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Note

The Influence of Heterocyclic Ring Size of Tertiary 2,2-Diphenyl-4-amino-butyramides on Parasympatholytic Activity

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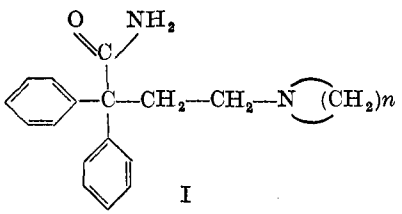
Introduction

It has previously been shown that the tertiary base 2,2-diphenyl-4-piperidino-butyramide (R 14: I, $n=5$) is about twice as active as an atropine-like compound as the pyrrolidine derivative R 13 (I, $n=4$).[1-5]



I

Continuing our experimental programme in this field we found that further expansion of the heterocyclic ring in I leads to maximal atropine-like activity when $n=6$ (R 658, 2,2-diphenyl-4-hexamethyleniminobutyramide). Cyclic bases of type I with more than 6 methylene groups in the ring ($n>6$) become progressively less active.

In an effort to correlate chemical, physical and pharmacological properties, four crystalline bases of type I [$n=4$ (R 13), 5 (R 14), 6 (R 658), 7 (R 937)] were studied in detail.

Methods and Results

Preparation of the Compounds

The compounds with the exception of I, $n=6$, have been described elsewhere[1-5]; the synthesis of this compound (R 658) is described below.

2, 2-*diphenyl*-4-*hexamethyleneiminobutyramide*.—A solution of 33 g of diphenylacetonitrile in 80 ml of benzene was slowly added with stirring to a suspension of 7 g of sodamide in 100 ml of benzene at 30 to 35°. The mixture was then refluxed for 45 min, cooled, 28 g of hexamethyleneiminoethyl chloride in 40 ml of xylene added dropwise and then the mixture refluxed for 3 hours. After cooling, the solution was washed with water and the base extracted with dilute hydrochloric acid. The base was liberated with sodium hydroxide solution, extracted with ether, the solution evaporated and the residue recrystallized from petroleum ether to yield 37 g of 2, 2-*diphenyl*-4-*hexamethyleneiminobutyronitrile* m.p. 52 to 55°.

Anal. Calcd. for $C_{22}H_{26}N_2$: C, 82·97; H, 8·23; N, 8·80%, Equiv. 318·5. Found: C, 82·80; H, 8·25; N, 8·80%. Equiv. 318.

2, 2-*diphenyl*-4-*hexamethyleneiminobutyramide* (I; $n=6$) 20 g of the above nitrile was dissolved in 40 ml of 90% sulphuric acid and the solution refluxed for 3 hours, cooled and poured into water containing ice. The solution was made alkaline with sodium hydroxide solution, the precipitate filtered, washed with water and recrystallized from isopropanol to yield 2, 2-diphenyl-4-hexamethyleneiminobutyramide m.p. 141 to 142°. *Anal.* Calcd. for $C_{22}H_{28}N_2O$: C, 78·53; H, 8·39; N, 8·33%; Equiv. 336·5. Found: C, 78·50; H, 8·40; N, 8·34%; Equiv. 336.

Physicochemical Properties

Melting points and pK/values. The melting points (Herzberg apparatus,[6]) and pK'a values (in 50 per cent CH_3OH,[7]) of four bases of type I are summarized in Fig. 1. A significant negative correlation between both sets of figures is observed.

Solubility. The solubilities of R 13, R 14 and R 658 (I : $n=4$, 5, 6), as determined in nine solvents (20 ± 1°C), are graphically summarized in Fig. 2. The pyrrolidine derivative shows the

highest solubility, and the piperidine derivative the lowest solubility in all solvents. Chloroform is the best solvent of the series, followed by methanol. The piperidine derivative, there-

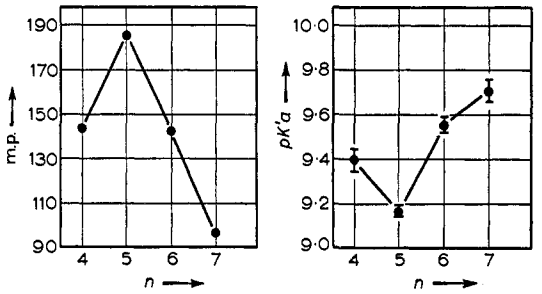


Fig. 1. Melting points (°C) and pK'a values of four bases of type I

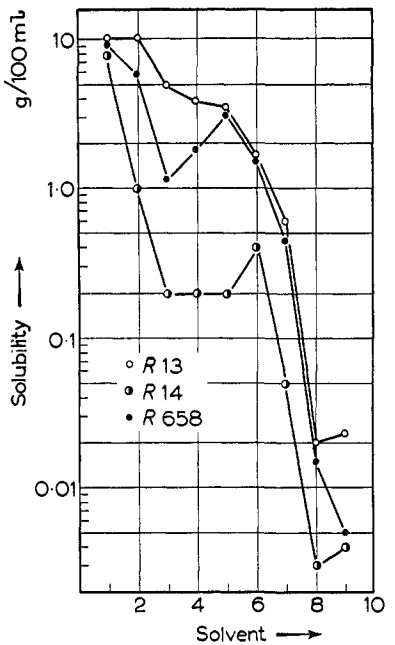


Fig. 2. Solubility of three bases of type I in nine solvents

(1) Chloroform; (2) methanol; (3) isopropanol; (4) acetone; (5) benzene; (6) ethyl acetate; (7) ether; (8) hexane; (9) water

fore, is the weakest base with the highest melting point and the lowest solubility of the series.

Spectrophotometry. Ultraviolet and infrared spectra of the four bases of type I were determined as follows:

(1) Recording spectrophotometers: 0·2–3 μ—Beckman DK–2; 3–15 μ—Beckman Infracord.

(2) Solvents and concentration: 0·2–0·8 μ: 10 ml HCl 0·01N + 90 ml *iso*propanol (2 millimols of 1 per l. of solvent). 1–3 μ: 6 ± 1 millimols of 1 per l. CCl_4; 3–15 μ: pellets: 1 mg of I in 300 mg KBr.

The ultraviolet spectra of the four bases of type I ($n = 4, 5, 6, 7$) are identical:

maxima: (1) $254 \cdot 7 \pm 1 \cdot 5$ mμ: $\epsilon = 390 \pm 20$; (2) $260 \cdot 5 \pm 1 \cdot 5$ mμ: $\epsilon = 430 \pm 20$; (3) $266 \cdot 5 \pm 1 \cdot 5$ mμ: $\epsilon = 325 \pm 20$.

minima: (*a*) $251 \cdot 5 \pm 1 \cdot 5$ mμ: $\epsilon = 350 \pm 20$; (*b*) $257 \cdot 0 \pm 1 \cdot 5$ mμ: $\epsilon = 345 \pm 20$; (*c*) $265 \cdot 0 \pm 1 \cdot 5$ mμ: $\epsilon = 310 \pm 20$.

The most important differences between the infrared spectra of the bases of type I are due to various methylene- and ring-vibrations.

Absorptions due to the primary amide group in I were observed at the following wavelengths:

	$n=4$ μ	$n=5$ μ	$n=6$ μ	$n=7$ μ	vibration
1	2·816	2·818	2·816	2·816	NH
2	2·850	2·852	2·850	2·850	NH
3	2·881	2·881	2·881	2·881	NH
4	2·918	2·918	2·918	2·918	NH
5	3·22	3·19	3·19	3·20	NH
6	6·15	6·10	6·10	6·12	C=O
7	6·37	6·32	6·30	6·32	NH
8	7·48	7·42	7·46	7·49	C—N (?)

Obviously the differences between these four sets of figures are small, and significant only in a few instances. The absorption

maxima of the pyrrolidine derivative ($n = 4$) and, to a lesser extent, those of the heptamethylenimine derivative ($n = 7$), located between 3 and 7·5 μ, are shifted to higher wavelengths.

Atropine-like Activity

The acetylcholine-stimulated isolated ileum of the rabbit was used for determining the following potency ratios:[2, 3, 5]

atropine sulphate	1·0
R 13	0·59 (0·43–0·82)
R 14	1·06 (0·88–1·27)
R 658	1·20 (0·98–1·46)
R 937	0·90 (0·63–1·27)
homatropine HBr	0·11 (0·08–0·15)
scopolamine HBr	1·10 (0·93–1·31)

The mydriatic activity in mice and rats was determined using a method which is described in a previous paper.[8] The substances were subcutaneously injected or locally applied in the left eye (one drop; contact of 30 sec). The ED50 values with their fiducial limits (P 0·05) are listed in Table I and the potency ratios (atropine = 1·0) are graphically represented in Fig. 3.

Table I. Mydriatic activity in mice and rats
(ED50 values and fiducial limits)

	Mice		Rats
	subcutaneous injection, mg/kg	local administration, mg/100 ml	
Atropine	0·096 (0·084–0·11)	1·32 (1·02–1·70)	5·10 (4·20–6·20)
Homatropine	2·40 (1·92–3·00)	17·1 (11·5–25·5)	86·0 (70–105)
Scopolamine	0·024 (0·016–0·036)	0·15 (0·11–0·20)	0·54 (0·45–0·64)
R 13	0·55 (0·47–0·64)	2·80 (1·90–4·20)	19·9 (16·4–24·1)
R 14	0·18 (0·16–0·22)	0·56 (0·35–0·90)	4·60 (3·97–5·34)
R 658	0·096 (0·070–0·13)	0·33 (0·22–0·49)	1·85 (1·50–2·28)
R 937	0·85 (0·61–1·19)	0·68 (0·48–0·97)	5·40 (4·10–7·10)

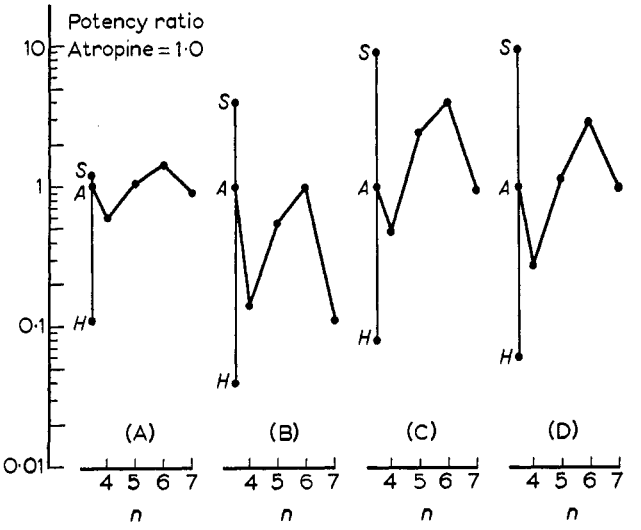


Fig. 3. Potency ratios of four bases of type I ($n = 4$, 5, 6 and 7), scopolamine (S), homatropine (H) and atropine (A + 1·0) in four experimental conditions

(A) Isolated intestine, (B) (C) and (D) mydriatic activity; (B) and (C) in mice, (D) in rats
(B) Subcutaneous injection. (C) and (D) local application

Discussion

The quantitative symbol used for expressing the 'activity' of a compound depends on many factors, such as species, route of administration, criteria of activity, method of statistical analysis, etc. Some of these factors are probably the expression of other factors, such as the metabolism of the compound in a given organism, amount and nature of the solvent used, age, weight, sex, race, and solubility of the compound in the body fluids, etc.

Fig. 4 shows satisfactory agreement between the mydriatic ED50 values in mice and rats obtained with locally applied compounds, the ratios for the seven sets of values varying only between 4 and 8. The compounds may therefore be placed in the following order of local mydriatic activity: scopolamine > R 658 > R 14 = R 937 ≥ atropine > R 13 > homatropine. However, after subcutaneous injection in mice, the order of the mydriatic activities is different: scopolamine > R 658 = atropine > R 14 > R 13 ≥ R 937 > homatropine.

Compared with atropine, therefore, the four basic amides of type I are significantly more active in mice after local administration than after subcutaneous injection. The route of administration is thus a more important factor than the species in these experimental conditions and for these compounds.

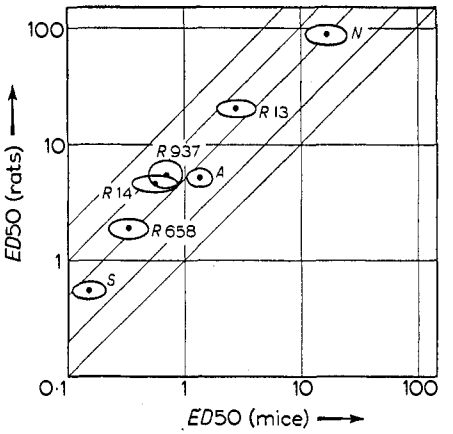


Fig. 4. Local mydriatic activity (ED50 values in mg per 100 ml) in mice and in rats of four bases of type I (n=4, 5, 6 and 7), scopolamine (S), atropine (A) and homatropine (H)

The differences between the atropine-like activities of R 658, scopolamine, R 14, atropine and R 937 as determined *in vitro* are hardly significant; in these tests R 13 is about twice and homatropine about ten times less active than the other five compounds.

No obvious correlation is found between the physicochemical properties (pK'a, solubility, spectra) and the atropine-like activity figures of the four members of series I.

From the practical point of view, the pronounced local mydriatic activity of R 658 (I, $n = 6$) is of interest. This compound was further investigated and clinically used as a local mydriatic. A 0·5 per cent solution in man is non-irritating and somewhat longer acting than atropine. The compound was well tolerated by patients who were hypersensitive to atropine and related esters.[9]

Summary. The influence of the number of methylene groups in the heterocyclic amino ring in tertiary 2,2-diphenyl-4-*cyclo*amino-butyramides

on the parasympatholytic activity and some physicochemical properties of these compounds is described. 2, 2-Diphenyl-4-hexamethyleneimino-butyramide is the most active atropine-like compound of this series.

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