8b) in 28 ml of $POCl_3$ was heated at reflux for 1 hr. Evaporation of the $POCl_3$ gave a residue which was taken up with iced water; after alkalinization with diluted Na_2CO_3 the oil which separated was extracted several times with ethyl acetate. Removal of the solvent yielded a residue which was crystallized from ethyl acetate–*n*-hexane (**4b**) or ether (**4c**).

Acknowledgment. We thank the Italian National Research Council (C.N.R. ROME) for financial support of this research and Professor M. Cardellini for helpful discussions.

Registry No.—**1a**, 234-72-0; **1b**, 52747-78-1; **1c**, 52747-79-2; **1d**, 30391-78-7; **1e**, 52747-80-5; **3a**, 27114-97-2; **3b**, 52747-81-6; **3c**, 52747-82-7; **3d**, 52747-83-8; **3e**, 52747-84-9; **3f**, 52747-85-0; **4a**, 1010-62-4; **4b**, 52747-86-1; **4c**, 52747-87-2; **4d**, 52747-88-3; **4e**, 52747-89-4; **4f**, 52747-90-7; **4g**, 52747-91-8; **8a**, 52747-92-9; **8b**, 52747-93-0; 4-chloroquinazoline, 5190-68-1; aziridine, 151-56-4; 2-phenylaziridine, 1499-00-9; *cis*-2,3-dimethylaziridine, 930-19-8; *trans*-2,3-dimethylaziridine, 930-20-1; *cis*-2,3-diphenylaziridine, 1605-06-7; 2-methylaziridine, 75-55-8; 2-aminopropanol, 78-91-1; 1-phenyl-2-aminoethanol, 7568-93-6.

Supplementary Material Available. Analytical data for compounds **1b,c,e**, **3b–f**, and **4a–g**, nmr data for compounds **1b,c,e** and **4a–c**, and uv data for compounds **1b,c,e** and **4a–f** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3508.

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Quinuclidine Chemistry. I. Configuration and Chemistry of 2-Substituted Benzylidene-3-quinuclidinones

E. J. Warawa* and John R. Campbell

Research Laboratories of the Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233

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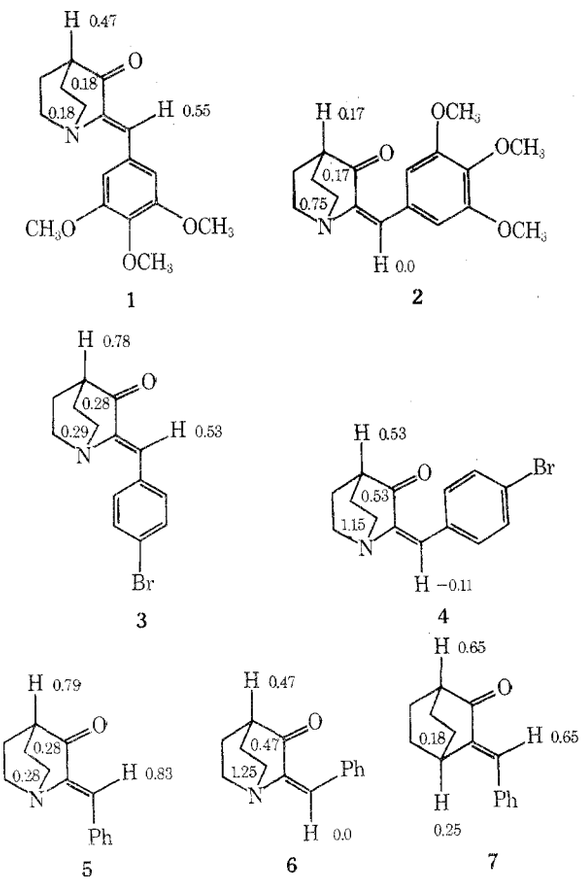
The base-catalyzed condensation of 3-quinuclidinone with several aromatic aldehydes which gives rise to 2-benzylidene-3-quinuclidinones as single geometrical isomers (kinetic products) is discussed. These isomers rapidly isomerize with HCl in $CHCl_3$ to the hydrochloride salts of the other geometrical isomers and in the case of 2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone the isomerization is quantitative. The latter also spontaneously isomerizes to the thermodynamic isomer. The configuration of these isomeric 2-benzylidene-3-quinuclidinones was determined from nmr shift reagent [$Eu(DPM)_3$] studies and the kinetic products were shown to have the *Z* configuration. Reduction of (*E*)-2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone with $NaBH_4$ gave a crystalline allylic alcohol which, by catalytic hydrogenation, gave predominantly *trans*-2-(3,4,5-trimethoxybenzyl)-3-quinuclidinol. Aluminum isopropoxide reduction of 2-(3,4,5-trimethoxybenzyl)-3-quinuclidinone under nonequilibrating conditions gave exclusively the cis alcohol. Reduction of the same ketone with sodium and isopropyl alcohol gave predominantly *trans*-2-(3,5-dimethoxybenzyl)-3-quinuclidinol, the 4-methoxy group being removed in the process. The *cis*-2-(3,5-dimethoxybenzyl)-3-quinuclidinol was formed by reduction of 2-(3,5-dimethoxybenzyl)-3-quinuclidinone with aluminum isopropoxide under nonequilibrating conditions.

In the course of our work with quinuclidines as medicinal agents we required 2-substituted benzylidene-3-quinuclidinones as intermediates. These ketones were prepared by condensation of aromatic aldehydes with 3-quinuclidinone under base catalysis.[1-3] We wish to report on the nature of this condensation, the configurational assignment of several benzylidenequinuclidinones, and some of the reactions which they undergo.

The reaction of 3-quinuclidinone with 3,4,5-trimethoxybenzaldehyde gave a single isomer, (*Z*)-2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone (**1**) (see Chart I). The configuration of **1** was established by nmr using a lanthanide shift reagent (discussion to follow) and was confirmed by correlation with an X-ray crystallographic determination[4] of (*Z*)-2-*p*-bromobenzylidene-3-quinuclidinone (**3**). When a chloroform solution of **1** was treated with hydrogen chloride a facile isomerization occured to give the hydrochloride salt of **2**, complete isomerization being indicated by a single vinyl proton resonance in the nmr spectrum. Such an isomerization by an acid is easily rationalized as proceeding through a carbonium ion and is indicative of a product formed by a kinetically controlled process isomerizing to the thermodynamically more stable form. Treatment of this salt with base gave **2** which contained 6% **1** (by nmr) as a result of base-induced reverse isomerization and exhibited a vinyl proton resonance at δ 7.10 compared with 6.93 for **1**. That **1** is the kinetic product was verified by observing its spontaneous isomerization to **2**, using nmr. After 68 hr at room temperature there was no evidence of further change with 12.5% **1** and 87.5% **2** being present. This isom-

erization could be followed qualitatively by tlc for, if **1** was allowed to stand in methylene chloride, benzene, or ethanol, a change to **2** was evidenced within 1 hr. After 1 day the equilibrium had shifted past the midpoint. On the other hand **2** showed no change by nmr after 48 hr at 26°.

Chart I
Slopes of Plots of Observed Changes in Chemical Shift *vs.* Molar Ratio of Eu(DPM)$_3$ and Substrate

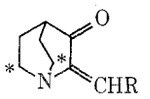


The reaction of 3-quinuclidinone with *p*-bromobenzaldehyde and benzaldehyde gave, respectively, single isomers, (*Z*)-2-*p*-bromobenzylidene-3-quinuclidinone (**3**) and (*Z*)-2-benzylidene-3-quinuclidinone[1] (**5**). Each isomerized rapidly with hydrogen chloride to the corresponding *E* isomer, **4** and **6**. Unfortunately, the resonances of the vinyl protons of the hydrochloride salts of **4** and **6** overlapped those of two aromatic protons so that it cannot be stated with certainty by nmr that complete conversion had occurred. The spontaneous isomerization of **3** and **5** (see Experimental Section) was very much slower than **1** in which the rate of isomerization is undoubtedly enhanced by resonance effects which are weaker in the former compounds.

Examination of the properties of these 2-benzylidene-3-quinuclidinones by the usual physical methods provided little assistance in assigning definitive configurations.[5,6] *Lanthanide shift reagents such as tris(dipivaloylmethanato)*europium(III) [Eu(DMP)$_3$] have found wide application in nmr spectroscopy.[7,8] In this study we have attempted to relate the observed changes in chemical shifts of various protons to a particular configuration of the europium–substituent complex.

In Table I it can be seen that there are large differences between isomers in induced shifts for both the vinyl protons and the methylene protons adjacent to the nitrogen atom. With the lanthanide complexing at nitrogen, one would expect large induced shifts for the methylene protons adjacent to the nitrogen atom and might also, on consideration of the distance term alone,[8] expect a large shift for a vinyl proton syn and a small shift for a vinyl proton anti to the nitrogen atom. However, Dreiding models indicate that the lobe of the nitrogen electron pair and the syn vinyl proton are coplanar and parallel. With nitrogen being complexed, the angle N–Eu–vinyl hydrogen is greater than 54.5° (the condition for a negative pseudocontact shift[8]) resulting in a small or even upfield shift for the vinyl proton. Thus, compounds **2**, **4**, and **6** having vinyl protons syn to the nitrogen atom bind the lanthanide at the nitrogen atom to show large shifts for the methylene protons adjacent to the nitrogen atom and nil or negative shifts for the vinyl protons.

Table I
Induced Chemical Shifts (Slopes[a])



Compd[a]	*R*	Vinyl H	CH_2*
1	3,4,5-$(OCH_3)_3$Ph	0.55	0.18
2	3,4,5-$(OCH_3)_3$Ph	0.0	0.75
3	*p*-BrPh	0.53	0.29
4	*p*-BrPh	−0.11	1.15
5	Ph	0.83	0.28
6	Ph	0.00	1.25

[a] See Chart I.

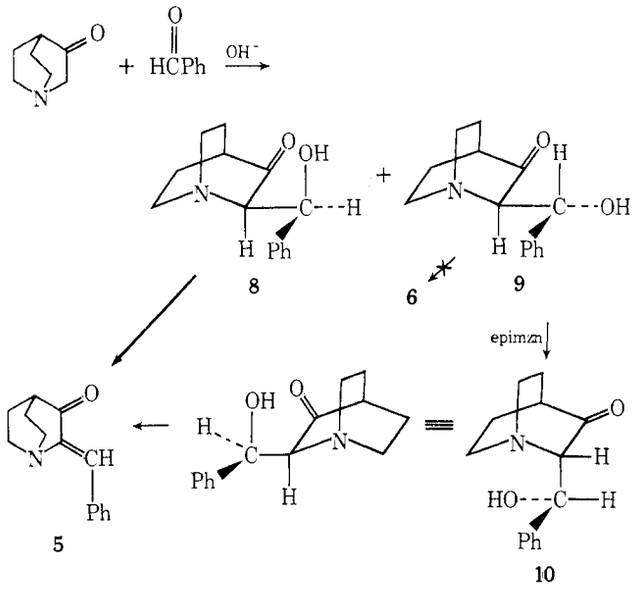
Table I also shows that **1**, **3**, and **5** have small shifts for the methylene protons adjacent to nitrogen but have large vinyl proton shifts as does (*E*)-3-benzylidenebicyclo-[2.2.2]octan-3-one[9] (**7**, Chart I), a result of the lanthanide complexing at the carbonyl group. That this is so can be seen from the induced shifts of the bridgehead protons (Chart I) which indicate the same spatial relationship to the site of complexation as do the vinyl protons. The fact that the lanthanide does not complex exclusively at nitrogen as might be expected on basicity considerations alone indicates that determination of configuration using lanthanide shift reagents must be approached with caution in complex systems containing several sites for complexation.

(*E*)-3-Benzylidenebicyclo[2.2.2]octan-2-one (**7**) showed a single vinyl resonance by nmr which did not change on standing in $CDCl_3$, nor was any change evident by tlc after the solution was treated with hydrogen chloride.

We now consider the reason that a single benzylidene isomer is formed under base catalysis. The formation of the intermediate β-hydroxy ketone generates a new asymmetric center so that this ketone exists as two diastereoisomers (Scheme I). In diastereoisomer **8** the hydrogen at the 2 position and the hydroxyl group can easily line up trans and coplanar for elimination to **5**. In diastereoisomer **9** rotation about the benzyl carbon is necessary for the 2 hydrogen and the hydroxyl group to be trans and coplanar, but this rotation requires the phenyl group to move past the carbonyl group. Elimination of water would now give **6**. The fact that this does not happen indicates that the rotational energy barrier is sufficiently high that a second pathway, a consequence of the symmetry of the quinuclidine molecule, predominates. Thus, epimerization of **9** to **10** requires no more energy than the actual enolization for the axial and equatorial positions are equivalent. The 2 hydrogen and the hydroxyl group can now easily line up trans and coplanar resulting in elimination to **5**.

Michael addition of hydroxide ion to the symmetrical **6** would again give **8** and **9**, both of which culminate in **5**.

Scheme I



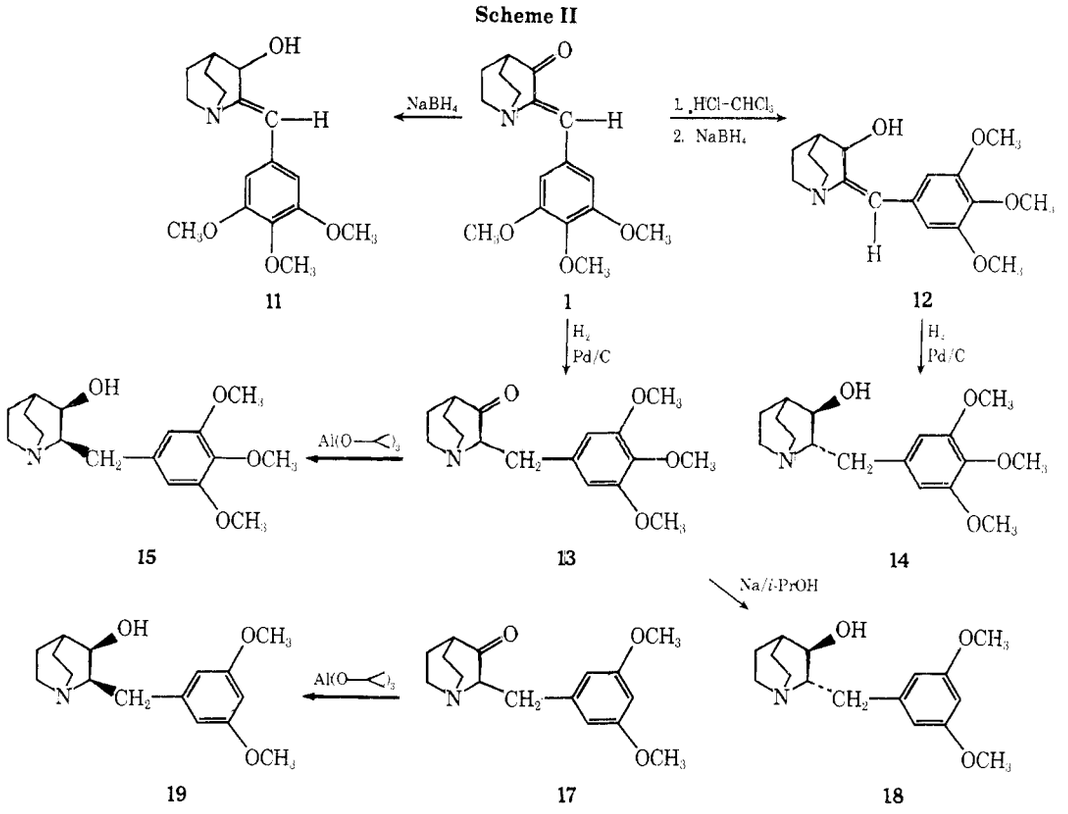
The spontaneous isomerization of **1** to **2** is most likely an effort to reduce the aryl–N electron pair interaction which must be greater than the aryl–carbonyl interaction. In the hydrochloride salt of **1** there would be an even greater interaction between the $^{+}$N–H bond and the aryl group and this interaction would be increased by solvation of the charged molecule.

Sodium borohydride reduction of **1** gave a single allylic alcohol **11** as an oil (Scheme II). Isomerization of **1** to the hydrochloride salt of **2** followed by sodium borohydride reduction gave crystalline **12.** Some **11** was formed in this reaction indicating competitive rates of simple reduction to **12** and Michael addition resulting in reversal to **1** which was then reduced to **11.** In the nmr spectrum **12** displayed a vinyl proton resonance at δ 6.56 and 3-H resonance centered at 4.47. For isomer **11** the vinyl proton resonance appeared as an unresolved doublet at δ 6.16 while the 3-H resonance appeared at 4.38. The splitting was not due to the interaction of the 3-H with the vinyl proton for no nuclear Overhauser effect was observed. Had such an effect been observed, it would have provided a basis for establishing the configuration of the benzylidene ketones.

Sodium borohydride reduction of **13,** which was obtained from **1** by catalytic hydrogenation, gave a mixture of cis and trans alcohols which was extremely difficult to separate by chromatography. Aluminum isopropoxide reduction of **13** under nonequilibrating conditions where the resulting acetone was continuously removed gave exclusively the cis alcohol **15.** The stereochemistry is a result of hydride transfer occurring from the least hindered side, *i.e.*, trans to the benzyl group. Surprisingly, the allylic alcohol **12** was a key intermediate for the preparation of the trans alcohol **14.** By hydrogenation with Pd/C catalyst hydrogen was introduced predominantly from the side of the hydroxyl group and **14** was readily purified by recrystallization. The diastereomeric alcohols **14** and **15** were homogeneous by tlc.

Reduction of **13** by sodium in isopropyl alcohol (equilibrating conditions) gave predominantly *trans*-2-(3,5-dimethoxybenzyl)-3-quinuclidinol (**18**), the 4-methoxy group being removed in the process. Hydrogenation of 2-(3,5-dimethoxybenzylidene)-3-quinuclidinone (**16**) to the ketone **17** followed by aluminum isopropoxide reduction under nonequilibrating conditions gave the cis isomer **19.** The isomers **18** and **19** were homogeneous by tlc. In the nmr spectra the 3-H of **18** appears unresolved and centered at δ 3.48 with a half-height peak width of 6.5 Hz, whereas the 3-H of **19** appears at δ 3.86 with half-height peak width of 11 Hz. These values compare favorably with the coupling constants of 8.2 Hz for *trans*-3-*p*-chlorophenyl-2-cyanobicyclo[2.2.2]octane and 11.0 Hz for the cis isomer,[10] and trans and cis coupling of 2.8 and 9.0 Hz, respectively, in bi-

Scheme II



cyclo[2.2.2]octanol.[11] The 3-H of **15** overlapped the methyl proton resonances, affording no coupling information.

Experimental Section

(*Z*)-2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinone (1). A solution of 5.0 g (0.04 mol) of 3-quinuclidinone, 8.50 g (0.04 mol) of 3,4,5-trimethoxybenzaldehyde, and one pellet of sodium hydroxide in EtOH was refluxed for 3 hr and stirred overnight at room temperature. The yellow solid was collected by filtration, washed with ethanol, and dried to give 8.6 g, mp 111–113°. A second crop of 1.9 g showed mp 112–114°. The analytical specimen was obtained by recrystallization of a portion of the first crop: mp 112–113°; ir max (Nujol) 5.88 (s), 6.17 (s), and 6.33 (s) μ; tlc showed one component (alumina developed with methylene chloride); uv max (MeOH) 240 nm (ϵ 10,343), 342 (21,364); nmr ($CDCl_3$) δ 2.07 [m, 4 H $(CH_2)_2C$], 2.60 (q, 1 H, bridgehead H), 3.08 [m, 4 H, $(CH_2)_2N$], 3.90 (br s, 9 H, OCH_3), 6.93 (s, 1 H, =CH), 7.55 (s, 2 H, aromatic H).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.01; H, 7.06; N, 4.49.

(*E*)-2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinone (2). A. Hydrochloride. Compound **1**, 1.0 g, was dissolved in chloroform and treated with hydrogen chloride for a few minutes. The solvent was removed *in vacuo* to give a pale yellow solid which was dried to give a quantitative yield: mp 203.5–204.5° dec; nmr ($CDCl_3$) δ 2.1–2.5 [m, 4 H, $(CH_2)_2C$], 3.05 (q, 1 H, bridgehead H), 3.2–3.9 [m, 4 H, $(CH_2)_2N$], 3.95, 3.96 (s, 9 H, OCH_3), 7.58 (s, 2 H, aromatic H), 8.07 (s, 1 H, =CH).

Anal. Calcd for $C_{17}H_{22}ClNO_4$: C, 60.10; H, 6.52; N, 4.12. Found: C, 60.38; H, 6.36; N, 4.00.

B. Free Base. The hydrochloride salt above was dissolved in methylene chloride, shaken with aqueous potassium carbonate solution and the organic phase was quickly separated, washed with saturated saline solution, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave an oil which crystallized upon scratching: mp (softens at 92°) 99–103°; tlc (alumina with methylene chloride) showed predominantly one component with a lower R_f than isomer **1** along with some of isomer **1** (6% by nmr); ir max (Nujol) 5.92 (s), 6.17 (w), 6.38 (s) μ; uv max (MeOH) 240 nm (infl, ϵ 8060), and 329 (15,500); nmr ($CDCl_3$) δ 2.10 [m, 4 H, $(CH_2)_2C$], 2.80 (q, 1 H, bridgehead H), 3.30 [m, 4 H, $(CH_2)_2N$], 4.00 (br s, 9 H, OCH_3), 7.10 (s, 1 H, =CH), 7.60 (s, 2 H, aromatic H).

(*Z*)-2-*p*-Bromobenzylidene-3-quinuclidinone (3). 3-Quinuclidinone, 7.10 g (0.056 mol), *p*-bromobenzaldehyde, 10.48 g (0.056 mol), and two pellets of sodium hydroxide were refluxed in 30 ml of ethanol for 3.5 hr and stirred overnight at room temperature. The yellow solid was collected by filtration, washed with ethanol, and dried to give 13.96 g (84.5%): mp 125–126°; ir max (Nujol) 5.88 (s), 6.14 (s), 6.32 (w) μ; tlc (alumina with benzene) showed a single component; uv max (MeOH) 225 nm (infl, ϵ 7885), 230 (7730), 301 (28,070); nmr ($CDCl_3$) δ 2.00 [m, 4 H, $(CH_2)_2C$], 2.55 (q, 1 H, bridgehead H), 2.95 [m, 4 H, $(CH_2)_2N$], 6.95 (s, 1 H, =CH), 7.40–7.80 (AA′BB′, 4 H, aromatic H).

Anal. Calcd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.80; Br, 27.35. Found: C, 57.37; H, 4.90; N, 4.59; Br, 27.25.

Crystallographic Data.[4] (*Z*)-2-*p*-Bromobenzylidene-3-quinuclidinone (p-$BrC_6H_4CH{=}CC(O)NC_5H_9$): orthorhombic; $P2_12_12_1$; a = 5.8770 (4) Å, b = 10.0866 (8) Å, c = 21.0373 (22) Å; ρ_{obsvd} = 1.34 (1) g cm^{-3} *vs.* ρ_{calcd} = 1.36 g cm^{-3} for Z = 4. Least-squares refinement with anisotropic thermal parameters for all nonhydrogen atoms (and with ideally positioned hydrogen atoms as fixed, isotropic contributors to the structure factors) gave $R_1(F)$ = 5.4% and $R_2(F)$ = 5.5% for 1143 independent diffractometry-collected data with $I \geq 2\sigma(I)$. (See paragraph at end of paper.)

(*E*)-2-*p*-Bromobenzylidene-3-quinuclidinone (4). A. Hydrochloride. Compound **3**, 1.0 g, was dissolved in chloroform and treated with HCl (g) for a few minutes. Removal of the solvent *in vacuo* gave a solid which was dried *in vacuo:* mp 207–208°.

Anal. Calcd for $C_{14}H_{15}BrClNO$: C, 51.17; H, 4.62; N, 4.26. Found: C, 50.90; H, 4.52; N, 4.06.

B. Free Base. The above hydrochloride salt was dissolved in methylene chloride and shaken with dilute potassium carbonate solution. The organic phase was quickly separated, washed with saturated saline solution and dried with $MgSO_4$. Removal of the solvent *in vacuo* gave an oil which crystallized upon scratching: mp 90–101°; tlc (micro alumina plate–benzene) indicated predominantly one component with a smaller R_f than isomer **3** along with some of isomer **3** (nmr indicated 10% **3**); ir max (Nujol) 5.90 (s), 6.13 (w), 6.24 (s), 6.32 (s) μ; uv max (MeOH) 240 nm (infl, ϵ 8060), 329 (15500); nmr ($CDCl_3$) δ 2.07 [m, 4 H, $(CH_2)_2C$], 2.67 (q, 1 H, bridgehead H), 3.14 [m, 4 H, $(CH_2)_2N$], 6.77 (s, 1 H, =CH), 7.40–7.90 (AA′BB′, 4 H, aromatic H).

(*Z*)-2-Benzylidene-3-quinuclidinone (5). 3-Quinuclidinone, 20.9 g (0.167 mol), benzaldehyde, 17.7 g (0.167 mol), and one pellet of sodium hydroxide in 75 ml of ethanol were refluxed for 1.5 hr. After the solution was cooled, the yellow solid was collected, washed with ethanol, and dried to give 32.5 g (91.2%): mp 130–132° (lit.[1] mp 133°); ir max (Nujol) 5.88 (s), 6.17 (s) μ; tlc (alumina plate with benzene) showed one component; nmr ($CDCl_3$) δ 2.05 [m, 4 H, $(CH_2)_2C$], 2.62 (q, 1 H, bridgehead H), 3.05 [m, 4 H, $(CH_2)_2N$], 7.01 (s, 1 H, =CH), 7.30–8.10 (m, 5 H, aromatic H).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.73; H, 7.14; N, 6.57.

(*E*)-2-Benzylidene-3-quinuclidinone (6). A. Hydrochloride. Compound **5**, 3.0 g, was dissolved in chloroform and treated with HCl (g) for a few minutes and the solvent was removed *in vacuo* to give 3.1 g: mp 175–177°; nmr ($CDCl_3$) δ 2.0–2.5 [m, 4 H, $(CH_2)_2C$], 3.00 (q, 1 H, bridgehead H), 3.2–4.3 [m, 4 H, $(CH_2)_2N$], 7.33–7.77 (m, 3 H, aromatic H), 7.9–8.2 (m, 3 H, aromatic H and =CH; C=CH at 8.18).

Anal. Calcd for $C_{14}H_{16}ClNO$: C, 67.34; H, 6.46; N, 5.62. Found: C, 67.59; H, 6.39; N, 5.50.

B. Free Base. The above hydrochloride salt was dissolved in methylene chloride and shaken with aqueous potassium carbonate. The organic phase was quickly separated, washed with saturated saline solution, and dried with $MgSO_4$. Removal of solvent *in vacuo* gave an oil which solidified on scratching: mp 65–69°; ir max (Nujol) 5.91 (s), 6.17 (s) μ; tlc (alumina with benzene) showed a major component with a smaller R_f than isomer **5** along with some isomer **5** (nmr indicated 8%); nmr ($CDCl_3$) δ 1.97 [m, 4 H, $(CH_2)_2C$], 2.62 (q, 1 H, bridgehead H), 3.05 [m, 4 H, $(CH_2)_2N$], 6.80 (s, 1 H, =CH), 7.25–7.85 (m, 5 H, aromatic H).

Equilibration Studies. Isomerization of ketones **1**, **3**, and **5** in $CDCl_3$ was followed by nmr, the proportion of the two isomers being obtained from integration of the vinyl hydrogen resonance.

A. 2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinone. Compound **1** to **2:** after 68 hr at 26° apparent equilibrium had been reached; no further change was effected by heating at 60° for 36 hr; the mixture now consisted of 12.5% **1** and 87.5% **2.** Compound **2** to **1:** no change was observed at 26° after 48 hr.

B. 2-*p*-Bromobenzylidene-3-quinuclidinone. Compound **3** to **4:** after 60 hr at 26° and warming to 60° for 36 hr the proportion of **4** had increased to 23%; no further change was observed at room temperature after 24 hr. Compound **4** to **3:** after 48 hr at 26° isomer **3** increased by only 3%; warming at 60° for 24 hr increased this isomer another 7% for a total change of 10%.

C. 2-Benzylidene-3-quinuclidinone. Compound **5** to **6:** after 36 hr at 60° only 10% **6** had formed; addition of a catalytic amount of HCl in $CHCl_3$ gave no change after 24 hr at room temperature. Compound **6** to **5:** after 48 hr at room temperature no change was observed; warming at 60° for 24 hr gave a 2% increase in **5.**

Studies of Induced Nmr Shifts with Eu(DMP)$_3$. Nmr spectra were measured at the probe temperature of a Perkin-Elmer R-24 spectrometer (~26°).

Solutions of substrate and $Eu(DPM)_3$ were separately prepared using $CDCl_3$ dried over molecular sieves. These studies were performed by monitoring the effects of adding aliquots of the $CDCl_3$ solution (0.05 M) of $Eu(DPM)_3$ to a $CDCl_3$ solution (0.50 M) of the substrate. Thus, 100 μl of the $Eu(DPM)_3$ was added to the substrate solution and the spectrum was recorded. This process was repeated four more times, adding 100 μl of $Eu(DPM)_3$ solution each time. For each proton of interest, the induced shift was plotted *vs.* the molar ratio of $Eu(DPM)_3$ to substrate to give a straight line whose slope is shown in Chart I.

(*E*)-3-Benzylidenebicyclo[2.2.2]octan-2-one (7). Bicyclo[2.2.2]octanone, 2.48 g (0.02 mol), and benzaldehyde, 2.12 g (0.02 mol), were dissolved in 15 ml of ethanol, treated with two pellets of potassium hydroxide, and refluxed for 6 hr. The solution was cooled to give 2.60 g. The filtrate was diluted with water to give a second crop of 0.72 g. The two crops were combined and recrystallized from ethanol to give 2.68 g after drying: mp 96–98° (lit.[9] mp 101°); ir max (Nujol) 5.91 (s), 6.17 (s) μ; tlc (alumina with methylene chloride) showed a single component: nmr ($CDCl_3$) δ 1.80 [v br s, 8 H, $(CH_2)_2C$], 2.45 [v br s, 1 H, =CH—C(=O)], 3.30 [v br s, 1 H, $(CH_2)_3CH$], 7.48 (s, 1 H, =CH), 7.40 (br s, 5 H, aromatic H).

(*Z*)-2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinol (11). 2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinone, 3.0 g (0.01

mol), was dissolved in 150 ml of methanol and treated portionwise with 2.5 g of sodium borohydride. At the completion of the addition the colorless solution was concentrated *in vacuo*. The residue was treated with water and a little ammonium hydroxide and extracted with methylene chloride and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave 2.97 g of a viscous oil; tlc analysis on alumina with ethyl acetate showed a single component. A 270-mg portion was distilled *in vacuo* in a kugelrohr to give quantitatively a pale yellow glassy material: bp 155° (3×10^{-4} mm); ir max ($CHCl_3$) 2.90 (m), 6.03 (w), 6.33 (s), 8.87 (s) μ; tlc analysis showed that this material was unchanged by distillation; nmr ($CDCl_3$) δ 6.16 (d, 1 H, =CH), 4.38 (m, 1 H, H_3).

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.83; H, 7.59; N, 4.59. Found: C, 66.61; H, 7.49; N, 4.55.

The remainder of the material was then distilled as above to yield 2.3 g which was dissolved in ether and treated with HCl (g). The resulting solid was quickly collected by filtration, dissolved in ethanol, treated with ether to the cloud point, and left at room temperature overnight. The solid was collected by filtration and dried to give 2.32 g. [A few crystals were converted to the free base and analysis by tlc (conditions cited) showed that treatment with HCl (g) had effected no change.] The analytical specimen was obtained by drying the solid in a drying pistol with refluxing methanol: mp 162–164°; ir max (Nujol) 3.12–2.15 (m), 6.33 (s) μ.

Anal. Calcd for $C_{17}H_{24}ClNO_4$: C, 59.73; H, 7.07; N, 4.10; Cl, 10.38. Found: C, 59.88; H, 7.09; N, 4.00; Cl, 10.38.

(*E*)-2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinol (12). To a solution of 3.4 g (0.01 mol) of 2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone hydrochloride in methanol, cooled in ice-water bath, was added 1.5 g of sodium borohydride portionwise over 30 min at which time the yellow color disappeared. The solvent was removed *in vacuo* and the residue was triturated with water to give a solid which was collected by filtration and dried to yield 2.45 g. Recrystallization from isopropyl alcohol gave 1.75 g which was dried in a drying pistol over refluxing methanol to give the analytical specimen: mp (melts at 143°, solidifies at 145°) 160–160.5°; ir max (Nujol) 3.09 (s) μ; uv max (MeOH) 220 nm (ϵ 28,500), 270 (17,800); nmr ($CDCl_3$) δ 6.56 (s, 1 H, =CH), 4.47 (m, 1 H, H_3).

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.21; H, 7.59; N, 4.60.

2-(3,4,5-Trimethoxybenzyl)-3-quinuclidinone (13). 2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinone, 5.3 g (0.0175 mol), was dissolved in 50 ml of methanol containing 8.75 ml of 2 *N* HCl (aqueous) and hydrogenated at atmospheric pressure and room temperature with 300 mg of 10% Pd/C catalyst. When the theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was treated with dilute sodium hydroxide solution, extracted with methylene chloride, and dried ($MgSO_4$). Removal of solvent gave 4.9 g, mp 118–122°. The analytical specimen, prepared by recrystallization of a portion from ethanol, exhibited mp 124–126.5°; ir max (Nujol) 5.82 (s), 6.27 (s), 8.05 (s), 8.87 (s) μ.

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.70; H, 7.54; N, 4.56.

***cis*-2-(3,4,5-Trimethoxybenzyl)-3-quinuclidinol (15).** In a 100-ml, 3-necked flask equipped with a gas inlet tube and a short Vigreux column with a drying tube ($CaCl_2$) was placed 1.0 g (0.0032 mol) of 2-(3,4,5-trimethoxybenzyl)-3-quinuclidinone, 2.0 g (0.01 mol) of aluminum isopropoxide, and 30 ml of isopropyl alcohol. The solution was heated to near reflux with removal of acetone assisted by a current of nitrogen. After 2.5 hr no acetone could be detected in the distillate with a 2,4-DNP test solution (1.0 g of 2,4-dinitrophenylhydrazine in 1 l. of 1 *N* HCl). The solution was then concentrated *in vacuo;* the residue was diluted with water and 10 ml of 50% sodium hydroxide solution, extracted with methylene chloride, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave an oil which solidified to give 0.9 g, mp 119–122°; tlc analysis using alumina and ethyl acetate showed only one component. Recrystallization from ethyl acetate gave 0.56 g after drying: mp 125–127°; ir max (Nujol) 3.20 (s), 6.30 (s) μ.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.79; H, 8.21; N, 4.55.

***trans*-2-(3,4,5-Trimethoxybenzyl)-3-quinuclidinol (14).** (*E*)-2-(3,4,5-Trimethoxybenzylidene)-3-quinuclidinol (12), 5.0 g (0.0164 mol), was hydrogenated at atmospheric pressure and 21° in 100 ml of methanol and 2.75 ml of 6 *N* HCl with 500 mg of 10% Pd/C catalyst. Uptake of hydrogen slowed considerably toward the end of the reaction which was terminated after 422 ml (theoretically 430 ml) of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was treated with dilute sodium hydroxide solution, extracted with methylene chloride, and dried with magnesium sulfate. Removal of the solvent *in vacuo* gave an oil which solidified on standing; tlc analysis on alumina with ethyl acetate showed this material to be predominantly the trans isomer with a small amount of the cis isomer. This material, 4.5 g, was treated with 200 ml of hot cyclohexane and decanted, and this procedure was repeated three times, leaving 0.55 g of a residue. The cyclohexane solution was concentrated to 250 ml and left at room temperature to deposit 3.36 g after drying: mp 109–111°; ir max (Nujol) 3.25 (sh, m), 6.30 (s) μ. No cis isomer was present by tlc.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.75; H, 8.21; N, 4.46.

(*Z*)-2-(3,5-Dimethoxybenzylidene)-3-quinuclidinone (16). 3-Quinuclidinone, 3.13 g (0.025 mol), and 3,5-dimethoxybenzaldehyde, 5.0 g (0.03 mol), were mixed in 25 ml of ethanol with one pellet of potassium hydroxide and the solution was refluxed for 3 hr. The yellow solid which formed on cooling was collected by filtration, washed well with water, and dried to give 6.4 g, mp 127–128.5°. The analytical specimen was obtained by recrystallization of 1.5 g from ethanol to yield 1.4 g after drying: mp 128–129°; ir max (nujol) 5.87 (m), 6.16 (s), 6.29 (s) μ.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.63; H, 7.01; N, 5.07.

2-(3,5-Dimethoxybenzyl)-3-quinuclidinone (17). A solution of 4.9 g (0.018 mol) of 2-(3,5-dimethoxybenzylidene)-3-quinuclidinone in 60 ml of methanol containing 3 ml of 6 *N* HCl was hydrogenated at atmospheric pressure and 23° in the presence of 500 mg of 10% Pd/C catalyst. Uptake of hydrogen was rapid and was terminated when the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was treated with dilute alkali, extracted with methylene chloride, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave 5.01 g of a solid; tlc analysis on alumina with methylene chloride showed one component. Recrystallization from ethyl acetate gave 2.44 g after drying: mp 90–92°; ir max (Nujol) 5.84 (s), 6.20 (sh, s), 6.28 (s) μ.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.13; H, 7.75; N, 4.99.

***trans*-2-(3,5-Dimethoxybenzyl)-3-quinuclidinol (18).** To a refluxing solution of 8.2 g of 2-(3,4,5-trimethoxybenzyl)-3-quinuclidinone in 30 ml of isopropyl alcohol was added 4 g of sodium portionwise and heating was continued until all of the sodium had reacted. The resulting cooled mass was diluted with water, extracted several times with methylene chloride, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave 6.92 g of an oil whose ir spectrum showed the absence of a carbonyl group; tlc analysis on alumina with ethyl acetate showed two components, the more mobile in preponderance. This material was dissolved in methylene chloride, treated with HCl (g), and concentrated *in vacuo* to yield a solid which was recrystallized from 30 ml of ethanol. A first crop of 5.85 g, mp 204–212°, was collected. A portion, 100 mg, was converted to the free base which, by tlc, still contained a small amount of the cis isomer. The remaining material was again recrystallized from 30 ml of ethanol to give 4.57 g, mp 217–219°. Conversion of a portion to the free base and tlc analysis showed complete absence of the cis isomer. Of this salt, 3.7 g was treated with dilute alkali, extracted with methylene chloride, and dried ($MgSO_4$). Concentration *in vacuo* gave 3.3 g of a solid. The analytical specimen was obtained by recrystallizing 0.5 g from cyclohexane to give 0.44 g after drying: mp 111–113°; ir max (Nujol) 3.23 (m), 6.28 (s) μ; nmr ($CDCl_3$) δ 3.48 (br m, 1 H, H_3), 3.76 [s, 6 H, $(OCH_3)_2$].

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.45; H, 8.59; N, 5.11.

***cis*-2-(3,5-Dimethoxybenzyl)-3-quinuclidinol (19).** 2-(3,5-Dimethoxybenzyl)-3-quinuclidinone, 1.77 g (0.0064 mol), and aluminum isopropoxide, 4.08 g (0.02 mol), were mixed in 25 ml of isopropyl alcohol in a 3-necked flask having a short Vigreux column with a distillation head. Heating commenced while nitrogen was passed into the solution until no acetone could be detected in the distillate by a 2,4-DNP reagent. Solvent was removed *in vacuo;* the residue was treated with 50% sodium hydroxide solution, diluted with water, extracted with methylene chloride, and dried ($MgSO_4$). Removal of solvent *in vacuo* gave 1.65 g, mp 118.5–120°; tlc analysis on alumina with ethyl acetate indicated complete absence of the trans isomer. This material was recrystallized from cyclohexane to give 1.34 g after drying: mp 121–122°; ir max (Nujol) 3.25 (s), 6.27 (s) μ; nmr ($CDCl_3$) δ 3.86 (br m, 1 H, H_3), 3.76 [s, 6 H, $(OCH_3)_2$].

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.60; H, 8.46; N, 4.94.

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Registry No.—**1,** 52455-66-0; **2,** 52455-67-1; **2** HCl, 52455-68-2; **3,** 52455-69-3; **4,** 52455-70-6; **4** HCl, 52539-61-4; **5,** 52455-71-7; **6,** 52455-72-8; **6** HCl, 52455-73-9; **7,** 52455-74-0; **11,** 52455-75-1; **11** HCl, 52455-76-2; **12,** 52455-77-3; **13,** 52539-62-5; **14,** 52455-78-4; **15,** 52539-63-6; **16,** 52455-79-5; **17,** 52455-80-8; **18,** 52455-81-9; **18** HCl, 52455-82-0; **19,** 52455-83-1; 3,4,5-trimethoxybenzaldehyde, 86-81-7; *p*-bromobenzaldehyde, 1122-91-4; benzaldehyde, 100-52-7; bicyclo[2.2.2]octanone, 2716-23-6; 3-quinuclidinone, 3731-38-2.

Supplementary Material. A listing of atomic coordinates will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3511.

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Reaction of Carbodiimide with Aldehyde

Iwao Yamamoto* and Haruo Gotoh

Faculty of Textile Science and Technology, Shinshu University, Ueda, Nagano 386, Japan

Toru Minami, Yoshiki Ohshiro, and Toshio Agawa

Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Yamada-kami, Suita, Osaka 565, Japan

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Reactions of carbodiimide with aromatic aldehyde gave rise to the formation of isocyanate and Schiff base *via* 1,2 cycloaddition. In the reaction of diphenylcarbodiimide with aliphatic aldehyde, no isocyanate and Schiff base were obtained but 4-anilino-3-alkylquinoline (**7a–c**), 2,4-dianilino-3-alkylquinoline (**8a,b**), and 1,3-diphenyl-2,4-diphenylimino-5-alkylpyrimidine (**11**) were formed. The formation mechanisms of these products were discussed.

Studies on the reaction of aldehydes with heterocumulenes such as isocyanates,[1] *N*-sulfinylamines,[2] sulfurdiimides,[3] and ketenes[4] have been reported. These reactions can be generalized as [2 + 2] cycloadditions to the carbonyl group of aldehydes, followed by decomposition into olefins.

$$RN{=}X{=}Y + R'CHO \longrightarrow RN{=}CHR' + Y{=}X{=}O$$

a, X = C; Y = O b, X = S; Y = O c, X = S; Y = NR

$$R_2C{=}C{=}O + R'CHO \longrightarrow R_2C{=}CHR' + CO_2$$

These reactions are mainly limited to aromatic aldehydes except for the reaction with ketene[4] and sulfonylisocyanate.[5] We now report some reactions of carbodiimides with various aldehydes and the dependence of the reaction products on substituents in the aldehydes.

Results and Discussion

Aromatic Aldehydes. The reaction of dipenylcarbodiimide (**1a**) with benzaldehyde (**2a**) at 200° gave phenyl isocyanate (**3a**) and benzylideneaniline (**4a**) in 16 and 33% yields. The reaction using dicyclohexyl- (**1b**) and dibutylcarbodiimide (**1c**) in place of **1a** similarly afforded corresponding isocyanates, **3b,c,** and imines, **4c,d,** respectively (Table I). The formation of these compounds may be explained by analogy with the reaction of other heterocumulenes with aldehydes.

Table I
The Reaction of Carbodiimide with Aromatic Aldehyde[a]

$$RN{=}C{=}NR + ArCHO \longrightarrow RN{=}C{=}O + RN{=}CHAr$$
1 2 3 4

R	Ar	Time	Yields, %[b] 3	4
C_6H_5 (**1a**)	C_6H_5 (**2a**)	6	16	33
C_6H_5	4-Cl-C_6H_4 (**2b**)	5	19	40
cyclo-C_6H_{11} (**1b**)	C_6H_5	7	18	42
n-C_4H_9 (**1c**)	C_6H_5	7	9	20

[a] Reaction temperature 200°. [b] Based on aldehyde.

The significant difference in yields between isocyanates **3** and imines **4** suggests that **3** formed initially reacts further with aldehydes to give **4.** This is also supported by the