Journal of Medicinal Chemistry, 1974, Vol. 17, No. 7 685

Quinoline Derivatives as Antiallergy Agents†

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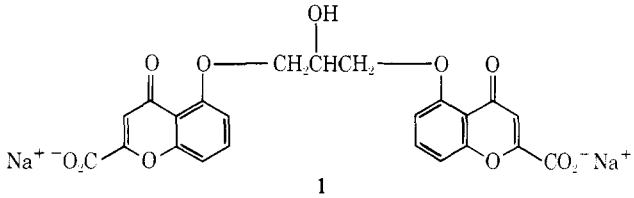
A series of 1,4-dihydro-4-oxoquinolinecarboxylic acids was synthesized and tested in the rat passive cutaneous anaphylaxis (PCA) assay as potential antiallergy agents. Many of the compounds of this series showed significant activity in this assay. 7-Amino-1,4-dihydro-8-methyl-4-oxoquinaldic acid (**6h**) and 7-amino-1,4-dihydro-4-oxobenz-[*h*]quinoline-2-carboxylic acid (**6r**) were very active (ID_{50} = 0.1 mg/kg). The synthesis and biological results are described.

The sequence of biological events preceding an allergic attack is generally thought to include attachment of IgE antibody to a mast cell, interaction of this antibody with an antigen to which it is specific, and the subsequent release of the mediators of immediate hypersensitivity, which include histamine, 5-hydroxytryptamine (5-HT), and the slow reacting substance of anaphylaxis (SRS-A) by the cell. These mediators then interact with the end organ smooth muscle or mucous membranes to produce the clinical manifestations of the allergic disease. Traditional chemotherapy of the allergic patient has utilized "end organ" antagonists, that is, agents (antihistamines, bronchodilators, steroids) which appear to block the receptors for the mediators on the affected tissues but may have little to do with the basic allergic process. In principle, an alternate mode of therapy would be the prevention of mediator release.

Recently, the introduction of cromolyn sodium (**1**) has confirmed that inhibition of mediator release is a viable means of prophylactically treating the allergic patient.[1] Our interest in this approach to therapy led us to investigate other chemical classes of compounds as potential antiallergy agent as judged by their ability to inhibit an animal model of allergic diseases [rat passive cutaneous anaphylaxis (PCA) assay]. The results of some of these studies are described below.



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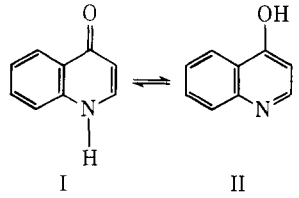
Early screening results indicated that certain substituted 1,4-dihydro-4-oxoquinolines possessed moderate activity in the rat PCA assay. Furthermore, the presence of a carboxy group in the hetero ring enhanced the biological activity. While 1,4-dihydro-4-oxoquinolines possess certain structural features in common with chromones, their ability to exist in two tautomeric forms, I and II, gives them distinct physical, chemical, and perhaps biological properties.‡ Accordingly, we undertook the synthesis and testing of a series of 1,4-dihydro-4-oxoquinolinecarboxylic acids as potential antiallergy agents.



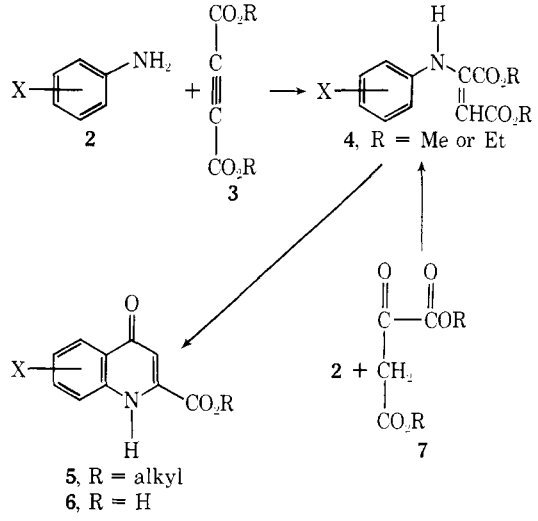
I II

† This work has been presented in part at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1973, Abstracts, MEDI 13.

‡ Sufficient data to specify the relative concentration of the two tautomers under physiological conditions are not available. For convenience, only the 4-oxo form will be referred to in the text.

Chemistry. 1,4-Dihydro-4-oxoquinoline-2-carboxylic acids (quinaldic acids) may be prepared readily by either of two routes[2,3] (Scheme I). Reaction of the appropriate aniline **2** with dimethyl acetylenedicarboxylate (**3**) or diethyl oxalacetate (**7**) gave an anilino butenedioate **4** in good yield. The anilinobutenedioates were formed initially

Scheme I



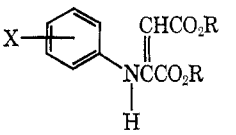
as a mixture of geometrical isomers (*E*, *Z*);[4a] however, purification or solution in nonpolar solvents gave essentially the pure *Z* isomer.[4b] Although the *Z* isomer is required sterically for ring closure, a mixture of the isomers may be used since isomerization apparently occurred readily at elevated temperatures. Ring closure was effected at ~250° in a high boiling solvent such as Dowtherm A or diphenyl ether to give **5**. Hydrolysis of the carboalkoxy group was achieved by stirring **5** in 1 *N* NaOH until solution occurred and then acidifying with hydrochloric acid to pH 3. The desired quinaldic acid **6** precipitated in good yield.

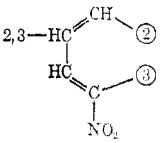
The 1,4-dihydro-4-oxoquinoline-3-carboxylic acids **11** were prepared as shown in Scheme II.[5] The aniline **2** was condensed with diethyl methoxymethylenemalonate (**8**). The resulting anilinomethylenemalonate was cyclized thermally at ~250°. Hydrolysis with dilute NaOH followed by acidification gave **11**.

It was of interest to study the effect on biological activity of linking two quinaldic acid nuclei. Both the length of the bridge and the bridging position were varied. The synthesis of these compounds is outlined in Scheme III. The diamine **12** reacted smoothly with **3** to give a 1:2 adduct **13** which underwent thermal cyclization smoothly at ~250° to give **14**. Hydrolysis gave **15** in good yield.

Biological Methods. The compounds shown in Tables I–V were tested for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in rats passively sensitized to egg albumin as follows.[6]

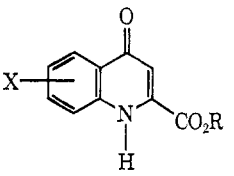
Table I. Anilinobutenedioates

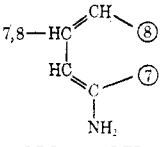
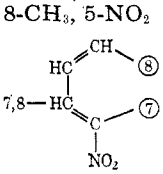


Compd	Substituent(s)	R	Formula	Mp, °C	Yield, % (method)	Recrystn solv[a]	Analyses
4a	4-OH	CH_3	$C_{12}H_{13}NO_5$	*b*	(A)	L	
4b	4-NO_2	CH_3	$C_{12}H_{12}O_6N_2$	120–121.5	59 (A)	A	C, H, N
4c	2-CH_3, 3-$NHSO_2CH_3$	CH_3	$C_{14}H_{18}N_2O_6S$	168–169	71 (A)	F	C, H, N, S
4d	2-CH_3, 3-NO_2	CH_3	$C_{13}H_{13}N_2O_6$	99–100	91 (A)	F	C, H, N
4e	5-NO_2, 2-CH_3	CH_3	$C_{13}H_{13}N_2O_6$	130–131	83 (A)	L	C, H, N
4f	4-$CH_2CO_2C_2H_5$	CH_3	$C_{16}H_{19}NO_6$	Oil	*a* (A)	L	
4g	2-CH_3, 3-*p*-$NHSO_2C_6H_4CH_3$	CH_3	$C_{20}H_{22}N_2O_6S$	119–121	56 (A)	L	*c*
4h	4-*p*-$CONHC_6H_4CO_2CH_3$	CH_3	$C_{21}H_{20}N_2O_7$	159–160	63 (A)	A	C, H, N
4i	4-$NHSO_2CH_3$	CH_3	$C_{13}H_{16}N_2O_6S$	141–142	34 (A)	A	C, H, N, S
4j	4-CO_2H	CH_3	$C_{13}H_{13}NO_6$	159	71 (A)	K	C, H, N
4k	2,3- 	CH_3	$C_{16}H_{14}N_2O_2$	189–190	87 (A)	B	C, H, N
4l	2-CH_3, 4-NO_2	CH_3	$C_{13}H_{14}N_2O_6$	116–117	65 (A)	A	C, H, N
4m	2-Cl, 5-NO_2	CH_3	$C_{12}H_{11}ClN_2O_6$	157–158	89 (A)	A	C, H, N

[a]Recrystallization solvent code given in the Experimental Section. [b]Used without isolation. [c]Used without purification.

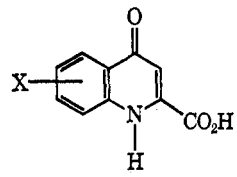
Table II. Alkyl Quinaldates

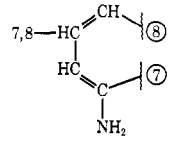


Compd	Substituent(s)	R	Formula	Mp, °C	Yield, %	Recrystn solv[a]	Analyses
5a	6-Br	C_2H_5	$C_{12}H_{10}O_3NBr$	256–257 dec[b]	34	A	C, H, N, Br
5b	6-OCH_3	C_2H_5	$C_{13}H_{13}NO_4$	222–223.5[c]	21	A	H, N; C[d]
5c	6-OH	CH_3	$C_{11}H_9O_4N$	279.5–281 dec	73	A	H, N; C[e]
5d	6-NO_2	CH_3	$C_{10}H_6N_2O_4$	297–300 dec[f]	96	B	C, H, N
5e	8-CH_3, 7-$NHSO_2CH_3$	CH_3	$C_{13}H_{14}N_2O_6S$	258 dec	84	G	C, H, N, S
5f	7-NH_2, 8-CH_3	CH_3	$C_{12}H_{12}N_2O_3$	238	77	F	C, H, N
5g	5-NH_2, 8-CH_3	CH_3	$C_{12}H_{10}N_2O_5$	187–188	88	B	C, H, N
5h	6-$CH_2CO_2C_2H_5$	CH_3	$C_{15}H_{15}N_2O_5$	186–187	26	F	C, H, N
5i	8-CH_3, 7-*p*-$NHSO_2C_6H_4CH_3$	CH_3	$C_{19}H_{18}N_2SO_5$	265	83	H	C, H, N, S
5j	6-NH_2	CH_3	$C_{11}H_{10}N_2O_5$	235 dec	100	L	
5k	6-*p*-$CONHC_6H_4CO_2CH_3$	CH_3	$C_{20}H_{16}N_2O_6$	>320	47	L	C, H, N
5l	6-$NHSO_2CH_3$	CH_3	$C_{12}H_{12}N_2O_5S$	310 dec	86	L	C, H, N, S
5m	7,8-$(CH_3)_2$	CH_3	$C_{13}H_{13}O_3N$	200–201	53	A	C, H, N
5n	6-*p*-$OC_6H_4CO_2CH_3$	CH_3	$C_{19}H_{15}NO_6$	237–238	68	H	C, H, N
5o	6-CO_2H	CH_3	$C_{12}H_9NO_5$	319	92	D	C, H, N
5p	7,8- 	CH_3	$C_{15}H_{12}N_2O_3$	245 dec	88	L	H, N; C[g]
5q	6-NO_2, 8-CH_3	CH_3	$C_{12}H_{10}N_2O_5$	270 dec	80	H	C, H, N
5r	6-NH_2, 8-CH_3	CH_3	$C_{12}H_{12}N_2O_3$	236 dec	59	A	H, N; C[h]
5s	8-Cl, 5-NO_2	CH_3	$C_{11}H_7ClN_2O_5$	197–198	82	L	C, H, Cl, N
5t	5-NH_2, 8-Cl	CH_3	$C_{11}H_9ClN_2O_3$	175–176	45	A	C, H, N
5u	8-CH_3, 5-NO_2	CH_3	$C_{12}H_{10}N_2O_5$	213–214	72	L	C, H, N
5v		CH_3	$C_{15}H_{10}N_2O_5$	251–252	87	D	C, H, N

[a]Recrystallization solvent code given in the Experimental Section. [b]Mp 245–251°: E. Vanloock, G. L'abbe, and G. Smets, *J. Org. Chem.*, **36,** 2520 (1971). [c]Mp 202–205°: British Patent 942,524 (1963). [d]C: calcd, 63.15; found, 62.64. [e]C: calcd, 60.27; found, 59.88. [f]Mp 295–297°: N. D. Heindel, I. S. Bechma, T. F. Lemke, and V. B. Fish, *J. Org. Chem.*, **32,** 4155 (1967). [g]C: calcd, 67.15; found, 66.18. [h]C: calcd, 62.06; found, 61.54.

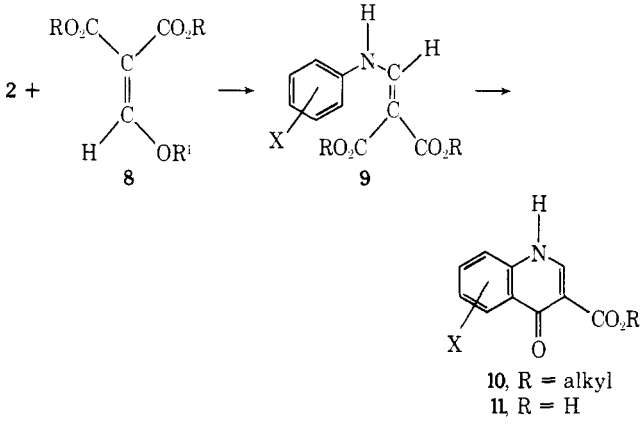
Table III. Quinaldic Acids



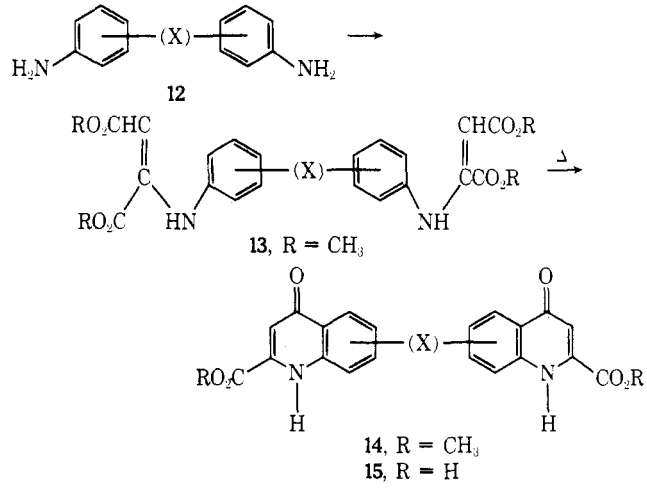
Compd	Substituent(s)	Formula	Mp, °C	Yield, %	Recrystn solv[a]	Analyses
6a	H	$C_{10}H_7NO_3$	*b*		L	
6b	8-OH	$C_{10}H_7NO_4$	*b*		L	
6c	6-Br	$C_{10}H_6O_3$	296–297 dec[c]		B	C, H, N, Br
6d	6-OCH_3	$C_{11}H_9NO_4$	294–295 dec[d]	100	L	
6e	6-OH (as Na^+ salt)	$C_{10}H_6O_4NNa \cdot H_2O$	>320	77	C	C, H, N
6f	6-NO_2	$C_{10}H_6O_5N_2$	290–291 dec	92	L	
6g	8-CH_3, 7-$NHSO_2CH_3$	$C_{12}H_{12}N_2O_5S \cdot 0.5H_2O$	310 dec	96	L	C, H, N, S
6h	7-NH_2, 8-CH_3	$C_{11}H_{10}N_2O_3$	310 dec	100	L	H, N; C[e]
6i	5-NH_2, 8-CH_3	$C_{11}H_{10}N_2O_3$	296 dec	92	L	C, H, N
6j	6-CH_2CO_2H	$C_{12}H_9NO_5 \cdot 0.5H_2O$	302 dec	92	L	C, H, N
6k	8-CH_3, 7-*p*-$NHSO_2C_6H_4CH_3$	$C_{19}H_{18}N_2SO_5$	273 dec	82	L	C, H, N, S
6l	6-NH_2	$C_{10}H_8N_2O_3$	308[f]	92	L	
6m	6-*p*-$CONHC_6H_4CO_2H$	$C_{18}H_{12}N_2O_6 \cdot 0.5H_2O$	>320 dec	84	L	H, N, S; C[g]
6n	6-$NHSO_2CH_3$	$C_{11}H_{10}N_2O_5 \cdot H_2O$	290 dec	81	L	C, H, N, S
6o	7,8-$(CH_3)_2$	$C_{12}H_{11}O_3N$	274–276[h]	100	L	
6p	6-*p*-$OC_6H_4CO_2H$	$C_{17}H_{11}NO_6 \cdot 0.5H_2O$	312 dec	92	L	C, H, N
6q	6-CO_2H	$C_{11}H_7NO_5$	>320	100	L	*i*
6r		$C_{14}H_{10}N_2O_3$	283 dec	60	I	H, N; C[j]

[a]Recrystallization solvent code given in the Experimental Section. [b]Aldrich Chemical Co. [c]Mp 287–288°: D. K. Wald and M. M. Joullié, *J. Org. Chem.*, **31**, 3369 (1966). [d]Mp 288–289°: British Patent 942,524 (1963). [e]C: calcd, 60.54; found, 59.65. [f]Mp 308°: W. O. Kermack and A. P. Whitehead, *J. Chem. Soc.*, 1164 (1940). [g]C: calcd, 59.83; found, 59.24. [h]Mp 275–276° dec: W. German Patent 2,130,408 (1971). [i]Low solubility prevented recrystallization. [j]C: calcd, 66.13; found, 65.26.

Scheme II



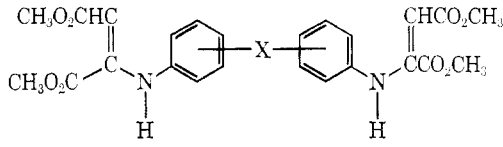
Scheme III



Rat homocytotropic antibody was elicited to egg albumin (EA) by the injection (ip) of 0.5 mg of EA + 0.5 cc of *H. pertussis* vaccine (Michigan Department of Public Health, 4.5 × 10^{10} heat killed organisms) per rat. After 18–20 days the serum was collected and frozen until use. The antibody was shown to be of the 72-hr latency type and to be destroyed by heating 1.0 hr at 56°. Five 0.1-ml volumes of an appropriate dilution of this serum were inoculated into the shaved dorsal surface of a 200-g Sprague–Dawley rat. Saline controls were run and showed less than 4-mm spots. After 72 hr the rat was challenged iv with 4 mg per animal of EA + 0.5% Evans Blue dye. In the case of drug-treated animals the materials were given iv at the time of antigen challenge or the materials were given ip 30 min before challenge with antigen. Results were reported as the inhibition of the number of spots per animal (regardless of size) that were seen at five dilutions of serum. The number of spots from a number of sensitization sites in drug-treated animals was compared with the spot score (number of total spots divided by the number of animals) obtained from the same number of sites in untreated animals. The per cent inhibition of the PCA reaction was then calculated.

The significance of the difference between treated and control in this PCA test has been analyzed and found to be significant with a P value of <0.001. The procedure is to find the highest dilution of the controls for which some of the animals do not have spots and some of the animals have spots. The number of animals not having spots at the next higher dilution of serum is counted and added to past control data. A new average is taken. We then

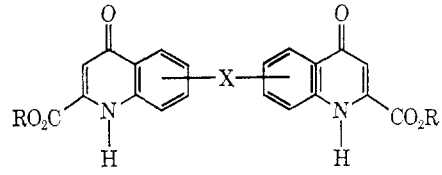
Table IV. Diphenylylenediiminodbutenedioates



Compd	Linkage	Formula	Mp, °C	Yield, %	Recrystn solv[a]	Analyses
13a	6-6′	$C_{24}H_{24}N_2O_8$	136–138	57	A	C, H, N
13b	6-CH_2-6′	$C_{25}H_{26}N_2O_8$	Glass	*b*	L	
13c	6-O$(CH_2)_3$O-6′	$C_{27}H_{36}N_2O_{10}$	Glass	*b*	L	
13d	8-8′	$C_{24}H_{24}N_2O_8$	105–106.5[c]	69	L	
13e	6-O-6′	$C_{24}H_{24}O_9N_2$	115–117	75	A	C, H, N

[a]Recrystallization solvent code given in the Experimental Section. [b]The compound was used without purification. [c]Mp 105°: S. K. Khetan and M. V. George, *Can. J. Chem.*, **47**, 3545 (1969).

Table V. Bis(1,4-dihydro-4-oxoquinaldic acids and esters)



Compd	Linkage	R	Formula	Mp, °C	Yield, %	Recrystn solv[a]	Analyses
14a	6-6′	CH_3	$C_{22}H_{16}N_2O_6$	>300	85	L	*b*
15a	6-6′	H	$C_{20}H_{10}O_6Na_2 \cdot 3H_2O$	>310	89	C	C, N; H[c]
14b	6-$CH_2$6,	CH_3	$C_{23}H_{18}N_2O_6$	304 dec	66[d]	L	*b*
15b	6-$CH_2$6′	H	$C_{21}H_{14}N_2O_6$	>310	100	L	*b*
14c	6-O$(CH_2)_3$O-6′	CH_3	$C_{25}H_{22}O_8N_2$	280 dec	48	E	H, N; C[e]
15c	6-O$(CH_2)_3$O-6′	H	$C_{23}H_{18}N_2O_8$	290 dec[f]	100	L	
14d	8-8′	CH_3	$C_{22}H_{16}N_2O_6$	240–242[g]	86	J	
15d	8-8′	H	$C_{20}H_{12}N_2O_6$	>310	81	L	*b*
14e	6-O-6′	CH_3	$C_{22}H_{16}N_2O_7$	318–320	100	D	H, N; C[h]
15e	6-O-7′	H	$C_{20}H_{12}N_2O_7$	>320[i]	100	L	

[a]Recrystallization solvent code given in the Experimental Section. [b]Low solubility prevented recrystallization. [c]H: calcd, 3.40; found, 2.99. [d]From the diamine. [e]C: calcd, 62.76; found, 61.86. [f]Mp 260° dec: W. German Patent 2,145,423 (1972). [g]Mp 225–226°; S. K. Khetan and M. V. George, *Can. J. Chem.*, **47**, 3545 (1969). [h] C: calcd, 62.86; found, 61.44. [i]Mp 270° dec: W. German Patent 2,145,423 (1972).

graphed the probability of not getting a spot at this dilution *vs.* the sample size and got a probability of about 0.1. This probability $p = (0.1)^3$ or N for the number of animals gives a degree of certainty of assuming there is a difference in control and treated. This was done for cromolyn sodium and the P value was <0.001.

Biological Results and Discussion. The results of the biological testing are tabulated in Tables VI and VII as the doses which inhibited 50% of the PCA reaction in rats. While no clear structure-activity relationship emerged, it is clear that a number of the substituted quinaldic acids possessed significant activity and that several were very potent inhibitors of the PCA reaction. Most noteworthy were **6h** (ID_{50} = 0.1 mg/kg) and **6r** (ID_{50} = 0.1 mg/kg), which were 25 times as active as cromolyn sodium (**1**, ID_{50} = 2.5 mg/kg) in this assay. Of the quinoline-3-carboxylic acids **11**, however, most showed only low activity and only **11g** showed an interesting level of activity.

The degree of enhancement obtained by linking two quinaldic acids was a function of both the nature and the location of the bridge. Direct linkage of the two quinaldic acid nuclei between the 6 and 6′ positions (**15a**) resulted in an approximately 50-fold increase in biological activity over that of the unsubstituted quinaldic acid **2a**, while the 8–8′ linked analog **15d** increased the activity by only a factor of 2 to 3.

In summary, many compounds described in this report inhibited the PCA reaction and, therefore, may be potential antiallergy agents. Several examples were significantly more active than the currently available cromolyn sodium (**1**).

Experimental Section

The melting points (capillary) are uncorrected. The ir spectra were measured on a Perkin-Elmer Infracord spectrometer. For those compounds with sufficient solubility in D_2O, DMSO-d_6, or $DCCl_3$, the nmr spectra were measured on a Varian A-60 or a Varian T-60 spectrometer. The ir and nmr spectra were consistent with the assigned structure in all cases. The results of elemental analysis were within ±0.4% of the theoretical values except where noted. Compounds **6a,b**, **10a,b**, and **11a,c,d–f** were obtained from Aldrich Chemical Co. Compound **11b** was obtained from K and K Laboratories. The following solvents were used for recrystallization of the compounds given in Tables I–V: A = methanol, B = ethanol, C = water, D = dimethylformamide, E = dimethyl sulfoxide, F = ethanol-water, G = dimethylformamide-ethanol, H = dimethylformamide-methanol, I = dimethylformamide-water, J = acetic acid, K = benzene-petroleum ether B, L = not recrystallized.

Anilinobutenedioates. The anilinobutenedioates were readily prepared by either of two procedures. Typical reaction conditions are given below.

Procedure A. To a solution (suspension) of the appropriate aniline (0.10 mol) in methanol (150 ml) was added dimethyl acetylenedicarboxylate (0.11 mol). The reaction mixture was stirred at room temperature for 24 hr. The desired product was isolated by filtration or removal of the solvent followed by recrystallization.

Procedure B. A mixture of the appropriate aniline (0.1 mol), diethyl oxalacetate sodium salt (0.1 mol), and glacial acetic acid

Table VI. Inhibition of the Rat PCA Reaction. 1,4-Dihydro-4-oxoquinaldic Acids

Compd	ID_{50}, mg/kg	Route of admin[a]
1	2.5	iv
6a	~50	iv (Na^+)
6b	>50	ip (Na^+)
6c	10	iv (Na^+)
6d	~50	iv (Na^+)
6e	10	iv (Na^+)
6f	10	iv (Na^+)
6g	1	iv (Na^+)
6h	0.1	iv ($THAM^+$)
6i	1	iv ($THAM^+$)
6j	>10	iv ($THAM^+$)
6k	5	iv ($THAM^+$)
6l	5	iv (Na^+)
6m	1	iv ($THAM^+$)
6n	>10	iv ($THAM^+$)
6o	>10	iv ($THAM^+$)
6p	10	iv ($THAM^+$)
6q	>10	iv ($THAM^+$)
6r	0.1	iv ($THAM^+$)
5a	>50	ip
5b	>50	ip
5r	5	iv (HCl salt)
5s	>10	ip
5t	1	iv (HCl salt)
15a	1	iv (Na^+)
15b	>10	iv (Na^+)
15c	10	iv (Na^+)
15d	20	iv (Na^+)
15e	>10	iv ($THAM^+$)

[a]Those compounds which were administered intravenously were done so as the sodium salt or the salt of tris(hydroxymethyl)aminomethane (THAM) or as the hydrochloride salt (**5r** and **5t**).

(60 ml) was heated for 6 hr at 40–50°. The reaction mixture was poured into ice water and the pH of the solution was adjusted to pH 8 with 35% sodium hydroxide. The resulting mixture was extracted with ether (3 × 200 ml). The combined ether extracts were washed sequentially with 0.5 *N* HCl (4 × 200 ml) and 0.5 *N* NaOH (4 × 200 ml). After the organic phase had been dried with anhydrous Na_2SO_4, the solvent was removed under reduced pressure to give the desired product as a crude oil. The oil was used in the subsequent reaction without further purification.

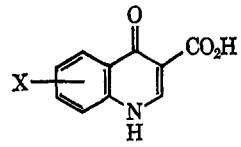
Alkyl 1,4-dihydro-4-oxoquinaldates were prepared by the general procedure described below. The anilinobutenedioate was added carefully to refluxing Dowtherm A. The reaction mixture was heated at reflux for 5–10 min. Upon cooling, the product precipitated and was collected by filtration. Recrystallization gave the desired ester in a pure state.

1,4-Dihydro-4-oxoquinaldic acids were prepared by the following method. The ester was stirred at room temperature in 1.0 *N* NaOH solution, until it was all dissolved. The resulting solution was acidified to pH ≈ 3. The desired acid precipitated and was collected by filtration. Several of the quinoline-2-carboxylic acids were sufficiently insoluble in common solvents to preclude recrystallization. In these cases meaningful elemental analyses were not obtained; however, the spectral properties of these compounds were consistent with the assigned structure.

3-Amino-*p*-toluenesulfono-*o*-toluidide. To a solution of 24.43 g (0.2 mol) of 2,6-diaminotoluene in 100 ml of dry pyridine was added, dropwise, a solution of 19.00 g (0.1 mol) of *p*-toluenesulfonyl chloride in 30 ml of pyridine. The resulting mixture was heated under reflux for 3 hr and the pyridine was removed by distillation under reduced pressure. The residue was dissolved in water and diluted HCl was added until the mixture was strongly acidic. The mixture was filtered, and the filtrate was made basic by the addition of 5% NaOH solution. The mixture was filtered and to the filtrate was added Dry Ice. The resulting gray precipitate was removed by filtration and recrystallized from ethanol. There was obtained 17.7 g (64%) of prisms melting at 139–141°. *Anal.* ($C_{14}H_{16}N_2O_2S$) C, H, N, S.

3′-Aminomethanesulfono-*o*-toluidide. To a stirred solution of 24.43 g (0.2 mol) of 2,6-diaminotoluene in 100 ml of dry pyridine was added, dropwise, 11.46 g (0.1 mol) of methanesulfonyl chloride. The solution was heated on the steam bath for 1 hr. The

Table VII. Inhibition of the Rat PCA Reaction. 1,4-Dihydro-4-oxoquinoline-3-carboxylic Acids



Compd	Substituent	ID_{50}, mg/kg	Route of admin[a]
11a	6-Cl	>50	iv
11b	7-CF_3	>50	ip
11c	6-NO_2	>50	ip
11d	7-OCH_3	~50	iv
11e	2-Ph	>50	ip
10a	8-CF_3 (Et ester)	>50	ip
11f	8-CF_3	50	iv
11g	8-Cl	10	iv
10b	8-Cl (Et ester)	>50	ip
10c	H (Et ester)	>50	ip

[a]Those compounds which were administered iv were done so as their sodium salt.

pyridine was removed by distillation under reduced pressure. To the residue was added water; the mixture was acidified with dilute HCl and filtered. The filtrate was basified with a 5% NaOH solution and filtered and the filtrate was treated with solid CO_2. The precipitate was removed by filtration and recrystallized from ethanol to give 11.90 g (60%) of gray needles melting at 125–126°. *Anal.* ($C_8H_{12}N_2O_2S$) H, N, S; C: calcd, 47.98; found, 47.52.

1,1′-(Trimethylenedioxy)bis(4-nitrobenzene). A mixture of *p*-nitrophenol (27.8 g, 0.2 mol), 1,3-dibromopropane (20.2 g, 0.1 mol), potassium carbonate (27.6 g, 0.2 mol), and acetone (300 ml) was refluxed for 6 days. The reaction mixture was poured into water (1 l.) and the insoluble white solid was collected by filtration and washed thoroughly with water (27.3 g, 83%, mp 128°). Recrystallization from ethanol gave white needles. *Anal.* ($C_{15}H_{14}N_2O_6$) C, H, N.

4,4′-(Trimethylenedioxy)dianiline. 1,1′-(Trimethylenedioxy)bis(4-nitrobenzene) (10.0 g) was dissolved in absolute ethanol (200 ml) and 1.0 g of platinum oxide was added. Reduction was carried out on a Parr hydrogenator for 2 hr. The solution was filtered with suction and the catalyst was washed with a few milliliters of ethanol. A light tan precipitate formed on cooling and was collected by filtration (6.45 g, mp 102–104°, 79% yield). Recrystallization of 200 mg from methanol gave a material melting at 104–105°. *Anal.* ($C_{15}H_{18}O_2N_2$) C, H, N.

Methyl 6-Amino-1,4-dihydro-8-methyl-4-oxoquinaldate (5r). A suspension of 5.24 g (0.02 mol) of methyl 1,4-dihydro-8-methyl-6-nitro-4-oxoquinaldate, 1 g of 10% palladium-on-charcoal catalyst, and 40 ml of DMF was hydrogenated at a pressure of 3 atm of hydrogen. The catalyst was removed by filtration and the filtrate was poured into water. The precipitate was removed by filtration and recrystallized from methanol. There was obtained 2.72 g (59%) of yellow prisms melting at 236° dec. *Anal.* ($C_{12}H_{12}N_2O_3$) H, N; C: calcd, 62.06; found, 61.54.

Methyl 5-Amino-1,4-dihydro-8-methyl-4-oxoquinaldate (5g). To a suspension of 9.82 g (0.0375 mol) of methyl 1,4-dihydro-8-methyl-4-oxo-5-nitroquinaldate in 100 ml of DMF was added 1 g of 10% palladium-on-charcoal catalyst. The mixture was hydrogenated at 3 atm of hydrogen. The catalyst was removed by filtration and the filtrate was poured into water. The precipitate was removed by filtration. There was obtained 7.68 g (88%) of yellow needles melting at 186–188°. Recrystallization from ethanol raised the melting point to 187–188°. *Anal.* ($C_{12}H_{12}N_2O_3$) C, H, N.

Methyl 7-Amino-1,4-dihydro-8-methyl-4-oxoquinaldate (5f). A solution of 29.3 g (0.1 mol) of dimethyl (3-nitro-*o*-toluidino)butenedioate in 200 ml of hot Dowtherm A was added to 200 ml of refluxing Dowtherm A. The reaction mixture was heated under reflux for 15 min and cooled to room temperature, and the product was removed by filtration. A suspension of the material obtained [22.5 g (86%)] in 390 ml of DMF was hydrogenated at 3 atm of hydrogen using 2.1 g of 10% palladium-on-charcoal catalyst. The catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. The residue upon recrystallization from ethanol–water gave 15.4 g (77%) of yellow prisms melting at 238°. *Anal.* ($C_{12}H_{12}N_2O_3$) C, H, N.

Methyl 1,4-Dihydro-7-amino-4-oxobenzo[*h*]quinoline-2-car-

boxylate (5e). To a solution of 12.6 g (0.042 mol) of methyl 1,4-dihydro-7-nitro-4-oxobenzo[*h*]quinoline-2-carboxylate in 1 l. of methyl cellosolve was added 1 g of 10% palladium-on-charcoal catalyst and the mixture was hydrogenated at 3 atm of hydrogen. When the theoretical amount of hydrogen was absorbed then the catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. There was obtained 10.0 g (88%) of a yellow-orange solid melting at 245° dec. *Anal.* ($C_{15}H_{12}N_2O_3$) H, N; C: calcd, 67.15; found, 66.18.

Methyl 5-Amino-8-chloro-1,4-dihydro-4-oxoquinaldate (5t). A mixture of 6.06 g (0.0214 mol) of methyl 8-chloro-1,4-dihydro-5-nitro-4-oxoquinaldate, 150 ml of methanol, and 6 g of Raney nickel catalyst was hydrogenated at 3 atm of hydrogen pressure. The catalyst was removed by filtration and the solvent was removed by distillation under reduced pressure. The residue was recrystallized from methanol. There was obtained 2.45 g (45%) of red needles melting at 175–176°. *Anal.* ($C_{11}H_9ClN_2O_3$) C, H, N.

Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (10c) was prepared by the method of Riegel, *et al.*[7]

6-Chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (11g) was prepared by the method of Tarbell.[8]

Acknowledgment. We are grateful to the Physical and Analytical Department of The Upjohn Company for determining the elemental analyses and for measuring the ir and uv spectra. We also express our gratitude to Miss Christine VanHout, Mr. Charles E. Fultz, Mr. Robert L. Griffin, Mr. Nelson Major, and Mr. Arlen Taylor for providing expert technical assistance.

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D-(*R*)- and L-(*S*)-3-Alkylaminopyrrolidino-Substituted Dihydrodibenzo[*b,f*]- and -[*b,e*]thiepins, Xanthenes, and Diphenylmethanes†

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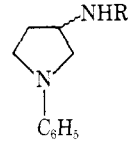
Received December 3, 1973

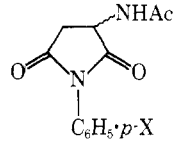
Based upon classical structure–activity relationships, the chiral aminopyrrolidines indicated in the title may be anticipated to exhibit a variety of central and peripheral actions. For these reasons, analogs of known absolute configuration were synthesized in order to assess stereoselective differences in antipsychotic (neuroleptic), antidepressant, anti-Parkinson, antihistaminic, and anticholinergic activities. In fact, few stereoselective differences were observed. Within this series dihydrodibenzo[*b,f*]thiepins would appear to serve as the better lead for the future design of antipsychotic drugs. Structural requirements for H_1 histamine antagonists *in vitro* are discussed.

Recent studies in this laboratory have been concerned with the synthesis and pharmacological evaluation of enantiomorphic drugs synthesized from amino acids of known absolute configuration.[1-4] From a theoretical point of view such compounds may serve as biological probes to study pharmacological receptor sites. For example, this laboratory reported the stereoselective synthesis[1] of L-(*S*)-3-amino-1-phenylpyrrolidine (**1**) from L-(*S*)-aspartic acid as well as the antihistaminic and anticholinergic properties of the L-(*S*)- and D-(*R*)-3-ethylamino analogs **2** determined *in vitro*.[1,2] While L-(*S*)-**2** possessed ten times greater antihistaminic potency than D-(*R*)-**2**, only the latter enantiomorph had measurable anticholinergic activity. In another study having potential therapeutic significance we synthesized a series of para-substituted *N*-acetyl-L-(*S*)- and D-(*R*)-α-amino-*N*-phenylsuccinimides (**3**) and glutarimides (**4**) from amino acids of known absolute configuration.[3] Assessment of the anticonvulsant properties[3,4] within these two series of imides revealed that they also exhibited stereoselective biological activity with the magnitude of the activity difference between isomers a function of the para substituent on the phenyl ring.

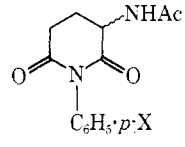
In an attempt to provide leads for the future design of



L-(*S*) or D-(*R*)
1, R = H
2, R = Et



L-(*S*) or D-(*R*)
3



L-(*S*) or D-(*R*)
4

clinically useful drugs, the synthesis and pharmacological evaluation of selected tricyclic and diphenylmethane analogs (**5–9**) containing chiral aminopyrrolidino side chains are described in this article. Based upon classical structure–activity relationships[5-7] it may be anticipated that such analogs should exhibit one or more of the following actions: antipsychotic (neuroleptic), antidepressant, anti-Parkinson, antihistaminic, and anticholinergic activities. The comparative properties of these compounds are discussed in light of results obtained by others studying similar tricyclic or diphenylmethyl systems substituted with other alkylamino side chains.

Synthetic Aspects. D-(*R*)- and L-(*S*)-aminopyrrolidino analogs **5–9** were synthesized from *N*-acetyl-D-(*R*)- or -L-(*S*)-aspartic anhydride (**10**) and the appropriate aryl amine **11–14** according to methods similar to the one reported for the preparation of D-(*R*)- or L-(*S*)-**2** from D-(*R*)- or L-(*S*)-**10** and aniline[1] (Scheme I). The dihydrodibenzo[*b,f*]thiepin **11**, prepared according to the method of Jilek and coworkers,[8] served as starting material for the

†The authors gratefully acknowledge support of this work through Grants NS-10203 from the National Institute of Neurological Diseases and Stroke and MH-22570 from the National Institute of Mental Health, U. S. Public Health Service. R. K. G. gratefully acknowledges support on Medicinal Chemistry Training Grant GM-1949 from the National Institutes of Health. Competent technical assistance was provided by Karen Alberts.