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IMPROVED DELIVERY THROUGH BIOLOGICAL MEMBRANES VI. * POTENT SYMPATHOMIMETIC ADRENALONE DERIVATIVES **

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SUMMARY

A series of diesters of adrenalone were synthesized and their ocular sympathomimetic activities tested. Most of the transient derivatives resulted in a dramatic increase in the activity (mydriatic response and reducing intraocular pressure) of the almost inactive adrenalone. Some derivatives (dibutyryl, dihexanoyl and diisovaleryl esters) are more potent mydriatics than epinephrine or its more active prodrug, dipivalylepinephrine. Use of the new compounds as potent short-term mydriatics or in the treatment of glaucoma is suggested.

INTRODUCTION

Adrenalone (1), the synthetic precursor of epinephrine (2), is known to have very weak sympathomimetic activity, as compared to (2). Thus, a 2% adrenalone solution did not cause any reduction in ocular tension of patients suffering from glaucoma, while L-epinephrine is quite effective (Weekers et al., 1955).

It was recently shown that the delivery, and consequently the activity, of epinephrine can be increased by the prodrug approach (Hussain and Truelove, 1976). Dipivalylepinephrine (3), a prodrug of (2), for example, is significantly more active in reducing intraocular pressure than epinephrine itself (McClure, 1975; Mandell and Podos, 1977). It can be assumed that appropriate transient changes in the molecule of adrenalone can also lead to improved delivery and subsequently increased activity. The present paper reports the synthesis and relative sympathomimetic activities of a series of novel adrenalone derivatives (4)–(13).

* This paper is dedicated to Professor Takeru Higuchi on the occasion of his 60th birthday.
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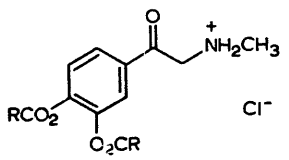

R

(4) $-C(CH_3)_3$
(5) $-CH_2CH_2CH_3$
(6) $-(CH_2)_4CH_3$
(7) $-(CH_2)_6CH_3$
(8) $-(CH_2)_{10}CH_3$
(9) $-CH_2CH(CH_3)_2$
(10) $-CH_2C(CH_3)_3$
(11) $-CHCH_2CH_2CH_3$
CH_3
(12) $-C-CH_2CH_3$
CH_3
(13) 

The sympathomimetic activities of the adrenalone derivatives were evaluated by measuring their mydriatic effect on rabbits' eyes. Limited studies on the effects of one of the derivatives on the ocular tension were also performed.

MATERIALS AND METHODS

(A) Synthesis

The adrenalone hydrochloride (1) was supplied by Roussell-Uclaf Company. The dipivalylepinephrine hydrochloride (3) used was synthesized by us according to a new synthetic procedure (Bodor and Yuan, 1977). This method was applied for the synthesis of the new adrenalone esters (4)–(13), as follows.

Dipivalyladrenalone hydrochloride (4)

To a mixture of 21.75 g (0.1 mol) adrenalone hydrochloride in 150 ml ethyl acetate containing 200 ml pivaloyl chloride was added dropwise with stirring 14.3 g of 70% perchloric acid. The mixture was heated under reflux for 5 hr. Upon cooling to room temperature, the yellow solution afforded a white crystalline solid. The solid was isolated by filtration, thoroughly washed with anhydrous ether and dried in vacuo at room temperature over anhydrous calcium sulfate to give 33 g (0.07 mol), 70%, dipivalyladrenalone hydroperchlorate, m.p. 174–176°C; IR (KBr) 3200, 2960, 1750, 1705, 1595, and 1050 cm^{-1}; PMR (CD_3COCD_3) δ 8.2 (bs, 2H) 8.0–7.4 (AB, 2H), 7.9 (s, 1H), 5.0 (t, 2H), 3.0 (t, 3H) and 1.3 (s, 18H) ppm.

Analysis. Calculated for $C_{19}H_{28}ClNO_9$: C, 50.72; H, 6.27; N, 3.11. Found: C, 50.51; H, 6.12; N, 3.00.

Dipivalyladrenalone hydroperchlorate 18 g (0.04 mol) was dissolved in 100 ml methanol and stirred at 0°C while 6.83 g (0.04 mol) cesium chloride in 300 ml warm methanol was added dropwise. After stirring for 1 hr at 0°C, the cesium perchlorate was removed by filtration and the methanol evaporated under reduced pressure. Recrystallization from isopropanol (80 ml) gave 12.3 g (0.03 mol), 75%, dipivalyladrenalone hydrochloride, m.p. 201–203°C; $R_f = 0.65$ (silica gel/chloroform : methanol : formic acid, 30 : 10 : 1 v/v);

IR (KBr) 3400, 2960, 1750, 1690, 1250 and 1100 cm^{-1}; PMR ($CD_3COCD_3 \cdot D_2O$) δ 7.7–6.7 (3H), 4.4 (s, 2H), 2.4 (s, 3H) and 0.9 (s, 18H) ppm.

Analysis. Calculated for $C_{19}H_{28}ClNO_5$: C, 59.13; H, 7.31; N, 3.63. Found: C, 59.19; H, 7.22; N, 3.76.

Using the procedure described for the preparation of dipivalyladrenalone hydrochloride (4), the following diacyladrenalone hydrochlorides were prepared:

Dibutyryladrenalone hydrochloride (5)

m.p. 178–180°C; $R_f = 0.67$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v); IR (KBr) 2960, 2680, 1760, 1675, 1260, 1105 and 860 cm^{-1}; PMR ($CDCl_3$) δ 8.0–7.2 (3H), 4.8 (bs, 2H), 3.0 (s, 3H), 2.8–2.4 (m, 4H), 2.2–1.6 (m, 4H) and 1.2 (t, 6H) ppm.

Analysis. Calculated for $C_{17}H_{24}ClNO_5$: C, 57.06; H, 6.76; N, 3.92. Found: C, 56.75; H, 6.67; N, 3.93.

Dihexanoyladrenalone hydrochloride (6)

m.p. 155–158°C; $R_f = 0.71$ (chloroform:methanol:formic acid; 30 : 10 : 1 v/v); IR (KBr) 2950, 2650, 1750, 1670, 1400, 1250, 1090 and 860 cm^{-1}; PMR ($CDCl_3$) δ 8.0–7.2 (3H), 4.6 (bs, 2H), 3.0–2.1 (7H), 2.0–1.1 (12H) and 0.9 (bt, 6H) ppm.

Analysis. Calculated for $C_{21}H_{32}ClNO_5$: C, 60.92; H, 7.79; N, 3.38. Found: C, 60.56; H, 7.45; N, 3.27.

Dioctanoyladrenalone hydrochloride (7)

m.p. 144–147°C; $R_f = 0.78$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v); IR (KBr) 2920, 2660, 1740, 1630, 1460, 1250, 1100 and 880 cm^{-1}; PMR ($CDCl_3$) δ 8.0–7.1 (3H), 4.7 (bs, 2H), 3.1–2.2 (7H) and 2.0–0.9 (26H) ppm.

Analysis. Calculated for $C_{25}H_{40}ClNO_5$: C, 63.88; H, 8.58; N, 2.98. Found: C, 63.67; H, 8.27; N, 2.78.

Didodecanoyladrenalone hydrochloride (8)

m.p. 136–140°C; $R_f = 0.84$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v); IR (KBr) 2920, 2620, 2680, 1765, 1600, 1420, 1200, 1100, 930 and 800 cm^{-1}; PMR ($CDCl_3$) δ 8.0–7.0 (3H), 3.5 (bs, 2H), 3.0–2.2 (7H), 1.2 (bs, 36H) and 0.9 (bt, 6H) ppm.

Analysis. Calculated for $C_{33}H_{56}ClNO_5$: C, 68.07; H, 9.69; N, 2.41. Found: C, 67.87; H, 9.69; N, 2.32.

Diisovaleryladrenalone hydrochloride (9)

m.p. 176–179°C; $R_f = 0.55$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v); IR (KBr) 2900, 2660, 1750, 1675, 1400, 1255, 1200, 975 and 850 cm^{-1}; PMR ($CD_3COCD_3 \cdot D_2O$) δ 7.8–6.9 (3H), 4.4 (s, 2H), 3.65 (bs, 2H), 2.6 (s, 3H), 2.0 (6H) and 0.6 (d, 12H) ppm.

Analysis. Calculated for $C_{19}H_{28}ClNO_5$: C, 59.13; H, 7.31; N, 3.63. Found. C, 58.86; H, 7.40; N, 3.43.

Di-tert-butylacetyladrenalone hydrochloride (10)

m.p. 176–178°C, $R_f = 0.60$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v);

IR (KBr) 2950, 2690, 1755, 1690, 1380, 1260, 1120 and 950 cm^{-1}; PMR (CD_3COCD_3 · D_2O) δ 7.8–6.9 (3H), 4.5 (s, 2H), 3.4 (b, 2H), 2.5 (s, 3H), 2.0 (s, 4H) and 0.7 (s, 18H) ppm.

Analysis. Calculated for $C_{21}H_{32}ClNO_5$: C, 60.93; H, 7.79; N, 3.38. Found: C, 60.66; H, 7.71; N, 3.06.

Di-2-methylvaleryladrenalone hydrochloride (11)

m.p. 144–147°C, $R_f = 0.65$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v); IR (KBr) 2920, 2680, 1750, 1680, 1410, 1260, 1100 and 860 cm^{-1}; PMR (CD_3COCD_3 · D_2O) δ 7.8–6.9 (3H), 4.6 (s, 2H), 3.6 (b, 2H), 2.6 (s, 3H), 2.3 (2H), 1.2 (8H), 0.9 (d, 6H), and 0.6 (bt, 6H) ppm.

Analysis. Calculated for $C_{21}H_{32}ClNO_5$: C, 60.93; H, 7.79; N, 3.38. Found: C, 60.55; H, 7.74; N, 3.13.

Di-2,2-dimethylbutryladrenalone hydrochloride (12)

m.p. 186–189°C, $R_f = 0.72$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v), IR (KBr) 2950, 2660, 1740, 1680, 1450, 1250, 1100 and 860 cm^{-1}; PMR (CD_3COCD_3 · D_2O) δ 7.6–6.8 (3H), 4.4 (s, 2H), 3.0 (b, 2H), 2.4 (s, 3H), 1.2 (q, 4H), 0.9 (s, 12H) and 0.4 (t, 6H) ppm.

Analysis. Calculated for $C_{21}H_{32}ClNO_5$: C, 60.93; H, 7.79; N, 3.38. Found: C, 61.00; H, 7.61; N, 3.21.

Dicyclopentylcarbonyladrenalone hydrochloride (13)

m.p. 190–193°C; $R_f = 0.61$ (chloroform : methanol : formic acid; 30 : 10 : 1 v/v); IR (KBr) 2940, 2660, 1750, 1670, 1400, 1260, 1100 and 850 cm^{-1}; PMR (CD_3COCD_3 · D_2O) δ 7.7–6.8 (3H), 4.4 (s, 2H), 3.6 (b, 2H), 2.45 (s, 3H), 2.5 (2H) and 1.3 (16H) ppm.

Analysis. Calculated for $C_{21}H_{28}ClNO_5$: C, 61.53; H, 6.89; N, 3.42. Found: C, 61.72; H, 6.86; N, 3.19.

(B) Mydriatic studies

Compounds (4)–(13) were evaluated in 0.9% saline solutions at concentrations equivalent to 0.05% adrenalone. The only exception was the didodecanoyl derivative (8), which formed a suspension at this concentration. Norman New Zealand albino rabbits of either sex, weighing about 2 kg, were used in the studies. The animals were placed in wooden restraining boxes. Standard doses of 50 μl were applied to the rabbits' eyes and pupillary changes were measured in a light- and temperature-controlled room. Amounts of dilation, in millimeters, were measured with a Starrett micrometer held at constant distance at various time intervals. The differences in the same animals between the pupil diameter of the eye with drug applied against the other eye with saline were observed. Each point is the average obtained on 3–6 animals. The observed results are summarized in Table 1.

(C) Intraocular pressure studies

Six unanesthetized, restrained New Zealand white rabbits were used, after examination for ocular defects that might preclude their use. The intraocular pressures were measured

TABLE 1

MYDRIATIC RESPONSE [a] OF DIACYLADRENALONE HYDROCHLORIDES [b] IN ALBINO RABBITS

Time (min)	1 [c]	3	4	5	6	7
10	0.33 ± 0.33	0.67 ± 0.33	0.083 ± 0.08	0.67 ± 0.33	0.67 ± 0.67	0.50 ± 0.50
20	0.33 ± 0.33	1.0 ± 0.44	1.58 ± 0.55	3.17 ± 1.01	3.33 ± 0.67	1.17 ± 0.33
30	0.33 ± 0.33	2.50 ± 0.67	2.33 ± 0.49	4.33 ± 0.67	4.0 ± 0.58	1.0 ± 0
60	1.0 ± 0.58	3.33 ± 0.63	2.83 ± 0.48	4.17 ± 0.83	4.17 ± 0.44	1.0 ± 0.58
120	1.0 ± 0.58	3.50 ± 0.68	1.50 ± 0.56	4.33 ± 0.67	4.33 ± 0.33	1.0 ± 0.58
180	0.67 ± 0.67	2.67 ± 1.05	0.83 ± 0.40	0.33 ± 0.33	1.17 ± 0.60	0.33 ± 0.33
240	0.67 ± 0.67	2.75 ± 0.73	0.67 ± 0.33	0	1.33 ± 0.67	1.33 ± 0.33
300	0.33 ± 0.33	2.25 ± 0.65	0		0.33 ± 0.33	0.50 ± 0.29
360		1.50 ± 0.50			0	0
420		0.50 ± 0.34				
480		0.67 ± 0.33				

Time (min)	9	10	11	12	13
10	0	0	0	0	0
20	3.0 ± 0.58	0	2.0 ± 1.0	0	1.67 ± 1.20
30	4.33 ± 0.33	0.50 ± 0.29	3.0 ± 0.58	1.67 ± 0.33	2.67 ± 1.20
60	4.33 ± 0.33	0.67 ± 0.33	3.17 ± 0.33	3.50 ± 0.50	3.67 ± 0.88
120	3.0 ± 1.0	0.33 ± 0.17	1.0 ± 0.58	1.33 ± 0.33	2.17 ± 1.50
180	0.67 ± 0.67	0	0	0	0.83 ± 0.83

[a] Mydriatic response mm ($\bar{X}$ ± S.E.) for each compound was determined using a dose equivalent to 0.05% of the parent compound.

[b] The numbers identify the compounds as in text.

[c] Mydriatic response for a 2% adrenalone hydrochloride solution.

TABLE 2

THE EFFECT OF DIPIVALYLADRENALONE · HCl (4) ON THE INTRAOCULAR PRESSURE IN NORMAL ALBINO RABBITS

Concentration	Time (hr)							
	0	1	2	4	6	8	10	23
	Intraocular pressure mm Hg ($\bar{X}$ ± S.E.)							
0%	24.8 ±0.8	25.2 ±1.0	24.2 ±1.2	24.8 ±1.0	24.7 ±1.4	24.8 ±1.2	25.2 ±0.7	26.2 ±0.7
0.01%	26.2 ±0.9	22.8 ±2.1	17.7 ±1.8	20.5 ±2.1	20.7 ±2.2	22.7 ±1.8	22.2 ±1.1	27.2 ±0.4
0.1%	25.2 ±0.9	24.7 ±1.3	18.7 ±1.8	16.5 ±1.0	15.2 ±1.6	16.8 ±0.7	19.3 ±0.9	25.5 ±0.8
0.5%	25.2 ±0.6	22.7 ±1.1	22.5 ±1.4	17.8 ±2.3	13.5 ±1.1	13.0 ±0.9	15.7 ±0.8	25.2 ±0.8
1%	24.3 ±1.1	21.8 ±1.1	23.8 ±1.0	18.3 ±1.7	14.5 ±0.4	14.8 ±1.0	13.2 ±0.6	22.2 ±1.3

with a modified Mackay–Marg-type tonometer. Prior to each pneumatonometry, the eye was given one drop of proparacaine · HCl, 0.5%, diluted 1 : 1 with normal saline prior to the installation, which was washed out a few seconds later with normal saline. The results of the dose–response studies on the dipivalyl derivative (4) are shown in Table 2.

RESULTS AND DISCUSSION

Preliminary mydriatic stuides have indicated that some of the compounds are extremely active at the concentration (2%) used (Weekers et al., 1955) for the parent adrenalone. Thus, for a direct comparison, the concentrations have to be reduced to 0.05% (in adrenalone equivalent). Dipivalylepinephrine (3) was also included in the studies due to its well known high activity.

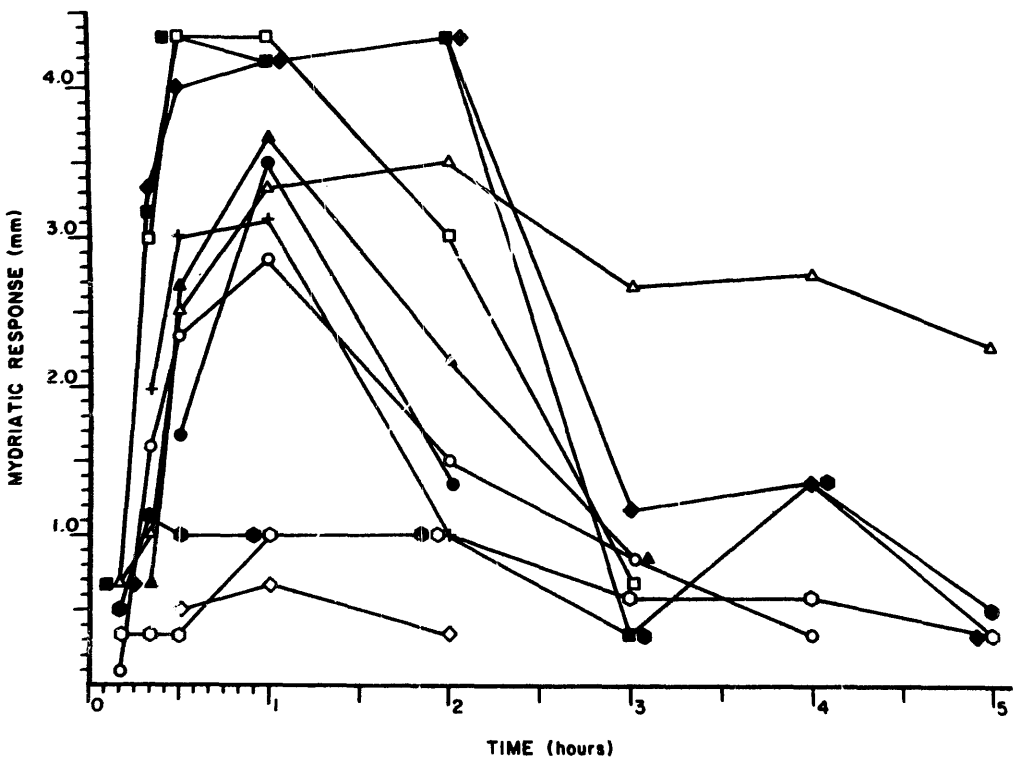

Fig. 1. ○ Adrenalone Hydrochloride, 1, 2 %
△ Dipivalylepinephrine Hydrochloride, 3, 0.05 %
○ Dipivalyladrenalone Hydrochloride, 4, 0.05 %
■ Dibutyryladrenalone Hydrochloride, 5, 0.05 %
◆ Dihexanoyladrenalone Hydrochloride, 6, 0.05 %
● Dioctanoyladrenalone Hydrochloride, 7, 0.05 %
□ Diisovaleryladrenalone Hydrochloride, 9, 0.05 %
◇ Di-tert-butylacetyladrenalone Hydrochloride, 10, 0.05 %
+ Di-2-methylvaleryladrenalone Hydrochloride, 11, 0.05 %
● Di-2,2-dimethylbutyryladrenalone Hydrochloride, 12, 0.05 %
▲ Dicyclopentylcarbonyladrenalone Hydrochloride, 13, 0.05 %

The results are summarized in Fig. 1. The results for (8) are not given since it could not be solubilized at 0.05% concentration. The solution obtained after filtering the suspension did not produce measurable mydriasis.

It can be seen that the increase in the activity of most of the compounds as compared to adrenalone is dramatic. Essentially all derivatives (except perhaps the didodecanoyl (8), which is very water insoluble) are significantly more active than (1) at a concentration of 1/40th of the adrenalone. Some of them are significantly more active even than the highly effective dipivalylepinephrine (3). The dibutyryl, dihexanoyl and diisovaleryl derivatives are extremely potent mydriatics.

The mechanism of this unexpected high activity is not clear. Based on the inactivity of intact dipivalylepinephrine (3), one can assume that, similarly, the diacyladrenalones are inactive as such (prodrugs). Thus, the results imply a significantly increased delivery of the slightly active adrenalone, or possibly epinephrine, by a reduction process of the keto substrate(s) in the eye. It is interesting that the mydriatic response to the diacyladrenalones is much shorter than that observed with the dipivalylepinephrine (3). This would indicate at least one possible important application: as short-term potent mydriatics.

Since the activity–time curves of the various diacyladrenalones are quite similar in the time reaching the peak and in the duration of the activity, a qualitative structure–activity relationship based on the peak heights and apparent duration (see Fig. 1) can be worked out, as follows:

$$(5) \cong (6) > (9) > (13) \geqslant (12) \geqslant (11) \geqslant (4) \gg (7) > (10) > (8) > (1)$$

Integration of the areas under the curve gave essentially the same order. A semiquantitative evaluation of the areas indicate that the most potent (5) and (6) are 4.5 times more active at 0.05% concentration than 2% adrenalone.

Interestingly enough, the straight chain and the most labile (based on in vitro plasma hydrolysis results: unpublished data from our laboratories on the analogous epinephrine esters series) dibutyryl (5) and dihexanoyl (6) derivatives are the most potent, followed by the diisovaleryl ester (9). The branced esters (13), (12), (11) and (4) do not essentially differ in activity, while the longer chain dioctanoyl (7) is significantly less active. The didodecanoyl (8) seems to be inactive (probably due to its insolubility in water). It is curious, however, that the di-*tert*-butylacetyl derivative (10) is much less active than the other branched esters.

On the other hand, as expected from the observed mydriatic response, the compounds should be very active in reducing intraocular pressure (IOP). For a direct comparison with the already established dipivalylepinephrine, the corresponding dipivalyladrenalone (4) was studied for its activity in reducing IOP. As shown in Table 2, the derivative (4) is highly active, indeed. Even a 0.01% solution reduces the IOP, while adrenalone at 2% is inactive (Weekers et al., 1955). Due to the known low systemic activity of adrenalone, a possible use in controlling IOP in glaucoma is also suggested using one of the more potent proadrenalones.

In conclusion, transient derivatization of adrenalone resulted in dramatic enhancement of its ocular sympathomimetic activity. Some of the derivatives could be used as potent short-term mydriatics or for reducing IOP.

ACKNOWLEDGEMENTS

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