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Derivatives of 3-Pyrrolidinols—III. The Chemistry, Pharmacology, and Toxicology of some *N*-Substituted-3-Pyrrolidyl α-Substituted Phenylacetates

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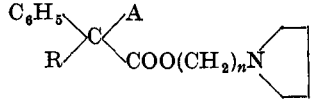
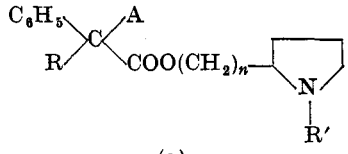
Introduction

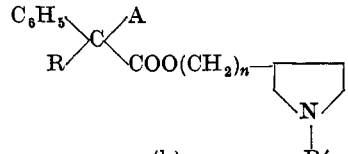
The pyrrolidine nucleus has been incorporated into many anticholinergic drugs as the basic moiety of the dialkylaminoalkyl substituted-phenylacetate type. These compounds can be divided into two main structural categories—those in which pyrrolidine serves as the terminal basic group of the alkyl chain (I); and those in which the nucleus itself is part of the aminoalkyl chain (II).[1-4]



(I)



(a)

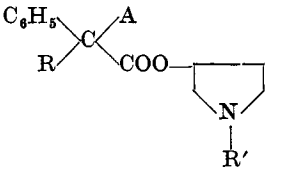


(b)

(II)

This paper is concerned with compounds of the second structural category. The synthesis, pharmacology and toxicology of a series

of type (IIb) esters, which are derivatives of 3-pyrrolidinols ($n = 0$) (III), are reported.



(III)

The quaternary salts of the benzilate esters of both 2-(1-methylpyrrolidyl)-methanol (IIa; R = C_6H_5, R′ = CH_3, A = OH, $n = 1$)[2,3] and the isomeric 3-pyrrolidyl compounds (IIb; R = C_6H_5, R′ = CH_3, A = OH, $n = 1$)[4,5] have been described as potent, orally effective anticholinergic substances.

Our interest in the 3-pyrrolidyl system where $n = 0$ stemmed from the fact that the degree of movement of the nitrogen centre with respect to the oxygen is limited by the rigidity of the five-membered ring and its derivatives might therefore be expected to act more selectively at physiological receptor sites. It has already been demonstrated that the benzhydryl ethers of the 3-pyrrolidinols are superior antihistaminic substances as compared with the corresponding open-chain dialkylaminoethyl analogues.[6] Similarly, as determined in several animal assays, the benzoates and substituted benzoates are more potent as local anaesthetics than the open-chain analogues.[7] Results of the present investigation show that the 3-pyrrolidyl-substituted phenylacetate esters are highly effective anticholinergic drugs.

Chemistry

The 1-alkyl-3-pyrrolidinols were prepared by condensation of primary amines with 1,4-dibromo-2-butanol.[6] They were then converted to the esters by the usual methods to give diphenylacetates (III; R = C_6H_5, A = H), α-phenylcyclopentaneacetates (III; R = cyclo-C_5H_9, A = H), α-phenylcyclohexaneacetates (III; R = cyclo-C_6H_{11}, A = H), benzilates (III; R = C_6H_5, A = OH), α-phenylcyclohexaneglycolates (III; R = cyclo-C_6H_{11}, A = OH),

and α-phenylcyclopentaneglycolates (III; R = cyclo-C_5H_9, A = OH). The physical properties and analytical data for these compounds are summarized in Table I.

Also prepared was a small series of xanthene-9-carboxylate esters which are listed in Table II.

The esters were synthesized by conventional means. The diphenylacetates and α-phenylcycloalkaneacetates (A = H) were most conveniently prepared from the acid chloride. The benzilates and α-phenylcycloalkaneglycolates (A = OH) were prepared from the methyl esters by a transesterification reaction. The pyrrolidyl xanthene-9-carboxylate esters were prepared by either synthetic route.

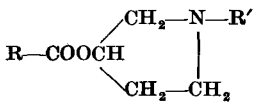
The substituted phenylglycolates could not be prepared by reaction of the free acid with the 3-chloro-1-alkylpyrrolidine in refluxing 2-propanol. This reaction has been used successfully, for example, in the preparation of diethylaminoethyl benzilate from diethylaminoethyl chloride and benzilic acid,[8] and in the preparation of the cyclic derivative, 1-ethyl-3-piperidyl benzilate,[9] from 3-chloro-1-ethylpiperidine and benzilic acid.

The failure of the 3-chloropyrrolidines to participate in this esterification reaction was anticipated because of their surprising stability, especially when compared with the usual nitrogen mustard compounds. An example of their stability is manifested by the fact that they can be distilled at atmospheric pressure without decomposition. They can be stored indefinitely at room temperature without appreciable inter- or intramolecular quaternization.

This stability can be accounted for by the fact that the nitrogen is unable to approach the carbon carrying the halogen with subsequent formation of a reactive ethylenimmonium ion. Further, the location of the negative centre in the vicinity of the approach of an external attacking base should decrease the reactivity of the halogen. The chemistry of these compounds will be the subject of a subsequent communication.

In most cases where the possibility of diastereoisomers existed, only a single compound was isolated; however, both forms of 1-ethyl-3-pyrrolidyl α-phenylcyclohexaneglycolate were obtained.

Table I. 1-Substituted-3-pyrrolidyl α-substituted phenylacetates



Code AHR no.	R	R′	b.p.[a] °C	Pressure, mm	Yield,[a] %	Salt	m.p. °C	Analysis		
								Elementary formula	Halogen %	
									Calcd.	Found
276	$(C_6H_5)_2CH$—	CH_3	170–176	0·4	63	HCl	152–153[b]	$C_{19}H_{21}NO_2.HCl$	10·68	10·68
261	$(C_6H_5)_2CH$—	CH_3	–	–	–	CH_3Br	171–173[b]	$C_{20}H_{24}NO_2.Br$	20·47	20·46
279	$(C_6H_5)_2CH$—	C_2H_5	164–166	0·2	70	HCl	136·5–137·5[c]	$C_{20}H_{23}NO_2.HCl$	10·25	9·98
262	$(C_6H_5)_2CH$—	C_2H_5	–	–	–	CH_3Br	143–146[d]	$C_{21}H_{26}NO_2.Br$	19·76	19·55
280	$(C_6H_5)_2CH$—	n-C_3H_7	168–169	0·17	63	HCl	97–98·5[e]	$C_{21}H_{25}NO_2.HCl$	9·85	9·68
281	$(C_6H_5)_2CH$—	i-C_3H_7	171–174	0·2	78	HCl	102–103·5[e]	$C_{21}H_{25}NO_2.HCl$	9·85	9·74
251	$(C_6H_5)_2CH$—	n-C_4H_9	178–180	0·5	82	HCl	115·5–116·5[e]	$C_{22}H_{27}NO_2.HCl$	9·48	9·41
291	$(C_6H_5)_2CH$—	i-C_4H_9	–	–	–	HCl	83·5–84·5[e]	$C_{22}H_{27}NO_2.HCl$	9·48	9·50
250	$(C_6H_5)_2CH$—	t-C_4H_9	178	0·7	42	HCl	137–138[f]	$C_{22}H_{27}NO_2.HCl$	9·48	9·28
278	$(C_6H_5)_2CH$—	$cyclo$-C_6H_{11}	204–209	0·05	66	HCl	150–151[e]	$C_{24}H_{29}NO_2.HCl$	8·87	8·83
235	$(C_6H_5)_2CH$—	$C_6H_5CH_2$	202–205	0·03	64	HCl	153–154·5[f]	$C_{25}H_{25}NO_2.HCl$	8·69	8·42
348	C_6H_5 / C_5H_9 >CH	CH_3	144–147	0·03	63	HCl	114–115·5[g]	$C_{18}H_{25}NO_2.HCl$	10·95	10·93
350	C_6H_5 / C_5H_9 >CH	CH_3	–	–	–	CH_3Br	166·5–168[d]	$C_{19}H_{28}NO_2.Br$	20·90	21·13
351	C_6H_5 / C_5H_9 >CH	C_2H_5	158–160	0·2	70	HCl	113–114[e]	$C_{19}H_{27}NO_2.HCl$	10·49	10·31
354	C_6H_5 / C_5H_9 >CH	C_2H_5	–	–	–	CH_3Br	152·5–154[g]	$C_{20}H_{30}NO_2.Br$	20·16	20·14

357	C_6H_5, C_5H_9>CH	*n*-C_4H_9	150–155	0·1	67	HCl	107·5–109·5[e]	$C_{21}H_{31}NO_2$.HCl	9·69	9·67
358	C_6H_5, C_5H_9>CH	*n*-C_4H_9	–	–	–	CH_3Br	107·5–108·5[d]	$C_{22}H_{34}NO_2$.Br	18·83	18·72
347	C_6H_5, C_5H_9>CH	*cyclo*-C_6H_{11}	184–187	0·5	56	HCl	191–192·5[c]	$C_{23}H_{33}NO_2$.HCl	9·05	8·90
356	C_6H_5, C_5H_9>CH	*cyclo*-C_6H_{11}	–	–	–	CH_3Br	191·5–193[d]	$C_{24}H_{36}NO_2$.Br	17·74	18·01
355	C_6H_5, C_5H_9>CH	$C_6H_5CH_2$	120–125	0·1	80	HCl	138–139[c]	$C_{24}H_{29}NO_2$.HCl	8·87	8·70
362	C_6H_5, C_5H_9>CH	$C_6H_5CH_2$	–	–	–	CH_3Br	175·5–176·5[c]	$C_{25}H_{32}NO_2$.Br	17·43	17·67
255	C_6H_5, C_6H_{11}>CH	CH_3	144–147	0·1	56	HCl	153·5–154·5[d]	$C_{19}H_{27}NO_2$.HCl	10·49	10·46
259	C_6H_5, C_6H_{11}>CH	CH_3	–	–	–	CH_3I	169·5–170·5[d]	$C_{20}H_{30}NO_2$.I	28·62	28·67
246	C_6H_5, C_6H_{11}>CH	C_2H_5	159–162	0·2	69	HCl	125–127·5[d]	$C_{20}H_{29}NO_2$.HCl	10·07	10·14
260	C_6H_5, C_6H_{11}>CH	C_2H_5	–	–	–	CH_3I	130–133[b]	$C_{21}H_{32}NO_2$.I	27·75	27·70
247	C_6H_5, C_6H_{11}>CH	*i*-C_3H_7	144–146	0·02	48	HCl	164–167[e]	$C_{21}H_{31}NO_2$.HCl	9·69	9·67
219	C_6H_5, C_6H_{11}>CH	*n*-C_4H_9	173–175	0·2	58	HCl	150–151[e]	$C_{22}H_{33}NO_2$.HCl	9·33	9·28
248	C_6H_5, C_6H_{11}>CH	*i*-C_4H_9	156–158	0·1	54	HCl	139·5–141·5[c]	$C_{22}H_{33}NO_2$.HCl	9·33	9·27
283	C_6H_5, C_6H_{11}>CH	*i*-C_4H_9	–	–	–	CH_3Br	168·5–170[d]	$C_{23}H_{36}NO_2$.Br	18·22	17·93
249	C_6H_5, C_6H_{11}>CH	*t*-C_4H_9	172–174	0·3	73	HCl	141–142[e]	$C_{22}H_{33}NO_2$.HCl	9·33	9·43
284	C_6H_5, C_6H_{11}>CH	*t*-C_4H_9	–	–	–	CH_3Br	177–178[d]	$C_{23}H_{36}NO_2$.Br	18·23	18·12

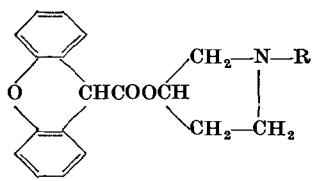
Table I—*continued*

Code AHR no.	R	R′	b.p.[a] °C	Pressure, mm	Yield,[a] %	Salt	m.p. °C	Analysis: Elementary formula	Analysis: Halogen % Calcd.	Analysis: Halogen % Found
271	C_6H_5 / C_6H_{11} >CH	*cyclo*-C_6H_{11}	168–174	0·02	66	HCl	226–227·5[f]	$C_{24}H_{35}NO_2$.HCl	8·73	8·62
256	C_6H_5 / C_6H_{11} >CH	$C_6H_5CH_2$	187–189	0·01	40	HCl	142–143·5[d]	$C_{25}H_{31}NO_2$.HCl	8·57	8·69
282	C_6H_5 / C_6H_{11} >CH	$C_6H_5CH_2$	–	–	–	CH_3Br	183–185[g]	$C_{26}H_{34}NO_2$.Br	16·92	16·62
326	$(C_6H_5)_2COH$	CH_3	–	–	–	HCl	176–177[h]	$C_{19}H_{21}NO_3$.HCl	10·19	10·12
327	$(C_6H_5)_2COH$	CH_3	–	–	–	CH_3Br	211–212·5[h]	$C_{20}H_{24}NO_3$.Br	19·67	19·79
324	$(C_6H_5)_2COH$	C_2H_5	179–181	0·08	78	HCl	148–149[d]	$C_{20}H_{23}NO_3$.HCl	9·80	9·79
329	$(C_6H_5)_2COH$	C_2H_5	–	–	–	CH_3Br	150–152[d]	$C_{21}H_{26}NO_3$.Br	19·01	19·30
325	$(C_6H_5)_2COH$	*i*-C_3H_7	141–143	0·2	54	HCl	191·5–193[d]	$C_{21}H_{25}NO_3$.HCl	9·43	9·19
341	$(C_6H_5)_2COH$	*i*-C_3H_7	–	–	–	CH_3Br	169–170·5[b]	$C_{22}H_{26}NO_3$.Br	18·40	18·33
317	$(C_6H_5)_2COH$	*n*-C_4H_9	–	–	–	HCl	179–180·5[h]	$C_{22}H_{27}NO_3$.HCl	9·09	9·16
320	$(C_6H_5)_2COH$	*n*-C_4H_9	–	–	–	CH_3Br	179–180·5[d]	$C_{23}H_{30}NO_3$.Br	17·82	17·97
308	$(C_6H_5)_2COH$	*i*-C_4H_9	179–182	0·15	71	HCl	155–155·5[h]	$C_{22}H_{27}NO_3$.HCl	9·09	8·86
315	$(C_6H_5)_2COH$	*i*-C_4H_9	–	–	–	CH_3Br	153·5–155[h]	$C_{23}H_{30}NO_3$.Br	17·82	17·62
313	$(C_6H_5)_2COH$	*cyclo*-C_6H_{11}	–	–	–	HCl	204·5–206·5[f]	$C_{24}H_{29}NO_3$.HCl	8·52	8·16
342	$(C_6H_5)_2COH$	*cyclo*-C_6H_{11}	–	–	–	CH_3Br	185·5–187[f]	$C_{25}H_{32}NO_3$.Br	16·84	16·48
337	$(C_6H_5)_2COH$	$C_6H_5CH_2$	220–225	0·05	43	HCl	154·5–156[b]	$C_{25}H_{25}NO_3$.HCl	8·36	8·16
340	$(C_6H_5)_2COH$	$C_6H_5CH_2$	–	–	–	CH_3Br	186–187·5[d]	$C_{26}H_{28}NO_3$.Br	16·57	16·23

376	C_6H_5, C_5H_9>COH	CH_3	137–140	0·07	75	HCl	170–171·5[d]	$C_{18}H_{25}NO_3$.HCl	10·43	10·30
504	C_6H_5, C_5H_9>COH	CH_3	–	–	–	CH_3Br	193·2–194·5[d]	$C_{19}H_{28}NO_3$.Br	20·06	19·78
379	C_6H_5, C_5H_9>COH	C_2H_5	162–165	0·25	30	HCl	160–161·5[d]	$C_{19}H_{27}NO_3$.HCl	10·02	9·82
371	C_6H_5, C_5H_9>COH	*n*-C_4H_9	160–165	0·04	80	HCl	129–130[d]	$C_{21}H_{31}NO_3$.HCl	9·28	9·17
372	C_6H_5, C_5H_9>COH	*n*-C_4H_9	–	–	–	CH_3Br	176–177·5[d]	$C_{22}H_{34}NO_3$.Br	18·15	17·98
451	C_6H_5, C_5H_9>COH	*cyclo*-C_6H_{11}	193–194	0·04	37	HCl	212–213·5[i]	$C_{23}H_{33}NO_3$.HCl	8·69	8·81
481	C_6H_5, C_5H_9>COH	*cyclo*-C_6H_{11}	–	–	–	CH_3Br	193–196[d]	$C_{24}H_{36}NO_3$.Br	17·13	16·92
480	C_6H_5, C_5H_9>COH	$C_6H_5CH_2$	200–203	0·03	74	–	–	$C_{24}H_{29}NO_3$	N, 3·69	N, 3·76
479	C_6H_5, C_5H_9>COH	$C_6H_5CH_2$	–	–	–	CH_3Br	173–175[d]	$C_{25}H_{32}NO_3$.Br	16·84	16·88
482	C_6H_5, C_6H_{11}>COH	CH_3	160–163	0·3	68	HCl	206–207[b]	$C_{19}H_{27}NO_3$.HCl	10·02	10·00
483	C_6H_5, C_6H_{11}>COH	CH_3	–	–	–	CH_3Br	253–255[d]	$C_{20}H_{30}NO_3$.Br	19·38	19·27
484[j]	C_6H_5, C_6H_{11}>COH	C_2H_5	157–160	0·05	60	HCl	219–220·5[d]	$C_{20}H_{29}NO_3$.HCl	9·64	9·65
487[j]	C_6H_5, C_6H_{11}>COH	C_2H_5	–	–	–	HCl	184-185[c]	$C_{20}H_{29}NO_3$.HCl	9-64	9·68
485	C_6H_5, C_6H_{11}>COH	C_2H_5	–	–	–	CH_3Br	181–182·5[b]	$C_{21}H_{32}NO_3$.Br	18·74	18·59

[a] B.p. and % yield refer to base; m.p. refers to salt. Recrystallized from: [b] butanone–methanol; [c] ethyl acetate; [d] butanone; [e] butanone–ethyl ether; [f] 2-propanol; [g] ethyl acetate–methanol; [h] ethyl acetate–ethanol; [i] ethanol; [j] 484 and 487 are diastereoisomers.

Table II. 1-Substituted-3-pyrrolidyl xanthene-9-carboxylates



Code AHR no.	R	Salt	m.p. °C	Analysis: Elementary formula	Analysis: % Calcd.	Analysis: % Found
361	CH_3	H_2SO_4	221–223[a]	$C_{19}H_{19}NO_3 . H_2SO_4$	C, 56·00 H, 5·19	C, 55·91 H, 5·21
389	CH_3	$(CH_3)_2SO_4$	105–107[a]	$C_{20}H_{22}NO_3 . CH_3SO_4$	C, 57·91 H, 5·78	C, 57·96 H, 5·96
360	C_2H_5	H_2SO_4	197–200[a]	$C_{20}H_{21}NO_3 . H_2SO_4$	C, 56·99 H, 5·50	C, 57·23 H, 5·47
353	C_4H_9	HCl	139–141[b]	$C_{22}H_{25}NO_3 . HCl$	Cl, 9·14	Cl, 9·27
346	*cyclo*-C_6H_{11}	HCl	186–188[a]	$C_{24}H_{27}NO_3 . HCl$	Cl, 8·56	Cl, 8·52
349	*cyclo*-C_6H_{11}	CH_3Br	185–189[a]	$C_{25}H_{30}NO_3 . Br$	Br, 16·91	Br, 16·71
343	$C_6H_5CH_2$	HCl	156–158[c]	$C_{25}H_{23}NO_3 . HCl$	Cl, 8·40	Cl, 8·56

Recrystallized from: [a] butanone–methanol; [b] benzene-ethyl ether; [c] butanone.

Synthesis*

The preparation of the 1-substituted-3-pyrrolidinols from 1,4-dibromo-2-butanol and primary amines was described earlier.[6] The α-phenylcyclohexaneacetyl and α-phenylcyclopentaneacetyl chloride were prepared by the method of Weston;[10] the α-phenylcyclohexane- and α-phenylcyclopentane-glycolic acids, by the method of Hoffmann and Schellenberg.[11] They were converted to their methyl esters by refluxing in methanol in the presence of catalytic amounts of *p*-toluenesulphonic acid. The following are examples of the procedures used for preparing the pyrrolidyl esters.

Method A. 1-Ethyl-3-pyrrolidyl diphenylacetate. A solution of 1-ethyl-3-pyrrolidinol (57·6 g, 0·5 mole) in benzene (200 ml) was added dropwise with stirring to a solution of diphenylacetyl chloride (115·3 g, 0·5 mole) in benzene (200 ml) with cooling so that the temperature did not exceed 35°. After addition was complete, the mixture was refluxed for two hours, cooled and extracted with 3N hydrochloric acid. The acid extract was made alkaline with concentrated sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed, dried over sodium sulphate, and concentrated, and the residue was distilled under reduced pressure. Yield, 109 g (70 per cent); b.p. 164–166°/0·2 mm.

The hydrochloride was precipitated from an ethereal solution of the base with ethereal hydrogen chloride and crystallized from ethyl acetate; m.p. 136·5–137·5°.

The methobromide quaternary salt precipitated from an ethereal solution of the base and methyl bromide after standing for several hours. It was crystallized from butanone; m.p. 143–146°.

Method B. 1-Methyl-3-pyrrolidyl α-phenylcyclopentaneglycolate. A solution of methyl α-phenylcyclopentaneglycolate (65 g, 0·28 mole) and *N*-methyl-3-pyrrolidinol (39·4 g, 0·39 mole) in *n*-heptane (1 l.) was heated until *ca.* 450 ml of heptane had distilled. Approximately 0·1 g of sodium was added, and the mixture was stirred and heated for two hours as the distillation was continued;

* All melting points are corrected. Carbon and hydrogen analysis by Schwarzkopf Microanalytical Laboratory, 56-19, 37th Avenue, Woodside, N.Y.

more heptane was added at such a rate as to keep the reaction volume constant. An additional piece of sodium was added at the end of an hour. The solution was then cooled and extracted with 3N hydrochloric acid. The acid extract was made alkaline with concentrated sodium hydroxide solution and extracted with ether. The ether extract was washed, dried (Na_2SO_4 anhyd.), concentrated, and the residue was distilled. Yield, 63·5 g (75 per cent); b.p. 137–140°/0·07 mm.

The hydrochloride was precipitated from a butanone solution of the base by addition of anhydrous hydrogen chloride, and was crystallized from an ethyl acetate–methanol mixture; m.p. 171–171·5°. Yield, 53 per cent.

The methobromide quaternary salt was precipitated from a solution of the base (175 g, 0·58 mole) and methyl bromide (59 g, 0·62 mole) in dry butanone (1800 ml) after standing at room temperature for 24 h. Yield, 226 g (98 per cent); m.p. 157–172°. After several crystallizations from a butanone–methanol mixture the melting point was 193–194·5°. Yield, 60 g (26 per cent).

Anal. Calcd. for $C_{19}H_{28}BrNO_3$: C, 57·28; H, 7·08. Found: C, 57·52; H, 7·19.

1-Ethyl-3-pyrrolidyl α-phenylcyclohexaneglycolate hydrochloride. Following Method B, in a 0·2 mole run, a 60 per cent yield of 1-ethyl-3-pyrrolidyl α-phenylcyclohexaneglycolate was obtained; b.p. 157–160°/0·05 mm. The hydrochloride was precipitated from an ethereal solution of the base with ethereal hydrogen chloride, and then fractionally crystallized from butanone and an ethyl acetate–methanol mixture. Two isomers were obtained: 2·5 g, m.p. 184–185°; and 13·8 g, m.p. 219–220·5° A mixture of the two melted at 178–182°.

Anal. Calcd. for $C_{20}H_{29}NO_3.HCl$: C, 65·28; H, 8·22. Found for higher melting isomer: C, 65·45; H, 8·39. Found for lower melting isomer: C, 65·55; H, 8·33.

3-Chloro-1-isobutylpyrrolidine. Hydrogen chloride gas was passed into a solution of 1-isobutyl-3-pyrrolidinol (318·6 g, 2·22 moles) in chloroform (1300 ml) until the solution was acidic. A solution of thionyl chloride (292 g, 2·46 moles) was then added dropwise with stirring. After addition was complete the solution was refluxed for 4 h, poured onto ice and made basic with sodium carbonate. The chloroform layer was separated, dried (Na_2SO_4

anhyd.) and concentrated. The residue was distilled at 99–105°/39 mm; yield, 233·7 g (65 per cent); n_D^{25} 1·4538.

Anal. Calcd. for $C_8H_{16}ClN$: C, 59·42; H, 9·99; N, 8·66. Found: C, 60·71; H, 10·62; N, 8·32.

The picrate salt after crystallization from absolute ethanol melted at 119–120°.

Anal. Calcd. for $C_8H_{16}ClN.C_6H_3NO_7$: C, 43·02; H, 4·90. Found: C, 43·15; H, 4·87.

Pharmacology and Toxicology

Methods and Results

Acute pharmacodynamic study. Sixty-one mongrel dogs (8–20 kg, either sex) were used. The animals were fasted for 16 to 20 h and anaesthetized by intravenous injection of 30 mg/kg of pentobarbital sodium with supplements as required to maintain a relatively constant level of anaesthesia. The right vagus nerve was sectioned and arranged so that the peripheral stump could be stimulated using a Harvard inductorium. Recordings of blood pressure, respiration and intestinal motility were made, the latter by means of a balloon-tambour system using a section of ileum which was approached through a longitudinal midline abdominal incision.

Although quantitative differences were noted, the following statements pertain to compounds in this series. With the intravenous administration of 10 μg/kg, spontaneous intestinal motility was greatly decreased or abolished. At 50 μg/kg these agents antagonized the depressor response induced by acetylcholine bromide (10 μg/kg intravenously) or methacholine chloride (2 μg/kg intravenously), and that produced by submaximal electrical stimulation of the peripheral stump of the sectioned vagus. They had essentially no effect on the pressor response resulting from bilateral carotid occlusion or from intravenous DMPP* (10 μg/kg). There was slight to moderate enhancement of the pressor response resulting from intravenously administered epinephrine hydrochloride (1 μg/kg). Oral administration of 0·5–5 mg/kg had the same qualitative effect on these challenges. The 50 μg/kg intravenous dose of the test compounds produced no apparent change

* 1,1-Dimethyl-4-phenylpiperazinium iodide.

in blood pressure or the pattern of respiration, but doses which were within the lethal range caused prompt, severe depressor responses and respiratory arrest.

In vitro *screening for cholinolytic activity.* Terminal sections of guinea-pig ileum were suspended in a 100-ml bath containing Tyrode's solution maintained at 38°. Gas containing 95 per cent oxygen and 5 per cent carbon dioxide was bubbled continuously through the bath. Muscle activity was recorded by an ink-writing pen yielding five-fold magnification.

All compounds were found to be potent acetylcholine antagonists in this preparation. Many effectively relaxed the induced spasms in concentrations of 0·01 μg/ml (Table III). Minimum effective concentrations were not determined. Methantheline bromide,* used as a control, was equally effective at a concentration of 0·02 μg/ml.

In vivo *inhibitory effect on intestinal motility in the rat.* The intestinal progression distances of a standardized charcoal test meal (10 per cent purified charcoal and 10 per cent acacia in water) in saline-treated control animals and in groups of rats pretreated with the test compounds were compared. This method was a slight modification of that reported by Macht and Barba-Gose.[12] Each agent was administered orally using a minimum of three dose levels per compound and six animals per dose level. The animals were fasted 16 to 20 h prior to use. The test meal, 2·5 ml/100 g, was given via a stomach tube 15 min after administration of the test compound, the concentration of which was adjusted so that each animal received 0·2 ml/100 g. The animals were sacrificed 30 min after receiving the test meal. The small intestine from the pylorus to the cecum was removed immediately, and the total length and the length through which the test meal had progressed were measured. The dose of each compound which could be expected to limit progression to 50 per cent of the total intestinal length was determined by calculation of linear regression.

The majority of the compounds were effective inhibitors of gastrointestinal propulsion in the unanaesthetized rat (see Table III) and appeared to be more potent than methantheline bromide. Several compounds were as effective as isopropamide iodide†

* Diethylaminoethyl xanthene-9-carboxylate methobromide.

† 4-(*N*,*N*-Diisopropylamino)-2,2-diphenylbutyramide methiodide.

and at least two compounds, 1-methyl-3-pyrrolidyl α-phenylcyclopentaneglycolate hydrochloride (AHR-376) and 1-ethyl-3-pyrrolidyl α-phenylcyclohexaneglycolate hydrochloride (AHR–487), compared favourably with the combination of belladonna alkaloids, the most effective of the positive reference standards used in this procedure.

The results of a few experiments suggested that the gastrointestinal anti-motor effect of 1-methyl-3-pyrrolidyl benzilate methobromide (AHR–327) as well as that of 1-methyl-3-pyrrolidyl α-phenylcyclopentaneglycolate hydrochloride (AHR–376) and of the analogous 1-ethyl-compound (AHR–379) was of long duration. A significant decrease in charcoal meal propulsion was noted 6 h after oral administration of the drug. Several of the compounds produced mydriasis in the animals treated; however, this occurred only with the administration of high doses.

In vivo *inhibitory effect on intestinal motility in the Thiry-Vella dog.* Five trained, unanaesthetized Thiry-Vella dogs[13] were used. The test compounds were administered in intravenous doses of 50 μg/kg, and a few compounds were given in oral doses of 1 to 5 mg/kg. Intestinal activity was recorded by means of a closed pressure system and respiration was followed with a conventional pneumograph. In addition to examination of the effects on spontaneous intestinal motility, observations were made on heart rate, pupil size, on the state of the oral mucous membranes, and, in a few instances, on intestinal hypermotility induced by methacholine chloride.

Table III presents the duration of a definitely recordable effect for each of the test compounds on intestinal motility and/or tone after parenteral administration. At the same dosage level AHR–259, –260, –282, –324, –327, –350, –354, –372, –379, –481 and –487 were equal or superior to methantheline bromide, isopropamideiodide, the belladonna alkaloids and the other AHR compounds. The α-phenylcycloalkaneglycolates, the benzilates and α-phenylcycloalkaneacetates were longer acting in the Thiry-Vella preparation than the diphenylacetates. With most of the compounds, a definite tachycardia was noted, but only with a few was a grossly observable mydriasis or xerostomia presented. 1-Methyl-3-pyrrolidyl benzilate methobromide (AHR–327), 1-methyl-3-pyrrolidyl α-phenylcyclopentaneglycolate hydrochloride (AHR–

Table III. Summary of the effects on the gastrointestinal tract and acute LD_{50}'s of some *N*-substituted-3-pyrrolidyl α-substituted phenylacetates

Code AHR no.	Effects on the gastrointestinal tract					Approx. acute LD_{50} in mice[c] (mg/kg)	
	Isolated guinea-pig ileum—inhibition of ACh spasm by 0·01 μg/ml[a]	Charcoal meal progression in rats. Oral ID_{50}[b] (mg/kg)	Thiry-Vella dog. Approximate duration (min) of effects 50 μg/kg i.v.	5-h Shay Rat 1 mg/kg i.p.			
				% decrease in volume of secretions	pH of secretions (control av. = 1·41)	IP	Oral
246	+	24·6	7	20·8	1·24	160	775
259	+	50·2	10	0	0·93	50	470
260	+	51·1	12	11·2	1·45	25	400
282	+	>1000·0	10	0	0·92	40	>800
324	+	33·0	15–30	24·3	1·16	110	400
326	+	23·6	0	0	1·10	140	500
327	+	45·0	30	50·6	2·22	105	1000
329	+	24·0	1–2	61·4	1·41	65	400
343		1854·0	0	14·5	1·33	897	–
346		96·1	0	0	1·28	153	–
349	–	136·4	0	23·4	1·68	75	400
350	+	108·6	10	58·8	–	25	400
353		40·4	0	20·8	1·52	92	–
354	+	275·3	15	72·6	2·29	42	450
360	+	38·5	0	0	1·18	170	850

361	–	37·2	0	0	1·93	205	600
371		14·0	0	0	1·15	151	–
372	–	51·3	10	13·2	1·96	32	400
376	+	0·7	6–7	69·1	1·66	250	500
379	+	2·9	25–30	35·9	1·54	230	480
389		1350·0	4	0	1·37	112	–
451		19·4	0	0	1·32	155	–
479		42·0	5	11·4	1·20	72	–
480		2·5	0	7·8	1·14	254	–
481		53·9	25	71·8	1·62	115	–
482		2·0	1	71·6	2·44	160	–
483		20·7	7	62·1	–	79	–
484	+	2·9	0	46·6	1·68	149	–
487	+	0·8	30–60	–	–	–	–
504	+	6·9	5	70·0	2·30	90	570
Methantheline bromide	+	117·1	3	52·2	1·67	55	1000
Isopropamide iodide	+	18·4	1	35·8	1·51	55	–
Belladonna alkaloids[d]		0·38	10	67·8	2·60	–	–

[a] Lowest concentration studied. [b] Oral dose which could be expected to limit progression of the test meal to 50% of the control progression distance. [c] Toxicity data by Woodard Research Corp., Herndon, Virginia. [d] Hyoscyamine sulphate, atropine sulphate and scopolamine hydrobromide in the ratio of 20·74 : 3·88 : 1·30 dissolved in 25% alcohol.

376), and the corresponding methobromide quaternary of the latter (AHR–504) in intravenous doses of 10 μg/kg abolished the intestinal hyperactivity and copious salivation caused by subcutaneous methacholine chloride.

The administration of relatively large doses (two to five times that required for inhibiting intestinal motility) of 1-methyl- (AHR–376) and 1-ethyl-3-pyrrolidyl α-phenylcyclopentaneglycolate (AHR–379) produced signs of CNS impairment such as hyperactivity, phonation and disorientation. Similar signs were not observed after administration of AHR–504, the quaternary salt corresponding to AHR–376.

AHR–327, –354, and –504, when administered orally to the Thiry-Vella dog in doses of 1 to 5 mg/kg, effectively abolished intestinal activity.

Antisecretory activity in the rat. Inhibition of gastric secretion in the rat was investigated using the surgical technique described by Shay *et al.*[14] The animals, weighing 120 to 195 g, were fasted for 18 to 20 h. Immediately following pyloric ligation each test compound or reference standard was tested in at least six animals in intraperitoneal doses of 1 mg/kg. The animals were sacrificed after 5 h and the centrifuged contents were analysed. Twenty control groups totalling 120 rats were run in parallel experiments. Control animals received a comparable volume of physiological saline.

Table III shows that AHR–327, –329, –350, –354, –376, –481, –482, –483 and –504 were potent inhibitors of gastric secretory activity in this preparation. AHR–327, –354, –376 and –504 were also found to be effective inhibitors upon oral administration of 50 mg/kg.

Several compounds induced an increase in the pH of the gastric contents. Table III presents the data obtained after intraperitoneal administration of 1 mg/kg. Oral doses (50 mg/kg) of AHR–327, –354 and –504 had the same effect on the acidity of gastric secretions.

Antisecretory activity in the gastric fistula dog. In dogs prepared with chronic gastric fistuli, AHR–329, –354, –484, –504 and the reference standard, methantheline bromide, decreased gastric secretory hyperactivity when administered in a subcutaneous dose of 0·2 mg/kg. Gastric hypersecretion was induced with

5-ethyl-5-(1,3-dimethyl-1-butenyl)-barbituric acid which has been reported to produce this effect through a central action.[15]

*Toxicology.** The approximate LD_{50} was estimated in mice by intraperitoneal administration and, with several compounds, by the oral route. These values are listed in Table III. Clonic convulsions, mydriasis and a deep, laboured respiration were observed in many of these animals. Deaths apparently resulted from respiratory failure. Autopsy of about 25 per cent of the animals revealed no grossly observable pathological changes.

Discussion

The *N*-substituted-3-pyrrolidyl α-substituted phenylacetates generally possess a high order of anticholinergic effect on the gastrointestinal tract. In each series of esters the compounds with lower alkyl substituents on the nitrogen of the pyrrolidine ring were more potent than those with higher alkyl, cycloalkyl or aralkyl substituents. The presence of the α-hydroxyl group as well as saturation of one of the aryl nuclei in either the diphenylacetates or benzilates enhanced the anticholinergic activity. The more promising compounds of the entire series were the benzilates and α-phenylcycloalkaneglycolates. The diphenylacetates were the least active in these tests.

In general, the tertiary salts were more potent than the quaternary salts as antispasmodic agents. The tertiary α-phenylcycloalkaneglycolates produced signs of CNS impairment in rats, mice and dogs. This phenomenon has also been observed in man when 1-methyl-3-pyrrolidyl α-phenylcyclopentaneglycolate hydrochloride (AHR–376) was administered orally.

The high potency of the 3-pyrrolidyl α-substituted phenylacetates as anticholinergic substances, the 3-pyrrolidyl ethers as antihistaminics,[6] and the 3-pyrrolidyl benzoates as local anaesthetics[7] emphasizes the desirability of further investigation of the 3-pyrrolidyl system as a substitute for the open-chain dialkylaminoethyl group in physiologically active drugs.

The results of the studies reported here have led to the selection of three compounds for clinical trial: 1-methyl-3-pyrrolidyl α-phenylcylcopentaneglycolate methobromide (AHR–504), 1-

* The major part of the toxicity data was determined by the Woodard Research Corporation, Herndon, Virginia.

methyl-3-pyrrolidyl benzilate methobromide (AHR–327), and 1-ethyl-3-pyrrolidyl α-phenylcyclopentaneacetate methobromide (AHR–354).

Summary. As part of a study of derivatives of *N*-substituted-3-pyrrolidinols, a series of esters has been prepared and examined for anticholinergic activity on the gastrointestinal tract. The diphenylacetates, benzilates, α-phenylcycloalkaneacetates and α-phenylcycloalkaneglycolates are reported. Most of these compounds were examined for their acute pharmacodynamic activity in dogs, cholinolytic activity on the isolated guinea-pig ileum, *in vivo* inhibitory effect on intestinal motility in the rat and Thiry-Vella dog, antisecretory activity in the rat and gastric fistula dog, and acute intraperitoneal and oral toxicity in mice.

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