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Quinuclidine Chemistry. 3.[1] β-*cis*-2-(4′-Chlorobenzhydryl)-3-quinuclidinol, a New Central Nervous System Stimulant. Importance of the Benzhydryl Configuration

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The 1,4 addition of *p*-chlorophenylmagnesium bromide to 2-benzylidene-3-quinuclidinone gave 2-(4-chlorobenzhydryl)-3-quinuclidinone as two diastereoisomers. Selective reduction of this ketone with aluminum isopropoxide gave the two *cis*-2-(4-chlorobenzhydryl)-3-quinuclidinols, which differ only in the configuration of the benzhydryl group, designated α and β in order of their elution on chromatography. Reduction with $NaBH_4$ gave a mixture of four isomeric alcohols, of which the two cis isomers were selectively oxidized. The two *trans*-2-(4-chlorobenzhydryl)-3-quinuclidinols were chromatographically separated and designated α and β in order of elution. Only the β-cis and β-trans alcohols showed CNS stimulant properties. The β-cis isomer was shown to be related both qualitatively and quantitatively more to methylphenidate (Ritalin) than to *d*-amphetamine.

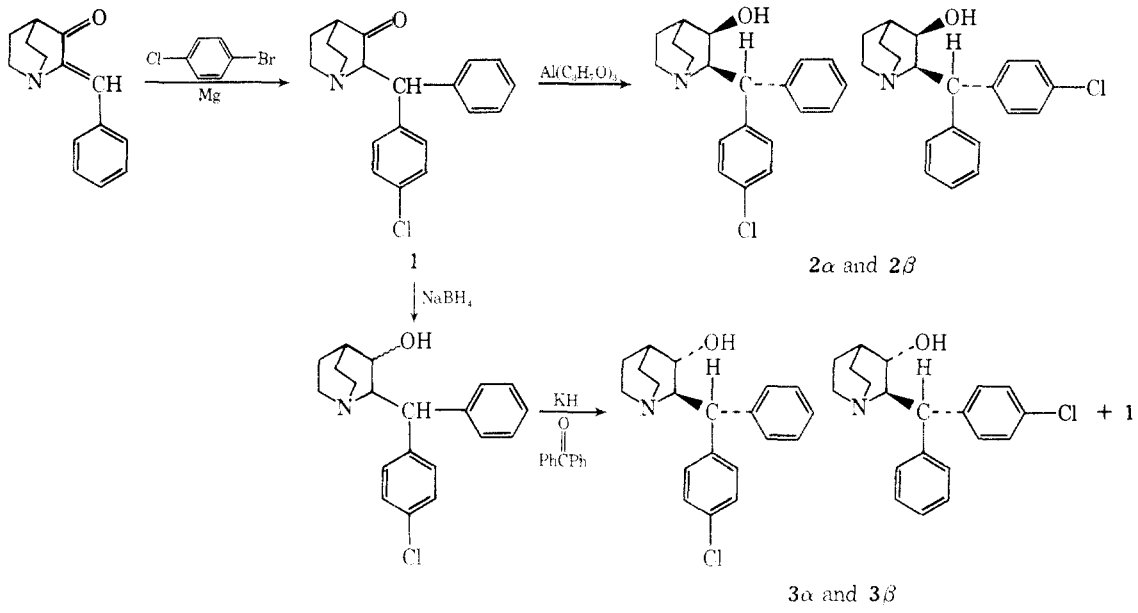
Our interest in quinuclidines as medicinal agents led to the discovery of the antiinflammatory properties of *cis*-2-(4,4′-difluorobenzhydryl)-3-quinuclidinol.[1] This compound was devoid of any effects on the central nervous system (CNS). We now report the synthesis of a potent CNS stimulant, β-*cis*-2-(4′-chlorobenzhydryl)-3-quinuclidinol (**2**), in which activity is critically dependent upon the configuration of the benzhydryl moiety.

Chemistry. The reaction of 2-benzylidene-3-quinuclidinone[2,3] with *p*-chlorophenylmagnesium bromide (see Scheme I) gave, by 1,4 addition, the ketone **1** as a mixture of two diastereoisomers. Reduction of **1** with aluminum isopropoxide under conditions where the resulting acetone was immediately removed to prevent equilibration gave selectively the two isomeric cis alcohols **2** in approximately equal amounts as detected by tlc analysis. The cis configuration is a consequence of hydride transfer to the carbonyl from the least hindered side, *i.e.*, trans to the benzhydryl group.† These isomers were separated by column chromatography and were designated **2**α and **2**β in order of their elution. These alcohols differ only in the configuration of the benzhydryl moiety.

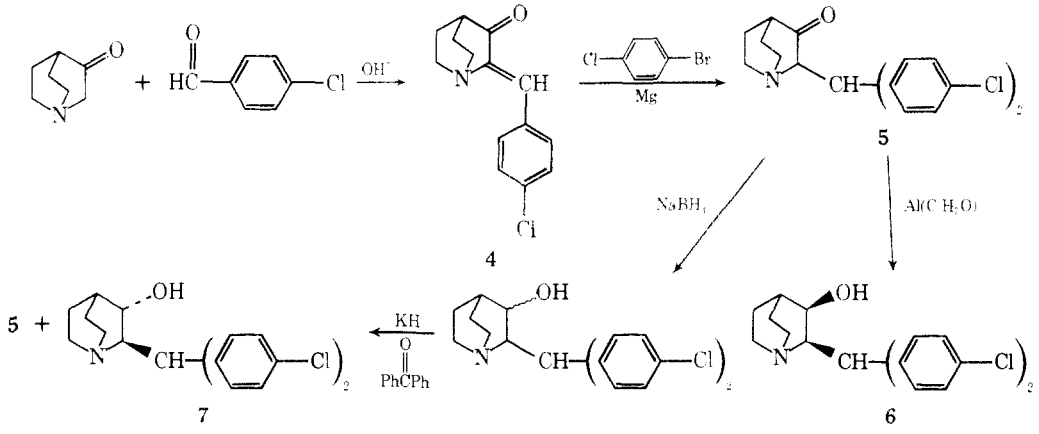
Reduction of ketone **1** with sodium borohydride gave a

† See ref 1 and 2 for additional examples of selective reduction of 2-substituted 3-quinuclidinones with aluminum isopropoxide to the cis alcohols.

Scheme I



Scheme II



mixture of four isomeric racemic alcohols as detected by tlc analysis. Modified Oppenauer oxidation[1,4] of this mixture using at least 2 equiv of potassium or sodium hydride and excess benzophenone resulted in preferential oxidation of the two cis alcohols (higher R_f values on tlc), leaving the two trans alcohols **3** and the ketone **1**.‡ Since the newly formed ketone **1** is trapped as its enolate, equilibration is prevented. This reduction–oxidation sequence was repeated two times and the trans alcohols were isolated by column chromatography to give, in order of elution, 3α and 3β.

2-*p*-Chlorobenzylidene-3-quinuclidinone (**4**) was prepared from 3-quinuclidinone and *p*-chlorobenzaldehyde under base catalysis (Scheme II). Reaction of **4** with *p*-chlorophenylmagnesium bromide gave the ketone **5** which was reduced selectively with aluminum isopropoxide to the cis alcohol **6**. Reduction of **5** with sodium borohydride gave a mixture of cis and trans alcohols and oxidation of this mixture as above gave the trans alcohol **7** which was isolated by column chromatography.

Structure–Activity Relationships. Among these 2-benzhydryl-3-quinuclidinols stimulation of the central nervous system was confined to the compounds bearing a monochlorinated benzhydryl group, and within this class only select isomers were active. The cis isomer 2β was active at 10 mg/kg po (MSD; see Table I) in the mouse, whereas the cis isomer 2α did not have any significant activity at doses at high as 100 mg/kg po. In the trans series 3β (MSD 6 mg/kg po) exhibited the same potency range as 2β (MSD 10 mg/kg po), but 3α showed no stimulation at 40 mg/kg po. Thus, activity in either the cis or trans series is governed principally by the configuration of the benzhydryl group which we conclude to be the same in 2β and 3β. Introduction of chlorine into each of the phenyls of the benzhydryl group was detrimental to activity for both **6** (MSD >50 mg/kg po) and **7** (MSD >80 mg/kg po) were definitely weaker. Although these two compounds are closely related to *cis*-2-(4,4′-difluorobenzhydryl)-3-quinuclidinol, a potent antiinflammatory,[1] **6** at 150 mg/kg po and **7** at 80 mg/kg po were inactive in the rat paw carrageenan edema test.[5]

A comparison of the pharmacology of 2β with methylphenidate (Ritalin) and *d*-amphetamine is presented in Table I. In testing for anorexia in rats 2β failed to inhibit food intake significantly (*i.e.*, >50%) in a wide dose range (2.5–20 mg/kg po) while *d*-amphetamine at 1 and 2 mg/kg po caused 60 and 100% inhibition for 2 hr, respectively. Methylphenidate at 10 mg/kg po inhibited food intake by 60% for 1 hr only. In the dog studies, all dogs tested with the highest dose (10 mg/kg po) of 2β and methylphenidate consumed their food within 30 min, while the dogs tested with *d*-amphetamine at 1 and 2 mg/kg po, but not at 0.5

‡ See ref 1 for a discussion of the ease of oxidation of *cis*- and *trans*-2-benzhydryl-3-quinuclidinols.

Table I. Comparative Pharmacology of 2β, Methylphenidate, and *d*-Amphetamine

	2β	Methylphenidate HCl	*d*-Amphetamine H_2SO_4
Acute toxicity			
Isolated mice, LD_{50}	225 mg/kg po } Ratio	450 mg/kg po } Ratio	60 mg/kg po } Ratio
Aggregated mice, LD_{50}	75 mg/kg po } 3:1	60 mg/kg po } 7.5:1	10 mg/kg po } 6:1
Gross behavioral stimulation			
Mouse, minimal stimulation dose (MSD)	10 mg/kg po	20 mg/kg po	5 mg/kg po
Squirrel monkey, MSD	5 mg/kg po	2.5 mg/kg po	1 mg/kg po
Anorectic activity			
Rat, ED_{50}	>20 mg/kg po	10 mg/kg po	1 mg/kg po
Dog, ED_{50}	>10 mg/kg po (stimulation, toxic)	>10 mg/kg po (stimulation)	1 mg/kg po (stimulation)
Mean arterial blood pressure			
Increase >10%, anesthetized dog (n^a)	>5 mg/kg iv (2)	>4 mg/kg iv (3)	0.1 mg/kg iv (3) (30% increase)

[a] n = number of determinations.

mg/kg po, failed to complete their meal within 5 hr. At the highest dose (10 mg/kg po) of 2β and methylphenidate mg/kg iv) and methylphenidate (4 mg/kg iv) failed to produce a significant effect (>10%) while *d*-amphetamine at 0.1 mg/kg iv caused a 30% increase.

Conclusions

On the basis of the presented results 2β, methylphenidate, and *d*-amphetamine were CNS stimulants in laboratory animals. The compounds can be listed in the order of decreasing potencies in several tests: (a) acute toxicity, *d*-amphetamine > 2β > methylphenidate; (b) stimulant activity, *d*-amphetamine > 2β > methylphenidate; (c) anorectic activity, *d*-amphetamine > methylphenidate > 2β; (d) pressor activity, *d*-amphetamine > 2β = methylphenidate. Thus, 2β appears to be related, both qualitatively and quantitatively, more to methylphenidate than to *d*-amphetamine.

Experimental Section

Pharmacology. Acute Toxicity. Swiss albino male mice were treated orally with graded doses of test compounds (four mice/dose) and observed 3–4 hr postadministration for deaths. Animals were kept in 1000-ml glass beakers either individually (isolated) or in groups of four (aggregated). If in the course of determining aggregated toxicity some animals died, they were replaced by similarly treated mice in order to maintain the constant aggregation. Only the original four mice were used for establishment of LD_{50} which was determined by graphical means.

Gross Behavior Stimulation. Swiss albino male mice were treated orally with graded doses (three mice/dose) and observed for gross behavioral effects in plastic cages for a period of 3 hr and the minimal stimulant dose (MSD) was determined. The modified scoring procedure as described by Irwin[6] was used. Male squirrel monkeys (600–1000 g), housed in communal cages allowing free movements and animal interaction, were treated orally with graded doses (two monkeys/dose) and the minimal stimulant dose was established. The drug effects on social interaction, locomotor activity, body movements, motor coordination, and response to handling were studied.

Anorectic Activity. Albino male rats in groups of four were starved overnight and allowed to eat (Purina rat chow) for 5 hr the next morning for 3 days prior to the testing. On the test day they were dosed orally with graded doses of test compounds 60 min prior to food exposure (four rats/dose) and their food consumption was measured for 5 hr at 60-min intervals. Reduction of food intake by 50% in comparison to saline groups was considered as a significant drug effect.

Mongrel dogs (10–15 kg) were starved overnight and allowed to consume their food in a 30-min time interval. Only those animals which exhibited such a consistent eating performance were used for the drug test. On the test day dogs were dosed orally with graded doses (three dogs/dose) 60 min prior to food exposure (1 lb of canned dog food). Failure to complete food within 30 min was considered as a drug effect.

Mean Arterial Blood Pressure. Mongrel dogs (10–15 kg) were prepared for the recording of arterial blood pressure under pentobarbital anesthesia. A 10% increase in mean arterial pressure was considered as a significant drug effect.

Chemistry. 2-(4-Chlorobenzhydryl)-3-quinuclidinone (1). A Grignard reagent was prepared in the usual way from 8.10 g (0.042 mol) of 4-bromochlorobenzene and 1.12 g (0.046 g-atom) of magnesium in 50 ml of ether and then cooled in cold water. A solution of 6.0 g (0.028 mol) of 2-benzylidene-3-quinuclidinone[2,3] in 150 ml of benzene was added dropwise over 1 hr and the solution was stirred overnight at room temperature. Water was added and the solution was filtered through Celite, the salts being washed with THF, and the filtrate was concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 and dried ($MgSO_4$), concentrated, and crystallized from ethanol to give 2.72 g (30%): ir max (Nujol) 5.82 μ (s). Recrystallization from cyclohexane gave the analytical specimen: 2.0 g; mp (softens 175) 184–187°. *Anal.* ($C_{20}H_{20}ClNO$) C, H, N.

α- and β-*cis*-2-(4-Chlorobenzhydryl)-3-quinuclidinol (2). In a flask equipped with a short Vigreux column and distillation head was heated a solution of 13.53 g (0.0416 mol) of 2-(4-chlorobenzhydryl)-3-quinuclidinone and 25 g of aluminum isopropoxide in 300 ml of 2-propanol. Nitrogen was passed into the solution to facilitate removal of the acetone. After 4 hr the distillate gave a negative test with 2,4-DNP reagent and the solvent was removed *in vacuo*. The residue was treated with dilute sodium hydroxide solution, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration *in vacuo* gave 13.5 g of a white solid which by tlc (alumina with CH_2Cl_2) was an equal mixture of two cis isomers. This material was chromatographed on 1.3 kg of activity II neutral alumina monitored by tlc using gradient elution by adding benzene to a reservoir of 2 l. of petroleum ether. Eluted in order were 4.0 g of the α-cis isomer, 4.7 g of a mixture of α and β isomers, and 5.24 g of the β-cis isomer.

The α isomer was recrystallized from methanol to give 3.04 g: mp 168–170°; ir max (Nujol) 3.03 μ. *Anal.* ($C_{20}H_{22}ClNO$) C, H, N, Cl.

The β isomer, 2.24 g, was recrystallized from methanol to give 1.76 g: mp 235–236°; ir max (Nujol) 3.07 μ. *Anal.* ($C_{20}H_{22}ClNO$) C, H, N, Cl.

α- and β-*trans*-2-(4-Chlorobenzhydryl)-3-quinuclidinol (3). A solution of 9.0 g (0.028 mol) of 2-(4-chlorobenzhydryl)-3-quinuclidinone in 200 ml of methanol and 100 ml of CH_2Cl_2 was reduced with 4.0 g of $NaBH_4$ in the usual way to yield 8.6 g; tlc (alumina with ether) showed four components.

This material (0.027 mol) in 200 ml of benzene was added to a refluxing solution of 2.37 g (0.06 mol) of potassium hydride and 16.4 g (0.09 mol) of benzophenone. After refluxing for 2 hr the solution was cooled and treated cautiously with ethanol and the solvent was removed *in vacuo*. The residue was treated with excess aqueous 2 *N* HCl and extracted with ether. The aqueous phase was made alkaline with dilute sodium hydroxide, extracted with CH_2Cl_2, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave 7.90 g; tlc showed the two least mobile of the four alcohols and the more mobile ketone 1.

A second $NaBH_4$ reduction of the above material gave 8.46 g which was oxidized to yield 8.0 g of the alcohol-ketone mixture. A third reduction gave 8.0 g and oxidation gave 7.55 g. Of this mixture, 5.68 g was chromatographed on 450 g of activity IV neutral alumina using gradient elution by adding benzene to a reservoir of 2.5 l. of petroleum ether. Eluted in order were 0.5 g of the ketone 1, 2.80 g of the α isomer, and 2.09 g of the β isomer.

The α isomer was recrystallized from ethanol to yield 1.31 g: mp 201–202°; ir max (Nujol) 3.02 μ (m). *Anal.* ($C_{20}H_{22}ClNO$) C, H, N, Cl.

The β isomer was recrystallized from ethanol to give 1.40 g: mp 215–216.5°; ir max (Nujol) 3.10 μ (m). *Anal.* ($C_{20}H_{22}ClNO$) C, H, N.

2-*p*-Chlorobenzylidene-3-quinuclidinone (4). A solution of 6.25 g (0.05 mol) of 3-quinuclidinone and 7.04 g (0.05 mol) of *p*-chlorobenzaldehyde in 15 ml of ethanol was treated with two pellets of KOH and refluxed for 4 hr. The yellow precipitate was collected, washed with ethanol, and dried to give 10.85 g (87.7%), mp 110–113°. A portion of this material, 1.50 g, was recrystallized from ethanol to give 1.03 g: mp 112.5–114.5°; ir max (Nujol) 5.85 (s) and 6.11 μ (s). *Anal.* ($C_{14}H_{14}ClNO$) C, H, N.

2-(4,4′-Dichlorobenzhydryl)-3-quinuclidinone (5). A Grignard reagent was prepared in the usual way from 5.23 g (0.0273 mol) of *p*-bromochlorobenzene and 0.66 g (0.0273 g-atom) of magnesium in 60 ml of ether and cooled with cold water. A solution of 4.50 g (0.0182 mol) of 2-*p*-chlorobenzylidene-3-quinuclidinone in 100 ml of benzene was added dropwise over 1 hr and the reaction mixture was stirred at ambient temperature overnight. After the addition of water the mixture was filtered through Celite, the salts being thoroughly washed with THF. Removal of the solvent *in vacuo* left a residue which was dissolved in CH_2Cl_2 and dried ($MgSO_4$). Solvent was removed *in vacuo* and the residue was recrystallized from ethanol to give 3.62 g (55.5%): mp 167.5–170°; ir max (Nujol) 5.81 μ. *Anal.* ($C_{20}H_{19}Cl_2NO$) C, H, N, Cl.

***cis*-2-(4,4′-Dichlorobenzhydryl)-3-quinuclidinol (6).** A solution of 13.12 g (0.0364 mol) of 2-(4,4′-dichlorobenzhydryl)-3-quinuclidinone and 20.0 g (0.098 mol) of aluminum isopropoxide in 300 ml of 2-propanol was heated in a flask bearing a short distillation column while nitrogen was passed into the solution. After 4.5 hr no acetone could be detected in the distillate with 2,4-DNP solution and the solvent was removed *in vacuo*. The residue was diluted with water, made alkaline with 50% sodium hydroxide, extracted with CH_2Cl_2, and dried ($MgSO_4$). Removal of solvent left 12.9 g of a white solid, mp 200–201°. Recrystallization from methanol gave 11.73 g: mp 201–202°; ir max (Nujol) 2.99 μ. *Anal.* ($C_{20}H_{21}Cl_2NO$) C, H, N, Cl.

***trans*-2-(4,4′-Dichlorobenzhydryl)-2-quinuclidinol (7).** 2-(4,4′-Dichlorobenzhydryl)-3-quinuclidinone, 6.0 g (0.0166 mol), was reduced with 1.9 g of $NaBH_4$ in the usual way in methanol-CH_2Cl_2 (1:1) to give 6.19 g of about an equal mixture of cis and trans alcohols. This product was refluxed with 2.46 g (0.051 mol) of NaH (50% in mineral oil) and 15.5 g (0.085 mol) of benzophenone in 100 ml of benzene for 7.5 hr and stirred overnight at room temperature. Excess NaH was destroyed by the cautious addition of ethanol and the solvent was removed *in vacuo*. The residue was treated with aqueous 2 *N* HCl and extracted with ether. The aqueous phase was then made alkaline with sodium hydroxide, extracted with CH_2Cl_2, washed, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave 4.92 g of a solid which by tlc (alumina with ether) was a mixture of the trans alcohol **7** and ketone **5**. The two components were separated by chromatography using 120 g of neutral alumina. Elution with 50% benzene–petroleum ether gave 2.16 g of **5** and 0.50 g of a mixture of **5** and **7**. Elution with benzene and ether–benzene gave 1.85 g of **7**. The analytical specimen was prepared by recrystallization from cyclohexane and exhibited mp 220–221°; ir max (Nujol) 3.04 μ. *Anal.* ($C_{20}H_{21}Cl_2NO$) C, H, N, Cl.

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Pyrido[2,3-*d*]pyrimidine Antibacterial Agents. 3.[1] 8-Alkyl- and 8-Vinyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic Acids and Their Derivatives

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The preparation and antibacterial activity of a series of the title compounds (21–73) are described. These compounds were prepared from the 2-methylthio derivatives **2** and **3** *via* the 2-methylthio-8-substituted compounds **4–20**; compounds **4–20** easily underwent displacement reactions with a variety of piperazines to afford 2-(4-substituted or unsubstituted 1-piperazinyl) derivatives **21–56**, of which **21**, **22**, **27**, and **51** with unsubstituted piperazinyl group at position 2 are converted subsequently into **57–73** by alkylation, acylation, sulfonylation, or addition of isocyanates to the piperazine nitrogen. The hexahydro-1*H*-1,4-diazepinyl analog **74** was also prepared. The most active members in this series of compounds were found to be 8-ethyl- and 8-vinyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acids (**22** and **51**), both of which are more active *in vitro* and *in vivo* against gram-negative bacteria, including *Pseudomonas aeruginosa*, than piromidic acid (**1**). Structure–activity relationships are discussed.

Our recent finding of piromidic acid (**1**)[1] (generic name of 8-ethyl-5,8-dihydro-5-oxo-2-pyrrolidinopyrido[2,3-*d*]pyrimidine-6-carboxylic acid), which possesses an excellent *in vitro* and *in vivo* activity[2] against staphylococci and gram-negative bacteria except *Pseudomonas aeruginosa*, prompted an extension of our study on the pyrido[2,3-*d*]pyrimidine in hopes of further enhancing the activity and broadening the antibacterial spectrum possessed by **1**. In view of the structure–activity relationship[1] that a secondary amino group at position 2 seemed to play an important role in enhancing the activity, we prepared a series of compounds having a piperazinyl group at position 2 as well as a variety of substituents at position 8 on 5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid.

Chemistry. Easily accessible compounds, 5,8-dihydro-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**2**) and its ethyl ester **3**,[3] served as starting materials in our project. Compounds **21–74** were prepared as shown in Scheme I by modifications of the procedures described previously.[1,3]

Compounds **2** and **3** were subjected to alkylation with an appropriate alkyl halide in dimethylformamide in the presence of potassium carbonate or sodium hydride to give the corresponding 8-alkyl derivatives **4–18**; acid **17** was