$). The per cent of ketone tautomer (Ia) in the 2-phenacylthioimidazolinium bromides was detd by comparison of the integral of the singlet due to the $CH_2$ group in the ketonic form with the total integral of the arom protons.

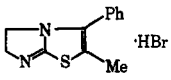
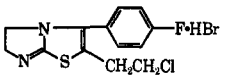
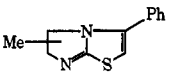
2-Phenacylthioimidazoline and 3-phenyl-5,6-dihydroimidazo-[2,1-*b*]thiazole free bases could be differentiated by tlc (silica, MeOH), $R_f$ values *ca.* 0.8 and 0.4, resp.

**Bromomethyl ketones** (Table II) were prepd[15] by the action of $CuBr_2$ on the appropriate ketone, and traces of inorg material were removed from the product by filtering an $Et_2O$ soln (or for 3,4-methylenedioxyacetophenone, an EtOAc soln).

**2-Phenacylthioimidazolines and Related Compounds (Tables III and IV).**—The halomethyl ketone (0.01 mole) in $Me_2CO$ (25 ml) was added to a soln of 2-mercaptoimidazoline (0.01 mole) in $Me_2CO$ (150 ml). After 30 min (or the time shown in Table

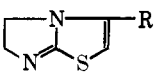
(15) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 2025 (1964).

TABLE V

| No. | Structure | % yield | Mp, °C dec | Formula[e] | Reserpine reversal[f] |
|---|---|---|---|---|---|
| 48 |  | 77[a] | 238–240 | $C_{12}H_{13}BrN_2S$ | 10.1 |
| 49 |  | 66[b,c] | 222–223 | | 11.2 |
| 50 |  | 80[d] | 192–193 | $C_{12}H_{13}BrN_2S$ | I |

[a] W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955). [b] See ref 2. [c] Prepd by lit. method. [d] *i*-PrOH used as solvent. [e,f] See footnotes *c* and *d*, Table IV.

TABLE VI



| No. | R | Salt | Yield, % | Mp, °C | Recrystn Solvent | Formula[f] | Reserpine reversal[g] |
|---|---|---|---|---|---|---|---|
| 51 | $C_6H_5$ | HBr | 89[a,b] | 251–253 dec | | | 16 |
| | | Base | | 112–113 | $C_6H_6$–petr ether | | |
| 52 | 2-$ClC_6H_4$ | HBr | 45 | 178–180 dec | | $C_{11}H_{10}BrClN_2S$ | 5.0 |
| 53 | 3-$ClC_6H_4$ | HBr | 54[c] | 198.5–199 dec | | $C_{11}H_{10}BrClN_2S$ | 3.2 |
| | | Base | | 148–149 | $C_6H_6$–petr ether | $C_{11}H_9ClN_2S$ | |
| 54 | 4-$ClC_6H_4$ | HBr | 87[a] | 276–279 dec | | | 1.5 |
| 55 | 3,4-$Cl_2C_6H_3$ | HBr | 69 | 251–253 dec | | | |
| | | Base | | 146–147 | Aq EtOH | $C_{11}H_8Cl_2N_2S$ | 2.0 |
| 56 | 2,4-$Cl_2C_6H_3$ | Base | 60[d] | 152–153 | Petr ether (100–120°) | $C_{11}H_8Cl_2N_2S$ | 2.9 |
| 57 | 2,5-$Cl_2C_6H_3$ | Base | 80[d] | 126–127 | Petr ether (100–120°) | $C_{11}H_8Cl_2N_2S$ | 1.9 |
| 58 | 4-$BrC_6H_4$ | HBr | 89[a] | 301–303 dec | | | 1.6 |
| 59 | 2,4-$F_2C_6H_3$ | HBr | 40 | 242–243 dec | EtOH | $C_{11}H_9BrF_2N_2S$ | I |
| 60 | 2-$MeC_6H_4$ | HBr | 59[e] | 216 dec | | $C_{12}H_{13}BrN_2S$ | 5.8 |
| 61 | 3-$MeC_6H_4$ | Base | 52[d] | 119–120 | Petr ether (100–120°) | $C_{12}H_{12}N_2S$ | 7.2 |
| 62 | 4-$MeC_6H_4$ | HBr | 94 | 270–272 dec | | $C_{12}H_{13}BrN_2S$ | 6.8 |
| 63 | 2,4-$Me_2C_6H_3$ | HCl | 75[e] | 211–212 dec | | $C_{13}H_{15}ClN_2S$ | 4.5 |
| 64 | 3,4-$Me_2C_6H_3$ | HBr | 62 | 232–233 dec | | $C_{13}H_{15}BrN_2S$ | 4.5 |
| 65 | 4-$C_5H_5C_6H_4$ | HBr | 87 | 323–324 dec | | $C_{17}H_{15}BrN_2S$ | 9 |
| 66 | 4-$CNC_6H_4$ | Base | 70[d] | 183–185 | $C_6H_6$–petr ether | $C_{12}H_9N_3S$ | 4 |
| 67 | 4-$HO_2CC_6H_4$ | HBr | 82[e] | 300–301 dec | | $C_{12}H_{11}BrN_2O_2S$ | I |
| 68 | 4-$NH_2C_6H_4$ | HCl | 50[h] | 254–256 dec | | $C_{11}H_{12}ClN_3S$ | 2.5 |
| 69 | 2-$MeOC_6H_4$ | HBr | 76[i] | 202–203 dec | | $C_{12}H_{13}BrN_2OS$ | 6.8 |
| 70 | 3-$MeOC_6H_4$ | HBr | 67 | 215.5–216.5 dec | | $C_{12}H_{13}BrN_2OS$ | 12.5 |
| 71 | 4 $MeOC_6H_4$ | HBr | 86[i] | 272–273 dec | | $C_{12}H_{13}BrN_2OS$ | 7.2 |
| 72 | 3,4-$CH_2O_2C_6H_3$ | HBr | 40[h] | 259–260 dec | $H_2O$ | $C_{12}H_{11}BrN_2O_2S$ | 6.4 |
| 73 | 2-$HOC_6H_4$ | HBr | 88 | 250–251 dec | | $C_{11}H_{11}BrN_2OS$ | 17 |
| 74 | 3-$HOC_6H_4$ | HBr | 57 | 259–262 dec | | $C_{11}H_{11}BrN_2OS$ | *Ca.* 25 |
| 75 | 4-$HOC_6H_4$ | HBr | 76[i] | 311–313 dec | | $C_{11}H_{11}BrN_2OS$ | 15 |
| 76 | 3,4-$(HO)_2C_6H_3$ | HCl | 94[i] | 251–252 dec | | $C_{11}H_{11}ClN_2O_2S$ | I |
| 77 | 2-HO-4-$MeOC_6H_3$ | HBr | 23[h] | 197–198 dec | | $C_{12}H_{13}BrN_2O_2S$ | I |
| 78 | 3-HO-4-$MeOC_6H_3$ | HBr | 70 | 255–256 dec | | $C_{12}H_{13}BrN_2O_2S$ | *Ca.* 12.5 |
| 79 | 4-HO-3-$MeOC_6H_3$ | HBr | 70 | 224–226 dec | | $C_{12}H_{13}BrN_2O_2S$ | *Ca.* 25 |
| 80 | 4-HO-3-$ClC_6H_3$ | HBr | 66 | 226–227 dec | | $C_{11}H_{10}BrClN_2OS$ | *Ca.* 25 |
| 81 | 4-HO-3-$MeC_6H_3$ | HBr | 65 | 217–218 dec | | $C_{12}H_{13}BrN_2OS$ | 23.5 |
| 82 | 1-Adamantyl | HBr | 84 | 312–314 dec | | $C_{15}H_{21}BrN_2S$ | I |
| 83 | α-Naphthyl | HBr | 27[h] | 282–284 dec | EtOH | $C_{15}H_{13}BrN_2S$ | 2.4 |
| 84 | β-Naphthyl | HBr | 75[h] | 242–248 dec | | $C_{15}H_{13}BrN_2S$ | 4.6 |
| 85 | 2-Furyl | HBr | 58[c] | 239–240 dec | EtOH | $C_9H_9BrN_2OS$ | 26 |
| 86 | 2-Thienyl | HBr | 59[h] | 243–244 dec | EtOH | $C_9H_9BrN_2S_2$ | 15 |
| 87 | 2-Pyridyl | HBr | 60[d] | 222–225 dec | EtOH | $C_{10}H_{10}BrN_3S$ | 13.5 |
| 88 | 3-Pyridyl | HBr | 60[d] | 223 dec | EtOH | $C_{10}H_{10}BrN_3S$ | 23 |
| 89 | 4-**P**yridyl | 2HBr | 20[k] | 310–312 dec | EtOH–$H_2O$ (2:1) | $C_{10}H_{11}Br_2N_3S$ | 14 |

[a] See ref 3. [b] See footnote *a*, Table V. [c] Heat under reflux 12 hr. [d] Dehydrated by heating in AcOH (method b). [e] Heat under reflux 6 hr. [f,g] See footnotes *c* and *d*, Table IV. [h] Heat under reflux 4 hr. [i] Prepd by treating 2-methoxyphenylacyl bromide in $Me_2CO$ with 2-mercaptoimidazoline and heating the product in *i*-PrOH for 2 hr. [j] Hydrochloride described by C. P. Krimmel, U. S. Patent 2,969,369 (1961). [k] See details in Experimental Section.

III or IV) the salt was collected and washed with $Me_2CO$. Some salts which gave incorrect analyses were dissolved in $H_2O$ (*ca.* 150 ml/g) and treated with dil $NH_4OH$ to pH 7 to ppt the base.

**2-Imidazolylthiomethyl 2-Pyridyl Ketone·HBr.**—2-(ω-Bromoacetyl)pyridine·HBr, prepd from 2-acetylpyridine (0.02 mole),[16] was treated with $NaHCO_3$ soln. An $Et_2O$ ext of the base was washed ($H_2O$), dried ($MgSO_4$), and added to a soln of 2-mercaptoimidazoline (0.02 mole) in $Me_2CO$ (300 ml). The $Et_2O$ was evapd and the product filtered off (Table IV).

The corresponding 3- and 4-pyridyl ketones were obtained similarly starting with hydrobromides of 3-bromoacetylpyridine[17] and 4-bromoacetylpyridine.[18]

**3-Substituted-5,6-dihydroimidazo[2,1-*b*]thiazoles (Tables V and VI). a.**—The halomethyl ketone (0.01 mole), 2-mercaptoimidazoline (0.01 mole), and EtOH (10 ml) were heated under reflux for 2 hr. Usually a ppt formed rapidly than gradually dissolved and the hydrohalide crystd on cooling (variations to this procedure are indicated in Tables V and VI).

**b.**—The intermediate 2-phenacylthioimidazolinium salt or related compd (0.01 mole) and AcOH (10 ml) were heated under reflux for 16 hr and the soln was evapd. The salt was either recrystd or treated with aq $NaHCO_3$, and the base was extd with EtOAc. The EtOAc was washed ($H_2O$), dried ($MgSO_4$), and evapd, and the residue was recrystd.

**3-(4-Pyridyl)-5,6-dihydroimidazo[2,1-*b*]thiazole·2HBr.**—2-Imidazolylthiomethyl 4-pyridyl ketone·HBr and a mixt of AcOH and 48% HBr (1:1) were heated under reflux for 4 hr. The soln was evapd and the residue was recrystd.

***N*-Acetyl-2-phenacylthioimidazoline.**—2-Phenacylthioimidazoline (0.6 g), THF (10 ml), and $Ac_2O$ (0.3 ml) were stirred 16 hr. The soln was evapd and the residue was partitioned between aq $NaHCO_3$ and EtOAc (*ca.* 150 ml). The EtOAc was washed ($H_2O$), dried ($MgSO_4$), and cond to give 0.45 g, mp 149.0–149.5°, $\nu_{max}$ 1670 $cm^{-1}$. *Anal.* ($C_{13}H_{14}N_2O_2S$) C, H, N.

**2-(3,4-Dichlorophenoxymethyl)imidazolinium Chloride.**—Treatment of 3,4-dichlorophenol with chloracetonitrile[19] and purification of the crude product by chromatog on alumina with $C_6H_6$ gave 73% 3,4-dichlorophenoxyacetonitrile, mp 63–64° (petr ether, 80–100°). *Anal.* ($C_8H_6Cl_2NO$) C, H, N. Treatment of the product with ethylenediamine tosylate by the general method[19] gave the imidazoline, isolated as the hydrochloride *in 45% yield*, mp 243–244° (*i*-PrOH). *Anal.* ($C_9H_{11}Cl_2N_2O$) C, H, N.

(16) G. R. Clemo, W. McG. Morgand, and R. Raper, *J. Chem. Soc.*, 965 (1937).

(17) H. McKennis, Jr., L. B. Turnbull, E. R. Bowman, and E. Tamaki, *J. Org. Chem.*, **28**, 383 (1963).

(18) L. Polo Friz, *Farmaco Ed. Sci.*, **18**, 972 (1963).

(19) W. B. Neely, H. C. White, and A. Rudzik, *J. Pharm. Sci.*, **57**, 1176 (1968).

# Chemistry and Pharmacology of 5-Methylene-4-substituted Dibenzo[*a*,*d*]cycloheptenes

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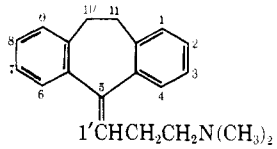
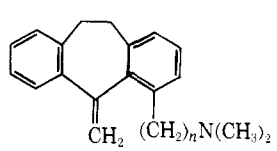
Methods are described, utilizing the Hofmann degradation of *N*,*N*-dimethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-*d*,*e*]isoquinolinium hydroxide, which allow the synthesis of 5-methylene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes bearing basic side chains, of varying lengths, at the 4 position. The lack of antidepressant activity in these compds shows that the presence of a $C_5$–$C_{1'}$ trigonal center, and of a basic side chain attached to the 4 position are insufficient for retention of amitriptyline-like activity.

This work stems from our wish to examine the hypothesis that the $C_5$–$C_1'$ trigonal center, and the basic center of the antidepressant amitriptyline, **1**, need not be joined through a 2-C alkylene chain. More particularly, in molecules of type **2**, in which the basic center is attached to position 4 of the dibenzo[*a*,*d*]-cycloheptene nucleus through alkylene chains of various lengths from $n = 1$ to $n = 3$, examination of molecular models shows that conformations exist in which the positions that can be assumed by the basic center relative to the nucleus, can, in turn, coincide with virtually all of those which are permissible for amitriptyline. These features of the molecules of type **2**, along with the retention of an exocyclic double bond at C-5, make them attractive candidates for pharmacological investigation.




1




2

Chemical methods have thus been developed allowing the syntheses of the compds **2** with $n = 1, 2, 3$. Intermediates available have permitted the preparation of desmethyl, and of 5,1′-dihydro derivatives, and compounds of these types have also been made for pharmacological examination.

**Chemistry.**—Recent work from this laboratory[1] has made available *N*-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-*d*,*e*]isoquinoline, **3**. The corresponding methohydroxide **4b**, prepared from the methiodide **4a** by ion-exchange chromatog, undergoes an extraordinarily facile Hofmann degradation in high yield to afford the 5-methylene-4-methyldimethylamine (**5**), one of the desired final products.

The Gadamer–Knoch[2] modification of the von Braun degradation, using ethyl chloroformate instead of BrCN, when applied to **5** proceeds with exclusive cleavage between the N and the benzylic C to give the benzyl chloride **6**. This key intermediate, **6**, has been transformed by conventional series of reactions into desired final products **7** (**14**, **15**), **8** (**17**, **18**, **19**), **9**, **10** (**14**, **15**, **16**), and **11**. The required 5,1′-dihydro derivative **12** was obtained by reduction of **5**, in high yield

(1) L. G. Humber, M. A. Davis, R. A. Thomas, R. Otson, and J. R. Watson, *J. Heterocycl. Chem.*, **3**, 247 (1966).

(2) J. Gadamer and F. Knoch, *Arch. Pharm. (Weinheim)*, **259**, 135 (1921).