Quinuclidine Chemistry. 4.[1] Diuretic Properties of *cis*-3-Amino-2-benzhydrylquinuclidine

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A number of 3-amino-2-benzhydrylquinuclidines were tested for diuretic activity in both rats and dogs. The Schiff base formed from 2-benzhydryl-3-quinuclidinone and benzylamine was reduced with $NaBH_4$ to a mixture of isomers, the cis isomer being preponderant. *cis*-2-Benzhydryl-3-benzylaminoquinuclidine was isolated by chromatography and debenzylated to *cis*-3-amino-2-benzhydrylquinuclidine, the most active compound in this series. The corresponding trans isomer was considerably less active. It was made by reacting the mesylate of *cis*-2-benzhydryl-3-quinuclidinol with NaN_3 to form *trans*-3-azido-2-benzhydrylquinuclidine which was reduced with $LiAlH_4$. In dose–response studies (sodium excretion as a function of dose) in rats the maximal or ceiling effect of *cis*-3-amino-2-benzhydrylquinuclidine was considerably greater than that of hydroflumethiazide but less than that of furosemide. An unusual biphasic dose–response was seen in dogs with *cis*-3-amino-2-benzhydrylquinuclidine, centering around 10 mg/kg.

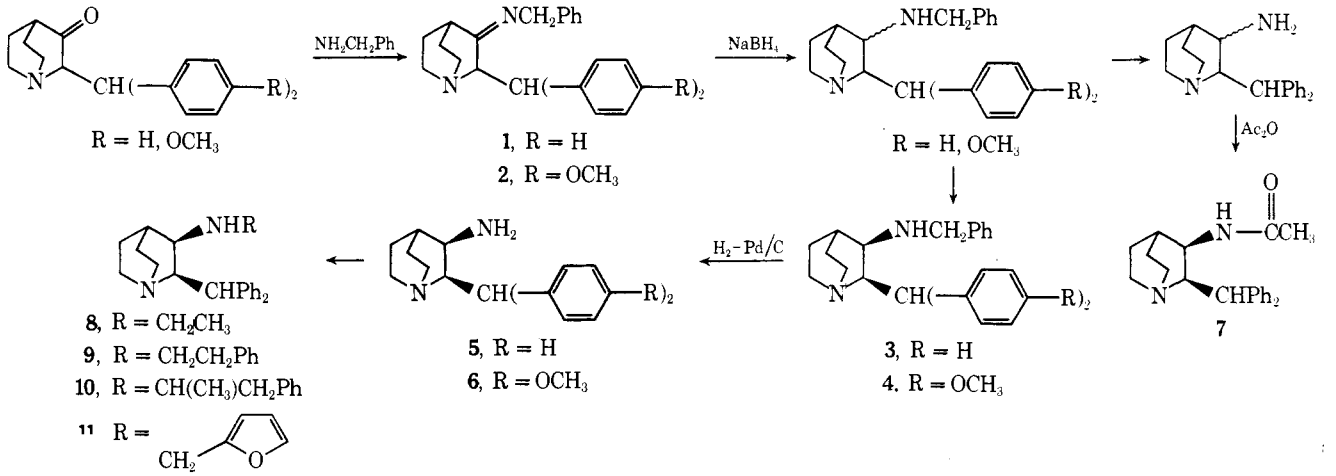
Our interest in the chemistry of quinuclidines led to the synthesis of 2-(substituted)benzhydryl-3-quinuclidinols. Among these compounds *cis*-2-(4,4′-difluorobenzhydryl)-3-quinuclidinol was found to be a potent antiinflammatory[2] and β-*cis*-2-(4-chlorobenzhydryl)-3-quinuclidinol was found to be a central nervous system stimulant,[1] related more to methylphenidate than to *d*-amphetamine. We now report the diuretic properties of *cis*-3-amino-2-benzhydrylquinuclidine (**5**) and analogs thereof.

Chemistry. We have reported previously the synthesis of 2-(substituted)benzhydryl-3-quinuclidinones[2] by 1,4 addition of aromatic Grignard reagents to 2-(substituted)benzylidene-3-quinuclidinones.[3,4] As outlined in Scheme I, 2-benzhydryl-3-quinuclidinone reacted with benzylamine to yield the Schiff base. Reduction with $NaBH_4$ followed by crystallization from 2-propanol gave a mixture of 2-benzhydryl-3-benzylaminoquinuclidines, which by GC was 79.7% of the cis isomer **3** and 20.3% of the trans isomer **26**. Approximately the same ratio could be estimated by TLC analysis. Stereochemical assignment, made on the basis of the ease of approach of the hydride to the benzylimino group, was unequivocally verified by an independent synthesis of **26** which will be presented in this discussion. The cis isomer **3** was isolated by chromatography and subsequently debenzylated to *cis*-3-amino-2-benzhydrylquinuclidine (**5**). Alternately, the mixture of benzylamines was debenzylated and the product was acylated with acetic anhydride. Two recrystallizations from 2-propanol gave the cis acetamide **7** which on acid hydrolysis yielded the cis isomer **5**.

The trans amines in this series were prepared according to Scheme II. The appropriate *cis*-2-benzhydryl-3-quinuclidinol[2] was converted to its methanesulfonate I. Although an excess of methanesulfonyl chloride was used, the crude product invariably contained a considerable amount of unreacted alcohol and a second treatment with methanesulfonyl chloride was necessary. In contrast, mesylation of the trans alcohol **24** proceeded smoothly, inferring that the stereochemistry of the alcohol plays a role in this reaction.

The methanesulfonate I reacted with sodium azide in dimethylacetamide containing 4% water.[5] Analysis of the crude product by TLC showed that all I had reacted but, in addition to the mobile azide II, a less mobile impurity was present. This impurity had the same R_f value as the corresponding trans alcohol[2] so that solvolysis of the mesylate was a competing reaction (Tables I and II). The pure azide was readily obtained by recrystallization, and reduction with $LiAlH_4$ at room temperature proceeded smoothly to the trans amine III in excellent yield. The yields in Table III reflect losses on recrystallization. The trans amine **20** reacted with benzaldehyde to form the Schiff base which was reduced with $NaBH_4$ to **26**, thus confirming our stereochemical assignments of the 2-benzhydryl-3-benzylaminoquinuclidines.

Scheme I



Scheme II

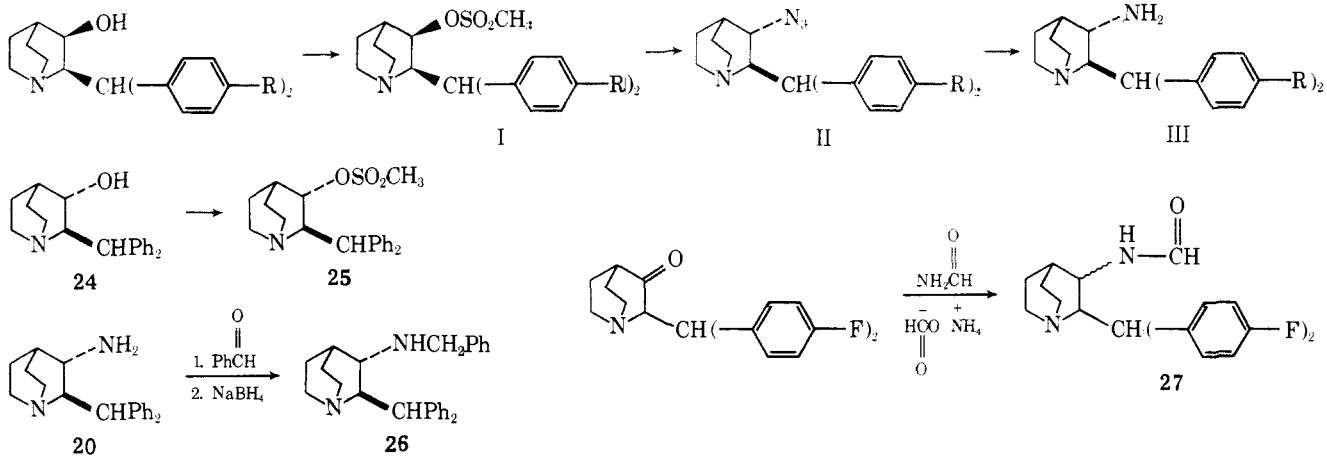
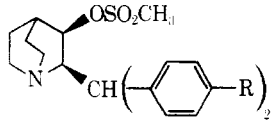


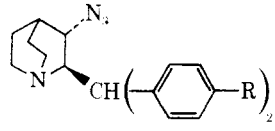
Table I. *cis*-2-Benzhydryl-3-*O*-methanesulfonylquinuclidinols (I)



No.	R	Formula	Mp, °C (solvent)	Yield, %	Analyses
12	H	$C_{21}H_{25}NSO_3$	196–198 (EtOH)	43.4	C, H, N, S
13	F	$C_{21}H_{23}F_2NO_3S$	204–205[a] (EtOH)	45.8	C, H, N, S
14	Cl	$C_{21}H_{23}Cl_2NO_3S$	182.0–183.5 (cyclohexane)	40.7	C, H, N, S
15	OCH_3	$C_{21}H_{25}NO_5S$	176–176.5 (2-propanol)	40.5	C, H, N, S

[a] First melts at 182–183° but resolidifies.

Table II. *trans*-3-Azido-2-benzhydrylquinuclidines (II)

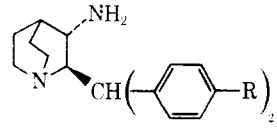


No.	R	Formula	Mp, °C (solvent)	Yield, %	Analyses
16	H	$C_{20}H_{22}N_4$	156–157 (EtOH)	53.6	C, H, N
17	F	$C_{20}H_{22}F_2N_4$	145[a] (EtOH)	62.3	C, H, N
18	Cl	$C_{20}H_{20}Cl_2N_4$	173–174 (2-propanol)	53.6	C, H, N
19	OCH_3	$C_{22}H_{26}N_4O_2$	119–120 (2-propanol)	59.3	C, H, N

[a] First melts at 139–140° but resolidifies.

2-Benzhydryl-3-quinuclidinone[2] readily underwent the Leuckart reaction to give a mixture of isomers. This reaction was especially important when the benzhydryl group was substituted with a halogen which could be reductively removed by the approach in Scheme I. Thus, reaction of 2-(4,4′-difluorobenzhydryl)-3-quinuclidinone with formamide and ammonium formate gave **27** as a mixture of ap-

Table III. *trans*-3-Amino-2-benzhydrylquinuclidines (III)



No.	R	Formula	Mp, °C (solvent)	Yield, %	Analyses
20	H	$C_{20}H_{24}N_2$	136–138	95.1[a]	C, H, N
21	F	$C_{20}H_{22}F_2N_2 \cdot 2HCl \cdot H_2O$	235–237 (EtOH)	43.2	C, H, N, Cl
22	Cl	$C_{20}H_{22}Cl_2N_2$	165–167 (cyclohexane)	77.0	C, H, N, Cl
23	OCH_3	$C_{22}H_{28}N_2O_2$	145–147 (cyclohexane)	64.0	C, H, N

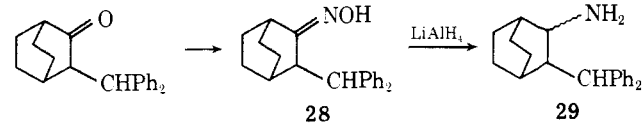
[a] Too soluble in all organic solvents, including petroleum ether; material was simply dried in vacuo to obtain the analytical specimen.

proximately equal amounts of cis and trans isomers as determined by TLC. Acid hydrolysis of **27** then gave a mixture of the amines.

Through reaction with an aldehyde and reduction with a borohydride, the primary amino group of **5** was converted to a secondary amine. The Schiff bases formed with acetaldehyde, phenylacetaldehyde, and phenylacetone required KBH_4 to effect complete reduction to **8**, **9**, and **10**, respectively. The latter exists as a mixture of diastereoisomers. The Schiff base from furfural was readily reduced with $NaBH_4$ to **11**.

In order to assess the role of the quinuclidine nitrogen on activity, the corresponding carbon analog **29** was prepared according to Scheme III.

Scheme III



Structure–Activity Relationships. According to our protocol, compounds were evaluated in the primary rat screen at a dose of 25 mg/kg po and were considered to be of sufficient interest to warrant further study only if they were more active than the reference agent, hydroflumethia-

zide. In this series of quinuclidine compounds the unsubstituted 3-amino-2-benzhydrylquinuclidine (**5**) was more active than hydroflumethiazide and considerably more active than the other analogs. The exact degree of difference among the analogs was not determined. The superiority of the cis isomer **5** over the trans isomer **20** was clearly established in 4.5-hr diuretic studies in the dog, where, at an oral dose of 10 mg/kg, sodium ion excretion (μequiv/min/kg) for **5** was 3.22 compared to 1.35 for **20**.

Dose–response data obtained from rat studies indicate that **5** at low doses is less potent than hydroflumethiazide but that its maximal or ceiling effect is considerably greater. In comparing furosemide to hydroflumethiazide, the same observation was made, although furosemide achieves even a higher ceiling effect than **5**. These data, depicting sodium excretion as a function of oral dose, are represented in Figure 1. One might conclude from these data that furosemide and **5** act upon the renal tubule at other sites in addition to those affected by hydroflumethiazide. An overall view of these dose–response studies is seen in Table IV where urine volume, sodium and potassium excretion, and sodium–potassium excretion ratios are compared for the three compounds over rather broad dosage ranges. Neither furosemide nor **5** appears to offer much of an advantage over hydroflumethiazide in terms of the maximal sodium–potassium excretion ratio achievable. However, the maximal effect of either furosemide or **5** on both urine production and sodium excretion clearly exceeds that achieved with hydroflumethiazide.

In order to learn more about the renal site of action for these compounds, studies were run in which either furosemide or **5** at 10 and 32 mg/kg was combined with a dose of hydroflumethiazide well along the ceiling plateau, 10 mg/kg. At each of the two doses, both furosemide and **5** combined with the thiazide produced a greater effect on sodium excretion than either compound alone. However, the combined effect was much less than additive.

Dose–response studies in dogs (see Figure 2) revealed a biphasic curve in the case of **5**. Peak activity was reached at an oral dose of 10 mg/kg, while both 5 and 20 mg/kg produced only moderate increases in sodium excretion over controls. Urine production, potassium excretion, chloride excretion, and sodium–potassium excretion ratio all followed the same biphasic pattern (see Table IV). Hydroflumethiazide produced a dose–response pattern similar to that seen in rats, in that the ceiling effect was reached at 1 mg/kg or less and was at a lower level than that seen with either furosemide or **5**.

The time course of urine production, sodium excretion, renal blood flow, and glomerular filtration rate was studied in the dog at the 10 mg/kg dose for each of the three compounds tested and for the control group. While urine production was stimulated in all groups due to the water load, sodium excretion patterns offered greater contrasts. In the case of furosemide a dramatic naturesis occurred, reaching a peak during the third hour. Both hydroflumethiazide and **5** led to a much milder naturesis, with the maximum sodium excretion generally being attained already following the first collection period and subsequently maintained. Renal clearances of creatinine and *p*-aminohippuric acid indicated that glomerular filtration rate and renal blood flow remained within normal ranges in all groups of animals studied. While urinary pH tended to increase slightly with increasing naturesis and free water clearance tended to decrease slightly, these changes were not marked and appeared to offer little information regarding tubular sites of drug action.

Although the halogenated derivatives of **5** were not of sufficient activity, some interesting qualitative differences appeared in the primary rat screen. Thus, relative to hydroflumethiazide (1.00),† the fluorinated derivative **21** had a score of 0.74 compared to 1.04 for the chlorinated compound **22**. The *cis*- and *trans*-3-amino-2-(4,4′-dimethoxybenzhydryl)quinuclidines (**6** and **23**) were also tested in the dog but showed no significant activity at 10 mg/kg po. Substitution of the 3-amino group as in **3**, **4**, **7**–**11**, and **26** did not result in any compound with greater activity than hydroflumethiazide. The quinuclidine nitrogen was again[2] essential for activity, for 2-amino-3-benzhydrylbicyclo[2.2.2]octane (**29**) was less active than hydroflumethiazide.

Our studies on quinuclidine chemistry[1,2] have demonstrated that specific activities can be obtained with appropriately substituted quinuclidines. The compounds we have presented here may represent a new class of diuretics.

Experimental Section

Methodology. Male, Sprague–Dawley rats were fasted for 18 hr prior to receiving the desired compound dissolved or suspended in a hydration volume of 25 ml/kg of 0.9% sodium chloride. Urine was then collected over a 6-hr period from groups of four rats per metabolism cage. Urinary sodium and potassium determinations, using an Instrumentation Laboratories flame photometer, Model 143, were made on the pooled urine sample from each group of four rats.

Mongrel dogs of both sexes with surgically implanted bladder cannulae were fasted for 18 hr prior to receiving the desired compound orally in a gelatin capsule and a hydration water load of 25 ml/kg. Urine was collected for analysis throughout each of six consecutive 1-hr clearance periods. Sodium and potassium levels were determined by the above-mentioned flame photometer method, while urine chloride was determined according to the method of Schales.[6]

2-Benzhydryl-3-benzyliminoquinuclidine (1). A solution of 2.4 g (0.0083 mol) of 2-benzhydryl-3-quinuclidinone[2] and 1.4 g (0.0131 mol) of benzylamine in toluene was refluxed azeotropically overnight in the presence of *p*-toluenesulfonic acid. After concentration in vacuo the residue was triturated with EtOH to give 2.03 g (64.4%) of a solid: ir max (Nujol) 5.99 μ. The analytical specimen was obtained by recrystallization from EtOH to give 1.25 g (39.7%), mp 162–165°. Anal. $C_{27}H_{28}N_2$) C, H, N.

***cis*-2-Benzhydryl-3-benzylaminoquinuclidine** (3). A solution of 200 g (0.687 mol) of 2-benzhydryl-3-quinuclidinone,[2] 147 g (1.37 mol) of benzylamine, and 0.10 g of *p*-toluenesulfonic acid in 800 ml of toluene was refluxed azeotropically, giving 12.5 ml (theoretical, 12.4 ml) of water in 13.5 hr. Concentration in vacuo left a pale yellow solid [ir max (Nujol) 6.00 μ (no carbonyl)] which was dissolved in 700 ml of CH_2Cl_2 and 700 ml of EtOH, cooled in an ice bath, and treated with 40 g (1.13 mol) of $NaBH_4$ over 2 hr. After stirring the reaction mixture overnight at room temperature, the solvent was removed in vacuo. The solid residue was triturated with 2 l. of water, collected by filtration, dissolved in 1 l. of CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo left 263.3 g (theoretical, 262 g) of a solid which was dissolved in a hot solution of 100 ml of MeOH and 2650 ml of 2-propanol which was then concentrated to 2 l. and left at room temperature. The resulting solid was collected by filtration and dried to yield 212.3 g: mp 141–145°; TLC analysis on alumina with ether showed a major, more mobile component and a less mobile minor component; VPC analysis (6 ft × 0.25 in., 3% XE-60 column at 230°) indicated two peaks with nearly base line separation, i.e., 79.7% of the lower retention cis isomer and 20.3% of the trans isomer.

Of the above mixture of isomers, 25 g was adsorbed on 150 g of neutral alumina by mixing in CH_2Cl_2 and removal of solvent in vacuo. This material was applied to a column of 1850 g of neutral alumina packed in petroleum ether. The column was eluted with 1 l. of petroleum ether, 2 l. of 5% benzene–petroleum ether, 3 l. of 10% benzene–petroleum ether, 4 l. of 15% benzene–petroleum ether, 2 l. of 25% benzene–petroleum ether, and 2 l. of 50% benzene–petroleum ether. After 1 l. of benzene, the cis isomer began to elute. Continued elution with benzene gave 14.5 g of the pure cis isomer as indicated by TLC (conditions cited), mp 149–151°. The analytical specimen, obtained by recrystallization from 2-propanol, exhibited mp 151.5–152°. Anal. ($C_{27}H_{30}N_2$) C, H, N.

†6-hr sodium excretion score of hydroflumethiazide.

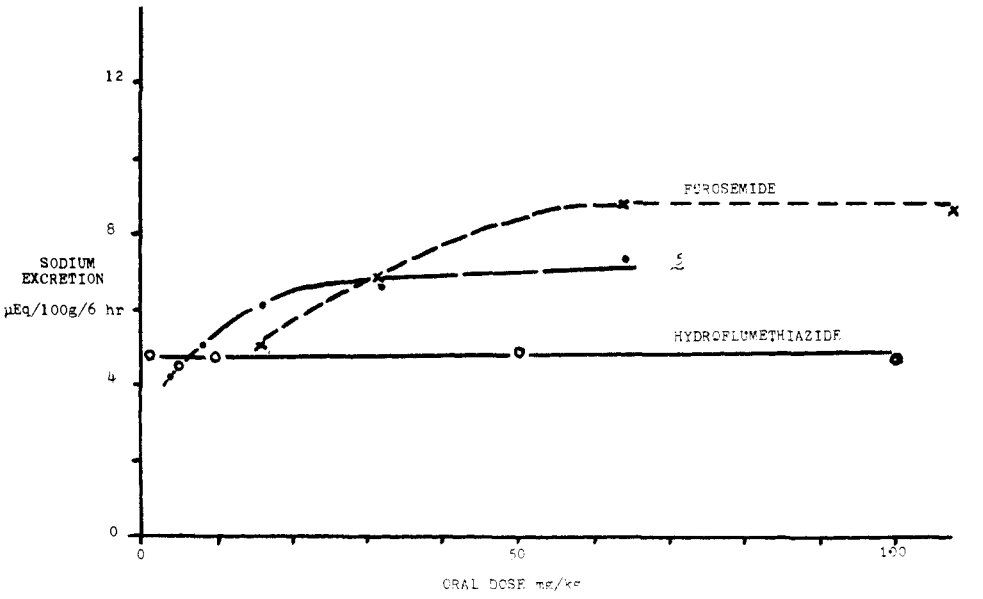


Figure 1. Dose–response curves in rats.

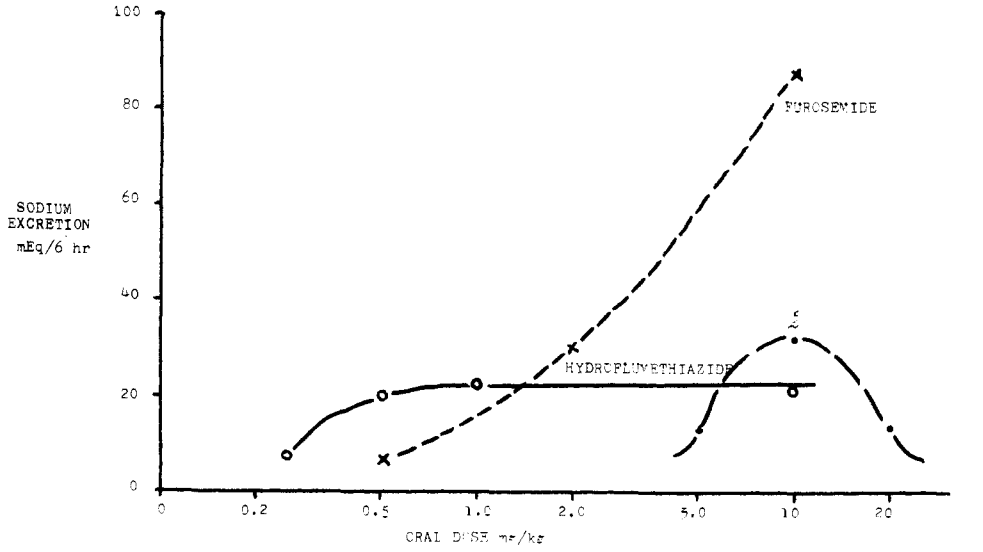


Figure 2. Dose–response curves in dogs.

***cis*-2-Benzhydryl-3-aminoquinuclidine (5).** (**A**) *cis*-2-Benzhydryl-3-benzylaminoquinuclidine, 6.0 g, was dissolved in MeOH, treated with HCl(g) slightly in excess of 2 equiv, and hydrogenated with 4 g of 10% Pd/C catalyst at 100 psi and 100° for 6 hr. The catalyst was removed by filtration, the filtrate was concentrated in vacuo, and the residue was treated with dilute NaOH solution and extracted with CH_2Cl_2. This organic extract was washed with saturated saline solution and dried ($MgSO_4$). Concentration in vacuo gave 4.36 g (95%): mp 181–183°; TLC analysis on alumina with ether showed complete absence of the *N*-benzyl precursor and with 5% 2-propanol–ether showed only the presence of this cis isomer; VPC analysis (6 ft × 0.25 in., 3% OV-17 column at 220°) gave a single peak. The analytical specimen was obtained by recrystallization from 1-butanol and exhibited mp 182–184°. Anal. ($C_{20}H_{24}N_2$) C, H, N.

(**B**) To a suspension of 28.0 g (0.0733 mol) of *cis*- and *trans*-2-benzhydryl-3-benzylaminoquinuclidine (ca. 4:1) in 250 ml of MeOH was added HCl(g) until solution was effected. Then the solvent and excess HCl were removed in vacuo, leaving a light yellow oil which was dissolved in 300 ml of MeOH and hydrogenated at 90° and 350 psi for 4.25 hr using 14.0 g of 10% Pd/C catalyst. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give an oil which was dissolved in water, made alkaline with dilute NaOH, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo gave 21.2 g (99%) of a white solid which by TLC on alumina with ether indicated complete debenzylation and with 2.5% 2-propanol–ether showed ca. 4:1 mixture of the cis and trans amines.

A solution of the above amine mixture and 74 g (0.726 mol) of acetic anhydride in 450 ml of anhydrous pyridine was heated at 85° for 6.5 hr using an oil bath and then stirred overnight at room temperature. The reaction mixture was cooled with an ice bath; dilute NaOH solution was added until alkaline, stirred for 0.5 hr, extracted with CH_2Cl_2, washed with water and saturated saline solution, and dried ($MgSO_4$). Concentration in vacuo left 24.7 g of a yellow solid; TLC on alumina with 5% 2-propanol–ether showed two components (isomeric amides) and a trace of the starting amines. Recrystallization from 2-propanol gave 15.2 g of a white solid: mp 258–263°; TLC (conditions cited) now showed only a trace of the amide which was the least predominent in the crude material. Another recrystallization from 2-propanol gave 11.0 g (45.4%) of **7**: mp 264–266°; homogeneous by TLC; ir max (Nujol) 3.02 (m), 6.03 (m), 6.10 μ (s). Anal. ($C_{22}H_{26}N_2O$) C, H, N.

A solution of 10.9 g (0.0324 mol) of **7** in 60 ml of 6 *N* HCl was refluxed for 23 hr, cooled, made alkaline with dilute NaOH solution, extracted with CH_2Cl_2, and dried ($MgSO_4$). Removal of solvent in vacuo gave 9.8 g of a white solid: mp 179–183°; TLC on alumina with 2.5% 2-propanol–ether showed a homogeneous material with the same R_f value of the previously obtained cis isomer.

(**C**) **Fumarate.** *cis*-2-Benzhydryl-3-aminoquinuclidine, 42.1 g (0.144 mol), was dissolved in 1200 ml of hot 2-propanol. A solution of 16.7 g (0.144 mol) of fumaric acid was prepared by treating the

Table IV. Comparison of Diuretic Activity of **5**, Hydroflumethiazide, and Furosemide in Unanesthetized Rats and Dogs. Oral Dosing

Drug and dose, mg/kg	6-hr urinary excretion (pooled values)			
	Urine vol, ml	Urine electrolytes, μequiv/100 g		Ratio
		Na^+	K^+	Na^+/K^+
	Rats (N = 8 per group)			
5				
4.0	56.0	4.23	1.33	3.2
8.0	63.2	5.05	1.46	3.5
16.0	76.4	6.17	1.64	3.8
32.0	81.6	6.60	1.28	5.2
64.0	94.4	7.40	1.33	5.6
Hydroflumethiazide				
1.0	48.4	4.84	1.00	4.8
5.0	53.6	4.46	1.42	3.1
10.0	48.2	4.75	0.88	5.4
50.0	46.0	4.99	0.95	5.3
100.0	48.0	4.76	0.94	5.1
Furosemide				
16.0	58.8	5.07	1.29	3.9
32.0	80.8	6.95	1.51	4.6
64.0	104.6	8.85	2.08	4.3
128.0	102.6	8.74	1.61	5.4
Saline controls, n = 24	32.4	3.04	0.90	3.4

Drug and dose, mg/kg	6-hr urinary excretion				
	Urine vol, ml	Urine electrolytes, mequiv			Ratio
		Na^+	K^+	Cl^-	Na^+/K^+
	Dogs (N = 5 per group)				
5					
5.0	626	13.7	6.5	19.0	2.1
10.0	942	32.8[a]	12.0	54.6	2.7
20.0	644	14.0	7.1	22.2	2.0
Hydroflumethiazide					
0.25	522	7.1	6.5	33.2	1.1
0.5	652	20.0[a]	11.8	48.8	1.7
1.0	637	22.5[a]	14.0	49.0	1.6
10.0	614	21.5[a]	15.5	74.1	1.4
Furosemide					
0.5	594	6.4	5.3	21.6	1.2
2.0	821	31.4[a]	12.9	46.9	2.4
10.0	1256	88.7[a]	22.4	85.1	4.0
Controls	659	6.3	4.8	32.0	1.3

[a] Significantly greater than controls ($p < 0.05$).

acid with 425 ml of 2-propanol and concentrating to 225 ml. The hot amine solution was then added to the hot fumaric acid solution. Within a few minutes the solution became turbid and a solid started to separate and the solution was refrigerated overnight. The solid was collected and dried in a vacuum oven at 70–75° to yield 53.0 g (91.3%), mp 215–217°. Anal. ($C_{24}H_{28}N_2O_4$) C, H, N.

3-Benzylimino-2-(4,4′-dimethoxybenzhydryl)quinuclidine (2). A solution of 4.0 g (0.0142 mol) of 2-(4,4′-dimethoxybenzhydryl)-3-quinuclidinone,[2] 3.05 g (0.0285 mol) of benzylamine, and a catalytic amount of *p*-toluenesulfonic acid in 30 ml of toluene was refluxed azeotropically overnight. Concentration in vacuo and trituration of the residue with 2-propanol gave 5.18 g (82.9%) of a white solid: ir max (Nujol) 6.01 μ. A 2.0-g sample was recrystallized from 2-propanol to give 1.19 g, mp 123–128°. Anal. ($C_{29}H_{32}N_2O_2$) C, H, N.

***cis*-3-Benzylamino-2-(4,4′-dimethoxybenzhydryl)quinuclidine (4).** While a solution of 4.38 g (0.00996 mol) of 2-(4,4′-dimethoxybenzhydryl)-3-benzyliminoquinuclidine in 50 ml of CH_2Cl_2 and 75 ml of EtOH was cooled in an ice bath, 1.0 g (0.026 mol) of $NaBH_4$ was added portionwise over 0.5 hr. The reaction mixture was then stirred at ice-bath temperature for 1 hr and at room temperature overnight. The solvent was removed in vacuo, leaving a white solid which was treated with water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo gave 4.41 g of a gum which by TLC on alumina with ether was about 60% of the cis isomer and 40% of the trans isomer. This material was adsorbed on 20 g of neutral alumina and applied to a column of 380 g of neutral alumina packed in petroleum ether. The column was eluted with petroleum ether, petroleum ether–benzene, benzene, benzene–CH_2Cl_2, and CH_2Cl_2. The cis isomer was subsequently eluted with ether–CH_2Cl_2 to give 2.0 g (47.1%). Recrystallization from 2-propanol gave 1.44 g of a white solid, mp 154–155°. Anal.

($C_{29}H_{34}N_2O_2$) C, H, N.

Elution with ether gave 1.95 g of a mixture of the cis and trans isomers.

***cis*-3-Amino-2-(4,4'-dimethoxybenzhydryl)quinuclidine (6).** The hydrochloride salt of 1.56 g (0.00353 mol) of *cis*-3-benzylamino-2-(4,4'-dimethoxybenzhydryl)quinuclidine was prepared by passing HCl(g) into a MeOH solution of the amine. The salt was then hydrogenated in MeOH at 250 psi and 90° for 5.5 hr with 1.5 g of 10% Pd/C catalyst. The catalyst was removed by filtration and concentration in vacuo gave 1.4 g of a brown glass which was treated with dilute NaOH, extracted with CH_2Cl_2, and dried ($MgSO_4$). Removal of solvent in vacuo gave 0.78 g (62.9%) of a brown solid. Recrystallization from cyclohexane (charcoal) gave 0.60 g (48.3%) of a white solid: mp 154–156°; ir max (Nujol) 2.97 μ (w); TLC on alumina with 5% 2-propanol–ether showed one component. Anal. ($C_{22}H_{28}N_2O_2$) C, H, N.

***cis*-2-Benzhydryl-3-ethylaminoquinuclidine (8).** *cis*-3-Amino-2-benzhydrylquinuclidine, 2.0 g (0.00685 mol), and acetaldehyde, 0.33 g (0.0075 mol), were mixed in 30 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid and stirred at room temperature overnight in the presence of molecular sieves. Since TLC analysis indicated that the reaction was incomplete, an additional 0.45 g of acetaldehyde was added and the reaction proceeded overnight. Removal of the molecular sieves by filtration and concentration in vacuo gave a white solid which was dissolved in 15 ml of CH_2Cl_2 and 15 ml of MeOH. This solution was cooled in an ice–water bath, treated with 1.5 g of KBH_4 over 2 hr, and stirred overnight at room temperature. Removal of solvent in vacuo gave a white solid which was treated with water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Removal of solvent gave 2.0 g of a solid; TLC on alumina with ether showed a major, very mobile component and five minor impurities near the origin. Recrystallization from 2-propanol gave 1.43 g, mp 132–141°. This material was chromatographed on 60 g of neutral alumina and elution with benzene–ether gave 1.3 g (59.4%) of a solid which was homogeneous by TLC. Recrystallization from 15 ml of 2-propanol gave 1.0 g (45.7%), mp 139–142°. Anal. ($C_{22}H_{28}N_2$) C, H, N.

***cis*-2-Benzhydryl-3-β-phenethylaminoquinuclidine (9).** *cis*-3-Amino-2-benzhydrylquinuclidine, 2.0 g (0.00685 mol), phenylacetaldehyde, 1.0 g (0.0083 mol), and a catalytic amount of *p*-toluenesulfonic acid were mixed in 40 ml of benzene and stirred overnight in the presence of molecular sieves. The molecular sieves were removed by filtration and the filtrate was concentrated in vacuo to get a pale yellow solid: ir max (Nujol) 6.08 μ (m). This material was dissolved in 30 ml of CH_2Cl_2–MeOH (1:1) and cooled with cold water, 2.3 g of KHB_4 was added portionwise over 1 hr, and the reaction was stirred overnight at room temperature. Concentration in vacuo gave a solid residue which was treated with water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo gave a solid which was recrystallized from 10 ml of 2-propanol (charcoal) to give 1.82 g, mp 101–104°. Anal. ($C_{28}H_{32}N_2$) C, H, N.

***cis*-2-Benzhydryl-3-(1'-phenyl)isopropylaminoquinuclidine (10).** *cis*-3-Amino-2-benzhydrylquinuclidine, 2.0 g (0.00685 mol), and phenylacetone, 1.02 g (0.0076 mol), were mixed in 50 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid and refluxed azeotropically overnight. Removal of solvent in vacuo yielded an oil: ir max (film) 6.03 μ. This material was dissolved in 15 ml of CH_2Cl_2 and 15 ml of MeOH and cooled in ice–water, and 2.0 g of KHB_4 was added over 1 hr. After stirring overnight, the solvent was removed in vacuo and the residue was treated with water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo gave an oil which solidified on scratching; TLC on alumina with CH_2Cl_2 indicated only two components (diastereoisomers). Recrystallization from 2-propanol gave 1.27 g (46.3%), mp 92–96°. Anal. ($C_{29}H_{34}N_2$) C, H, N.

***cis*-2-Benzhydryl-3-furfurylaminoquinuclidine (11).** A solution of 1.00 g (0.00343 mol) of *cis*-3-amino-2-benzhydrylquinuclidine, 0.36 g (0.00377 mol) of furfural, and a catalytic amount of *p*-tohuenesulfonic acid in 25 ml of benzene was refluxed azeotropically under nitrogen overnight. Concentration in vacuo gave a yellow solid: mp 167–169.5°; ir max (Nujol) 6.10 μ. This material was dissolved in 50 ml of EtOH and 20 ml of CH_2Cl_2, cooled in an ice bath, and treated with 0.38 g of $NaBH_4$ over 15 min. The reaction was kept cold for 1.75 hr and then left at room temperature overnight. Solvent was removed in vacuo and the residue was diluted with water, extracted with CH_2Cl_2, and dried ($MgSO_4$). Concentration in vacuo gave 1.33 g of an oil which slowly solidified but the infrared spectrum indicated unreduced Schiff base. The reduction with $NaBH_4$ was repeated as above and work-up gave 1.30 g of a white solid. The 6.10 μ band was now absent. This material was recrystallized from 10 ml of 2-propanol (with charcoal treatment) to give 1.04 g (81.9%) after drying and exhibited mp 137.5–138.5°. Anal. ($C_{25}H_{28}N_2O$) C, H, N.

***cis*-2-Benzhydryl-3-*O*-methanesulfonylquinuclidine (12).** A solution of 6.0 g (0.02 mol) of *cis*-2-benzhydryl-3-quinuclidinol[2] in 60 ml of pyridine was cooled in an ice–water mixture and treated with 5.5 ml (0.07 mol) of methanesulfonyl chloride. After stirring for 15 min in the cold, the solution was left at room temperature overnight. It was again cooled to 0–5° and treated with 1, 1, 1, 2, and 5 ml of water at 5-min intervals and then poured into 1 l. of water. Excess potassium carbonate was added and the solution was extracted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). Concentration in vacuo gave 6.4 g of a brown solid. TLC analysis on alumina (microplate) with CH_2Cl_2 showed a major mobile component, a less mobile impurity, and unreacted alcohol near the origin. Thus, this material was again allowed to react with methanesulfonyl chloride as outlined above. The same work-up yielded a residue which on trituration with ether yielded 6.4 g of a solid; TLC analysis now showed a minute amount of the starting alcohol. This material was recrystallized from EtOH by concentration to 125 ml when a solid started to separate. The resulting solid, 3.75 g (mp 189–192°), showed a small impurity by TLC. A second recrystallization from EtOH (100 ml) gave after drying the analytical sample which exhibited mp 196–198°; yield 3.22 g (43.4%). Anal. ($C_{21}H_{25}NSO_3$) C, H, N, S.

The above is the general procedure used for the preparation of the quinuclidines in Table I.

***trans*-2-Benzhydryl-3-*O*-methanesulfonylquinuclidine (25).** A solution of 0.60 g (0.002 mol) of *trans*-2-benzhydryl-3-quinuclidinol[2] in 10 ml of dry pyridine, cooled in an ice–water mixture, was treated with 0.5 ml (ca. 0.006 mol) of methanesulfonyl chloride. After stirring for 10 min in the cold, the solution was left at room temperature overnight. The solution was again cooled in ice, treated with a few drops of water several times at 5-min intervals followed by 2 ml of water, and poured into 200 ml of cold water. The resulting solid was collected by filtration and dried to yield 0.62 g (83.8%); TLC analysis on alumina (microplate) with CH_2Cl_2 showed only one component; ir max (Nujol) 8.54 μ (s). This material was more mobile than the cis isomer 12 on alumina (2 × 8 in. plate) using 10% ethyl acetate–benzene. The analytical specimen was obtained by recrystallization from EtOH: 0.45 g (60.8%); mp 190° dec. Anal. ($C_{21}H_{25}NSO_3$) C, H, N, S.

***trans*-3-Azido-2-benzhydrylquinuclidine (16).** *cis*-2-Benzhydryl-3-*O*-methanesulfonylquinuclidine, 2.4 g (0.00646 mol), and sodium azide, 1.26 g (0.0194 mol), were mixed in 40 ml of dimethylacetamide and 1.6 ml of water.[5] This solution was heated overnight in an oil bath at 105°. The cooled solution was poured into 1 l. of water and stirred for 30 min. The resulting solid was collected by filtration and dried to give 1.57 g; TLC on alumina (microplate) with CH_2Cl_2 showed a major mobile component with a slight amount of a less mobile impurity. Recrystallization from EtOH and drying in vacuo gave the analytical specimen: 1.1 g (53.6%); mp 156–157°; TLC (conditions cited) showed one component; ir max (Nujol) 4.78 μ (s). Anal. ($C_{20}H_{22}N_4$) C, H, N.

The above is a general procedure for the preparation of the azidoquinuclidines in Table II.

***trans*-3-Amino-2-(4,4'-dichlorobenzhydryl)quinuclidine (22).** To a suspension of 400 mg (0.010 mol) of $LiAlH_4$ in a small amount of ether was added dropwise 1.24 g (0.0035 mol) of *trans*-3-azido-2-(4,4'-dichlorobenzhydryl)quinuclidine in 100 ml of ether. Upon completion of the addition (20 min), the reaction mixture was stirred at room temperature for 3.5 hr, decomposed with saturated sodium sulfate solution, filtered, and dried ($MgSO_4$). Concentration in vacuo gave 1.21 g (96%) of a white solid: mp 163.5–167°; ir max (Nujol) 2.98 (w), 3.02 μ (w); TLC on alumina (microplate) with 5% 2-propanol–ether showed only a major component with a trace of impurity at the origin. Recrystallization from cyclohexane and drying gave the analytical specimen: 0.97 g (77%); mp 165–167°; ir unchanged. Anal. ($C_{20}H_{22}Cl_2N_2$) C, H, N, Cl.

The above is a general procedure for the preparation of the *trans*-2-benzhydryl-3-aminoquinuclidines in Table III.

***trans*-2-Benzhydryl-3-benzylaminoquinuclidine (26).** A solution of 1.0 g (0.0034 mol) of *trans*-2-benzhydryl-3-aminoquinuclidine and 0.72 g (0.0068 mol) of benzaldehyde in 30 ml of benzene with a catalytic amount of *p*-toluenesulfonic acid was refluxed azeotropically for 2 hr and concentrated in vacuo. The residue was dissolved in 10 ml of CH_2Cl_2 and 10 ml of MeOH, cooled in an ice–water bath, treated portionwise with 0.5 g of $NaBH_4$, and stirred overnight at room temperature. Solvent was removed in vacuo and

trituration of the residue with water gave a solid which was dried to yield 1.17 g (90.7%); TLC on alumina (microplate) with ether showed only the desired **26**. This material was recrystallized from 2-propanol (15 ml) and dried to give 0.90 g (69.7%), mp 154–155°. Anal. ($C_{27}H_{30}N_2$) C, H, N.

***cis*- and *trans*-2-(4,4′-Difluorobenzhydryl)-3-formamidoquinuclidine (27).** A solution of 6.0 g (0.0183 mol) of 2-(4,4′-difluorobenzhydryl)-3-quinuclidinone[2] in 40 ml of formamide was treated with 6.0 g of ammonium formate and heated overnight at 172° in an oil bath. The cooled solution was treated with excess potassium carbonate and poured into 1 l. of water. This solution was extracted several times with ether, which was then dried ($MgSO_4$) and concentrated in vacuo to yield 5.39 g of a glassy material: ir max ($CHCl_3$) 5.95 μ (s); TLC on alumina (microplate) with 5% 2-propanol–ether showed two components in about equal amounts. Recrystallization from 2-propanol gave 3.40 g: mp 179–190°; ir max (Nujol) 3.08 (m), 5.94 (s), 6.05 μ (s); ir max ($CHCl_3$) 5.93 μ (s). Anal. ($C_{21}H_{22}F_2N_2O$) C, H, N.

3-Benzhydrylbicyclo[2.2.2]octan-2-one Oxime (28). 3-Benzhydrylbicyclo[2.2.2]octan-2-one,[2] 1.0 g (0.0034 mol), was treated with 7 ml of water, 7 ml of 10% aqueous potassium hydroxide solution, 15 ml of ethanol, and 1.7 g of hydroxylamine hydrochloride and refluxed for 45 min. The solution was cooled and the resulting solid was collected and dried to yield 0.95 g: mp 185–190°; ir max (Nujol) 3.08–3.25 μ (s). Anal. ($C_{21}H_{23}NO$) C, H, N.

2-Amino-3-benzhydrylbicyclo[2.2.2]octane (29). A solution of 2.9 g (0.0095 mol) of 3-benzhydrylbicyclo[2.2.2]octan-2-one oxime in 50 ml of THF was added dropwise to a refluxing suspension of 2.5 g (0.065 mol) of $LiAlH_4$ in 50 ml of THF and refluxing was continued overnight. The cooled solution was treated with saturated sodium sulfate solution and the salts were removed by filtration and washed with THF. The filtrate was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 and dried ($MgSO_4$). Removal of solvent in vacuo gave 1.8 g of a slightly yellow solid residue. This material was combined with 1.0 g from a previous run and sublimed on a kugelrohr at 120–130° (10×10^{-5} mm) to give 1.5 g of a white solid, mp 130–132°. Anal. ($C_{21}H_{25}N$) C, H, N.

References and Notes

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Butyrophenones as Hypotensive Agents. Derivatives of 4-Aryl-4-(hydroxymethyl)cyclohexylamine

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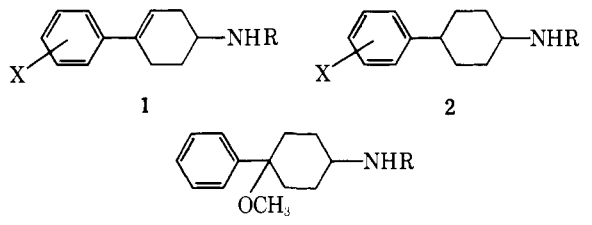
The preparation of butyrophenone derivatives of 4-aryl-4-(hydroxymethyl)cyclohex-1-ylamines starting from the corresponding 4-cyano-4-phenylcyclohexan-1-ones is described. Substitution was varied in both rings; both isomers of 4-phenyl-4-(hydroxymethyl)cyclohex-1-ylamine were characterized. Those derivatives which carried *p*-fluoro substitution on the butyrophenone exhibited hypotensive activity in the rat with diminished CNS activity compared to compounds lacking the hydroxymethyl group. The effect of substitution on the 4-aryl ring is discussed.

It has been shown previously that the butyrophenone derivatives of the amines **1–3** [R = $CH_2CH_2CH_2C(=O)(p\text{-}C_6H_4F)$] exhibit interesting neuroleptic activity in various animal screens.[1] In theory at least, these compounds are metabolically intraconvertible by well-known pathways. Thus, reduction of the styrene double bond of **1** leads into series **2**; the benzylic *tert*-methoxyl group of **3** could, under acidic conditions, eliminate to afford the olefin **1**.



We thus considered it of some interest to ascertain the effect on biological activity of blocking these potential intraconversions. Such simple reactions should be prevented by attachment of an additional carbon atom to the benzilic position. We chose as our initial goal compounds in which this additional substituent was present as a hydroxymethyl group.

Synthesis. Hydroxyacetate **4** was converted to its mesylate in straightforward manner by means of mesyl chloride in pyridine. Treatment of **5** with sodium azide in DMF followed by reduction of the crude intermediate with lithium aluminum hydride led to reduction of both the azide and acetate groups; there was obtained amino alcohol **6** in which the configuration about C_1 had been inverted. The isomeric hydroxyacetate **8** was subjected to the same series of reactions to afford an amino alcohol (**10**) which was clearly different from **6** (Scheme I). Each of these compounds was then converted to the butyrophenone by condensation with the 2,2-dimethylpropylene ketal of 4′-chloro(*p*-fluoro)butyrophenone, followed by deketalization. General screening revealed that **7** elicited a blood pressure lowering effect in the rat while the CNS responses to this agent were markedly reduced from the prototypes **1–3** (see Table I). The isomeric compound **11**, on the other hand, failed to lower blood pressure at the standard screening dose of 50 mg/kg. This observation led us to study the effect of substitution on the aromatic rings of **7** on biological activity.

The key intermediates to this series, the cyano ketones **15**, were prepared by a modification of a previously reported route,[2] which involves decarboxylation of the product of Dieckmann cyclization (**14**) of the double Michael adducts of methyl acrylate and arylacetonitriles (**13**). Treatment of the cyano ketone with ethylene glycol in refluxing benzene afforded the ketals **16**. In view of the hindered nature of the nitrile, it is perhaps not surprising that reflux in ethylene glycol with base was required to effect hydrolysis of these last to the acids.[3] Reduction with lithium aluminum hydride[4] followed by deketalization and