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# THE PHARMACOLOGY OF SOME BASIC KETONES AND RELATED COMPOUNDS

BY

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Five series of compounds are included in this study :

*Series I.*—$\beta$-dialkylaminoketones (Mannich bases).

*Series II.*—Bispidines (bi-cyclic $\beta$-aminoketones).

*Series III.*—$\gamma$-dialkylaminoketones.

*Series IV.*—$\gamma$-dialkylaminobutyramidines.

*Series V.*—2-($\gamma$-dialkylaminopropyl) dihydroglyoxalines.

The chemistry of Series I will be described by Wilson and Kyi (in preparation) ; that of Series II has been described by Kyi and Wilson (1951) ; and that of Series IV and V by Wilson (1950). The chemical structures of the compounds are given in Table I, and henceforth in the text compounds are referred to by the serial numbers assigned to them in this Table. Quaternary salts (methiodides) of compounds 1 and 9 were also included in the studies.

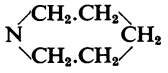
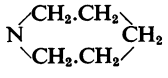
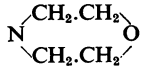
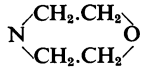
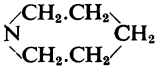
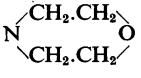
Most of the compounds were supplied as crystalline hydrochlorides. Compounds which would not form crystallizable salts were supplied as bases, and were dissolved in equivalent quantities of hydrochloric acid as required. Two compounds (23 and 24) were supplied as salts of toluene-*p*-sulphonic acid. The compounds, as salts, were sufficiently soluble in water for most of the pharmacological tests, though a few were not soluble enough for local anaesthetic tests. Compound 15 was completely insoluble and therefore could not be included in any of the tests.

## METHODS

*Spasmolytic* action was determined on isolated guinea-pig ileum suspended in oxygenated Tyrode's solution in a 2.5 ml. bath, movements of the gut being recorded on smoked paper by a frontal writing lever. Submaximal muscle contractions were produced by histamine, acetylcholine, potassium chloride, and barium chloride. The spasmogen was added to the bath every 2 min., and doses of the compounds half a minute before the spasmogen. After each spasmolytic effect, doses of spasmogen alone were continued at 2-min. intervals until the response returned to the original level. Since the method of Schild (1947) was found to be impracticable for measuring inhibition of potassium or barium contractions, all spasmolytic activities were measured as the amount of compound which produced a 50 per cent inhibition of the contraction induced by the spasmogen.

TABLE I

CLASSIFICATION OF COMPOUNDS

| Series and general formula | Serial No. | R | $NR'_2$ |
|---|---|---|---|
| SERIES I | 1 | $CH_3$ | $N(CH_3)_2$ |
| β-dialkylaminoketones | 2 | $CH_3$ | $N(C_2H_5)_2$ |
| (Mannich bases) | 3 | $C_6H_5CH_2$ | $N(CH_3)_2$ |
| | 4 | $C_6H_5CH_2$ | $N(C_2H_5)_2$ |
| $R.CO.CH(C_6H_5).CH_2NR'_2$ | 5 | $CH_3$ |  |
| (all hydrochlorides) | 6 | $C_6H_5CH_2$ |  |
| | 7 | $CH_3$ |  |
| | 8 | $C_6H_5CH_2$ |  |
| | | | $NR_2$ |
| | 9 | | $N(CH_3)_2$ |
| | 10 | | $N(C_2H_5)_2$ |
| $(C_6H_5)_2CH.CO.CH_2CH_2NR_2$ | 11 | |  |
| (all hydrochlorides) | 12 | |  |

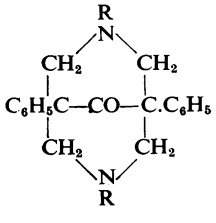
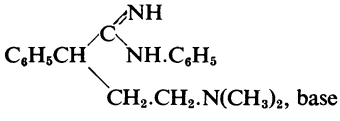
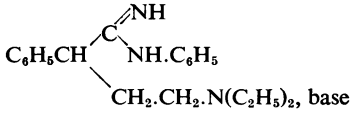
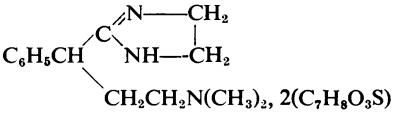
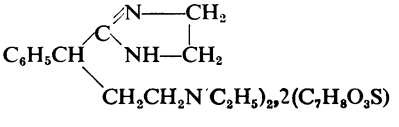
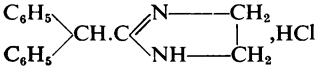
| SERIES II Bispidines (bi-cyclic β-aminoketones) | | R | Salt |
|---|---|---|---|
|  | 13 | H | HCl |
| | 14 | $CH_3$ | 2HCl |
| | 15 | $C_6H_5CH_2$ | HCl |
| | 16 | $CH_2CH_2OH$ | HCl, $H_2O$ |
| | 17 | $CH_2CH_2Cl$ | 2HCl |

TABLE I—*cont.*

| Series and general formula | Serial No. | R | R′ | Salt |
|---|---|---|---|---|
| SERIES III | | | | |
| γ-dialkylaminoketones | 18 | $CH_3$ | $CH_3$ | base |
| $R.CO.CH(C_6H_5).CH_2CH_2NR'_2$ | 19 | $C_6H_5CH_2$ | $CH_3$ | HCl |
| | 20 | $C_6H_5CH(CH_2CH_2N(CH_3)_2)$ | $CH_3$ | 2HCl |
| SERIES IV | | | | |
| γ-dialkylaminobutyramidines | 21 |  | | |
| | 22 |  | | |
| SERIES V | | | | |
| 2-(γ-dialkylaminopropyl) dihydroglyoxalines | 23 |  | | |
| | 24 |  | | |
| | 25 |  | | |

*Analgesic* action was determined in mice subjected to a painful stimulus of constant magnitude applied to the tail by an electrically heated wire. The apparatus and method were similar to those described for rats by Davies, Raventos, and Walpole (1946). The maximum reaction time allowed was 15 sec., in order to avoid burning the tail. Compounds were administered by subcutaneous injection, and the mice tested for analgesia 20 min. after dosing.

*Local anaesthetic* potency was measured by the intracutaneous weal method of Bülbring and Wajda (1945) on guinea-pigs. *Surface anaesthesia* was assessed on the

guinea-pig cornea by a method similar to that of Chance and Lobstein (1944). Two drops of solution were instilled into the eye, and the blink responses to ten stimuli of the cornea by a horse hair were recorded at intervals up to 30 min.

*Anti-adrenaline* action was measured as the degree of protection of mice to a lethal dose of adrenaline. The method was similar to that described by Loew and Micetich (1948). A dose of adrenaline hydrochloride, which would produce a high mortality, was given intraperitoneally to groups of ten mice 30 min. after intraperitoneal injection of the compound under test. The reduction in percentage mortality was recorded.

*Neuromuscular blocking* action was measured on the isolated rat phrenic nerve-diaphragm preparation by the method of Bülbring (1946).

General systemic effects of the compounds on blood pressure, spleen volume, and respiration were observed after intravenous injection into cats anaesthetized with chloralose (80 mg. per kg. body weight). Blood pressure was recorded from the carotid artery by mercury manometer and float, spleen volume by plethysmograph and piston recorder, and respiration by recording movements of the abdomen by thread and pulley system.

## RESULTS

*Spasmolytic action.*—All the compounds inhibited contractions of the isolated guinea-pig ileum induced by histamine, acetylcholine, potassium, or barium. Table II shows the relative spasmolytic potencies against these spasmogens. Two compounds (9 and 10) showed fairly high activity, which was not, however, specific for any one spasmogen. It was therefore concluded that the compounds were general spasmolytics, and did not possess any specific antihistamine or atropine-like actions. Quaternization of compound 9 reduced its activity against all spasmogens except acetylcholine, thus introducing some degree of specific anti-acetylcholine effect.

*Analgesic action.*—None of the compounds showed any analgesic action when injected subcutaneously into mice.

*Local anaesthesia.*—Local anaesthetic action was well marked in many of the compounds (Table III). When tested by the intracutaneous method in guinea-pigs, ten compounds showed activity greater than that of procaine, and two compounds (6 and 9) were about half as active as cinchocaine.

The more active compounds were tested for surface anaesthetic action on the guinea-pig cornea. In preliminary tests, compounds 4, 9, 19, 21, and 22 were found to have only low activity. Compound 6 was more active, and was tested more fully in comparison with cinchocaine. The median effective concentration for compound 6 was 0.34 per cent, that for cinchocaine 0.04 per cent. This compound had therefore about one-eighth the surface anaesthetic action of cinchocaine.

*Anti-adrenaline action.*—It was thought that the chloro-compound 17 might, like dibenamine, antagonize the effects of adrenaline. In protection tests against lethal doses of adrenaline in mice, this compound showed some action, of the order of 1/16th the potency of dibenamine (Table IV). This activity was absent in compound 16, in which there was no chloro-substitution.

*Neuromuscular blocking action.*—None of the compounds showed any depressant action on the rat diaphragm preparation. The quaternized derivatives of 1 and 9 showed no activity themselves, but there was slight potentiation of the action of *d*-tubocurarine by these compounds.

TABLE II

SPASMOLYTIC ACTION

Isolated guinea-pig ileum in 2.5 ml. bath. Contractions produced by histamine (0.1 μg.), acetylcholine (0.1 μg.), potassium chloride (2 mg.), barium chloride (1 mg.)

| Compound | μg. required for 50% inhibition of spasms produced by | | | |
|---|---|---|---|---|
| | histamine | acetylcholine | potassium | barium |
| *Series I* | | | | |
| 1 | >200 | >200 | >200 | >200 |
| 1 MeI | >200 | >200 | >200 | >200 |
| 2 | 20 | 25 | 9 | 50 |
| 3 | 70 | >200 | 25 | 50 |
| 4 | 45 | 50 | 25 | 9 |
| 5 | 100 | 130 | 50 | >200 |
| 6 | 70 | 50 | 9 | 25 |
| 7 | 15 | >200 | >200 | >200 |
| 8 | 30 | >200 | 75 | 50 |
| 9 | 7.5 | 2.5 | 12 | 6 |
| 9 MeI | 80 | 2.0 | 50 | 50 |
| 10 | 5 | 1.5 | 9 | 18 |
| 11 | 2.0 | 2.5 | 18 | 20 |
| 12 | 15 | 30 | 75 | 100 |
| *Series II* | | | | |
| 13 | 40 | 45 | >200 | >200 |
| 14 | 40 | 80 | 20 | 50 |
| 15 | insol. | insol. | insol. | insol. |
| 16 | 40 | 50 | 150 | 75 |
| 17 | 75 | 90 | >200 | >200 |
| *Series III* | | | | |
| 18 | 20 | 50 | 75 | >200 |
| 19 | 40 | 80 | 8 | 12 |
| 20 | 40 | 70 | 10 | 20 |
| *Series IV* | | | | |
| 21 | 20 | 15 | 10 | 50 |
| 22 | 50 | 10 | 10 | 18 |
| *Series V* | | | | |
| 23 | 10 | 100 | >200 | >200 |
| 24 | 100 | 50 | >200 | >200 |
| 25 | 100 | 75 | 20 | 40 |
| Anthisan | 0.03 | 25 | 12 | 18 |
| Atropine | 5 | 0.0004 | >200 | >200 |
| Trasentin | 5 | 0.004 | 18 | 22 |

*General systemic effects.*—Representative compounds from each series were tested by intravenous injection into cats under chloralose anaesthesia. Compounds of Series I, represented by numbers 1, 4, and 9, produced a transient fall in blood pressure, which increased in magnitude with increasing complexity of the derivatives. They produced contraction of the spleen, in this case more marked in the less complex compounds. Since spleen and blood pressure effects were not proportionate, some of the splenic contraction was probably due to direct rather than reflex action. Respiration was unaffected except for very slight depression and slowing at the

TABLE III

LOCAL ANAESTHETIC ACTION

Guinea-pig intracutaneous weal

| Compound | Median effective dose (mg.) | Activity compared with | |
|---|---|---|---|
| | | Procaine = 1.0 | Cinchocaine = 1.0 |
| *Series I* | | | |
| 1 | 2.40 | 0.30 | 0.03 |
| 1 MeI | >2.50 | <0.29 | <0.03 |
| 2 | 7.94 | 0.09 | 0.01 |
| 3 | 0.45 | 1.60 | 0.17 |
| 4 | 0.22 | 3.28 | 0.35 |
| 5 | 2.80 | 0.26 | 0.03 |
| 6 | 0.14 | 5.15 | 0.54 |
| 7 | >5.00 | <0.14 | <0.02 |
| 8 | >1.00 | <0.72 | <0.08 |
| 9 | 0.16 | 4.50 | 0.48 |
| 9 MeI | insol. | — | — |
| 10 | 0.60 | 1.20 | 0.13 |
| 11 | 2.50 | 0.29 | 0.03 |
| 12 | 2.00 | 0.36 | 0.04 |
| *Series II* | | | |
| 13 | insol. | — | — |
| 14 | 0.58 | 1.24 | 0.13 |
| 15 | insol. | — | — |
| 16 | 0.60 | 1.20 | 0.13 |
| 17 | 5.75 | 0.13 | 0.01 |
| *Series III* | | | |
| 18 | >2.50 | <0.29 | <0.03 |
| 19 | 0.19 | 3.88 | 0.41 |
| 20 | 0.89 | 0.81 | 0.09 |
| *Series IV* | | | |
| 21 | 0.33 | 2.18 | 0.23 |
| 22 | 0.27 | 2.66 | 0.28 |
| *Series V* | | | |
| 23 | >2.50 | <0.29 | <0.03 |
| 24 | >5.00 | <0.14 | <0.02 |
| 25 | 1.25 | 0.58 | 0.06 |
| Procaine | 0.72 | 1.00 | 0.11 |
| Cinchocaine | 0.08 | 9.50 | 1.00 |

moment of injection. Compounds 19 and 21 produced transient fall in blood pressure with very slight dilatation of the spleen. Compounds 23 and 25 had little effect on blood pressure, but produced marked dilatation of the spleen. Again, respiratory effects were insignificant.

Fig. 1 shows the effects of similar doses of the local anaesthetic compound 6 and cinchocaine. A dose of 2 mg. compound 6 produced only transient effects on blood pressure, spleen, and respiration, whereas a similar dose of cinchocaine produced complete collapse from which the animal failed to recover, even after artificial respiration and intravenous adrenaline. The primary effect appeared to be respiratory paralysis, and was accompanied by a severe fall in blood pressure.

TABLE IV

ANTI-ADRENALINE ACTION

Protection of mice against lethal doses of adrenaline. Compounds given (i.p.) 30 min. before adrenaline (i.p.)

| Adrenaline mg./20 g. | Compound | Dose mg./20 g. | Mortality |
|---|---|---|---|
| *1st Test* | | | |
| 0.2 | — | — | 9/10 |
| 0.2 | 17 | 1.0* | 4/10 |
| 0.2 | 17 | 2.0* | 1/10 |
| — | 16 | 2.0 | 10/10 |
| 0.2 | dibenamine | 0.5 | 0/10 |
| 0.2 | dibenamine | 1.0 | 0/10 |
| *2nd Test* | | | |
| 0.4 | — | — | 5/10 |
| 0.4 | 16 | 1.0 | 4/10 |
| 0.4 | 16 | 0.5 | 6/10 |
| 0.4 | dibenamine | 0.125 | 1/10 |

* In suspension.

## DISCUSSION

The compounds described in this paper were synthesized with the object of extending the field of possible analgesic drugs. It was therefore disappointing that none of the compounds showed any analgesic activity.

Spasmolytic activity was shown by nearly all the compounds. There was little differentiation between the degrees of inhibition of acetylcholine, histamine, and the "direct" acting spasmogens, as compared with that shown by atropine or anthisan, in which highly specific inhibition of acetylcholine and histamine, respectively, is clearly seen (Table II). Spasmolytic action in the compounds studied was more akin to that of trasentin, though even in this drug, usually regarded as a general spasmolytic, a high degree of specificity for acetylcholine is apparent. It may be concluded, then, that the compounds show spasmolytic activity, which is definitely of the non-specific general type.

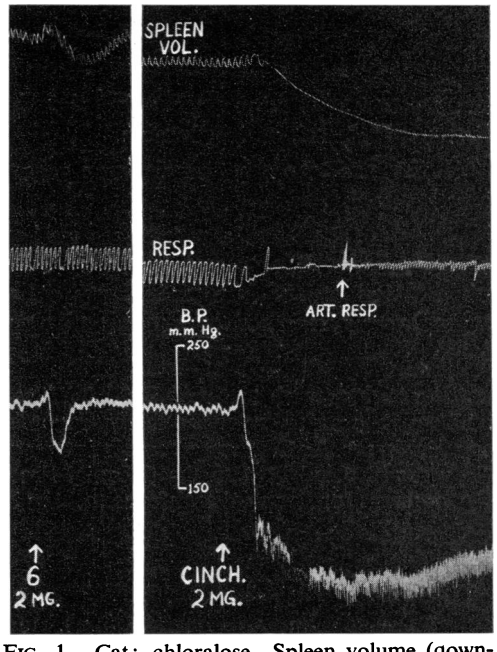



FIG. 1.—Cat; chloralose. Spleen volume (downstrokes = contraction); respiration (downstrokes = inspiration); blood pressure. Comparison of effects of compound 6 and cinchocaine; 2 mg. of each, intravenously.

The most interesting property shown by these compounds is local anaesthetic activity. Ten compounds were more active than procaine and two were about half as active as cinchocaine, when injected intracutaneously. Surface anaesthesia, tested on the guinea-pig cornea, was less marked, compound 6 being about one-eighth as active as cinchocaine in this respect. This compound was much less toxic than cinchocaine when injected intravenously into cats.

An interesting observation on local anaesthetic activity in these compounds is the marked increase in potency produced by substituting a phenyl group on the ketone side-chain. This effect is seen between pairs of compounds 1 and 3, 2 and 4, 5 and 6, and 18 and 19, where the phenyl substitution increases local anaesthetic potency by as much as thirtyfold. In compounds 9 to 12, where two phenyl groups are substituted in this terminal position, local anaesthetic activity is increased only in the compounds with relatively simple substitution in the amino-group. This suggests that local anaesthetic activity may be related to an optimum "balance" between the aromatic and basic groupings at either end of the molecule.

The high local anaesthetic activity of these compounds justifies more detailed investigation, results of which will be published subsequently.

## SUMMARY

1. Twenty-five basic ketones and related compounds have been tested pharmacologically.

2. The compounds showed no analgesic or neuromuscular blocking actions, and no very marked action on blood pressure, spleen volume, or respiration.

3. One compound, containing a $\beta$-chloroethyl group attached to nitrogen, had some protective action against lethal doses of adrenaline in mice. Its potency was about 1/16th that of dibenamine.

4. Most of the compounds were spasmolytics, having non-specific, direct action on plain muscle.

5. Local anaesthetic action was well marked in many of the compounds. Ten compounds were more active than procaine, two were half as active as cinchocaine, when tested by the intracutaneous weal method. Surface anaesthesia (guinea-pig cornea) was less marked, the most active compound being 1/16th as active as cinchocaine.

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