Quinuclidine Chemistry. 2.[1] Synthesis and Antiinflammatory Properties of 2-Substituted Benzhydryl-3-quinuclidinols

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A number of 2-benzhydryl-3-quinuclidinols were tested for their antiinflammatory activity. The cis isomers were prepared selectively by aluminum isopropoxide reduction of the ketones which were made by the addition of aromatic Grignard reagents to 2-benzylidene-3-quinuclidinones. The most active compound was *cis*-2-(4,4′-difluorobenzhydryl)-3-quinuclidinol. The trans alcohol was less active than the cis isomer. It was made by selectively oxidizing the cis alcohol in a mixture of cis and trans alcohols (formed by $NaBH_4$ reduction of the ketone) followed by chromatography. The two diastereoisomers of the monofluorinated alcohol, *cis*-2-(4-fluorobenzhydryl)-3-quinuclidinol, showed activity but were markedly less active than the difluorinated alcohol. The quinuclidine nitrogen was vital for activity for *cis*-3-(4,4-difluorobenzhydryl)bicyclo[2.2.2]octan-2-one showed only marginal activity.

Physiological properties have long been associated with quinuclidine derivatives, both naturally occurring and synthetic.[2] As part of our work on quinuclidine-containing compounds we prepared a number of benzhydryl-substituted quinuclidines. We now report the synthesis and antiinflammatory properties of *cis*-2-(4,4′-difluorobenzhydryl)-3-quinuclidinol (**17**), a departure from the usually acidic, nonsteroidal antiinflammatory agents, and analogs.

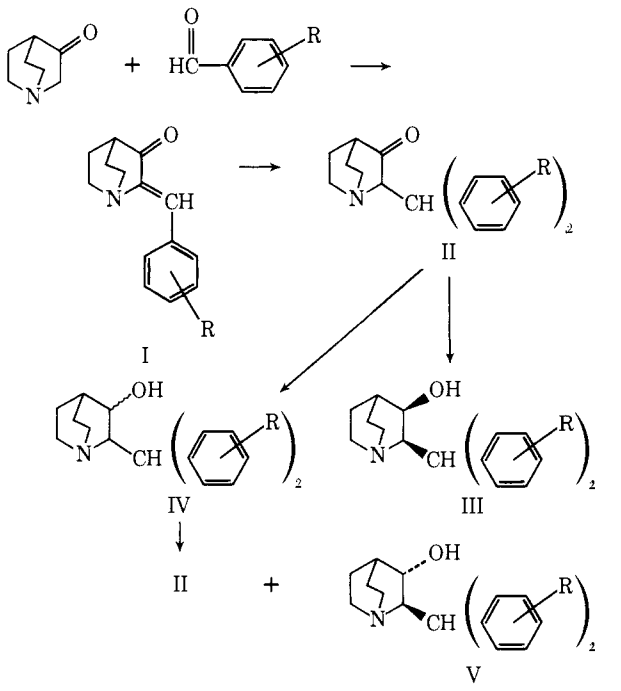
Chemistry. Reaction of an appropriately substituted benzaldehyde with 3-quinuclidinone under base catalysis[1,3] readily gave the corresponding 2-benzylidene-3-quinuclidinone I (see Scheme I and Table I). This α,β-unsaturated ketone was found to undergo 1,4 addition to a considerable extent with Grignard reagents to give the ketone II (Table II). Ketone II was reduced with sodium borohydride to a mixture of cis and trans isomers IV with slight preponderance of the former as estimated by tlc. However, reduction with aluminum isopropoxide under conditions where the acetone is removed as quickly as possible resulted in essentially one isomer. The almost exclusive formation of the cis isomer III results from hydride transfer to the carbonyl group from the least hindered side, *i.e.*, trans to the benzhydryl group.† In all cases the amount of trans isomer was minute. The isolated yields (Table III) of the cis alcohols do not reflect the great specificity of this reduction.

Since the cis alcohol was stereoselectively formed by reduction with aluminum isopropoxide, it seemed possible that under Oppenauer conditions the cis alcohol would oxidize at a greater rate than the trans alcohol. Hydride transfer trans to the bulky benzhydryl group should be more feasible and this was the case. The mixture of cis and trans alcohols obtained by borohydride reduction was oxidized by the Woodward[4] modification of the Oppenauer oxidation using benzophenone. We used the very reactive KH to generate the alkoxide anion of III with a second equivalent to trap the resulting ketone as its enolate, thus preventing possible equilibration. After a reaction time of about 1 hr, the product consisted of only the trans alcohol V and the ketone II. At this point the alcohol and ketone were separated by chromatography or recycled with sodium borohydride to a mixture of alcohols now greatly enriched in the trans isomer. This mixture was again oxidized and the trans alcohol was separated from the ketone by chromatography. For large-scale reactions we found that sodium hydride was a suitable replacement for potassium hydride.

The above reduction–oxidation sequence to afford the trans alcohol is especially useful for benzhydryl groups bearing halogens which might be reductively removed by reagents such as sodium in alcohol.

† See ref 1 for a discussion of stereochemical assignments and nmr data on analogous 2-benzyl-3-quinuclidinols.

Scheme I

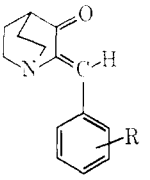


The susceptibility of the trans alcohol to oxidation under these Oppenauer conditions was tested by allowing *trans*-2-benzhydryl-3-quinuclidinol (**24**) to react at reflux overnight. Tlc analysis indicated that only 10–15% conversion of **24** to ketone **16** had occurred.

Addition of *p*-fluorophenylmagnesium bromide (see Scheme II) to 2-benzylidene-3-quinuclidinone[3] (**6**) gave, by 1,4 addition, the ketone **25** as a mixture of diastereoisomers. Reduction of **25** with aluminum isopropoxide proceeded selectively to yield two cis alcohols **26α** and **26β**, differing only in the configuration of the phenyl and the *p*-fluorophenyl groups in the benzhydryl moiety. These isomers were readily separated by chromatography and are designated α and β in the order of their elution.

The importance of the nitrogen atom in regard to the biological properties of these quinuclidine compounds was tested by the synthesis (see Scheme III) of the bicyclo[2.2.2]octane analog. 3-*p*-Fluorobenzylidenebicyclo[2.2.2]octan-2-one (**27**) underwent 1,4 addition with *p*-fluorophenylmagnesium bromide to give ketone **28**. This ketone was also reduced selectively with aluminum isopropoxide to the cis alcohol **29**.

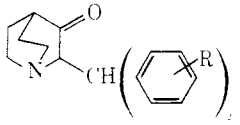
Table I. 2-Benzylidene-3-quinuclidinones (I)



No.	R	Formula	Mp, °C	Yield, %	Analyses
1	*p*-F	$C_{14}H_{14}FNO$	118.5–120.5	91	C, H, N
2	*p*-Br	$C_{14}H_{14}BrNO$	125–126	84.5	C, H, N
3	*p*-OCH_3	$C_{15}H_{17}NO_2$	125–126.5	84.5	C, H, N
4	*m*-F	$C_{14}H_{14}FNO$	103–105	93	C, H, N
5	*p*-CF_3	$C_{15}H_{14}F_3NO$	105.0–106.5	63.8	C, H, N
6	H	$C_{14}H_{15}NO$	130–132	91	C, H, N
7	*p*-Ph	$C_{20}H_{19}NO$	157.0–158.5	91	H, N; C[a]
8	*p*-OPh	$C_{20}H_{19}NO_2$	176–177	60	C, H, N

[a]C: calcd, 83.01; found, 83.50.

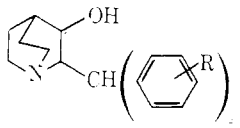
Table II. 2-Benzhydryl-3-quinuclidinones (II)



No.	R	Formula	Mp, °C (solvent)	Yield, %	Analyses
9	*p*-F	$C_{20}H_{19}F_2NO$	163.0–164.5 (EtOH)	43.6	C, H, N
10	*p*-Br	$C_{20}H_{19}Br_2NO$	191.0–192 (EtOH)	32	C, H, N
11	*p*-CF_3	$C_{22}H_{19}F_6NO$	147–148 (EtOH)	50.8	C, H, N
12	*p*-OCH_3	$C_{22}H_{25}NO_3$	144.5–146 (EtOH)	40.8	C, H, N
13	*p*-OPh	$C_{32}H_{29}NO_3$	132.5–133.5 (EtOH)	31.6	C, H, N
14	*p*-Ph	$C_{32}H_{29}NO \cdot HCl$	247.5–248.5 (EtOH–Et_2O)	28[a]	C, H, N, Cl
15	*m*-F	$C_{20}H_{19}F_2NO$	117–118.5 (cyclohexane)	48.4	C, H, N
16	H	$C_{20}H_{21}NO$	117–118 (EtOH)	39	C, H. N

[a]Yield of base.

Table III. 2-Benzhydryl-3-quinuclidinols (III and V)



No.	R	Configuration	Formula	Mp, °C (solvent)	Yield, %	Analyses	Inhibn of carrageenin-induced edema, MED (mg/kg oral)
17	*p*-F	Cis	$C_{20}H_{21}F_2NO$	198–199 (MeOH)[a]	81.8	C, H, N	4 (135)[b]
			$C_{24}H_{25}FNO_5$ (fumarate)	261–262		C, H, N	
		Trans	$C_{20}H_{21}F_2NO$	190–192 (cyclohexane)	36.8	C, H, N	6 (80)
			$C_{24}H_{25}FNO_5$ (fumarate)	235		C, H, N	
18	*p*-Br	Cis	$C_{20}H_{21}Br_2NO$	205–206 (MeOH)	68.3	C, H, N, Br	64 (10)
		Trans	$C_{20}H_{21}Br_2NO$	212–216 (MeOH)		C, H, N, Br	128 (5)
19	*p*-CF_3	Cis	$C_{22}H_{21}F_6NO$	175–176 (cyclohexane)	91.8	C, H, N	Inactive 150 (5)
20	*p*-OCH_3	Cis	$C_{22}H_{27}NO_3$	175–176 (MeOH)	65.6	C, H, N	132 (35)
		Trans	$C_{22}H_{27}NO_3$	206.5–207.5 (2-propanol)	54.5	C, H, N	80 (35)
21	*p*-Ph	Cis	$C_{32}H_{39}NO_2 \cdot C_3H_7OH$[b]	190–191[c] (2-propanol)	68.5	C, H, N	Inactive 150 (5)
22	*p*-OPh	Cis	$C_{32}H_{31}NO_3 \cdot HCl$	271 (EtOH)		C, H, N, Cl	Inactive 64 (5)
		Trans	$C_{32}H_{31}NO_3 \cdot HCl$	206.5–208		C, H, N, Cl	Inactive 75 (5)
23	*m*-F	Cis	$C_{20}H_{21}F_2NO$	163–164 (2-propanol)	83	C, H, N	Inactive 32 (5)
24	H	Cis	$C_{20}H_{23}NO$	196–198 (MeOH)	73	C, H, N	Inactive 150 (5)
		Trans[d]	$C_{20}H_{23}NO$	194.5–197 (MeOH)		C, H, N	Inactive 40 (5)
Indomethacin							1 (80)
Phenylbutazone							16 (84)
Hydrocortisone							8 (60)

[a]First melts at 191–192° with resolidification. [b]Number of rats tested. [c]Crystallized as a solvate. [d]Prepared by Na–EtOH reduction; isolated by chromatography.

Table IV. Inhibition of Carrageenin-Induced Foot Edema in Adrenalectomized Rats by *cis*-**17**

Dose, mg/kg	No. of rats	7 days postadrenalectomy: Edema, ml ± S.E.	Inhibition of edema, %	t[a]	p
64	5	0.72 ± 0.15	37	2.10	=0.05
32	10	0.82 ± 0.15	28	1.81	<0.1
16	8	0.63 ± 0.06	45	4.47	<0.001
8	10	0.74 ± 0.06	35	3.54	<0.01
Control	10	1.14 ± 0.13			

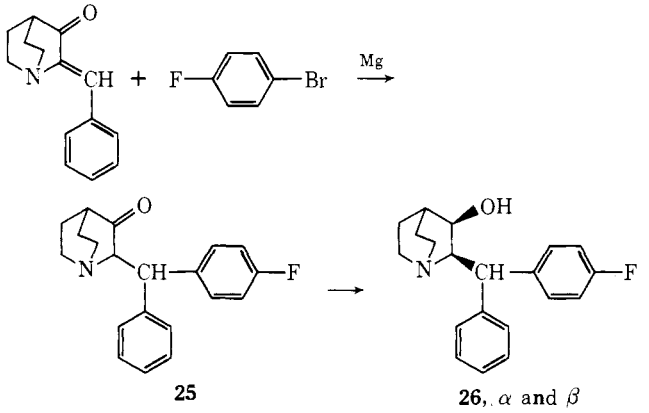
[a]Student's t test.

Table V. Effect of Orally Administered *cis*-**17** on Granuloma Pouch Exudate Formation

Drug	Dose, mg/kg b.f.d., 4 days	No. of rats	Mean body wt change, g	Vol of exudate, ml ± S.E.	Inhibition, %	t[a]	p
17	32	10	0	2.0 ± 0.7	71	2.24	<0.05
Control		10	+23	7.0 ± 1.3			
17	16	10	+1	2.9 ± 0.8	66	5.23	<0.001
Control		10	+31	8.6 ± 0.6			
17	8	10	+9	2.9 ± 1.0	55	2.59	<0.02
Control		10	+24	6.7 ± 1.1			

[a]Student's t test.

Scheme II



Resolution of racemic *cis*-**17** was effected by fractional crystallization of its dextrorotary mandelate salt prepared with (+)-mandelic acid. Regeneration of the base gave (+)-*cis*-2-(4,4′difluorobenzhydryl)-3-quinuclidinol, the hydrochloride of which was levorotary. The use of (−)-mandelic acid gave the levorotary base, whose hydrochloride salt was dextrorotary.

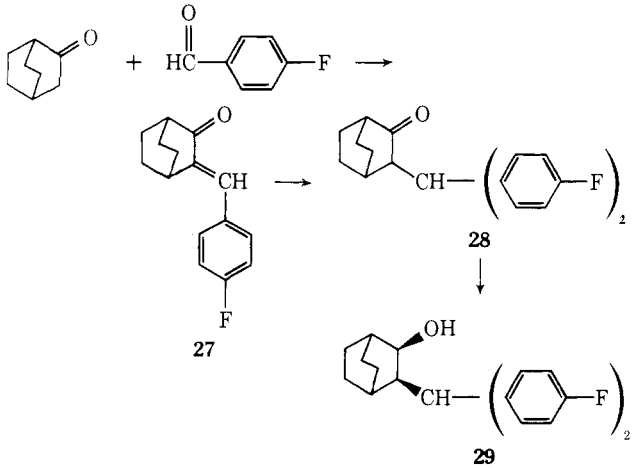
Structure-Activity Relationships. The carrageenin-induced edema test is a widely used procedure for screening compounds for antiinflammatory activity.[5] As shown in Table III *cis*-**17**, as well as the other known antiinflammatory drugs, effectively inhibited the edema caused by the injection of carrageenin. Based on the minimal effective dose (MED) the relative potency of the test drugs was indomethacin > *cis*-**17** > hydrocortisone > phenylbutazone. To determine whether the activity against carrageenin-induced edema in the rat was an indirect effect due to adrenal stimulation, *cis*-**17** was tested in rats 7 days after adrenalectomy. The data from one experiment are summarized in Table IV and demonstrate that *cis*-**17** was effective in inhibiting carrageenin-induced edema even in the absence of the adrenals. Antiedema activity was also found for both antipodes of *cis*-**17** but the dextrorotary base was more active than the levorotary antipode or the racemate. The trans isomer was also quite active (see Table III).

Examination of the data reported in Table V shows that *cis*-**17** produced a significant dose-related reduction in granulomatus exudate.[6,7] Although the effect of *cis*-**17** on exudate formation was associated with some depression in growth rate, no other sign of toxicity was apparent. Significant inhibition of exudate formation was observed with hydrocortisone at dose levels as low as 2 mg/kg b.i.d. Decreased growth was also evident in the hydrocortisone-treated rats. Indomethacin produced some inhibition of exudate formation at 1 mg/kg b.i.d. with little adverse effect on growth rate. Phenylbutazone was ineffective at dose levels as high as 32 mg/kg b.i.d.

In tests against the development of cotton pellet induced granuloma[8,9] and adjuvant arthritis,[10,11] activity with *cis*-**17** was either lacking or marginal.

Replacement of the fluorine atom in **17** by other groups did not enhance activity and only the dibromo analog **18** approached **17** in potency (see Table III). Since *cis*-2-(3,3′-difluorobenzhydryl)-3-quinuclidinol (**23**) was inactive the fluorine atoms must occupy the 4 and 4′ positions of the benzhydryl group, as in **17**, to maximize activity. Substitution of the benzhydryl group by only one fluorine atom still resulted in antiedema activity with **26α** showing activity at 32 mg/kg po and **26β** at 8–16 mg/kg po, but both were markedly less active than *cis*-**17**.

Scheme III



The quinuclidine nitrogen atom was vital for activity. Substitution of nitrogen in **17** by carbon caused loss of activity for *cis*-2-(4,4′-difluorobenzhydryl)bicyclo[2.2.2]octan-3-ol (**29**) showed only marginal activity.

Unlike the acidic, nonsteroidal antiinflammatory drugs, *cis*-**17** did not cause any gastrointestinal lesions in normal animals on either acute or chronic treatment schedules.

Experimental Section

Pharmacology. The salts of the 2-(substituted)benzhydryl-3-quinuclidinols were freely soluble in water and thus were administered as solutions. The base forms were administered as suspensions in a 0.25% Tween 80, distilled water vehicle. The data obtained with both forms of *cis*-**17** were combined, since no difference in activity was observed in various test models. The drugs included for comparison, indomethacin, phenylbutazone, and hydrocortisone, were suspended in the 0.25% Tween 80, aqueous vehicle and administered as suspensions. All *cis*-**17** doses are expressed in terms of the free base and the reference agents in terms of the free acid.

Carrageenin-Induced Edema. Antiedema activity was evaluated by the method of Winter, *et al.*[5] Young, male Sprague-Dawley rats of 160–190-g body weight were used. Food was withheld for 18 hr before the start of the experiment. Water was withheld only during the experiment. All animals received 3 ml/100 g of body weight of distilled water by stomach tube, in which the drug-treated animals received the test material. One hour after oral dosing carrageenin, 0.1 ml of a 1.0% solution, was injected in one hind paw and physiological saline in the other. The degree of edema was measured after 3 hr. Paw volumes were measured by means of a volume differential meter (mercury displacement). The volume difference between the irritant-injected paw and the saline-injected paw was recorded as the degree of edema. Possible adrenal stimulation was assessed by employing the carrageenin-induced edema model in rats adrenalectomized and maintained on physiologic saline in the place of drinking water.

Granuloma Pouch. The granuloma pouch technique of Selye and Jasmin[6] as modified by Robert and Nezamis[7] was used to assess antiphlogistic activity. Animals were dosed orally twice daily for 4 days and sacrificed on the 5th day.

Chemistry. 2-*p*-Fluorobenzylidene-3-quinuclidinone (1). A solution of 12.50 g (0.10 mol) of 3-quinuclidinone and 12.40 g (0.10 mol) of *p*-fluorobenzaldehyde in 25 ml of ethanol was treated with one pellet of sodium hydroxide, refluxed for 2.5 hr, and stirred overnight at room temperature. The yellow solid which formed on cooling was washed with water and ethanol and dried to yield 20.90 g (91%): mp 118.5–120.5°; ir max (Nujol) 5.89 μ (s). *Anal.* ($C_{14}H_{14}FNO$) C, H, N. This is a typical procedure for the preparation of compounds listed in Table I.

2-(4,4′-Difluorobenzhydryl)-3-quinuclidinone (9). A Grignard reagent from 6.61 g (0.0378 mol) of *p*-bromofluorobenzene and 1.01 g (0.0416 g-atom) of magnesium turnings was prepared in the usual way in 40 ml of ether. While the above solution was cooled with a cold water bath, 5.80 g (0.025 mol) of 2-*p*-fluorobenzylidene-3-quinuclidinone in 50 ml of benzene was added dropwise over 1.5 hr. The solution was then stirred overnight at room temperature and decomposed with water. The reaction mixture was then filtered through Celite, solvent was removed *in vacuo*, and the residue was extracted with methylene chloride and dried ($MgSO_4$). Evaporation of solvent left a solid which was recrystallized from ethanol to give 3.59 g (43.6%): mp 163.0–164.5°; ir max (Nujol) 5.82 μ. *Anal.* ($C_{20}H_{19}F_2NO$) C, H, N. This is a typical procedure for the preparation of compounds listed in Table II.

***cis*-2-(4,4′-Difluorobenzhydryl)-2-quinuclidinol (17).** 2-(4,4′-Difluorobenzhydryl)-2-quinuclidinone, 35 g (0.108 mol), and aluminum isopropoxide, 67.3 g (0.33 mol), in 400 ml of 2-propanol were heated in a flask equipped with a 6-in. Vigreux column and distillation head while nitrogen was passed into the solution. After 2.5 hr no acetone could be detected in the distillate by 2,4-DNP solution. Heating was continued for another 30 min and the solvent was removed *in vacuo*. The residue was treated with 60 ml of 50% NaOH solution and 175 ml of water, extracted with methylene chloride, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave 33.9 g of a solid which by tlc (alumina plate with ether) showed a major component with a trace of a second component. Recrystallization from methanol gave 28.9 g (81.8%): mp (191–192° with resolidification) 198–199°; ir max (Nujol) 3.00 μ (m). *Anal.* ($C_{20}H_{21}F_2NO$) C, H, N. This is a typical procedure for the preparation of the cis compounds listed in Table III.

***trans*-2-(4,4′-Difluorobenzhydryl)-2-quinuclidinol (17).** 2-(4,4′-Difluorobenzhydryl)-3-quinuclidinone, 5.0 g (0.0153 mol), was reduced with 1.5 g of sodium borohydride in ethanol in the usual way to give 5.31 g of a mixture of cis and trans isomers. This mixture of alcohols in 45 ml of benzene was added to a mixture of 11.56 g (0.063 mol) of benzophenone and 1.42 g (0.035 mol) of potassium hydride in 35 ml of benzene. After refluxing for 0.75 hr the solution was cooled, treated with ethanol to decompose the excess hydride, and concentrated *in vacuo*. The residue was treated with 2 *N* HCl (aqueous) and extracted with ether. This aqueous phase was treated with dilute sodium hydroxide solution, extracted with methylene chloride, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave 4.69 g of a mixture of **9** and **17**. This mixture was again reduced with sodium borohydride to give 3.94 g of a mixture of isomeric alcohols which was oxidized as above to give 3.42 g of the trans alcohol **17** and ketone **9**. Chromatography using 100 g of neutral alumina gave 1.01 g of the ketone **9** by elution with 50% benzene-petroleum ether followed by 0.32 g of a mixture of **9** and **17**. Elution with 10% ether-benzene gave 1.85 g (36.8%) of the trans alcohol **17**. The analytical specimen was obtained by recrystallization from cyclohexane and exhibited mp 190–192°. *Anal.* ($C_{20}H_{21}F_2NO$) C, H, N. This is a typical procedure for the preparation of the trans isomers listed in Table III. The starting mixture of cis and trans alcohol was prepared by Na-ethanol reduction in **20** and **22**.

2-(4-Fluorobenzhydryl)-3-quinuclidinone (25). A Grignard reagent was prepared in the usual way in ether from 17.5 g (0.10 mol) of *p*-fluorobromobenzene and 2.64 g (0.11 g-atom) of magnesium and cooled with a cold water bath. 2-Benzylidene-3-quinuclidinone,[3] 15 g (0.07 mol), in 200 ml of benzene was added dropwise over 1.5 hr and the solution was then stirred overnight at room temperature. After decomposition with water the solution was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in methylene chloride, dried ($MgSO_4$), and concentrated to give an oil which crystallized by treatment with ethanol. This solid was recrystallized from ethanol to give 9.4 g (30.6%): mp 132–138°; ir max (Nujol) 5.82 μ (s). *Anal.* ($C_{20}H_{20}FNO$) C, H, N.

α- and β-*cis*-2-(4-Fluorobenzhydryl)-3-quinuclidinol (26). 2-(4-Fluorobenzhydryl)-3-quinuclidinone, 11.1 g (0.036 mol), aluminum isopropoxide, 22 g (0.108 mol), and 150 ml of 2-propanol were heated in a flask equipped with a 6-in. Vigreux column and distillation head. Nitrogen was passed through the solution and the solvent was distilled (*ca.* 72°). After 40 min no acetone could be detected in the distillate with a 2,4-DNP solution. Heating was continued for an additional 30 min and the solvent was then removed *in vacuo*. The residue was treated with 50 ml of water and 60 ml of 50% NaOH solution, extracted twice with methylene chloride, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave 11.1 g; tlc (alumina with ether) showed only two components in approximately equal amounts; ir (Nujol) no carbonyl.

This mixture of alcohols was chromatographed on 450 g of neutral activity IV alumina packed in petroleum ether using a gradient elution by adding benzene to a reservoir of 2.5 l. of petroleum ether. Elution, monitored by tlc, gave 2.72 g of the α isomer followed by 2.23 g of the β isomer.

The α isomer was recrystallized from 15 ml of ethanol to give 2.23 g: mp 165–167°; ir max (Nujol) 3.06 μ (s). *Anal.* ($C_{20}H_{22}FNO$) C, H, N.

The β isomer was recrystallized from 25 ml of ethanol to give 1.92 g: mp 201–203°; ir max (Nujol) 3.03 μ (s). *Anal.* ($C_{20}H_{22}FNO$) C, H, N.

3-*p*-Fluorobenzylidenebicyclo[2.2.2]octan-2-one (27). A mixture of 8.7 g (0.07 mol) of bicyclo[2.2.2]octanone and 8.7 g (0.07 mol) of *p*-fluorobenzaldehyde in 25 ml of ethanol was treated with six pellets of potassium hydroxide and refluxed overnight. The solution was cooled and allowed to stand for 3 days, resulting in 6.0 g (37.1%) of a solid: mp 84.0–84.5°; ir max (Nujol) 5.90 (s), 6.20 (s), and 6.25 μ (s). *Anal.* ($C_{15}H_{15}FO$) C, H.

3-(4,4′-Difluorobenzhydryl)bicyclo[2.2.2]octan-2-one (28). A Grignard reagent was prepared in the usual way in ether from 8.1 g (0.046 mol) of *p*-bromofluorobenzene and 1.2 g (0.05 g-atom) of magnesium. 3-*p*-Fluorobenzylidenebicyclo[2.2.2]octan-2-one, 5.3 g (0.023 mol), in 35 ml of ether was added dropwise and the solution was stirred overnight at room temperature. After decomposition with water and dilute hydrochloric acid, the ether was separated, washed, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a solid which was recrystallized from 2-propanol to give 4.5 g (60.8%): mp 142.5–144°; ir max (Nujol) 5.85 μ (s). *Anal.* ($C_{21}H_{20}F_2O$) C, H.

***cis*-3-(4,4′-Difluorobenzhydryl)bicyclo[2.2.2]octan-2-ol (29).** A

mixture of 1.5 g (0.0046 mol) of 3-(4,4'-difluorobenzhydryl)bicyclo[2.2.2]octan-2-one and 4.1 g (0.02 mol) of aluminum isopropoxide in 100 ml of 2-propanol was refluxed in a flask equipped with a 6-in. Vigreux column and distillation head. A stream of nitrogen was passed into the solution to facilitate removal of acetone. When the distillate gave a negative 2,4-DNP test, the solvent was removed *in vacuo*. The residue was diluted with 50 ml of water and 7 ml of 50% sodium hydroxide solution, extracted with methylene chloride, and dried ($MgSO_4$). Removal of solvent gave 1.5 g of a white solid; tlc (silica gel with methylene chloride) showed a trace of the trans isomer. Recrystallization from methanol gave 1.3 g: mp 180–182°; ir max (Nujol) 2.85 μ (s). *Anal.* ($C_{21}H_{22}FO$) C, H.

Resolution of (±)-*cis*-2-(4,4'-Difluorobenzhydryl)-3-quinuclidinol (17). (±)-*cis*-2-(4,4'-Difluorobenzhydryl)-3-quinuclidinol, 2.0 g (0.0068 mol), in 60 ml of warm acetone was treated with 0.92 g (0.0068 mol) of (+)-mandelic acid in 20 ml of acetone and left overnight at room temperature to deposit 2.37 g of the mandelate salt, mp 215–218° dec. An amount sufficient for melting point determination was converted to the free base: mp 198–199° (unchanged). Three fractional recrystallizations from acetone gave 0.52 g: mp 228–229°; $[\alpha]^{20}D$ +26.3° (*c* 0.64 in MeOH). Of this material 380 mg was converted to the free base and recrystallized from 1 ml of methanol to give 166 mg: mp 185–186°; $[\alpha]^{20}D$ +21.4° (*c* 2.06 in MeOH); $[\alpha]^{25}D$ −30° (*c* 1.13 in 0.06 *N* HCl).

A similar resolution with 0.92 g (0.0068 mol) of (−)-mandelic acid gave 2.58 g of the salt: mp 217–222° dec (base, mp 198–199°). Four recrystallizations from acetone gave 0.38 g: mp 228–230° dec; $[\alpha]^{20}D$ −30.3° (*c* 0.79 in MeOH). This salt was converted to the free base which was recrystallized from methanol to give 99 mg: mp 185–186°; $[\alpha]^{20}D$ −20° (*c* 1.0 in MeOH); $[\alpha]^{25}D$ +27° (*c* 1.0 in 0.06 *N* HCl).

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Molecular Orbital Studies on the Mechanism of Drug-Receptor Interaction. 1. Adrenergic Drugs. Conformation and Reactivity of Isoproterenol and 1-(*p*-Nitrophenyl)-2-isopropylaminoethanol

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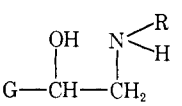
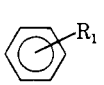
Quantum mechanical calculations were performed by the molecular orbital CNDO method on conformations and reactivities of two typical β-adrenergic drugs, isoproterenol and INPEA, the first with a stimulant activity and the second with a blocking one. A theoretical approach to explain the drug-receptor interaction was attempted on the basis of the electrostatic molecular potentials of the drugs. The interactions with possible receptor site models essentially confirm the gas-phase conformational analysis. The significance of the results obtained is discussed within the framework of current knowledge and theories of β-adrenergic agonist-antagonist activity.

Adrenergic β-receptor antagonists, a class of highly selective blocking drugs, are, with very few exceptions, derivatives of ethanolamine (I) or of oxypropanolamine (II), the only difference between the two types of compounds being the introduction of an OCH_2 group between the aromatic moiety and the ethanolamine chain. As regards derivatives I, a comparison of their structures with those of β-adrenergic drugs shows that the structural requirements necessary for eliciting β-adrenergic blocking activity are parallel to a remarkable degree to those required for adrenergic receptor stimulation. The nature and position of the substituents at the phenyl group or the type of the aromatic group confers β-adrenergic or β-adrenolitic properties. In derivatives II the aromatic portion can range from a substituted phenyl or naphthyl group to an aromatic ring fused to a heterocyclic system or a single heterocyclic ring, without appreciable change in the β-blocking activity.



I, G =  or different group

II, G = CH_2O–  or CH_2O–different aromatic group

Although β-blocking agents have been extensively studied especially in recent years,[1] together with their structural relationship with β-adrenergic agonists, no satisfactory explanation has so far been given of the way in which the nature of the aromatic moiety in derivative I can affect the β activity and of the mechanism with which compounds II elicit their β-blocking activity.

The adrenergic drug-receptor interaction generally involves rather weak bonds, such as ionic interactions, hydrogen bonds, dispersion forces, and hydrophobic bonds; stable covalent bonds are probably not involved.[1e,2-4] In fact, the nature of the adrenergic action is highly reversible, as is demonstrated not only by the rapid termination